(−)-(3*S*)-3-(Tosylamino)butano-4-lactone, a Versatile Chiral Synthon for the Enantioselective Synthesis of Different Types of Polyamine Macrocycles: Determination of the Absolute Configuration of (−)-(*R*)-Budmunchiamine A

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(−)-(3*S*)-3-(Tosylamino)butano-4-lactone (**1**) and its derivative ethyl (−)-(3*S*)-4-iodo-3-(tosylamino)butanoate (**2**) are presented as easily accessible chiral building blocks for the construction of a range of different macrolactam frameworks important for the synthesis of naturally occurring polyamine alkaloids as well as for establishing a substance library of such compounds, including S-containing derivatives for biological tests. In addition to that, the absolute configuration of the spermine alkaloid (−)-(*R*)-budmunchiamine A (**3**) from *Albizia amara* was determined by total synthesis according to the new methodology.

Introduction. – Polyamine alkaloids, either in their open-chain, or, more importantly for this report, in their macrolactam form, are natural products that are widely but rather unsystematically distributed throughout the plant and animal kingdom.

In the course of our polyamine-chemistry studies, we were searching for a universal synthetic method that would allow the construction of different types of naturally occurring macrolactams by a handful of similar and – even more important in this context – simple reactions, starting from a single central starting material. So far, all known naturally occurring polyamine macrolactams were isolated in pure enantiomeric form. The desired synthon, therefore, has to have a defined center of chirality, enabling the synthesis of enantiomerically pure products from the very beginning. It is our purpose to show in this report, that (−)-(3*S*)-3-(tosylamino)butano-4-lactone (**1**) could serve as such a highly versatile starting material – which itself is easily obtainable in a well-known three-step sequence from inexpensive L-aspartic acid – making it possible to synthesize a greater range of optically active polyamine macrolactams of different ring sizes. Besides the successful synthesis of some unnatural spermine and spermidine macrocycles, we could test this new method especially in verifying the proposed, but still unknown, absolute configuration of the spermine alkaloid budmunchiamine A (**3**), which was isolated from the seeds of *Albizia amara* BOLV. (Leguminosae) [1] and from stem bark of *A. schimperana* OLIV. [2].

Results and Discussion. – The preparation of lactone **1** from L-aspartic acid is well known in the literature [3–7]; therefore, multigram amounts of this material were easily accessible for us. Furthermore, *Jefford* and *Wang* [3] described a method to

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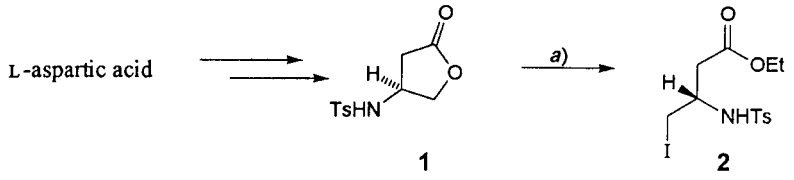
[1]) Part of the Ph.D. Thesis of *R. D.*, University of Zürich, 2002.
[2]) Part of the Ph.D. Thesis of *K. P.*, University of Zürich, 1999.

transform **1** into ethyl (−)-(3*S*)-4-iodo-3-(tosylamino)butanoate (**2**), the second important synthon, with iodotrimethylsilane in CH_2Cl_2/EtOH under mild conditions, providing us also with enough of **2** to establish the usefulness of the two mentioned reagents for our synthetic purposes (*Scheme 1*).

Scheme 1



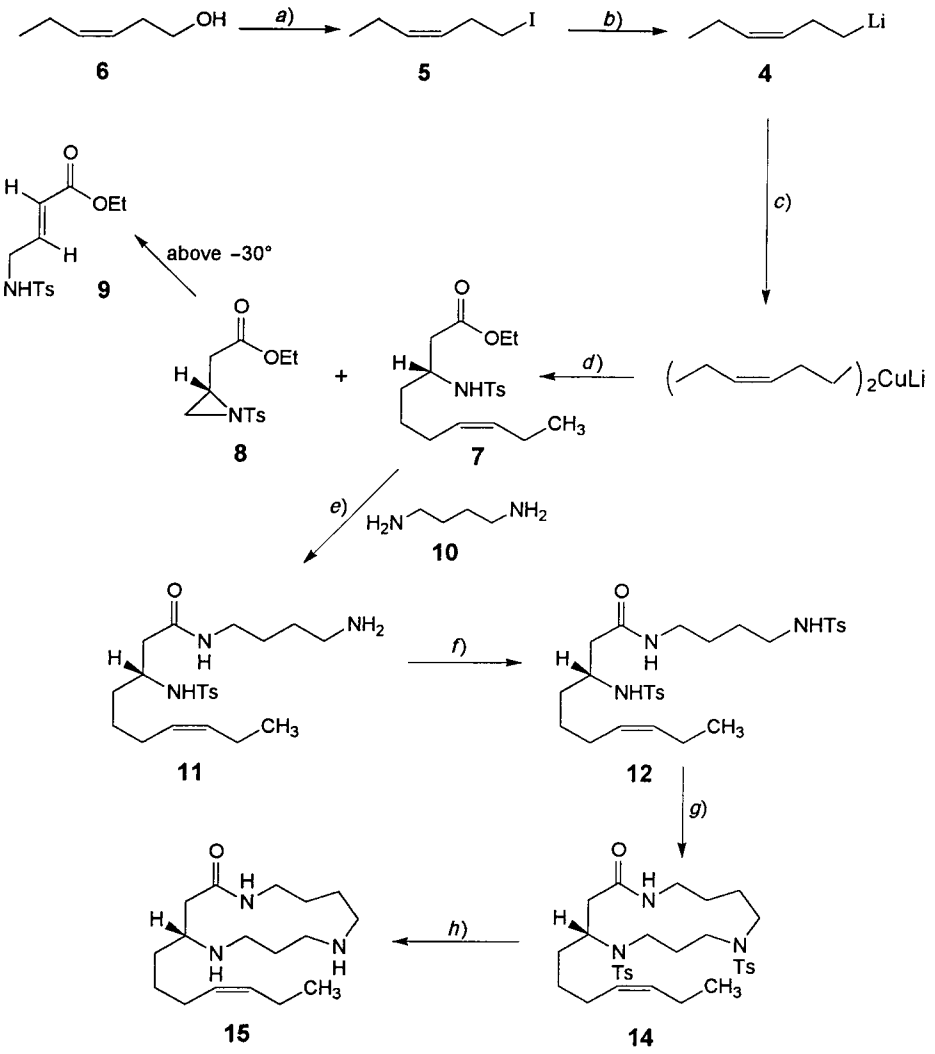
a) Me_3SiI, EtOH/CH_2Cl_2, 0° → r.t, 4 h, 78%.

Special attention should be drawn to the usage of the tosyl group, which, on the one hand, serves as a protecting group of outstanding stability, but, on the other hand enables the highly fruitful nucleophilic substitutions necessary to built up the aspired macrolactam framework of the target structures.

Inspired by one of our synthetic projects, we first examined the possibility to prolong the C-skeleton of iodo ester **2** by a cuprate reaction (see *Scheme 2*). In principle, this prolongation by use of commercially available organolithium compounds has been described [3][4][6]. In our hands, we found it somewhat tricky to work out the experimental details of the cuprate forming, which allowed the use of *in situ* prepared (3*Z*)-hex-3-enyllithium (**4**) from (3*Z*)-1-iodohex-3-ene (**5**). The latter was easily obtained by a simple transformation from commercially available (3*Z*)-3-hexen-1-ol (**6**). Finally, we succeeded in preparing the tosylated β-amino acid **7** from **4** and **2** using freshly prepared $CuBr \cdot Me_2S$ as the copper-reagent precursor, a special temperature protocol, and a solvent mixture of Et_2O and THF. As a side reaction, we always observed the formation of the aziridinacetate **8**, which even rearranged under the basic working conditions at a temperature above −30° to the α,β-unsaturated derivative **9**. The ester functionality in **7** furnished, after $Cu(OAc)_2$-assisted aminolysis with excess putrescine (**10**), the amide **11**, which itself could be easily tosylated to the ditosyl-protected derivative **12**, the definite ring precursor. Following ideas from the literature [8–10], we decided to accomplish the ring closure using propane-1,3-diol bis(*p*-toluenesulfonate) (**13**), which was synthesized by a known procedure [11], and cesium carbonate as a base in DMF at elevated temperature. The two-fold substitution occurred smoothly under these conditions, enabling us to isolate the desired macrolactam **14** in 78% yield for the last step. Besides the normal spectroscopic characterization, the structure of **14** was firmly established by an X-ray single-crystal analysis (see *Fig. 1*). Detosylation by a very well-established electrochemical method [12][13] yielded the free spermidine macrolactam **15** after simple extractive workup (see *Scheme 2*).

Motivated by this rapid access to **15**, we found it now challenging to examine lactone **1** in the aminolysis reaction with different polyamines (see *Scheme 3*). First of all, we observed a smooth reaction of **1** and putrescine (**10**) under somewhat forced conditions, which yielded amino-hydroxy-amide **16**; the same was true for the use of

Scheme 2



a) PPh_3, 1*H*-imidazole, I_2, CH_2Cl_2, r.t., 1 h; 89%. *b*) ^{t}BuLi, Et_2O, −78° → r.t., 2 h. *c*) CuBr·Me_2S, Et_2O/THF, −78° → −20°, 30 min. *d*) **2**, Et_2O/THF, −60° → −10°, 3 h; 75%. *e*) $H_2N(CH_2)_4NH_2$ (**10**), $Cu(OAc)_2$, r.t., 8 h; quant. *f*) TsCl, Et_3N, $CHCl_3$, r.t, 2 h; 93%. *g*) $TsO(CH_2)_3OTs$ (**13**), Cs_2CO_3, DMF, 65°, 24 h, 78%. *h*) Electrolysis, EtOH, 5°; 92%.

propane-1,3-diamine, which resulted in formation of the homologous compound **17**. Both substances led, after tosylation of the free amino group, *i.e.*, of the more nucleophilic and therefore reactive site in comparison with the OH group, to the corresponding ditosyl-protected derivatives **18** and **19**. For **18**, ring closure to **20** was accomplished as mentioned above, *i.e.*, **13** was again used as electrophile. To build up a spermidine macrocycle from **19**, we, of course, had to switch from **13** to a CH_2-elongated reagent with

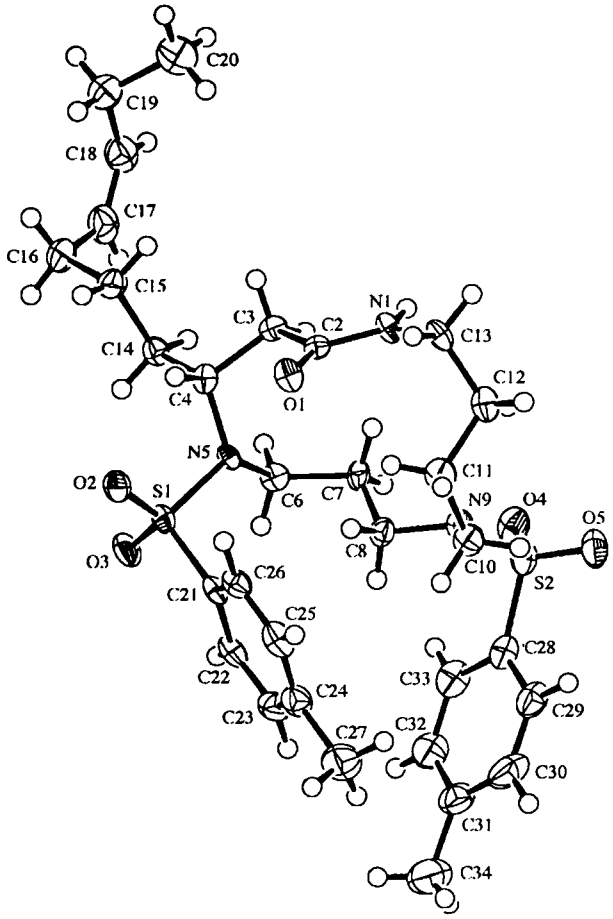
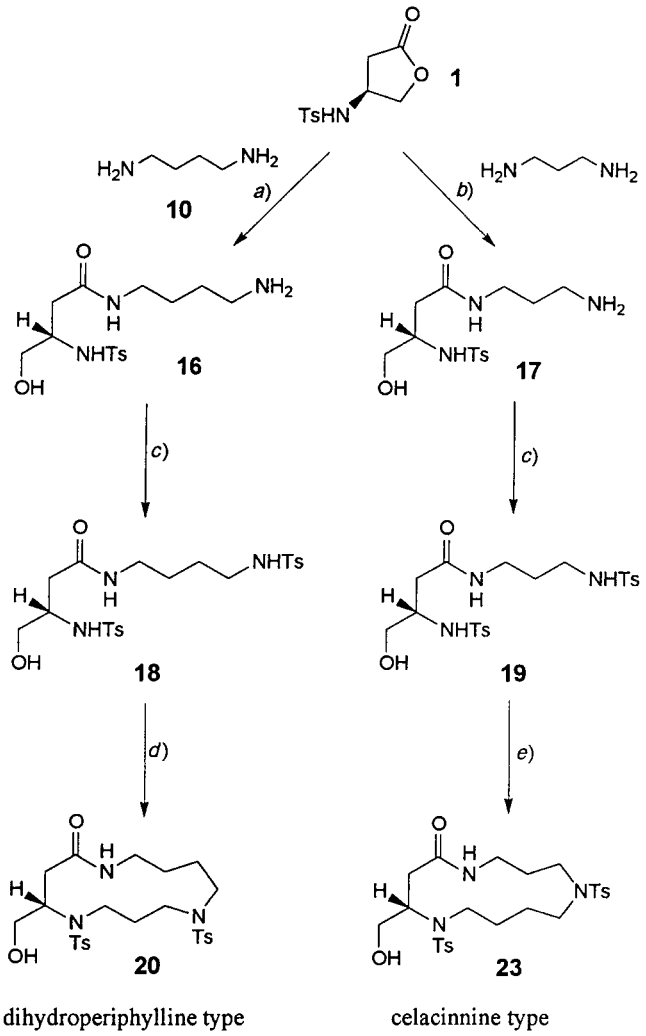


Figure. *ORTEP* [14] *Plot of the doubly* N-*tosylated macrolactam* ***14***

two α,ω-leaving groups, *e.g.*, butan-1,4-diol bis(*p*-toluenesulfonate) (**21**) or butan-1,4-diol bis(methane-sulfonate) (**22**) [11]. This finally generated in macrolactam **23**.

