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

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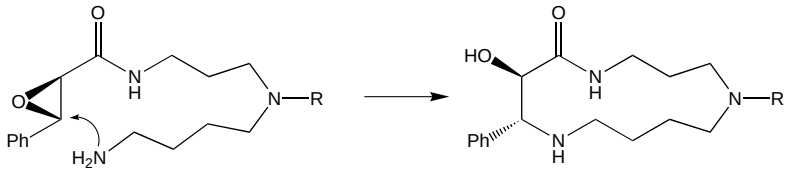
Dedicated to Dr. *Annalaura Lorenzi-Riacci* on the occasion of her 70th birthday

The two epimers (−)-**1a** and (−)-**1b** of the macrocyclic lactam alkaloid 3-hydroxycelacinnine with the (2*R*,3*R*) and (2*R*,3*S*) 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 (2*R*,3*R*)-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 $NaNO_2$ led to (2*R*,3*S*)-macrocycles. The synthesized (−)-(2*R*,3*S*)-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.

Scheme 1. *Proposed Biosynthetic Macrocyclization*



In the previous paper, we described the eight-step synthesis of (±)-(2*RS*,3*RS*)-3-hydroxycelacinnine ((±)-**1a**) in 10% overall yield starting from potassium *trans*-phenylglycidate ((±)-**5**) [5]. The key transformations involved stereo- and regioselective oxirane-ring opening with $Mg(N_3)_2$ and macrocyclic coupling of ditosylated

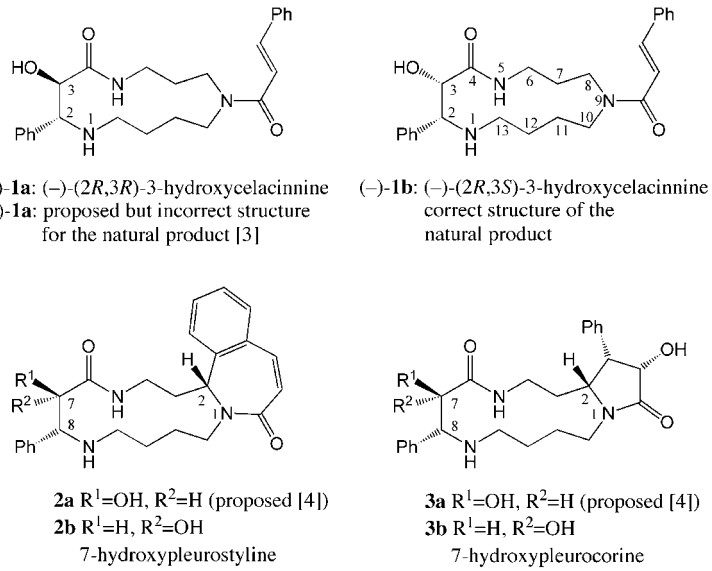


Fig. 1. *Proposed structures of the novel hydroxylated alkaloids 3-hydroxycelacinnine* ((±)-**1a**)*, 7-hydroxypleurostyline* (**2a**)*, and 7-hydroxypleurocorine* (**3a**) *from* Pleurostylia opposita [3][4] *and their corrected structures* (–)-**1b**, **2b**, *and* **3b** (this work)

diamine precursor with 1,4-dibromobutane promoted by Cs_2CO_3 in DMF. NMR Data of the synthesized (±)-**1a** suggested that the natural 3-hydroxycelacinnine is the *cis*-epimer **1b** with the (2*R**,3*S**) 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 ^{1}H- and ^{13}C-NMR data for the β-amino-α-hydroxy-lactam moiety (*Fig. 1*) [3][4]. In addition, despite the reported zero $[\alpha]_D$ value and the absence of CD effect for the natural 3-hydroxycelacinnine [3], we have proposed (2*R*,3*S*) 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 (–)-(2*R*,3*R*)-3-hydroxycelacinnine ((–)-**1a**) and (–)-(2*R*,3*S*)-3-hydroxycelacinnine ((–)-**1b**) *via* the more efficient 'biomimetic' route (*Scheme 1*) and confirm the assumed (2*R*,3*S*) 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 (2*R*,3*R*) configuration with excellent yields (up to 85%). However, reaction of the corresponding *cis*-oxiranes led only to numerous by-products for steric

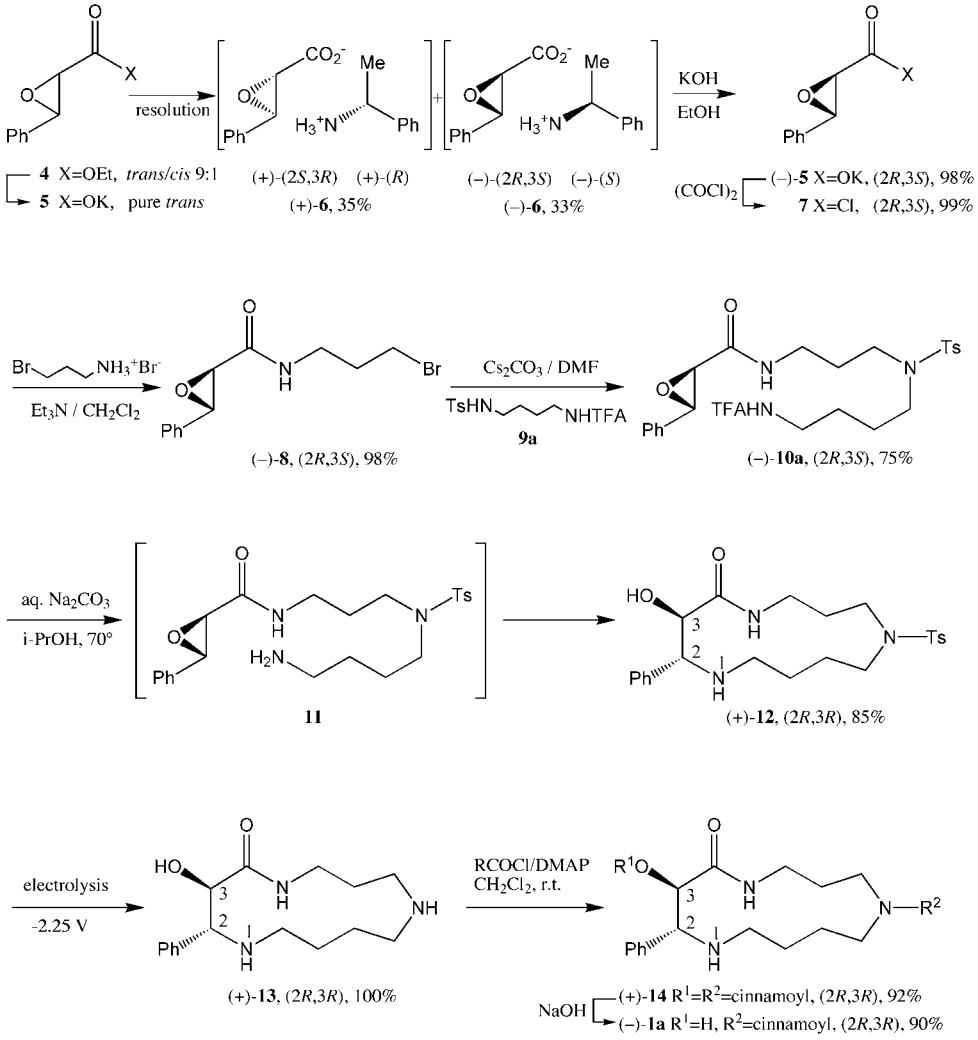
reasons. This suggests an alternative biosynthetic formation of (−)-**1b**. Macrocycles with the natural (2*R*,3*S*) configuration were finally obtained from epimeric (2*R*,3*R*)-precursors by mean of inversion at C(3) involving nucleophilic displacement of a cyclic sulfamidate derivative. To the best 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; (±)-**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 (2*R*,3*S*)- and (2*S*,3*R*)-potassium phenylglycidates ((−)- and (+)-**5**, resp.) were regenerated from (−)- and (+)-**6**, respectively, by quantitative (98%) precipitation from EtOH with ethanolic KOH and Et_2O. 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 (2*R*,3*R*)-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 (±)-**5** for optimization. The latter was converted to amide (±)-**8** [5] *via* acid chloride (±)-**7** [11] followed by Cs_2CO_3-promoted 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 CF_3CO-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**–**f** were easily prepared according to general or published procedures from putrescine in one to three steps as described in the *Exper. Part*. Alternatively, acid chloride (±)-**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 CF_3CO) in acyclic precursors **10a**–**e**,**h**, the best yields of the desired macrocyclic products (up to 85%, *Table 1*) were achieved with the CF_3CO 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

Scheme 2. *Synthesis of (–)-(2*R*,3*R*)-3-Hydroxycelacinnine* ((–)-**1a**)

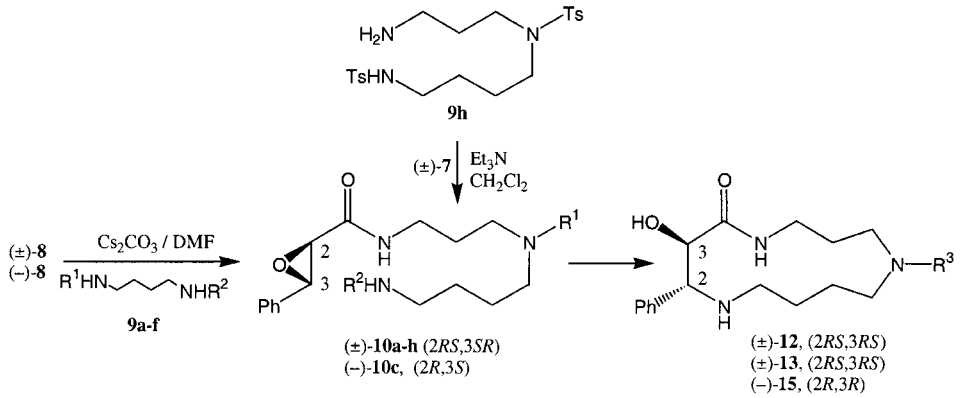


TFA = CF_3CO, Ts = 4-$MeC_6H_4SO_2$, cinnanoyl = (2*E*)-PhCH=CHCO

of **16a** and **16b** (*Scheme 3*). In case of Boc-protected **10e**, either both Boc and oxirane (with CF_3COOH in CH_2Cl_2 or Me_3SiCl/PhOH in CH_2Cl_2) or only the oxirane were cleaved (*Amberlyst-15* (H^+-form) in CH_2Cl_2) 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 KH_2PO_4/Na_2HPO_4) for 4 h followed by reflux in biphasic THF/aqueous Na_2CO_3 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

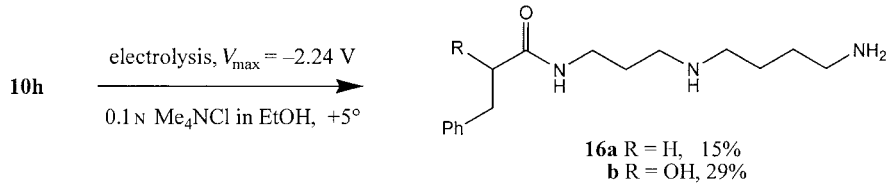
Table 1. *Preparation of the Acyclic Precursors, their Deprotection, and Macrocyclization*



9	R^1	R^2	10 (yield [%])	R^3	Macrocycle (yield [%])
9a	Ts	CF_3CO	**10a** (75)	Ts	**12** (85)[a][b])
9b	CF_3CO	CF_3CO	**10b** (17)	H	**13** (67)[a]
9c	β-$C_{10}H_7SO_2$	CF_3CO	**10c** (79)	β-$C_{10}H_7SO_2$	**15** (85)[a])
9d	Ts	Troc (= Cl_3CCH_2OCO)	**10d** (63)	Ts	**12** (53)[c])
9e	Ts	Boc	**10e** (74)[d])		
9f	Ts	H	**10f** (> 50)[e])		
9g	H	H	**10g** (0)[f])		
9h	Ts	Ts	**10h** (92)[g])		

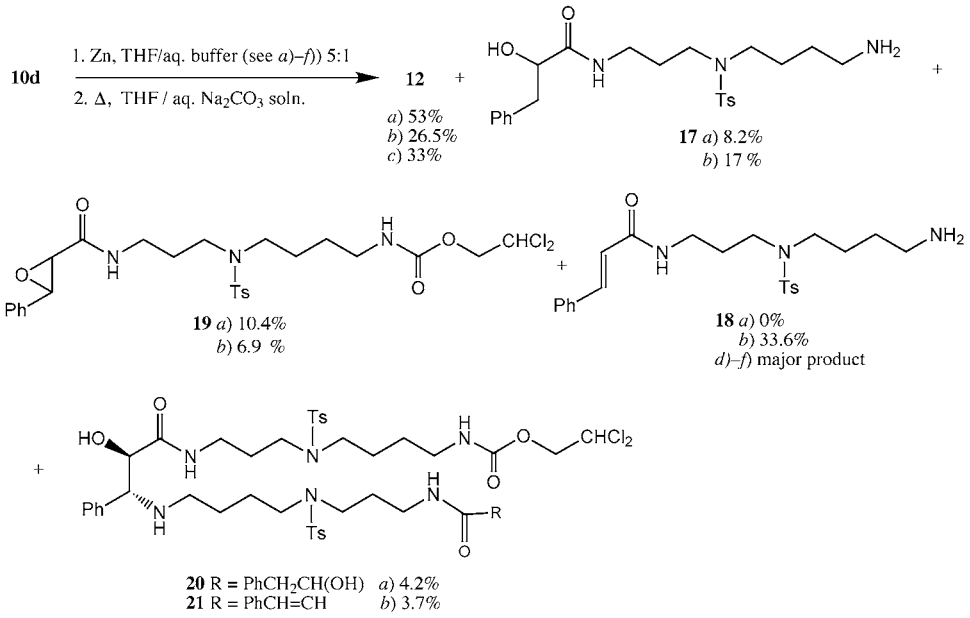
[a]) Optimized conditions: aq. Na_2CO_3 soln./i-PrOH 70°, 36 h. [b]) For details, see discussion and *Exper. Part*; for product distribution, see also *Scheme 5*. [c]) Optimized conditions: 1. Zn/sat. aq. Na_2HPO_4 soln./THF 2. Δ; for product distribution under different pH conditions, see *Scheme 4*. [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/Na_2CO_3 under heating failed. [g]) Electrochemical tosyl deprotection also led to complete oxirane cleavage.

