Abiotic Anion Receptor Functions. A Facile and Dependable Access to Chiral Guanidinium Anchor Groups

H. Kurzmeier and F. P. Schmidtchen*

Lehrstuhl für Org. Chemie und Biochemie der Techn. Univ., München, Lichtenbergstr. 4, D-8046 Garching, FRG

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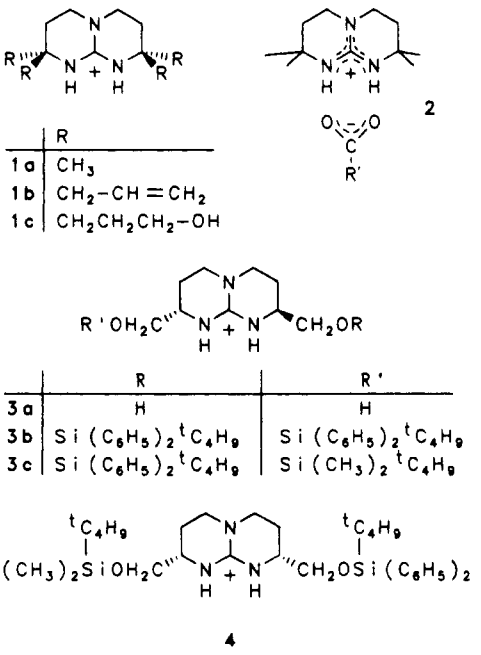
We describe the synthesis of the chiral bicyclic guanidinium salts **3** and **4**, which may be useful as anchor modules for oxoanionic functions of molecular guest species complexed by polytopic artificial receptors. Starting from the chiral amino acids asparagine and methionine a convergent strategy is followed to produce a thiourea compound **15** containing all the atoms necessary to construct the bicyclic skeleton. The key reaction is the double cyclization process of this thiourea initiated by S-alkylation. In a four-step one-pot reaction the Tos-protected bicyclic guanidines **18** are obtained, which are finally deprotected by electrolyses or aluminum amalgam reduction to give the target compounds. This route matches an older one with respect to the availability of chiral educts and the reliability of the stereochemical outcome, but is distinctly superior in terms of yield, managable scale, rapidity, and experimental ease.

Preorganization of binding functions has been recognized as the vital concept of host–guest binding to artificial receptors.[1] This notion has led to the extensive use[2] of macro(poly)cyclic frameworks which allow in principle the precise placement of binding groups in space. In our continuing effort to design synthetically more easily accessible alternatives we follow an approach in which anchor groups are linearly connected to give a polymodular chain receptor.[3] Its capability to selectively complex molecular guest species depends on strong and dedicated interactions of the structural epitopes of the guest with binding modules of the host, which have to be oriented by a folding process. A particularly promising module for binding oxoanionic functions would be the guanidinium moiety which is known to participate in anion binding in proteins.[4] Based on this principle the bicyclic guanidinium salts **1a–c** (Chart I) have been designed[5,6] as artificial anchor groups to exploit the unique and well known[7] interaction pattern of guanidines with oxoanionic functions. Theoretical studies[8] as well as experimental findings from site-directed mutagenesis, e.g. of lactate dehydrogenase,[9] attest this binding mode (e.g. **2**) an extraordinary stability. Above all, this leads to an unambiguous definition of the relative positions and orientations of host and guest ions, that are clearly observed in the respective X-ray crystal structures.[3b,6,10] To be useful as building blocks in linear polytopic receptors, the bicyclic guanidinium salts have to be supplemented with connective functions. First choice

