77. Anion-Receptor Molecules: Synthesis of a Chiral and Functionalized Binding Subunit, a Bicyclic Guanidinium Group Derived from L- or D-Asparagine[1])

by **Antonio Echavarren**[2]), **Amalia Galán**, **Javier de Mendoza***, and **Armando Salmerón**

Departamento de Química, Universidad Autónoma de Madrid, Cantoblanco, E-28049 Madrid

and **Jean-Marie Lehn**

Institut Le Bel, Université Louis Pasteur, 4, rue Blaise Pascal, F-67000 Strasbourg

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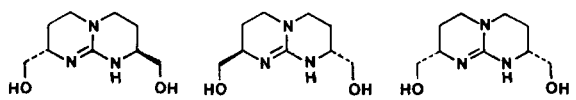
The optically active (4*S*,8*S*)-4,8-bis(hydroxymethyl)-1,5,7-triazabicyclo[4.4.0]dec-5-ene ((*S*,*S*)-**1**) has been synthesized in nine steps from L-asparagine with a total yield of 5.1%. Similarly, the enantiomer (*R*,*R*)-**1** has been prepared from D-asparagine. (*S*,*S*)- and (*R*,*R*)-**1** are representative examples of rigid and functionalized bicyclic guanidine systems and constitute useful intermediates in the construction of chiral and selective anion-receptor molecules.

Introduction. – Guanidinium units may serve as binding sites for anionic functional groups. Such is the role of the guanidinium function of arginine residues in biological receptor sites. Polyguanidinium ions act as anion complexones [1], and macrocycles containing guanidinium groups have been synthesized for anion-binding purposes [2].

In order to maintain the structure of the guanidinium groups and to enhance its binding abilities, one may incorporate it into a rigid bicyclic framework. Some natural products contain the guanidino functionality as part of a cyclic or bicyclic system. For example, the puffer fish poison tetrodotoxin [3], the paralytic shellfish poison saxitoxin [4], the peptide antibiotics capreomycin, viomycin, and tuberactinomycin [5], the antifungal agent stendomycin [6], and the *Alchornea* alkaloids alchorneine and isoalchorneine [7]. Some abiotic bicyclic amidinium [8] and guanidinium [9–12] compounds have been prepared synthetically, but none is endowed with appropriate functional groups so as to allow its subsequent introduction into macrocyclic and macropolycyclic anion-receptor molecules. This could be accomplished by means of the bicyclic guanidine targets (*S*,*S*)-, (*R*,*R*)-, and (*R*,*S*)-**1**, which can be assembled from chiral amino acids.



(*S*,*S*)-**1** (*R*,*R*)-**1** (*R*,*S*)-**1**

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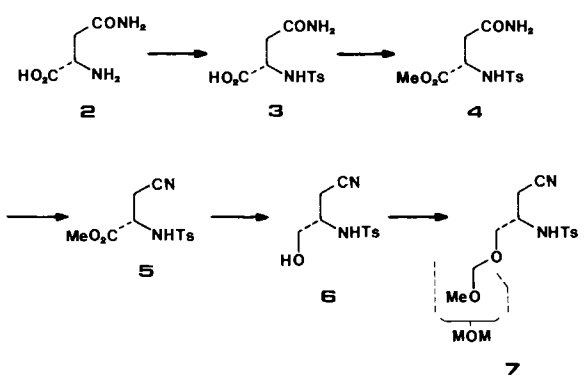
[2]) Present address: Instituto de Química Orgánica, CSIC, Juan de la Cierva, 3, E-28006 Madrid.

Moreover, the optically active subunits (*S*,*S*)- and (*R*,*R*)-**1** would be of interest for chiral recognition of substrates bearing appropriate anionic functional groups, as carboxylic acids or phosphates. We report herein the synthesis of (*S*,*S*)- and (*R*,*R*)-**1** from L- and D-asparagine, respectively. A similar methodology, combining both precursors, could be easily adapted for the preparation of the *meso*-isomer (*R*,*S*)-**1**.

Syntheses. – Despite the wide number of methods available for the preparation of guanidines [13], few can be adapted to the synthesis of bicyclic systems, and only two are of general value. One is the intramolecular *N*-alkylation of a monocyclic guanidine, reported first by *McKay et al.* [9] and recently improved by *Esser via* aminomercuriation [12]. The second, developped by *Schmidtchen,* is based on the introduction of the central guanidine C-atom in an acyclic triamine precursor. Direct reaction with methyl orthocarbonate was only achieved with an unsubstituted triamine, whereas stepwise formation of the guanidine through the corresponding thiourea (activated as a thiouronium salt) was employed with more hindered systems, containing methyl and allyl substituents adjacent to the terminal groups [11]. Owing to the symmetry axis present in our target molecules (a symmetry plane in the case of the *meso*-isomer), we selected this last strategy as the most convenient, for it allows a fully convergent synthetic entry to the system.