Macrolactams such as **20**, with a 4-3 incorporation of the spermidine subunit, are known as representatives of the so-called dihydroperiphylline type of polyamine-class alkaloids. On the contrary, a 3-4 incorporation as in **23** classifies this principle structure as belonging to the group of celacinnine-type macrolactams. It was interesting to note that the 90% yield for the ring closure to **20** was surprisingly high for the formation of a 13-membered ring. A matching template effect of the cesium cation *may* contribute to this success, as well as the presence of the two sulfonamide groups, whose location obviously seems to favor the ring closure in this case. On the other hand, the yield for the ring closure of **19** to **23** was always significantly lower, *ca.* 50%, although we varied the reaction conditions in a broad manner. The best results were observed with **21** as an electrophile in DMSO at 45° and – surprisingly – potassium carbonate as a base.

Scheme 3



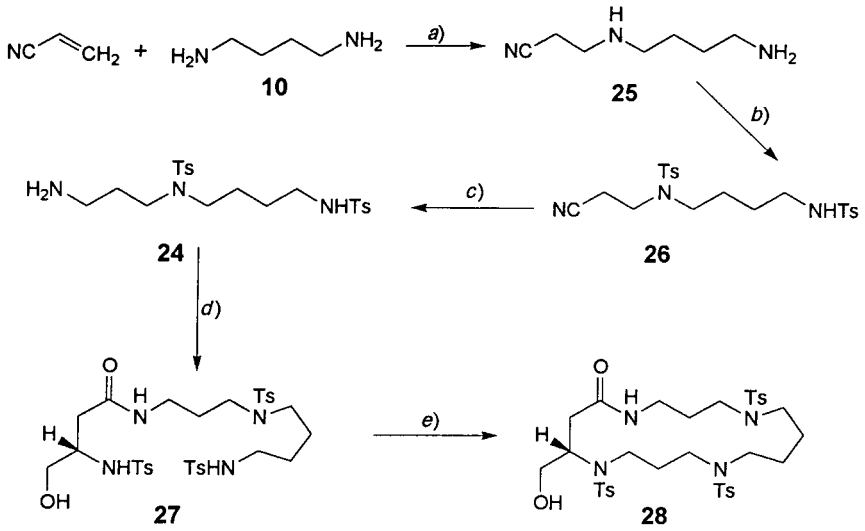
a) $Cu(OAc)_2$, $CHCl_3$, 6 h, reflux; 91%. *b*) $CHCl_3$, r.t., 8 h; 96%. *c*) TsCl, DMF, r.t., 5 h; 81%. *d*) $TsO(CH_2)_3OTs$ (**13**), Cs_2CO_3, DMF, 65°, 24 h; 90%. *e*) $TsO(CH_2)_4OTs$ (**21**), K_2CO_3, DMSO, 45°, 48 h; 48%.

We want to point out that this simple reaction sequence, starting with the chiral lactone **1**, allowed rapid access to both above-mentioned principle types of naturally occurring spermidine macrocycles or of their precursors. Until now, *preliminary* experiments to convert the primary OH group of **20** or **23** to a leaving-group functionality have been so far unsuccessful (*Scheme 3*).

Strongly encouraged by these results, we next expanded the method for synthesis of the principle skeleton of spermine macrolactams, also widespread in nature. For this,

we first prepared the partially protected amine **24**, needed for aminolysis (see *Scheme 4*), by aza-*Michael* addition of putrescine (**10**) to acrylonitrile (→ **25**) and two-fold tosylation *via* **26**. The desired **24** could be isolated in almost quantitative yield, by application of a method for reducing nitriles with a mixture of $NaBH_4$ and CF_3COOH in THF [15]. Successful aminolysis of **1** with amine **24** to ring precursor **27** could be achieved in good yield by refluxing both components in ^{i}PrOH for a prolonged time. The use of EtOH instead of ^{i}PrOH seems to result in some transesterification and, therefore, decreased yields. With **27** in hand, ring closure to **28**, the desired spermine analog of macrocycles **20** and **23**, could be accomplished in moderate yield. We want to emphasize at this point that we do not have to use high-dilution conditions, which are often considered as unavoidable for synthesizing large rings. It had not escaped our notice that this approach should also be highly useful in the construction of other 13- and 17-membered macrolactams, in addition to those mentioned.

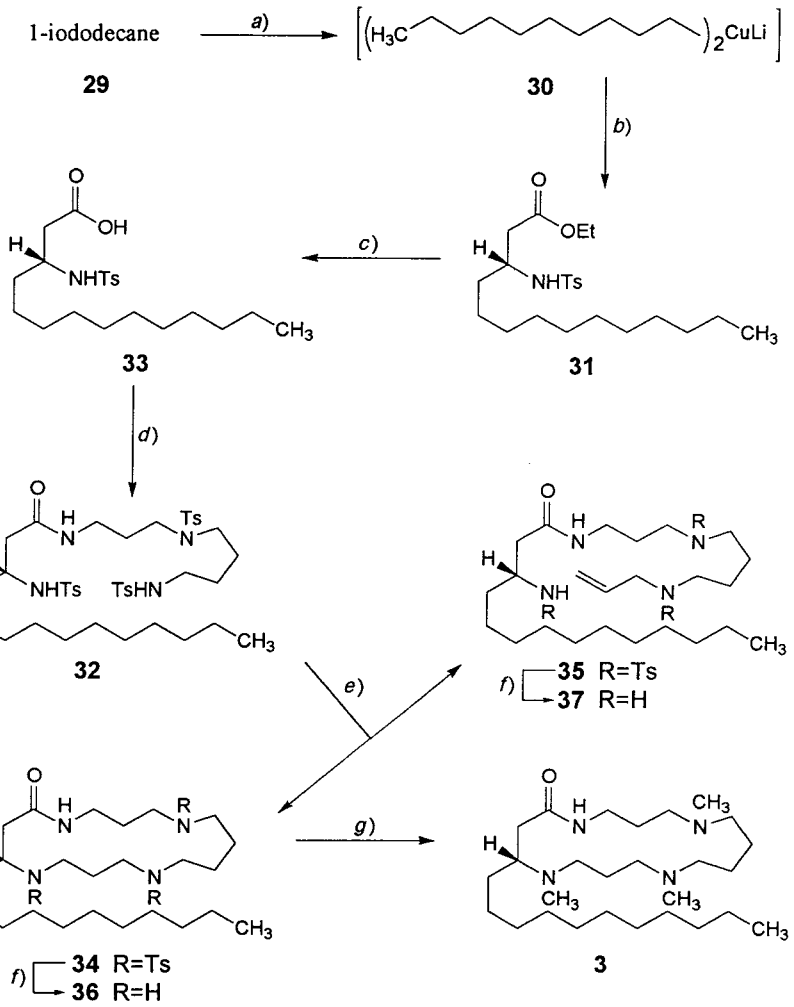
Scheme 4



a) MeOH, r.t., 8 h; 84%. *b*) TsCl, Et_3N, THF, r.t., 6 h; 99%. *c*) $NaBH_4$, CF_3COOH, THF, r.t., 3 h; 98%. *d*) **1**, $Cu(OAc)_2$, ^{i}PrOH, r.t., 4 d; 71%. *e*) $TsO(CH_2)_3OTs$ (**13**), Cs_2CO_3, DMSO, r.t., 24 h; 48%.

Looking for some application of this enantioselective procedure in the field of polyamine alkaloids, we focused on the *Albizia amara* alkaloid budmunchiamine A (**3**). Recently, we reported the racemic synthesis [16] of this alkaloid. We decided to synthesize **3** again (see *Scheme 5*), but now in an enantioselective manner, to compare the chiroptical properties of the natural and synthetic compounds, therefore enabling a conclusion about its absolute configuration. To this end, we could profit from our experience obtained in synthesizing **7** for a similar cuprate reaction. Now commercially available 1-iododecane (**29**) was subjected to an iodo-lithium exchange reaction. The resulting organolithium compound was transformed *in situ* into the appropriate low-order cuprate **30**, which gave in a nucleophilic substitution on **2** the tosylated β-amino acid derivative **31** in 75% yield, based on **29**. For the following amidation,

Scheme 5



a) 1. *t*BuLi, Et_2O, $-78° \rightarrow$ r.t., 2 h; 2. $CuBr \cdot Me_2S$, THF/Et_2O, $-78° \rightarrow -20°$, 30 min. *b*) **2**, THF/Et_2O, $-78° \rightarrow$ r.t.; 75%. *c*) aq. NaOH soln./EtOH, r.t.; 98%. *d*) **24**, DCC, DMAP, CH_2Cl_2, r.t.; 94%. *e*) 1,3-dibromopropane, Cs_2CO_3, DMF, r.t. *f*) Electrolysis, EtOH, 5°; 47%. *g*) 1. 37% formalin, AcOH, 0°; 2. $NaCNBH_3$, 0°; 91%.

the highest yields of ring precursor **32** could be achieved in a classical manner, *i.e.*, first by saponification of the ethyl ester **31** to the free acid **33** and subsequent coupling with **24** by usual DCC/DMAP (dicyclohexylcarbodiimide/*N*,*N*-dimethylpyridin-4-amine) activation. Cyclization of **32** was achieved by deprotonation with 2.0 equiv. of cesium carbonate, followed by treatment with 1.0 equiv. of a diluted 1,3-dibromopropane solution in DMF. Deprotection of the resulting tritosyl-substituted amide mixture **34**/**35**, which was again performed by electrolysis, yielded, after purification of the crude product, the desired macrocyclic lactam **36** in 47% yield. The relatively low yield is due

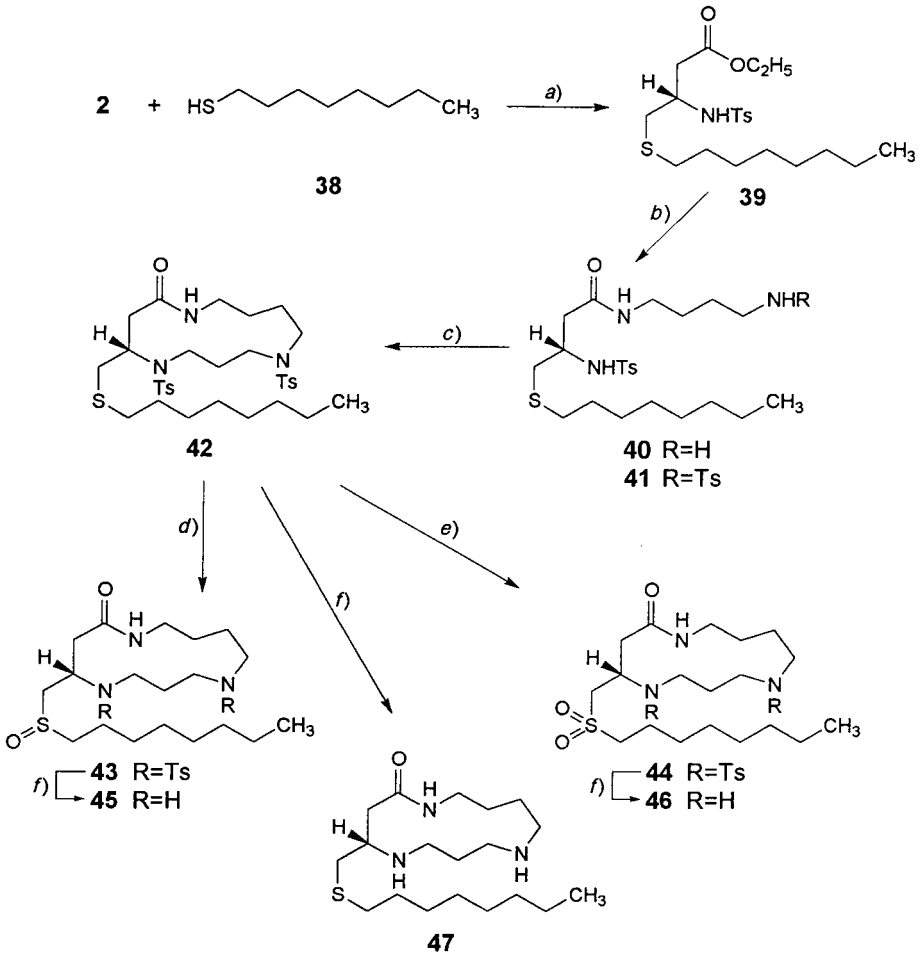
to the concomitant elimination reaction producing the allyl amine **37** as by-product in 41% yield. Separation of **36**/**37** could be achieved by standard column chromatography. The completion of the budmunchiamine A (**3**) synthesis required the methylation of all three secondary-amino functionalities. For this purpose, **36** was treated for 7 min with 37% aqueous formaldehyde (formalin) and AcOH at 0°. Then $NaCNBH_3$ was added and the mixture stirred overnight at room temperature. Final column chromatography of the crude product afforded the target compound **3** in 88% yield. Synthetic (−)-(*R*)-budmunchiamine A (**3**) was characterized by IR, mass, ^{1}H- and ^{13}C-NMR spectra and found to be identical with the natural product and with the formerly obtained synthetic (±)-budmunchiamine A [16]. Determination of the enantiomer purity of **3** by NMR spectroscopy showed that no epimerization had occurred during its synthesis. Both, the synthetic and the natural compound showed the same specific rotation; therefore, the absolute configuration of (−)-(*R*)-budmunchiamine A (**3**) has been established.