Chart I



as target structures were the disubstituted derivatives **3** and **4**, which should meet the requirements in terms of interaction mode, chirality, and stability and hold the option for regioselective attachment of further anchor groups. Moreover, they may be prepared by chiral synthesis from readily available components of the "chiral pool". In fact, the compounds **3a** and **3b** have been synthesized by independent routes starting from L-asparagine.[11,12] Though both approaches make use of the same general strategy to construct the bicyclic skeleton, i.e. the cyclization of an open chain triamine with a C_1-synthon,[5] they differ in most steps on the way and in the final outcome. While the de Mendoza/Lehn synthesis[11] furnishes **3a** in 5–10% overall yield depending on the particular pathway, our route[12] gives the same compound in 20% yield. Moreover, in the light of the optical rotation data,[13] the former route leads to loss of the stereochemical

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(3) (a) Schmidtchen, F. P. *J. Am. Chem. Soc.* **1986**, *108*, 8249–8255. (b) Schmidtchen, F. P.; Gleich, A.; Schummer, A. *Pure Appl. Chem.* **1989**, *61*, 1535–1546. For a similar reasoning, see: (c) Rheingold, A. L.; Staley, D. L.; Iimori, T.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 3439–3440. (d) Imori, T.; Erickson, S. D.; Rheingold, A. L.; Still, W. C. *Tetrahedron Lett.* **1989**, *30*, 6947–6950.
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(12) Gleich, A.; Schmidtchen, F. P. *Chem. Ber.*, in press. Gleich, A. Dissertation, Techn. Univ. München, 1989.
(13) The specific optical rotation $[\alpha]^{20}_D$ = +61.8° (H_2O, c = 1.3) of **3a**·Cl^- is the only stereochemical feature reported.[11] This is significantly smaller than the one found by us $[\alpha]^{20}_D$ = +96.8° (H_2O, c = 0.2) for the same compound as the product of our synthesis, which was shown to be stereochemically pure (de >98%).[12]

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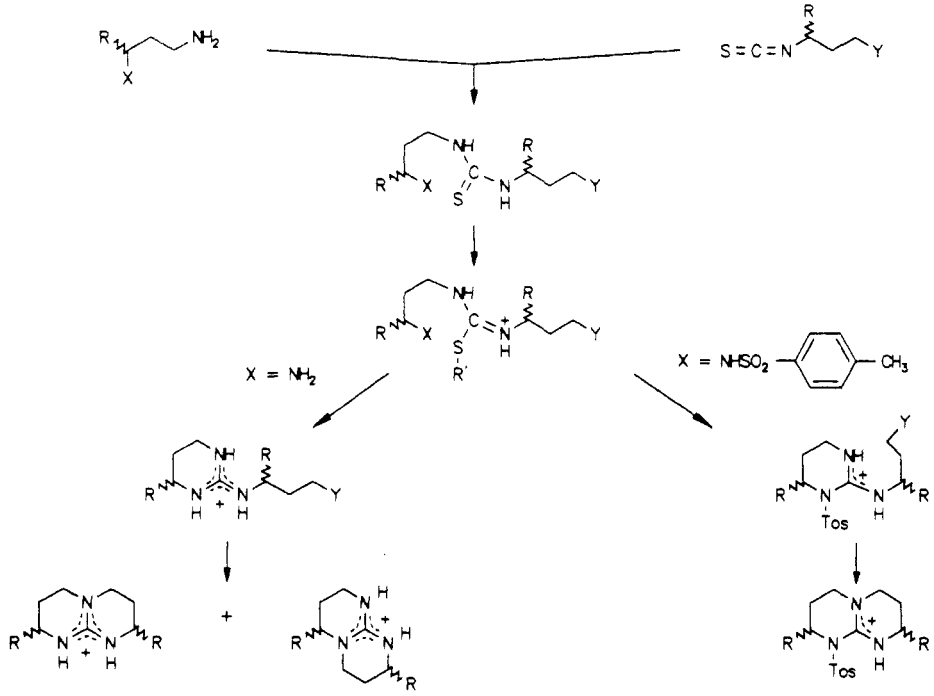
Scheme I



integrity of the product. In addition, if one includes experimental considerations (e.g. rapidity, amenability to scale up, etc.), neither of these pathways provides an easy access route to chiral bicyclic guanidinium anchor groups.