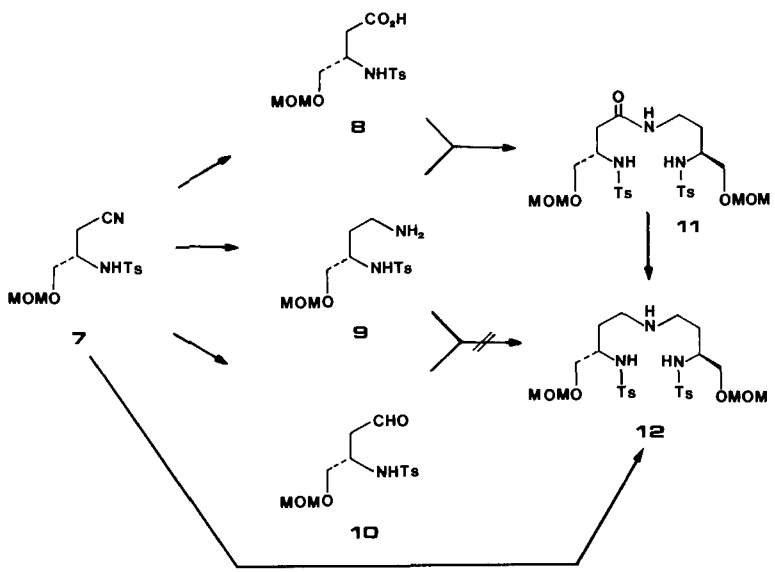
Asparagine (**2**) was selected as the choice precursor, since it contains all the atoms present in **1** but the central quaternary C-atom. Asparagine was transformed in few steps (⇉ **3**–**7**, *Scheme 1*) into the reduced and protected derivative **7** of cyanoalaninol. For the dehydration step **4**→**5**, the *Mai-Patil* method [14], based on the use of $ClCOOCCl_3$, was found superior to the reported transformation with TsCl in pyridine [15], especially for small-scale preparations, affording **5** in quantitative yield.

Scheme 1



The Ts and the methoxymethyl (MOM) group [16] were found to be the best protecting groups for the NH_2 and OH functions, respectively. Use of other protecting groups for the primary alcohol like tetrahydropyranyl or (methylthio)methyl [17] gave poorer yields in subsequent steps of the synthesis. Similarly, protection of the amine as carbamate using the (benzyloxy)carbonyl (Cbz) or (trichloroethoxy)carbonyl (Troc) [18] group was unpractical due to the partial or complete loss of the latter in the following nitrile-reduction step.

Scheme 2



Intermediate **7** was transformed quantitatively into the carboxylic acid **8** by LiOH. Similarly, amine **9** resulted in 75% yield from the reduction of **7** with $NaBH_4/CoCl_2$ [19], whereas reduction with diisobutylaluminium hydride (DIBAL) afforded aldehyde **10** in 95% yield *(Scheme 2)*. Unexpectedly, reductive condensation of (*S*)-**9** and (*S*)-**10** with $NaB(CN)H_3$ to give the secondary amine (*S,S*)-**12** was unsuccessful, as were all attempts to carry the reaction stepwise, condensing first the amine and the aldehyde to an imine intermediate. Hence, we took a somewhat longer way, *via* the amide intermediate (*S,S*)-**11**, which was obtained in 70% yield by condensation of acid (*S*)-**8** with amine (*S*)-**9** in the presence of carbonyl-diimidazole *(Scheme 2)*[3]). The amide was then successfully reduced to the amine (*S,S*)-**12** with $LiACH_4$ in THF, though in only 41% yield[4]).

At the same time, we tried also a direct route from the nitrile **7**. It is well known that catalytic hydrogenation of nitriles affords variable amounts of secondary amines. This reaction has always been considered as an undesirable side reaction, and no examples are known of its use as a synthetic tool. However, H_2 reduction of **7** using rhodium/alumina in AcOH gave a 60% yield of the desired secondary amine, in a one-pot reaction, which has been found of general use [20].

Removal of the Ts groups from (*S,S*)-**12** to give triamine (*S,S*)-**13** was easily performed by Na/NH_3 [21] in a 70% yield, and we were finally ready to introduce the last central C-atom of the guanidine target. We undertook first a stepwise approach, *via* a thiourea intermediate *(Scheme 3)*. However, both the direct formation of the thiourea

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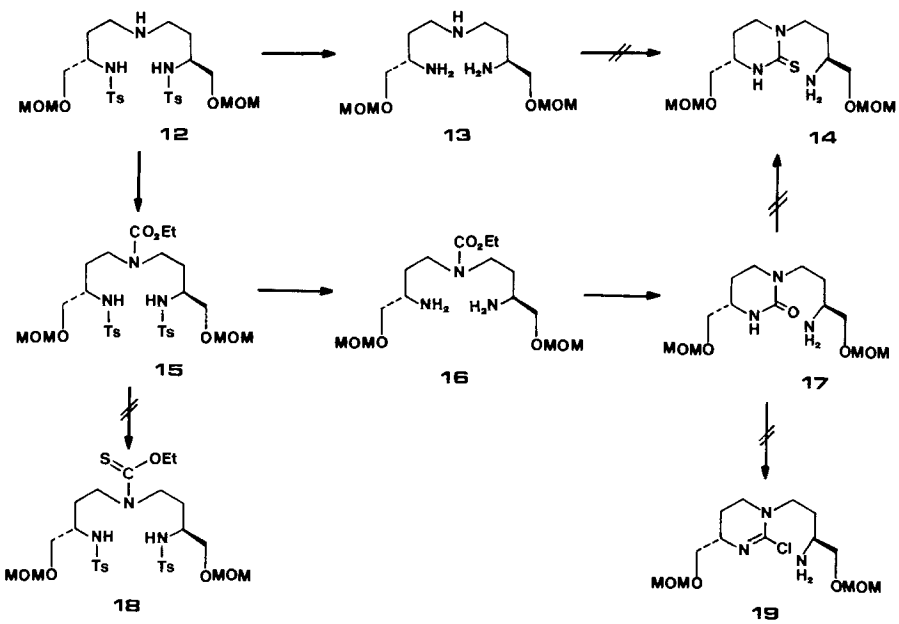
[3]) Use of 1,3-dicyclohexylcarbodiimide afforded (*S,S*)-**11** in only 53% yield.

