Synthesis of the Spermidine Alkaloids (-)-(2*R*,3*R*)- and (-)-(2*R*,3*S*)-3-Hydroxycelacinnine: Macrocyclization with Oxirane-Ring Opening and Inversion *via* Cyclic Sulfamidates

by Nikolai A. Khanjin and Manfred Hesse*

Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich

Dedicated to Dr. Annalaura Lorenzi-Riacci on the occasion of her 70th birthday

The two epimers (-)-1a and (-)-1b of the macrocyclic lactam alkaloid 3-hydroxycelacinnine with the (2R,3R) and (2R,3S) absolute configurations, respectively, were synthesized by an alternative route involving macrocyclization with the regio- and stereoselective oxirane-ring opening by the terminal amino group (*Schemes 2* and 6). Properly *N*-protected chiral *trans*-oxirane precursors provided (2R,3R)-macrocycles after a one-pot deprotection-macrocyclization step under moderate dilution (0.005-0.01M). The best yields (65-85%) were achieved with trifluoroacetyl protection. Macrocyclization of the corresponding *cis*-oxiranes was unsuccessful for steric reasons. Inversion at OH-C(3) *via* nucleophilic displacement of the cyclic sulfamidate derivative with NaNO₂ led to (2R,3S)-macrocycles. The synthesized (-)-(2R,3S)-3-hydroxycelacinnine ((-)-1b) was identical to the natural alkaloid.

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





In the previous paper, we described the eight-step synthesis of (\pm) -(2RS,3RS)-3hydroxycelacinnine $((\pm)$ -**1a**) in 10% overall yield starting from potassium *trans*phenylglycidate $((\pm)$ -**5**) [5]. The key transformations involved stereo- and regioselective oxirane-ring opening with Mg(N₃)₂ and macrocyclic coupling of ditosylated



Fig. 1. Proposed structures of the novel hydroxylated alkaloids 3-hydroxycelacinnine $((\pm)-1\mathbf{a})$, 7-hydroxypleurostyline (2a), and 7-hydroxypleurocorine (3a) from Pleurostylia opposita [3][4] and their corrected structures $(-)-1\mathbf{b}$, 2b, and 3b (this work)

diamine precursor with 1,4-dibromobutane promoted by Cs_2CO_3 in DMF. NMR Data of the synthesized (\pm)-**1a** suggested that the natural 3-hydroxycelacinnine is the *cis*epimer **1b** with the ($2R^*,3S^*$) relative configuration (*Fig. 1*). The same conclusion holds for 7-hydroxypleurostyline (**2**) and 7-hydroxypleurocorine (**3**) as well since all three natural alkaloids had almost identical ¹H- and ¹³C-NMR data for the β -amino- α hydroxy-lactam moiety (*Fig. 1*) [3][4]. In addition, despite the reported zero [α]_D value and the absence of CD effect for the natural 3-hydroxycelacinnine [3], we have proposed (2R,3S) absolute configuration (as in (-)-**1b**) for the natural alkaloid. This assumption was based on the observation that all macrocyclic spermine and spermidine alkaloids with the 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) [6]. The assumption should also be extended to alkaloids **2** and **3**. Thus, the newly assumed absolute configuration at the β -amino- α hydroxy-lactam moiety in all three alkaloids requires further confirmation.

In this paper, we report the preparation of (-)-(2R,3R)-3-hydroxycelacinnine ((-)-1a) and (-)-(2R,3S)-3-hydroxycelacinnine ((-)-1b) via the more efficient 'biomimetic' route (*Scheme 1*) and confirm the assumed (2R,3S) absolute configuration for the natural alkaloid (-)-1b. Without any precedent literature data for the intramolecular macrocyclic oxirane-ring opening with amines, we investigated such a novel macrocyclization method with *trans*- and *cis*-oxirane precursors. The macrocyclization with *trans*-oxiranes went smoothly under moderate dilution (0.01M) to give macrocycles with the unnatural (2R,3R) configuration with excellent yields (up to 85%). However, reaction of the corresponding *cis*-oxiranes led only to numerous by-products for steric

reasons. This suggests an alternative biosynthetic formation of (-)-**1b**. Macrocycles with the natural (2R,3S) configuration were finally obtained from epimeric (2R,3R)-precursors by mean of inversion at C(3) involving nucleophilic displacement of a cyclic sulfamidate derivative. To the best of our knowledge, this is the first application of cyclic sulfamidates for epimerization of vicinal amino alcohols (for an example of epimerization of the taxol side chain *via* dihydrooxazole, see [7][8]). It might be an efficient method for epimerization of β -amino- α -hydroxy acids and their derivatives in general.

Synthesis of 1a. – The optimized synthetic route to (-)-1a is depicted in *Scheme 2*. Saponification of the commercially available 3-phenylglycidate 4 (*trans/cis* 9:1) with KOH in EtOH led to precipitation of pure potassium *trans*-3-phenylglycidate (= potassium *trans*-3-phenyloxirane-2-carboxylate; (\pm) -5) [5][9]. It was resolved *via* diastereoisomeric salts with (-)-(*S*)-phenylethylamine to give crystalline (-)-6 and then with (+)-(*R*)-phenylethylamine to give (+)-6 according to a described procedure [9][10]. The optically pure (2R,3S)- and (2S,3R)-potassium phenylglycidates ((-)- and (+)-5, resp.) were regenerated from (-)- and (+)-6, respectively, by quantitative (98%) precipitation from EtOH with ethanolic KOH and Et₂O. It is interesting to note that the use of NaOH led to gel formation instead of precipitation of the corresponding nonracemic sodium phenylglycidate. Glycidate (-)-5 (2*R*,3*S*) was required for the generation of (2R,3R)-macrocycles including (-)-1a after intramolecular opening with the terminal amine.

Initially, we prepared several N-protected phenylglycidic spermidines 10a-f,h for the desired macrocyclization step starting from racemic (\pm) -5 for optimization. The latter was converted to amide (\pm) -8 [5] via acid chloride (\pm) -7 [11] followed by Cs₂CO₃promoted N,C-coupling with a slight excess of N,N'-protected putrescines **9a.c-f** (1.2-1.5 equiv.) in a minimal amount of DMF (2 ml for 1 g of 8). The yields are summarized in Table 1. Initial attempts to carry out the N,C-coupling promoted by anhydrous K_2CO_3 in DMSO led to a slow reaction and undesired hydrolysis of the bromide functionality of 8. However, in the presence of Cs_2CO_3 in DMF, the reaction proceeded smoothly with all N-sulfonylated putrescines 9a,c-f. Due to the lower acidity of CF₃CO-protected amines, bis-trifluoroacetylated putrescine 9b reacted much slower under the same conditions with significant formation of N-allyl-phenylglycidamide from the competitive base-promoted HBr elimination. N-Protected putrescines 9a - fwere easily prepared according to general or published procedures from putrescine in one to three steps as described in the *Exper. Part.* Alternatively, acid chloride (\pm) -7 was coupled with ditosylated spermidine **9h** [12] in the presence of Et_3N in CH_2Cl_2 to give (phenylglycidyl)spermidine 10h in 92% yield.

The results of deprotection and subsequent macrocyclization of 10a-h are summarized in *Table 1*. From several protective groups tested for the terminal primary amine (Boc ((*tert*-butoxy)carbonyl), Ts ((4-methylphenyl)sulfonyl), Troc ((2,2,2-trichloroethoxy)carbonyl), and CF₃CO) in acyclic precursors 10a-e,h, the best yields of the desired macrocyclic products (up to 85%, *Table 1*) were achieved with the CF₃CO group. Deprotection of other groups were accompanied either by complete (Ts, Boc) or by partial oxirane cleavage (Troc). In particular, electrochemical detosylation of 10h also led to non-regioselective oxirane reduction with the formation





 $TFA = CF_3CO, Ts = 4-MeC_6H_4SO_2, cinnanoyl = (2E)-PhCH = CHCO$

of **16a** and **16b** (*Scheme 3*). In case of Boc-protected **10e**, either both Boc and oxirane (with CF₃COOH in CH₂Cl₂ or Me₃SiCl/PhOH in CH₂Cl₂) or only the oxirane were cleaved (*Amberlyst-15* (H⁺-form) in CH₂Cl₂) under acidic conditions.

With the Troc-protected **10d**, initial deprotection with Zn in THF/1M aqueous buffer 5:1 [13] at pH 5.5 (aqueous 1M KH₂PO₄/Na₂HPO₄) for 4 h followed by reflux in biphasic THF/aqueous Na₂CO₃ solution gave the desired macrocycle **12** in 26.5% yield. By-products from the oxirane and Troc reduction were also isolated including the hydroxy-amino-amide **17** (17% yield), aminocinnamamide **18** (33.6%), and the dichloroethyl oxiranylcarbamate **19** (7%), as well as product **21** (3.7%) from coupling





^a) Optimized conditions: aq. Na₂CO₃ soln./i-PrOH 70°, 36 h. ^b) For details, see discussion and *Exper. Part*; for product distribution, see also *Scheme 5*. ^c) Optimized conditions: 1. Zn/sat. aq. Na₂HPO₄ soln./THF 2. Δ ; for product distribution under different pH conditions, see *Scheme 4*. ^d) Boc deprotection also led to complete oxirane cleavage. ^e) **10f** was observed on TLC as the major product, but one-pot macrocyclization in DMF at 70° failed. ^f) Direct macrocyclization between putrescine and (±)-8 to give **13** in EtOH/Na₂CO₃ under heating failed. ^g) Electrochemical tosyl deprotection also led to complete oxirane cleavage.



of **18** and **19** (*Scheme 4*). In the presence of NH₄OAc buffer (pH 7), deprotectionmacrocyclization proceeded with a better yield of **12** (33%). The oxirane cleavage was minimized (*Scheme 4*), and the yield of **12** was improved to 53% when Troc deprotection was performed very slowly at pH 8 (sat. aqueous Na₂HPO₄ solution, 22 h), followed by macrocyclization. In this case, cinnamamide **18** could not be detected in the reaction mixture (<1%), but other by-products were isolated from it, including **17** (8.2%), **19** (10.4%), and **20** (4.2%). However, **18** was the major product



a) Sat. aq. Na₂HPO₄ soln., pH 8 22 h. *b*) 0.5M KH₂PO₄/0.5M Na₂HPO₄, pH 5.5, 4 h. *c*) 1M NH₄OAc, pH 7, 16 h. *d*) 1M AcOH, pH 3, 10 min. *e*) 1M KH₂PO₄, 85 min. *f*) 1M NaOH.

when deprotection was performed at a faster rate and thus in uncontrolled fashion under higher-(1M NaOH) or lower-pH conditions (1M AcOH or 1M KH₂PO₄).

With the CF₃CO-protected substrates, the best yields of macrocyclic products (85%) were observed after one-pot deprotection-macrocyclization at 70° for 36 h in aqueous Na₂CO₃/i-PrOH. In contrast to many other macrocyclization reactions, highdilution conditions were not required in this case. The reaction could easily be performed on a 1-g scale under moderate dilution (0.01M or 1 g in ca. 200 ml). The bimacrocyclic product 23 (Scheme 5) was observed in only 1.1% yield after deprotection-macrocyclization at 0.005M dilution in aqueous Na₂CO₃/EtOH at reflux for 22 h. In this case, the yield of **12** was also excellent (85%). However, unlike with the more hindered i-PrOH solvent, product 22 from oxirane opening by the solvent was also observed in 7% yield (Scheme 5). Also, heating at higher temperature (e.g., reflux) for a longer reaction time led to a small decrease in yield due to partial lactam hydrolysis and other competive side reactions. In a biphasic THF/aq. Na₂CO₃ system, the initial CF₃CO deprotection proceeded very slowly and resulted in a higher ratio of by-products after reflux for 3 days with the decreased 65% yield of **12**. To accelerate the initial deprotection step, it was found necessary to use diluted aqueous Na₂CO₃ solution (3 times from sat. aqueous Na₂CO₃ solution in case of EtOH or i-PrOH, and 10 times in case of THF). Otherwise CF₃CO cleavage proceeded slowly in these biphasic systems. The intermediate free amino-amide **11** could be separated when CF₃CO removal was performed at room temperature with K_2CO_3 in MeOH. However, product 11 was not



stable in pure form due to slow self-condensation between the oxirane and amino moieties present in the same molecule.

With the bis-trifluoroacetyl precursor **10b**, deprotection-macrocyclization proceeded with lower yield (67.5%) under formation of unprotected macrocycle **13** (*Table 1*). Several minor by-products were observed in this case due to the release of two unprotected N-atoms both capable of oxirane opening. Unprotected macrocycle **13** could be converted directly to the final product **1a** without additional deprotection as in case of the monotosylated lactam **12**. However, the preparation of **10b** and the purification of **13** should be further optimized.

After optimization of the reaction conditions, the synthesis was repeated starting from (-)-5 to give optically pure (+)-12 with the (2R,3R) absolute configuration. Quantitative electrochemical removal of the Ts group according to a general procedure of *Guggisberg et al.* [14] as we used in the previous synthesis of (\pm) -1a [5] provided unprotected lactam (+)-13. To avoid electrochemical detosylation, the β -naphthylsulfonyl protecting group was used instead of Ts such as in (-)-15, which was obtained by the same synthetic route as tosylated (+)-12 (*Table 1*). The reductive cleavage of the β naphthylsulfonyl group requires a lower potential, or this group can be removed chemically with Mg/MeOH [15]. But, of course, other easily cleaved sulfonyl groups, *e.g.*, 2-nitrophenylsulfonyl, can be used instead.

Unprotected lactam (+)-13 was selectively diacylated at the less hindered N(10) and OH–C(3) with an excess of cinnamoyl chloride promoted by *N*,*N*-dimethylpyridin-4-amine (DMAP) in CH₂Cl₂ or CDCl₃ to give (+)-14. Although the conditions for such N(10) over N(1) regioselection require low temperatures according to *Yamamoto* and *Maruoka* [16], no acylation took place at the more hindered N(1) of (+)-13 at room temperature. On the contrary, excess cinnamoyl chloride led to complete *O*-acylation of the basic OH–C(3). Thus, (+)-13 was diacylated at room temperature to (+)-14 (92% isolated yield) followed by one-pot saponification with NaOH in MeOH to the final (-)-(2*R*,3*R*)-3-hydroxycelacinnine ((-)-1a) (90% yield).

Synthesis of (-)-1b. – The optimized synthetic route to (-)-1b from (+)-12 via inversion at C(3) is depicted in *Scheme 6*. To quickly confirm our hypothesis concerning the $(2R^*,3S^*)$ relative configuration of the natural 3-hydroxycelacinnine, we obtained the racemic C(3) epimer (\pm)-35 of (\pm)-12 by means of a nucleophilic displacement of its cyclic sulfamidate derivative (\pm)-33 (see below). The small ¹H-NMR H–C(2)–C(3)–H coupling constant and corresponding chemical shifts in the epimer (\pm)-35 were in excellent agreement with the values of the natural alkaloid. However, the preparation of (\pm)-33 required further optimization. Then we attempted to reproduce the above 'biomimetic' synthetic route starting from corresponding *cis*oxirane derivatives (*Scheme 7*) and investigated other methods for epimerization (*Scheme 9*).





 $Ts = 4-MeC_6H_4SO_2$, R = (E) - PhCH = CH

First, we attempted to convert *trans*-oxiranecarboxamide (\pm)-**10a** to *cis*-isomer (\pm)-**30a** by the procedure of *Tung* and *Speziale* [17] for the conversion of *trans*-*N*,*N*-diethyl-3-phenylglycidamide or *trans*-ester **4** to corresponding *cis*-oxirane derivatives *via* chlorohydrins. Unfortunately, oxirane opening with HCl proceeded with almost no *threo-erythro* stereoselectivity in case of the secondary amide (\pm)-**10a**. However, we found that the *erythro*-chlorohydrin could be kinetically resolved with 100% selectivity from the reaction mixture by conversion back to the *trans*-oxirane under the mild basic conditions (aqueous NaHCO₃ solution/EtOH, room temperature, 30 min). The desired unreacted *threo*-isomer could be separated by chromatography and converted to the *cis*-oxirane under more-basic conditions (aqueous NaOH solution/benzene or *Amberlite IRA 420*/OH⁻ form) or at higher temperature (50° in aqueous Na₂CO₃ solution/ acetone). However, the procedure seemed impractical. We also attempted to use TsOH, camphorsulfonic acid, and polymer-supported sulfonic acid, *e.g.*, *Amberlyst-15*,

Scheme 7. Synthesis of the Acyclic cis-Oxirane Precursors and their Attempted Macrocyclization



 $TFA = CF_3CO, Ts = 4-MeC_6H_4SO_2$

for oxirane opening on solid support. The *threo-erythro* stereoselectivity was also poor in this case. In addition, selective cleavage of the *trans*-oxiranecarboxamide (\pm) -**10a** from the polymer-supported intermediate *threo/erythro* hydroxysulfonates with NaHCO₃ failed due to a faster and uncontrolled ring closure to a mixture of both oxiranes (\pm) -**10a** and (\pm) -**35a**. Thus, the *trans*- to *cis*-oxirane isomerization had to be initiated at the beginning of the synthetic route starting from *trans*-**4** according to the original procedure of *Tung* and *Speziale* [17].

Instead of a three-step procedure for the preparation of pure *trans*-4 [10], commercial 4 was treated directly with HCl in toluene at 0° to give a 4:1 mixture of *threo*- and *erythro*-chlorohydrin derivatives 24a and 24b, respectively, followed by

2036

Scheme 8. Rationalization of the Successful and Unsuccessful Macrocyclization of trans- and cis-Oxiranecarboxamides: Restricting the Phenyl Group in cis-Oxirane Derivatives Prevents the Formation of the (2R,3S)-Macrocycle



crystallization of pure *threo*-isomer **24a** in 52% yield (*Scheme 7*). Addition of HCl to *trans*-**4** proceeded predominantly with double inversion at C(3) involving neighboring ester O-atom participation. Compound **24a** was closed to *cis*-oxiranecarboxylate **25** with aqueous Na₂CO₃ solution in acetone as described for the corresponding bromohydrin [10]. Then **25** was saponified with KOH to **26** and resolved with (+)-and (-)-ephedrines according to *Harada* and *Nakajima* [10][18] to give the ephedrine salts (+)-**27b** and (-)-**27a**. The latter was converted directly to the intermediate acid chloride **28** with (COCl)₂. Then CF₃CO-protected *cis*-oxiranecarboxamides (+)-**30a** and **30b** were prepared *via* (+)-**29** as described above for the corresponding *trans*-oxiranecarboxamides **10a** and **10b**.

Treatment of **30a** and **30b** under the conditions described above for the macrocyclization of **10a** and **10b** led to complete decomposition of the starting *cis*oxiranecarboxamides into a complex mixture of products without formation of the desired macrocycles. Thus the CF₃CO group of **30a** was cleaved with the formation of free amino-*cis*-oxiranecarboxamide **31** as described for amino-*trans*-oxiranecarboxamide **11**. Unlike the latter, **31** was stable at room temperature in pure form and remained unreacted under the macrocyclization conditions after a short period of time. However, longer reaction time or heating at reflux in various solvents (THF, dioxane, EtOH, toluene) led to complete degradation of **31** without formation of the desired macrocycle **35**. The unsuccessful macrocyclization can be rationalized by the blocking of the nucleophilic approach by the restricting phenyl group in the *cis*-arrangement to the amide function (*Scheme* 8). Therefore, $S_N 2$ oxirane opening in case of *cis*-oxirane derivatives **35a** and **35b** is sterically unfavored, leading to a mixture of competitive byproducts presumably from $S_N 1$ opening and eliminative oxirane cleavage.

This *in vitro* model reaction of the proposed biosynthetic formation of **1b** suggests that the macrocyclization with *cis*-oxirane derivatives does not occur spontaneously *in*

vivo and perhaps would require an enzymatic influence. Nevertheless, it is conceivable to propose an alternative biosynthetic pathway that involves mono-oxidation of the naturally occurring (2*R*)-celacinnine into (2*R*,3*S*)-3-hydroxycelacinnine assisted by cytochrome P-450. Enzymatic radical monooxidation involving intramolecular addition of the forming intermediate radical to a C=C bond of the cinnamoyl group or the phenyl ring of **1b** may also explain the formation of alkaloids with an unusual bicyclic structure with a five- or seven-membered ring such as in caesalpinine [19], pleurostyline, 7-hydroxypleurostyline (**2**), and 7-hydroxypleurocorine (**3**). Alternatively, the oxidation may simply occur by air during storage. But of course, these proposals require further investigation.

The desired epimer **1b** could be obtained by nucleophilic inversion at the activated HO-C(3). To avoid neighboring N(1) participation as a potential competitive side reaction in classical methods with inversion of sulfonates or *Mitsunobu* betains, we attempted to prepare and displace cyclic sulfamidate (-)-**33** (*Scheme 6*). In this case, the N-atom is protected, and, at the same time, the O-atom is activated for the nucleophilic displacement. Using a described two-step procedure for the preparation of cyclic sulfamidates [20], we were able to isolate the desired intermediate sulfamidite (\pm)-**32** in only 20% yield after the first step due to unexpected neighboring N-atom participation in the formation of aziridine derivative (\pm)-**38** in 31% yield (*Scheme 9*). The latter is presumably formed from the intermediate **37** with the O-atom activated by the positively charged Et₃N+S(O)-O-C(3) as a good leaving group. Aziridine



derivative (\pm) -**38** was also formed as the major product (79% yield) after an attempt to prepare tosyloxy derivative (\pm) -**39** from (\pm) -**12**. In this case, N(1) remained intact due to the steric hindrance, and tosylation occurred only at the O-atom to form unstable intermediate (\pm) -**39**, which was never observed in a reaction mixture.