Scheme 3



of **18** and **19** (*Scheme 4*). In the presence of NH_4OAc buffer (pH 7), deprotection-macrocyclization 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 Na_2HPO_4 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

Scheme 4

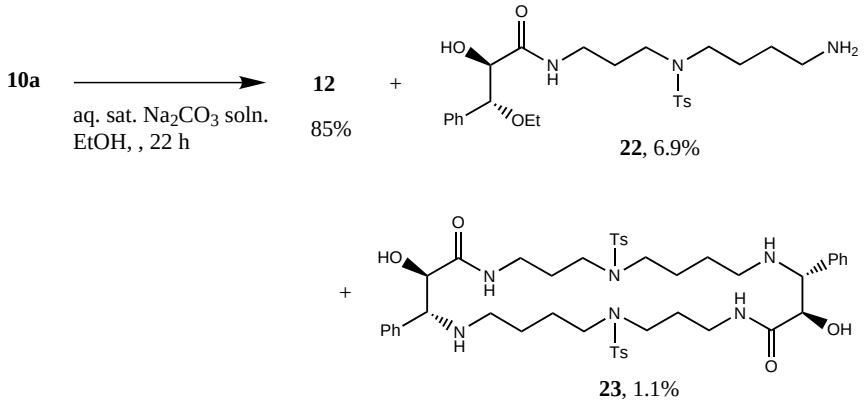


a) Sat. aq. Na_2HPO_4 soln., pH 8 22 h. *b*) 0.5M KH_2PO_4/0.5M Na_2HPO_4, pH 5.5, 4 h. *c*) 1M NH_4OAc, pH 7, 16 h. *d*) 1M AcOH, pH 3, 10 min. *e*) 1M KH_2PO_4, 85 min. *f*) 1M NaOH.

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 KH_2PO_4).

With the CF_3CO-protected substrates, the best yields of macrocyclic products (85%) were observed after one-pot deprotection-macrocyclization at 70° for 36 h in aqueous Na_2CO_3/i-PrOH. In contrast to many other macrocyclization reactions, high-dilution 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 Na_2CO_3/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. Na_2CO_3 system, the initial CF_3CO 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 Na_2CO_3 solution (3 times from sat. aqueous Na_2CO_3 solution in case of EtOH or i-PrOH, and 10 times in case of THF). Otherwise CF_3CO cleavage proceeded slowly in these biphasic systems. The intermediate free amino-amide **11** could be separated when CF_3CO removal was performed at room temperature with K_2CO_3 in MeOH. However, product **11** was not

Scheme 5



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

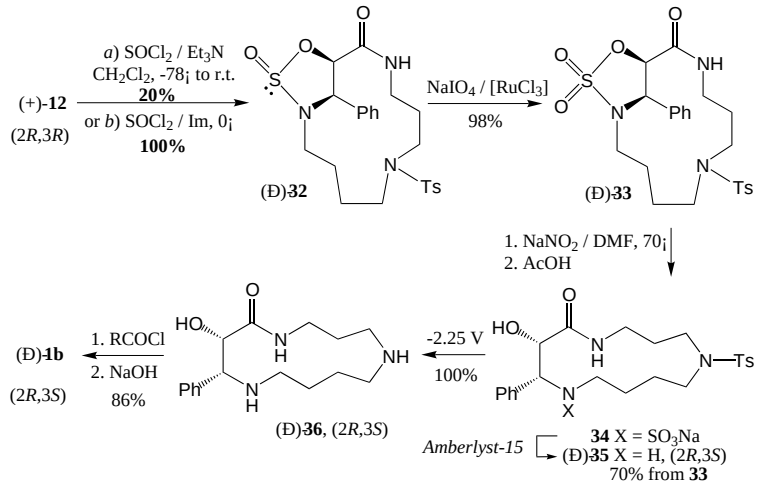
With the bis-trifluoroacetyl precursor **10b**, deprotection-macrocyclization proceeded with lower yield (67.5%) under formation of unprotected macrocycle **13** (*Table 1*). Several minor by-products were observed in this case due to the release of two unprotected N-atoms both capable of oxirane opening. 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 (2*R*,3*R*) 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 (±)-**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 CH_2Cl_2 or $CDCl_3$ 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).

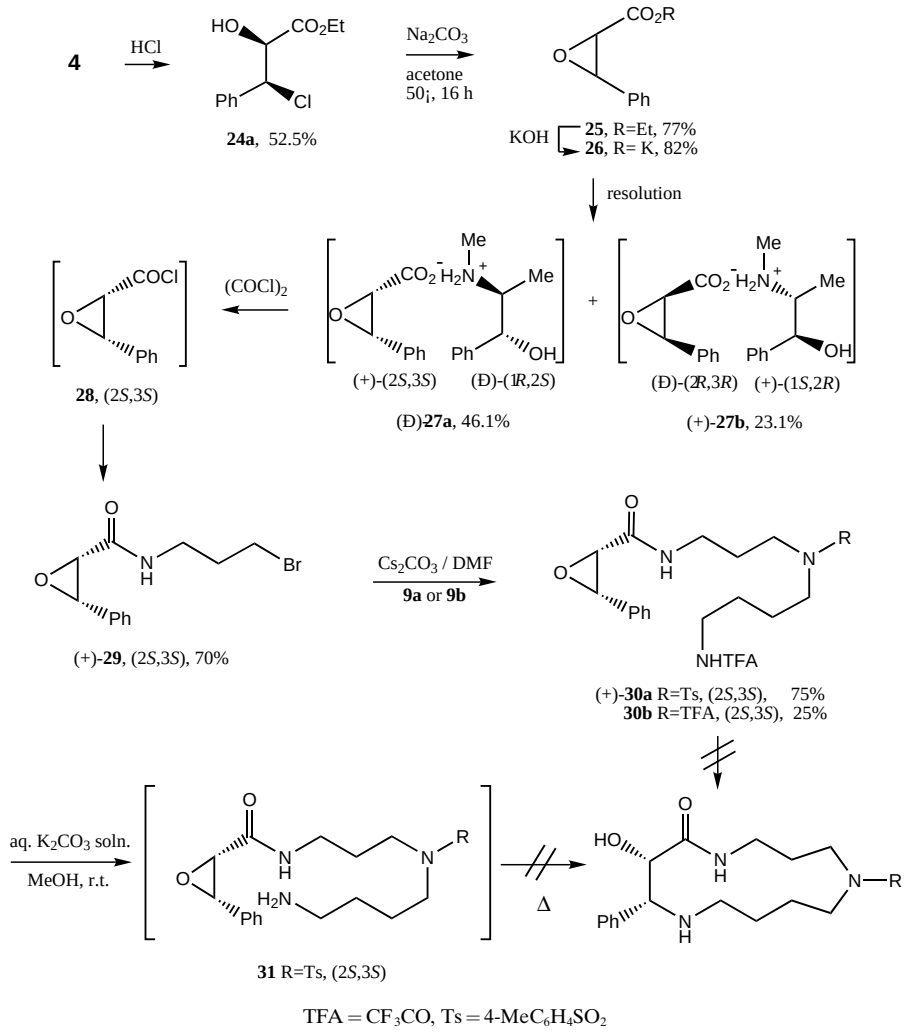
Synthesis of (–)-1b. – The optimized synthetic route to (–)-**1b** from (+)-**12** *via* inversion at C(3) is depicted in *Scheme 6*. To quickly confirm our hypothesis concerning the (2*R**,3*S**) relative configuration of the natural 3-hydroxycelacinnine, we obtained the racemic C(3) epimer (±)-**35** of (±)-**12** by means of a nucleophilic displacement of its cyclic sulfamidate derivative (±)-**33** (see below). The small ^{1}H-NMR H–C(2)–C(3)–H coupling constant and corresponding chemical shifts in the epimer (±)-**35** were in excellent agreement with the values of the natural alkaloid. However, the preparation of (±)-**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*).

Scheme 6. *Synthesis of (–)-(2*R,*3*S*)-3-Hydroxycelacinnine* ((–)-**1b**)



First, we attempted to convert *trans*-oxiranecarboxamide (±)-**10a** to *cis*-isomer (±)-**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 (±)-**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 $NaHCO_3$ 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 Na_2CO_3 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*

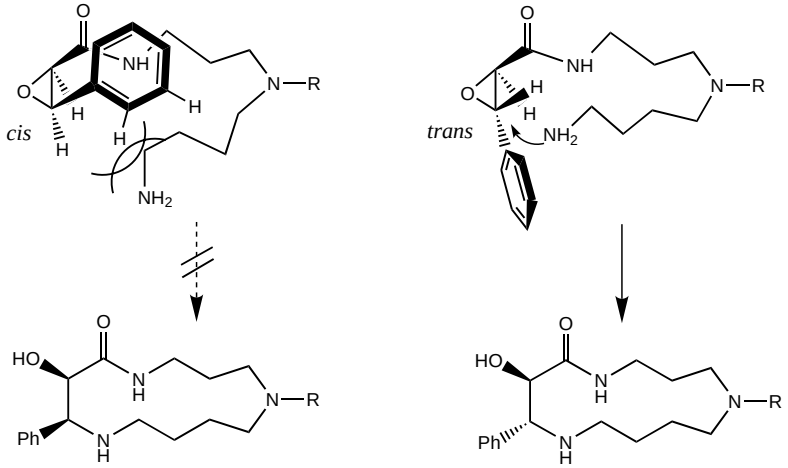


TFA = CF_3CO, Ts = 4-$MeC_6H_4SO_2$

for oxirane opening on solid support. The *threo-erythro* stereoselectivity was also poor in this case. In addition, selective cleavage of the *trans*-oxiranecarboxamide (±)-**10a** from the polymer-supported intermediate *threo/erythro* hydroxysulfonates with $NaHCO_3$ failed due to a faster and uncontrolled ring closure to a mixture of both oxiranes (±)-**10a** and (±)-**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

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 (2*R,*3*S*)-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 Na_2CO_3 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 CF_3CO-protected *cis*-oxiranecarboxamides (+)-**30a** and **30b** were prepared *via* (+)-**29** as described above for the corresponding *trans*-oxiranecarboxamides **10a** and **10b**.

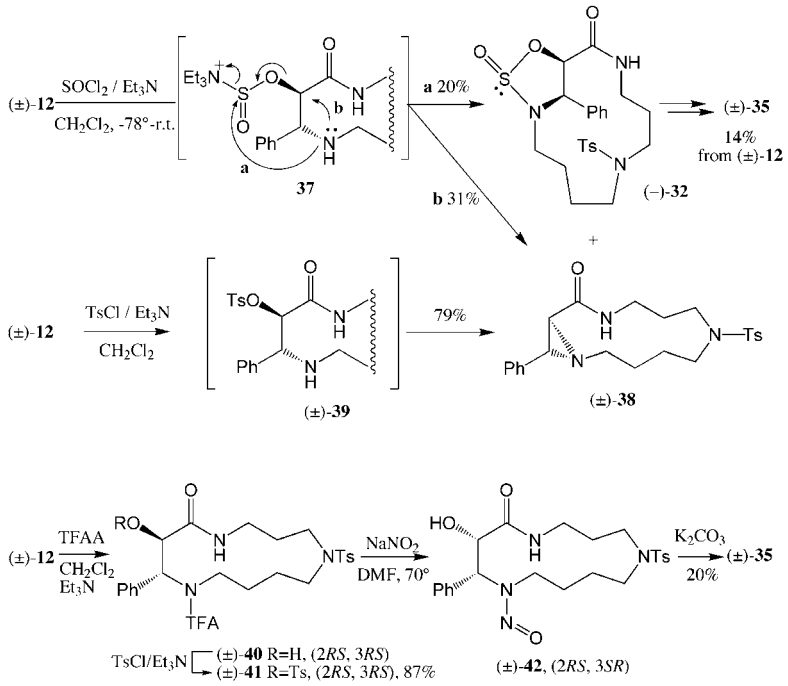
Treatment of **30a** and **30b** under the conditions described above for the macrocyclization of **10a** and **10b** led to complete decomposition of the starting *cis*-oxiranecarboxamides into a complex mixture of products without formation of the desired macrocycles. Thus the CF_3CO group of **30a** 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_N2 oxirane opening in case of *cis*-oxirane derivatives **35a** and **35b** is sterically unfavored, leading to a mixture of competitive by-products presumably from S_N1 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 (±)-**32** in only 20% yield after the first step due to unexpected neighboring N-atom participation in the formation of aziridine derivative (±)-**38** in 31% yield (*Scheme 9*). The latter is presumably formed from the intermediate **37** with the O-atom activated by the positively charged $Et_3N^+S(O)–O–C(3)$ as a good leaving group. Aziridine

Scheme 9



Ts = 4-$MeC_6H_4SO_2$, TFA = CF_3CO, TFAA = $(CF_3CO)_2O$

derivative (±)-**38** was also formed as the major product (79% yield) after an attempt to prepare tosyloxy derivative (±)-**39** from (±)-**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 (±)-**39**, which was never observed in a reaction mixture.

The isolated sulfamidite (±)-**32** was oxidized to cyclic sulfamidate (±)-**33** and displaced with $NaNO_2$ ($\rightarrow$ (±)-**34**) according to a general procedure (for displacement of sulfonates with KNO_2, see [21]; for displacement of cyclic sulfates with KNO_2, see [22]). The desired *cis*-epimer (±)-**35** was isolated in 14% overall yield from *trans*-epimer (±)-**12** after acidic workup. The ^{1}H-NMR data of (±)-**35** (H−C(3) at δ 4.05, H−C(2) at δ 4.16, and a small ^3J(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.).

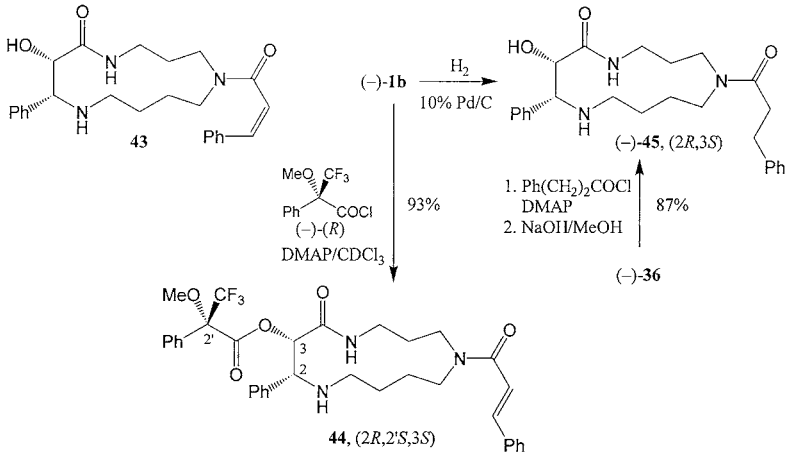
Alternatively, N(1) could be protected with CF_3CO (($CF_3CO)_2O$/Et_3N, CH_2Cl_2) to give (±)-**40** followed by *O*-tosylation with formation of (±)-**41** (87% yield) (*Scheme 9*). The tosyloxy group of (±)-**41** was displaced with $NaNO_2$ in DMF (14 h, 70°) to give epimeric *N*-nitroso-*cis*-macrocycle (±)-**42** in *ca.* 85% yield according to the analysis of the reaction mixture after workup. Again the typical ^{1}H-NMR data were observed (^3J(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 (±)-**42** was troublesome and gave only 20% yield of (±)-**35** after heating with K_2CO_3 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 ^{t}BuMe$_2$Si 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[1*H*-imidazole] (room temperature) generated *in situ* from $SOCl_2$ and 1*H*-imidazole (*Scheme 6*). Unlike with Et_3N 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 $NaNO_2$ 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 *trans*-epimer (+)-**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 ^{1}H-NMR data (*Scheme 10*).