[4]) The preparation of amide (*S,S*)-**11** and amine (*S,S*)-**12** (or their respective enantiomers of the *R* series), with two chiral centres, provided an easy way to check the optical purity of the compounds, since no splitting of any signal was observed in the ^{1}H-NMR spectra. On the contrary, repetition of the synthesis with racemic asparagine afforded **11** and **12** as a diastereoisomeric mixture with well differentiated ^{1}H-NMR signals.

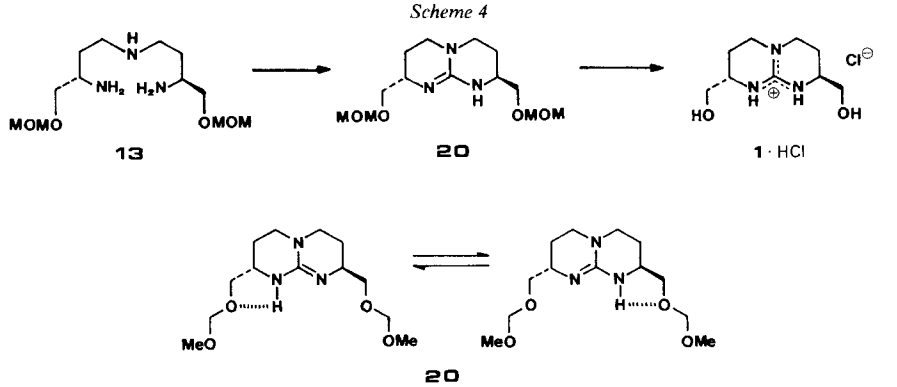
Scheme 3



(*S,S*)-**14** from (*S,S*)-**13** with thiophosgene [11] or the O/S exchange in the urea (*S,S*)-**17** (obtained from (*S,S*)-**12** *via* the carbamates **15** and **16**) by P_2S_5 treatment under sonication [22] or with the *Lawesson* reagent [23] failed. Other ways of activation as formation of the thiocarbamate (*S,S*)-**18** from carbamate (*S,S*)-**15** with P_2S_5 of the chloroimine (*S,S*)-**19** from urea (*S,S*)-**17** with $POCl_3$ were also unsuccessful.

However, use of (thiocarbonyl)diimidazole on triamine (*S,S*)-**13** afforded directly guanidine (*S,S*)-**20** in *ca.* 60% yield. Presumably, the reaction took place *via* thiourea (*S,S*)-**14** as intermediate, but no activation of this intermediate was therefore necessary to achieve cyclisation *(Scheme 4)*. This represents, to our knowledge, one of the few examples of guanidine synthesis from thioureas not requiring activation to thiouronium

Scheme 4



derivatives[5]), a fact that could be interpreted by the intramolecular character of the reaction.

A direct introduction of the guanidinium C-atom into (*S,S*)-**13** by orthocarbonate esters was an attractive alternative. Our first attempts, following literature conditions (acid catalysis, dimethyl sulfoxide) [11] were unsuccessful, but on removal of the catalyst and use of an excess of reagent, the guanidine (*S,S*)-**20** was obtained in 40% yield.

It is noteworthy that two signals of the ^{13}C-NMR spectrum of **20** in $CDCl_3$ or in DMSO are split, namely those corresponding to CH_3O and OCH_2O of the lateral chain. This could be explained by a slow tautomeric exchange of the guanidinic proton, due to chelation. Thus, the splitting is not observed in a protic solvent like CD_3OD.

The final elimination of the MOM protecting groups was performed under acidic conditions, with formation of the corresponding salt of (*S,S*)-**1** in 50% yield. Thus, we have developed a nine-step synthesis of a chiral rigid bicyclic guanidine from L-asparagine. The same sequence was also performed with the low-cost enantiomer D-asparagine.

Studies towards the construction of anion-receptor molecules by incorporation of the bicyclic subunit **1** into macropolycyclic frameworks have been undertaken.

Experimental Part

General. Most chemicals were purchased from *Aldrich Co.* and used as received without further purification. Org. solvents were purified by standard procedures. Anh. THF was distilled from benzophenone and Na under Ar, immediately prior to use. Flash chromatography (FC): silica gel *Merck* 230–400 mesh. TLC: *DC-Alufolien 60*; visualization by UV light, ninhydrin, phosphomolybdic acid, or (2,4-dinitrophenyl)hydrazine. Ion-exchange chromatography: *Amberlite CG-50(H)* (100–200 mesh) following the method described in [1]. M.p.: uncorrected. $[\alpha]_D$: *Perkin Elmer 141* polarimeter. ^{1}H- and ^{13}C-NMR spectra: *Bruker WP 200 SY* instrument. MS (*m/z* (rel. abundance)): *Hewlett-Packard 5985* and *Hitachi-Perkin-Elmer RMU-6MG* (70 eV, EI and CI modes). Elemental analyses were carried out at the Instituto de Química Orgánica General, CSIC, Madrid.

*Methyl 3-Cyano-2-[(*p*-toluenesulfonyl)amino]propionate* (**5**; Caution). In a well ventilated hood, $ClCOOCCl_3$[6]) (0.07 ml) was added dropwise to a cold (0–5°), stirred soln. of *N*-(*p*-toluenesulfonyl)asparagine methyl ester [15] (**4**; 0.100 g, 0.33 mmol) in $PO(OMe)_3$ (0.2 ml). The mixture was then slowly heated to 60° for 5 min to ensure the completion of the reaction and to eliminate any generated phosgene. To ensure the dehydration, the mixture was cooled to 10°, an additional amount (0.03 ml) of $ClCOOCCl_3$ was added, and heating was resumed for another 5 min. After cooling in an ice-water bath, the mixture was vigorously stirred and ice-water (0.5 g) added to destroy any trace of phosgene and $ClCOOCCl_3$. The resulting solid was filtered, washed with H_2O to eliminate all traces of HCl and $PO(OMe)_3$, and air-dried. Yield of **5** *ca.* 100%. M.p. 116° ([15]: 119–120°). $[\alpha]_D^{20} = -10.3$ for (*S*)-**5**, $[\alpha]_D^{20} = +11.7$ for (*R*)-**5** (*c* = 1.00, acetone).