Thus, an alternative approach was very desirable which combines the attractive features of the older synthesis (availability of chiral starting materials of either configuration, optical purity of the product) with a more rapid, high yield, and experimentally easy to handle strategy. An optimal pathway has been found,[14] and we now report on the experimental details and the synthetic options which govern this approach.

Results and Discussion

Central to our considerations was the high-yield construction of the guanidinium functionality, since this step was one of the major flaws in the published approaches.[11,12] According to a literature survey[15] one of the most reliable methods is the reaction of isothiuronium salts with *N*-nucleophiles even if the nitrogen atom is part of a sulfonamide moiety[16] (Scheme I). Isothiuronium salts are easily obtained by alkylation of the parent thioureas as is well known from classic mercaptane synthesis.[17] As thioureas in turn are readily prepared by the addition of amines to isothiocyanates, the sequence thiourea, isothiuronium salt, (tosyl)guanidine was selected as the backbone of a promising high-yield strategy to build up the guanidinium moiety. Further elaboration to the bicyclic skeleton can be achieved by intramolecular N-alkylation of a suitably functionalized derivative, a route chosen by McKay and Kreling in their synthesis of the parent ring system.[18]

For this pathway to work out as planned, two components are required which contribute all carbon and nitrogen atoms of the target compounds: The amino component contains two amino groups of differential reactivity in order to introduce them stepwise in the guanidine formation. In addition, a third functional group, which itself is not involved in the chemistry of cyclization but ends up as the exocyclic substituent, renders this building block chiral. The second component is chiral as well and contains the exocyclic substituent attached to the other ring. An isothiocyanate function in γ-position to a potential leaving group are built-in features of this compound. Thus, both components are trifunctional chiral substances comprising substitution patterns that should be readily derived from natural chiral amino acids.

The convergent layout of this synthetic strategy warrants high flexibility in terms of the choice of configurations, functionalized substituents attached to the bicyclic ring system, and their covalent protection. We therefore expect this basic route to be adaptable by minor modifications to the changing demands in the construction of a variable set of polytopic molecular hosts. In the present case protected alcoholic functions occur at equivalent positions in both rings of the target compounds **3** and **4**. For the high yield transformation into polymodular hosts, the sides of the bicycle must be distinguishable which mandates their differential protection. Among the huge variety of useful hydroxy protecting groups, silyl ether functions appeared most attractive. They can be introduced and cleaved under very mild conditions,[19] yet their reactivity can be tuned to render them stable in the ring-forming processes but sufficiently labile in regioselective deprotection.[20]

Another point of general concern is the deprotection of the tosylated guanidines that are primarily obtained. Though a number of methods are available[21,22] which conduct guanidine detosylation under much milder conditions than necessary for sulfonamide cleavage, some risk

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(15) (Houben-Weyl) Methoden der Organischen Chemie, Bd. E4, p 608, Thieme, Stuttgart, 1983.
(16) Senning, A. *Acta Chim. Scand.* **1967**, *21*, 1293–1296.
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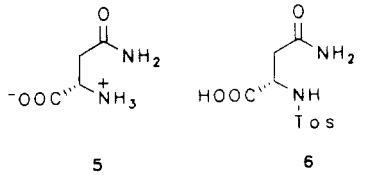
Chart II



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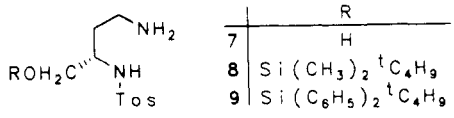
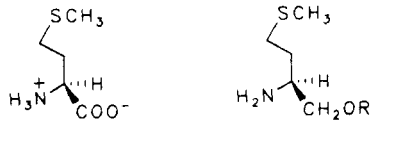
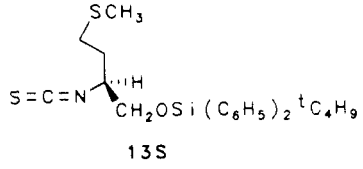


	R
7	H
8	$Si(CH_3)_2{}^tC_4H_9$
9	$Si(C_6H_5)_2{}^tC_4H_9$



10S

	R
11S	H
12S	$Si(C_6H_5)_2{}^tC_4H_9$



13S

remains as to the survival of silyl ethers. Nevertheless at this stage, we felt confident that our electrochemical reductive method, which had been useful in sulfonamide cleavage in the presence of silyl ethers,[12] should bring about this selective deprotection, too.