Characterization and Comparison with the Natural Sample. – ^{1}H- and ^{13}C-NMR-signal 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 ^{1}H- and

Scheme 10



^{13}C-NMR signals of (−)-**1b** in $CDCl_3$ were broad, overlapped, or doubled with the approximate integral ratio 2 : 3. The exact ^{1}H- and ^{13}C-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, ^{1}H-, and ^{13}C-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 H_2O, CD_3OD, 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 ^{1}H-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_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 ($[M((-)\text{-}\mathbf{1b})+1]^+$), identical fragmentation with isomeric (−)-**1b** in the MS/MS experiment, hypsochromic and hypochromic UV shift (λ_{max} 255 nm for **43**, *vs.* λ_{max} 287 nm for (−)-**1b**), and the presence of characteristic. ^{1}H-NMR olefin signals of the (*Z*)-cinnamoyl moiety (δ 6.56, 6.57 (2 *d* of two rotamers, $^3J_{cis} = 12.6$ Hz) and δ 5.98, 5.99 (2 *d* of 2 rotamers, $^3J_{cis} = 12.6$ Hz). Presumably, **A** was formed from 3-hydroxycelacinnine after light-induced (*E*) → (*Z*) C=C bond isomerization upon long-time storage. Component **B** (t_R 11.3 min) with *m/z* 438 ($[M((-)\text{-}\mathbf{1b})+16+1]^+$) and a UV $\lambda_{max} < 215$ 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 (−)-(2*R,*3*S*)-3-Hydroxycelacinnine* ((−)-**1b**), *and* (−)-**35**

	1b [3][a]		(−)-**1b**, (2*R*,3*S*) (this work)[b]		(−)-**35**, (2*R*,3*S*) (this work)[c]	
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
H−C(2)	4.27 (*d*, *J*(2,3) = 1.2)	64.01, 64.38	4.31 (br. *s* (unres. *d*), *J*(2,3) < 1.5)	64.08, 64.38	4.16 (*s* (unres. *d*), *J*(2,3) < 1.5)	63.94
H−C(3)	4.16 (*d*, *J*(2,3) = 1.2)	76.16, 76.16	4.18 (br. *s* (unres. *d*), *J*(2,3) < 1.5)	75.94	4.05 (*s* (unres. *d*), *J*(2,3) < 1.5)	75.61
C(4)		172.50, 172.34	–	173.98, 173.91		173.21
NH(5)	7.00 (*t*)		7.09 (br. *s*, 0.4 H) 7.03 (br. *s*, 0.6 H)	–	7.16 (br. *t*)	–
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 (*m*), 1.70 (*m*)	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 (*m*), 3.43 (*m*)	43.03, 44.59[d]	3.63, 3.55 3.69, 3.45	44.37, 43.38	3.25 (*t*, *J* = 7.7, 2 H)	46.19
CH_2(10)	3.57 (*m*), 3.38 (*m*)	44.01, 46.80[d]	3.53, 3.38 3.52, 3.39	44.96 46.56	3.3 (*m*) 2.91 (*m*)	47.69
CH_2(11)	1.92 (*m*), 1.62 (*m*)	24.88[e], 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[e], 26.06	1.47, 1.58	24.64	1.42 (*m*, 2 H)	25.59
CH_2(13)	2.86 (*m*), 2.31 (*m*)	46.55, 46.46	2.46, 2.82 2.46, 2.82	46.18, 47.04	2.69 (*dt* (*ddd*), ^2J = 12.2, ^3J = 4.8) 2.33 (*m*)	45.56
OH−C(3)			–	–	–	–
Phenyl:						
C(1′)		142.35, 142.44	–	140.82, 140.54	–	141.17
H−C(2′), H−C(6′)	7.35 (*m*)	127.76[f]	7.37	127.35	7.32	127.19
H−C(3′), H−C(5′)	7.35 (*m*)	126.99[f]	7.37	128.57	7.33	128.88
H−C(4′)	7.35 (*m*)	127.56[f]	7.30	127.88	7.26	127.72
Cinnamoyl or tosyl:						
O=C		165.16, 165.82	–	166.66, 166.38	–	–
CH=C*H*CO	6.30 (*d*, *J*(2,3) = 15.4)	117.53	6.80 (br. (*d*, *J* = 15.5)	117.46	–	–
C*H*=CHCO	7.66 (*d*, *J*(2,3) = 15.4)	140.79	7.66 (*d*, *J* = 15.5)	142.78, 142.65	–	–
C(1″)		135.41	–	135.35	–	137.15
H−C(2″), H−C(6″)	7.52 (*m*)	128.78	7.51 (br. *d*)	127.88	7.67 (*d*, *J* = 8.2)	127.3
H−C(3″), H−C(5″)	7.35 (*m*)	128.78	7.37	128.88	7.29 (*d*, *J* = 8.2)	129.88
H−C(4″)	7.35 (*m*)	129.49	7.36	129.72	–	143.34
Me−C(4″)					2.42	21.68

[a]) Spectra in $CDCl_3$ at room temperature with $SiMe_4$ as internal reference; ^{1}H- and ^{13}C-NMR at 270 and 67.5 MHz, resp. [b]) ^{1}H- and ^{13}C-NMR and 2D NMR: 6 mg in 0.8 ml of $CDCl_3$, δ($SiMe_4$) 0.00(^{1}H, 500 MHz), δ($CDCl_3$) 77.23 (^{13}C, 125 MHz). Due to a low sample concentration, some ^{13}C-NMR signals were not resolved: these δ are based on a more concentrated sample of (−)-**1b**: 40 mg in 0.6 ml of $CDCl_3$ + 0.05 ml of CD_3OD, δ($CDCl_3$) 77.23 (^{13}C, 75 MHz). [c]) 38 mg in 0.7 ml of $CDCl_3$, 300 K, δ(Me_4Si) 0.00 (^{1}H, 600 MHz), δ($CDCl_3$) 77.23 (^{13}C, 150 MHz). [d])[e])[f]) Interchangeable 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 ((−)-**1b**) and 3-hydroxycelallocinnine (**43** or **A**) from the natural sample into the same compound, *i.e.*, dihydro-3-hydroxycelacinnine (−)-**45**, after hydrogenation with H_2 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 (−)-**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 ^{1}H-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 ^{1}H-NMR. Thus, the absolute configuration of natural 3-hydroxycelacinnine is (2*R*,3*S*) as in the identical synthetic (−)-(2*R*,3*S*)-3-hydroxycelacinnine ((−)-**1b**).

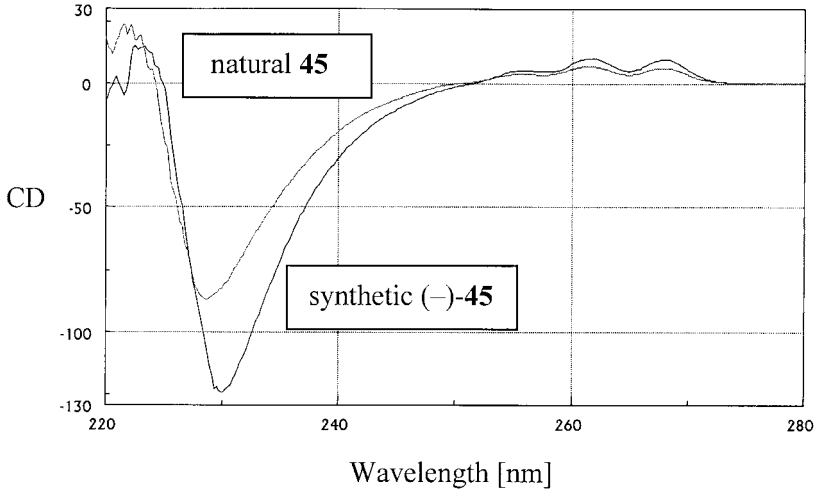


Fig. 2. *CD Curves of synthetic* (−)-**45**) *and hydrogenated natural 3-hydroxycelacinnine*

Conformational Analysis of Epimeric Macrocycles. – The relative (2*R**,3*R**) *trans*-configuration in **1a** and *cis*-configuration (2*R**,3*S**) 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*-

averaged ^{1}H-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 $^3J(2,3)$ of *trans*-macrocycles **1a**, **12**–**15**, **40**, and **41** were practically identical ($^3J(2,3) = 9-10$ Hz) as well as those of *cis*-macrocycles **1b**, **34**–**36**, **42**, and **44** ($^3J(2,3) <$ 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) (*anti*-periplanar) 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 $^3J(2,3)$ (*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 $^3J(2,3)$ (0.8–2 Hz, depending on the force field), in excellent agreement with the observed values for *cis*-macrocycles including (–)-**1b**.

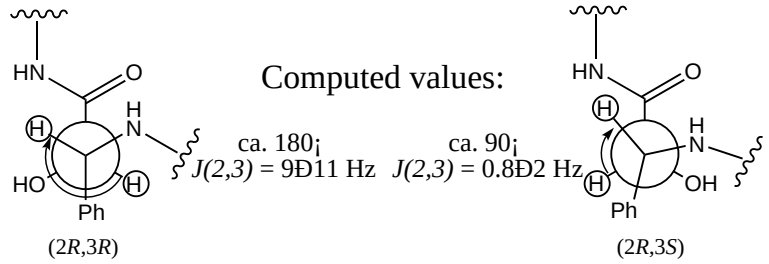


Fig. 3. *Lowest-energy conformations around C(2)–C(3) and calculated* Boltzmann-*averaged* J*(2,3) for (2*R*,3*R*)- and (2*R*,3*S*)-macrocycles*

Conclusions. – We confirmed the absolute configuration of the natural 3-hydroxycelacinnine by means of the total synthesis of its two diastereoisomers (–)-(2*R*,3*R*)- and (–)-(2*R*,3*S*)-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 (−)-(2*R*)-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 (±)-**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%; $[\alpha]_D = +125.8$ ($c = 1.14$, 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%; $[\alpha]_D = -124$) according to *Thijs et al.* [10].

*Potassium (−)-(2*R,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 Et_2O to give 9.19 g of (−)-**5** ($[\alpha]_D = -139.5$ ($c = 1.14$, H_2O)). The supernatant gave additional 970 mg of the product ($[\alpha]_D = -138.2$ ($c = 1.24$)) after quenching with Et_2O. ^{1}H-NMR (300 MHz, 20 mg in 0.6 ml of D_2O; 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)). ^{13}C-NMR (75 MHz): 175.32 (CO); 135.62 (C_{ipso}); 128.95 (C_p); 128.75 (C_m); 126.03 (C_o); 58.86, 57.47 (C(2), (C(3)).

*(−)-(2*R,3S*)*-trans-N-*(3-Bromopropyl)-3-phenyloxiranecarboxamide* ((−)-**8**) was obtained from (−)-**5** by the same procedure as (±)-**8** [5]. An anal. sample was prepared after purification by FC (SiO_2, 35% AcOEt/hexane) and crystallization from AcOEt/hexane. Colorless fibers. M.p. 100.0–100.3°. $[\alpha]_D = -46.8$ ($c = 1.4$, $CHCl_3$). Other data: completely identical with those of (±)-**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 CH_2Cl_2 (15 ml), $(CF_3CO)_2O$ (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 CH_2Cl_2 (80 ml), $(CF_3CO)_2O$ (15 ml) was added, followed by dropwise addition of CF_3COOH (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 H_2O (300 ml): **9a** (7.002 g, 87.9%). M.p. 95–101°. FT-IR (KBr): 3314*s* (N–H), 3254*s* (N–H), 3104*w*, 3070*w*, 2968*m*, 2954*m*, 2932*m*, 2892*w*, 2865*m*, 2760*w*, 1924*w*, 1698*s* (C=O), 1600*m*, 1561*s*, 1496*w*, 1475*m*, 1441*m*, 1400*w*, 1381*w*, 1353*m*, 1322*s*, 1306*s*, 1292*m*, 1246*m*, 1212*s*, 1183*s*, 1159*s*, 1091*m*, 1065*m*, 1038*m*, 1019*w*, 896*m*, 815*s*, 803*w*, 744*m*, 726*s*, 706*m*, 660*m*, 634*w*, 596*w*, 571*s*, 550*s*, 520*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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*, $J = 6.6$, CH_2NHCO); 2.94 (*t*, $J = 6.5$, CH_2NHTs); 2.42 (*s*, Me); 1.61, 1.53 (2 *m*, 2 CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$; $\delta(CDCl_3)$ 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*, $J = 288$, CF_3); 42.44 (CH_2NHTs); 39.23 (br., CH_2NHCO); 26.43, 25.65 (CH_2CH_2); 21.33 (Me). ESI-MS: 361 ($[M + Na]^+$).

N,N′-*Butane-1,4-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*. ^{1}H-NMR (300 MHz, 31 mg in 0.6 ml (D_6)DMSO; δ((D_6)DMSO) 2.5): 9.37 (br. *t*, NHCO); 3.19 (unresolved *m*, 2 CH_2N); 1.48 (*quint.*, $J = 3.2$, 2 CH_2). ^{13}C-NMR (75 MHz, (D_6)DMSO; δ((D_6)DMSO) 39.38): 156.08 (*q*, $J = 36.5$, NHCO); 115.82 (*q*, $J = 288$, CF_3); 38.58 (CH_2NH); 25.36 (CH_2).

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 Et_3N (4 ml) in CH_2Cl_2 (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 $CHCl_3$, and the soln. washed with 10% citric acid (2 × 20 ml), then with sat. aq. $NaHCO_3$ soln. The org. phase was dried (Na_2SO_4) 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 $(CF_3CO)_2O/CF_3COOH$ as described above for **9a** (*Method B*) and crystallized from hot EtOH/H_2O: **9c** (2.5 g, 77%). White crystals. M.p. 100–102°. FT-IR (KBr): 3265*s*, 3111*m*, 3061*w*, 2981*w*, 2924*m*, 2865*m*, 1716*s*, 1697*s*, 1626*w*, 1570*s*, 1503*w*, 1470*w*, 1457*m*, 1441*m*, 1370*m*, 1351*m*, 1316*s*, 1216*s*, 1186*s*, 1154*s*, 1126*s*, 1077*m*, 1061*s*, 1017*w*, 971*w*, 958*w*, 947*w*, 910*m*, 877*m*, 827*s*, 748*s*, 722*s*, 702*s*, 657*m*, 640*m*, 617*w*, 561*w*, 534*w*, 517*w*, 484*m*. ^{1}H-NMR (300 MHz, 10 mg in 0.5 ml of $CDCl_3$): 8.43 (*d*, *J* = 1.2, 1 H); 7.80–8.04 (*m*, 4 H); 7.63 (*m*, 2 H); 6.66 (br. *s*, $NHCOCF_3$); 5.08 (br. *t*, *J* = 5.8, $NHSO_2$); 3.32 (*q*, *J* = 6.7, 2 H); 3.01 (*q*, *J* = 5.4, 2 H); 1.48–1.7 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$; $\delta(CDCl_3)$ 76.90): 157.32 (*q*, *J* = 36.6, *C*OCF_3); 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 (CH_2NHS); 39.21 (*C*H_2NHCO); 26.58, 25.74 (CH_2CH_2). 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 CH_2Cl_2 (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 CH_2Cl_2, the org. phase washed with sat. aq. $NaHCO_3$ soln., dried (Na_2CO_3), 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*, 1284*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*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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, $NHCO_2$); 4.70 (overlapping *s*, CH_2O); 3.20 (*q*, *J* = 6.4, C*H*$_2$NHCO); 2.96 (*q*, *J* = 6.4, C*H*$_2$NHTs); 2.43 (*s*, Me of Ts); 1.47–1.63 (2 overlapping *quint.*, CH_2CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$; $\delta(CDCl_3)$ 76.89): 154.56 (C=O); 143.37 (C_p); 136.84 (C_{ipso}); 129.63 (C_m); 126.97 (C_o); 42.60 (*C*H_2NHTs); 40.5 (*C*H_2NHCO); 26.70, 26.59 (CH_2CH_2); 21.38 (Me). ESI-MS: 439, 441, 443, 445 (100, 95, 45, 4 $[M+Na]^+$). CI-MS (NH_3): 286 ($[TsNH(CH_2)_4NHCONH_2]^+$).