The isolated sulfamidite (\pm) -32 was oxidized to cyclic sulfamidate (\pm) -33 and displaced with NaNO₂ (\rightarrow (\pm)-34) according to a general procedure (for displacement of sulfonates with KNO₂, see [21]; for displacement of cyclic sulfates with KNO₂, see [22]). The desired *cis*-epimer (\pm)-35 was isolated in 14% overall yield from *trans*-epimer (\pm)-12 after acidic workup. The ¹H-NMR data of (\pm)-35 (H–C(3) at δ 4.05, H–C(2) at δ 4.16, and a small ³*J*(2,3) of 0.93 Hz) were in excellent agreement with the data of natural 3-hydroxycelacinnine (δ 4.16, δ 4.27, and *J* = 1.2 Hz, resp.).

Alternatively, N(1) could be protected with CF₃CO ((CF₃CO)₂O/Et₃N, CH₂Cl₂) to give (\pm)-**40** followed by *O*-tosylation with formation of (\pm)-**41** (87% yield) (*Scheme 9*). The tosyloxy group of (\pm)-**41** was displaced with NaNO₂ in DMF (14 h, 70°) to give epimeric *N*-nitroso-*cis*-macrocycle (\pm)-**42** in *ca*. 85% yield according to the analysis of the reaction mixture after workup. Again the typical ¹H-NMR data were observed (³*J*(2,3) = 1.9, H-C(2) at δ 6.12, and H-C(3) at δ 4.86). Cleavage of the *N*-nitroso function of (\pm)-**42** was troublesome and gave only 20% yield of (\pm)-**35** after heating with K₂CO₃ in MeOH. Thus, this route should be further investigated and optimized.

Cyclic sulfamidates can be obtained from hydroxy-*N*-triflates by base-promoted cyclization into sulfamidate under CF_3 elimination [23][24]. However, smooth protection of OH-C(3) with 'BuMe₂Si followed by *N*-triflation was not achieved in good yield.

Finally, the desired cyclic sulfamidate (-)-33 was prepared by treating (+)-12 with 1,1'-sulfinylbis[1H-imidazole] (room temperature) generated in situ from SOCl₂ and 1H-imidazole (Scheme 6). Unlike with Et₃N as base, the formation of the positively charged leaving group such as in 37 (see Scheme 9) was avoided and allowed to prepare sulfamidate (-)-33 in almost quantitative overall yield (98%) from (+)-12 via intermediate sulfamidite (-)-32. The obtained sulfamidate (-)-33 was then treated with NaNO₂ under heating in DMF at 70° for 15 h. The intermediate nitrite was instantly cleaved to give 34 after mild acidic workup with AcOH. The remaining monosulfamidate function of 34 was then smoothly removed by treatment with Amberlyst-15 (H⁺ form) as described by Khanjin and Montero for monosulfate cleavage [25]. Thus, cis-epimer (-)-35 was isolated in 70% yield. No starting transepimer (+)-12 was detectable by NMR, thus confirming a highly stereoselective inversion. Finally, (-)-1b was obtained from (-)-35 by quantitative electrochemical detosylation $(\rightarrow (-)-36)$ followed by acylation with cinnamoyl chloride as described above for (-)-1a. The optical purity of (-)-1b is assumed to be 100% based on the optical purity of the starting (-)-5 and on the diastereoisomer purity of the Mosher ester derivative 44 as determined by its ¹H-NMR data (Scheme 10).

Characterization and Comparison with the Natural Sample. - ¹H- and ¹³C-NMRsignal assignments for the synthesized (–)-**1b** and monotosylated precursor (–)-**35** were obtained from the 2D NMR data (COSY, HMBC, and HSQC). They are summarized in *Table 2* and compared with the original data of natural 3-hydroxycelacinnine [3]. Due to the restricted rotation in the cinnamamide moiety, many ¹H- and



¹³C-NMR signals of (–)-**1b** in CDCl₃ were broad, overlapped, or doubled with the approximate integral ratio 2:3. The exact ¹H- and ¹³C-NMR chemical shifts for each nucleus of both rotamers were obtained mostly from the HSQC data. Prof. *Richomme* (University d'Angers) kindly provided original hardcopies of the 2D, ¹H-, and ¹³C-NMR spectra of 3-hydroxycelacinnine [26]. They were identical to those of synthesized (–)-**1b**, except for some very minor differences due to the temperature and concentration dependence of chemical shifts (especially those of the amide NH), and sensitivity to H₂O, CD₃OD, or other H-bonding impurities.

The original 10-year old sample of 3-hydroxycelacinnine was also provided by Prof. *Richomme* and compared with the synthesized (-)-**1b** by ¹H-NMR and HPLC-MS/MS. In addition to the major component **1b** in the sample, the NMR data indicated the presence of at least two other minor components A and B in the molar ratio 1b/A/B of ca. 4:1:1 in agreement with HPLC. The retention times of the synthesized (-)-1b and the major component of the natural sample were completely identical and reproducible $(t_{\rm R}$ 14.55 min) after several runs with both individual samples and their mixtures. For comparison, the *trans*-epimer (-)-1a had t_R of 15.35 min under the same gradient conditions and was nicely separable by HPLC from the prepared mixture with the synthesized (-)-1b and the natural sample. Fragmentation of (-)-1a and (-)-1b in the MS/MS experiment were completely identical. Component A (t_R 13.55 min) was identified as 3-hydroxycelallocinnine (43; see Scheme 10) with the (Z)-cinnamoyl group according to the same m/z 422 ($[M((-)-\mathbf{1b})+1]^+$), identical fragmentation with isomeric (-)-1b in the MS/MS experiment, hypsochromic and hypochromic UV shift $(\lambda_{\text{max}} 255 \text{ nm for } 43, vs. \lambda_{\text{max}} 287 \text{ nm for } (-)-1b)$, and the presence of characteristic. ¹H-NMR olefin signals of the (Z)-cinnamoyl moiety (δ 6.56, 6.57 (2 d of two rotamers, ${}^{3}J_{cis} = 12.6$ Hz) and δ 5.98, 5.99 (2 d of 2 rotamers, ${}^{3}J_{cis} = 12.6$ Hz). Presumably, A was formed from 3-hydroxycelacinnine after light-induced $(E) \rightarrow (Z)$ C=C bond isomerization upon long-time storage. Component **B** (t_R 11.3 min) with m/z 438 ([M((-)-(1b) + 16 + 1]⁺) and a UV λ_{max} < 215 nm might correspond to some unidentified monooxidized derivative, for example 3-hydroxyleurocorine (3a,b). Components A, B, and

Table 2. Comparison of ¹ H- and ¹³ C-NMR Data of Natural 3-Hydroxycelacinnine [3] the Synthesized ($-$	
	d(-)-
	*()
(2R.3S)-3-Hydroxycelacinnine $((-)$ -1b), and $(-)$ -35	

	1b [3] ^a)		(-)- 1b , $(2R, 3S)$ (this work) ^b)		(-)- 35 , (2 <i>R</i> ,3 <i>S</i>) (this work) ^c)	
	¹ H	¹³ C	$^{1}\mathrm{H}$	¹³ C	¹ H	¹³ C
H-C(2)	$\begin{array}{c} 4.27 \\ (d, J(2,3) = 1.2) \end{array}$	64.01,	4.31 (br. s (unres. d), J(2,3) < 1.5)	64.08,	4.16 (s (unres. d), J(2,3) < 1.5)	63.94
H-C(3)	4.16 (d, J(2,3) = 1.2)	64.38 76.16	4.18 (br. <i>s</i> (unres. <i>d</i>), <i>J</i> (2,3) < 1.5)	64.38 75.94	4.05 (s (unres. d), J(2,3) < 1.5)	75.61
C(4)		76.16 172.50, 172.34	-	173.98, 173.91		173.21
NH(5)	7.00 (<i>t</i>)	172.34	7.09 (br. <i>s</i> , 0.4 H) 7.03 (br. <i>s</i> , 0.6 H)	-	7.16 (br. <i>t</i>)	-
CH ₂ (6)	3.80(m), 3.00(m)	36.72, 36.16	3.78, 2.98 3.79, 2.99	36.59, 36.13	3.65(m) 2.91(m)	36.99
CH ₂ (7)	2.25 (<i>m</i>), 1.70 (<i>m</i>)	27.92, 30.39	2.22, 1.67 2.20, 1.68	27.99, 30.26	2.06(m) 1.62(m)	29.6
CH ₂ (8)	3.75 (<i>m</i>),	43.03,	3.63, 3.55	44.37,	3.25 (<i>t</i> , <i>J</i> = 7.7, 2 H)	46.19
CH ₂ (10)	3.43 (m) 3.57 (m), 3.38 (m)	44.59 ^a) 44.01, 46.80 ^d)	3.69, 3.45 3.53, 3.38 3.52, 3.39	43.38 44.96 46.56	3.3(m)	47.69
CH ₂ (11)	1.92(m), 1.62(m)	24.88°), 25.12	1.92, 1.56 1.92, 1.63	24.42, 26.18	1.82 (m) 1.55 (m)	24.20
CH ₂ (12)	1.65(m), 1.45(m)	24.22°), 26.06	1.47, 1.58	24.64	1.42 (<i>m</i> , 2 H)	25.59
CH ₂ (13)	2.86 (<i>m</i>), 2.31 (<i>m</i>)	46.55, 46.46	2.46, 2.82 2.46, 2.82	46.18, 47.04	2.69 (dt (ddd), ² $J = 12.2$, ³ $J = 4.8$) 2.33 (m)	45.56
OH-C(3)			-	-	- -	-
$\begin{array}{l} Phenyl: \\ C(1') \end{array}$		142.35,	-	140.82, 140.54	-	141.17
H-C(2'), H-C(6')	7.35 (<i>m</i>)	142.44 127.76 ^f)	7.37	127.35	7.32	127.19
H - C(3'), H - C(5')	7.35 (<i>m</i>)	126.99 ^f)	7.37	128.57	7.33	128.88
H–C(4') Cinnamoyl or	7.35 (m) • tosyl:	127.56 ^f)	7.30	127.88	7.26	127.72
O=C		165.16, 165.82	-	166.66, 166.38	-	-
CH=CHCO	$\begin{array}{c} 6.30 \\ (d, J(2,3) = 15.4) \end{array}$	117.53	6.80 (br. $(d, J = 15.5)$	117.46	_	-
CH=CHCO	7.66 (d, J(2,3) = 15.4)	140.79	7.66 $(d, J = 15.5)$	142.78,	-	-
C(1")		135.41	-	142.65 135.35	_	137.15
H-C(2''), H-C(6'')	7.52 (<i>m</i>)	128.78	7.51 (br. <i>d</i>)	127.88	7.67 $(d, J = 8.2)$	127.3
H-C(3''), H-C(5'')	7.35 (<i>m</i>)	128.78	7.37	128.88	7.29 $(d, J = 8.2)$	129.88
$ \begin{array}{c} H-C(4'') \\ Me-C(4'') \end{array} $	7.35 (<i>m</i>)	129.49	7.36	129.72	- 2.42	143.34 21.68

^{a)} Spectra in CDCl₃ at room temperature with SiMe₄ as internal reference; ¹H- and ¹³C-NMR at 270 and 67.5 MHz, resp. ^b) ¹H- and ¹³C-NMR and 2D NMR: 6 mg in 0.8 ml of CDCl₃, δ (SiMe₄) 0.00(¹H, 500 MHz), δ (CDCl₃) 77.23 (¹³C, 125 MHz). Due to a low sample concentration, some ¹³C-NMR signals were not resolved: these δ are based on a more concentrated sample of (–)-**1b**: 40 mg in 0.6 ml of CDCl₃ + 0.05 ml of CD₃OD, δ (CDCl₃) 77.23 (¹³C, 75 MHz). ^c) 38 mg in 0.7 ml of CDCl₃, 300 K, δ (Me₄Si) 0.00 (¹H, 600 MHz), δ (CDCl₃) 77.23 (¹³C, 75 MHz). ^c) 1 nterchangeable values each.

1b were poorly separable by prep. TLC with several eluent systems investigated. Thus, it was not possible to make a pure sample of natural **1b** and to make a definite conclusion about the absolute configuration based on $[\alpha]_D$ values of the synthetic (-)-**1b** ($[\alpha]_D = -38.5$) and the old natural sample ($[\alpha]_D = -18$) due to impurities.

However, it was possible to convert both 3-hydroxycelacinnine $((-)-\mathbf{1b})$ and 3-hydroxycelallocinnine (43 or A) from the natural sample into the same compound, *i.e.*, dihydro-3-hydroxycelacinnine (-)-45, after hydrogenation with H₂ over Pd/C (*Scheme 10*). The latter compound was also prepared either from the unprotected lactam (-)-36 by acylation with 3-phenylpropanoyl chloride or by hydrogenation of the synthesized $(-)-\mathbf{1b}$. Component B remained unchanged upon catalytic hydrogenation and was not separable by prep. TLC. However, it remained a minor component (*ca.* 15%) in the mixture with 45 according to ¹H-NMR.

Crude natural **45** and synthesized (-)-**45** (5.0 mg each in 10 ml MeOH) gave nearly identical CD curves (*Fig.* 2). The difference in amplitude between their CD spectra corresponds exactly to a lower amount of **45** (*ca.* 80%) in the hydrogenated natural sample. It should be noted that it was not possible to record CD spectra of (-)-**1b** with a reasonable signal-to-noise ratio due to the strong UV-absorbing cinnamoyl group at N(9) distant from the chiral center at C(2) with the weakly absorbing Ph group. Moreover, crude (*S*)-*Mosher* esters prepared from both synthesized (-)-**1b** (see **44**) and from the crude natural **1b** were completely identical and diastereoisomerically pure by ¹H-NMR. Thus, the absolute configuration of natural 3-hydroxycelacinnine is (2R,3S) as in the identical synthetic (-)-(2R,3S)-3-hydroxycelacinnine ((-)-**1b**).



Fig. 2. CD Curves of synthetic (-)-45) and hydrogenated natural 3-hydroxycelacinnine

Conformational Analysis of Epimeric Macrocycles. – The relative $(2R^*, 3R^*)$ transconfiguration in **1a** and *cis*-configuration $(2R^*, 3S^*)$ in **1b** can be indirectly confirmed by means of a Monte Carlo Multiple Minimum (MCMM) conformational search with MM2*, MM3*, and Amber force fields, followed by calculation of the *Boltzmann*-

2042

averaged ¹H-NMR ³J(2,3) coupling constants based on the *Altona* modification [27] of the Karplus equation all implemented in MacroModel [28]. Since the experimental values of ${}^{3}J(2,3)$ of *trans*-macrocycles **1a**, **12–15**, **40**, and **41** were practically identical $({}^{3}J(2,3) = 9 - 10 \text{ Hz})$ as well as those of *cis*-macrocycles **1b**, **34**-**36**, **42**, and **44** $({}^{3}J(2,3) < 10^{-10} \text{ Hz})$ 2 Hz), the conformational search on all rotatable bonds was performed only with the lowest-molecular-mass representatives 13 and 36. MCMM on these structures generated several thousands of conformers within a 25-kcal/mol energy window relative to the found global minimum. Although all three force fields predicted three different global minima and conformation-energy distributions for each epimer, one family of conformers distinguished by the dihedral angle around C(2)-C(3) (antiperiplanar) was more stable than the other (gauche). Anti conformers of 13 or 36 with ca. 180° torsion between the two bulky substituents Ph at C(3) and CONHR at C(3) were calculated to be more stable by 3-7 kcal/mol (depending on the force field) than corresponding gauche conformers. Thus, an ideal anti-periplanar arrangement of Ph and CONH forces the two vicinal H-C(2) and H-C(3) to the anti-periplanar arrangement in case of trans-macrocycle 13 corresponding to a very large calculated and experimental ${}^{3}J(2,3)$ (Fig. 3). In the case of the *cis*-macrocycle **36**, the theoretical 60° torsion between vicinal H-atoms is distorted due to the repulsive interaction between remaining substituents OH and NHR in the gauche arrangement to Ph and CONHR, respectively. Thus, vicinal H-atoms are in ca. 90° torsion corresponding to a very small calculated ${}^{3}J(2,3)$ (0.8–2 Hz, depending on the force field), in excellent agreement with the observed values for cis-macrocycles including (-)-1b.



Fig. 3. Lowest-energy conformations around C(2)-C(3) and calculated Boltzmann-averaged J(2,3) for (2R,3R)- and (2R,3S)-macrocycles

Conclusions. – We confirmed the absolute configuration of the natural 3-hydroxycelacinnine by means of the total synthesis of its two diastereoisomers (-)-(2R,3R)- and (-)-(2R,3S)-3-hydroxycelacinnine ((-)-**1a** and (-)-**1b**, resp.). A new macrocyclization method *via* oxirane opening by the terminal amino group was developed. Also, a new inversion method of vicinal amino alcohols *via* cyclic sulfamidates was discovered. Synthesized (-)-**1b** was identical in every respect with the natural alkaloid. In the light of our negative results with the macrocyclization of *cis*-oxirane precursors **30a**, **30b**, and **31**, we conclude that the proposed biosynthetic pathway might work for the unnatural (-)-**1a** generated from *trans*-oxirane (*Scheme 1*), but it is unlike for the epimeric natural (-)-**1b**, which should be formed from *cis*-oxirane. The alkaloid (-)-**1b** as well as bicyclic alkaloids **2** and **3** from the same

natural source are presumably synthesized *in vivo* by an alternative pathway, for example, by oxidation of (-)-(2R)-celacinnine in the presence of some mono-oxygenase enzyme or simply on exposure to air.

We greatfully acknowledge the *Swiss National Science Foundation* for the generous support of this work and for the postdoctoral fellowship award to *N.A.K.* Special thanks go to Professor *P. Richomme* (University d'Angers) for providing the original data and sample of 3-hydroxycelacinnine and to Dr. *K. Drandarov* for his help with CD measurements.

Experimental Part

General. See [5]. HPLC: t_R in min. $[\alpha]_D$: *Perkin-Elmer 241* polarimeter. UV: λ_{max} in nm. CD Spectra: *Jasco J-715* spectropolarimeter.

Chiral Resolution of Potassium trans-3-Phenyloxiranecarboxylate (5) with Phenylethylamine. Salt (\pm)-5 [5][9] (34.02 g, 168.4 mmol) was resolved with (+)-(*R*)-phenylethylamine, which crystallized with the (+)-(2*S*,3*R*)-acid to give (+)-6 (16.5 g, 34.3%; [α]_D = +125.8 (*c* = 1.14, EtOH); [10]: +125.4) and then with (-)-(*S*)-phenylethylamine to give with the (-)-(2*R*,3*S*)-acid a crystalline salt (-)-6 (15.55 g, 32.4%; [α]_D = -124) according to *Thijs et al.* [10].

Potassium (-)-(2R,3S)-trans-3-Phenyloxiranecarboxylate ((-)-5). The suspension of (-)-6 (14.59 g, 51.2 mmol) in EtOH (200 ml) was sonicated for 5 min followed by addition of KOH (3.77 g, 67.3 mmol) in EtOH (50 ml) and cooled in an ice/water bath. The precipitate was filtered, washed with EtOH, acetone, and Et₂O to give 9.19 g of (-)-5 ($[\alpha]_D = -139.5$ (c = 1.14, H₂O)). The supernatant gave additional 970 mg of the product ($[\alpha]_D = -138.2$ (c = 1.24)) after quenching with Et₂O. ¹H-NMR (300 MHz, 20 mg in 0.6 ml of D₂O; δ (DHO) 4.8): 7.43-7.58 (m, 5 arom. H); 4.08 (d, J = 1.9, H–C(3)); 3.67 (d, J = 1.9, H–C(2)). ¹³C-NMR (75 MHz): 175.32 (CO); 135.62 (C₁₉₅₀); 128.95 (C_p); 128.75 (C_m); 126.03 (C_o); 58.86, 57.47 (C(2), (C(3))).

(-)-(2R,3S)-trans-N-(3-Bromopropyl)-3-phenyloxiranecarboxamide ((-)-8) was obtained from (-)-5 by the same procedure as (\pm) -8 [5]. An anal. sample was prepared after purification by FC (SiO₂, 35% AcOEt/hexane) and crystallization from AcOEt/hexane. Colorless fibers. M.p. $100.0-100.3^{\circ}$. $[\alpha]_{\rm D} = -46.8$ (c = 1.4, CHCl₃). Other data: completely identical with those of (\pm) -8 [5].

2,2,2-Trifluoro-N-[4-{[(4-methylphenyl)sulfonyl]amino]butyl]acetamide (**9a**). Method A: To a stirred soln. of N-(4-aminobutyl)-4-methyl benzenesulfonamide (**9f**) [29] (860 mg, 3.554 mmol) in CH₂Cl₂ (15 ml), (CF₃CO)₂O (0.583 ml, 4.19 mmol) was added dropwise during 1 min. After 25 min, the mixture was evaporated under h.v. to give 1.27 g of colorless crystalline solid. The product was crystallized from EtOH/0.5M aq. HCl to give a white powder (82.6% yield).