According to the outlined strategy, the synthesis of our target compounds required the preparation of a diamino alcohol as a partially protected derivative **7**, **8**, or **9** (Chart II). Based on the substitution pattern of this chiral C_4-skeleton, it can be derived from L-asparagine **5**. Tosylation of this natural amino acid gives the known[23] N^{α}-Tos derivative **6** in 80% yield. Reduction of both the primary carboxamide and the carboxylic acid at the same time can be achieved with borane in THF,[12] but the reaction is very sluggish due to the insolubility of the starting materials and intermediate borane complexes. Therefore an alternative procedure was highly welcome, that could convert the polar amino acid derivatives to the desired amino alcohol **7**. Using the method of Giannis and Sandhoff[24] ($LiBH_4/ClSi(CH)_3/THF$) we obtained **7** in 77% yield as a crystalline compound which was identical in every respect with the material prepared by the former method and characterized to be optically pure.[12] Two silyl ether derivatives **8** and **9** were prepared by standard silylation techniques ($ClSiR_3$, imidazole, DMF), but they were contaminated by another more hydrophobic byproduct (≈10%), so that tedious purification by extraction was required. Switching the solvent to acetonitrile or CH_2Cl_2 removed this side reaction, so that quantitative yields of the respective silyl ethers resulted.

The isothiocyanate intended as the coupling partner of the primary amino components **7** to **9** must have a moiety in γ-position that can serve as a leaving group on activation, but must remain unharmed in the presence of a strong intramolecular nucleophile like a thiourea moiety. Fortunately, the substitution pattern of natural methionine is optimally suited for our purpose. Being a chiral C_4-compound, it contains the usually very robust thioether function in the proper distance to the amino group. However, on alkylation thioethers are converted to the corresponding sulfonium salts, which will make excellent leaving groups in intramolecular nucleophilic substitutions. This scheme is exploited in the standard cyanogen bromide cleavage of proteins at Met sites. It has the extra virtue in the present case that no special activation steps are needed, since S-alkylation of the intermediate thiourea is a constitutive reaction in the sequence anyhow.

Though commercially available, economics dictated the preparation of methioninol **11** by borane reduction of the corresponding chiral methionine **10**. Silylation of this amino alcohol exclusively gave the silyl ether **12**, which was transformed into the isothiocyanate **13** by standard thiophosgene/base treatment in a two-phase mixture. By HPLC analysis, the crude material was >95% pure, so that we abandoned further purification.

The subsequent addition reactions of the amino components **7**, **8**, or **9** onto the isothiocyanate **13** were clean, but their rate was solvent dependent. The best choice involved a small excess of the amino compound in acetonitrile to assure complete conversion of the isothiocyanate. The separation of excess amine by mild extraction was easily accomplished but led to the partial removal of the silyl ether protection in **15**. To circumvent this difficulty, the addition of the unprotected amino alcohol **7** was tried. The suspected competition between the amino and the hydroxy nucleophilic moieties did not substantialize, and the desired thiourea **14** formed in quantitative yield. It was subsequently silylated to furnish the completely protected thiourea **15** (Chart III).