1,1-Dimethylethyl {4-{[(4-Methylphenyl)sulfonyl]amino}butyl}carbamate (**9e**) [31]. R_f (AcOEt/hexane 1:1) 0.62. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.74 (*d*, *J* = 8.3, 2 H_o); 7.29 (*d*, *J* = 8.1, 2 H_m); 5.08 (br. *s*, N*H*Ts); 4.6 (br. *s*, N*H*Boc); 3.05 (br. *s*, C*H*$_2$NHBoc); 2.93 (br. *s*, C*H*$_2$NHTs); 2.42 (*s*, Me of Ts); 1.44–1.52 (*m*, 2 CH_2); 1.42 (*s*, *Me*$_3$C). ^{13}C-NMR (75 MHz, $CDCl_3$; $\delta(CDCl_3)$ 76.93): 155.89 (C=O); 143.19 (C_p); 136.94 (C_{ipso}); 129.56 (C_m); 126.96 (C_o); 79.13 (Me_3C); 42.69 (*C*H_2NHTs); 39.82 (br., *C*H_2NHCO); 28.28 (*Me*$_3$C); 27.04, 26.61 (CH_2CH_2); 21.35 (Me of Ts).

N-*[4-Aminobutyl]4-methylbenzenesulfonamide* (**9f**) [29]. ^{1}H-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, N*H*Ts); 2.92 (*t*, *J* = 6.45, C*H*$_2$NHTs); 2.67 (*t*, *J* = 6.3, C*H*$_2$$NH_2$); 2.42 (*s*, Me of Ts); 1.4–1.6 (2 *m*, 2 CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$; $\delta(CDCl_3)$ 76.94): 142.93 (C_p); 137.25 (C_{ipso}); 129.49 (C_m); 126.91 (C_o); 42.9 (CH_2NH); 41.17 (CH_2NH_2); 30.21, 27.25 (2 CH_2); 21.34 (Me).

N-*(3-Aminopropyl)-4-methyl*-N-*{4-{[(4-methylphenyl)sulfonyl]amino}butyl}benzenesulfonamide* (**9h**) [12]. R_f (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 90:9:1) 0.3. ^{1}H-NMR (300 MHz, 30 mg in 0.7 ml of $CDCl_3$): 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, N*H*Ts, NH_2, H_2O); 3.1–3.25 (*m*, C*H*$_2$N(Ts)C*H*$_2$); 2.98 (*t*, *J* = 7.2, C*H*$_2$$NH_2$); 2.88 (*t*, *J* = 6.0, C*H*$_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). ^{13}C-NMR (75 MHz, $CDCl_3$; $\delta(CDCl_3)$ 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 (*C*H_2N*C*H_2); 42.41 (*C*H_2NHTs); 37.95 (CH_2NH_2); 27.29 ($NCH_2CH_2CH_2N$); 26.38 (overlapping 2 CH_2); 21.32 (2 Me of 2 Ts).

*(±)-(2*RS,*3*SR*)*-N-*{3-[(4-Methylphenyl)sulfonyl]{4-[(trifluoroacetyl)amino]butyl}amino}propyl}-3-phenyloxiranecarboxamide* ((±)-**10a**). A mixture of (±)-**8** (845 mg, 2.975 mmol), **9a** (1.09 g, 3.22 mmol), Cs_2CO_3 (1.11 g, 3.407 mmol), and DMF (3.5 ml) was stirred at r.t. under N_2 for 7 h and partitioned between H_2O (100 ml) and CH_2Cl_2 (75 ml). The aq. layer was extracted with CH_2Cl_2 (2 × 40 ml) and the combined org. phase dried (Na_2SO_4) and evaporated under h.v. (12 h, r.t.): 2.015 g of brown oil. The oil was dissolved in CH_2Cl_2/CCl_4 1:1 (6 ml) and submitted to FC (SiO_2 (100 ml), AcOEt/hexane 1:1 (500 ml), then 6:4 (200 ml): pure (±)-**10a** (1.055 g, 65.5%). White foam. R_f (AcOEt/hexane 1:1) 0.15. FT-IR (neat, NaCl): 3325*s* (br., N–H), 3088*m*,

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*. ^{1}H-NMR (300 MHz, 45 mg in 0.6 ml of $CDCl_3$): 7.66 (*d*, *J* = 8.3, 2 H_o of Ts); 7.23–7.4 (*m*, 7 arom. H, $NHCOCF_3$); 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, $NCH_2CH_2CH_2N$); 1.64 (2 overlapping *m*, CH_2CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$; $\delta(CDCl_3)$ 76.93): 167.85 (CONH); 157.35 (*q*, *J* = 36.5, CF_3CO); 143.57 (C_p of Ts); 135.7 (C_{ipso} 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_o of Ts); 125.67 (C_o of Ph); 115.86 (*q*, *J* = 288, CF_3); 58.87, 58.77 (overlapping C(2), C(3)); 49.08, 46.88 (CH_2NCH_2); 39.12 ($CH_2NHCOCF_3$); 36.26 (CH_2NHCO); 28.74 ($NCH_2CH_2CH_2N$); 26.16, 25.79 (CH_2CH_2); 21.33 (Me). ESI-MS: 564 ($[M+Na]^+$).

*(–)-(2*R*,3*R*)-*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. $[\alpha]_D = -25.7$ (*c* = 1.6, $CHCl_3$).

*(±)-(2*RS,*3*SR*)-3-Phenyl*-N-*{3-{(trifluoroacetyl){4-[(trifluoroacetyl)amino]butyl}amino}propyl}oxiranecarboxamide* (**10b**). A mixture of (±)-**8** (500 mg, 1.76 mmol), **9b** (2.03 g, 7.25 mmol), Cs_2CO_3 (2.23 g, 7.04 mmol), and DMF (4 ml) was stirred at r.t. under N_2 for 38 h. The mixture was quenched with H_2O/CH_2Cl_2, and the excess **9b** was filtered off. The aq. layer was extracted with $CHCl_3$ (4×), dried, and evaporated. The residue (283 mg) was chromatographed by FC (SiO_2 (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): 3313*s* (br., N–H), 3094*m*, 2948*m*, 2869*m*, 2253*w*, 1715*s* (C=O), 1682*s* (C=O), 1546*s*, 1498*w*, 1460*m*, 1443*m*, 1383*m*, 1330*w*, 1313*w*, 1285*w*, 1202*s*, 1183*s*, 1152*s*, 1118*m*, 1028*w*, 912*m*, 893*m*, 859*w*, 758*m*, 735*s*, 698*m*, 666*w*, 649*w*, 597*w*. ^{1}H-NMR (300 MHz, 30 mg in 0.5 ml of $CDCl_3$; 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*, N*H*$COCF_3$ 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*); 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, $NCH_2CH_2CH_2N$); 1.55–1.76 (*m*, CH_2CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$; $\delta(CDCl_3)$ 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 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, CF_3); 115.83 (*q*, *J* = 288, CF_3CONH); 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 (CH_2NCH_2 of *A* and *B*); 38.99, 38.93 (CH_2NHTFA of *B* and *A*, resp.); 36.1, 36.0 (CH_2NHCO of *B* and *A*, resp.); 28.90, 27.31 ($NCH_2CH_2CH_2N$ of *B* and *A*, resp.); 25.86, 25.79, 25.65, 23.9 (CH_2CH_2 of *A* and *B*). ESI-MS: 506 ($[M+Na]^+$).

*(–)-(2*R*,3*S*)-*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), and Cs_2CO_3 (1.094 g, 3.358 mmol) in DMF (2 ml) was stirred at r.t. for 60 h. Usual workup and purification by FC (SiO_2 (100 ml), AcOEt/hexane 65:35) provided (–)-**10c** (1.136 g, 9.4%). Amorphous glass-like solid. M.p. 38–47°. R_f (AcOEt/hexane 1:1) 0.15. $[\alpha]_D = -27.9$ (*c* = 1.29, $CHCl_3$). FT-IR (KBr): 3378*s* (br., N–H), 3091*w*, 3067*w*, 2939*m*, 2872*m*, 1718*s* (C=O), 1667*s* (C=O), 1545*s*, 1503*w*, 1460*m*, 1419*w*, 1382*w*, 1335*s*, 1211*s*, 1184*s*, 1155*s*, 1130*s*, 1073*m*, 1020*w*, 965*w*, 889*w*, 857*w*, 818*w*, 754*m*, 722*m*, 698*m*, 651*w*, 615*w*, 597*w*, 547*m*, 477*w*. ^{1}H-NMR (300 MHz, 45 mg in 0.6 ml of $CDCl_3$): 8.37 (*d*, *J* = 1.4, H_α of naphth.); 7.97 (*d*, *J* = 8.4, 2 H); 7.91 (*d*, *J* = 7.6, 1 H); 7.75 (*dd*, *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, $NHCOCF_3$); 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, $NCH_2CH_2CH_2N$); 1.68 (*m*, CH_2CH_2). ^{13}C-NMR (75 MHz; $\delta(CDCl_3)$ 76.92): 167.88 (CONH); 157.35 (*q*, *J* = 37, CF_3CO); 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, CF_3); 58.94, 58.80 (C(2), C(3)); 49.22, 47.04 (CH_2NCH_2); 39.13 ($CH_2NHCOCF_3$); 36.33 (CH_2NHCO); 28.82 ($NCH_2CH_2CH_2N$); 26.30, 25.81 (CH_2CH_2). ESI-MS: 600 ($[M+Na]^+$).

*(±)-(2*RS,*3*SR*)-*N*-{3-{[(4-Methylphenyl)sulfonyl]{4-{[(2,2,2-trichloroethoxy)carbonyl]amino}butyl}amino}propyl}-3-phenyloxiranecarboxamide* (**10d**). A mixture of (±)-**8** (549 mg, 1.933 mmol), **9d** (1.049 g, 2.513 mmol), and Cs_2CO_3 (819 mg, 2.513 mmol) in DMF (5 ml) was stirred at r.t. for 60 h. The mixture was quenched with CH_2Cl_2 (200 ml) and washed with 5% aq. citric acid (60 ml), the org. phase dried (Na_2CO_3) and evaporated, and the obtained brown oil (1.44 g) dissolved in a small amount of CH_2Cl_2/CCl_4 1:1 and chromatographed (SiO_2 (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_f (AcOEt/hexane 1:1) 0.16. FT-IR (neat, NaCl): 3353*m* (br., N–H), 3064*w*, 2946*m*, 2871*w*, 1737*s* (amide C=O), 1671*s* (carbamate C=O), 1598*w*, 1537*s*, 1460*m*, 1335*s*, 1306*m*, 1242*s*, 1157*s*, 1090*m*, 1030*w*, 955*w*, 889*w*, 816*m*, 758*m*, 734*s*, 700*m*, 654*m*, 598*w*, 571*w*, 549*m*. ^{1}H-NMR

(300 MHz, 25 mg in 0.6 ml of $CDCl_3$): 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*, N*H*Troc); 4.73, 4.68 (2 '*d*' (*AB*), ^2J = 12, CH_2O); 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, CH_2NHCO); 3.02–3.29 (overlapping *m*, 2 CH_2N); 3.24 (overlapping *q*, *J* = 6.4, CH_2N); 2.42 (*s*, Me); 1.79 (*quint.*, *J* = 6.7, $NCH_2CH_2CH_2N$); 1.5–1.68 (2 overlapping *m*, CH_2CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$; δ($CDCl_3$) 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 (CCl_3); 74.35 (CH_2O); 58.92 (overlapping C(2) and C(3)); 48.90, 46.41 (CH_2NCH_2); 40.53 (CH_2NHTroc); 35.87 (CH_2NHCO); 28.70 ($NCH_2CH_2CH_2N$); 26.79, 26.1 (CH_2CH_2); 21.37 (Me of Ts). ESI-MS: 642, 644, 646, 648 (100, 95, 35, 7, $[M+Na]^+$).

*(±)-(2*RS,*3*SR*)*-N-*{3-{[4-{[(1,1-Dimethylethoxy)carbonyl]amino}butyl][(4-methylphenyl)sulfonyl]amino}propyl}-3-phenyloxiranecarboxamide* (**10e**). A mixture of (±)-**8** (491 mg, 1.729 mmol), **9e** (1.183 g, 3.458 mmol), and anh. Cs_2CO_3 (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/$CHCl_3$). After partitioning between H_2O (100 ml) and CH_2Cl_2 (75 ml), the aq. layer was extracted with CH_2Cl_2 (2 × 40 ml), the combined org. phase dried (Na_2CO_3) and evaporated under h.v., and the obtained pale brown oil (1.92 g) dissolved in a small amount of CH_2Cl_2/CCl_4 1:1 and submitted to FC (SiO_2 (150 ml), AcOEt/hexane 1:1 (500 ml; → unreacted **9e**), then 7:3): **10e** (700 mg, 74.3%). White foam, glass-like oil. R_f (AcOEt/hexane 1:1) 0.18. FT-IR (neat, NaCl): 3339*s* (N–H), 3065*s*, 2976*s*, 2934*s*, 2870*s*, 1694*s* (C=O), 1598*m*, 1537*s*, 1460*s*, 1392*m*, 1366*m*, 1335*s*, 1253*s*, 1170*s*, 1090*m*, 1020*m*, 999*m*, 889*m*, 864*w*, 816*m*, 758*s*, 736*s*, 699*m*, 654*m*, 598*w*, 574*m*, 549*m*. ^{1}H-NMR (300 MHz, 25 mg in 0.6 ml of $CDCl_3$): 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*, N*H*Boc); 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*, ^3J = 6, CH_2NHCO); 3.03–3.25 (*m*, 3 CH_2N); 2.42 (*s*, Me); 1.79 (*quint.*, *J* = 6.7, $NCH_2CH_2CH_2N$); 1.4–1.65 (2 overlapping *m*, CH_2CH_2); 1.43 (*s*, Me_3C). ^{13}C-NMR (75 MHz, $CDCl_3$; δ($CDCl_3$) 76.91): 167.63 (CONH); 155.91 (OCONH); 143.35 (C_p of Ts); 136.14 (C_{ipso} of Ts); 135.02 (C_{ipso} of Ph); 129.68 (C_m of Ts); 128.80 (C_p of Ph); 128.48 (C_m of Ph); 127.0 (C_o of Ts); 125.71 (C_o of Ph); 79.08 (Me_3C); 58.87 (overlapping C(2), C(3)); 48.78, 46.02 (CH_2NCH_2); 39.81 (br., CH_2NHBoc); 35.61 (CH_2NHCO); 28.60 ($NCH_2CH_2CH_2N$); 28.3 (Me_3C); 27.23, 26.07 (CH_2CH_2); 21.36 (Me of Ts). CI-MS (NH_3): 563 (4, $[M+NH_4]^+$), 546 (6, $[M+H]^+$), 446 (100, $[M-t$-BuOCO + 2 H$]^+$).