Finally, we want to present the possibility of incorporating an S-atom in the side chain of the macrolactams in order to obtain some analogs with a heteroatom (see *Scheme 6*). This intention was motivated by the potential biological activity of such compounds. Once again, iodo ester **2** represented an ideal starting material, enabling a very smooth reaction with a range of thiols, firstly deprotonated with KOH in EtOH. To present one concrete example, octane-1-thiol (**38**) reacted in a 89% yield with **2** to derivative **39**. The usual procedure of setting up the macrolactam, *i.e.*, aminolysis to **40**, tosylation, and ring closure of intermediate **41** showed no problems, the tosylated macrocycle **42** being isolated in a 45% overall yield, starting from **2**. Oxidation at the S-atom offers the possibility to tune the polarity of the compounds; so careful treatment with 1.0 equiv. of *m*CPBA (*m*-chloroperbenzoic acid) at −20° resulted in sulfoxide derivative **43**, whereas an excess of *m*CPBA at room temperature led to the sulfone **44**. The corresponding deprotected macrocycles **45**–**47** were achieved by final electrochemical detosylation.

Conclusions. – The chiral (−)-(3*S*)-3-(tosylamino)butano-4-lactone (**1**) – easily accessable from very cheap L-aspartic acid – was used for the straightforward synthesis of different polyamine macrocycles, whose macrolactam framework is incorporated in naturally occurring spermidine and spermine alkaloids. For this purpose, **1**, or its synthetic successor, iodo ester **2**, provided the needed reactivity and chirality, furnishing the targeted macrocycles by always the same reaction sequence under easy reaction conditions, *i.e.*, in a user-friendly way. Different ring sizes were realized by simply varying the chain length of the involved amines and electrophiles, without departing from the general synthetic strategy. Furthermore, heteroatoms such as an S-atom could be incorporated in the molecules, enabling a broader range of compounds for biological tests. Finally, this method was successfully used in performing the enantioselective synthesis of (−)-(*R*)-budmunchiamine A (**3**).

We thank the analytical departments of our institute for all measurements and the *Swiss National Science Foundation* for generous financial support. Dr. *K. Drandarov* is thanked for his suggestion to use $Cu(OAc)_2$ as a catalyst for the aminolysis reactions and especially Dr. *A. Linden* for X-ray structure determination.

Scheme 6



a) KOH, EtOH, r.t., 15 min; 89%. *b*) 1. $H_2N(CH_2)_4NH_2$ (**10**), $Cu(OAc)_2$, r.t., 8 h; quant.; 2. TsCl, Et_3N, $CHCl_3$, r.t., 2 h; quant. *c*) $TsO(CH_2)_3OTs$ (**13**), Cs_2CO_3, DMF, 50°, 24 h; 81%. *d*) *m*CPBA (1.0 equiv.), CH_2Cl_2, $-45° \rightarrow -20°$, 1 h; 87%. *e*) *m*CPBA (2.5 equiv.), CH_2Cl_2, r.t., 4 h; 94%. *f*) Electrolysis, EtOH, 5°; 92%.

Experimental Part

General. All commercially available reagents were used without further purification. Solvents were either *puriss. p.a.* grade (*Fluka*) or distilled prior to use. THF and Et_2O for the cuprate reaction were dried over Na-benzophenone and freshly distilled before use. Dry DMSO was purchased from *Fluka* and stored over 4-Å molecular sieves. $CuBr \cdot Me_2S$ was prepared by recrystallization of CuBr from Me_2S. Reactions were normally *not* carried out under N_2, unless otherwise stated; they were monitored by TLC (*Merck* precoated plates, silica gel *60* F_{254}). All extracts were dried before evaporation over $MgSO_4$, unless otherwise stated. Column chromatography (CC): silica gel *60* (230–400 mesh ASTM) from *Merck*. M.p. *Mettler FP5*. Optical rotations $[\alpha]_D^{21}$: in $CHCl_3$ (*Fluka* for IR spectroscopy), except where noted; *Perkin-Elmer 241* polarimeter. IR Spectra [cm^{-1}]: in $CHCl_3$ (*Fluka* for IR spectroscopy); *Perkin-Elmer 781*. NMR Spectra: in $CDCl_3$, except where noted; *Bruker ARX-300* (300 (^1H) and 75 (^{13}C) MHz) or *Bruker DRX-600* (600 (^1H) and 150 (^{13}C) MHz); chemical

shifts δ in ppm rel. to Me_4Si as internal standard; coupling constants J in Hz. MS: *Finnigan SSQ-700* for chemical ionization (CI) with NH_3, *Finnigan MAT-90* for electron impact (EI, 70 eV), and *Finnigan TSQ-700* for electrospray ionization (ESI); m/z (rel. int. in %).

(3Z)-1-Iodohex-3-ene (**5**). A soln. of PPh_3 (13.35 g, 51.0 mmol) and 1*H*-imidazole (3.47 g, 51.0 mmol) in CH_2Cl_2 (50 ml) was treated slowly with I_2 (12.9 g, 51.0 mmol). To this heterogeneous mixture, commercially available (3*Z*)-hex-3-en-1-ol (**6**; 4.25 g, 42.4 mmol, 5.0 ml) was added dropwise. After stirring at r.t. for 1 h, the solvent was mostly evaporated and the residue filtered over silica gel (pentane/Et_2O 4:1): 8.1 g (91%) of **5**. Pale red liquid, which was considered sufficiently pure for use in the next step. IR: 3000*m*, 2960*s*, 2930*s*, 2880*s*, 1650*m*, 1460*s*, 1425*s*, 1400*m*, 1375*m*, 1310*m*, 1300*m*, 1240*s*, 1170*s*, 1110*w*, 1070*m*, 1025*w*, 985*m*, 920*m*, 895*w*, 865*m*. ^{1}H-NMR ($CDCl_3$): 5.58–5.48 (*m*, 1 H); 5.33–5.24 (*m*, 1 H); 3.13 (*t*, J = 7.3, 2 H); 2.65 (*dq*, 2 H); 2.09–2.01 (*quint.*-like *m*, 2 H); 0.98 (*t*, J = 7.5, 3 H). ^{13}C-NMR ($CDCl_3$): 134.2 (*d*); 127.2 (*d*); 31.4 (*t*); 20.7 (*t*); 14.1 (*q*); 5.5 (*t*).

*Ethyl (+)-(3*R*,7Z)-3-{[(4-Methylphenyl)sulfonyl]amino}dec-7-enoate* (**7**). ^{t}BuLi (12.4 mmol) was added to a soln. of **5** in dry Et_2O (10 ml) at $-78°$ under N_2. After 10 min at $-78°$, the mixture was allowed to warm to r.t. for 1.5 h. After recooling to $-78°$ and diluting with dry THF (20 ml), $CuBr \cdot Me_2S$ (0.64 g, 3.10 mmol) was added, the cooling bath removed, and the mixture allowed to warm up until all crystalline $CuBr \cdot Me_2S$ was dissolved (which normally happened below $-40°$), yielding a dark red soln. of the cuprate. Once again, this soln. was cooled to $-78°$ and treated dropwise with **2** (1.27 g, 3.10 mmol) in dry THF (5 ml). The temp. was slowly raised until TLC showed no more educt. Then, the mixture was quenched with sat. aq. NH_4Cl soln. and extracted with Et_2O. Evaporation and purification of the residue by CC (SiO_2, hexane/AcOEt 4:1) yielded 0.85 g (75%) of **7**. Colorless oil. $[\alpha]_D$ = +13.56 (c = 1.60, $CHCl_3$). IR: 3540*w*, 3370*m*, 3020*w*, 2960*s*, 2920*s*, 2860*m*, 1725*s*, 1600*m*, 1440*w*, 1420*w*, 1390*w*, 1370*s*, 1330*s*, 1300*w*, 1250*s*, 1155*s*, 1090*s*, 1040*s*, 950*w*, 910*s*, 845*w*, 810*w*, 650*m*. ^{1}H-NMR ($CDCl_3$): 7.75 (*d*, J = 8.3, 2 H); 7.28 (*d*, J = 8.3, 2 H); 5.35–5.29 (*m*, 1 H); 5.23–5.14 (*m*, *d*, 2 H); 4.11–4.03 (*m*, 2 H); 3.54–3.51 (*m*, 1 H); 2.45–2.40 (*dd*, *s*, 4 H); 2.36 (*dd*, J = 4.7, 2.4, 1 H); 2.02–1.87 (*sept.*-like *m*, 4 H); 1.51–1.20 (*m*, 4 H); 1.22 (*t*, J = 7.1, 3 H); 0.92 (*t*, J = 7.5, 3 H). ^{13}C-NMR ($CDCl_3$): 171.4 (*s*); 143.3 (*s*); 138.3 (*s*); 132.3 (*d*); 129.7 (*d*); 128.2 (*d*); 127.1 (*d*); 60.7 (*t*); 50.7 (*d*); 38.7 (*t*); 34.2 (*t*); 26.4 (*t*); 25.8 (*t*); 21.5 (*q*); 20.5 (*t*); 14.3 (*q*); 14.1 (*q*).

*(3*R*,7Z)-*N*-(4-Aminobutyl)-3-{[(4-methylphenyl)sulfonyl]amino}dec-7-enamide* (**11**). At r.t., **7** (0.80 g, 2.18 mmol) was added to liquified butane-1,4-diamine (= putrescine; **10**; 4.0 g, 45 mmol). The aminolysis was supported by a cat. amount of $Cu(OAc)_2$. After stirring for 8 h at r.t., the mixture was taken up in H_2O and extracted vigorously with CH_2Cl_2. The org. layer was subsequently washed with H_2O and dil. aq. NH_3 soln. Drying (Na_2SO_4) and evaporation resulted in 0.89 g (quant.) of **11**. Colorless, but slightly turbid oil, which was pure enough for the next step. $[\alpha]_D$ = +6.17 (c = 1.12, $CHCl_3$). IR: 3400–3050(br.), 3000*w*, 2930*s*, 2860*m*, 1655*s*, 1600*w*, 1520*m*, 1410*m*, 1330*m*, 1305*w*, 1290*w*, 1260*w*, 1160*s*, 1090*m*, 1020*w*, 950*w*. ^{1}H-NMR ($CDCl_3$): 7.75 (*d*, J = 8.1, 2 H); 7.28 (*d*, J = 8.1, 2 H); 6.55 (br. *t*, 1 H); 5.35–5.27 (*m*, 1 H); 5.20–5.08 (*m*, 1 H); 3.50–3.42 (*m*, 1 H); 3.28–3.15 (*m*, 4 H); 2.42 (*s*, 3 H); 2.22 (*dd*, J = 14.6, 4.6, 2 H); 2.0–1.82 (*m*, 4 H); 1.60–1.40 (*m*, 6 H); 1.35–1.13 (*m*, 2 H); 0.92 (*t*, J = 7.5, 3 H). ^{13}C-NMR ($CDCl_3$): 170.6 (*s*); 143.2 (*s*); 138.3 (*s*); 132.1 (*d*); 129.6 (*d*); 128.3 (*d*); 127.1 (*d*); 51.5 (*d*); 40.0 (*t*); 39.3 (*t*); 34.2 (*t*); 27.5 (*t*); 26.5 (*t*); 26.0 (*t*); 21.5 (*q*); 20.5 (*t*); 14.3 (*q*)[3]). ESI-MS: 432 (5, $[M + Na]^+$), 410 (100, $[M + H]^+$).