Method B: To a stirred soln. of **9e** (8.058 g, 23.56 mmol) in CH₂Cl₂ (80 ml), (CF₃CO)₂O (15 ml) was added, followed by dropwise addition of CF₃COOH (10 ml) at 0°. After 17 h at r.t., the mixture was evaporated to give 10.13 g of a pale brown solid, which was crystallized from EtOH (50 ml) and H₂O (300 ml): **9a** (7.002 g, 87.9%). M.p. 95–101°. FT-IR (KBr): 3314s (N–H), 3254s (N–H), 3104w, 3070w, 2968m, 2954m, 2932m, 2892w, 2865m, 2760w, 1924w, 1698s (C=O), 1600m, 1561s, 1496w, 1475m, 1441m, 1400w, 1381w, 1353m, 1322s, 1306s, 1292m, 1246m, 1212s, 1183s, 1159s, 1091m, 1065m, 1038m, 1019w, 896m, 815s, 803w, 744m, 726s, 706m, 660m, 634w, 596w, 571s, 550s, 520m. ¹H-NMR (300 MHz, CDCl₃): 7.72 (d, J = 8.3, H_o); 7.30 (d, J = 8.0, 2 H_m); 6.94 (br. t, NHCO); 5.19 (br. s, NHTs); 3.31 (q, J = 6.6, CH₂NHCO); 2.94 (t, J = 6.5, CH₂NHTs); 2.42 (s, Me); 1.61, 1.53 (2m, 2 CH₂). ¹³C-NMR (75 MHz, CDCl₃) δ (CDCl₃) 76.91): 157.39 (q, J = 36.7, NHCO); 143.57 (C_p of Ts); 136.47 (C_{ipso} of Ts); 129.68 (C_m of Ts); 126.88 (C_o of Ts); 115.75 (q, J = 288, CF₃); 42.44 (CH₂NHTs); 39.23 (br., CH₂NHCO); 26.43, 25.65 (CH₂CH₂); 21.33 (Me). ESI-MS: 361 ([M + Na]⁺).

N,N'-Butane-I,4-diylbis[2,2,2-trifluoroacetamide] (9b). To a cold (ice/water bath) stirred soln. of $(CF_3CO)_2O$ (31.4 g, 149.6 mmol) in CH_2Cl_2 (150 ml), putrescine (= butane-1,4-diamine; 5.276 g, 59.85 mmol) in CH_2Cl_2 (75 ml) was added. The mixture was stirred for 60 min and evaporated to give a solid mixture of two products. The latter was dissolved in hot EtOH (100 ml). Then 1N aq. HCl was added (20 ml) and the mixture slowly diluted with hot H_2O (125 ml), allowed to cool in an ice/water bath, and filtered. The solid was washed with H_2O and dried under h.v.: **9b** (7.06 g, 42%). M.p. 154.4–154.6°. FT-IR (KBr): 3312*s*, 3115*m*, 2993*w*, 2968*m*, 2936*w*, 2904*w*, 2869*w*, 1705*s*, 1566*s*, 1450*m*, 1375*m*, 1346*w*, 1324*w*, 1245*s*, 1205*s*, 1177*s*, 1044*w*, 986*m*, 944*m*, 838*w*, 767*w*, 722*s*, 700*s*, 526*w*, 477*w*. ¹H-NMR (300 MHz, 31 mg in 0.6 ml (D₆)DMSO; $\delta((D_6)DMSO)$ 2.5): 9.37 (br. *t*, NHCO); 3.19 (unresolved *m*, 2 CH₂N); 1.48 (*quint*, *J* = 3.2, 2 CH₂). ¹³C-NMR (75 MHz, (D₆)DMSO; $\delta((D_6)DMSO)$ 39.38): 156.08 (*q*, *J* = 36.5, NHCO); 115.82 (*q*, *J* = 288, CF₃); 38.58 (CH₂NH); 25.36 (CH₂).

2,2.2-Trifluoro-N-[4-[(naphthalen-2-ylsulfonyl)amino]butyl]acetamide (9c). To a soln. of monoprotected N-[(tert-butoxy)carbonyl]putrescine [30] (1.615 g, 8.59 mmol) and Et₃N (4 ml) in CH₂Cl₂ (25 ml), naphthalene-2-sulfonyl chloride (1.947 g, 8.59 mmol) was added in portions and stirred for 60 min. The mixture was evaporated, the residue dissolved in CHCl₃, and the soln. washed with 10% citric acid (2 × 20 ml), then with sat. aq. NaHCO₃ soln. The org. phase was dried (Na₂SO₄) and evaporated under h.v. to give 3.449 g of pale brown oil used in the next step without further purification. This oil was treated with an excess of (CF₃CO)₂O/CF₃COOH as described above for **9a** (*Method B*) and crystallized from hot EtOH/H₂O: **9c** (2.5 g, 77%). White crystals. M.p. 100–102°. FT-IR (KBr): 3265s, 3111m, 3061w, 2981w, 2924m, 2865m, 1716s, 1697s, 1626w, 1570s, 1503w, 1470w, 1457m, 1441m, 1370m, 1351m, 1316s, 1216s, 1186s, 1154s, 1126s, 1077m, 1061s, 1017w, 971w, 958w, 947w, 910m, 877m, 827s, 748s, 722s, 702s, 657m, 640m, 617w, 561w, 534w, 517w, 484m. ¹H-NMR (300 MHz, 10 mg in 0.5 ml of CDCl₃): 8.43 (d, J = 1.2, 1 H); 7.80–8.04 (m, 4 H); 7.63 (m, 2 H); 6.66 (br. s, NHCOCF₃); 5.08 (br. t, J = 5.8, NHSO₂); 3.32 (q, J = 6.7, 2 H); 3.01 (q, J = 5.4, 2 H); 1.48–1.7 (m, 4 H). ¹³C-NMR (75 MHz, CDCl₃; δ (CDCl₃) 76.90): 157.32 (q, J = 36.6, COCF₃); 136.31, 134.75, 132.05 (3 quat. arom. C); 129.53, 129.1, 128.8, 128.32, 127.82, 127.57, 122.02 (7 arom. CH); 42.51 (CH₂NHS); 39.21 (CH₂NHCO); 26.58, 25.74 (CH₂CH₂). ESI-MS: 397 (100, [M + Na]⁺), 771 (95, [2M + Na]⁺).

2,2.2-Trichloroethyl [4-[[(4-Methylphenyl)sulfonyl]amino]butyl/carbamate (9d). To a cold (ice/water bath) stirred soln. of 9f [29] (1.2 g, 4.959 mmol) and DMAP (0.606 g, 4.959 mmol) in CH₂Cl₂ (20 ml), 2,2.2-trichloroethyl carbonochloridate (TrocCl; 0.669 ml, 4.959 mmol) was added dropwise. After 3 h, the mixture was evaporated, the residue partitioned between 10% citric acid (2 × 20 ml) and CH₂Cl₂, the org. phase washed with sat. aq. NaHCO₃ soln., dried (Na₂CO₃), and evaporated under h.v., and the pale brown oil (2.317 g) crystallized: 9d (2.069 g, 100%), which was used in the next step without further purification. M.p. 89–91°. R_f (AcOEt/hexane 1:1) 0.6. FT-IR (KBr): 3351*m* (N–H), 3226*m* (N–H), 3048*w*, 2952*w*, 2937*w*, 2878*w*, 1906*w*, 1725*s* (C=O), 1600*w*, 1536*s*, 1494*w*, 1479*w*, 1459*w*, 1451*w*, 1441*w*, 1379*w*, 1356*w*, 1323*s*, 1304*m*, 1245*s*, 1184*w*, 1157*s*, 1131*m*, 1086*m*, 1056*m*, 1025*w*, 986*w*, 952*w*, 916*w*, 864*w*, 848*w*, 810*s*, 771*w*, 733*s*, 704*m*, 694*m*, 657*w*, 569*m*, 551*m*, 524*m*. ¹H-NMR (300 MHz, CDCl₃): 7.74 (*d*, *J* = 8.3, 2 H_o of Ts); 7.31 (*d*, *J* = 8.2, 2 H_m of Ts); 5.04 (br. *t*, NHTs); 4.73 (overlapping br. *t*, *J* = 6.3, NHCO₂); 4.70 (overlapping *s*, CH₂O); 3.20 (*q*, *J* = 6.4, CH₂NHCO); 2.96 (*q*, *J* = 6.4, CH₂NHTS); 2.43 (*s*, Me of Ts); 1.47–1.63 (2 overlapping *quint*, CH₂CH₂). ¹³C-NMR (75 MHz, CDCl₃); $\delta(CDCl_3)$, 76.89): 154.56 (C=O); 143.37 (C_p); 136.84 (C_{mpo}); 129.63 (C_m); 126.97 (C_o); 42.60 (CH₂NHTS); 4.05 (CH₂NHCO); 26.70, 26.59 (CH₂CH₂); 21.38 (Me). ESI-MS: 439, 441, 443, 445 (100, 95, 45, 4 [*M* + Na]⁺). CI-MS (NH₃): 286 ([TsNH(CH₂)₄NHCONH₂]⁺).

1,1-Dimethylethyl [4-[[(4-Methylphenyl)sulfonyl]amino]butyl]carbamate (9e) [31]. R_f (AcOEt/hexane 1:1) 0.62. ¹H-NMR (300 MHz, CDCl₃): 7.74 ($d, J = 8.3, 2 H_o$); 7.29 ($d, J = 8.1, 2 H_m$); 5.08 (br. s, NHTs); 4.6 (br. s, NHBoc); 3.05 (br. s, CH₂NHBoc); 2.93 (br. s, CH₂NHTs); 2.42 (s, Me of Ts); 1.44–1.52 ($m, 2 CH_2$); 1.42 (s, Me_3C). ¹³C-NMR (75 MHz, CDCl₃; δ (CDCl₃) 76.93): 155.89 (C=O); 143.19 (C_p); 136.94 (C_{ipso}); 129.56 (Cm); 126.96 (C_o); 79.13 (Me₃C); 42.69 (CH₂NHTs); 39.82 (br., CH₂NHCO); 28.28 (Me_3C); 27.04, 26.61 (CH₂CH₂); 21.35 (Me of Ts).

 $\begin{array}{l} \text{N-}[4\text{-}Aminobutyl]$4\text{-}methylbenzenesulfonamide (9f) [29]. 1H-NMR (10 mg in 0.6 ml of CDCl_{3}, 300 MHz): $7.74 (d, J = 8.3, 2 H_{o})$; $7.29 (d, J = 8.1, 2 H_{m})$; $2.8-3.2 (br., NH_{2}, NHTs)$; $2.92 (t, J = 6.45, CH_{2}NHTs)$; $2.67 (t, J = 6.3, CH_{2}NH_{2})$; $2.42 (s, Me of Ts)$; $1.4-1.6 (2 m, 2 CH_{2}). 1C-NMR (75 MHz, CDCl_{3}; $0(CDCl_{3}) 76.94)$: $142.93 (C_{p})$; $137.25 (C_{ipso})$; $129.49 (C_{m})$; $126.91 (C_{o})$; $42.9 (CH_{2}NH)$; $41.17 (CH_{2}NH_{2})$; $30.21, $27.25 (2 CH_{2})$; $21.34 (Me)$. $ \end{array}$

N-(3-Aminopropyl)-4-methyl-N-[4-[[(4-methylphenyl)sulfonyl]amino]butyl]benzenesulfonamide (**9h**) [12]. $R_{\rm f}$ (CH₂Cl₂/MeOH/25% aq. NH₃ soln. 90 :9 :1) 0.3. ¹H-NMR (300 MHz, 30 mg in 0.7 ml of CDCl₃): 7.77 ($d, J = 8.3, 2 H_o$ of TsNH); 7.63 ($d, J = 8.3, 2 H_o$ of TsN); 7.26 ($d, J = 8.1, 2 H_m$ of TsNH); 7.23 ($d, J = 8.3, 2 H_m$ of TsN); 6.6–7.0 (br. *s*, 4 H, NHTs, NH₂, H₂O); 3.1–3.25 (m, CH_2 N(Ts)CH₂); 2.98 ($t, J = 7.2, CH_2$ NH₂); 2.88 ($t, J = 6.0, CH_2$ NHTs); 2.36, 2.37 (2*s*, 2 Me of 2 Ts); 2.15 (*quint*, $J = 7.1, NCH_2CH_2CH_2N$); 1.63 (unres. *quint*, $J = 6.5, CH_2$); 1.46 (unres. m, CH_2). ¹³C-NMR (75 MHz, CDCl₃; δ (CDCl₃) 76.90): 143.27 (C_p of TsN); 143.04 (C_p of TsNH); 136.98 (C_{ipso} of TsNH); 135.50 (C_{ipso} of TsN); 129.68, 129.62 (4 C_m of 2 Ts); 127.1, 126.99 (4 C_o of 2 Ts); 49.54, 46.79 (CH₂NCH₂); 42.41 (CH₂NHTs); 37.95 (CH₂NH₂); 27.29 (NCH₂CH₂CH₂N); 26.38 (overlapping 2 CH₂); 21.32 (2 Me of 2 Ts).

 (\pm) -(2RS,3SR)-N-[3-[[(4-Methylphenyl)sulfonyl][4-[(trifluoroacetyl)amino]butyl]amino]propyl]-3-phenyloxiranecarboxamide ((\pm)-10a). A mixture of (\pm)-8 (845 mg, 2.975 mmol), 9a (1.09 g, 3.22 mmol), Cs₂CO₃ (1.11 g, 3.407 mmol), and DMF (3.5 ml) was stirred at r.t. under N₂ for 7 h and partitioned between H₂O (100 ml) and CH₂Cl₂ (75 ml). The aq. layer was extracted with CH₂Cl₂ (2 × 40 ml) and the combined org. phase dried (Na₂SO₄) and evaporated under h.v. (12 h, r.t.): 2.015 g of brown oil. The oil was dissolved in CH₂Cl₂/CCl₄ 1:1 (6 ml) and submitted to FC (SiO₂ (100 ml), AcOEt/hexane 1:1 (500 ml), then 6:4 (200 ml): pure (\pm)-10a (1.055 g, 65.5%). White foam. R₁ (AcOEt/hexane 1:1) 0.15. FT-IR (neat, NaCl): 3325s (br., N–H), 3088m, 3066*m*, 2942*m*, 2872*m*, 1717*s* (C=O), 1668*s* (C=O), 1598*w*, 1540*s*, 1496*m*, 1459*m*, 1380*m*, 1335*s*, 1306*w*, 1289*w*, 1267*w*, 1210*s*, 1184*s*, 1157*s*, 1090*m*, 1020*w*, 890*w*, 860*w*, 815*m*, 757*w*, 736*m*, 699*m*, 653*w*, 597*w*, 573*w*, 548*w*. ¹H-NMR (300 MHz, 45 mg in 0.6 ml of CDCl₃): 7.66 (d, J = 8.3, 2 H_o of Ts); 7.23 – 7.4 (m, 7 arom. H, NHCOCF₃); 6.80 (br. t, J = 6.1, NHCO); 3.94 (d, J = 1.9, H–C(3)); 3.48 (d, J = 1.9, H–C(2)); 3.31 – 3.46 (m, 4 H); 3.02 – 3.23 (m, 4 H); 2.41 (s, Me); 1.78 (*quint*, J = 6.7, NCH₂CH₂CH₂N); 1.64 (2 overlapping *m*, CH₂CH₂). ¹³C-NMR (75 MHz, CDCl₃; δ (CDCl₃) 76.93): 167.85 (CONH); 157.35 (q, J = 36.5, CF₃CO); 143.57 (C_p of Ts); 125.67 (C_o of Ts); 134.85 (C_{ipso} of Ph); 129.75 (C_m of Ts); 128.88 (C_p of Ph); 128.52 (C_m of Ph); 126.98 (C_1 , 07 Ts); 125.67 (C_o of Ph); 115.86 (q, J = 288, CF₃); 58.87, 58.77 (overlapping C(2), C(3)); 49.08, 46.88 (CH₂NCH₂); 39.12 (CH₂NHCOCF₃); 36.26 (CH₂NHCO); 28.74 (NCH₂CH₂CH₂N); 26.16, 25.79 (CH₂CH₂); 21.33 (Me). ESI-MS: 564 ($[M + Na]^+$).

(-)-(2R,3R)-N-(3-[(4-Methylphenyl)sulfonyl]/4-[(trifluoroacetyl)amino]butyl]amino]propyl]-3-phenyloxiranecarboxamide ((-)-10a) was prepared from (-)-8 by the same procedure as (±)-10a and was identical to $the latter. <math>[a]_{\rm D} = -25.7$ (c = 1.6, CHCl₃).

 (\pm) -(2RS,3SR)-3-Phenyl-N-{3-{(trifluoroacetyl)}/4-{(trifluoroacetyl)amino]butyl]amino]propyl]oxirane*carboxamide* (10b). A mixture of (\pm)-8 (500 mg, 1.76 mmol), 9b (2.03 g, 7.25 mmol), Cs₂CO₃ (2.23 g, 7.04 mmol), and DMF (4 ml) was stirred at r.t. under N₂ for 38 h. The mixture was quenched with H₂O/CH₂Cl₂, and the excess **9b** was filtered off. The aq. layer was extracted with $CHCl_3(4\times)$, dried, and evaporated. The residue (283 mg) was chromatographed by FC (SiO₂ (25 ml), gradient of 20-70% AcOEt/hexane): 10b (146 mg, 17.2%). White foam. R_f (AcOEt/hexane 1:1) 0.15. FT-IR (neat, NaCl): 3313s (br., N-H), 3094m, 2948m, 2869m, 2253w, 1715s (C=O), 1682s (C=O), 1546s, 1498w, 1460m, 1443m, 1383m, 1330w, 1313w, 1285w, 1202s, 1183s, 1152s, 1118m, 1028w, 912m, 893m, 859w, 758m, 735s, 698m, 666w, 649w, 597w. ¹H-NMR (300 MHz, 30 mg in 0.5 ml of CDCl₃; rotamers A/B 6:4): 7.32-7.39 (m, 3 arom. H); 7.23-7.30 (m, 2 arom. H); 7.04-7.20 (br. m, NHCOCF₃ of A and B); 6.77 (br. t, J = 6.1, 0.6 H, NHCO of A); 6.52 (br. t, J = 6, 0.4 H, NHCO of B); 3.92 (d, J = 1.9, 0.6 H, H - C(3) of A); 3.87 (d, J = 1.9, 0.4 H, H - C(3) of B); 3.51 (d, J = 1.9, 0.4 H, H - C(2) of B)B); 3.49 (d, J=1.9, 0.6 H, H-C(2) of A); 3.36-3.50 (m, 6 H); 3.20-3.36 (m, 2 H); 1.78-1.94 (m, 2 H, NCH₂CH₂CH₂N); 1.55–1.76 (*m*, CH₂CH₂). ¹³C-NMR (75 MHz, CDCl₃; δ(CDCl₃) 76.96); 167.94 (CONH); $157.49 (q, J = 37.2, CF_3CONH); 157.18 (q, J = 36, CF_3CONH); 156.7 (q, J = 36, CF_3CO); 134.75, 134.52 (C_{ipso} of C_{ipso}); 134.75, 134.52 (C_{ipso}); 135.75 (C_{ipso}); 134.75, 134.52 (C_{ipso}); 134.75 (C_{ipso}); 135.75 (C_{ipso}); 134.75 (C_{ipso}); 13$ Ph of A and B, resp.); 129.05, 128.92 (C_p of Ph of B and A, resp.); 128.6, 128.53 (C_m of Ph of B and A, resp.); 125.65 (C_o of Ph); 116.36 (q, J=288, CF₃); 115.83 (q, J=288, CF₃CONH); 58.83, 58.80, 58.70, 58.65 (overlapping C(2), C(3) of A and B); 47.18, 46.53, 45.41, 44.27 (CH₂NCH₂ of A and B); 38.99, 38.93 (CH₂NHTFA of B and A, resp.); 36.1, 36.0 (CH₂NHCO of B and A, resp.); 28.90, 27.31 (NCH₂CH₂CH₂N of B and A, resp.); 25.86, 25.79, 25.65, 23.9 (CH₂CH₂ of A and B). ESI-MS: 506 ([M+Na]⁺).