*(±)-(2*RS,*3*SR*)*-N-*{3-{[(4-Methylphenyl)sulfonyl]{4-{[(4-methylphenyl)sulfonyl]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 CH_2Cl_2 (20 ml) and allowed to cool (ice/water bath). After addition of amine **9h** (2.265 g, 5.0 mmol) in CH_2Cl_2 (20 ml) and Et_3N (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 × 30 ml), H_2O (2 × 20 ml), and sat. aq. $NaHCO_3$ soln. (2 × 30 ml), dried (Na_2CO_3) and evaporated under h.v. (40°, 60 min): pure **10h** (2.755 g, 92%). White solid. FT-IR (KBr): 3350*m* (N–H), 3287*m* (N–H), 3065*w*, 2938*m*, 2870*m*, 1667*s* (C=O), 1598*m*, 1539*s*, 1495*w*, 1459*m*, 1381*w*, 1330*s*, 1306*m*, 1289*m*, 1229*w*, 1159*s*, 1091*s*, 1020*w*, 889*w*, 860*w*, 815*m*, 757*m*, 726*m*, 699*m*, 655*m*, 570*m*, 550*s*. ^{1}H-NMR (300 MHz, 38 mg in 0.7 ml of $CDCl_3$): 7.71 (*d*, *J* = 8.3, 2 H_o of TsNH); 7.65 (*d*, *J* = 8.3, 2 H_o of TsN); 7.22–7.4 (*m*, 9 arom. H); 6.80 (br. *t*, *J* = 6.1, NHCO); 5.20 (*t*, *J* = 6.25, N*H*Ts); 3.97 (*d*, *J* = 2.0, H–C(3)); 3.51 (*d*, *J* = 2.0, H–C(2)); 3.29–3.48 (*m*, ^3J = 6.8, CH_2NHCO); 3.0–3.2 (*m*, overlapping 2 CH_2N); 2.92 (*q* (*ddd*), *J* = 6.5, CH_2NHTs); 2.39, 2.41 (2 *s*, 2 Me); 1.79 (*quint.*, *J* = 6.6, $NCH_2CH_2CH_2N$); 1.45–1.66 (2 overlapping *m*, 4 H, CH_2CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$; δ($CDCl_3$) 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 (C_{ipso} of TsN); 135.0 (C_{ipso} of Ph); 129.72, 129.57 (4 C_m of 2 Ts); 128.80 (C_p of Ph); 128.48 (C_m of Ph); 127.01, 126.89 (4 C_o of 2 Ts); 125.76 (C_o of Ph); 58.86 (overlapping C(2), C(3)); 48.91, 46.57 (CH_2NCH_2); 42.48 (CH_2NHTs); 36.07 (CH_2NHCO); 28.73 ($NCH_2CH_2CH_2N$); 26.42, 25.96 (CH_2CH_2); 21.36 (2 Me of 2 Ts). ESI-MS: 622 ($[M+Na]^+$).

*(±)-(2*RS,*3*SR*)*-N-*{3-{[(4-Methylphenyl)sulfonyl](4-aminobutyl)amino}propyl}-3-phenyloxiranecarboxamide* (**11**). A soln. of **10a** (52 mg, 0.096 mmol), K_2CO_3 (145 mg) in MeOH (5 ml), and H_2O (2 ml) was stirred at r.t. and monitored by TLC (8 h), then quenched with sat. aq. Na_2CO_3 soln. (10 ml) followed by extraction with CH_2Cl_2 (3 × 10 ml). The combined org. soln. gave 44 mg of oil after drying (Na_2CO_3) and evaporation under h.v. The product was slowly converted to the dimer after intermolecular oxirane opening with amine. R_f ($CHCl_3$/MeOH/25% aq. NH_3 soln. 90:9:1) 0.15. ^{1}H-NMR (300 MHz, 44 mg in 0.6 ml of $CDCl_3$; 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, CH_2NH_2); 2.42

(*s*, Me); 1.79 (*quint.*, $J = 6.7$, $NCH_2CH_2CH_2N$); 1.57 (*quint.* (unres. *m*), $J = 7.3$, 2 H); 1.40 (*quint.* (unres. *m*), $J = 7.3$, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$; $\delta(CDCl_3)$ 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 (CH_2NCH_2); 41.5 (CH_2NH_2); 35.59 (CH_2NHCO); 30.62 ($NCH_2CH_2CH_2N$); 28.54, 26.16 (CH_2CH_2); 21.35 (Me). ESI-MS: 446 (100, $[M+H]^+$), 468 (10, $[M+Na]^+$), 891 (16, $[2M+H]^+$), 913 (4, $[2M+Na]^+$).

*One-Pot Deprotection-Macrocyclization of (±)-***10a** *in EtOH under Reflux*. A biphasic mixture of (±)-**10a** (374 mg, 0.691 mmol) in EtOH (150 ml), sat. aq. Na_2CO_3 soln. (15 ml), and H_2O (15 ml) was stirred under reflux and N_2 for 22 h. Evaporation to a small volume, dilution with H_2O (30 ml), and extraction with $CHCl_3$ (4×20 ml) yielded an org. soln. that was dried (Na_2CO_3) and evaporated. The crude product was analyzed by ^{1}H-NMR. FC (SiO_2 (25 ml), 2% MeOH/$CHCl_3$ (100 ml; → (±)-**12** (264 g, 85.8%; see below)), then 4% MeOH/$CHCl_3$ (50 ml), $CHCl_3$/MeOH/25% aq. NH_3 soln. 90 : 9 : 1 (100 ml), and $CHCl_3$/MeOH/25% aq. NH_3 soln. 85 : 14 : 1 (100 ml)) gave crude **22** (25 mg, 6.9% by NMR) contaminated with dimeric macrocycle **23** (1.1% by ^{1}H-NMR).

*Data of (±)-(*α*RS,*β*RS)-N-{3-[(4-Aminobutyl)[(4-methylphenyl)sulfonyl]amino}propyl]-*β*-ethoxy-*α*-hydroxybenzenepropanamide* (**22**). R_f ($CHCl_3$/MeOH/25% aq. NH_3 soln. 85 : 14 : 1) 0.13. ^{1}H-NMR (300 MHz, 20 mg in 0.6 ml of $CDCl_3$): 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, $J = 7$, OCH_2Me); 3.29 (*dt* (*dddd*), $^3J = 6.5$, $^2J = 14$, CH_2NHCO); 2.92–3.20 (*m*, 3 H); 2.81 (*t* with fine splitting, $J = 6.5$, CH_2N); 2.68 (*t*, $J = 6.7$, CH_2NH_2); 2.43 (*s*, Me of Ts); 1.34–1.66 (*m*, 3 CH_2); 1.20 (*t*, $J = 6.9$, Me of Et). ^{13}C-NMR (75 MHz; $\delta(CDCl_3)$ 76.90): 170.88 (CONH); 143.16 (C_p of Ts); 137.09 (C_{ipso} of Ts); 136.29 (C_{ipso} of Ph); 129.55 (C_m of Ts); 127.84 (overlapping C_p, C_m, C_o of Ph); 127.02 (C_o of Ts); 81.57 (C(*β*)); 74.09 (C(*α*)); 64.45 (CH_2O); 48.81, 45.63 (CH_2NCH_2); 41.29 (CH_2NH_2); 35.43 (CH_2NHCO); 30.06 ($NCH_2CH_2CH_2N$); 28.49, 26.14 (CH_2CH_2); 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 ^{1}H-NMR of crude **22**): ^{1}H-NMR (selected δ): 4.61 (*d*, $J = 3.9$, PhC*H*); 4.09 (*d*, $J = 3.9$, C*H*OH). ESI-MS: 913 ($[M+Na]^+$), 891 ($[M+H]^+$).

*One-Pot Deprotection-Macrocyclization of (±)-***10a** *in i-PrOH under Reflux*. Concentration of (±)-**10a** and workup as described in the previous experiment with EtOH. A soln. of (±)-**10a** (157 mg, 0.290 mmol) in i-PrOH (63 ml), sat. aq. Na_2CO_3 soln. (6.3 ml) and H_2O (6.3 ml) was stirred under reflux for 23 h. FC after workup gave (±)-**12** (105 mg, 81.3%). A crude mixture of at least three by-products (24 mg) was eluted with $CHCl_3$/MeOH/25% aq. NH_3 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. Na_2CO_3 soln. (30 ml), and H_2O (90 ml) was stirred at 70° for 36 h. FC after workup gave (+)-**12** (382 mg, 85%).

*One-Pot Deprotection-Macrocyclization of (±)-***10a** *in THF at Reflux*. A mixture of (±)-**10a** (119 mg, 0.220 mmol) in THF (30 ml), sat. aq. Na_2CO_3 soln. (5 ml), and H_2O (45 ml) was stirred under reflux and N_2 until no (±)-**10a** or the intermediate amine **11** could be observed (48 h). FC after workup gave (±)-**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 N_2 for 22 h. The mixture was quenched with i-PrOH (500 ml), sat. aq. Na_2CO_3 soln. (50 ml), and H_2O (150 ml) and stirred at 70° for 48 h. Usual workup and FC gave (+)-**12** (1.647 g, 52.4%).

*Data of (±)-(2*RS*,3*RS*)-3-Hydroxy-9-[(4-methylphenyl)sulfonyl]2-phenyl-1,5,9-triazacyclotridecan-4-one* ((±)-**12**): For ^{1}H- and ^{13}C-NMR assignments from 2D NMR data (600 MHz), see also [5]. White foam. M.p. 80–92° (reproducible and reversible). R_f (5% MeOH/$CHCl_3$) 0.2. FT-IR (neat, NaCl): 3375*s* (br.), 3313*s* (br.), 3064*w*, 3029*w*, 2931*s*, 2858*m*, 2254*w*, 1919*w*, 1810*w*, 1652*s* (C=O), 1599*w*, 1538*s*, 1494*w*, 1454*s*, 1402*w*, 1331*s*, 1306*m*, 1231*w*, 1197*w*, 1155*s*, 1122*m*, 1106*m*, 1089*m*, 1063*m*, 1030*m*, 981*w*, 912*m*, 816*m*, 731*s*, 701*m*, 656*m*, 564*m*, 548*m*. ^{1}H-NMR (600 MHz, 38 mg in 0.7 ml of $CDCl_3$): 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*, CH_2(7)); 1.83 (*m*, 1 H–C(11)); 1.69 (*m*, 1 H–C(11)); 1.48, 1.41 (2*m*, CH_2(12)). ^{1}H-NMR (300 MHz, 9 mg in 0.7 ml of $CDCl_3$; 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) = 2.5,

OH); 3.48 (*d*, $^3J(2,3) = 10.1$, H–C(2)). ^{1}H-NMR (300 MHz, 30 mg in 0.6 ml of (D_6)DMSO; δ((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)). ^{13}C-NMR (75 MHz, $CDCl_3$, δ($SiMe_4$) 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 (CH_2(10)); 46.59 (CH_2(8)); 43.96 (CH_2(13)); 37.36 (CH_2(6)); 29.08 (CH_2(7)); 25.29 (CH_2(12)); 24.20 (CH_2(11)); 21.69 (Me). ESI-MS: 446 (100, $[M+H]^+$), 468 (8, $[M+Na]^+$).

*Data of (+)-(2*R*,3*R*)-3-Hydroxy-9-[(4-methylphenyl)sulfonyl]-2-phenyl-1,5,9-triazacyclotridecan-4-one* ((+)-**12**): Amorphous glass-like solid. M.p. 87–93° (irreversible). $[\alpha]_D = +10.3$ ($c = 1.02$, $CHCl_3$). FT-IR (KBr): 3381*s* (br., N–H), 3062*w*, 3027*w*, 2928*s*, 2860*m*, 1656*s* (C=O), 1599*w*, 1550*s*, 1495*w*, 1454*m*, 1402*w*, 1333*s*, 1305*m*, 1224*w*, 1195*w*, 1156*s*, 1108*w*, 1089*m*, 1058*m*, 1029*m*, 980*w*, 816*m*, 752*m*, 701*m*, 655*m*, 564*m*, 547*m*. NMR: identical to those of (±)-**12**. ESI-MS: 446 (100, $[M+H]^+$), 468 (35, $[M+Na]^+$).

*(±)-(2*RS*,3*RS*)-3-Hydroxy-2-phenyl-1,5,9-triazacyclotridecan-4-one* ((±)-**13**). The biphasic mixture of (±)-**10b** (43 mg, 0.089 mmol) in EtOH (20 ml), sat. aq. Na_2CO_3 soln. (2 ml), and H_2O (4 ml) was stirred at 60° under N_2 for 72 h. After evaporation to a small volume, the mixture was quenched with sat. aq. Na_2CO_3 soln. (20 ml) and extracted with $CHCl_3$ (4 × 20 ml) and the combined org. phase dried (Na_2CO_3) and evaporated under h.v.: crude (±)-**13** (29 mg, 70% by NMR). FC (Al_2O_3 (20 ml), $CHCl_3$/MeOH/aq. 25% NH_3 soln. 95 : 4.5 : 0.5 (50 ml), then $CHCl_3$/MeOH/aq. 25% NH_3 soln. 90 : 9 : 1 (100 ml)) gave (±)-**13** (17.5 mg, 67.5%). Data completely identical to those of (+)-**13**; see also [5].

*(+)-(2*R*,3*R*)-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 H_2O (40 ml) and sat. aq. Na_2CO_3 soln. (40 ml) followed by extraction with CH_2Cl_2 (4 × 15 ml). The combined org. phase was dried (Na_2CO_3) 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_f (SiO_2, $CHCl_3$/MeOH/aq. 25%. NH_3 soln. 70 : 25 : 5) 0.15. R_f (Al_2O_3, $CHCl_3$/MeOH/aq. 25% NH_3 soln. 90 : 9 : 1) 0.25. $[\alpha]_D = +10.0$ ($c = 1.07$, $CHCl_3$). FT-IR (KBr): 3390*s* (br.), 3288*s* (br.), 3081*m*, 3062*m*, 3028*m*, 2924*s*, 2852*s*, 1653v*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*. ^{1}H-NMR (300 MHz, 12 mg in 0.6 ml of $CDCl_3$): 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*, CH_2(8)); 2.63–2.72 (*m*, CH_2(10)); 2.58 (*ddd*, $J = 2.7$, 5.8, 11.7, 1 H–C(13)); 2.43 (*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). ^{13}C-NMR (75 MHz; δ($CDCl_3$) 76.93): 172.92 (CONH); 140.77 (C_{ipso}); 128.44 (C_m); 127.36 (overlapping C_o, C_p); 72.24 (C(3)); 66.25 (C(2)); 49.93, 48.33 (C(8), C(10)); 45.47 (C(13)); 40.21 (C(6)); 27.72, 27.67, 27.57 (overlapping C(7), C(11), C(12)). ESI-MS: 292 (100, $[M+H]^+$), 304 (15, $[M+Na]^+$).