N-*(1-Cyano-3-hydroxypropan-2-yl)*-p-*toluenesulfonamide* (**6**). Nitrile **5** (0.90 g, 3.2 mmol) was added to a soln. of $NaBH_4$ (0.85 g, 22.5 mmol) in MeOH (25 ml). The mixture was refluxed for 10 min, cooled, acidified with 1M HCl, and extracted with AcOEt (3 × 100 ml). The extract was dried (Na_2SO_4) and evaporated to give **6** (0.77 g, 90%), colorless crystals. M.p. 121°. $[\alpha]_D^{20} = +24.0$ for (*S*)-**6**, $[\alpha]_D^{20} = -25.0$ for (*R*)-**6** (*c* = 1.00, acetone). ^{1}H-NMR ($CDCl_3$): 7.78, 7.33 (*AA'BB'*, $J_{AB} = 8.2$, Ts); 5.71 (*d*, *J* = 7.7); 3.60 (*m*, CH_2CH); 2.64 (*m*, CH_2CN); 2.43 (*s*, CH_3);

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[5]) For other examples of direct guanidine formation from thioureas in the presence of a metal oxide (PbO), see [24].

[6]) $ClCOOCCl_3$ is a highly toxic reagent. Paper soaked with a soln. of 10% *p*-(dimethylamino)benzaldehyde and colorless diphenylamine in EtOH, then dried, will turn from yellow to deep orange in the presence of the maximum allowable concentration of this liquid 'diphosgene'. See the *Merck Index* for further details and precautions.

2.57 (br. *s*, OH). ^{13}C-NMR ($CDCl_3$): 144.3, 136.7, 130.0, 127.1 (arom.); 117.0 (CN); 62.6 (CH_2OH); 51.2 (CH); 21.6, 20.9 (CH_2CN, CH_3). EI-MS: 256 (3.2, $M^+ + 2$), 254 (0.8, M^+), 223 (26.5), 155 (74.2), 99 (3.3), 91 (100). Anal. calc. for $C_{11}H_{14}N_2O_3S$ (154.3): C 51.95, H 5.55, N 11.01, S 12.61; found: C 51.93, H 5.29, N 10.99, S 12.52.

*N-[1-Cyano-3-(methoxymethoxy)propan-2-yl]-*p*-toluenesulfonamide* (**7**). To a soln. of **6** (5.40 g, 21.0 mmol) in CH_2Cl_2 (60 ml) was added dimethoxymethane (80.0 ml, 0.9 mol), P_2O_5 (1.0 g), and 4 Å molecular sieves. The mixture was stirred at r.t. for 5 days and was then poured into aq. $NaHCO_3$ soln. (sat. soln. of $NaHCO_3/H_2O$ 1:1), and extracted with CH_2Cl_2 (6 × 40 ml). The extract was washed with brine, dried (Na_2SO_4), and evaporated to give **7** as an oil. FC (AcOEt/hexane 1:1 containing 1% of Et_3N) afforded pure **7** (5.50 g, 87%); oil which solidified on standing. M.p. 54°. $[\alpha]_D^{20} = +10.7$ for (*S*)-**7**, $[\alpha]_D^{20} = -12.0$ for (*R*)-**7** (*c* = 1.00, acetone). ^{1}H-NMR ($CDCl_3$): 7.77, 7.33 (*AA'BB'*, $J_{AB} = 8.3$, Ts); 5.24 (*d*, *J* = 8.1, NH); 4.55 (*s*, OCH_2O); 3.64 (*m*, CH); 3.44 (*m*, CH_2O); 3.34 (*s*, CH_3O); 2.67 (*d*, *J* = 6.0, CH_2CN); 2.44 (*s*, CH_3). ^{13}C-NMR ($CDCl_3$): 144.0, 137.2, 129.9, 127.1 (arom.); 116.4 (CN); 96.9 (OCH_2O); 67.9 (CH_2O); 55.7 (CH_3O); 49.8 (CH); 21.4 (CH_2CN, CH_3, DEPT-analyzed). EI-MS: 283 (0.2, $M^+ - CH_3$), 267 (3.9), 223 (25.5), 155 (37.2), 91 (59.6), 45 (100). Anal. calc. for $C_{13}H_{18}N_2O_4S$ (298.3): C 52.33, H 6.08, N 9.38; found: C 52.05, H 6.03, N 9.34.