(-)-(2R,3S)-N-(3-((Naphthalen-2-ylsulfonyl)/4-[(trifluoroacetyl)amino]butyl]amino]propyl]-3-phenyloxiranecarboxamide ((-)-10c). A mixture of (-)-8 (704 mg, 2.479 mmol), 9c (1.134 mg, 3.032 mmol), andCs₂CO₃ (1.094 g, 3.358 mmol) in DMF (2 ml) was stirred at r.t. for 60 h. Usual workup and purification by FC(SiO₂ (100 ml), AcOEt/hexane 65 :35) provided (-)-10c (1.136 g, 9.4%). Amorphous glass-like solid. M.p. 38– $47°. <math>R_{\rm f}$ (AcOEt/hexane 1:1) 0.15. $[a]_{\rm D} = -27.9$ (c = 1.29, CHCl₃). FT-IR (KBr): 3378s (br., N-H), 3091w, 3067w, 2939m, 2872m, 1718s (C=O), 1667s (C=O), 1545s, 1503w, 1460m, 1419w, 1382w, 1335s, 1211s, 1184s, 1155s, 1130s, 1073m, 1020w, 965w, 889w, 857w, 818w, 754m, 722m, 698m, 651w, 615w, 597w, 547m, 477w. ¹H-NMR (300 MHz, 45 mg in 0.6 ml of CDCl₃): 8.37 (d, J = 1.4, H_a of naphth.); 7.97 (d, J = 8.4, 2 H); 7.91 (d, J = 7.6, 1 H); 7.75 (d, J = 1.7, 8.6, 1 H); 7.63 (dquint., J = 1.5, 7, 2 H); 7.31 – 7.39 (m, 3 H of Ph); 7.24 – 7.30 (m, 2 H of Ph); 7.22 (br. t, NHCO); 6.79 (br. t, J = 6.1, NHCOCF₃); 3.94 (d, J = 1.9, H - C(3)); 3.49 (d, J = 1.9, H - C(2)); 3.33 – 3.51 (m, 4 H); 3.08 – 3.32 (m, 4 H); 1.81 (quint., J = 6.7, NCH₂CH₂CH₂N); 1.68 (m, CH₂CH₂). ¹³C-NMR (75 MHz; δ (CDCl₃) 76.92): 167.88 (CONH); 157.35 (q, J = 37, CF₃CO); 135.58, 134.80, 134.71, 132.11 (4 quat. arom. C); 129.50, 129.11, 128.91, 128.81, 128.54, 128.40, 127.81, 127.62, 125.68, 122.12 (arom. CH); 115.85 (q, J = 288, CF₃); 58.94, 58.80 (C(2), C(3)); 49.22, 47.04 (CH₂NCH₂); 39.13 (CH₂NHCOCF₃); 36.33 (CH₂NHCO); 28.82 (NCH₂CH₂CH₂N); 26.30, 25.81 (CH₂CH₂). ESI-MS: 600 ([M + Na]⁺).

 (\pm) -(2RS,3SR)-N-[3-[[(4-Methylphenyl)sulfonyl][4-[[(2,2,2-trichloroethoxy)carbonyl]amino]butyl]amino]propyl]-3-phenyloxiranecarboxamide (**10d**). A mixture of (\pm) -**8** (549 mg, 1.933 mmol), **9d** (1.049 g, 2.513 mmol), and Cs₂CO₃ (819 mg, 2.513 mmol) in DMF (5 ml) was stirred at r.t. for 60 h. The mixture was quenched with CH₂Cl₂ (200 ml) and washed with 5% aq. citric acid (60 ml), the org. phase dried (Na₂CO₃) and evaporated, and the obtained brown oil (1.44 g) dissolved in a small amount of CH₂Cl₂/CCl₄ 1:1 and chromatographed (SiO₂ (150 ml), with AcOEt/hexane 1:1 (800 ml)): unreacted **9d**, then **10d** (760 mg, 63.3%). Colorless foam, amorphous solid. M.p. 39–40°. $R_{\rm f}$ (AcOEt/hexane 1:1) 0.16. FT-IR (neat, NaCl): 3353m (br., N–H), 3064w, 2946m, 2871w, 1737s (amide C=O), 1671s (carbamate C=O), 1598w, 1537s, 1460m, 1335s, 1306m, 1242s, 1157s, 1090m, 1030w, 955w, 889w, 816m, 758m, 734s, 700m, 654m, 598w, 571w, 549m. ¹H-NMR

(300 MHz, 25 mg in 0.6 ml of CDCl₃): 7.68 ($d, J = 8.3, 2 H_o$ of Ts); 7.25 – 7.38 (m, 7 arom. H); 6.78 (br. t, J = 6.0, NHCO); 5.32 (br. t, NHTroc); 4.73, 4.68 (2 'd' (AB), ²J = 12, CH₂O); 3.95 (d, J = 2.0, H-C(3)); 3.51 (d, J = 2.0, H-C(2)); 3.30 – 3.52 (2 overlapping m, ³J = 6.6, CH₂NHCO); 3.02 – 3.29 (overlapping m, 2 CH₂N); 3.24 (overlapping $q, J = 6.4, \text{CH}_2$ N); 2.42 (s, Me); 1.79 ($quint. J = 6.7, \text{NCH}_2\text{CH}_2\text{CH}_2$ N); 1.5 – 1.68 (2 overlapping m, CH₂CH₂). ¹³C-NMR (75 MHz, CDCl₃; δ (CDCl₃) 76.91): 167.69 (CONH); 154.62 (OCONH); 143.44 (C_p of Ts); 135.99 (C_{ipso} of Ts); 134.94 (C_{ipso} of Ph); 129.71 (C_m of Ts); 128.85 (C_p of Ph); 128.51 (C_m of Ph); 127.02 (C_o of Ts); 125.71 (C_o of Ph); 95.61 (CCl₃); 74.35 (CH₂O); 58.92 (overlapping C(2) and C(3)); 48.90, 46.41 (CH₂NCH₂); 40.53 (CH₂NHTroc); 35.87 (CH₂NHCO); 28.70 (NCH₂CH₂CH₂N); 26.79, 26.1 (CH₂CH₂); 21.37 (Me of Ts). ESI-MS: 642, 644, 646, 648 (100, 95, 35, 7, [M + Na]⁺).

 (\pm) -(2RS,3SR)-N-{3-{[4-{[(1,1-Dimethylethoxy)carbonyl]amino]butyl][(4-methylphenyl)sulfonyl]amino]butyl][(4-methylphenyl]amino]butyl][(4-methylph no]propyl]-3-phenyloxiranecarboxamide (10e). A mixture of (±)-8 (491 mg, 1.729 mmol), 9e (1.183 g, 3.458 mmol), and anh. Cs₂CO₃ (1.127 g, 3.458 mmol) in anh. DMF (16 ml) was stirred at r.t. until full consumption of starting 8 (17 h) monitored by TLC (5% MeOH/CHCl₃). After partitioning between H₂O (100 ml) and CH₂Cl₂ (75 ml), the aq. layer was extracted with CH₂Cl₂ (2×40 ml), the combined org. phase dried (Na₂CO₃) and evaporated under h.v., and the obtained pale brown oil (1.92 g) dissolved in a small amount of CH₂Cl₂/CCl₄ 1:1 and submitted to FC (SiO₂ (150 ml), AcOEt/hexane 1:1 (500 ml; \rightarrow unreacted **9e**), then 7:3): 10e (700 mg, 74.3%). White foam, glass-like oil. R_t (AcOEt/hexane 1:1) 0.18. FT-IR (neat, NaCl): 3339s (N-H), 3065s, 2976s, 2934s, 2870s, 1694s (C=O), 1598m, 1537s, 1460s, 1392m, 1366m, 1335s, 1253s, 1170s, 1090m, 1020m, 999m, 889m, 864w, 816m, 758s, 736s, 699m, 654m, 598w, 574m, 549m. ¹H-NMR (300 MHz, 25 mg in 0.6 ml of CDCl₃): 7.68 (d, J = 8.3, 2 H_o of Ts); 7.25 - 7.37 (m, 7 arom. H); 6.84 (br. t, J = 6.0, NHCO); 4.64 (br. s, NHBoc); 3.96 (d, J = 2.0, H-C(3)); 3.50 (d, J = 2.0, H-C(2)); 3.30-3.51 (2 overlapping m, ${}^{3}J = 6$, CH₂NHCO); 3.03-3.25 (*m*, 3 CH₂N); 2.42 (*s*, Me); 1.79 (*quint*, *J*=6.7, NCH₂CH₂CH₂N); 1.4-1.65 (2 overlapping m, CH₂CH₂); 1.43 (s, Me₃C). ¹³C-NMR (75 MHz, CDCl₃; δ (CDCl₃) 76.91): 167.63 (CONH); 155.91 (OCONH); 143.35 (Cp of Ts); 136.14 (Cipso of Ts); 135.02 (Cipso of Ph); 129.68 (Cm of Ts); 128.80 (Cp of Ph); 128.48 (C_m of Ph); 127.0 (C_o of Ts); 125.71 (C_o of Ph); 79.08 (Me₃C); 58.87 (overlapping C(2), C(3)); 48.78, 46.02 (CH₂NCH₂); 39.81 (br., CH₂NHBoc); 35.61 (CH₂NHCO); 28.60 (NCH₂CH₂CH₂N); 28.3 (Me₃C); 27.23, 26.07 (CH₂CH₂); 21.36 (Me of Ts). CI-MS (NH₃): 563 (4, $[M + NH_4]^+$), 546 (6, $[M + H]^+$), 446 (100, $[M - t-t]^+$) $BuOCO + 2H]^+$).

 $(\pm)-(2RS,3SR)-N-\{3-\{[(4-Methylphenyl)sulfonyl]\{4-\{[(4-methylphenyl)sulfonyl]amino\}butyl\}amino\}-(2RS,3SR)-N-\{3-\{[(4-Methylphenyl)sulfonyl]\{4-\{[(4-methylphenyl)sulfonyl]amino\}butyl\}amino\}-(2RS,3SR)-N-\{3-\{[(4-Methylphenyl)sulfonyl]\{4-\{[(4-methylphenyl)sulfonyl]amino\}butyl\}amino\}-(2RS,3SR)-N-\{3-\{[(4-Methylphenyl)sulfonyl]\{4-\{[(4-methylphenyl)sulfonyl]amino\}butyl\}amino\}-(2RS,3SR)-N-\{3-\{[(4-Methylphenyl)sulfonyl]\{4-\{[(4-methylphenyl)sulfonyl]amino\}butyl\}amino\}-(3RS,3SR)-N-\{3-\{[(4-Methylphenyl)sulfonyl]amino\}butyl]amino\}-(3RS,3SR)-N-\{3-\{[(4-Methylphenyl)sulfonyl]amino\}butyl]amino\}-(3RS,3SR)-N-\{3-\{[(4-Methylphenyl)sulfonyl]amino\}butyl]amino\}-(3RS,3SR)-N-\{3-\{[(4-Methylphenyl]amino]butyl]amino\}-(3RS,3SR)-N-\{3-\{[(4-Methylphenyl]amino]butyl]amino\}-(3RS,3SR)-N-\{3-\{[(4-Methylphenyl]amino]butyl]amino\}-(3RS,3SR)-N-\{3-\{[(4-Methylphenyl]amino]butyl]amino\}-(3RS,3SR)-N-\{3-\{[(4-Methylphenyl]amino]butyl]amino\}-(3RS,3SR)-N-\{3-\{[(4-Methylphenyl]amino]butyl]amino\}-(3RS,3SR)-N-\{3-\{[(4-Methylphenyl]amino]butyl]amino\}-(3RS,3SR)-N-\{3-\{[(4-Methylphenyl]amino]butyl]amino\}-(3RS,3SR)-N-\{3-\{[(4-Methylphenyl]amino]butyl]amino\}-(3RS,3SR)-N-\{3-\{[(4-Methylphenyl]amino]butyl]amino\}-(3RS,3SR)-N-\{3-\{[(4-Methylphenyl]amino]butyl]amino\}-(3RS,3SR)-N-\{3-\{[(4-Methylphenyl]amino]butyl]amino\}-(3RS,3SR)-N-\{3-\{[(4-Methylphenyl]amino]butyl]amino\}-(3RS,3SR)-N-\{3-\{[(4-Methylphenyl]amino]butyl]amino]butyl]amino]butyl]amino]$ propyl]-3-phenyloxiranecarboxamide (10h). Oxalyl chloride (0.429 ml, 2 equiv.) was added to a cold (ice/water bath) suspension of 5 (1.009 g, 5.0 mmol) in THF. The cold bath was removed and stirring continued until the gas evolution ceased (30 min). After evaporation under h.v., the solid colorless mixture of acid chloride 7 and KCl [5] was dissolved in CH₂Cl₂ (20 ml) and allowed to cool (ice/water bath). After addition of amine 9h (2.265 g, 5.0 mmol) in CH₂Cl₂ (20 ml) and Et₃N (3 ml), the bath was removed and the mixture stirred at r.t. for 20 min, then evaporated. The residue was partitioned between Et_2O and H_2O and the org. layer washed with aq. 5% citric acid $(2 \times 30 \text{ ml})$, H₂O $(2 \times 20 \text{ ml})$, and sat. aq. NaHCO₃ soln. $(2 \times 30 \text{ ml})$, dried (Na₂CO₃) and evaporated under h.v. (40°, 60 min): pure 10h (2.755 g, 92%). White solid. FT-IR (KBr): 3350m (N-H), 3287m (N-H), 3065w, 2938m, 2870m, 1667s (C=O), 1598m, 1539s, 1495w, 1459m, 1381w, 1330s, 1306m, 1289m, 1229w, 1159s, 1091s, 1020w, 889w, 860w, 815m, 757m, 726m, 699m, 655m, 570m, 550s. ¹H-NMR (300 MHz, 38 mg in 0.7 ml of CDCl₃): 7.71 (d, $J = 8.3, 2 \text{ H}_a$ of TsNH); 7.65 (d, $J = 8.3, 2 \text{ H}_a$ of TsN); 7.22 – 7.4 (m, 9 arom. H); 6.80 (br. t, J = 6.1, NHCO); 5.20 (t, J = 6.25, NHTs); 3.97 (d, J = 2.0, H - C(3)); 3.51 (d, J = 2.0, H - C(2)); 3.29 - 3.48Me); 1.79 (quint., J = 6.6, NCH₂CH₂CH₂N); 1.45 – 1.66 (2 overlapping m, 4 H, CH₂CH₂). ¹³C-NMR (75 MHz, $CDCl_3$; $\delta(CDCl_3)$ 76.93): 167.82 (CONH); 143.42 (C_p of TsN); 143.14 (C_p of TsNH); 136.99 (C_{ipso} of TsNH); 135.86 (Ciase of TsN); 135.0 (Ciase of Ph); 129.72, 129.57 (4 Cm of 2 Ts); 128.80 (Cp of Ph); 128.48 (Cm of Ph); 127.01, 126.89 (4 Co of 2 Ts); 125.76 (Co of Ph); 58.86 (overlapping C(2), C(3)); 48.91, 46.57 (CH₂NCH₂); 42.48 (CH₂NHTs); 36.07 (CH₂NHCO); 28.73 (NCH₂CH₂CH₂N); 26.42, 25.96 (CH₂CH₂); 21.36 (2 Me of 2 Ts). ESI-MS: 622 ($[M + Na]^+$).

 (\pm) -(2RS,3SR)-N-[3-[[(4-Methylphenyl)sulfonyl](4-aminobutyl)amino]propyl]-3-phenyloxiranecarboxamide (11). A soln. of 10a (52 mg, 0.096 mmol), K₂CO₃ (145 mg) in MeOH (5 ml), and H₂O (2 ml) was stirred at r.t. and monitored by TLC (8 h), then quenched with sat. aq. Na₂CO₃ soln. (10 ml) followed by extraction with CH₂Cl₂ (3 × 10 ml). The combined org. soln. gave 44 mg of oil after drying (Na₂CO₃) and evaporation under h.v. The product was slowly converted to the dimer after intermolecular oxirane opening with amine. R_f (CHCl₃/ MeOH/25% aq. NH₃ soln. 90:9:1) 0.15. ¹H-NMR (300 MHz, 44 mg in 0.6 ml of CDCl₃; contains *ca*. 25% of the dimer): 7.68 (d, J = 8.3, 2 H_o of Ts); 7.24–7.4 (m, 7 arom. H); 6.86 (br. t, J = 6.2, NHCO); 3.95 (d, J = 1.9, H–C(3)); 3.5 (d, J = 1.9, H–C(2)); 3.30–3.49 (m, 2 H); 3.05–3.25 (m, 4 H); 2.67 (t, J = 6.7, CH₂NH₂); 2.42 (*s*, Me); 1.79 (*quint*. J = 6.7, NCH₂CH₂CH₂N); 1.57 (*quint*. (unres. *m*), J = 7.3, 2 H); 1.40 (*quint*. (unres. *m*), J = 7.3, 2 H). ¹³C-NMR (75 MHz, CDCl₃; δ (CDCl₃) 76.93): 167.60 (CONH); 143.30 (C_p of Ts); 136.26 (C_{ipso} of Ts); 135.01 (C_{ipso} of Ph); 129.65 (C_m of Ts); 128.79 (C_p of Ph); 128.48 (C_m of Ph); 126.99 (C_o of Ts); 125.7 (C_o of Ph); 58.85 (overlapping C(2), C(3)); 48.88, 45.79 (CH₂NCH₂); 41.5 (CH₂NH₂); 35.59 (CH₂NHCO); 30.62 (NCH₂CH₂CH₂N); 28.54, 26.16 (CH₂CH₂); 21.35 (Me). ESI-MS: 446 (100, [*M* + H]⁺), 468 (10, [*M* + Na]⁺), 891 (16, [2*M* + H]⁺), 913 (4, [2*M* + Na]⁺).

One-Pot Deprotection-Macrocyclization of (\pm) -10a in EtOH under Reflux. A biphasic mixture of (\pm) -10a (374 mg, 0.691 mmol) in EtOH (150 ml), sat. aq. Na₂CO₃ soln. (15 ml), and H₂O (15 ml) was stirred under reflux and N₂ for 22 h. Evaporation to a small volume, dilution with H₂O (30 ml), and extraction with CHCl₃ (4 × 20 ml) yielded an org. soln. that was dried (Na₂CO₃) and evaporated. The crude product was analyzed by ¹H-NMR. FC (SiO₂ (25 ml), 2% MeOH/CHCl₃ (100 ml; \rightarrow (\pm)-12 (264 g, 85.8%; see below)), then 4% MeOH/CHCl₃ (50 ml), CHCl₃/MeOH/25% aq. NH₃ soln. 90:9:1 (100 ml), and CHCl₃/MeOH/25% aq. NH₃ soln. 85:14:1 (100 ml)) gave crude 22 (25 mg, 6.9% by NMR) contaminated with dimeric macrocycle 23 (1.1% by ¹H-NMR).

Data of (±)-(*α*RS,*β*RS)-N-[*3*-[(*4*-*Aminobutyl*)][(*4*-*methylphenyl*)*sulfonyl*]*amino*]*propyl*]-*β*-*ethoxy*-*α*-*hy*-*droxybenzenepropanamide* (**22**). *R*_t (CHCl₃/MeOH/25% aq. NH₃ soln. 85 :14 :1) 0.13. ¹H-NMR (300 MHz, 20 mg in 0.6 ml of CDCl₃): 7.61 (*d*, *J* = 8.2, 2 H_o of Ts); 7.20 – 7.36 (*m*, 7 arom. H); 6.92 (br. *t*, *J* = 6.1, NHCO); 4.67 (*d*, *J* = 4.4, H−C(*β*)); 4.41 (*d*, *J* = 4.9, H−C(*α*)); 3.47 (*q* with fine splitting, *J* = 7, OCH₂Me); 3.29 (*dt* (*dddd*), ³*J* = 6.5, ²*J* = 14, CH₂NHCO); 2.92 – 3.20 (*m*, 3 H); 2.81 (*t* with fine splitting, *J* = 6.5, CH₂N); 2.68 (*t*, *J* = 6.7, CH₂NH₂); 2.43 (*s*, Me of Ts); 1.34 – 1.66 (*m*, 3 CH₂); 1.20 (*t*, *J* = 6.9, Me of Et). ¹³C-NMR (75 MHz; δ(CDCl₃) 76.90): 170.88 (CONH); 143.16 (C_ρ of Ts); 137.09 (C_{ipso} of Ts); 136.29 (C_{ipso} of Ph); 129.55 (C_m of Ts); 127.84 (overlapping C_ρ, C_m, C_o of Ph); 127.02 (C_o of Ts); 81.57 (C(*β*)); 74.09 (C(*α*)); 64.45 (CH₂O); 48.81, 45.63 (CH₂NCH₂); 41.29 (CH₂NH₂); 35.43 (CH₂NHCO); 30.06 (NCH₂CH₂CH₂N); 2.849, 26.14 (CH₂CH₂); 21.36 (Me of Ts); 15.17 (Me of Et). ESI-MS: 492 (100, [M + H]⁺), 514 (95, [M + Na]⁺).

Data of **23** (extracted from the ¹H-NMR of crude **22**): ¹H-NMR (selected δ): 4.61 (*d*, *J* = 3.9, PhCH); 4.09 (*d*, *J* = 3.9, CHOH). ESI-MS: 913 ([*M* + Na]⁺), 891 ([*M* + H]⁺).

One-Pot Deprotection-Macrocyclization of (\pm) -**10a** in *i*-PrOH under Reflux. Concentration of (\pm) -**10a** and workup as described in the previous experiment with EtOH. A soln. of (\pm) -**10a** (157 mg, 0.290 mmol) in *i*-PrOH (63 ml), sat. aq. Na₂CO₃ soln. (6.3 ml) and H₂O (6.3 ml) was stirred under reflux for 23 h. FC after workup gave (\pm) -**12** (105 mg, 81.3%). A crude mixture of at least three by-products (24 mg) was eluted with CHCl₃/MeOH/ 25% aq. NH₃ soln. 85 :14 :1.