*(3*R*,7Z)-3-{[(4-Methylphenyl)sulfonyl]amino}-*N*-(4-{[(4-methylphenyl)sulfonyl]amino}butyl)dec-7-enamide* (**12**). To a soln. of **11** (0.80 g, 1.95 mmol) and Et_3N (0.36 g, 3.6 mmol, 0.50 ml) in $CHCl_3$ (10 ml), TsCl (0.372 g, 1.95 mmol) was added at r.t. After stirring for 1 h, the mixture was diluted with H_2O and extracted with CH_2Cl_2. Evaporation and purification by CC (SiO_2, CH_2Cl_2/MeOH 19:1) yielded **12** (1.10 g, 93%). Colorless oil. $[\alpha]_D$ = −1.45 (c = 1.10, $CHCl_3$). IR: 3480*s*, 3280*s*, 3020*w*, 3000*m*, 2930*s*, 2860*m*, 1655*s*, 1600*m*, 1525*m*, 1410*m*, 1330*s*, 1305*w*, 1290*w*, 1160*s*, 1090*s*, 1020*w*, 950*w*. ^{1}H-NMR ($CDCl_3$): 7.76–7.72 (2*d*, 4 H); 7.31–7.28 (2*d*, 4 H); 6.17 (br. *t*, 1 H); 5.86 (*d*, J = 8.2, 1 H); 5.31–5.24 (*m*, 2 H); 5.11–5.07 (*m*, 1 H); 3.55–3.42 (*m*, 1 H); 3.25–3.10 (*m*, 2 H); 2.97–2.88 (*m*, 2 H); 2.42 (*s*, 3 H); 2.41 (*s*, 3 H); 2.28 (*dd*, J = 14.6, 4.8, 2 H); 1.95–1.79 (*m*, 4 H); 1.58–1.50 (*m*, 4 H); 1.45–1.35 (*m*, 2 H); 1.28–1.08 (*m*, 2 H); 0.90 (*t*, J = 7.5, 3 H). ^{13}C-NMR ($CDCl_3$): 170.9 (*s*); 143.4 (*s*); 143.3 (*s*); 138.1 (*s*); 136.8 (*s*); 132.1 (*d*); 129.7 (*d*); 129.6 (*d*); 128.3 (*d*); 127.1 (2*d*); 51.7 (*d*); 42.9 (*t*); 40.5 (*t*); 38.8 (*t*); 34.2 (*t*); 26.8 (*t*); 26.5 (*t*); 26.4 (*t*); 25.8 (*t*); 21.5 (2*q*); 20.5 (*t*); 14.3 (*q*). ESI-MS: 586 (100, $[M + Na]^+$), 564 (19, $[M + H]^+$).

*(+)-(4*R*)-4-[(4Z)-Hept-4-enyl]-5,9-bis[(4-methylphenyl)-sulfonyl]-1,5,9-triazacyclotridecan-2-one* (**14**). A mixture of **12** (1.0 g, 1.0 equiv., 1.77 mmol) and Cs_2CO_3 (1.27 g, 2.2 equiv., 3.90 mmol) in DMF (20 ml) was

[3]) Due to signal overlap, two CH_2 signals are not reported.

stirred at 65° for 5 min; then, 0.82 g (1.20 equiv., 2.12 mmol) of propane-1,3-diol bis(4-methylbenzenesulfonate] (**13**)[4]) were introduced, and the mixture was stirred at 65° for 24 h. Finally, the DMF was evaporated. The residue was dissolved in H_2O and extracted with CH_2Cl_2. Evaporation and purification of the crude product by CC (SiO_2, AcOEt/hexane 2:1) gave 0.83 g (78%) of **14**. Colorless oil, which was crystallized for X-ray analysis from EtOH. M.p. 141–142° (EtOH). $[\alpha]_D = +10.0$ ($c = 2.0$, $CHCl_3$). IR: 3540(br.), 3440*m*, 3380*m*, 3020*w*, 3000*m*, 2930*s*, 2860*s*, 1660*s*, 1600*m*, 1520*m*, 1490*w*, 1455*m*, 1400*w*, 1330*s*, 1300*s*, 1290*m*, 1150*s*, 1090*m*, 1020*w*, 950*w*, 910*m*, 810*m*. ^{1}H-NMR ($CDCl_3$, 310 K): 7.72–7.62 (2 *d*, 4 H); 7.30–7.24 (2 *d*, 4 H); 6.28 (br. *t*, 1 H); 5.34–5.22 (*m*, 1 H); 5.20–4.98 (*m*, 1 H); 3.80–3.55 (*m*, 3 H); 3.30–2.90 (*m*, 6 H); 2.45–2.30 (2*s*, *dd*, 7 H); 2.00–1.10 (*m*, 15 H); 0.90 (*t*, $J = 7.5$, 3 H). ^{13}C-NMR ($CDCl_3$, 310 K): 170.9 (*s*); 143.6 (*s*); 142.9 (*s*); 138.3 (*s*); 136.5 (*s*); 132.2 (*d*); 129.6 (*d*); 129.5 (*d*); 127.8 (*d*); 127.5 (*d*); 127.2 (*d*); 60.2 (*d*); 47.5 (*t*); 44.6 (*t*); 41.4 (*t*); 37.8 (*t*); 31.4 (*t*); 29.7 (*t*); 26.5 (2*t*); 25.6 (*t*); 25.0 (*t*); 23.1 (*t*); 21.4 (2*q*); 20.4 (*t*); 14.2 (*q*). CI-MS: 604 (100, $[M+H]^+$), 448 (8, $[M - C_7H_7SO_2]^+$).

*(4*S*)-[(4*Z*)-4-Hept-4-enyl]-1,5,9-triazacyclotridecan-2-one* (**15**). The electrochemical detosylation of **14** (400 mg) in EtOH soln. was performed according to [13]. The reaction was carried out under Ar at 5°. After evaporation of the catholyte, the residue was dissolved in aq. K_2CO_3 soln. and extracted exhaustively with CH_2Cl_2. Evaporation of the extract yielded **15** (180 mg, 92%). Colorless oil. ^{1}H-NMR ($CDCl_3$): 8.62 (br. *t*, 1 H); 5.42–5.25 (*m*, 2 H); 3.50–3.38 (*m*, 1 H); 3.30–3.20 (*m*, 1 H); 3.15–3.05 (*m*, 1 H); 2.95–2.80 (*m*, 3 H); 2.79–2.55 (*m*, 4 H); 2.41 (*dd*, $J = 14.6$, 2.8, 1 H); 2.18 (*dd*, $J = 14.6$, 9.1; 1 H); 2.07–1.95 (*m*, 4 H); 1.80–1.30 (*m*, 11 H); 0.95 (*t*, $J = 7.5$, 3 H). ^{13}C-NMR ($CDCl_3$): 172.1 (*s*); 132.0 (*d*); 128.4 (*d*); 55.3 (*d*); 49.2 (*t*); 48.0 (*t*); 44.2 (*t*); 40.6 (*t*); 39.3 (*t*); 33.2 (*t*); 27.8 (*t*); 26.9 (*t*); 26.7 (*t*); 26.6 (*t*); 25.7 (*t*); 20.4 (*t*); 14.2 (*q*). CI-MS: 296 ($[M+H]^+$).

*(3*S*)-*N*-(4-Aminobutyl)-4-hydroxy-3-{[(4-methylphenyl)sulfonyl]amino}butanamide* (**16**). A soln. of **1** (3.0 g, 11.7 mmol), **10** (1.95 g, 22.1 mmol), and a cat. amount of $Cu(OAc)_2$ in $CHCl_3$ (30 ml) was heated under gentle reflux for 6 h. After evaporation, the residue was purified by CC (SiO_2, MeOH/25% aq. NH_3 soln. 20:1): 3.66 g (91%) of pure **16**. Colorless solid. M.p. 136–138°. IR (KBr): 3317*s*, 3260*s*, 2930*s*, 2873*m*, 1651*s*, 1611*m*, 1552*s*, 1495*w*, 1448*m*, 1431*m*, 1330*m*, 1315*s*, 1263*w*, 1237*w*, 1205*w*, 1185*w*, 1159*s*, 1090*s*, 1044*s*, 1020*m*, 975*m*, 945*w*, 911*w*, 855*m*, 819*s*. ^{1}H-NMR ((D$_6$)DMSO): 7.67 (br. *t*, 1 H); 7.72 (*d*, $J = 8.2$, 2 H); 7.29 (*d*, $J = 8.1$, 2 H); 3.53–3.43 (br. *m*, 5 H); 3.18 (*dd*, $J = 10.8$, 4.8, 2 H); 2.93–2.78 (*m*, 2 H); 2.53–2.38 (*m*, 2 H); 2.31 (*s*, 3 H); 2.21 (*dd*, $J = 14.5$, 7.2, 1 H); 1.99 (*dd*, $J = 14.5$, 6.2, 1 H); 1.35–1.13 (*m*, 4 H). ^{13}C-NMR ((D$_6$)DMSO): 169.6 (*s*); 142.3 (*s*); 139.1 (*s*); 129.5 (*d*); 126.5 (*d*); 63.0 (*t*); 52.7 (*d*); 41.2 (*t*); 38.5 (*t*); 37.6 (*t*); 30.5 (*t*); 26.5 (*t*), 21.0 (*q*). CI-MS: 344 (100, $[M+H]^+$), 189 (25, $[M - C_7H_7SO_2]^+$).

*(+)-(3*S*)-4-Hydroxy-3-{[(4-methylphenyl)sulfonyl]amino}-*N*-(4-{[(4-methylphenyl)sulfonyl]amino}butyl)butanamide* (**18**). At r.t., **16** (10.34 g, 30 mmol) was treated with TsCl (6.30 g, 33 mmol) in DMF (75 ml) in the presence of Et_3N (6.07 g, 60 mmol). After stirring for 5 h, the DMF was evaporated. The residue was dissolved in aq. NaCl soln. and extracted with AcOEt. After washing with aq. NaCl soln. and evaporation, the crude product was further purified by recrystallization from CH_2Cl_2/hexane: 12.0 g (81%) of **18**. Colorless crystalline mass. $[\alpha]_D = +5.29$ ($c = 1.02$, MeOH). IR (KBr): 3544*m*, 3331*s*, 3257*s*, 3066*w*, 2930*m*, 2867*m*, 1638*s*, 1597*w*, 1539*s*, 1495*w*, 1480*w*, 1449*m*, 1420*m*, 1385*w*, 1321*s*, 1229*w*, 1156*s*, 1091*s*, 1050*m*, 995*m*, 921*w*, 852*w*, 813*s*. ^{1}H-NMR ((D$_6$)DMSO): 7.70–7.60 (*m*, 5 H); 7.45 (*t*, $J = 5.9$, 1 H); 7.40–7.32 (2 *d*, 4 H); 4.66 (*t*, $J = 5.6$, 1 H); 3.55–3.40 (*m*, 1 H); 3.33 (*s*, 1 H); 3.35–3.15 (*m*, 2 H); 2.92–2.80 (*m*, 2 H); 2.75–2.65 (*m*, 2 H); 2.38 (*s*, 3 H); 2.36 (*s*, 3 H); 2.26 (*dd*, $J = 14.6$, 7.3, 1 H); 2.03 (*dd*, $J = 14.6$, 6.1, 1 H); 1.40–1.20 (*m*, 4 H). ^{13}C-NMR ((D$_6$)DMSO): 169.5 (*s*); 142.4 (*s*); 142.2 (*s*); 138.9 (*s*); 137.6 (*s*); 129.5 (*d*); 129.4 (*d*); 126.45 (*d*); 126.41 (*d*); 63.0 (*t*); 52.6 (*d*); 42.2 (*t*); 37.9 (*t*); 37.5 (*t*); 26.4 (*t*); 26.1 (*t*); 20.9 (2*q*). ESI-MS: 520 (42, $[M+Na]^+$), 498 (100, $[M+H]^+$), 480 (10, $[M - H_2O + H]^+$).

*(+)-(4*S*)-4-(Hydroxymethyl)-5,9-bis[(4-methylphenyl)sulfonyl]-1,5,9-triazacyclotridecan-2-one* (**20**). As described for **14**, with 0.20 g (0.40 mmol) of **18**. CC (SiO_2, CH_2Cl_2/MeOH 14:1) gave 0.19 g (90%) of **20**. Colorless foam. $[\alpha]_D = +9.72$ ($c = 1.05$, $CHCl_3$). IR: 3500–3200(br.), 3020*m*, 2940*m*, 2860*w*, 1650*s*, 1600*m*, 1530*m*, 1490*w*, 1460*m*, 1400*w*, 1330*s*, 1300*w*, 1290*w*, 1160*s*, 1090*s*, 1040*w*, 1020*w*, 950*w*. ^{1}H-NMR ($CDCl_3$): 7.73 (*d*, $J = 8.3$, 2 H); 7.64 (*d*, $J = 8.3$, 2 H); 7.32–7.22 (2*d*, 4 H); 6.65 (*t*, $J = 6.3$, 1 H); 4.00–2.80 (*m*, 13 H); 2.49 (*dd*, $J = 14.9$, 2.3, 1 H); 2.42 (*s*, 3 H); 2.39 (*s*, 3 H); 1.99–1.82 (*m*, 2 H); 1.80–1.40 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$): 171.5 (*s*); 143.8 (*s*); 143.1 (*s*); 137.6 (*s*); 135.7 (*s*); 129.4 (*d*); 129.6 (*d*); 127.3 (*d*); 127.1 (*d*); 62.5 (*t*); 60.2 (*d*); 48.4 (*t*); 46.4 (*t*); 45.5 (*t*); 38.8 (*t*); 38.1 (*t*); 30.2 (*t*); 25.0 (*t*); 23.6 (*t*); 21.4 (2*q*). CI-MS: 538 (100, $[M+H]^+$), 520 (10, $[M - H_2O + H]^+$).

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[4]) Preparation by a known procedure [11].