*(+)-(2*R*,3*R*)-9-[(2*E*)-1-Oxo-3-phenylprop-2-enyl]-3-{[(2*E*)-1-oxo-3-phenylprop-2-enyl]oxy}-2-phenyl-1,5,9-triazacyclotridecan-4-one* ((+)-**14**). To a cold (ice/water bath) soln. of (+)-**13** (40.1 mg, 0.138 mmol) in CH_2Cl_2 (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 (SiO_2 (20 ml), gradient $CH_2Cl_2 \rightarrow 2\%$ MeOH/CH_2Cl_2): (+)-**14** (70 mg, 92%). Glass-like amorphous solid. R_f (5% MeOH/$CHCl_3$) 0.3. $[\alpha]_D = +35.0$ ($c = 1.0$, $CHCl_3$). FT-IR (KBr): 3418*m* (br., N–H), 3299*s* (br., N–H), 3083*w*, 3060*m*, 3027*m*, 2926*s*, 2853*m*, 1955*w*, 1886*w*, 1715*s*, 1679*s*, 1648v*s*, 1599*s*, 1578*m*, 1553*m*, 1496*m*, 1450*s*, 1437*s*, 1377*m*, 1332*s*, 1306*m*, 1281*m*, 1244*s*, 1202*s*, 1164*s*, 1125*m*, 1072*m*, 1060*m*, 1027*m*, 976*m*, 915*w*, 861*m*, 764*s*, 734*w*, 701*s*, 684*m*, 613*w*, 590*w*, 557*w*, 537*m*, 484*w*. ^{1}H-NMR (300 MHz, 60 mg in 0.6 ml of $CDCl_3$): 7.71 (*m*, $J_{trans} = 15.5$, PhC*H*=CHCON); 7.50 (*m*, 2 H of P*h*CH=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=C*H*CON); 6.21 (*m*, $J_{trans} = 16$, PhCH=C*H*CO_2); 5.28 (2*d*, $J = 10$, 0.5 + 0.5 H, CH–O); 4.11 (*d*, $J = 10.2$, PhC*H*NH); 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). ^{13}C-NMR (75 MHz; δ($CDCl_3$) 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_{ipso}); 135.28, 133.93 (2 C_{ipso} of 2 P*h*CH=); 130.4, 129.43 (2 C_p of 2 P*h*CH=); 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 CH_2N of *A* and *B*); 37.13, 36.65 (*C*H_2NHCO of *A* and *B*); 27.48, 25.65, 24.46, 23.67, 23.57, 23.7 (3 CH_2 of *A* and *B*). ESI-MS: 552 (100, $[M+H]^+$), 574 (100, $[M+Na]^+$).

*(−)-(2*R*,3*R*)-3-Hydroxy-9-[(2*E*)-1-oxo-3-phenylprop-2-enyl]-2-phenyl-1,5,9-triazacyclotridecan-4-one* (=*(−)-(2*R*,3*R*)-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 H_2O (30 ml) and CH_2Cl_2 (4 × 10 ml), the org. phase dried (Na_2CO_3) and evaporated, and the residue (50 mg) purified by FC

(SiO_2 (20 ml), 5% MeOH/$CHCl_3$): (−)-**1a** (46 mg, 90%). Colorless glass-like amorphous solid. M.p. 112–114°, irreversible. $[\alpha]_D = -3.2$ ($c = 0.73$, $CHCl_3$/MeOH 30:1). FT-IR and NMR: identical to the data of (±)-**1a** [5]. ESI-MS: 422 (100, $[M+H]^+$), 444 (65, $[M+Na]^+$).

*(−)-(2*R*,3*R*)-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. Na_2CO_3 soln. (30 ml), and H_2O (100 ml) was stirred at 70° for 22 h. Usual workup and FC (SiO_2 (50 ml), 2% MeOH/$CHCl_3$) gave (−)-**15** (772 mg, 84.8%). Amorphous solid. M.p. 96–100°. $[\alpha]_D = -1.5$ ($c = 1.14$, $CHCl_3$). FT-IR (KBr): 3383*s* (br.), 3057*w*, 3026*w*, 2929*s*, 2858*m*, 1656*s* (C=O), 1589*w*, 1547*s*, 1503*w*, 1454*m*, 1331*s*, 1269*w*, 1196*w*, 1154*s*, 1128*s*, 1073*s*, 1027*m*, 981*w*, 951*w*, 858*w*, 819*w*, 751*s*, 700*s*, 653*s*, 615*m*, 545*s*, 477*w*. ^{1}H-NMR (300 MHz, 33 mg in 0.6 ml of $CDCl_3$): 8.44 (br. *t*, NHCO); 8.38 (*d*, $J = 1.4$, H–C(α) 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*, CH_2(8), H–C(6)); 2.97 (*ddd*, $^3J = 4.6, 9.2$, $^2J = 13.9$, 1 H–C(10)); 2.58 (*ddd*, $^3J = 4.6, 5.2$, $^2J = 12.6$, 1 H–C(13)); 2.35 (*ddd*, $^3J = 4.1, 9.2$, $^2J = 12.9$, 1 H–C(13)); 1.91–2.02 (*m*, CH_2(7)); 1.83 (*m*, 1 H–C(11)); 1.69 (*m*, 1 H–C(11)); 1.32–1.55 (2*m*, CH_2(12)). ^{13}C-NMR (75 MHz; $\delta(CDCl_3)$ 76.94): 173.3 (CONH); 140.05, 136.06, 134.68, 132.14 (4 quat. arom. C); 129.37, 129.1, 128.69, 128.62, 128.36, 127.82, 127.72, 127.52, 127.29, 122.38 (arom. CH); 72.37 (C(3)); 65.76 (C(2)); 48.23 (CH_2(10)); 46.25 (CH_2(8)); 43.69 (CH_2(13)); 37.06 (CH_2(6)); 28.87 (CH_2(7)); 24.89 (CH_2(12)); 23.93 (CH_2(11)). ESI-MS: 482 ($[M+H]^+$).

Electrochemical Detosylation of **10h**. A soln. of **10h** (411 mg, 0.686 mmol) in 0.1N Me_4NCl/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 (Na_2CO_3) and evaporated under h.v., and the hygroscopic solid (318 mg) submitted to FC (SiO_2 (50 ml), CH_2Cl_2/MeOH/aq. 25%. NH_3 soln. 70:25:5 (200 ml), followed by CH_2Cl_2/MeOH/aq. 25%. NH_3 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**): ^{1}H-NMR (300 MHz, 28 mg in 0.8 ml of $CDCl_3$): 7.14–7.33 (*m*, 5 arom. H); 6.88 (br. *s* (unres. *t*), NHCO); 3.29 (*q* (*dt*), $J = 6.0$, CH_2NHCO); 2.95 (*t*, $J = 7.7$, PhCH_2); 2.71 (*t*, $J = 6.1$, CH_2NH); 2.62, 2.57 (2 overlapping *t*, $J = 6.3$, 6.5, resp., CH_2NH, CH_2NH$_2$); 2.46 (*t*, $J = 7.7$, CH_2CO); 2.41 (br. *s*, NH, NH_2); 1.61 (*quint.*, $J = 6.1$, $NCH_2CH_2CH_2N$); 1.50, 1.51 (2 overlapping *quint.*, CCH_2CH_2C). ^{13}C-NMR (75 MHz, $CDCl_3$; $\delta(CDCl_3)$ 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 CH_2); 38.41 (2 overlapping CH_2); 31.71, 30.98, 28.4, 27.17 (4 CH_2).

*Data of (±)-*N-*{3-[(4-Aminobutyl)amino]propyl}-α-hydroxybenzenepropanamide* (**16b**): ^{1}H-NMR (300 MHz, 58 mg in 1 ml of $CDCl_3$): 7.56 (br. *t*, NHCO); 7.2–7.34 (*m*, 5 arom. H); 4.22 (*dd*, $J = 3.6$, 8.5, C*H*OH); 3.29 (br. *q*, $J = 5.7$, CH_2NHCO); 3.21 (*dd*, $^3J = 3.6$, $^2J = 13.8$, PhCH_2); 3.21 (*dd*, $^3J = 8.5$, $^2J = 13.8$, PhCH_2); 2.59 (overlapping *m*, 2 CH_2); 2.49 (overlapping *m*, CH_2); 2.3–2.7 (overlapping br. *s*, OH, NH, NH_2); 1.59 (*m*, $NCH_2CH_2CH_2N$); 1.42 (*m*, CCH_2CH_2C). ^{13}C-NMR (75 MHz, $CDCl_3$; $\delta(CDCl_3)$ 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 CH_2).

Reductive Troc Cleavage with Zn in the Presence of NH_4OAc Buffer (pH 7) [13] *Followed by Macrocyclization*. A mixture of Zn powder (1 g), 0.5M sat. aq. NH_4OAc soln. (5 ml), **10d** (160 mg, 0.258 mmol), and THF (25 ml) was stirred vigorously under N_2 for 16 h at r.t. After quenching with sat. aq. Na_2CO_3 soln. (10 ml), the mixture was refluxed for 36 h. The solid residue was filtered, the soln. extracted with CH_2Cl_2, the extract evaporated, and the oil (145 mg) submitted to FC (SiO_2 (25 ml), 5% MeOH/$CHCl_3$)): crude (±)-**12** (50 mg). Additional FC (SiO_2 (20 ml), $CHCl_3$ (40 ml), 1% MeOH/$CHCl_3$ (40 ml), and 2% MeOH/$CHCl_3$) 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. $NaHCO_3$ (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 (SiO_2 (25 ml). Elution with 2% MeOH/$CHCl_3$ (50 ml) gave **19** (13 mg, 6.9%), with 3% MeOH/$CHCl_3$ (50 ml) **12** (38 mg, 26.5%), and with $CHCl_3$/MeOH/aq. 25% NH_3 soln. 95:4.5:0.5 (50 ml) **21** (6 mg, 3.7%). After subsequent elution with $CHCl_3$/MeOH/aq. 25% NH_3 soln. 90:9:1 (100 ml), $CHCl_3$/MeOH/aq. 25% NH_3 soln. 85:14:1 (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}-α-hydroxybenzenepropanamide* (**17**): R_f ($CHCl_3$/MeOH/aq. 25% NH_3 soln. 85:14:1) 0.18. ^{1}H-NMR (300 MHz, 17 mg in 0.6 ml of $CDCl_3$): 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, C*H*OH); 3.24–3.43 (*m*, CH_2NHCO); 3.20 (*dd*, *J* = 3.8, 13.9, 1 H, PhCH_2); 2.95–3.13 (*m*, 2 CH_2N); 2.89 (*dd*, *J* = 8.1, 13.9, 1 H, PhCH_2); 2.63 (br. *t*, C$H_2$$NH_2$); 2.42 (*s*, Me); 1.71 (*m*, $NCH_2CH_2CH_2N$); 1.52, 1.38 (2*m*, CH_2CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$; δ($CDCl_3$) 76.90): 173.33 (CONH); 143.25 (C_p of Ts); 137.40 (C_{ipso} of Ts); 136.12 (C_{ipso} of Ph); 129.60, 129.52 (overlapping C_m of Ts and C_p of Ph); 128.31 (C_m of Ph); 127.01 (C_o of Ts); 126.54 (C_o of Ph); 72.57 (CHOH); 48.83, 45.93 (CH_2NCH_2); 41.23 (C$H_2$$NH_2$); 40.80 ($CH_2$); 35.73 (C$H_2$NHCO); 30.05 ($NCH_2CH_2CH_2N$); 28.64, 26.1 ($CH_2CH_2$); 21.35 (Me). ESI-MS: 448 (100, $[M+H]^+$), 470 (12, $[M+Na]^+$).

*Data of (2*E*)-*N*-{3-[(4-Aminobutyl)[(4-methylphenyl)sulfonyl]amino]propyl}-3-phenylprop-2-enamide* (**18**): R_f ($CHCl_3$/MeOH/aq. 25% NH_3 soln. 85:14:1) 0.22. ^{1}H-NMR (300 MHz, 29 mg in 0.8 ml of $CDCl_3$): 7.67 (*d*, *J* = 8.4, 2 H_o of Ts); 7.62 (*d*, *J* = 15.7, C*H*=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=C*H*); 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, C$H_2$$NH_2$); 2.41 (*s*, Me); 1.83 (*quint.*, *J* = 6.1, $NCH_2CH_2CH_2N$); 1.57,1.4 (2*m*, CH_2CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$; δ($CDCl_3$) 76.91): 165.98 (CONH); 143.36 (C_p of Ts); 140.53 (*C*H=CH); 136.18 (C_{ipso} of Ts); 134.86 (C_{ipso} of Ph); 129.68 (C_m of Ts); 129.44 (C_p of Ph); 128.66 (C_m of Ph); 127.69 (C_o of Ts); 126.93 (C_o of Ph); 120.98 (CH=*C*H); 48.89, 46.02 (CH_2NCH_2); 41.47 (C$H_2$$NH_2$); 36.05 (C$H_2$NHCO); 30.56 ($NCH_2CH_2CH_2N$); 28.24, 26.16 ($CH_2CH_2$); 21.35 (Me of Ts). ESI-MS: 430 ($[M+H]^+$).

*Data of (±)-(2*RS,*3*SR*)-*N*-{3-{[4-{[(2,2-Dichloroethoxy)carbonyl]amino}butyl][(4-methylphenyl)sulfonyl]-amino}propyl}-3-phenyloxiranecarboxamide* (=*(±)-2,2-Dichloroethyl {4-{[(4-Methylphenyl)sulfonyl]{3-{{[(2*RS,*3*SR*)-3-phenyloxiran-2-yl]carbonyl}amino}propyl}amino}butyl}carbamate*; **19**): Colorless syrup. ^{1}H-NMR (300 MHz, 13 mg in 0.7 ml of $CDCl_3$): 7.68 (*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, $CHCl_2$); 5.13 (br. *t*, $NHCO_2$); 4.38 (*d*, *J* = 6.0, CH_2OCO); 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, CH_2NHCO); 3.02–3.26 (*m*, 3 CH_2N); 2.43 (*s*, Me); 1.79 (*quint.*, *J* = 6.7, $NCH_2CH_2CH_2N$); 1.5–1.68 (*m*, CH_2CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$; δ($CDCl_3$) 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); 68.95 ($CHCl_2$); 68.62 (CH_2O); 58.93, 58.89 (overlapping C(2) and C(3)); 48.91, 46.43 (CH_2NCH_2); 40.41 (C$H_2$$NHCO_2$); 35.84 (C$H_2$NHCO); 28.71 ($NCH_2CH_2CH_2N$); 26.81, 26.14 ($CH_2CH_2$); 21.36 (Me of Ts). ESI-MS: 608, 610, 612 (100, 68, 15 $[M+Na]^+$).