One-Pot Deprotection-Macrocyclization of (-)-10a in i-PrOH at 70°. A soln. of (-)-10a (546 mg, 1.008 mmol) in i-PrOH (300 ml), sat. aq. Na₂CO₃ soln. (30 ml), and H₂O (90 ml) was stirred at 70° for 36 h. FC after workup gave (+)-12 (382 mg, 85%).

One-Pot Deprotection-Macrocyclization of (\pm) -10a in THF at Reflux. A mixture of (\pm) -10a (119 mg, 0.220 mmol) in THF (30 ml), sat. aq. Na₂CO₃ soln. (5 ml), and H₂O (45 ml) was stirred under reflux and N₂ until no (\pm) -10a or the intermediate amine 11 could be observed (48 h). FC after workup gave (\pm) -12 (64 mg, 65.4%).

Preparation of (+)-12 via One-Pot N,C Coupling, CF_3CO Deprotection, and Macrocyclization. (Bromopropyl)oxiranecarboxamide (-)-8 (2.004 g, 7.052 mmol), anh. Cs_2CO_3 (2.836 g, 1.25 equiv.), 9a (2.895 g, 1.2 equiv.), and anh. DMF were stirred at r.t. under N₂ for 22 h. The mixture was quenched with i-PrOH (500 ml), sat. aq. Na₂CO₃ soln. (50 ml), and H₂O (150 ml) and stirred at 70° for 48 h. Usual workup and FC gave (+)-12 (1.647 g, 52.4%).

Data of (\pm) -(2RS,3RS)-3-Hydroxy-9-[(4-methylphenyl)sulfonyl]2-phenyl-1,5,9-triazacyclotridecan-4-one $((\pm)$ -12): For ¹H- and ¹³C-NMR assignments from 2D NMR data (600 MHz), see also [5]. White foam. M.p. 80–92° (reproducible and reversible). R_t (5% MeOH/CHCl₃) 0.2. FT-IR (neat, NaCl): 3375s (br.), 3313s (br.), 3064w, 3029w, 2931s, 2858m, 2254w, 1919w, 1810w, 1652s (C=O), 1599w, 1538s, 1494w, 1454s, 1402w, 1331s, 1306m, 1231w, 1197w, 1155s, 1122m, 1106m, 1089m, 1063m, 1030m, 981w, 912m, 816m, 731s, 701m, 656m, 564m, 548m. ¹H-NMR (600 MHz, 38 mg in 0.7 ml of CDCl₃): 8.49 (br. t, NHCO); 7.68 (d, J = 8.2, 2 H_o of Ts); 7.37 (t, J = 7.5, 2 H_m of Ph); 7.32 (d, J = 8.3, 2 H_m of Ts); 7.29 (t, J = 7.4, H_p of Ph); 7.23 (d, J = 7.3, 2 H_o of Ph); 3.99 (m, J(2,3) = 10.1, H–C(3)); 3.70 (br. s, OH); 3.53 (m, 1 H–C(6)); 3.47 (d, J(2,3) = 10.1, H–C(2)); 3.39 (m, 1 H–C(10)); 3.28 (overlapping m, 1 H–C(8)); 3.25 (overlapping m, 1 H–C(6)); 3.16 (m, 1 H–C(8)); 2.88 (ddd, ³J = 4.6, 9.2, ²J = 13.9, 1 H–C(10)); 2.60 (ddd, ³J = 4.2, 5.6, ²J = 12.6, H–C(13)); 2.43 (s, Me); 2.35 (ddd, ³J = 4.1, 9.2, ²J = 12.9, H–C(13)); 1.90–1.99 (m, CH₂(7)); 1.83 (m, 1 H–C(11)); 1.69 (m, 1 H–C(11)); 1.48, 1.41 (2m, CH₂(12)). ¹H-NMR (300 MHz, 9 mg in 0.7 ml of CDCl₃; selected resonances, the rest is identical to the preceding spectrum): 3.99 (dd, ³J(2,3) = 10.1, ³J(CH,OH) = 2.5, H–C(3)); 3.69 (d, ³J(CH,OH) = 2

OH); 3.48 ($d, {}^{3}J(2,3) = 10.1, H-C(2)$). ¹H-NMR (300 MHz, 30 mg in 0.6 ml of (D₆)DMSO; $\delta((D_6)DMSO)$ 2.5, selected resonances): 7.92 (t, J = 5.8, NHCO); 5.06 (d, J = 6.4, OH); 3.74 (dd, J = 6.4, 9.5, H-C(3)); 3.47 (br. d, J = 9.1, H-C(2)). ¹³C-NMR (75 MHz, CDCl₃, $\delta(SiMe_4)$ 0): 173.61 (CONH); 143.60 (C_p of Ts); 140.46 (C_{ipso} of Ph); 136.32 (C_{ipso} of Ts); 129.95 (C_m of Ts); 128.91 (C_m of Ph); 128.0 (C_p of Ph); 127.56 (C_o of Ph); 127.40 (C_o of Ts); 72.61 (H-C(3)); 66.06 (H-C(2)); 48.55 (CH₂(10)); 46.59 (CH₂(8)); 43.96 (CH₂(13)); 37.36 (CH₂(6)); 29.08 (CH₂(7)); 25.29 (CH₂(12)); 24.20 (CH₂(11)); 21.69 (Me). ESI-MS: 446 (100, [M + H]⁺), 468 (8, [M + Na]⁺).

 (\pm) -(2RS,3RS)-3-Hydroxy-2-phenyl-1,5,9-triazacyclotridecan-4-one ((\pm)-13). The biphasic mixture of (\pm)-10b (43 mg, 0.089 mmol) in EtOH (20 ml), sat. aq. Na₂CO₃ soln. (2 ml), and H₂O (4 ml) was stirred at 60° under N₂ for 72 h. After evaporation to a small volume, the mixture was quenched with sat. aq. Na₂CO₃ soln. (20 ml) and extracted with CHCl₃ (4 × 20 ml) and the combined org. phase dried (Na₂CO₃) and evaporated under h.v.: crude (\pm)-13 (29 mg, 70% by NMR). FC (Al₂O₃ (20 ml), CHCl₃/MeOH/aq. 25% NH₃ soln. 95:4.5:0.5 (50 ml), then CHCl₃/MeOH/aq. 25% NH₃ soln. 90:9:1 (100 ml)) gave (\pm)-13 (17.5 mg, 67.5%). Data completely identical to those of (+)-13; see also [5].

(+)-(2R,3R)-3-Hydroxy-2-phenyl-1,5,9-triazacyclotridecan-4-one ((+)-13). According to [5], (+)-12 (210 mg, 0.471 mmol) was electrochemically detosylated (see also detosylation of 10h below). The obtained soln. after electrolysis was evaporated, treated with H₂O (40 ml) and sat. aq. Na₂CO₃ soln. (40 ml) followed by extraction with CH₂Cl₂ (4 × 15 ml). The combined org. phase was dried (Na₂CO₃) and evaporated under h.v.: (+)-13 (138 mg, 100%). White foam, >95% purity by NMR, which was used in the next step without further purification. $R_{\rm f}$ (SiO₂, CHCl₃/MeOH/aq. 25%. NH₃ soln. 70:25:5) 0.15. $R_{\rm f}$ (Al₂O₃, CHCl₃/MeOH/aq. 25% NH₃ soln. 90:9:1) 0.25. [a]_D = +10.0 (*c* = 1.07, CHCl₃). FT-IR (KBr): 3390*s* (br.), 3288*s* (br.), 3081*m*, 3062*m*, 3028*m*, 2924*s*, 2852*s*, 1653*s* (C=O), 1550*s*, 1496*m*, 1454*s*, 1437*s*, 1369*m*, 1305*m*, 1258*m*, 1230*m*, 1190*m*, 1122*s*, 1064*m*, 958*w*, 856*w*, 763*m*, 700*s*, 617*w*. ¹H-NMR (300 MHz, 12 mg in 0.6 ml of CDCl₃): 9.17 (br. *s*, NHCO); 7.33–7.41 (*m*, 2 arom. H); 7.26–7.32 (*m*, 3 arom. H); 3.99 (*d*, *J* = 10.0, H–C(3)); 3.68 (*m*, 1 H–C(6)); 3.56 (*d*, *J* = 10.0, H–C(2)); 3.34 (*m*, 1 H–C(6)); 2.76–2.92 (complex *m*, CH₂(8)); 2.63–2.72 (*m*, CH₂(10)); 2.58 (*ddd*, *J* = 2.7, 5.8, 11.7, 1 H–C(13)); 1.43 (*ddd*, *J* = 2.8, 9.5, 11.5, 1 H–C(13)); 1.67–1.8 (*m*, 2 H); 1.52–1.67 (*m*, 3 H); 1.36–1.52 (*m*, 1 H). ¹³C-NMR (75 MHz; δ (CDCl₃) 76.93): 172.92 (CONH); 140.77 (C₁₃₀); 142.41 (C₆); 2.772, 2.767, 27.57 (overlapping C(7), C(11), C(12)). ESI-MS: 292 (100, [*M*+H]⁺), 304 (15, [*M*+Na]⁺).

(+)-(2R,3R)-9-[(2E)-1-Oxo-3-phenylprop-2-enyl]-3-[[(2E)-1-oxo-3-phenylprop-2-enyl]oxy]-2-phenyl-oxo-3-phenylprop-2-enyl]oxy]-2-phenylprop-2-e1,5,9-triazacyclotridecan-4-one ((+)-14). To a cold (ice/water bath) soln. of (+)-13 (40.1 mg, 0.138 mmol) in CH₂Cl₂ (4 ml), cinnamoyl chloride (58 mg, 0.345 mmol), and DMAP (51 mg, 0.414 mmol) were added and stirred for 30 min. The obtained mixture was submitted to FC (SiO₂ (20 ml), gradient CH₂Cl₂ \rightarrow 2% MeOH/ CH₂Cl₂: (+)-14 (70 mg, 92%). Glass-like amorphous solid. R_f (5% MeOH/CHCl₃) 0.3. $[\alpha]_D = +35.0$ (c = 1.0, CHCl₃). FT-IR (KBr): 3418m (br., N-H), 3299s (br., N-H), 3083w, 3060m, 3027m, 2926s, 2853m, 1955w, 1886w, 1715s, 1679s, 1648vs, 1599s, 1578m, 1553m, 1496m, 1450s, 1437s, 1377m, 1332s, 1306m, 1281m, 1244s, 1202s, 1164s, 1125m, 1072m, 1060m, 1027m, 976m, 915w, 861m, 764s, 734w, 701s, 684m, 613w, 590w, 557w, 537m, 484w. ¹H-NMR (300 MHz, 60 mg in 0.6 ml of CDCl₃): 7.71 (*m*, *J*_{trans} = 15.5, PhCH=CHCON); 7.50 (*m*, 2 H of PhCH=CH); 7.2-7.45 (m, 14.5 H); 7.07 (br. s, 0.5 H, NHCO); 6.83 (d, J_{trans}=15.4, 1 H, PhCH=CHCON); 6.21 $(m, J_{trans} = 16, PhCH = CHCO_2); 5.28 (2d, J = 10, 0.5 + 0.5 H, CH - O); 4.11 (d, J = 10.2, PhCHNH); 5.25 - 5.85$ (br. m, 5 H); 3.1 (br. m, 1 H); 2.74 (br. m, 1 H); 2.48 (br. m, 1 H); 2.16 (br. m, 1 H); 1.76-2.03 (br. m, 2 H); 1.48 - 1.75 (br. m, 2 H); 1.39 (br. m, 1 H). ¹³C-NMR (75 MHz; δ (CDCl₃) 76.96, two rotamers A and B): 169.36 (C=O); 166.13 (C=O); 165.76 (C=O); 145.85 (CH=); 142.47, 142.26 (CH= of A and B); 140.13 (C_{inso}) ; 135.28, 133.93 (2 Cinso of 2 PhCH=); 130.4, 129.43 (2 Cn of 2 PhCH=); 128.73, 128.68, 128.56, 128.03, 127.69, 127.21 (arom. CH); 117.53, 116.76 (2 CH=); 76.25, 76.15 (CHO of A and B); 63.98, 63.86 (CHNH of A and B); 46.61, 45.74, 44.44, 44.07, 42.94 (3 CH₂N of A and B); 37.13, 36.65 (CH₂NHCO of A and B); 27.48, 25.65, 24.46, 23.67, 23.57, 23.7 (3 CH₂ of A and B). ESI-MS: 552 (100, $[M + H]^+$), 574 (100, $[M + Na]^+$).

(-)-(2R,3R)-3-Hydroxy-9-[(2E)-1-oxo-3-phenylprop-2-enyl]-2-phenyl-1,5,9-triazacyclotridecan-4-one (=(-)-(2R,3R)-3-Hydroxycelacinnine; (-)-1a). A soln. of (+)-14 (67 mg, 0.121 mmol) in MeOH (5 ml) and NaOH (250 mg) was stirred at r.t. for 60 min. Then the mixture was partitioned between H₂O (30 ml) and CH₂Cl₂ (4 × 10 ml), the org. phase dried (Na₂CO₃) and evaporated, and the residue (50 mg) purified by FC

 $(SiO_2 (20 \text{ ml}), 5\% \text{ MeOH/CHCl}_3): (-)-1a (46 \text{ mg}, 90\%).$ Colorless glass-like amorphous solid. M.p. $112-114^\circ$, irreversible. $[\alpha]_D = -3.2 (c = 0.73, \text{ CHCl}_3/\text{MeOH } 30:1).$ FT-IR and NMR: identical to the data of $(\pm)-1a$ [5]. ESI-MS: 422 (100, $[M + \text{H}]^+$), 444 (65, $[M + \text{Na}]^+$).

(-)-(2R,3R)-3-Hydroxy-9-(naphthalene-2-ylsulfonyl)-2-phenyl-1,5,9-triazacyclotridecan-4-one ((-)-15). A soln. of (-)-10c (1.092 g, 1.893 mmol) in i-PrOH (300 ml), sat. aq. Na₂CO₃ soln. (30 ml), and H₂O (100 ml) was stirred at 70° for 22 h. Usual workup and FC (SiO₂ (50 ml), 2% MeOH/CHCl₃) gave (-)-15 (772 mg, 84.8%). Amorphous solid. M.p. $96-100^{\circ}$. $[a]_{D} = -1.5$ (c = 1.14, CHCl₃). FT-IR (KBr): 3383s (br.), 3057w, 3026w, 2929s, 2858m, 1656s (C=O), 1589w, 1547s, 1503w, 1454m, 1331s, 1269w, 1196w, 1154s, 1128s, 1073s, 1027m, 981w, 951w, 858w, 819w, 751s, 700s, 653s, 615m, 545s, 477w. ¹H-NMR (300 MHz, 33 mg in 0.6 ml of CDCl₃): 8.44 (br. t, NHCO); 8.38 (d, J = 1.4, H-C(a) of naphth.); 7.84-8.0 (m, 3 H); 7.77 (dd, J = 1.7, 8.8, 1 H); 7.58-7.68 (m, 2 H); 7.20-7.40 (m, 5 H); 3.98 (d, J(2,3) = 10.1, H-C(3)); 3.67 (br. s, OH); 3.40-3.6 (overlapping, 1 H-C(6), 1 H-C(10)); 3.47 (overlapping d, J(2,3) = 10.1, H-C(2)); 3.17-3.40 (m, CH₂(8), H-C(6)); 2.97 (ddd, $^{3}J = 4.6, 9.2, ^{2}J = 13.9, 1$ H-C(10)); 2.58 (ddd, $^{3}J = 4.6, 5.2, ^{2}J = 12.6, 1$ H-C(13)); 2.35 (ddd, $^{3}J = 4.1, 9.2, ^{2}J = 12.9, 1$ H-C(13)); 1.91-2.02 (m, CH₂(7)); 1.83 (m, 1 H-C(11)); 1.69 (m, 1 H-C(11)); 1.32-1.55 (2m, CH₂(12)). ¹³C-NMR (75 MHz; δ (CDCl₃) 76.94: 173.3 (CONH); 140.05, 136.06, 134.68, 132.14 (4 quat. arom. C); 129.37, 129.1, 128.69, 128.66, 127.82, 127.72, 127.52, 127.29, 122.38 (arom. CH); 72.37 (C(3)); 65.76 (C(2)); 48.23 (CH₂(10)); 46.25 (CH₂(8)); 43.69 (CH₂(13)); 37.06 (CH₂(6)); 2.8.87 (CH₂(7)); 24.89 (CH₂(12)); 23.93 (CL₂(11)). ESI-MS: 482 ($[M + H]^+$).

Electrochemical Detosylation of **10h**. A soln. of **10h** (411 mg, 0.686 mmol) in 0.1N Me₄NCl/EtOH (200 ml) was electrolyzed according to [5] and evaporated to a small volume. The obtained soln. was acidified with aq. 10% citric acid soln. (15 ml), washed with CH_2Cl_2 (4 × 20 ml), saturated with K_2CO_3 , and extracted with CH_2Cl_2 (6 × 20 ml). The combined org. extract was dried (Na₂CO₃) and evaporated under h.v., and the hygroscopic solid (318 mg) submitted to FC (SiO₂ (50 ml), CH₂Cl₂/MeOH/aq. 25%. NH₃ soln. 70:25:5 (200 ml), followed by CH₂Cl₂/MeOH/aq. 25%. NH₃ soln. 65:28:7 (200 ml)): **16a** (28 mg, 15%) then **16b** (58 mg, 29%).

Data of N-[3-[(4-Aminobutyl)amino]propyl]benzenepropanamide (**16a**): ¹H-NMR (300 MHz, 28 mg in 0.8 ml of CDCl₃): 7.14–7.33 (m, 5 arom. H); 6.88 (br. s (unres. t), NHCO); 3.29 (q (dt), J = 6.0, CH_2 NHCO); 2.95 (t, J = 7.7, PhCH₂); 2.71 (t, J = 6.1, CH_2 NH); 2.62, 2.57 (2 overlapping t, J = 6.3, 6.5, resp., CH_2 NH, CH_2 NH₂); 2.46 (t, J = 7.7, CH₂CO); 2.41 (br. s, NH, NH₂); 1.61 (quint. J = 6.1, NCH₂CH₂CH₂N); 1.50, 1.51 (2 overlapping quint., CCH₂CH₂C). ¹³C-NMR (75 MHz, CDCl₃; δ (CDCl₃) 76.93): 172.05 (CONH); 140.95 (C_{ipso}); 128.32, 128.27 (C_o , C_m); 126.0 (C_p); 49.35, 47.70, 41.62 (3 CH₂); 38.41 (2 overlapping CH₂); 31.71, 30.98, 28.4, 27.17 (4 CH₂).

Data of (\pm) -N-{*3*-[(*4*-*Aminobutyl*)*amino*]*propyl*/-*a*-*hydroxybenzenepropanamide* (**16b**): ¹H-NMR (300 MHz, 58 mg in 1 ml of CDCl₃): 7.56 (br. *t*, NHCO); 7.2–7.34 (*m*, 5 arom. H); 4.22 (*dd*, *J*=3.6, 8.5, CHOH); 3.29 (br. *q*, *J*=5.7, CH₂NHCO); 3.21 (*dd*, ³*J*=3.6, ²*J*=13.8, PhCH₂); 3.21 (*dd*, ³*J*=8.5, ²*J*=13.8, PhCH₂); 2.59 (overlapping *m*, 2 CH₂); 2.49 (overlapping *m*, CH₂); 2.3–2.7 (overlapping br. *s*, OH, NH, NH₂); 1.59 (*m*, NCH₂CH₂CH₂N); 1.42 (*m*, CCH₂CH₂C). ¹³C-NMR (75 MHz, CDCl₃; δ (CDCl₃) 76.95): 173.66 (CONH); 138.21 (*C*_{*ipso*}); 129.54 (*C*_{*o*}); 128.12 (*C*_{*m*}); 126.27 (*C*_{*p*}); 72.47 (CHOH); 49.03, 47.76, 41.32, 41.01, 37.9, 30.34, 28.73, 26.83 (8 CH₂).

Reductive Troc Cleavage with Zn in the Presence of NH₄OAc Buffer (pH 7) [13] Followed by Macrocyclization. A mixture of Zn powder (1 g), 0.5m sat. aq. NH₄OAc soln. (5 ml), **10d** (160 mg, 0.258 mmol), and THF (25 ml) was stirred vigorously under N₂ for 16 h at r.t. After quenching with sat. aq. Na₂CO₃ soln. (10 ml), the mixture was refluxed for 36 h. The solid residue was filtered, the soln. extracted with CH₂Cl₂, the extract evaporated, and the oil (145 mg) submitted to FC (SiO₂ (25 ml), 5% MeOH/CHCl₃)): crude (±)-**12** (50 mg). Additional FC (SiO₂ (20 ml), CHCl₃ (40 ml), 1% MeOH/CHCl₃ (40 ml), and 2% MeOH/CHCl₃) gave (±)-**12** (38 mg, 33% yield).