(3S)-N-*(3-Aminopropyl)-4-hydroxy-3-{[(4-methylphenyl)sulfonyl]amino}butanamide* (**17**). A soln. of **1** (8.48 g, 33.2 mmol) in $CHCl_3$ (100 ml) was mixed with propane-1,3-diamine (6.16 g, 7.45 ml, 83 mmol). The mixture was stirred at r.t. for 8 h. The precipitation of product **17** was brought to completion by addition of some Et_2O. Filtration and subsequent washing with Et_2O gave 10.5 g (96%) of pure **17**. Fine colorless powder. IR (KBr): 3310*m*, 3263*s*, 2930*m*, 861*m*, 1643*s*, 1557*m*, 1428*m*, 1367*w*, 1305*m*, 1253*w*, 1189*w*, 1158*s*, 1088*m*, 1051*w*, 979*m*, 860*w*, 819*m*. ^{1}H-NMR ((D_6)DMSO): 7.68 (*m*, *d*, *J* = 8.2, 3 H); 7.35 (*d*, *J* = 8.1, 2 H); 4.25–3.85 (br., 4 H); 3.55–3.40 (*m*, 1 H); 3.27 (*dd*, *J* = 10.8, 4.8, 1 H); 3.18 (*dd*, *J* = 10.8, 6.0, 1 H); 3.05–2.85 (*m*, 2 H); 2.55–2.45 (*m*, 2 H); 2.37 (*s*, 3 H); 2.27 (*dd*, *J* = 14.6, 7.3, 1 H); 2.05 (*dd*, *J* = 14.6, 6.0, 1 H); 1.50–1.35 (*m*, 2 H). ^{13}C-NMR ((D_6)DMSO): 169.4 (*s*); 142.1 (*s*); 138.9 (*s*); 129.2 (*d*); 126.3 (*d*); 62.8 (*t*); 52.5 (*d*); 38.8 (*t*); 37.4 (*t*); 36.0 (*t*); 32.6 (*t*); 20.8 (*q*). CI-MS: 330 (87, $[M+H]^+$), 189 (100, $[TsNH_2+NH_4]^+$).

(+)-(3S)-4-Hydroxy-3-{[(4-methylphenyl)sulfonyl]amino}-N-*(3-{[(4-methylphenyl)sulfonyl]amino}propyl)butanamide* (**19**). As described for **18**, with **17** (4.0 g, 12.1 mmol). CC (SiO_2, CH_2Cl_2/MeOH 10:1) gave 4.74 g (81%) of **19**. $[\alpha]_D = +3.38$ (*c* = 1.07, MeOH). IR (KBr): 3550*m*, 3287*s*, 2927*m*, 2881*m*, 1641*s*, 1598*w*, 1538*m*, 1494*w*, 1451*w*, 1427*m*, 1327*s*, 1154*s*, 1091*s*, 1039*w*, 968*w*, 907*w*, 856*w*, 836*w*, 812*m*. ^{1}H-NMR ((D_6)DMSO): 7.69–7.59 (2*d*, 4 H); 7.45–7.30 (2*d*, *m*, 5 H); 4.64 (br. *t*, 1 H); 3.50–3.40 (*m*, 1 H); 3.20–3.10 (*m*, 2 H); 3.00–2.80 (*m*, 2 H); 2.75–2.60 (*m*, 2 H); 2.36 (*s*, 3 H); 2.34 (*s*, 3 H); 2.24 (*dd*, *J* = 14.6, 7.3, 1 H); 2.01 (*dd*, *J* = 14.6, 6.1, 1 H); 1.50–1.35 (*quint.*-like *m*, 2 H)[5]). ^{13}C-NMR ((D_6)DMSO): 169.5 (*s*); 142.4 (*s*); 142.1 (*s*); 138.8 (*s*); 137.4 (*s*); 129.5 (*d*); 129.2 (*d*); 126.35 (*d*); 126.29 (*d*); 62.9 (*t*); 52.4 (*d*); 40.3 (*t*); 37.4 (*t*); 35.9 (*t*); 29.0 (*t*); 20.8 (2*q*). ESI-MS: 484 (100, $[M+H]^+$), 466 (7, $[M-H_2O+H]^+$).

(−)-(2S)-2-(Hydroxymethyl)-1,9-bis[(4-methylphenyl)sulfonyl]-1,5,9-triazacyclotridecan-4-one (**23**). Into a soln. of **19** (0.70 g, 1.45 mmol) in DMSO (15 ml), subsequently K_2CO_3 (0.80 g; 5.78 mmol) and butan-1,4-diol bis(4-methylbenzenesulfonate)[6]) (**21**; 0.87 g, 2.20 mmol) were introduced. The mixture was heated to 45° for 48 h. Afterwards, H_2O was added and the mixture extracted exhaustively with AcOEt. Washing the org. phase with sat. NaCl soln. and evaporation gave a crude product, which was purified by CC (SiO_2, AcOEt): 0.37 g (48%) of **23**. Colorless foam. $[\alpha]_D = -4.88$ (*c* = 1.02, $CHCl_3$). IR: 3500–3200(br.), 3020*m*, 2920*m*, 2860*w*, 1650*s*, 1600*m*, 1520*s*, 1490*w*, 1460*w*, 1450*m*, 1400*w*, 1330*s*, 1305*m*, 1160*s*, 1120*w*, 1090*s*, 1050*w*, 980*w*. ^{1}H-NMR ($CDCl_3$): 7.76 (*d*, *J* = 8.3, 2 H); 7.73 (*d*, *J* = 8.2, 2 H); 7.30–7.25 (2*d*, 4 H); 6.93 (*t*, *J* = 5.5, 1 H); 4.24–4.17 (*m*, 1 H); 3.65–3.00 (*m*, 11 H); 2.76 (*dd*, *J* = 15.3, 9.6, 1 H); 2.50 (*dd*, *J* = 15.2, 2.5, 1 H); 2.42 (*s*, 3 H); 2.39 (*s*, 3 H); 1.95–1.40 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$): 170.8 (*s*); 143.5 (*s*); 143.4 (*s*); 137.7 (*s*); 135.0 (*s*); 129.7 (*d*); 129.6 (*d*); 127.4 (*d*); 127.1 (*d*); 62.2 (*t*); 57.7 (*d*); 50.9 (*t*); 49.6 (*t*); 45.6 (*t*); 38.7 (*t*); 38.2 (*t*); 28.5 (*t*); 27.8 (*t*); 25.9 (*t*); 21.5 (*q*); 21.4 (*q*). ESI-MS: 538 (100, $[M+H]^+$), 520 (45, $[M-H_2O+H]^+$).

3-[(4-Aminobutyl)amino]propanenitrile (**25**). To a soln. of **10** (55.0 g, 0.623 mol) in MeOH (300 ml), acrylonitrile (16.12 g, 20 ml, 0.30 mol) was added dropwise at r.t. during 1 h. After stirring for additional 7 h, the solvent was evaporated. The residue was fractionated at *ca.* 10 mbar, yielding (after recover of the excess of **10** at *ca.* 100°) 42.4 g (84%) of **25** (at *ca.* 130°). Colorless liquid. IR: 3500–3100(br.); 2960*s*, 2850*s*, 2240*m*, 1630*m*, 1580*m*, 1465*m*, 1420*w*, 1360*w*, 1240*m*, 1120*s*, 1050*w*, 960*m*. ^{1}H-NMR ($CDCl_3$): 2.76 (*t*, *J* = 6.6, 2 H); 2.54 (*t*, *J* = 6.7, 2 H); 2.49 (*t*, *J* = 6.8, 2 H); 2.36 (*t*, *J* = 6.6, 2 H); 1.42–1.26 (*m*, 4 H); 0.97 (br., 3 H). ^{13}C-NMR ($CDCl_3$): 118.6 (*s*); 48.8 (*t*); 44.8 (*t*); 41.8 (*t*); 31.2 (*t*); 27.2 (*t*); 18.5 (*t*). CI-MS: 142 ($[M+H]^+$).

N-*(2-Cyanoethyl)-4-methyl*-N-*(4-{[(4-methylphenyl)sulfonyl]amino}butyl)benzenesulfonamide* (**26**). To a mixture of **25** (10.19 g, 72 mmol) and Et_3N (14.60 g, 20.1 ml, 144 mmol) in THF (100 ml), a soln. of TsCl (27.52 g, 144 mmol) in THF (100 ml) was added dropwise at r.t. The precipitate was filtered off and discarded. The filtrate was subsequently washed with aq. 4N NaOH (in order to hydrolyze any unreacted TsCl) and aq. NaCl soln. Evaporation gave 32.0 g (99%) of **26**. Waxy solid. IR: 3400–3200(br.), 3020*m*, 2930*m*, 2870*w*, 2225*w*, 1600*m*, 1490*m*, 1455*m*, 1410*m*, 1330*s*, 1305*m*, 1290*w*, 1185*w*, 1160*s*, 1090*s*, 1020*w*, 960*m*, 815*s*. ^{1}H-NMR ($CDCl_3$): 7.73 (*d*, *J* = 8.3, 2 H); 7.67 (*d*, *J* = 8.3, 2 H); 7.33–7.29 (2*d*, 4 H); 4.92 (*t*, *J* = 6.0, 1 H); 3.31 (*t*, *J* = 7.0, 2 H); 3.11 (*t*, *J* = 7.1, 2 H); 2.97–2.91 (*q*-like *m*, 2 H); 2.69 (*t*, *J* = 7.0, 2 H); 2.43 (*s*, 3 H); 2.42 (*s*, 3 H); 1.70–1.45 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$): 144.0 (*s*); 143.3 (*s*); 136.8 (*s*); 135.2 (*s*); 129.9 (*d*); 129.6 (*d*); 127.2 (*d*); 126.9 (*d*); 117.7 (*s*); 49.2 (*t*); 44.6 (*t*); 42.4 (*t*); 26.2 (*t*); 25.4 (*t*); 21.40 (*q*); 21.38 (*q*); 19.0 (*t*). CI-MS: 467 (100, $[M+NH_4]^+$), 450 (10, $[M+H]^+$), 414 (36, $[M-CH_2{=}CHCN+NH_4]^+$).

N-*{3-Aminopropyl)-4-methyl*-N-*(4-{[(4-methylphenyl)sulfonyl]amino}butyl)benzenesulfonamide* (= N^5,N^{10}-*Ditosylspermidine*; **24**). A suspension of $NaBH_4$ (2.19 g, 57.8 mmol) in THF (30 ml) was treated dropwise with a soln. of CF_3COOH (6.59 g, 57.8 mmol, 4.42 ml) in THF (10 ml) at r.t. After 15 min, a soln. of **26**

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5) The signals of two exchangeable protons are not detectable in the ^{1}H-NMR spectra.

6) Preparation by a known procedure [11].

(5.2 g, 11.6 mmol) in THF (20 ml) was added dropwise, and the resulting mixture was stirred at r.t. for 2 h. Careful addition of H_2O and extraction with AcOEt gave, after separating the org. layer and evaporation, 5.15 g (98%) of **24**. Colorless oil. IR: 3480*m*, 2920*s*, 2850*s*, 1595*s*, 1450*s*, 1405*s*, 1330*s*, 1305*s*, 1290*s*, 1230*m*, 1150*s*, 1090*s*, 1035*m*, 965*m*, 880*s*, 810*s*. ^{1}H-NMR ($CDCl_3$): 7.74 (*d*, *J* = 8.2, 2 H); 7.63 (*d*, *J* = 8.2, 2 H); 7.32 – 7.25 (2*d*, 4 H); 3.12 (*t*, *J* = 7.1, 2 H); 3.03 (*t*, = 7.3, 2 H); 2.89 (*t*, = 6.5, 2 H); 2.82 (*t*, *J* = 6.9, 2 H); 2.39 (2*s*, 6 H); 1.80 – 1.68 (*m*, 2 H); 1.65 – 1.43 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$): 143.2 (*s*); 143.0 (*s*); 137.0 (*s*); 136.0 (*s*); 129.6 (*d*); 129.5 (*d*); 127.0 (*d*); 126.0 (*d*); 48.5 (*t*); 46.6 (*t*); 42.3 (*t*); 38.5 (*t*); 30.9 (*t*); 26.3 (*t*); 25.9 (*t*); 21.3 (2*q*). CI-MS: 454 ($[M+H]^+$).

*(+)-(3*S*)-4-Hydroxy-3-{[(4-methylphenyl)sulfonyl]amino}*-N-*{3-[[(4-methylphenyl)sulfonyl](4-{[(4-methylphenyl)sulfonyl]amino}butyl)amino]propyl}butanamide* (**27**). A soln. of **1** (1.20 g, 4.66 mmol) in ^{i}PrOH (45 ml) was stirred in the presence of **24** (2.12 g, 4.66 mmol) and a cat. amount of $Cu(OAc)_2$ for 4 days. After evaporation, the residue was dissolved in H_2O and extracted with AcOEt. Evaporation gave a crude product which was purified by CC (SiO_2, AcOEt), yielding 2.34 g (71%) of **27**. Yellowish waxy solid. $[\alpha]_D = +2.92$ (*c* = 1.37, MeOH). IR: 3500 – 3100(br.), 3030*m*, 2930*m*, 2870*w*, 1650*s*, 1600*m*, 1540*m*, 1490*w*, 1450*m*, 1410*m*, 1330*s*, 1300*m*, 1290*w*, 1185*w*, 1160*s*, 1090*s*, 1040*w*, 1020*w*. ^{1}H-NMR ($CDCl_3$): 7.76 (*d*, *J* = 8.2, 2 H); 7.71 (*d*, *J* = 8.3, 2 H); 7.65 (*d*, *J* = 8.3, 2 H); 7.32 – 7.22 (*m*, 6 H); 6.85 (br. *t*, 1 H); 6.21 (br. *d*, 1 H); 5.66 (*t*, *J* = 5.8, 1 H); 3.65 – 3.55 (*m*, 2 H); 3.52 – 3.42 (*m*, 1 H); 3.40 – 3.15 (*m*, 2 H); 3.11 (*t*, *J* = 6.7, 2 H); 3.02 (*t*, *J* = 7.3, 2 H); 3.95 – 3.85 (*m*, 2 H); 2.65 – 2.40 (*m*, 2 H); 2.40 (2*s*, 6 H); 2.39 (*s*, 3 H); 2.20 – 2.00 (br., 1 H); 1.83 – 1.70 (*m*, 2 H); 1.70 – 1.45 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$): 171.2 (*s*); 143.4 (*s*); 143.3 (*s*); 143.2 (*s*); 137.2 (*s*); 136.8 (*s*); 135.8 (*s*); 129.7 (2*d*); 129.6 (*d*); 127.0 (*d*); 126.95 (*d*); 126.89 (*d*); 64.0 (*t*); 52.2 (*d*); 48.8 (*t*); 46.7 (*t*); 42.4 (*t*); 38.9 (*t*); 36.8 (*t*); 28.6 (*t*); 26.3 (*t*); 25.9 (*t*); 21.4 (3*q*. ESI-MS: 747 (15, $[M+K]^+$), 731 (87, $[M+Na]^+$), 709 (100, $[M+H]^+$).