*4-(Methoxymethoxy)-3-[(*p*-toluenesulfonyl)amino]butanoic Acid* (**8**). LiOH (3.70 g, 8.8 mmol) was added to a soln. of **7** (1.20 g, 4.0 mmol) in H_2O (92 ml) and EtOH (64 ml). The mixture was heated to 100° for 4 days, allowed to cool, and washed with Et_2O (2 × 30 ml). AcOEt (45 ml) was added to the resulting aq. soln., and the mixture was cooled to 0°, slowly acidified with conc. HCl soln., and finally extracted with AcOEt (5 × 40 ml). The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated to give **8** (1.27 g, 100%) as an oil which was used directly in the next step without further purification. ^{1}H-NMR ($CDCl_3$): 7.77, 7.31 (*AA'BB'*, $J_{AB} = 8.3$, Ts); 5.53 (*d*, *J* = 8.9, NH); 4.49, 4.50 (*AB*, $J_{AB} = 6.9$, OCH_2O); 3.78 (*m*, CH); 3.54 (*dd*, *J* = 10.2, 4.2, 1 H, CH_2O); 3.43 (*dd*, *J* = 10.2, 5.4, 1 H, CH_2O); 3.30 (*s*, CH_3O); 2.68 (*dd*, *J* = 18.0, 5.6, 1 H, CH_2CO_2H); 2.56 (*dd*, *J* = 18.0, 5.6, 1 H, CH_2CO_2H); 2.43 (*s*, CH_3). EI-MS: 286 (1.4, $M^+ - CH_3O$), 242 (100), 197 (1.0), 162 (3.5), 155 (72.6), 91 (68.1), 45 (30.8).

*N-[4-Amino-1-(methoxymethoxy)butan-2-yl]-*p*-toluenesulfonamide* (**9**). $CoCl_2$ (2.50 g, 10.5 mmol) and $NaBH_4$ (0.10 g, 2.6 mmol) [19] were added to a soln. of **7** (1.50 g, 5.0 mmol) in dry MeOH (95 ml). After stirring the dark mixture for 15 min at r.t., and additional amount of $NaBH_4$ (0.95 g, 24.7 mmol) was added, and stirring was continued for 30 min. H_2O (10 ml) was added, and the mixture was filtered over *Celite*. The filtrate was evaporated and the residue dissolved in AcOEt (100 ml). The org. phase was washed with 10% NH_4OH soln. until the blue color had dissappeared and with brine until neutral pH. The soln. was dried (Na_2SO_4) and evaporated to give **9** (1.14 g, 75%), colorless oil. The N^4-(*tert*-butoxy)carbonyl derivative Boc-**9**, prepared as above, was used to record the anal. data. $[\alpha]_D^{20} = -3.9$ for (*S*)-Boc-**9**, $[\alpha]_D^{20} = +4.6$ for (*R*)-Boc-**9** (*c* = 1.00, acetone). ^{1}H-NMR ($CDCl_3$): 7.77, 7.31 (*AA'BB'*, $J_{AB} = 8.3$, Ts); 5.27 (*d*, *J* = 8.8, NHTs); 4.96 (*t*, *J* = 5.6, NHBoc); 4.43, 4.40 (*AB*, $J_{AB} = 6.5$, OCH_2O); 3.25 (*s*, CH_3O); 3.50–3.00 (*m*, CH, CH_2O, CH_2NHBoc); 2.43 (*s*, CH_3); 1.80–1.60 (*m*, $CHCH_2CH_2$). EI-MS: 346 (0.9, $M^+ - C_3H_7$), 327 (4.3), 286 (1.8), 271 (79.4), 210 (49.2), 155 (67.0), 91 (100), 57 (68.1). Anal. calc. for $C_{18}H_{30}N_2O_6S$ (402.5): C 53.71, H 7.51, N 6.96, S 7.97; found: C 53.70, H 7.55, N 6.90, S 7.94.

*N-[1-Formyl-3-(methoxymethoxy)propan-2-yl]-*p*-toluenesulfonamide* (**10**). To a soln. of **7** (0.10 g, 0.3 mmol) in CH_2Cl_2 (8 ml) was slowly added DIBAL (20% in hexane; 1.30 ml, 1.3 mmol) at −78°. The mixture was stirred at −78° for 0.5 h, and then MeOH (5 ml) and H_2O (0.5 ml) were added. After 15 min, the mixture was filtered over *Celite* and the filtrate dried (Na_2SO_4) and evaporated to give **10** (0.10 g, 95%), oil. ^{1}H-NMR ($CDCl_3$): 9.65 (*t*, *J* = 1.3, CHO); 7.76, 7.31 (*AA'BB'*, $J_{AB} = 8.3$, Ts); 5.29 (*d*, *J* = 8.6, NH); 4.48 (*s*, OCH_2O); 3.90 (*m*, CH); 3.51 (*dd*, *J* = 10.2, 4.0, 1 H, CH_2O); 3.37 (*dd*, *J* = 10.2, 4.6, 1 H, CH_2O); 3.28 (*s*, CH_3O); 2.72 (*m*, CH_2CHO); 2.43 (*s*, CH_3). EI-MS: 270 (1.1, $M^+ - CH_3O$), 256 (0.8), 241 (1.4), 226 (16.0), 171 (21.3), 155 (34.4), 91 (70.0), 45 (100). Anal. calc. for $C_{13}H_{19}NO_5S$ (301.3): C 51.81, H 6.35, N 4.65, S 10.64; found: C 51.63, H 6.30, N 4.55, S 10.60.