Reductive Troc Cleavage with Zn in the Presence of KH_2PO_4/Na_2HPO_4 Buffer (pH 5.5) [13] Followed by Macrocyclization. A mixture of Zn powder (1.1 g), 1M aq. KH_2PO_4 (2 ml), 1M aq. Na_2HPO_4 (2 ml), **10d** (200 mg, 0.322 mmol), and THF (20 ml) was stirred vigorously under N_2 for 4 h at r.t. After filtration, the residue was washed with THF. To the combined soln. (150 ml), sat. aq. NaHCO₃ (20 ml) and sat. aq. Na_2CO_3 soln. (20 ml) were added. The biphasic soln. was stirred at 55° for 21 h, then refluxed for 36 h. After evaporation of THF, the mixture was extracted with CH_2Cl_2 (3 × 20 ml), the extract dried (Na_2CO_3) and evaporated, and the colorless oil (143 mg) submitted to FC (SiO₂ (25 ml). Elution with 2% MeOH/CHCl₃ (50 ml) gave **19** (13 mg, 6.9%), with 3% MeOH/CHCl₃ (50 ml) **12** (38 mg, 26.5%), and with CHCl₃/MeOH/aq. 25% NH₃ soln. 95 : 4.5 : 0.5 (50 ml) **21** (6 mg, 3.7%). After subsequent elution with CHCl₃/MeOH/aq. 25% NH₃ soln. 95 : 14 : 1 (70 ml) eluted **18** (46.5 mg, 33.6%) and finally **17** (24.5 mg, 17%).

Data of (±)-N-[*3*-{(*4*-*Aminobutyl*)[(*4*-*methylphenyl*)*sulfonyl*]*amino*]*propyl*]-*a*-*hydroxybenzenepropanamide* (**17**): $R_{\rm f}$ (CHCl₃/MeOH/aq. 25% NH₃ soln. 85 :14 :1) 0.18. ¹H-NMR (300 MHz, 17 mg in 0.6 ml of CDCl₃): 7.63 (*d*, *J* = 8, 2 H_o of Ts); 7.24 – 7.33 (*m*, 7 arom. H); 7.08 (br. *t*, *J* = 6, NHCO); 4.28 (*dd*, *J* = 3.8, 8.1, CHOH); 3.24 – 3.43 (*m*, CH₂NHCO); 3.20 (*dd*, *J* = 3.8, 13.9, 1 H, PhCH₂); 2.95 – 3.13 (*m*, 2 CH₂N); 2.89 (*dd*, *J* = 8.1, 13.9, 1 H, PhCH₂); 2.63 (br. *t*, *CH*₂NH₂); 2.42 (*s*, Me); 1.71 (*m*, NCH₂CH₂CH₂N); 1.52, 1.38 (*2m*, CH₂CH₂). ¹³C-NMR (75 MHz, CDCl₃; δ (CDCl₃) 76.90): 173.33 (CONH); 143.25 (C_p of Ts); 137.40 (C_{ipso} of Ts); 136.12 (C_{ipso} of Ph); 129.60, 129.52 (overlapping C_m of Ts and C_p of Ph); 128.31 (C_m of Ph); 127.01 (C_o of Ts); 126.54 (C_o of Ph); 72.57 (CHOH); 48.83, 45.93 (CH₂NCH₂); 41.23 (CH₂NH₂); 40.80 (CH₂); 35.73 (CH₂NHCO); 30.05 (NCH₂CH₂CH₂N); 28.64, 26.1 (CH₂CH₂); 21.35 (Me). ESI-MS: 448 (100, [*M* + H]⁺), 470 (12, [*M* + Na]⁺).

Data of (2E)-N-{3-{(4-Aminobutyl)[(4-methylphenyl)sulfonyl]amino}propyl]-3-phenylprop-2-enamide (18): R_t (CHCl₃/MeOH/aq. 25% NH₃ soln. 85:14:1) 0.22. ¹H-NMR (300 MHz, 29 mg in 0.8 ml of CDCl₃): 7.67 ($d, J = 8.4, 2 H_o$ of Ts); 7.62 (d, J = 15.7, CH = CH); 7.48 – 7.54 (m, 2 arom. H); 7.25 – 7.39 (m, 5 arom. H); 6.64 (br. t, J = 5.7, NHCO); 6.45 (d, J = 15.6, CH = CH); 3.51 ($q, J = 6.1, CH_2NHCO$); 3.20 ($t, J = 6.4, CH_2N$); 3.11 ($t, J = 7.6, CH_2N$); 2.67 ($t, J = 6.8, CH_2NH_2$); 2.41 (s, Me); 1.83 ($quint, J = 6.1, NCH_2CH_2CH_2N$); 1.57,1.4 (2 m, CH_2CH_2). ¹³C-NMR (75 MHz, CDCl₃; δ (CDCl₃) 76.91): 165.98 (CONH); 143.36 (C_p of Ts); 140.53 (CH=CH); 136.18 (C_{ipso} of Ts); 134.86 (C_{ipso} of Ph); 129.68 (C_m of Ts); 129.44 (C_p of Ph); 128.66 (C_m of Ph); 127.69 (C_o of Ts); 126.93 (C_o of Ph); 120.98 (CH=CH); 48.89, 46.02 (CH₂NCH₂); 41.47 (CH₂NH₂); 36.05 (CH₂NHCO); 30.56 (NCH₂CH₂CH₂CH₂N); 28.24, 26.16 (CH₂CH₂); 21.35 (Me of Ts). ESI-MS: 430 ([M + H]⁺).

Data of (\pm) -(2RS,3SR)-N-{3-{[4-{[(2,2-Dichloroethoxy)carbonyl]amino]butyl][(4-methylphenyl)sulfonyl]amino]propyl]-3-phenyloxiranecarboxamide $(=(\pm)$ -2,2-Dichloroethyl [4-{[(4-Methylphenyl)sulfonyl]/3-{[[(2RS,3SR)-3-phenyloxiran-2-yl]carbonyl]amino]propyl]amino]butyl]carbamate; **19**): Colorless syrup. ¹H-NMR (300 MHz, 13 mg in 0.7 ml of CDCl₃): 768 (d, J = 8.3, 2 H_o of Ts); 7.25 – 7.40 (m, 7 arom. H); 6.76 (br. t, J = 6.2, amide NH); 5.81 (t, J = 6.0, CHCl₂); 5.13 (br. $t, NHCO_2$); 4.38 (d, J = 6.0, CH₂OCO); 3.95 (d, J = 2.0, H–C(3)); 3.51 (d, J = 2.0, H–C(2)); 3.30 – 3.52 (2 overlapping m, ³J = 6.6, CH₂NHCO); 3.02 – 3.26 (m, 3 CH₂N); 2.43 (s, Me); 1.79 (quint, J = 6.7, NCH₂CH₂CH₂N); 1.5 – 1.68 (m, CH_2CH_2). ¹³C-NMR (75 MHz, CDCl₃; δ (CDCl₃) 76.89): 167.69 (CONH); 154.75 (OCONH); 143.44 (C_p of Ts); 135.99 (C_{ipso} of Ts); 134.94 (C_{ipso} of Ph); 129.71 (C_m of Ts); 128.86 (C_p of Ph); 128.51 (C_m of Ph); 127.02 (C_o of Ts); 125.71 (C_o of Ph); 68.92 (CHCl₂); 68.62 (CH₂O); 58.93, 58.89 (overlapping C(2) and C(3)); 48.91, 46.43 (CH₂NCH₂); 40.41 (CH₂NHCO₂); 35.84 (CH₂NHCO); 28.71 (NCH₂CH₂CH₂N); 26.81, 26.14 (CH₂CH₂); 21.36 (Me of Ts). ESI-MS: 608, 610, 612 (100, 68, 15 [M + Na]⁺).

Data of (\pm) -2,2-Dichloroethyl {(11RS,12SR,24Z)-11-Hydroxy-5,18-bis[(4-methylphenyl)sulfonyl]10,23dioxo-12,25-diphenyl-5,9,13,18,22-pentaazapentacos-24-en-1-yl]carbamate (**21**): R_t (CHCl₃/MeOH/aq. 25% NH₃ soln. 85 : 14 : 1) 0.5. ¹H-NMR (300 MHz, 13 mg in 0.7 ml of CDCl₃): 7.67 ($d, J = 8.5, 2 H_o$ of Ts); 7.62 (overlapping d, J = 15, CH=CH); 7.48–7.53 (m, 2 arom. H); 7.20–7.40 (m, 12 arom. H); 7.16, 6.58 (2 br. t, 2 amide NH); 6.45 (d, J = 15.6, CH=CH); 5.84 (t, J = 6.0, CHCl₂); 5.24 (br. t, NHCO₂); 4.39 (d, J = 6.0, CH₂OCO); 4.33 (d, J = 5.1, CHOH); 4.04 (d, J = 5.0, CHNH); 3.50 (q, J = 6.1, CH₂NHCO); 2.88–3.28 (m, 10 H); 2.77 (m, 2 H); 2.57 (m, 2 H); 2.41, 2.43 (2s, 2 Me); 1.25–1.9 (m, 12 H). ESI-MS: 1015, 1017, 1019 (90, 100, 20, [M + H]⁺).

Reductive Troc Cleavage with Zn in the Presence of Na_2HPO_4 Buffer (pH 8) Followed by Macrocyclization. A mixture of Zn powder (230 mg), <1M sat. aq. Na₂HPO₄ soln. (1 ml), **10d** (143 mg, 0.23 mmol), and THF (5 ml) was stirred vigorously under N₂ for 22 h at r.t. After filtration, the residue was washed with THF, and the combined soln. diluted to 100 ml with THF. The mixture was heated under reflux for 30 h; however, macrocyclization proceeded slowly in pure THF. Then, sat. aq. Na₂CO₃ soln. (10 ml) was added and reflux continued for additional 36 h. After evaporation of THF, the aq. soln. was extracted with CH₂Cl₂ (5 × 10 ml), the extract dried (Na₂CO₃) and evaporated, and the residue (170 mg) submitted to FC (SiO₂ (25 ml). Elution with 2% MeOH/CHCl₃ (100 ml) gave **19** (14 mg, 10.4%) and lactam **12** (54 mg, 53%). After subsequent elution with 5% MeOH/CHCl₃ (100 ml) and CHCl₃/MeOH/aq. 25% NH₃ soln. 90:9:1 (100 ml) gave **20** (5 mg, 4.2%) and two unidentified crude products. Finally CHCl₃/MeOH/aq. 25% NH₃ soln. 85:14:1 (100 ml) eluted **17** (8.5 mg, 8.2%).

Data of (\pm) -2,2-Dichloroethyl {(11RS,12RS,24RS)- and (11RS,12RS,24SR)-11,24-Dihydroxy-5,18-bis[(4methylphenyl)sulfonyl]-10,23-dioxo-12,25-diphenyl-5,9,13,18,22-pentaazapentacos-1-yl]carbamate (20): ESI-MS: 1033 ($[M + H]^+$). ¹H-NMR (300 MHz, CDCl₃): in agreement with the proposed structure similar to 21; but 20 appeared as a *ca*. 1:1 mixture of two diastereoisomers.

Ethyl (\pm)-(α RS, β SR)- β -*Chloro-\alpha-hydroxybenzenepropanoate* (**24a**). Dry HCl gas was bubbled into a soln. of **4** (32.45 g, 0.169 mmol) in dry toluene (150 ml) in an ice/water bath until absorption of gas stopped (4 h). The mixture was allowed to warm to r.t. and evaporated. ¹H-NMR indicated the formation of a mixture of *threo*-

isomer **24a**, its *erythro*-isomer **24b**, and an unidentified olefin with the ratio 8:2:1. The mixture was treated with hot hexane and allowed to cool, and the separated solid was recrystallized from hot benzene (50 ml) and hexane (200 ml): pure crystalline **24a** (20.27 g, 52.5%). ¹H-NMR (300 MHz, 33 mg in 0.7 ml of CDCl₃): 7.51 (*m*, 2 H_o of Ph); 7.31–7.40 (*m*, 3 arom. H); 5.3 (*d*, J = 2.5, H - C(3)); 4.5 (br. *d* (unres. *dd*), H - C(2)); 4.26, 4.34 (2 overlapping dt, ²J = 10.7, ³J = 7, MeCH₂); 3.29 (br. *d*, J = 7, OH); 1.31 (t, J = 7, MeCH₂). ¹³C-NMR (75 MHz; δ (CDCl₃) 76.94): 171.08 (CO); 137.56 (C_{ipso} of Ph); 128.63 (C_p of Ph); 128.35 (C_m of Ph); 127.84 (C_o of Ph); 74.52 (C(2)); 63.72 (C(3)); 62.41 (CH₂); 14.0 (MeCH₂).

Potassium cis-3-*Phenyloxiranecarboxylate* (**26**). The biphasic mixture of **24a** (16.64 g, 72.77 mmol) in acetone (17 ml) and Na₂CO₃ (11.57 g, 109.1 mmol) in H₂O (100 ml) was stirred at 50°. After 8 h, additional Na₂CO₃ (5.75 g) was added and stirred at 35° for 12 h, then at 50° for 3 h. The mixture was diluted with H₂O and extracted with CHCl₃ (4×20 ml) and the combined org. phase dried (Na₂CO₃) and evaporated: crude **25** (10.8 g, 77.6%) as a pale yellow oil contaminated with *ca*. 10% of unreacted **24a**. The crude **25** (56.19 mmol) was stirred with KOH soln. (4.04 g, 72.1 mmol) in EtOH (100 ml) added by portions until full conversion (90 min) was achieved. The excess KOH was neutralized by bubbling CO₂ until the soln. turned from brown to pale yellow. After concentration to a small volume and quenching with Et₂O (100 ml), the solid was filtered: 9.3 g (82%) of pure **26**. White solid. ¹H-NMR (300 MHz, 30 mg in 0.7 ml of D₂O; δ (DHO) 4.8): 7.49–7.59 (*m*, 5 arom. H); 4.45 (*d*, *J* = 5.2, H–C(3)); 3.98 (*d*, *J* = 5.4, H–C(2)). ¹³C-NMR (75 MHz): 173.66 (CO); 134.43 (C_{*ipso*} of Ph); 128.3 (C_{*o*}, C_{*m*} of Ph); 128.3 (C_{*o*}, C_{*m*} of Ph); 126.33 (C_{*o*} of Ph); 58.53, 57.2 (C(2), (C(3)).

Data of Ethyl cis-3-*Phenyloxiranecarboxylate* (**25**): ¹H-NMR (300 MHz, 20 mg in 0.7 ml of CDCl₃): 7.41 ($m, 2 H_o$); 7.28–7.36 (m, 3 arom. H); 4.25 (d, J = 4.5, H-C(3)); 4.03, 3.96 (2 overlapping $dt, {}^{2}J = 10.9, {}^{3}J = 7$, MeCH₂); 3.81 (d, J = 4.6, H-C(2)); 1.01 ($t, J = 7, MeCH_2$). ¹³C-NMR (75 MHz, CDCl₃; δ (CDCl₃) 76.90): 166.5 (CO); 132.84 (C_{ipso} of Ph); 128.29 (C_p of Ph); 127.87 (C_m of Ph); 126.55 (C_o of Ph); 61.04 (MeCH₂); 57.25, 55.61 (C(2), (C(3))); 13.73 ($MeCH_2$).

Resolution of (\pm) -26 with (-)- and (+)-Ephedrine. Racemic 26 (9.3 g, 45.98 mmol) was resolved according to [10] to give ephedrine salts (-)-27a (6.98 g, 46.1%) from (-)-ephedrine and (+)-27b (3.5 g, 23%) from (+)-ephedrine.

Data of (-)-(1R,2S)-Ephedrine (2S,3S)-cis-3-Phenyloxiranecarboxylate ((-)-**27a**): $[a]_D = -27.2$ (c = 1.5, EtOH; [10]: -28.3). ¹H-NMR (300 MHz, 27 mg in 0.6 ml of D₂O; δ (DHO) 4.8): 7.40–7.60 (m, 10 arom. H); 5.19 (d, J = 3.4, CHOH); 4.37 (d, J = 5.2, H–C(3), oxirane); 3.90 (d, J = 5.2, H–C(2), oxirane); 3.58 (dq, J = 3.6, 6.7, CHMe); 2.82 (s, MeN); 1.19 (d, J = 6.9, MeCH). ¹³C-NMR (75 MHz): 173.52 (CO); 138.45 (C_{ipso} of ephedrine Ph); 134.33 (C_{ipso} of Ph); 128.74, 128.35, 128.21 (C_p , C_m of 2 Ph); 126.27, 126.01 ($4 C_o$ of 2 Ph); 71.30 (CHOH); 59.83 (CHNH); 58.47, 57.12 (CH–CH, oxirane); 30.62 (MeN); 9.60 (Me).

Data of (+)-(1S,2R)-Ephedrine (2R,3R)-cis-3-Phenyloxiranecarboxylate ((+)-**27b**): $[a]_D = +27.3$ (c = 1.5, EtOH).

(+)-(2S,3S)-N-(3-Bromopropyl)-3-phenyloxiranecarboxamide ((+)-29). Oxalyl chloride (0.775 ml, 9 mmol) was added to a cold (ice/water bath) stirred suspension of (-)-27a (1.52 g, 4.61 mmol) in anh. THF (45 ml). The cold bath was removed and the mixture stirred for 30 min. Additional oxalyl chloride (0.775 ml) was introduced followed by Et₃N (0.04 ml), and the mixture stirred for 30 min. The obtained suspension was poured into hexane (200 ml), stirred for 5 min, and filtered to give 852 mg (96%, corrected for purity) of the acid chloride 28 after evaporation under h.v. (1H-NMR: only ca. 5 mol-% of ephedrine derivative). To the obtained crude 28 in CH₂Cl₂ (24 ml), 3-bromopropanamine hydrobromide (1.41 g, 6.44 mmol) was added followed by Et₃N (1.79 ml, 12.88 mmol). After stirring at r.t. for 30 min, the mixture was diluted with CH₂Cl₂ (150 ml), the org. phase washed with 5% citric acid $(2 \times 50 \text{ ml})$ and NaHCO₃ soln. $(2 \times 50 \text{ ml})$, dried (Na₂CO₃), and evaporated under h.v.: (+)-29 (1.054 g, 69%), 86% purity by NMR. Crystalline solid, which was used in the next step without further purification. [$\alpha_D = +11.3$ (c = 1.64, CHCl₃). FT-IR (KBr): 3309s, 3068w, 3039w, 3014w, 2999w, 2969m, 2938m, 2860w, 1963w, 1899w, 1824w, 1653s (C=O), 1585w, 1544s, 1497m, 1441s, 1406m, 1368m, 1358m, 1340m, 1320m, 1292m, 1257s, 1212m, 1184w, 1162w, 1122w, 1079m, 1052w, 1030w, 924w, 896s, 846m, 799m, 773m, 746s, 698s, 650w, 620m, 594w, 530m, 481w, 470w. 1H-NMR (300 MHz, 29 mg in 0.5 ml of CDCl₃): 7.30 - 7.40 (*m*, 5 arom. H); 6.0 (br. *s*, NH); 4.33 (*d*, *J* = 4.7, H-C(3)); 3.78 (*d*, *J* = 4.8, H-C(2)); 3.33 (*dq* (*dddd*), 3.33 (*dq* (*dddd*)); 3.34 (*dq* (*dddd*); 3.34 (*dq* (*dddd*); 3.34 (*dq* (*dddd*)); 3.34 (*dq* (*dddd*); 3.34 (*dq* (*dddd*)); 3.34 (*dq* (*dddd*); 3.34 (*dq* (*dddd*)); 3.34 (*dq* (*dddd*); 3.34 (*dq* (*ddd*); 3.34 (*dq* (*dddd*); 3.34 (*dq* (*ddd*); ${}^{2}J = 13.7, {}^{3}J = 7, 1 \text{ H}, \text{C}H_2\text{NH}$; 2.97 (overlapping m, 1 H, CH₂NH); 2.92 (overlapping dt, ${}^{2}J = 10.1, {}^{3}J = 6.5, 1 \text{ H},$ CH₂Br); 2.66 (dt, ²J = 10.2, ³J = 6.7, 1 H, CH₂Br); 1.58 (quint. J = 6.5, CH₂). ¹³C-NMR (75 MHz; δ (CDCl₃) 76.93): 166.37 (CONH); 133.1 (C_{inso}); 128.56 (C_n); 128.40 (C_n); 126.4 (C_a); 57.93 (C(2)); 56.03 (C(3)); 36.95 $(18, [M - Br]^+).$

Data of (28,38)-3-Phenyloxiranecarbonyl Chloride (28): ¹H-NMR (300 MHz, CDCl₃): 7.31–7.41 (*m*, 5 arom. H); 4.48 (d, J = 4.5, H-C(3)); 4.25 (d, J = 4.5, H-C(2)). ¹³C-NMR (75 MHz; δ (CDCl₃) 76.92): 167.33 (COCl); 130.83 (C_{10x0}); 129.41 (C_p); 128.31 (C_m); 126.47 (C_o); 61.88 (C(2)); 59.04 (C(3)).