*(+)-(8*S*)-8-(Hydroxymethyl)-1,9,13-tris[(4-methylphenyl)sulfonyl]-1,5,9,13-tetraazacycloheptadecan-6-one* (**28**). As described for **14**, with DMSO at r.t. instead of DMF and **27** (0.45 g, 0.63 mmol). CC (SiO_2, CH_2Cl_2/MeOH 25 : 1) gave 0.23 g (48%) of **28**. Colorless foam. $[\alpha]_D = +17.0$ (*c* = 1.0, $CHCl_3$). IR: 3500 – 3300(br.), 3020*m*, 2930*m*, 2860*w*, 1665*s*, 1600*m*, 1530*m*, 1490*m*, 1460*m*, 1335*s*, 1300*m*, 1290*w*, 1160*s*, 1090*s*, 1020*w*. ^{1}H-NMR ($CDCl_3$): 7.76 (*d*, *J* = 8.2, 2 H); 7.67 (*d*, *J* = 8.1, 2 H); 7.60 (*d*, *J* = 8.3, 2 H); 7.34 – 7.24 (*m*, 6 H); 6.65 (br. *t*, 1 H); 4.22 – 4.12 (*m*, 1 H); 3.75 – 3.42 (*m*, 4 H); 3.32 – 2.55 (*m*, 13 H); 2.42 (2*s*, 6 H); 2.40 (*s*, 3 H); 2.00 – 1.65 (*m*, 4 H); 1.62 – 1.40 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$): 170.9 (*s*); 143.9 (*s*); 143.6 (*s*); 143.3 (*s*); 137.5 (*s*); 136.4 (*s*); 135.1 (*s*); 129.84 (*d*); 129.81 (*d*); 129.77 (*d*); 127.5 (*d*); 127.2 (*d*); 127.1 (*d*); 63.9 (*t*); 59.00 (*d*); 49.5 (*t*); 49.0 (*t*); 47.0 (2*t*); 45.2 (*t*); 37.9 (*t*); 37.2 (*t*); 30.5 (*t*); 30.0 (*t*); 25.9 (*t*); 25.8 (*t*); 21.5 (3*q*). ESI-MS: 787 (7, $[M+K]^+$), 771 (45, $[M+Na]^+$), 749 (100, $[M+H]^+$), 731 (13, $[M-H_2O+H]^+$).

*(+)-Ethyl (3*R*)-3-{[(4-Methylphenyl)sulfonyl]amino}tetradecanoate* (**31**). As described for **7**, with commercially available 1-iododecane (**29**; 2.19 g, 8.17 mmol). CC (SiO_2, AcOEt/hexane 1 : 6) gave 1.25 g (75%) of **31**. Colorless oil. $[\alpha]_D = +19.6$ (*c* = 1.10, $CHCl_3$). IR ($CHCl_3$): 2920, 2850, 1725, 1335, 1155. ^{1}H-NMR ($CDCl_3$): 7.76 (*d*, *J* = 8.3, 2 H); 7.28 (*d*, *J* = 8.4, 2 H); 5.23 (*d*, *J* = 9.1, 1 H); 4.06 (*dq*, *J* = 7.1, 2.4, 2 H); 3.60 – 3.45 (*m*, 1 H); 2.41 (*s*, 3 H); 2.40 – 2.32 (*m*, 2 H); 1.50 – 1.38 (*m*, 2 H); 1.35 – 1.05 (*m*, 21 H); 0.88 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR ($CDCl_3$): 171.2, 143.1, 138.1 (3*s*); 129.4, 126.9 (4*d*); 60.5 (*t*); 50.6 (*d*); 38.8, 34.6, 31.7, 29.5, 29.4, 29.3, 29.2, 28.9, 28.8, 25.6, 22.5 (11*t*); 21.3, 13.9, 13.8 (3*q*). CI-MS: 443 (100, $[M+NH_4]^+$); 426 (20, $[M+1]^+$).

*(+)-(3*R*)-3-{[(4-Methylphenyl)sulfonyl]amino}tetradecanoic Acid* (**33**). A soln. of **31** (1.0 g, 2.35 mmol) in aq. 3N NaOH (50 ml) and EtOH (50 ml) was stirred overnight at r.t. Then, the EtOH was evaporated and the residue extracted with AcOEt. The aq. layer was acidified with aq. 2N HCl to pH 1 and extracted with AcOEt and the extract washed with NaCl soln. and evaporated: 920 mg (98%) of **20**. Colorless powder. $[\alpha]_D = +18.3$ (*c* = 1.03, $CHCl_3$). IR ($CHCl_3$): 2920, 2850, 1710, 1305, 1150. ^{1}H-NMR ($CDCl_3$): 7.75 (*d*, *J* = 8.3, 2 H); 7.60 – 7.35 (br., 1 H); 7.29 (*d*, *J* = 8.4, 2 H); 5.45 – 5.30 (*m*, 1 H); 3.58 – 3.42 (*m*, 1 H); 2.49 (*d*, *J* = 5.2, 1 H); 2.42 (*s*, 3 H); 2.41 (*d*, *J* = 4.5, 1 H); 1.50 – 1.40 (*m*, 2 H); 1.35 – 1.00 (*m*, 18 H); 0.88 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR ($CDCl_3$): 176.2, 143.3, 137.7 (3*s*); 129.5, 126.9, 50.3 (3*d*, 5 CH); 21.4, 13.9 (2*q*); 38.6, 34.4, 31.8, 29.5, 29.4, 29.3, 29.2, 28.9, 28.8, 25.6, 22.5 (11*t*). CI-MS: 415 (100, $[M+NH_4]^+$), 398 (12, $[M+1]^+$).

*(+)-(3*R*)-3-{[(4-Methylphenyl)sulfonyl]amino}*-N-*{3-[[(4-methylphenyl)sulfonyl](4-{[(4-methylphenyl)-sulfonyl]amino}butyl)amino]propyl}tetradecanamide* (**32**). To a mixture of **33** (555 mg, 1.4 mmol), DCC (317 mg, 1.54 mmol), and DMAP (17 mg, 0.14 mmol) in CH_2Cl_2 (20 ml), a soln. of **24** (697 mg, 1.54 mmol) in CH_2Cl_2 (3 ml) was added at 5°. The mixture was stirred overnight at r.t., diluted with Et_2O, and filtered, and the filtrate washed with aq. 0.2N HCl. After separation, the org. layer was washed with NaCl soln. and evaporated. Purification by CC (SiO_2, CH_2Cl_2/MeOH 98 : 2) afforded 1.1 g (94%) of **32**. Colorless oil. $[\alpha]_D = +5.4$ (*c* = 2.06, $CHCl_3$). IR ($CHCl_3$): 2920, 2850, 1650, 1520. ^{1}H-NMR ($CDCl_3$): 7.75, 7.72, 7.64 (3*d*, *J* = 8.3, 6 H); 7.29 (3*d*, *J* = 7.5, 6 H); 6.53 (*t*, *J* = 5.9, 1 H); 5.95 (*d*, *J* = 8.0, 1 H); 5.50 (br. *t*, 1 H); 3.55 – 3.41 (*m*, 1 H); 3.33 – 3.23 (*m*, 2 H); 3.16 – 3.08 (*m*, 2 H); 3.03 (*t*, *J* = 7.3, 2 H); 2.95 – 2.85 (*q*-like *m*, 2 H); 2.41, 2.40 (2*s*, 9 H); 2.34 (*d*, *J* = 5.0, 1 H); 2.26 (*dd*, *J* = 14.6, 5.7, 1 H); 1.80 – 1.41 (*m*, 6 H); 1.40 – 1.00 (*m*, 20 H); 0.87 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR ($CDCl_3$):

170.9, 143.3, 143.0, 142.2, 138.0, 136.8, 135.8 (7*s*); 129.6, 129.5, 127.0, 126.9, 51.5 (5*d*, 13 CH); 48.8, 46.7, 42.4, 40.6, 36.4, 34.5, 31.8, 29.5, 29.4, 29.3, 29.2, 29.0, 28.6, 28.3, 26.5, 25.6, 22.5 (17*t*, 18 CH_2); 21.3, 14.0 (2*q*, 4 Me). ESI-MS: 855 (20, $[M+Na]^+$), 833 (100, $[M+1]^+$).

*(8*R*)-1,9,13-Tris[(4-methylphenyl)sulfonyl]-8-undecyl-1,5,9,13-tetraazacycloheptadecan-6-one* (**34**) *and (3*R*)-3-{[(4-Methylphenyl)sulfonyl]amino}-*N*-{3-[[(4-methylphenyl)sulfonyl](4-{[(4-methylphenyl)sulfonyl](prop-2-enyl)amino}butyl)amino]propyl}tetradecanamide* (**35**). To a suspension of **32** (1.0 g, 1.20 mmol) and Cs_2CO_3 (821 mg, 2.52 mmol) in DMF (300 ml), 1,3-dibromopropane (266 mg, 1.32 mmol) was added dropwise over *ca.* 12 h. The mixture was stirred for 20 h at r.t. After evaporation, the residue was dissolved in $CHCl_3$, the soln. washed with H_2O, dried (Na_2SO_4), and evaporated, and the residue submitted to CC (silica gel, CH_2Cl_2/MeOH 98:2): 870 mg (83%) of unseparable **34**/**35**. Colorless oil.

*(−)-(8*R*)-8-Undecyl-1,5,9,13-tetraazacycloheptadecan-6-one* (**36**) *and (−)-(3*R*)-3-Amino-*N*-(3-{[4-(prop-2-enylamino)butyl]amino}propyl)tetradecanamide* (**37**). As described for **15**, with **34**/**35**. CC (SiO_2, $CHCl_3$/MeOH/25% aq. NH_3 soln. 15:4:1) yielded 152 mg (47%) of **36** and 132 mg (41%) of **37**, both as colorless oils.

Data for **36**: $[\alpha]_D = -14.2$ ($c = 1.15$, $CHCl_3$). IR: 2920, 2850, 1640, 1520. ^{1}H-NMR ($CDCl_3$): 8.48 (br. *t*, 1 H); 3.49–3.22 (*m*, 2 H); 2.90–2.80 (*m*, 1 H); 2.80–2.60 (*m*, 10 H); 2.36 (*dd*, $J = 15.3$, 3.4, 1 H); 2.14 (*dd*, $J = 15.3$, 7.7, 1 H); 1.99 (br. *s*, 3 H); 1.75–1.40 (*m*, 8 H); 1.35–1.20 (*m*, 20 H); 0.88 (*t*, $J = 7.0$, 3 H). ^{13}C-NMR ($CDCl_3$): 172.3 (*s*); 55.6 (*d*); 48.6, 48.3, 48.2, 47.6, 45.9, 40.4, 37.8, 34.1, 31.9, 29.7, 29.6, 29.3, 29.0, 26.8, 25.9, 22.6 (16*t*, 21 CH_2); 14.1 (*q*). ESI-MS: 411 ($[M+1]^+$).

Data for **37**. IR: 2920, 2850, 1640, 1520. ^{1}H-NMR ($CDCl_3$): 7.74 (br. *s*, 1 H); 5.88 (*ddt*, $J = 17.1$, 10.2, 6.0, 1 H); 5.18 (*ddt*, $J = 17.1$, 1.6, 1 H); 5.08 (*ddt*, $J = 10.2$, 1.6, 1 H); 3.32 (*q*, $J = 6.1$, 2 H); 3.25 (*ddd*, $J = 6.0$, 1.3, 2 H); 3.11–3.09 (*m*, 1 H); 2.69 (*t*, $J = 6.5$, 2 H); 2.65–2.60 (*m*, 4 H); 2.31 (*dd*, $J = 15.0$, 3.3, 1 H); 2.06 (*dd*, $J = 15.0$, 9.2, 1 H); 1.84 (br. *s*, 4 H); 1.69 (*quint.*-like *m*, 2 H); 1.57–1.52 (*m*, 4 H); 1.32–1.20 (*m*, 20 H); 0.88 (*t*, $J = 6.5$, 3 H). ^{13}C-NMR ($CDCl_3$): 172.0 (*s*); 136.5 (*d*); 115.8, 52.2 (2*t*); 48.7 (*d*); 49.5, 48.9, 47.6, 43.7, 38.3, 37.7, 31.7, 29.4, 29.2, 29.0, 27.7, 27.6, 25.9, 22.5 (14*t*, 18 CH_2); 13.9 (*q*). ESI-MS: 41 ($[M+1]^+$).