*Data of (±)-2,2-Dichloroethyl {(11*RS,*12*SR,*24Z)-11-Hydroxy-5,18-bis[(4-methylphenyl)sulfonyl]10,23-dioxo-12,25-diphenyl-5,9,13,18,22-pentaazapentacos-24-en-1-yl}carbamate* (**21**): R_f ($CHCl_3$/MeOH/aq. 25% NH_3 soln. 85:14:1) 0.5. ^{1}H-NMR (300 MHz, 13 mg in 0.7 ml of $CDCl_3$): 7.67 (*d*, *J* = 8.5, 2 H_o of Ts); 7.62 (overlapping *d*, *J* = 8.4, 2 H_o of Ts); 7.61 (overlapping *d*, *J* = 15, C*H*=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=C*H*); 5.84 (*t*, *J* = 6.0, $CHCl_2$); 5.24 (br. *t*, $NHCO_2$); 4.39 (*d*, *J* = 6.0, CH_2OCO); 4.33 (*d*, *J* = 5.1, CHOH); 4.04 (*d*, *J* = 5.0, C*H*NH); 3.50 (*q*, *J* = 6.1, CH_2NHCO); 2.88–3.28 (*m*, 10 H); 2.77 (*m*, 2 H); 2.57 (*m*, 2 H); 2.41, 2.43 (2*s*, 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. Na_2HPO_4 soln. (1 ml), **10d** (143 mg, 0.23 mmol), and THF (5 ml) was stirred vigorously under N_2 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. Na_2CO_3 soln. (10 ml) was added and reflux continued for additional 36 h. After evaporation of THF, the aq. soln. was extracted with CH_2Cl_2 (5 × 10 ml), the extract dried (Na_2CO_3) and evaporated, and the residue (170 mg) submitted to FC (SiO_2 (25 ml). Elution with 2% MeOH/$CHCl_3$ (100 ml) gave **19** (14 mg, 10.4%) and lactam **12** (54 mg, 53%). After subsequent elution with 5% MeOH/$CHCl_3$ (100 ml) and $CHCl_3$/MeOH/aq. 25% NH_3 soln. 95:4.5:0.5 (50 ml), $CHCl_3$/MeOH/aq. 25% NH_3 soln. 90:9:1 (100 ml) gave **20** (5 mg, 4.2%) and two unidentified crude products. Finally $CHCl_3$/MeOH/aq. 25% NH_3 soln. 85:14:1 (100 ml) eluted **17** (8.5 mg, 8.2%).

*Data of (±)-2,2-Dichloroethyl {(11*RS,*12*RS,*24*RS*)- and (11*RS,*12*RS,*24*SR*)-11,24-Dihydroxy-5,18-bis[(4-methylphenyl)sulfonyl]-10,23-dioxo-12,25-diphenyl-5,9,13,18,22-pentaazapentacos-1-yl}carbamate* (**20**): ESI-MS: 1033 ($[M+H]^+$). ^{1}H-NMR (300 MHz, $CDCl_3$): in agreement with the proposed structure similar to **21**; but **20** appeared as a *ca.* 1:1 mixture of two diastereoisomers.

*Ethyl (±)-(α*RS,*β*SR*)-β-Chloro-α-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. ^{1}H-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%). ^{1}H-NMR (300 MHz, 33 mg in 0.7 ml of $CDCl_3$): 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, MeCH_2); 3.29 (br. *d*, *J* = 7, OH); 1.31 (*t*, *J* = 7, *Me*CH_2). ^{13}C-NMR (75 MHz; $\delta(CDCl_3)$ 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 (CH_2); 14.0 (*Me*CH_2).

Potassium cis-*3-Phenyloxiranecarboxylate* (**26**). The biphasic mixture of **24a** (16.64 g, 72.77 mmol) in acetone (17 ml) and Na_2CO_3 (11.57 g, 109.1 mmol) in H_2O (100 ml) was stirred at 50°. After 8 h, additional Na_2CO_3 (5.75 g) was added and stirred at 35° for 12 h, then at 50° for 3 h. The mixture was diluted with H_2O and extracted with $CHCl_3$ (4 × 20 ml) and the combined org. phase dried (Na_2CO_3) 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 CO_2 until the soln. turned from brown to pale yellow. After concentration to a small volume and quenching with Et_2O (100 ml), the solid was filtered: 9.3 g (82%) of pure **26**. White solid. ^{1}H-NMR (300 MHz, 30 mg in 0.7 ml of D_2O; 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)). ^{13}C-NMR (75 MHz): 173.66 (CO); 134.43 (C_{ipso} of Ph); 128.3 (C_p, 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**): ^{1}H-NMR (300 MHz, 20 mg in 0.7 ml of $CDCl_3$): 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*, ^2J = 10.9, ^3J = 7, MeCH_2); 3.81 (*d*, *J* = 4.6, H–C(2)); 1.01 (*t*, *J* = 7, *Me*CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$; $\delta(CDCl_3)$ 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 (MeCH_2); 57.25, 55.61 (C(2), (C(3)); 13.73 (*Me*CH_2).

*Resolution of (±)-***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 (–)-(1*R,*2*S*)-Ephedrine (2*S,*3*S*)*-cis-*3-Phenyloxiranecarboxylate* ((–)-**27a**): $[\alpha]_D = -27.2$ (*c* = 1.5, EtOH; [10]: –28.3). ^{1}H-NMR (300 MHz, 27 mg in 0.6 ml of D_2O; δ(DHO) 4.8): 7.40–7.60 (*m*, 10 arom. H); 5.19 (*d*, *J* = 3.4, C*H*OH); 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, C*H*Me); 2.82 (*s*, MeN); 1.19 (*d*, *J* = 6.9, *Me*CH). ^{13}C-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 (+)-(1*S,*2*R*)-Ephedrine (2*R,*3*R*)*-cis-*3-Phenyloxiranecarboxylate* ((+)-**27b**): $[\alpha]_D = +27.3$ (*c* = 1.5, EtOH).

*(+)-(2*S,*3*S*)*-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 Et_3N (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. (^{1}H-NMR: only *ca.* 5 mol-% of ephedrine derivative). To the obtained crude **28** in CH_2Cl_2 (24 ml), 3-bromopropanamine hydrobromide (1.41 g, 6.44 mmol) was added followed by Et_3N (1.79 ml, 12.88 mmol). After stirring at r.t. for 30 min, the mixture was diluted with CH_2Cl_2 (150 ml), the org. phase washed with 5% citric acid (2 × 50 ml) and $NaHCO_3$ soln. (2 × 50 ml), dried (Na_2CO_3), 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, $CHCl_3$). FT-IR (KBr): 3309*s*, 3068*w*, 3039*w*, 3014*w*, 2999*w*, 2969*m*, 2938*m*, 2860*w*, 1963*w*, 1899*w*, 1824*w*, 1653*s* (C=O), 1585*w*, 1544*s*, 1497*m*, 1441*s*, 1406*m*, 1368*m*, 1358*m*, 1340*m*, 1320*m*, 1292*m*, 1257*s*, 1212*m*, 1184*w*, 1162*w*, 1122*w*, 1079*m*, 1052*w*, 1030*w*, 924*w*, 896*s*, 846*m*, 799*m*, 773*m*, 746*s*, 698*s*, 650*w*, 620*m*, 594*w*, 530*m*, 481*w*, 470*w*. ^{1}H-NMR (300 MHz, 29 mg in 0.5 ml of $CDCl_3$): 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*), ^2J = 13.7, ^3J = 7, 1 H, CH_2NH); 2.97 (overlapping *m*, 1 H, CH_2NH); 2.92 (overlapping *dt*, ^2J = 10.1, ^3J = 6.5, 1 H, CH_2Br); 2.66 (*dt*, ^2J = 10.2, ^3J = 6.7, 1 H, CH_2Br); 1.58 (*quint.* *J* = 6.5, CH_2). ^{13}C-NMR (75 MHz; $\delta(CDCl_3)$ 76.93): 166.37 (CONH); 133.1 (C_{ipso}); 128.56 (C_p); 128.40 (C_m); 126.4 (C_o); 57.93 (C(2)); 56.03 (C(3)); 36.95 (CH_2NH); 31.75 (CH_2); 30.09 (CH_2Br). ESI-MS: 306, 308 (97, 100, $[M + Na]^+$), 284, 286 (15, 15, $[M + H]^+$), 204 (18, $[M - Br]^+$).

Data of (2S,3S)-3-Phenyloxiranecarbonyl Chloride (**28**): ^{1}H-NMR (300 MHz, $CDCl_3$): 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)). ^{13}C-NMR (75 MHz; $\delta(CDCl_3)$ 76.92): 167.33 (COCl); 130.83 (C_{ipso}); 129.41 (C_p); 128.31 (C_m); 126.47 (C_o); 61.88 (C(2)); 59.04 (C(3)).

(+)-(2S,3S)-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), Cs_2CO_3 (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 (Na_2CO_3) and evaporated under h.v. and the pale yellow oil (1.3 g) submitted to FC (SiO_2 (60 ml), 50 → 70% AcOEt/hexane): **30a** (500 mg, 74.7%). White foam. R_f (AcOEt/hexane 3:1) 0.35. $[\alpha]_D = +8.6$ (*c* = 1.5, $CHCl_3$). FT-IR (neat, NaCl): 3331*s* (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 CF_3CO), 1598*w*, 1541*s*, 1496*w*, 1452*s*, 1379*m*, 1335*s*, 1306*m*, 1290*w*, 1211*s*, 1184*s*, 1157*s*, 1090*m*, 1038*w*, 1020*w*, 1001*w*, 909*s*, 850*w*, 815*m*, 732*s*, 699*m*, 653*m*, 572*w*, 549*m*. ^{1}H-NMR (300 MHz, 45 mg in 0.6 ml of $CDCl_3$): 7.62 (*d*, *J* = 8.2, 2 H_o of Ts); 7.43 (br. *t*, $NHCOCF_3$); 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*, $CH_2NHCOCF_3$); 322 (*dq* (*dddd*), ^2J = 13.8, ^3J = 7, CH_2NHCO); 2.97–3.1 (*m*, 2 H); 2.73–2.87 (*m*, 2 H); 2.67 (*dt*, ^2J = 13.5, ^3J = 6.1, 1 H); 2.43 (*s*, Me); 1.44–1.62 (*m*, 4 H); 1.14–1.4 (*m*, 2 H). ^{13}C-NMR (75 MHz; $\delta(CDCl_3)$ 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 ($CH_2NHCOCF_3$); 35.48 (CH_2NHCO); 28.44 ($NCH_2CH_2CH_2N$); 26.14, 25.68 (CH_2CH_2); 21.33 (Me). ESI-MS: 564 ($[M+Na]^+$).

(2S,3S)-N-{3-{[(Trifluoroacetyl)amino]{4-[(trifluoroacetyl)amino]butyl}amino}propyl}-3-phenyloxiranecarboxamide (**30b**). A mixture of **29** (104 mg, 0.366 mmol), **9b** (277 mg, 1.098 mmol), and Cs_2CO_3 (239 mg, 0.732 mmol) in DMF (0.5 ml) was stirred at r.t. under N_2 for 28 h and partitioned between H_2O (10 ml) and $CHCl_3$ (4 × 10 ml). The combined org. phase was dried (Na_2SO_4) and evaporated and the residue (95 mg) submitted to FC (SiO_2 (25 ml), 50 → 70% AcOEt/hexane): **30b** (44 mg, 25%). Colorless oil. R_f (AcOEt/hexane 3:1) 0.15. ^{1}H-NMR (300 MHz, $CDCl_3$): 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**). CF_3CO-protected **30a** (149 mg) was treated with K_2CO_3 (300 mg) in H_2O (2 ml) and MeOH (5 ml). After stirring for 8 h, the mixture was quenched with sat. aq. Na_2CO_3 soln. and extracted with CH_2Cl_2 (5 × 10 ml). The extract was dried (Na_2CO_3), and a small portion was evaporated and the residue characterized. ^{1}H-NMR (300 MHz, 22 mg in 0.7 ml of $CDCl_3$): 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, CH_2NHCO); 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). ^{13}C-NMR (75 MHz; $\delta(CDCl_3)$ 76.91): 166.25 (CONH); 143.22 (C_p of Ts); 136.48 (C_{ipso} of Ts); 133.33 (C_{ipso} 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, (CH_2NCH_2); 41.48 (CH_2NH_2); 35.85 (CH_2NHCO); 30.56 ($NCH_2CH_2CH_2N$); 28.27, 26.12 (CH_2CH_2); 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 1*H*-imidazole (792 mg, 11.6 mmol) in CH_2Cl_2 (60 ml), $SOCl_2$ (0.169 ml, 2.328 mmol) was added dropwise. After 5 min, (+)-**12** (518 mg, 1.162 mmol) in CH_2Cl_2 (25 ml) was added slowly and stirred at +5° for 30 min. The mixture was quenched with H_2O (100 ml) and extracted with $CHCl_3$ (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_f (5% MeOH/$CHCl_3$) 0.5 (*A*), 0.75 (*B*). $[\alpha]_D = -242$ (*c* = 1.28, $CHCl_3$). FT-IR (KBr): 3385*s*, 3027*w*, 2933*m*, 2867*m*, 1675*s*, 1599*w*, 1529*s*, 1495*w*, 1456*s*, 1380*w*, 1336*s*, 1306*m*, 1207*w*, 1157*s*, 1117*w*, 1091*m*, 1030*m*, 997*m*, 969*s*, 933*w*, 870*w*, 816*m*, 750*s*, 704*s*, 655*m*, 631*w*, 558*m*. ^{1}H-NMR (300 MHz, 53 mg in 0.7 ml of $CDCl_3$; isomer *A*): 7.72 (*d*, *J* = 8.4, 2 H_o of Ts); 7.28–7.42 (*m*, 5 arom. H); 7.23 (*dd*, ^4J = 1.3, ^3J = 7.8, 2 H_o of Ph); 6.55 (br. *d* (*dd*), *J* = 8, NHCO); 5.13, 5.16 (2*d* of *AB*, *J* = 6.2, CHCH); 3.61–3.76 (*m*, 1 H); 3.3–3.44 (*m*, 2 H); 3.02–3.24 (*m*, 2 H); 2.96 (*dt*, ^2J = 13, ^3J = 3.2, 1 H); 2.6–2.83 (*m*, 2 H); 2.45 (*s*, Me); 1.86–2.04 (*m*, 2 H); 1.56–1.8 (*m*, 4 H). ^{13}C-NMR (75 MHz; $\delta(CDCl_3)$ 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 (CH_2(5)); 45.23 (CH_2(7)); 42.33 (CH_2(2)); 36.03 (CH_2(9)); 30.29 (CH_2(8)); 25.28,22.99 (CH_2(2), CH_2(3)); 21.41 (Me). ESI-MS: 514 (100, $[M+Na]^+$), 466 (10, $[M+Na-SO]^+$).