*4-(Methoxymethoxy)-*N*-{4-(methoxymethoxy)-3-[(*p*-toluenesulfonyl)amino]butyl}-3-[(*p*-toluenesulfonyl)amino]butanamide* ((*S,S*)- and (*R,R*)-**11**). *Method A.* To a soln. of **8** (0.130 g, 0.40 mmol) in anh. CH_2Cl_2 (5 ml), maintained at 0°, was added 1,3-dicyclohexylcarbodiimide (0.092 g, 0.44 mmol), and the mixture was stirred at 0° for 10 min. A soln. of **9** (of the same configuration as **8**; 0.130 g, 0.43 mmol) in anh. CH_2Cl_2 (10 ml) was then added slowly. The mixture was allowed to reach r.t. and stirred for 4 h. The 1,3-dicyclohexylurea was filtered off and the filtrate evaporated. FC (AcOEt/hexane 2:1→AcOEt) afforded (*S,S*)- or (*R,R*)-**11** as an oil which solidified on standing (0.130 g, 53%). M.p. 85–87°. $[\alpha]_D^{20} = -3.2$ (*c* = 1.00, acetone) for (*S,S*)-**11**; $[\alpha]_D^{20} = +2.7$ (*c* = 1.00, acetone) for (*R,R*)-**11**. ^{1}H-NMR ($CDCl_3$): 7.78, 7.77, 7.31, 7.30 (*AA'BB'*, $J_{AB} = 8.3$, 2 Ts); 6.61 (*t*, *J* = 6.1, NHCO); 6.00 (*d*, *J* = 8.2, NHTs); 5.56 (*d*, *J* = 9.3, NHTs); 4.46, 4.41 (*AB*, $J_{AB} = 6.4$, OCH_2O); 4.38, 4.33 (*AB*, $J_{AB} = 6.5$, OCH_2O); 3.92–3.73 (*m*, 2 CH); 3.60–3.00 (*m*, 8 H, CH_2O, CH_2CO, CH_2NHCO); 3.26 (*s*, CH_3O); 3.22 (*s*, CH_3O); 2.43 (*s*, CH_3); 2.42 (*s*, CH_3); 1.77–1.68 (*m*, $CHCH_2CH_2$). ^{13}C-NMR ($CDCl_3$): 170.2 (CONH); 143.4, 143.1,

137.8, 129.5, 129.4, 126.8, 126.7 (arom.); 96.4 (OCH_2O); 69.4, 69.0 (CH_2); 55.2, 55.1 (CH_3O); 51.7, 50.9 (CH); 38.0, 36.1 (CH_2CONH, CH_2NHCO); 31.8 ($CHCH_2CH_2$); 21.3 (CH_3). EI-MS: 526 (7.7, $M^+ - CH_2OMOM$), 494 (44.4), 446 (5.8), 285 (49.3), 271 (82.1), 226 (28.1), 210 (41.1), 155 (85.9), 91 (100). Anal. calc. for $C_{26}H_{39}N_3O_9S_2$ (601.7): C 51.89, H 6.53, N 6.98, S 10.66; found: C 51.72, H 6.36, N 7.13, S 10.69.

Method B. To a soln. of **8** (0.84 g, 2.6 mmol) in anh. CH_2Cl_2 (8 ml) was added 1,1'-carbonyldiimidazole (0.49 g, 2.7 mmol). After CO_2 evolution had ceased, the soln. was stirred for 1 h, and then a soln. of **9** (0.84 g, 2.8 mmol) in anh. CH_2Cl_2 (15 ml) was added. The mixture was maintained for 24 h at r.t. and evaporated. Workup as in *Method A* afforded (*S,S*)- or (*R,R*)-**11** (1.12 g, 70%).

N,N'-*{4,4'-Iminobis[1-(methoxymethoxy)butan-2-yl]}bis[*p-*toluenesulfonamide]* ((*S,S*)- and (*R,R*)-**12**). *Method A.* A soln. of **11** (0.30 g, 0.5 mmol) in THF (35 ml) was added slowly to a suspension of $LiAlH_4$ (0.08 g, 2.1 mmol) in THF (10 ml), at 0° under Ar. The mixture was heated to 60° for 24 h, cooled to r.t., and H_2O (5 ml) was added slowly, followed by LiOH (0.05 g), and Na_2SO_4 (0.05 g). The mixture was filtered over *Celite*, and the filtrate was dried (Na_2SO_4) and evaporated to give crude **12** (0.18 g, 60%), pure enough to be used in the next step. An anal. sample was obtained by FC (CH_2Cl_2/MeOH 9:1), colorless oil which solidified on addition of acetone or THF/Et_2O. M.p. 139–141°. $[\alpha]_D^{20} = +42.3$ for (*S,S*)-**12**, $[\alpha]_D^{20} = -44.3$ for (*R,R*)-**12** (*c* = 1.00, MeOH). ^{1}H-NMR ($CDCl_3$): 7.79, 7.30 (*AA'BB'*, $J_{AB} = 8.3$, 2 Ts); 5.85 (br. *s*, NH, 2 NHTs); 4.42, 4.39 (*AB*, $J_{AB} = 6.5$, 2 OCH_2O); 3.50 (*m*, 2 CH); 3.40 (*dd*, *J* = 10.1, 3.6, CH_2O); 3.24 (*s*, 2 CH_3O); 3.18 (*dd*, *J* = 10.1, 5.1, CH_2O); 2.91 (*m*, CH_2NHCH_2); 2.41 (*s*, 2 CH_3); 1.90 (*m*, 2 $CHCH_2CH_2$). ^{13}C-NMR ($CDCl_3$): 143.4, 137.7, 129.7, 127.0 (arom.); 96.6 (OCH_2O); 69.4 (CH_2O); 55.4 (CH_3O); 51.8 (CH); 45.5 (CH_2NH); 29.7 ($CHCH_2CH_2$); 21.5 (CH_3). EI-MS: 556 (3.3, $M^+ - CH_3O$), 542 (4.0), 417 (19.6), 357 (12.1), 329 (31.0), 315 (100), 283 (34.6), 255 (29.5), 155 (57.3), 91 (81.6). Anal. calc. for $C_{26}H_{41}N_3O_8S_2$ (587.7): C 53.13, H 7.03, N 7.15; found: C 53.00, H 7.05, N 7.19.