*(−)-(8*R*)-1,9,13-Trimethyl-8-undecyl-1,5,9,13-tetraazacycloheptadecan-6-one* (*=(−)-(*R*)-Budmunchiamine A*; **3**). To a stirred soln. of **36** (41 mg, 0.1 mmol) in AcOH (5 ml) at 0°, 37% formalin (1.5 ml) was added, and stirring was continued for 7 min. Then $NaCNBH_3$ (124 mg, 2 mmol) in MeOH (0.5 ml) was added and stirred overnight at r.t. The mixture was quenched with aq. 2N HCl and evaporated, the residue taken up in sat. aq. K_2CO_3, the mixture extracted with CH_2Cl_2, the org. phase dried (Na_2SO_4) and evaporated, and the residue purified by CC (SiO_2, $CHCl_3$/MeOH/25% aq. NH_3 soln. 90:10:0.7): 40 mg (88%) of **3**. Colorless oil. $[\alpha]_D = -16.3$ ($c = 1.01$, $CHCl_3$). IR: 3420, 2920, 2850, 2800, 1640, 1520. ^{1}H-NMR ($CDCl_3$): 8.42 (br. *t*, 1 H); 3.37 (*dt*, $J = 6.7$, 6.3, 2 H); 2.92–2.80 (*m*, 1 H); 2.64 (*dt*, $J = 12.0$, 7.0, 1 H); 2.50–2.23 (*m*, 14 H); 2.22 (*s*, 3 H); 2.21 (*s*, 3 H); 1.71–1.60 (*m*, 4 H); 1.56–1.52 (*m*, 4 H); 1.30–1.25 (*m*, 20 H); 0.88 (*t*, $J = 7.0$, 3 H). ^{13}C-NMR ($CDCl_3$): 172.6 (*s*); 61.2 (*d*); 56.4, 56.1, 55.5, 54.3, 51.3 (5*t*, 6 CH_2); 42.4, 42.1 (2*q*); 37.2, 37.4 (2*t*, 4 CH_2); 35.3 (*q*); 31.7, 29.7, 29.4, 29.1, 27.4, 27.3, 27.1, 25.2, 24.3, 23.2, 22.5 (11*t*); 13.9 (*q*). ESI-MS: 453 ($[M+1]^+$).

*Ethyl (+)-(3*S*)-3-[[(4-Methylphenyl)sulfonyl]amino}-4-(octylthio)butanoate* (**39**). To a soln. of KOH (0.41 g, 7.3 mmol) and octane-1-thiol (1.07 g, 1.27 ml, 7.3 mmol) in EtOH (15 ml) a soln. of **2** (2.0 g, 4.9 mmol) in EtOH (15 ml) was added slowly and dropwise at r.t. Then, the mixture was evaporated and the product separated by CC (hexane/AcOEt 4:1): 1.86 g (895) of **39**. Colorless oil. $[\alpha]_D = +9.50$ ($c = 1.00$, $CHCl_3$). IR: 3330*m*, 3020*w*, 2980*w*, 2950*m*, 2920*s*, 2850*m*, 1720*s*, 1600*m*, 1410*m*, 1375*m*, 1335*m*, 1300*m*, 1180*w*, 1160*s*, 1090*m*, 1060*w*, 1025*m*, 960*m*, 875*w*. ^{1}H-NMR ($CDCl_3$): 7.76 (*d*, $J = 8.3$, 2 H); 7.30 (*d*, $J = 7.9$, 2 H); 5.36 (*d*, $J = 7.8$, 1 H); 4.13–4.01 (*m*, 2 H); 3.68–3.60 (*m*, 1 H); 2.77 (*dd*, $J = 4.9$, 16.5, 1 H); 2.63 (*d*, $J = 4.9$, 2 H); 2.51 (*dd*, $J = 6.3$, 16.5, 1 H); 2.43 (*s*, 3 H); 2.33–2.24 (*m*, 2 H); 1.46–1.39 (*m*, 2 H); 1.33–1.19 (*m*, *t*, $J = 7.1$, 13 H); 0.89 (*t*, $J = 7.0$, 3 H). ^{13}C-NMR ($CDCl_3$): 170.9 (*s*); 143.4 (*s*); 137.4 (*s*); 129.6 (*d*); 127.1 (*d*); 60.7 (*t*); 49.8 (*d*); 37.4 (*t*); 36.2 (*t*); 32.3 (*t*); 31.7 (*t*); 29.3 (*t*); 29.0 (2*t*); 28.7 (*t*); 22.5 (*t*); 21.4 (*q*); 14.0 (2*q*). ESI-MS: 452 ($[M+Na]^+$).

*(+)-(3*S*)-*N*-(4-Aminobutyl)-3-[[(4-methylphenyl)sulfonyl]amino}4-(octylthio)butanamide* (**40**). As described for **11**, with **39** (1.86 g, 4.4 mmol): 2.03 g (quant.) of **40**. Colorless oil. $[\alpha]_D = +7.98$ ($c = 1.10$, MeOH). IR: 3500–3100(br.), 3440*m*, 3020*w*, 3000*m*, 2930*m*, 2860*s*, 1660*s*, 1600*w*, 1525*m*, 1470*m*, 1405*m*, 1380*w*, 1330*m*, 1305*w*, 1290*w*, 1220*w*, 1185*w*, 1160*s*, 1120*w*, 1095*s*, 1020*w*, 960*m*, 880*m*. ^{1}H-NMR ($CDCl_3$): 7.76 (*d*, $J = 8.3$, 2 H); 7.30 (*d*, $J = 8.0$, 2 H); 6.65 (br. *t*, 1 H); 3.58–3.50 (*m*, 1 H); 3.23–3.17 (*m*, 2 H); 2.80–2.44 (*m*, 8 H); 2.42–2.37 (*m*, *s*, 4 H); 2.32–2.20 (*m*, 2 H); 1.57–1.35 (*m*, 6 H); 1.33–1.20 (*m*, 10 H); 0.89 (*t*, $J = 7.0$, 3 H). ^{13}C-NMR ($CDCl_3$): 170.1 (*s*); 143.3 (*s*); 137.4 (*s*); 129.6 (*d*); 127.1 (*d*); 50.5 (*d*); 41.3 (*t*); 39.1 (*t*); 38.5 (*t*); 36.2 (*t*); 32.1 (*t*); 31.7 (*t*); 30.3 (*t*); 29.4 (*t*); 29.0 (2*t*); 28.7 (*t*); 26.66 (*t*); 22.5 (*t*); 21.4 (*q*); 13.9 (*q*). ESI-MS: 494 (18, $[M+Na]^+$), 472 (100, $[M+H]^+$).

*(+)-(3*S*)-3-[[(4-Methylphenyl)sulfonyl]amino}-*N*-(4-{[(4-methylphenyl)sulfonyl]amino}butyl)-4-(octylthio)butanamide* (**41**). As described for **12**, with **40** (0.88 g, 1.87 mmol): 1.17 g (quant.) of **41**. Colorless oil, which

slowly solidified. $[\alpha]_D = +5.22$ ($c = 1.48$, $CHCl_3$). IR: 3480–3100(br.), 2990*w*, 2920*s*, 2860*m*, 1660*s*, 1600*m*, 1520*m*, 1410*m*, 1330*s*, 1300*m*, 1290*w*, 1160*s*, 1120*w*, 1090*s*, 1020*w*, 950*w*. ^{1}H-NMR ($CDCl_3$): 7.78–7.73 (*t*-like *m*, 4 H); 7.30–7.28 (*d*-like *m*, 4 H); 6.27 (br. *t*, 1 H); 6.05 (br. *d*, 1 H); 5.37 (br. *t*, 1 H); 3.60–3.50 (*m*, 1 H); 3.20–3.10 (*m*, 2 H); 2.95–2.85 (*m*, 2 H); 2.65–2.45 (*m*, 4 H); 2.41 (*s*, 6 H); 2.26–2.15 (*m*, 2 H); 1.55–1.45 (*m*, 4 H); 1.43–1.32 (*m*, 2 H); 1.30–1.20 (*m*, 10 H); 0.88 (*t*, $J = 6.4$, 3 H). ^{13}C-NMR ($CDCl_3$): 170.3 (*s*); 143.4 (*s*); 143.2 (*s*); 137.3 (*s*); 136.7 (*s*); 129.6 (2*d*); 127.1 (*d*); 127.0 (*d*); 50.6 (*d*); 42.7 (*t*); 39.0 (*t*); 38.7 (*t*); 36.3 (*t*); 32.1 (*t*); 31.7 (*t*); 29.3 (*t*); 29.05 (2*t*); 28.7 (*t*); 26.6 (*t*); 26.2 (*t*); 22.5 (*t*); 21.4 (2*q*); 14.0 (*q*). ESI-MS: 648 ($[M+Na]^+$).

*(+)-(4*S*)-5,9-Bis[(4-methylphenyl)sulfonyl]4-[(octylthio)methyl]-1,5,9-triazacyclotridecan-2-one* (**42**). As described for **14**, with **41** (1.12 g, 1.79 mmol). CC (SiO_2, CH_2Cl_2/MeOH 9:1) gave 0.97 g (81%) of **42**. Yellowish oil. $[\alpha]_D = +20.7$ ($c = 1.1$, $CHCl_3$). IR: 3440*w*, 3380*w*, 3020*w*, 2920*s*, 2850*s*, 1660*s*, 1600*m*, 1520*m*, 1450*m*, 1330*s*, 1300*w*, 1155*s*, 1090*m*, 1035*w*, 990*w*, 950*w*, 915*w*. ^{1}H-NMR ($CDCl_3$): 7.72 (*d*, $J = 8.3$, 2 H); 7.64 (*d*, $J = 8.3$, 2 H); 7.29–7.27 (2*d*, 4 H); 6.40–6.36 (*m*, 1 H); 4.00–3.85 (*m*, 1 H); 3.72–3.58 (*m*, 1 H); 3.32–3.20 (*m*, 1 H); 3.15–2.85 (*m*, 8 H); 2.78 (*dd*, $J = 15.9$, 2.6, 1 H); 2.65–2.45 (*m*, 2 H); 2.42 (*s*, 3 H); 2.38 (*s*, 3 H); 2.35–2.28 (*m*, 1 H); 2.00–1.75 (*m*, 2 H); 1.72–1.35 (*m*, 6 H); 1.32–1.18 (*m*, 10 H); 0.88 (*t*, $J = 6.5$, 3 H). ^{13}C-NMR ($CDCl_3$): 170.7 (*s*); 143.7 (*s*); 142.9 (*s*); 137.8 (*s*); 136.2 (*s*); 129.6 (*d*); 129.5 (*d*); 127.6 (*d*); 127.0 (*d*); 59.0 (*d*); 47.5 (*t*); 46.7 (*t*); 45.7 (*t*); 44.7 (*t*); 39.6 (*t*); 37.4 (*t*); 34.2 (*t*); 32.3 (*t*); 31.6 (*t*); 29.6 (*t*); 29.3 (*t*); 29.0 (*t*); 28.7 (*t*); 25.1 (*t*); 23.0 (*t*); 22.5 (*t*); 21.3 (2*q*); 14.0 (*q*). ESI-MS: 666 ($[M+H]^+$).

*(4*S*)-5,9-Bis[(4-methylphenyl)sulfonyl]4-[(octylsulfinyl)methyl]-1,5,9-triazacyclotridecan-2-one* (**43**)[7]. A soln. of **42** (0.37 g, 0.56 mmol) in CH_2Cl_2 (20 ml) was cooled to $-45°$. Then *m*CPBA (96 mg, 0.56 mmol)[8]) was added and the temp. slowly raised to $-20°$ within 1 h. The cold mixture was quenched with aq. Na_2SO_3 soln. After addition of some aq. 2N NaOH, the mixture was extracted with CH_2Cl_2. Evaporation and CC (SiO_2, CH_2Cl_2/MeOH 20:1) gave 0.33 g (87%) of **43**. Colorless oil. IR: 3440*w*, 3390*w*, 3020*w*, 2980*m*, 2920*s*, 2860*m*, 1665*s*, 1600*m*, 1520*m*, 1450*m*, 1400*w*, 1335*s*, 1300*m*, 1290*w*, 1155*s*, 1090*m*, 1020*m*, 950*w*, 910*w*. ^{1}H-NMR ($CDCl_3$): 7.82–7.58 (*m*, 4 H); 7.35–7.20 (*m*, 4 H); 6.50–6.25 (*m*, 1 H); 4.60–4.25 (*m*, 1 H); 3.70–2.48 (*m*, 14 H); 2.45–2.35 (*m*, 6 H); 2.15–1.15 (*m*, 18 H); 0.88 (*t*, $J = 5.4$, 3 H). ESI-MS: 720 (38, $[M+K]^+$), 704 (100, $[M+Na]^+$), 682 (13, $[M+H]^+$).