(+)-(2\$,3\$)-N-[3-{[(4-Methylphenyl)sulfonyl]{4-[(trifluoroacetyl)amino]butyl}amino]propyl]-3-phenyloxiranecarboxamide ((+)-30a). A mixture of (+)-29 (414 mg, 1.458 mmol), 9a (739 mg, 2.187 mmol), Cs₂CO₃ (713 mg, 2.187 mmol), and DMF (2 ml) was stirred at r.t. under N_2 for 14 h and partitioned between 5% citric acid (20 ml) and CH_2Cl_2 (5 × 5 ml). The combined org. phase was dried (Na₂CO₃) and evaporated under h.v. and the pale yellow oil (1.3 g) submitted to FC (SiO₂ (60 ml), $50 \rightarrow 70\%$ AcOEt/hexane): **30a** (500 mg, 74.7%). White foam. $R_{\rm f}$ (AcOEt/hexane 3:1) 0.35. [α]_D = +8.6 (c = 1.5, CHCl₃). FT-IR (neat, NaCl): 3331s (br., N-H), 3091*m*, 3068*w*, 3034*w*, 2944*s*, 2873*m*, 2253*w*, 1917*w*, 1718*s* (C=O), 1666*s* (C=O of CF₃CO), 1598*w*, 1541*s*, 1496*w*, 1452s, 1379m, 1335s, 1306m, 1290w, 1211s, 1184s, 1157s, 1090m, 1038w, 1020w, 1001w, 909s, 850w, 815m, 732s, 699m, 653m, 572w, 549m. ¹H-NMR (300 MHz, 45 mg in 0.6 ml of CDCl₃): 7.62 (d, J = 8.2, 2 H_o of Ts); 7.43 (br. t, NHCOCF₃); 7.23 – 7.38 (*m*, 7 arom. H); 6.42 (br. *t*, *J* = 6.2, NHCO); 4.31 (*d*, *J* = 4.8, H–C(3)); 3.76 (*d*, *J* = 4.9, H-C(2); 3.27-3.38 (*m*, CH₂NHCOCF₃); 322 (*dq* (*ddd*), ²*J*=13.8, ³*J*=7, CH₂NHCO); 2.97-3.1 (*m*, 2 H); 2.73-2.87 (*m*, 2 H); 2.67 (*dt*, ${}^{2}J = 13.5$, ${}^{3}J = 6.1$, 1 H); 2.43 (*s*, Me); 1.44-1.62 (*m*, 4 H); 1.14-1.4 (*m*, 2 H). ¹³C-NMR (75 MHz; δ (CDCl₃) 76.95): 166.43 (CONH); 157.33 ($q, J = 36.5, COCF_3$); 143.48 (C_p of Ts); 135.82 (C_{ipso} of Ts); 133.17 (C_{ipso} of Ph); 129.66 (C_m of Ts); 128.28 (C_p of Ph); 128.19 (C_m of Ph); 126.93 (C_o of Ts); 126.46 (C_o of Ph); 115.89 ($q, J = 288, CF_3$);57.84 (C(2)); 56.14 (C(3)); 48.86, 46.34 (CH_2NCH_2); 39.12 (CH₂NHCOCF₃); 35.48 (CH₂NHCO); 28.44 (NCH₂CH₂CH₂CH₂N); 26.14, 25.68 (CH₂CH₂); 21.33 (Me). ESI-MS: 564 ($[M + Na]^+$).

(2S,3S)-N-[3-[(Trifluoroacetyl)amino][4-[(trifluoroacetyl)amino]butyl]amino]propyl]-3-phenyloxirane $carboxamide (30b). A mixture of 29 (104 mg, 0.366 mmol), 9b (277 mg, 1.098 mmol), and Cs₂CO₃ (239 mg, 0.732 mmol) in DMF (0.5 ml) was stirred at r.t. under N₂ for 28 h and partitioned between H₂O (10 ml) and CHCl₃ (4 × 10 ml). The combined org. phase was dried (Na₂SO₄) and evaporated and the residue (95 mg) submitted to FC (SiO₂ (25 ml), 50 <math>\rightarrow$ 70% AcOEt/hexane): 30b (44 mg, 25%). Colorless oil. R_f (AcOEt/hexane 3:1) 0.15. ¹H-NMR (300 MHz, CDCl₃): mixture of two rotamers with broad signals. ESI-MS: 506 ([M + Na]⁺).

(2S,3S)-N-[3-{[(4-Methylphenyl)sulfonyl][4-aminobutyl]amino]propyl]-3-phenyloxiranecarboxamide (**31**). CF₃CO-protected **30a** (149 mg) was treated with K₂CO₃ (300 mg) in H₂O (2 ml) and MeOH (5 ml). After stirring for 8 h, the mixture was quenched with sat. aq. Na₂CO₃ soln. and extracted with CH₂Cl₂ (5 × 10 ml). The extract was dried (Na₂CO₃), and a small portion was evaporated and the residue characterized. ¹H-NMR (300 MHz, 22 mg in 0.7 ml of CDCl₃): 7.65 (d, J = 8.3, 2 H_o of Ts); 7.39 (m, 2 H_o of Ph); 7.25 – 7.35 (m, 5 arom. H); 6.50 (br. t, J = 5.9, NHCO); 4.31 (d, J = 4.8, H–C(3)); 3.78 (d, J = 4.8, H–C(2)); 3.19 (dq (dddd), ²J = 13.5, ³J = 7, 1 H, CH₂NHCO); 2.95 – 3.09 (m, 3 H); 2.75 (m, 2 H); 2.66 (m, 2 H); 2.44 (s, Me); 1.30 – 1.50 (m, 5 H); 1.12 – 1.28 (m, 1 H). ¹³C-NMR (75 MHz; δ (CDCl₃) 76.91): 166.25 (CONH); 143.22 (C_p of Ts); 136.48 (C_{lipso} of Ts); 133.33 (C_{lipso} of Ph); 129.58 (C_m of Ts); 128.16 (overlapping C_p, C_m of Ph); 126.95 (C_o of Ts); 126.61 (C_o of Ph); 57.78 (C(2)); 56.18 (C(3)); 48.7, 45.37, (CH₂NCH₂); 41.48 (CH₂NH₂); 35.85 (CH₂NHCO); 30.56 (NCH₂CH₂CH₂N); 28.27, 26.12 (CH₂CH₂); 21.37 (Me). ESI-MS: 446 (100, [M + H]⁺), 468 (40, [M + Na]⁺).

(-)-(12R,15R)-6-[(4-Methylphenyl)sulfonyl]-15-phenyl-13-oxa-14-thia-1,6,10-triazabicyclo[10.2.1]pentadecan-11-one 14-Oxide ((-)-32). To a cold (ice/water bath) stirred soln. of 1H-imidazole (792 mg, 11.6 mmol) in CH₂Cl₂ (60 ml), SOCl₂ (0.169 ml, 2.328 mmol) was added dropwise. After 5 min, (+)-12 (518 mg, 1.162 mmol) in CH₂Cl₂ (25 ml) was added slowly and stirred at $+5^{\circ}$ for 30 min. The mixture was quenched with H₂O (100 ml) and extracted with CHCl₃ (3 × 20 ml). The combined org. phase was washed with aq. 1N HCl, dried (Na_2SO_4) , and evaporated under h.v.: (-)-32 (581 mg, >100%). White foam, which appeared to be a 6:1 mixture of two diastereoisomers A and B. $R_{\rm f}$ (5% MeOH/CHCl₃) 0.5 (A), 0.75 (B). $[a]_{\rm D} = -242$ (c = 1.28, CHCl₃). FT-IR (KBr): 3385s, 3027w, 2933m, 2867m, 1675s, 1599w, 1529s, 1495w, 1456s, 1380w, 1336s, 1306m, 1207w, 1157s, 1117w, 1091m, 1030m, 997m, 969s, 933w, 870w, 816m, 750s, 704s, 655m, 631w, 558m. ¹H-NMR (300 MHz, 53 mg in 0.7 ml of CDCl₃; isomer A): 7.72 (d, J = 8.4, 2 H_o of Ts); 7.28-7.42 (m, 5 arom. H); 7.23 $(dd, {}^{4}J = 1.3, {}^{3}J = 7.8, 2 H_{a} \text{ of Ph}); 6.55 (br. d (dd), J = 8, NHCO); 5.13, 5.16 (2d of AB, J = 6.2, CHCH); 3.61 - 100 (2d of A$ $3.76(m, 1 \text{ H}); 3.3-3.44(m, 2 \text{ H}); 3.02-3.24(m, 2 \text{ H}); 2.96(dt, {}^{2}J=13, {}^{3}J=3.2, 1 \text{ H}); 2.6-2.83(m, 2 \text{ H}); 2.45$ (s, Me); 1.86-2.04 (m, 2 H); 1.56-1.8 (m, 4 H). ¹³C-NMR (75 MHz; δ(CDCl₃) 76.96): 165.55 (CONH); 143.36 (C_p of Ts); 137.16 (C_{ipso} of Ts); 129.7 (C_m of Ts); 129.57 (C_{ipso} of Ph); 129.49 (overlapping C_m, C_p of Ph); 128.44 (C_o of Ph); 127.02 (C_o of Ts); 85.38 (H-C(12)); 64.89 (H-C(15)); 48.34 (CH₂(5)); 45.23 (CH₂(7)); 42.33 (CH₂(2)); 36.03 (CH₂(9)); 30.29 (CH₂(8)); 25.28,22.99 (CH₂(2), CH₂(3)); 21.41 (Me). ESI-MS: 514 (100, [M + $Na]^+$, 466 (10, $[M + Na - SO]^+$).

(-)-(12R,15R)-6-[(4-Methylphenyl)sulfonyl]-15-phenyl-13-oxa-14-thia-1,6,10-triazabicyclo[10.2.1]penta-1,0,10-triazabicyclo[10.2.1]penta-1,0,10-triazabicyclo[10.2.1]penta-1,0,10-triazabicyclo[10.2.1]penta-1,0,decan-11-one 14,14-Dioxide ((-)-33). Crude (-)-32 (527 mg, 1.053 mmol) was dissolved in CH₂Cl₂/MeCN/H₂O 1:1:1 (60 ml) followed by addition of NaIO₄ (915 mg, 4.3 mmol) and RuCl₃ (2.5 mg), and the mixture was stirred vigorously for 90 min with the formation of a single product. After quenching with H₂O (200 ml), the mixture was extracted with CH_2Cl_2 (4 × 20 ml), the combined org. phase dried (Na₂SO₄) and evaporated, and the residue dissolved in CH₂Cl₂ and filtered via a short plug of SiO₂ (2 g) with 2% MeOH/CHCl₃. Drying under h.v. gave (-)-33 (533 mg, 99%). White foam, amorphous colorless solid. $R_{\rm f}$ (5% MeOH/CHCl₃) 0.8. $[a]_{\rm D}$ = -154 (c = 1.18, CHCl₃). FT-IR (KBr): 3425s, 3060w, 3038w, 2938m, 2875m, 1688s (C=O), 1599w, 1536s, 1496w, 1459s, 1342s, 1269w, 1232w, 1215w, 1158s, 1183s, 1092m, 1032w, 971s, 932w, 909w, 870w, 813m, 785m, 760s, 739m, 717w, 700m, 655m, 571m, 559m, 548m, 526m. ¹H-NMR (300 MHz, 39 mg in 0.7 ml of CDCl₃): 7.70 (d, J = 8.2, $2 H_o$ of Ts); 7.38 - 7.48 (*m*, 3 arom. H); 7.32 (*d*, *J* = 7.8, 2 H); 7.26 (*dd*, ⁴*J* = 1.6, ³*J* = 7.8, 2 H_o of Ph); 7.05 (br. *d*) (dd), J=8.3, NHCO); 5.05, 5.02 (2 d of AB, J=5.6, CHCH); 3.92 (m, (dddd), 1 H); 3.67 (ddd, 1 H); 3.33 (ddd, 1 H); 3.16-3.26 (m, 2 H); 2.68-2.88 (m, 3 H); 2.44 (s, Me); 1.83-2.1 (m, 4 H); 1.52-1.76 (m, 2 H). 13 C-NMR (75 MHz; δ (CDCl₃) 76.94): 163.68 (CONH); 143.27 (C_p of Ts); 136.34 (C_{ipso} of Ts); 130.42 (C_p of Ph); $129.68 (C_m \text{ of } Ts); 129.32 (C_m \text{ of } Ph); 128.8 (C_o \text{ of } Ph); 128.59 (C_{ipso} \text{ of } Ph); 127.0 (C_o \text{ of } Ts); 83.27 (H-C(12)); 128.59 (C_{ipso} \text{ of } Ph); 128.59 (C$ 67.57 (H-C(15)); 50.58 (CH₂(5)); 45.97 (CH₂(7)); 43.73 (CH₂(2)); 36.2 (CH₂(9)); 31.97 (CH₂(8)); 24.48, 23.17 (CH₂(2), CH₂(3)); 21.38 (Me). NMR: *Table 2*. ESI-MS: 530 ([*M*+Na]⁺).

(-)-(2R,3S)-3-Hydroxy-9-[(4-methylphenyl)sulfonyl]-2-phenyl-1,5,9-triazacyclotridecan-4-one (((-)-35). A mixture of (-)-33 (513 mg, 1.011 mmol), NaNO₂ (1.25 g), and DMF (25 ml) was stirred at 70° under N₂ for 27 h and evaporated under h.v. A small portion of the residue was acidified with AcOH, then partitioned between H₂O and CHCl₃ to give the intermediate sulfate salt sodium (2R,3S)-3-hydroxy-9-[(4-methylphenyl)-sulfonyl]-4-oxo-2-phenyl-1,5,9-triazacyclotridecane-1-sulfonate (34) after evaporation of the aq. phase. The combined residue was dissolved in MeOH (25 ml) followed by addition of Amberlyst-15 (H⁺ form; 3 g) [25]. After stirring for 30 min, the mixture was quenched with 25% aq. NH₃ soln., stirred for 20 min, and extracted thoroughly with CHCl₃ (6 × 10 ml). The org. phase was washed with H₂O and sal. aq. Na₂CO₃ soln. and the aq. phase extracted with CHCl₃. The combined org. phase was dried (Na₂CO₃) and evaporated and the white foam, (356 mg) purified by FC (SiO₂ (50 ml), 300 ml of 2% MeOH/CHCl₃): (-)-**35** (315 mg, 70%). White foam, amorphous solid. M.p. 84–87°. [α]_D = - 30.0 (c = 1.11, CHCl₃). FT-IR (KBr): 3397s (br.), 3086w, 3061w, 3027w, 2930s, 2862m, 1650s (C=O), 1599w, 1534s, 1494w, 1454s, 1399w, 1333s, 1306m, 1289w, 1184w, 1156vs, 1090s, 1059w, 1032m, 990w, 963w, 929w, 890w, 816m, 744m, 705s, 655m, 568m, 548s. NMR: see *Table 2*. ESI-MS: 468 (100, [M + Na]⁺).

Data of **34**: ¹H-NMR (300 MHz, CD₃OD; selected resonances): 5.6 (d, J = 2.5, H-C(2)); 4.64 (d, J = 2.5, H-C(3)).

(-)-(2R,3S)-3-Hydroxy-2-phenyl-1,5,9-triazacyclotridecan-4-one ((-)-36). As described above for **10h**, (-)-35 (246 mg, 0.552 mmol) was electrochemically detosylated. The obtained soln. after electrolysis was evaporated, treated with H₂O (40 ml) and sat. aq. Na₂CO₃ soln. (40 ml), followed by extraction with CH₂Cl₂ (4 × 15 ml). The combined org. phase was dried (Na₂CO₃) and evaporated under h.v.: (-)-36 (159 mg, 99%) > 95% purity by NMR. White foam that was used in the next step without further purification. $R_{\rm f}$ (SiO₂, CHCl₃/MeOH/aq. 25% NH₃ soln. 70:25:5) 0.15. $[a]_{\rm D} = -39.8$ (c = 1.08, CHCl₃). FT-IR (KBr): 3388s (O-H), 3291m, 3061m, 3029m, 2927s, 2852s, 2669m (br., N-H), 1955w, 1656vs (C=O), 1585w, 1520s, 1455s, 1440s, 1363w, 1323m, 1298w, 1246w, 1190w, 1121s, 1087s, 1055w, 1031w, 1012w, 965w, 923w, 879w, 841w, 793w, 780w, 752w, 705s, 682w, 618w, 573m, 509m. ¹H-NMR (300 MHz, 20 mg in 0.6 ml of CDCl₃): 7.48 (br. d (unres. dd), NHCO); 7.30-7.40 (m, 4 arom. H); 7.22-7.29 (m, 1 arom. H); 4.21 (d, J = 1.6, H-C(2)); 4.05 (d, J = 1.6, H-C(3)); 3.80 (m, 1 H-C(6)); 2.7-3.6 (very br. s, NH,OH); 2.97 (m, 1 H-C(6)); 2.70 (m, CH₂(8)); 2.61 (m, 1 H-C(13)); 2.51 (m, CH₂(10)); 2.34 (m, 1 H-C(13)); 1.81 (m, 1 H-C(7)); 1.29-1.68 (m, 5 H). ¹³C-NMR (75 MHz; δ (CDCl₃) 76.91): 173.12 (CONH); 141.1 (c_{ipro}); 128.22 (c_m); 127.33 (c_o); 127.22 (c_p); 74.63 (C(3)); 64.0 (C(2)); 49.23 (overlapping C(8), C(10)); 46.49 (C(13)); 39.3 (C(6)); 2.811, 27.81, 27.54 (3 CH₂). ESI-MS: 292 ([M + H]⁺).

(-)-(2R,3S)-3-Hydroxy-9-[(2E)-1-oxo-3-phenylprop-2-enyl]-2-phenyl-1,5,9-triazacyclotridecan-4-one (=(-)-(2R,3S)-3-Hydroxycelacinnine; (-)-1b). To a cold (ice/water bath) stirred soln. of (-)-36 (40.4 mg, 0.139 mmol) and DMAP (34 mg, 0.278 mmol) in anh. CH₂Cl₂ (5 ml), cinnamoyl chloride (30 mg, 0.18 mmol) in CH₂Cl₂ (1 ml) was added dropwise. After 60 min, volatiles were evaporated, and the residue was treated with NaOH (100 mg) in MeOH (4 ml) for 60 min with stirring. The mixture was partitioned between H₂O (10 ml) and CH₂Cl₂ (4 × 5 ml), the combined org. phase dried (Na₂CO₃) and evaporated, and the crude product (100 mg) purified by FC (SiO₂ (25 ml), 7% MeOH/CHCl₃): (-)-1b (50 mg, 85.5%). Colorless amorphous solid. M.p. 234–244° (dec.). $[a]_D = -38.5$ (c = 1.09, CHCl₃/MeOH 30 :1). FT-IR (KBr): 3295s (br.), 3060w, 3026w,

2926m, 2847m, 1646vs (C=O), 1594s, 1530s, 1497m, 1443m, 1433s, 1376w, 1357w, 1323m, 1276w, 1264w, 1229w, 1196m, 1169w, 1132m, 1089m, 1074w, 1030w, 991m, 914w, 849m, 763s, 731m, 699s, 685m, 568m, 503w. ¹H-NMR (500 MHz, 6 mg in 0.8 ml of CDCl₃, 27°; two rotamers A and B): 7.66 (d, J=15.5, PhCH=CH); 7.51 (d, J=7.5, $2 H_{a}$ of PhCH=CH); 7.37 (overlapping m, $4 H_{m}$ of 2 Ph, $2 H_{a}$ of Ph-C(2)); 7.36 (overlapping m, H_{a} of PhCH=CH); 7.30 (m, H_p of Ph-C(2)); 7.09 (br. s, 0.4 H, NHCO); 7.03 (br. s, 0.6 H, NHCO); 6.80 (d, J=15.5, PhCH=CH; 4.31 (br. s (unres. d), H-C(2)); 4.18 (br. s (unresolved d), H-C(3)); 3.78, 3.79 (br., $1 H_A-C(6)$); 3.63, 3.69 (br., $1 H_A - C(8)$); 3.48 - 3.59 (overlapping 3 *m* at 3.55 (0.5 H, H'_B - C(8)), at 3.52 (0.5 H, H_A - C(10)), and at 3.53 (0.5 H, H_A-C(10)); 3.45 (br., 0.5 H, H'_A-C(8)); 3.39, 3.38 (br., 1 H'_B-C(10)); 2.98, 2.99 (br., $1 H_{B} - C(6)$; 2.82 (br., $1 H_{A} - C(13)$); 2.46 (m, $1 H_{B} - C(13)$); 2.22 (br., $1 H_{A} - C(7)$); 1.92 (br., $1 H_{A} - C(11)$); 1.67, 1.68 (br., $1 H_B - C(7)$); 1.56, 1.63 (br., $1 H_B - C(11)$); 1.58 (br., $1 H_A - C(12)$); 1.47 ($1 H_B - C(12)$). ^{13}C -NMR (75 MHz, 40 mg in 0.6 ml of CDCl₃+0.05 ml of CD₃OD; δ(CDCl₃) 77.23; 23°; two rotamers): 173.98, 173.91 (CONH); 166.66, 166.38 (C(O)CH=CH); 142.78, 142.65 (PhCH=CH); 140.82, 140.54 (C_{ipso} of Ph-C(2)); 135.35 (C_{ipso} of PhCH=CH); 129.72 (C_p of PhCH=CH); 128.88, 128.57 (C_m of 2 Ph); 127.88 (C_p of Ph-C(2)); 127.35 (C_a of Ph-C(2)); 117.46 (PhCH=CH); 75.94 (C(3)); 64.38, 64.08 (C(2)); 47.04, 46.18 (C(13)); 46.56, 44.96 (C(10)); 44.37, 43.38 (C(8)); 36.59, 36.13 (C(6)); 30.26, 27.99 (C(7)); 26.18, 24.42 (C(11)); 24.64 (C(12)). For ¹H- and ¹³C-NMR: see also *Table 2*. ESI-MS: 422 ($[M + H]^+$).