Method B. To a soln. of **7** (0.50 g, 1.7 mmol) in AcOH (5 ml) was added rhodium on alumina powder (0.65 g), and the mixture was stirred for 2 days at r.t. under H_2. Filtration over *Celite* and evaporation afforded a residue which was washed with a sat. aq. $NaHCO_3$ soln. and extracted with AcOEt (4 × 10 ml). The soln. was dried (Na_2SO_4) and evaporated to give crude **12** which was purified as above: 0.30 g (61%).

4,4'-Iminobis{[1-(methoxymethoxy)butan-2-yl]amine} ((*S,S*)- and (*R,R*)-**13**). A soln. of **12** (0.177 g, 0.30 mmol) in THF (15 ml) was slowly added to Na in liq. NH_3 (60 ml). Once the addition was finished, additional Na was added during 4 h in order to maintain the blue color of the soln. Finally, NH_4Cl was added, and the NH_3 was allowed to evaporate. The solvent was evaporated and the residue treated with dil. AcOH (0.1M, 25 ml), washed with Et_2O (2 × 15 ml), and evaporated again. Solid Na_2CO_3 was added and the whole mixture extracted with CH_2Cl_2 (5 × 20 ml). The soln. was dried (Na_2SO_4) and evaporated to give almost pure **13** (0.058 g, 70%), which was directly used in the next step without further purification, colorless oil. ^{1}H-NMR ($CDCl_3$): 4.64 (br. *s*, 2 OCH_2O); 3.50–3.25 (*m*, 2 CH_2O); 3.37 (*s*, 2 CH_3); 3.06 (*m*, 2 CH); 2.75 (*t*, *J* = 7.0, 2 CH_2NH); 1.82 (br. *s*, NH, 2 NH_2); 1.72–1.36 (*m*, 2 $CHCH_2CH_2$). ^{13}C-NMR ($CDCl_3$): 96.7 (OCH_2O); 73.6 (CH_2O); 55.2 (CH_3); 55.0 (CH); 47.4 (CH_2NH); 34.1 ($CHCH_2CH_2$). EI-MS: 215 (61.8, $M^+ - 2\ NH_3 - 2\ CH_3$), 159 (16.5), 145 (41.1), 96 (23.5), 84 (74.4), 83 (100.0), 70 (45.9).

*Ethyl Bis{4-(methoxymethoxy)-3-[(*p-*toluenesulfonyl)amino]butyl}carbamate* ((*S,S*)- and (*R,R*)-**15**). To a soln. of **12** (1.0 g, 1.7 mmol) in NaOH/MeOH (1M, 22.5 ml) was added ClCOOEt (0.34 ml, 3.5 mmol). After heating the mixture for 3 h at 50°, further ClCOOEt (1.2 ml, 12.5 mmol) was added and the temp. maintained at 50° for 24 h. H_2O (20 ml) and CH_2Cl_2 (50 ml) were added, and the org. phase was washed with H_2O, dried (Na_2SO_4), and evaporated. FC of the residue (AcOEt/hexane 1:1→AcOEt) afforded **15** (0.778 g, 70%), oil. $[\alpha]_D^{20} = +5.7$ (*c* = 1.30, acetone) for (*S,S*)-**15**. ^{1}H-NMR ($CDCl_3$): 7.77, 7.30 (*AA'BB'*, $J_{AB} = 8.3$, 2 Ts); 5.35 (br. *s*, 2 NHTs); 4.44, 4.38 (*AB*, $J_{AB} = 6.5$, 2 OCH_2O); 4.10 (*q*, *J* = 7.1, OCH_2CH_3); 3.49–3.14 (*m*, 10 H, CH, CH_2O, CH_2N); 3.25 (*s*, 2 CH_3O); 2.42 (br. *s*, 2 CH_3); 1.85–1.61 (*m*, 2 $CHCH_2CH_2$); 1.23 (*t*, *J* = 7.1, CH_3CH_2O). ^{13}C-NMR ($CDCl_3$): 156.3 ($NHCO_2$); 143.4, 138.3, 129.7, 126.9 (arom.); 96.7 (OCH_2O); 69.4 (CH_2O); 61.3 (OCH_2CH_3); 55.4 (CH_3O); 51.8 (CH); 43.5 (CH_2N); 30.1 ($CHCH_2CH_2$); 21.5 (CH_3); 14.7 (CH_3CH_2O). EI-MS: 584 (3.4, $M^+ - CH_2OMOM$), 504 (1.7), 375 (58.7), 355 (64.1), 343 (79.4), 297 (100), 183 (24.5), 155 (94.2), 91 (70.1). Anal. calc. for $C_{29}H_{45}N_3O_{10}S_2$ (659.8): C 52.79, H 6.87, N 6.37; found: C 52.62, H 6.91, N 6.33.

Ethyl Bis[3-amino-4-(methoxymethoxy)butyl]carbamate ((*S,S*)- and (*R,R*)-**16**). As described above for **12**, **15** (0.58 g, 0.88 mmol) was transformed into **16** (0.235 g, 74%); oil which was directly used in the next step. ^{1}H-NMR ($CDCl_3$): 4.63 (*s*, 2 OCH_2O); 4.13 (*q*, *J* = 7.1, OCH_2CH_3); 3.81–3.13 (*m*, 6 H, CH, CH_2O); 3.35 (*s*, 2 CH_3O); 2.92 (*m*, 2 CH_2N); 1.90 (br. *s*, 2 NH_2); 1.79–1.31 (*m*, 2 $CHCH_2CH_2$); 1.27 (*t*, *J* = 7.1, CH_3CH_2O). ^{13}C-NMR ($CDCl_3$): 156.1 ($NHCO_2$); 96.3 (OCH_2O); 72.8 (CH_2O); 60.9 (OCH_2CH_3); 54.9 (CH_3O); 48.3 (CH); 43.4 (CH_2N); 32.5 ($CHCH_2CH_2$); 14.3 (CH_3CH_2). EI-MS: 303 (1.1, $M^+ - NH_3 - OCH_3$), 286 (1.0), 276 (7.2), 247 (4.5), 230 (19.7), 221 (98.4), 175 (56.1), 155 (37.8), 56 (100).