*(−)-(12*R*,15*R*)-6-[(4-Methylphenyl)sulfonyl]-15-phenyl-13-oxa-14-thia-1,6,10-triazabicyclo[10.2.1]pentadecan-11-one 14,14-Dioxide* ((−)-**33**). Crude (−)-**32** (527 mg, 1.053 mmol) was dissolved in CH_2Cl_2/MeCN/H_2O 1:1:1 (60 ml) followed by addition of $NaIO_4$ (915 mg, 4.3 mmol) and $RuCl_3$ (2.5 mg), and the mixture was stirred vigorously for 90 min with the formation of a single product. After quenching with H_2O (200 ml), the mixture was extracted with CH_2Cl_2 (4 × 20 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the residue dissolved in CH_2Cl_2 and filtered *via* a short plug of SiO_2 (2 g) with 2% MeOH/$CHCl_3$. Drying under h.v. gave (−)-**33** (533 mg, 99%). White foam, amorphous colorless solid. R_f (5% MeOH/$CHCl_3$) 0.8. $[\alpha]_D = -154$ ($c = 1.18$, $CHCl_3$). FT-IR (KBr): 3425*s*, 3060*w*, 3038*w*, 2938*m*, 2875*m*, 1688*s* (C=O), 1599*w*, 1536*s*, 1496*w*, 1459*s*, 1342*s*, 1269*w*, 1232*w*, 1215*w*, 1158*s*, 1183*s*, 1092*m*, 1032*w*, 971*s*, 932*w*, 909*w*, 870*w*, 813*m*, 785*m*, 760*s*, 739*m*, 717*w*, 700*m*, 655*m*, 571*m*, 559*m*, 548*m*, 526*m*. ^{1}H-NMR (300 MHz, 39 mg in 0.7 ml of $CDCl_3$): 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*, $^4J = 1.6$, $^3J = 7.8$, 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($CDCl_3$) 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 of Ts); 129.32 (C_m of Ph); 128.8 (C_o of Ph); 128.59 (C_{ipso} of Ph); 127.0 (C_o of Ts); 83.27 (H−C(12)); 67.57 (H−C(15)); 50.58 (CH_2(5)); 45.97 (CH_2(7)); 43.73 (CH_2(2)); 36.2 (CH_2(9)); 31.97 (CH_2(8)); 24.48, 23.17 (CH_2(2), CH_2(3)); 21.38 (Me). NMR: *Table 2.* ESI-MS: 530 ([M + Na]$^+$).

*(−)-(2*R*,3*S*)-3-Hydroxy-9-[(4-methylphenyl)sulfonyl]-2-phenyl-1,5,9-triazacyclotridecan-4-one* ((−)-**35**). A mixture of (−)-**33** (513 mg, 1.011 mmol), $NaNO_2$ (1.25 g), and DMF (25 ml) was stirred at 70° under N_2 for 27 h and evaporated under h.v. A small portion of the residue was acidified with AcOH, then partitioned between H_2O and $CHCl_3$ to give the intermediate sulfate salt *sodium (2*R*,3*S*)-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. NH_3 soln., stirred for 20 min, and extracted thoroughly with $CHCl_3$ (6 × 10 ml). The org. phase was washed with H_2O and sat. aq. Na_2CO_3 soln. and the aq. phase extracted with $CHCl_3$. The combined org. phase was dried (Na_2CO_3) and evaporated and the white foam (356 mg) purified by FC (SiO_2 (50 ml), 300 ml of 2% MeOH/$CHCl_3$): (−)-**35** (315 mg, 70%). White foam, amorphous solid. M.p. 84–87°. $[\alpha]_D = -30.0$ ($c = 1.11$, $CHCl_3$). FT-IR (KBr): 3397*s* (br.), 3086*w*, 3061*w*, 3027*w*, 2930*s*, 2862*m*, 1650*s* (C=O), 1599*w*, 1534*s*, 1494*w*, 1454*s*, 1399*w*, 1333*s*, 1306*m*, 1289*w*, 1184*w*, 1156v*s*, 1090*s*, 1059*w*, 1032*m*, 990*w*, 963*w*, 929*w*, 890*w*, 816*m*, 744*m*, 705*s*, 655*m*, 568*m*, 548*s*. NMR: see *Table 2*. ESI-MS: 468 (100, [M + Na]$^+$).

Data of **34**: ^{1}H-NMR (300 MHz, CD_3OD; selected resonances): 5.6 (*d*, $J = 2.5$, H−C(2)); 4.64 (*d*, $J = 2.5$, H−C(3)).

*(−)-(2*R*,3*S*)-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 H_2O (40 ml) and sat. aq. Na_2CO_3 soln. (40 ml), followed by extraction with CH_2Cl_2 (4 × 15 ml). The combined org. phase was dried (Na_2CO_3) 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_f (SiO_2, $CHCl_3$/MeOH/aq. 25% NH_3 soln. 70:25:5) 0.15. $[\alpha]_D = -39.8$ ($c = 1.08$, $CHCl_3$). FT-IR (KBr): 3388*s* (O−H), 3291*m*, 3061*m*, 3029*m*, 2927*s*, 2852*s*, 2669*m* (br., N−H), 1955*w*, 1656v*s* (C=O), 1585*w*, 1520*s*, 1455*s*, 1440*s*, 1363*w*, 1323*m*, 1298*w*, 1246*w*, 1190*w*, 1121*s*, 1087*s*, 1055*w*, 1031*w*, 1012*w*, 965*w*, 923*w*, 879*w*, 841*w*, 793*w*, 780*w*, 752*w*, 705*s*, 682*w*, 618*w*, 573*m*, 509*m*. ^{1}H-NMR (300 MHz, 20 mg in 0.6 ml of $CDCl_3$): 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*, CH_2(8)); 2.61 (*m*, 1 H−C(13)); 2.51 (*m*, CH_2(10)); 2.34 (*m*, 1 H−C(13)); 1.81 (*m*, 1 H−C(7)); 1.29–1.68 (*m*, 5 H). ^{13}C-NMR (75 MHz; δ($CDCl_3$) 76.91): 173.12 (CONH); 141.1 (C_{ipso}); 128.32 (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)); 28.11, 27.81, 27.54 (3 CH_2). ESI-MS: 292 ([M + H]$^+$).

*(−)-(2*R*,3*S*)-3-Hydroxy-9-[(2*E*)-1-oxo-3-phenylprop-2-enyl]-2-phenyl-1,5,9-triazacyclotridecan-4-one* (=*(−)-(2*R*,3*S*)-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. CH_2Cl_2 (5 ml), cinnamoyl chloride (30 mg, 0.18 mmol) in CH_2Cl_2 (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 H_2O (10 ml) and CH_2Cl_2 (4 × 5 ml), the combined org. phase dried (Na_2CO_3) and evaporated, and the crude product (100 mg) purified by FC (SiO_2 (25 ml), 7% MeOH/$CHCl_3$): (−)-**1b** (50 mg, 85.5%). Colorless amorphous solid. M.p. 234–244° (dec.). $[\alpha]_D = -38.5$ ($c = 1.09$, $CHCl_3$/MeOH 30:1). FT-IR (KBr): 3295*s* (br.), 3060*w*, 3026*w*,

2926*m*, 2847*m*, 1646v*s* (C=O), 1594*s*, 1530*s*, 1497*m*, 1443*m*, 1433*s*, 1376*w*, 1357*w*, 1323*m*, 1276*w*, 1264*w*, 1229*w*, 1196*m*, 1169*w*, 1132*m*, 1089*m*, 1074*w*, 1030*w*, 991*m*, 914*w*, 849*m*, 763*s*, 731*m*, 699*s*, 685*m*, 568*m*, 503*w*. ^{1}H-NMR (500 MHz, 6 mg in 0.8 ml of $CDCl_3$, 27°; two rotamers A and B): 7.66 (*d*, *J* = 15.5, PhC*H*=CH); 7.51 (*d*, *J* = 7.5, 2 H_o of *Ph*CH=CH); 7.37 (overlapping *m*, 4 H_m of 2 Ph, 2 H_o of Ph–C(2)); 7.36 (overlapping *m*, H_p of *Ph*CH=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=C*H*); 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 $CDCl_3$ + 0.05 ml of CD_3OD; $\delta(CDCl_3)$ 77.23; 23°; two rotamers): 173.98, 173.91 (CONH); 166.66, 166.38 (*C*(O)CH=CH); 142.78, 142.65 (Ph*C*H=CH); 140.82, 140.54 (C_{ipso} of Ph–C(2)); 135.35 (C_{ipso} of *Ph*CH=CH); 129.72 (C_p of *Ph*CH=CH); 128.88, 128.57 (C_m of 2 Ph); 127.88 (C_p of *Ph*–C(2)); 127.35 (C_o of *Ph*–C(2)); 117.46 (PhCH=*C*H); 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 ^{1}H- and ^{13}C-NMR: see also *Table 2*. ESI-MS: 422 ($[M+H]^+$).

*(12*RS*,13*SR*)-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 CH_2Cl_2 (1 ml), TsCl (59.1 mg, 0.31 mmol) was added, followed by Et_3N (0.2 ml) and DMAP (45 mg). The mixture was stirred for 6 h and evaporated. FC (SiO_2 (25 ml), $CHCl_3$ (100 ml), then 1% MeOH/$CHCl_3$ (100 ml)) gave **38** (35 mg, 79%). ^{1}H-NMR (300 MHz, 35 mg in 0.6 ml of $CDCl_3$): 7.66 (*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*, ^3J = 5.1, ^2J = 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). ^{13}C-NMR (75 MHz; $\delta(CDCl_3)$ 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 $CDCl_3$); 49.16 (C(10)?); 47.85 (br., CH_2); 44.3 (br.); 38.9 (br.); 28.1 (br., CH_2); 26.69 (CH_2); 25.8 (br.); 21.35 (Me). ESI-MS: 428 ($[M+H]^+$).

*(±)-(2*RS*,3*RS*)-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 (±)-**12** (30.2 mg, 0.0677 mmol) and $(CF_3CO_2)_2O$ (57 mg, 0.271 mmol) in CH_2Cl_2 (1 ml), Et_3N (0.021 ml, 0.15 mol) was added and stirred for 40 min at r.t. The mixture was quenched with $CHCl_3$, the org. phase washed with 5% aq. citric acid and then aq. NH_3 soln., dried (Na_2CO_3), and evaporated: crude **40** (41 mg), which was used in the next step without purification. Crude **40** was dissolved in $CDCl_3$ (0.6 ml) followed by addition of TsCl (23 mg, 0.121 mmol) and Et_3N (0.023 ml). ^{1}H-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 $CHCl_3$, washed with aq. Na_2CO_3 soln., 1N aq. HCl, dried (Na_2CO_3), and evaporated (64 mg). Purification by FC (SiO_2 (20 ml), AcOEt/hexane 1:1) gave **41** (41 mg, 87%). White foam. R_f (AcOEt/hexane 1:1) 0.3. ^{1}H-NMR (300 MHz, 41 mg in 0.6 ml of $CDCl_3$): 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). ^{13}C-NMR (75 MHz; $\delta(CDCl_3)$ 76.92): 166.82 (CONH); 157.5 (*q*, *J* = 36.7, *C*OCF$_3$); 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_o of Ph); 128.33 (C_p of Ph); 127.91, 127.19 (4 C_o of 2 Ts); 116.08 (*q*, *J* = 289, CF_3); 76.54 (H–C(3)); 66.0 (br., H–C(2)); 52.3, 48.19 (2*s*, CH_2(13)); 51.12, 50.44 (C(8), C(10)); 39.69 (CH_2(6)); 27.63 (CH_2(7)); 25.76 (CH_2(12)); 24.67 (CH_2(11)); 21.46, 21.37 (2 Me). ESI-MS: 524 (100, $[M-TsO]^+$), 718 (12, $[M+Na]^+$).

*Data of (±)-(2*RS*,3*RS*)-3-Hydroxy-9-[(4-methylphenyl)sulfonyl]-2-phenyl-1-(trifluoroacetyl)-1,5,9-triaza-cyclotridecan-4-one* (**40**). ^{1}H-NMR (300 MHz, $CDCl_3$): 2:3 mixture of two rotamers. ESI-MS: 564 ($[M+Na]^+$).

*(±)-(2*RS*,3*SR*)-3-Hydroxy-9-[(4-meth ylphenyl)sulfonyl]-1-nitroso-2-phenyl-1,5,9-triazacyclotridecan-4-one* (**42**). The suspension of $NaNO_2$ (237 mg) and **41** (40 mg) in DMF (1 ml) was stirred at 70° for 14 h, quenched with H_2O (1 ml) and AcOH (0.2 ml), and extracted with Et_2O: crude **42** (34 mg) of *ca*. 85% purity by ^{1}H-NMR. Pale brown solid. R_f (5% MeOH/$CHCl_3$) 0.33. ^{1}H-NMR (300 MHz, 34 mg in 0.7 ml of $CDCl_3$): 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*, CH_2(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*), ^3J = 5, 5.6, ^2J = 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). ^{13}C-NMR (75 MHz; $\delta(CDCl_3)$ 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 (CH_2(10)); 48.02 (CH_2(8)); 44.36 (CH_2(13)); 38.19 (CH_2(6)); 28.24 (CH_2(7)); 25.74 (CH_2(12)); 24.96 (CH_2(11)); 21.38 (Me). ESI-MS: 497 (100, $[M+Na]^+$), 467 (20, $[M+Na-NO]^+$), 446 (40, $[M-NO+2H]^+$), 410 (40).

*(2*R*,3*S*)-9-[(2*E*)-1-Oxo-3-phenylprop-2-enyl]-2-phenyl-3-{[(2*S*)-3,3,3-trifluoro-2-methoxy-1-oxo-2-phenylpropyl]oxy}-1,5,9-triazacyclotridecan-4-one* (= (α*S*)-α-*Methoxy*-α-*(trifluoromethyl)benzeneacetic Acid (2*R*,3*S*)-4-Oxo-9-[(2*E*)-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 $CDCl_3$ (0.6 ml), (–)-(*R*)-*Mosher* acid chloride (7.5 mg, 0.0297 mmol) was added. ^{1}H-NMR indicated an immediate complete reaction. FC (SiO_2 (10 ml), 1% MeOH/$CHCl_3$) gave **44** (8.4 mg, 93%). Oil. R_f (5% MeOH/$CHCl_3$) 0.3. ^{1}H-NMR (300 MHz, 8.4 mg in 0.6 ml of $CDCl_3$): 7.69 (*d*, *J* = 15.5, PhC*H*=CH); 7.18–7.55 (15 arom. H); 6.80 (*d*, *J* = 15.4, PhCH=C*H*); 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 (^{1}H-NMR) and completely identical to synthetic **44**. ^{1}H-NMR: 5.59 (*s*, H–C(3)); 4.43 (*s*, H–C(2)); 3.28 (*s*, MeO).

*(–)-(2*R*,3*S*)-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 $CDCl_3$, 3-phenylpropanoyl chloride (25 mg) was added. ^{1}H-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. Na_2CO_3 soln. and CH_2Cl_2, followed by FC purification (SiO_2, 4% MeOH/$CHCl_3$) gave (–)-**45** (24 mg, 87%). White solid.

Method B. Synthetic (–)-**1b** (7 mg) was hydrogenated with H_2 over 10% Pd/C in MeOH. Filtration over a plug of SiO_2 and evaporation gave (–)-**45** in *ca.* 96% yield. M.p. 210–212°. R_f (5% MeOH/$CHCl_3$) 0.12. $[\alpha]_D$ = –22.9 (*c* = 0.48, $CHCl_3$). ^{1}H-NMR (300 MHz, 19 mg in 0.6 ml of $CDCl_3$): 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, PhCH_2); 2.87 (overlapping *m*, 1 H); 2.72 (br. *m*, 1 H); 2.54 (*m*, CH_2CO); 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 H_2 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-C$_{18}$* (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% HCO_2H in H_2O (solvent *A*) to 0.1% HCO_2H 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: N_2 nebulizer gas 40 psi; N_2 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 *m*/*z* 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_R 15.35. UV: 287. MS/MS of *m*/*z* 422 ($[M+1]^+$): 404 (6, $[M+1-H_2O]^+$), 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_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_R 11.3. UV: <215. MS/MS of *m*/*z* 438 ($[M+1]^+$): 420 (100, $[M+1-H_2O]^+$), 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.

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