*(−)-(4*S*)-5,9-Bis[(4-methylphenyl)sulfonyl]-4-[(octylsulfonyl)methyl]-1,5,9-triazacyclotridecan-2-one* (**44**). To a soln. of **42** (0.50 g, 0.75 mmol) in CH_2Cl_2 (20 ml) at r.t., *m*CPBA (0.32 g, 1.88 mmol) was added in one portion. After stirring for 4 h, the mixture was poured in aq. 2N NaOH and extracted with CH_2Cl_2. Evaporation and CC (SiO_2, CH_2Cl_2/MeOH 25:1) yielded 0.49 g (94%) of **44**. Colorless foam. $[\alpha]_D = -5.7$ ($c = 1.05$, $CHCl_3$). IR: 3540*w*, 3440*w*, 3380*m*, 3020*w*, 2920*s*, 2860*s*, 1665*s*, 1600*m*, 1520*m*, 1460*m*, 1400*w*, 1330*s*, 1155*s*, 1130*s*, 1090*s*, 1035*w*, 1020*w*, 950*w*, 910*w*. ^{1}H-NMR ($CDCl_3$): 7.78 (*d*, $J = 8.3$, 2 H); 7.61 (*d*, $J = 8.3$, 2 H); 7.30–7.22 (2*d*, 4 H); 6.48 (br. *t*, 1 H); 4.70–4.55 (*m*, 1 H); 3.80–3.65 (*m*, 1 H); 3.40–2.70 (*m*, 13 H); 2.42 (*s*, 3 H); 2.35 (*s*, 3 H); 2.05–1.85 (*m*, 2 H); 1.80–1.42 (*m*, 6 H); 1.40–1.20 (*m*, 10 H); 0.88 (*t*, $J = 6.5$, 3 H). ^{13}C-NMR ($CDCl_3$): 169.7 (*s*); 144.1 (*s*); 143.2 (*s*); 136.3 (*s*); 135.6 (*s*); 129.7 (*d*); 129.6 (*d*); 128.0 (*d*); 127.0 (*d*); 54.2 (*t*); 53.8 (*t*); 51.6 (*d*); 48.9 (*t*); 46.0 (*t*); 43.8 (*t*); 40.9 (*t*); 37.4 (*t*); 31.5 (*t*); 30.6 (*t*); 28.9 (*t*); 28.8 (*t*); 28.2 (*t*); 25.6 (*t*); 24.1 (*t*); 22.4 (*t*); 21.7 (*t*); 21.4 (2*q*); 13.9 (*q*). ESI-MS: 720 (100, $[M+Na]^+$); 698 (8, $[M+H]^+$).

*(4*S*)-4-[(Octylsulfinyl)methyl]-1,5,9-triazacyclotridecan-2-one* (**45**). As described for **15**: **45** (0.50 g, 1.34 mmol). IR: 3500–3120(br.), 2990*m*, 2955*s*, 2920*s*, 2850*s*, 1640*s*, 1540*m*, 1460*m*, 1430*m*, 1375*w*, 1300*w*, 1200*m*, 1130*m*, 1020*m*, 910*m*. ^{1}H-NMR ($CDCl_3$): 9.05–8.80 (*m*, 1 H); 3.50–3.32 (*m*, 2 H); 3.25–2.50 (*m*, 12 H); 2.32–2.15 (*m*, 1 H); 2.00–1.20 (*m*, 20 H); 0.88 (*t*, $J = 6.6$, 3 H). ^{13}C-NMR ($CDCl_3$): 170.3 (*s*); 170.0 (*s*); 56.4 (*t*); 56.0 (*t*); 53.2 (*t*); 52.8 (*t*); 52.6 (*d*); 50.5 (*d*); 49.9 (*t*); 49.8 (*t*); 47.8 (*t*); 47.5 (*t*); 44.0 (*t*); 39.9 (*t*); 39.6 (*t*); 31.5 (*t*); 28.9 (*t*); 28.8 (*t*); 28.7 (*t*); 28.6 (*t*); 28.4 (*t*); 28.3 (*t*); 27.7 (*t*); 27.4 (*t*); 27.3 (*t*); 22.4 (*t*); 22.2 (*t*); 13.9 (*q*). ESI-MS: 374 ($[M+H]^+$).

*(+)-(4*S*)-4-[(Octylsulfonyl)methyl]-1,5,9-triazacyclotridecan-2-one* (**46**). Electrochemical detosylation was performed as described for **15**: **46** (0.50 g, 1.28 mmol). $[\alpha]_D = +26.19$ ($c = 1.05$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 8.8 (br. *t*, 1 H); 3.70–3.55 (*m*, 1 H); 3.50–2.70 (*m*, 13 H); 2.29 (*dd*, $J = 14.0$, 6.6, 1 H); 1.90–1.50 (*m*, 8 H); 1.50–1.20 (*m*, 12 H); 0.88 (*t*, $J = 6.6$, 3 H). ^{13}C-NMR ($CDCl_3$): 170.2 (*s*); 55.0 (*t*); 54.5 (*t*); 50.3 (*d*); 49.5 (*t*); 48.3 (*t*); 44.2 (*t*); 40.5 (*t*); 39.5 (*t*); 31.5 (*t*); 28.9 (*t*); 28.8 (*t*); 28.3 (*t*); 27.7 (*t*); 27.0 (*t*); 26.8 (*t*); 22.4 (*t*); 21.8 (*t*); 13.9 (*q*). ESI-MS: 390 ($[M+H]^+$).

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[7]) Due to the newly formed stereogenic center at the S-atom, **43** is a mixture of two diastereoisomers. This restricted the spectroscopic characterization.

[8]) Commercially available *m*CPBA normally contains up to 20% of H_2O for safety reasons; the reported amounts are calculated for *pure m*CPBA.

*(+)-(4*S*)-4-(Octylthio)methyl-1,5,9-triazacyclotridecan-2-one* (**47**). Electrochemical detosylation was performed as described for **15**: **47** (0.50 g, 1.40 mmol). $[\alpha]_D = +28.9$ ($c = 1.2$, $CHCl_3$). IR: 3214*m*, 3019*m*, 2929*s*, 2855*s*, 1638*s*, 1544*s*, 1468*m*, 1437*m*, 1377*w*, 1342*w*, 1303*w*, 1220*m*, 1130*m*, 1051*w*, 957*w*, 905*w*, 825*w*. ^{1}H-NMR ($CDCl_3$): 8.78 (br. *t*, 1 H); 3.35–3.45 (*m*, 1 H); 3.18–3.05 (*m*, 1 H); 3.02–2.92 (*m*, 1 H); 2.90–2.78 (*m*, 2 H); 2.75–2.40 (*m*, 9 H); 2.22 (*dd*, $J = 15.0$, 8.2, 1 H); 1.80–1.45 (*m*, 10 H); 1.42–1.20 (*m*, 10 H); 0.88 (*t*, $J = 6.6$, 3 H). ^{13}C-NMR ($CDCl_3$): 171.3 (*s*); 54.3 (*d*); 49.3 (*t*); 47.3 (*t*); 43.6 (*t*); 40.2 (*t*); 39.4 (*t*); 36.6 (*t*); 32.7 (*t*); 31.7 (*t*); 29.7 (*t*); 29.0 (2*t*); 28.7 (2*t*); 27.3 (*t*); 26.9 (*t*); 22.5 (*t*); 13.9 (*q*). ESI-MS: 358 ($[M+H]^+$).

X-Ray Crystal-Structure Determination of **14**[9]). The data-collection and refinement parameters are summarized in the *Table*, and a view of the molecule is shown in the *Figure*. All measurements were made on a *Rigaku AFC5R* diffractometer with graphite-monochromated MoK_α radiation (λ 0.71069 Å) and a 12-kW rotating-anode generator. The ω scan mode was employed for data collection, which included the measurement of the *Friedel* opposites of all symmetry-unique reflections. The intensities were corrected for *Lorentz* and polarization effects, and an empirical absorption correction, based on azimuthal scans of several reflections [17], was also applied. Equivalent reflections other than *Friedel* pairs were merged. The structure was solved by direct methods with SIR92 [18], which revealed the positions of all non-H-atoms. There are two symmetry-independent molecules in the asymmetric unit. The atomic coordinates of the two molecules were tested carefully for a relationship from a higher-symmetry space group with the program PLATON [19], but none could be found. The non-H-atoms were refined anisotropically. All of the H-atoms were fixed in geometrically calculated positions (d(C–H) = 0.95 Å), and each was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent atom. Refinement of the structure was carried out on F with full-matrix least-squares procedures, which minimized the function $\Sigma w(|F_o| - |F_c|)^2$. A correction for secondary extinction was applied. The absolute configuration of the molecule was determined confidently by the diffraction experiment (absolute structure parameter = –0.06(6)) [20]. Neutral-atom scattering factors for non-H-atoms were taken from *Maslen et al.* [21a], and the scattering factors for H-atoms from *Stewart et al.* [22]. Anomalous dispersion effects were included in F_c [23]; the values for f' and f'' were those of *Creagh* and *McAuley* [20b]. The values of the mass attenuation coefficients are those of *Creagh* and *Hubbel* [20c]. All calculations were performed with the teXsan crystallographic software package [24].

Table. *Crystallographic Data of* **14**

Crystallized from	EtOH	D_x [g cm^{-3}]	1.261
Empirical formula	$C_{31}H_{45}N_3O_5S_2$	μ(MoK_α) [mm^{-1}]	0.210
Formula weight [g mol^{-1}]	603.83	$2\theta_{(max)}$ [°]	55
Crystal color, habit	colorless, plate	Transmission factors (min; max)	0.686; 1.000
Crystal dimensions [mm]	0.10 × 0.65 × 0.68	Total reflections measured	16224
Temperature [K]	173 (1)	Symmetry independent reflections	14538
Crystal system	monoclinic	Reflections used ($I > 2\sigma(I)$)	8900
Space group	$P2_1$	Parameters refined	738
Z	4	Final R	0.0521
Reflections for cell determination	25	wR	0.0427
2θ range for cell determination [°]	24–37	Weights:	$[\sigma^2(F_o) + (0.005\ F_o)^2]^{-1}$
Unit-cell parameters a [Å]	11.160 (8)	Goodness-of-fit	1.639
b [Å]	9.243 (6)	Final λ_{max}/σ	0.0009
c [Å]	30.874 (4)	$\Delta\rho$ (max; min) [e Å^{-3}]	0.38; –0.36
β [°]	92.97 (3)		
V [Å^3]	3180 (3)		

[9]) Crystallographic data (excluding structure factors) for the structure of **14** have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication No. CCDC-179449. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk).

REFERENCES

[1] J. M. Pezzuto, W. Mar, L.-Z. Lin, G. A. Cordell, A. Neszmelyi, H. Wagner, *Heterocycles* **1991**, *32*, 1961.
[2] G. M. Rukunga, P. G. Waterman, *Phytochemistry* **1996**, *42*, 1211.
[3] C. W. Jefford, J. Wang, *Tetrahedron Lett*. **1993**, *34*, 1111.
[4] C. W. Jefford, J. B. Wang, Z.-H. Lu, *Tetrahedron Lett*. **1993**, *34*, 7557.
[5] C. W. Jefford, J. McNulty, *Helv. Chim. Acta* **1994**, *77*, 2142.
[6] C. W. Jefford, J. McNulty, Z.-H. Lu, J. B. Wang, *Helv. Chim. Acta* **1996**, *79*, 1203.
[7] S. C. Bergmeier, W. K. Lee, H. Rapoport, *J. Org. Chem*. **1993**, *58*, 5019.
[8] J. E. Richman, T. J. Atkins, *J. Am. Chem. Soc*. **1974**, *96*, 2268.
[9] B. K. Vriesema, J. Buter, R. M. Kellogg, *J. Org. Chem*. **1984**, *49*, 110.
[10] F. Chavez, A. D. Sherry, *J. Org. Chem*. **1989**, *54*, 2990.
[11] M. Ouchi, Y. Inoue, Y. Liu, S. Nagamune, S. Nakamura, K. Wada, T. Hakushi, *Bull. Chem. Soc. Jpn*. **1990**, *63*, 1260.
[12] A. Guggisberg, P. v. d. Broek, M. Hesse, H. Schmid, F. Schneider, K. Bernauer, *Helv. Chim. Acta* **1976**, *59*, 3013.
[13] C. Goulaouic-Dubois, A. Guggisberg, M. Hesse, *J. Org. Chem*. **1995**, *60*, 5969.
[14] C. K. Johnson, 'ORTEP II', Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.
[15] N. Umino, T. Iwakuma, N. Itoh, *Tetrahedron Lett*. **1976**, *17*, 2875.
[16] K. Popaj, M. Hesse, *Helv. Chim. Acta* **2001**, *84*, 180.
[17] A. C. T. North, D. C. Phillips, F. S. Mathews, *Acta Crystallogr., Sect. A* **1968**, 351.
[18] A. Altomare, G. Gascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr*. **1994**, 435.
[19] A. L. Spek, 'PLATON, Program for the Analysis of Molecular Geometry', University of Utrecht, The Netherlands, 2001.
[20] a) H. D. Flack, *Acta Crystallogr., Sect. A* **1983**, *39*, 876; b) G. Bernardinelli, H. D. Flack, *Acta Crystallogr., Sect. A* **1985**, *41*, 500.
[21] a) E. N. Maslen, A. G. Fox, M. A. O'Keefe, in 'International Tables for Crystallography', A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, p. 477, Table 6.1.1.1; b) D. C. Creagh, W. J. McAuley, in 'International Tables for Crystallography', A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, p. 219, Table 4.2.6.8; c) D. C. Creagh, J. H. Hubbel, in 'International Tables for Crystallography', A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, p. 200, Table 4.2.4.3.
[22] R. F. Stewart, E. R. Davidson, W. T. Simpson, *J. Chem. Phys.* **1965**, *42*, 3175.
[23] J. A. Ibers, W. C. Hamilton, *Acta Crystallogr.* **1964**, *17*, 781.
[24] 'teXsan: Single Crystal Structure Analysis Software', Version 1.10b, Molecular Structure Corporation, The Woodlands, Texas, 1999.

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