(12RS,13SR)-6-[(4-Methylphenyl)sulfonyl]-13-phenyl-1,6,10-triazabicyclo[10.1.0]tridecan-11-one ((±)-38). To a soln. of (±)-12 (46 mg, 0.103 mmol) in CH₂Cl₂ (1 ml), TsCl (59.1 mg, 0.31 mmol) was added,followed by Et₃N (0.2 ml) and DMAP (45 mg). The mixture was stirred for 6 h and evaporated. FC (SiO₂(25 ml), CHCl₃ (100 ml), then 1% MeOH/CHCl₃ (100 ml)) gave**38**(35 mg, 79%). ¹H-NMR (300 MHz, 35 mgin 0.6 ml of CDCl₃): 7.66 (<math>d, J = 8.1, 2 H_o of Ts); 7.24 – 7.33 (m, 7 arom. H); 6.77 (br. s, 0.3 H); 3.8 (br. s, 0.3 H); 2.48 – 3.6 (several br. m, 8 H): 3.32 (br. s, ca. 2 H); 3.07 (br. dt, ${}^{3}J$ = 5.1, ${}^{2}J$ = 14.8, 1 H); 2.62 (d, J = 2.7, ca. 1 H); 2.57 (m, ca. 1 H); 2.43 (s, Me); 2.13 (br., 0.7 H); 1.4 – 2.0 (br., 5.3 H). ¹³C-NMR (75 MHz; δ (CDCl₃) 76.92, several br. signals): 143.31 (C_p of Ts); 135.65 (C_{ipso} of Ts); 129.63 (C_m of Ts); 128.20 (C_m of Ph); 127.14 (C_o of Ts); 126.3 (br.); 77.13, 76.34 (overlapping with CDCl₃); 49.16 (C(10)?); 47.85 (br., CH₂); 44.3 (br.); 38.9 (br.); 28.1 (br., CH₂); 26.69 (CH₂); 25.8 (br.); 21.35 (Me). ESI-MS: 428 ($[M + H]^+$).

 (\pm) -(2RS,3RS)-9-[(4-Methylphenyl)sulfonyl]-3-[[(4-methylphenyl)sulfonyl]oxy]-2-phenyl-1,5,9-triaza-1-(trifluoroacetyl)cyclotridecan-4-one (41). To a stirred soln. of (\pm) -12 (30.2 mg, 0.0677 mmol) and (CF₃CO₂)₂O (57 mg, 0.271 mmol) in CH₂Cl₂ (1 ml), Et₃N (0.021 ml, 0.15 mol) was added and stirred for 40 min at r.t. The mixture was quenched with CHCl₃, the org. phase washed with 5% aq. citric acid and then aq. NH₃ soln., dried (Na₂CO₃), and evaporated: crude 40 (41 mg), which was used in the next step without purification. Crude 40 was dissolved in CDCl₃ (0.6 ml) followed by addition of TsCl (23 mg, 0.121 mmol) and Et₃N (0.023 ml). ¹H-NMR indicated a very slow reaction. After 2 h, DMAP (11 mg) was added and the mixture kept at r.t. for 4 h. The obtained soln. was diluted with CHCl₃, washed with aq. Na₂CO₃ soln., 1N aq. HCl, dried (Na₂CO₃), and evaporated (64 mg). Purification by FC (SiO₂ (20 ml), AcOEt/hexane 1:1) gave 41 (41 mg, 87%). White foam. $R_{\rm f}$ (AcOEt/hexane 1:1) 0.3. ¹H-NMR (300 MHz, 41 mg in 0.6 ml of CDCl₃): 7.97 (d, J = 8.1, 0.3 H); 7.7 (overlapping d, J = 8.2, 2 H); 7.66 (overlapping d, J = 8, 0.3 H); 7.41 (overlapping br. d, J = 7.9, 1.7 H); 7.04 - 7.48 (m, 12 H); 6.12 (d, J = 10.3, 0.7 H); 5.75 (s, 0.3 H); 4.44 (br. s, 0.7 H); 3.6 - 4.04 (m, 2 H); 3.3 - 3.6 (m, 2 H);2.95-3.26 (*m*, 2 H); 2.7-2.92 (*m*, 4 H); 2.44 (*s*, 3.3 H, Me); 2.4 (*s*, 2.7 H, Me); 1.82-2.12 (*m*, 3 H); 1.52-1.82 (m, 3 H). ¹³C-NMR (75 MHz; δ (CDCl₃) 76.92): 166.82 (CONH); 157.5 ($q, J = 36.7, \text{ COCF}_3$); 144.72 (C_p of TsO); 143.74 (C_p of TsN); 134.83, 134.32, 132.08 (C_{ipso} of Ts, Ph); 129.91 (CH); 129.76, 129.61 (4 C_m of 2 Ts); 129.23 (br., 2 C_m of Ph); 128.42 (2 C_a of Ph); 128.33 (C_a of Ph); 127.91, 127.91 (4 C_a of 2 Ts); 116.08 (q, J = 289, CF₃); 76.54 (H-C(3)); 66.0 (br., H-C(2)); 52.3, 48.19 (2s, CH₂(13)); 51.12, 50.44 (C(8), C(10)); 39.69 (CH₂(6)); 27.63 (CH₂(7)); 25.76 (CH₂(12)); 24.67 (CH₂(11)); 21.46, 21.37 (2 Me). ESI-MS: 524 (100, [M- $TsO]^+$, 718 (12, $[M + Na]^+$).

Data of (\pm) -(2RS,3RS)-3-Hydroxy-9-[(4-methylphenyl)sulfonyl]-2-phenyl-1-(trifluoroacetyl)-1,5,9-triaza-cyclotridecan-4-one (40). ¹H-NMR (300 MHz, CDCl₃): 2:3 mixture of two rotamers. ESI-MS: 564 ([M + Na]⁺).

 (\pm) -(2RS,3SR)-3-Hydroxy-9-[(4-meth ylphenyl)sulfonyl]-1-nitroso-2-phenyl-1,5,9-triazacyclotridecan-4one (42). The suspension of NaNO₂ (237 mg) and 41 (40 mg) in DMF (1 ml) was stirred at 70° for 14 h, quenched with H₂O (1 ml) and AcOH (0.2 ml), and extracted with Et₂O: crude 42 (34 mg) of *ca*. 85% purity by ¹H-NMR. Pale brown solid. $R_{\rm f}$ (5% MeOH/CHCl₃) 0.33. ¹H-NMR (300 MHz, 34 mg in 0.7 ml of CDCl₃): 7.64 (*d*, *J* = 8.2, 2 H_o of Ts); 7.56 (br. *dd*, *J* = 4, 7.1 NH); 7.26–7.38 (7 H); 6.12 (*d*, *J*(2,3) = 1.9, H–C(2)); 4.86 (*d*, *J*(2,3) = 1.9, H–C(2)); 3.78–3.92 (*m*, CH₂(6)); 3.36 (*m*, 1 H–C(10)); 3.20 (*ddd*, *J* = 4, 8, 12.7, 1 H–C(8)); 2.98–3.14 (3 H); 2.60 (*dt* (*ddd*), ³*J* = 5, 5.6, ²*J* = 13.6); 2.43 (s, Me); 1.90–2.16 (*m*, 2 H); 1.45–1.7 (*m*, 2 H); 1.32–1.44 (*m*, 1 H); 0.8–0.92 (*m*, 1 H). ¹³C-NMR (75 MHz; δ (CDCl₃) 76.92): 171.89 (CONH); 143.49 (C_p of Ts); 135.93 (C_{ipso} of Ph); 135.4 (C_{ipso} of Ts); 129.7 (C_m of Ts); 128.94 (C_m of Ph); 128.48 (C_p of Ph); 127.27 (C_o of Ph); 127.11 (C_o of Ts); 75.55 (H–C(3)); 67.08 (H–C(2)); 50.15 (CH₂(10)); 48.02 (CH₂(8)); 44.36 (CH₂(13)); 38.19 (CH₂(6)); 28.24 (CH₂(7)); 25.74 (CH₂(12)); 24.96 (CH₂(11)); 21.38 (Me). ESI-MS: 497 (100, $[M + Na]^+$), 467 (20, $[M + Na - NO]^+$), 446 (40, $[M - NO + 2 H]^+$), 410 (40).

(2R,3S)-9-[(2E)-1-Oxo-3-phenylprop-2-enyl]-2-phenyl-3-[[(2S)-3,3,3-trifluoro-2-methoxy-1-oxo-2-phenylpropyl]oxyl-1,5,9-triazacyclotridecan-4-one (= (α S)- α -Methoxy- α -(trifluoromethyl)benzeneacetic Acid (2R,3S)-4-Oxo-9-[(2E)-1-oxo-3-phenylprop-2-enyl]-2-phenyl-1,5,9-triazacyclotridec-3-yl Ester **44**). To a soln. of **1b** (6 mg, 0.0142 mmol) and DMAP (5.7 mg, 0.0466 mmol) in CDCl₃ (0.6 ml), (-)-(R)-Mosher acid chloride (7.5 mg, 0.0297 mmol) was added. ¹H-NMR indicated an immediate complete reaction. FC (SiO₂ (10 ml), 1% MeOH/CHCl₃) gave **44** (8.4 mg, 93%). Oil. $R_{\rm f}$ (5% MeOH/CHCl₃) 0.3. ¹H-NMR (300 MHz, 8.4 mg in 0.6 ml of CDCl₃): 7.69 (d, J = 15.5, PhCH=CH); 7.18-7.55 (15 arom. H); 6.80 (d, J = 15.4, PhCH=CH); 5.93, 5.77 (2 br. s, 0.4 and 0.6 H, resp., NHCO); 5.59 (d, J = 1.8, H-C(3)); 4.43 (br. s, H-C(2)); 3.15-3.84 (overlapping br. m, 8 H); 3.63-3.84 (1.6 H); 3.44-3.63 (1.7 H); 3.31-3.44 (1.1 H); 3.28 (s, MeO); 2.79 (dt, 2J = 12, 3J = 4.3, 1 H); 2.71 (br. m, 1 H); 2.39 (br. m, 1 H); 2.19 (br. m, 1 H); 1.85 (br. m, 1 H); 1.34-1.76 (br. m, 4 H). ESI-MS: 638 ($[M+H]^+$).

Mosher *Esterification of the Natural Sample*. A crude natural sample of 3-hydroxycelacinnine (3 mg) was treated with (-)-(R)-*Mosher* acid chloride as described above for **44**. The mixture was purified by prep. TLC to give a crude product which was diastereoisomerically pure (¹H-NMR) and completely identical to synthetic **44**. ¹H-NMR: 5.59 (*s*, H–C(3)); 4.43 (*s*, H–C(2)); 3.28 (*s*, MeO).

(-)-(2R,3S)-3-Hydroxy-9-(1-oxo-3-phenylpropyl)-2-phenyl-1,5,9-triazacyclotridecan-4-one ((-)-45). Method A. To a soln. of (-)-36 (19 mg, 0.0652 mmol) and DMAP (27 mg) in CDCl₃, 3-phenylpropanoyl chloride (25 mg) was added. ¹H-NMR indicated a fully complete reaction after 5 min. The mixture was evaporated and the residue dissolved in MeOH (5 ml). Aq. 1N NaOH (1 ml) was added and the mixture stirred for 5 h. Partition between aq. Na₂CO₃ soln. and CH₂Cl₂, followed by FC purification (SiO₂, 4% MeOH/CHCl₃) gave (-)-45 (24 mg, 87%). White solid.

Method B. Synthetic (-)-**1b** (7 mg) was hydrogenated with H₂ over 10% Pd/C in MeOH. Filtration over a plug of SiO₂ and evaporation gave (-)-**45** in *ca.* 96% yield. M.p. 210–212°. R_f (5% MeOH/CHCl₃) 0.12. [α]_D = -22.9 (c = 0.48, CHCl₃). ¹H-NMR (300 MHz, 19 mg in 0.6 ml of CDCl₃): 7.15–7.38 (m, 10 arom. H); 7.04 (dd, J = 4.4, 7.7, 0.4 H, NHCO); 6.98 (dd, J = 4, 7.8, 0.6 H, NHCO); 4.20 (br., H–C(2)); 4.11 (br. s, H–C(3)); 3.47–3.76 (br. m, 2 H); 3.05–3.46 (br. m, 4 H); 2.91 (overlapping t, J = 8, PhCH₂); 2.87 (overlapping m, 1 H); 2.72 (br. m, 1 H); 2.54 (m, CH₂CO); 2.33 (br. m, 1 H); 1.9–2.18 (br. m, 1.4 H); 1.64–1.9 (br. m, 1.6 H); 1.22–1.63 (br. m, 4 H). ESI-MS: 424 ([M + H]⁺).

Hydrogenation of the Natural Sample. A crude natural sample of 3-hydroxycelacinnine (7.7 mg) was hydrogenated with H₂ over 10% Pd/C (3.7 mg) in MeOH (2 ml) and purified by prep. TLC: crude **45** (7 mg) of *ca.* 80% purity. ESI-MS: 424 (100, $[M + H]^+$), 437 (10, unidentified impurity). CD (5 mg in 10 ml of MeOH): *Fig.* 2.

HPLC-UV-MS/MS Studies of (-)-**1a**, (-)-**1b**, and the Natural Sample of 3-Hydroxycelacinnine. The HPLC-UV(DAD)-MS experiments were performed on an *HP1100* system (*Hewlett-Packard*, Palo Alto, CA, USA). HPLC: Uptisphere-UP3 HDO-C₁₈ (3 µm) column (200 mm long, 4.6 mm i.d.; Interchim, Montluçon, France) at 22°; flow rate 0.5 ml min⁻¹; diode-array detection (DAD), detector setting at 280 nm; mobile phase: gradient 0.1% HCO₂H in H₂O (solvent *A*) to 0.1% HCO₂H in MeCN (solvent *B*); gradient: within 30 min, 0–100% *B*. The APCI-MS (atmospheric-pressure-chemical-ionization mass spectrometry) detector was interfaced directly to the output of the UV detector. HPLC-UV(DAD)-tandem mass spectrometry (MS/MS): APCI-MS with a *Bruker Esquire-LC* quadrupole ion-trap instrument (*Bruker Daltonik*, Bremen, Germany) connected to an orthogonal electrospray ion source (*Hewlett-Packard*); MS detector: N₂ nebulizer gas 40 psi; N₂ dry gas 81 min⁻¹; dry temp. 300°; APCI temp. 350°, HV capillary 4770 V; HV end-plate offset -787 V; capillary exit 108.2 V; cap. exit offset 73.2 V; trap drive 40.4; auto MS/MS acquisitions under ion-charge-control (ICC) conditions (10'000) in the mass range from *mlz* 50 to 800; isolation width, 4 *m/z*; fragmentation amplitude, 1 V in the SmartFrag mode (20–200%).

HPLC-UV-MS/MS Data of (+)-**1a**: $t_{\rm R}$ 15.35. UV: 287. MS/MS of *m/z* 422 ([*M*+1]⁺): 404 (6, [*M*+1 - H₂O]⁺), 382 (10), 347 (3), 321 (20), 317 (21), 307 (60), 292 (5), 274 (13), 202 (30), 160 (100), 131 (13).

HPLC-UV-MS/MS Data of (-)-**1b**: $t_{\rm R}$ 14.55. UV: 287. MS/MS of m/z 422 ($[M+1]^+$): 404 (8, $[M+1-H_2O]^+$), 347 (5), 321 (11), 317 (17), 307 (77), 292 (5), 274 (11), 221 (5), 202 (40), 160 (100), 131 (11).

HPLC-UV-MS/MS Data of the Natural Sample: mixture of three components **1b**, **A** (= 3-hydroxycelallocinnine (**43**)), *and* **B** ca. 4:1:1. HPLC-UV-MS/MS was also performed with the prepared mixture of the natural sample with (-)-**1b** and (-)-**1a**. Data of natural **1b** were completely identical to the data of synthesized (-)-**1b**. *Data of* **43** (**A**): t_R 13.55 min. UV: 255. MS/MS of m/z 422 ($[M+1]^+$): 404 (7, $[M+1-H_2O]^+$), 321 (6), 317 (11), 307 (29), 292 (25), 274 (6), 221 (1), 202 (11), 188 (4), 160 (100), 131 (6).

Data of **B** (unidentified impurity): $t_{\rm R}$ 11.3. UV: <215. MS/MS of m/z 438 ([M+1]⁺): 420 (100, [M+1-H₂O]⁺), 361.6 (5), 332 (2), 290 (3), 261 (6), 218 (55), 203 (10), 196 (4), 160 (7), 154 (3), 143 (35), 128 (17).

REFERENCES

- [1] U. Bachrach, 'Function of Naturally Occurring Polyamines', Academic Press, New York, 1973.
- [2] A. Guggisberg, M. Hesse, in 'The Alkaloids', Vol. 50, Academic Press, New York, 1998, p. 219.
- [3] C. Séguineau, P. Richomme, J. Bruneton, J. Pusset, Helv. Chim. Acta 1992, 75, 2283.
- [4] C. Séguineau, P. Richomme, J. Bruneton, P. Meadows, Heterocycles 1994, 38, 181.
- [5] N. A. Khanjin, M. Hesse, Helv. Chim. Acta 2001, 84, 1253.
- [6] S. Bienz, R. Detterbeck, C. Ensch, A. Guggisberg, U. Häusermann, C. Meisterhans, B. Wendt, C. Werner, M. Hesse, in 'The Alkaloids', 2002, 58, 83.
- [7] D. M. Gou, Y. C. Liu, C. S. Chen, J. Org. Chem. 1993, 58, and ref. 14a,b cited therein.
- [8] I. Brackenridge, S. Davies, D. R. Fenwick, O. Ichihara, M. E. C. Polywka, *Tetrahedron* 1999, 55, 533 and ref. cit. therein.
- [9] K. Harada, J. Org. Chem. 1966, 31, 1407.
- [10] L. Thijs, J. J. M. Porskamp, A. A. W. M. van Loon, M. P. W. Derks, R. W. Feenstra, J. Legters, B. Zwanenburg, *Tetrahedron* 1990, 46, 2611.
- [11] J. M. Lemmens, W. J. M. Blommerde, L. Thijs, B. Zwanenburg, J. Org. Chem. 1984, 49, 2231.
- [12] R. Wälchli, A. Guggisberg, M. Hesse, Helv. Chim. Acta 1984, 61, 2178.
- [13] G. Just, K. Grozinger, Synthesis 1976, 457.
- [14] J. K. Pak, A. Guggisberg, M. Hesse, *Tetrahedron* 1998, 54, 8035; C. Goulaouic-Dubois, A. Guggisberg, M. Hesse, J. Org. Chem. 1995, 60, 5969.
- [15] B. Nyasse, L. Crehn, H. L. S. Maia, L. S. Monteiro, U. Ragnarsson, J. Org. Chem. 1999, 64, 7135.
- [16] H. Yamamoto, K. Maruoka, J. Am. Chem. Soc. 1982, 103, 6133.
- [17] C. C. Tung, A. J. Speziale, Chem. Ind. 1963, 1985; J. Org. Chem. 1963, 28, 2009; J. Am. Chem. Soc. 1965, 87, 2683.
- [18] K. Harada, Y. Nakajima, Bull. Chem. Soc. Jpn. 1974, 47, 2911.
- [19] S. B. Mahato, N. P. Sahu, P. Luger, J. Am. Chem. Soc. 1983, 105, 4441.
- [20] M. E. Van Dort, Y.-W. Jung, P. S. Sherman, M. R. Kilbourn, D. M. Wieland, J. Med. Chem. 1995, 38, 810.
- [21] B. Radüchel, Synthesis 1980, 292; R. Latrell, G. Lohaus, Liebigs Ann. Chem. 1974, 901.
- [22] A. Defoin, H. Sarazin, J. Streith, *Tetrahedron* 1997, 53, 12783.
- [23] T. A. Lyle, C. A. Magill, S. M. Pitzenberger, J. Am. Chem. Soc. 1987, 109, 7890.
- [24] K. W. Pankiewicz, B. C. Nawrot, K. A. Watanabe, J. Org. Chem. 1986, 51, 1525.
- [25] N. A. Khanjin, J.-L. Montero, Tetrahedron Lett. 2002, 43, 4017.
- [26] C. Séguineau, Ph.D. Thesis, personal communication.
- [27] C. A. G. Haasnoot, F. A. A. M. de Leeuw, C. Altona, Tetrahedron 1980, 36, 2783.
- [28] F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, J. Comput. Chem. 1990, 11, 440; http://www.schrodinger.com/macromodel2.html.
- [29] S. Chen, J. K. Coward, J. Org. Chem. 1998, 63, 502.
- [30] A. P. Krapcho, C. S. Kuell, Synth. Commun. 1990, 20, 2559.
- [31] L. Bigler, C. F. Schnider, W. Hu, M. Hesse, Helv. Chim. Acta 1996, 79, 2152.

Received August 22, 2002