3-[3-Amino-4-(methoxymethoxy)butyl]-3,4,5,6-tetrahydro-6-[(methoxymethoxy)methyl]-2(1H)-pyrimidone ((*S,S*)- and (*R,R*)-**17**). To a soln. of **16** (0.25 g, 0.7 mmol) in H_2O (20 ml) and EtOH (12 ml) was added LiOH (0.72 g, 17.1 mmol), and the mixture was refluxed for 7 h. Additional LiOH (0.55 g, 13.1 mmol) was added and the mixture further refluxed for 24 h. After cooling, the pH was adjusted to 8 with an NH_4OH soln., and the mixture was extracted with CH_2Cl_2 (5 × 15 ml). The soln. was dried (Na_2SO_4) and evaporated to give **17** (0.16 g, 76%), oil. ^{1}H-NMR ($CDCl_3$): 5.37 (br. *s*, NHCON); 4.65 (*s*, OCH_2O); 4.63 (*s*, OCH_2O); 4.01 (br. *s*, NH_2); 3.90–2.98 (*m*, 10 H, CH, CH_2O, CH_2N); 3.35 (*s*, 2 CH_3O); 2.02–1.48 (*m*, 2 $CHCH_2CH_2$). ^{13}C-NMR ($CDCl_3$): 155.7 (NHCON); 96.2 (OCH_2O); 72.9, 70.6 (CH_2O); 54.9, 54.7 (CH_3O); 49.9, 48.0 (CH); 43.4, 43.1 (CH_2N); 31.6, 24.3 ($CHCH_2CH_2$). EI-MS: 306 (0.5, $M^+ + H$), 305 (0.4, M^+), 290 (0.8), 274 (5.4), 230 (53.8), 175 (100), 155 (35.9), 143 (28.2), 45 (33.9).

4,8-Bis[(methoxymethoxy)methyl]-1,5,7-triazabicyclo[4.4.0]dec-5-ene ((*S,S*)- and (*R,R*)-**20**). *Method A.* To a stirred soln. of **13** (0.100 g, 0.36 mmol) in anh. CH_2Cl_2 (18 ml) was added, at −40° under Ar, a soln. of 1,1′-(thiocarbonyl)diimidazole (0.077 g, 0.43 mmol) in anh. CH_2Cl_2 (22 ml). The soln. was allowed to reach r.t. and stirring was continued for 4 days. The solvent was evaporated, and imidazole was washed off with CH_2Cl_2/Et_2O 1:1 (3 × 20 ml) giving almost pure **20** (0.060 g, 58%), containing traces of imidazole. ^{1}H-NMR (CD_3OD): 4.68 (*s*, 2 OCH_2O); 3.75–3.30 (*m*, 10 H, OCH_2CH, CH_2N); 3.39 (*s*, 2 CH_3); 2.20–1.80 (*m*, 2 $CHCH_2CH_2$). ^{13}C-NMR ((D_6)DMSO): 150.6 (N=C−N); 96.0, 95.9 (OCH_2O); 69.1 (CH_2O); 54.8, 54.6 (br., CH_3O); 47.7 (CH); 44.6 (CH_2N); 22.5 ($CHCH_2CH_2$). ^{13}C-NMR (CD_3OD): 151.6; 97.9; 70.1; 55.3; 50.1; 46.4; 24.0. Compound **20** was directly used in the next step.

Method B. To a soln. of **13** (0.100 g, 0.36 mmol) in anh. DMSO (0.7 ml) was added tetramethyl orthocarbonate (0.36 ml, 2.70 mmol), and the mixture was heated for 40 h to 120°. The solvent and excess orthocarbonate were evaporated *in vacuo* in a *Kugelrohr* apparatus, the residue was crude **20** (0.041 g, 40%). ^{1}H- and ^{13}C-NMR as above.

4,8-Bis(hydroxymethyl)-1,5,7-triazabicyclo[4.4.0]dec-5-ene ((*S,S*)- and (*R,R*)-**1**). To a soln. of crude **20** (0.130 g, 0.45 mmol) in MeOH/H_2O 85:15 (20 ml) was added 12M HCl (1.0 ml). The soln. was refluxed for 8 h, the solvent evaporated, and the residue purified by ion-exchange chromatography [1] to give **1**·HCl as a hygroscopic colorless solid (0.053 g, 50%). $[\alpha]_D^{20} = +61.8$ (*c* = 1.30, H_2O) for (*S,S*)-**1**·HCl, $[\alpha]_D^{20} = -66.4$ (*c* = 1.20, H_2O) for (*R,R*)-**1**·HCl. ^{1}H-NMR (D_2O): 3.39 (*dd*, *J* = 22.1, 6.1, CH_2O); 3.35 (*dd*, *J* = 22.1, 7.3, CH_2O); 3.19 (*m*, 2 CH); 3.14 (*t*, *J* = 5.5, 2 CH_2N); 1.90–1.49 (*m*, 2 $CHCH_2CH_2$). ^{13}C-NMR (D_2O): 151.6 (N=C−N); 64.0 (CH_2OH); 50.3 (CH); 45.5 (CH_2N); 22.7 ($CHCH_2CH_2$). Anal. calc. for $C_9H_{18}N_3O_2Cl \cdot H_2O$ (253.7): C 42.60, H 7.95, N 16.56; found: C 42.78, H 7.97, N 16.20.

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