For the following double cyclization process, absolute dryness of solvents and equipment was essential. In particular, when conducted on a large scale, azeotropic distillation of part of the CH_2Cl_2 solvent from the reaction mixture proved satisfactory. The four-step sequence does not require the isolation of intermediates, but can conveniently be monitored by HPLC analysis. Addition of a slight excess of methyl triflate[25] converted **15** very rapidly first to the isothiuronium salt, then more slowly to the dicationic compound **16**. If methyl iodide was taken as the alkylating agent, longer reaction times were required, and methylation on both sulfur sites appeared to proceed simultaneously. This led to the formation of some side products, which interfered with the purification later on. When alkylation was complete, a huge excess of ethyldiisopropylamine was added. Gentle refluxing of this mixture caused the two-step cyclization to commence, the first ring closure being distinctly faster (ca. 5–10-fold) than the second. From an analogous pilot run the monocycle **17** was isolated as the intermediate, suggesting that the alkylation of the isothiuronium salt preceds guanidine formation. The basicity of an aliphatic tertiary amine is needed to initiate the second step, since on employing imidazole as a base the process stopped at the monocyclic stage. Higher temperatures and more polar solvents did accelerate ring formation but at the same time fostered side reactions, too. An abundant byproduct in these reactions gave spectroscopic data compatible with structure **19**. This is indicative of an intermolecular demethylation prior to guanidine ring closure. Moreover *S*- to *N*-methyl group migrations are

(23) Ressler, C. *J. Am. Chem. Soc.* **1960**, *82*, 1641–1644.
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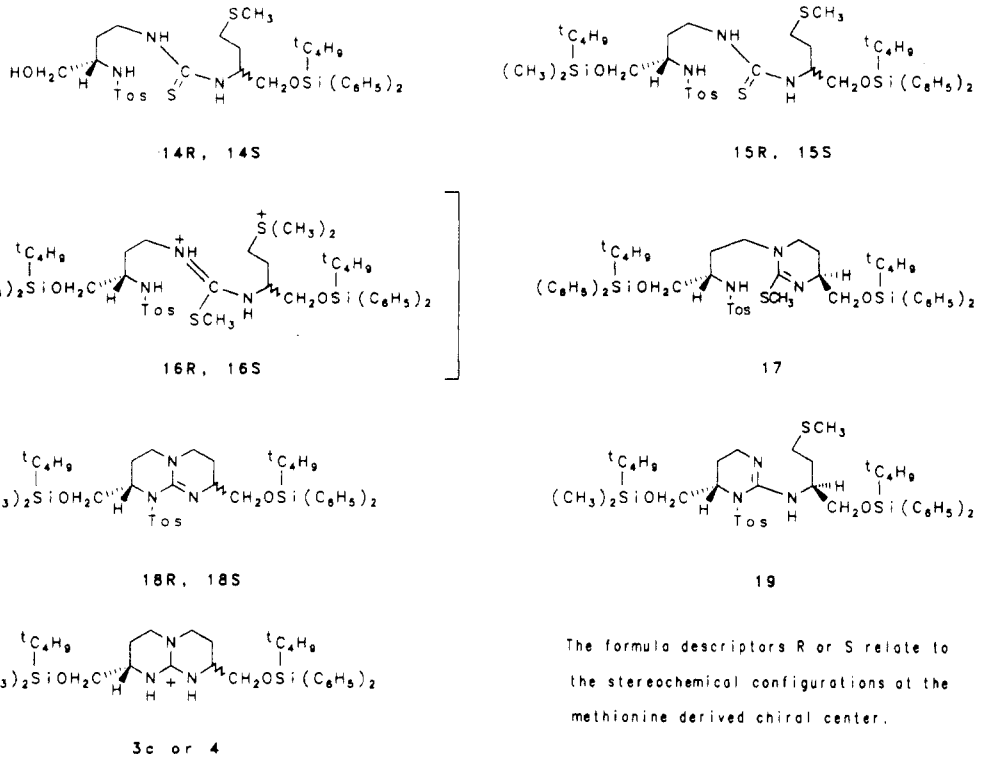
(25) The prior addition of 20 mol % ethyldiisopropylamine to neutralize any triflic acid which might be present in the reagent due to hydrolysis is advisable.

Chart III



expected to contribute to the product distribution.[26] Under our optimized conditions, the four-step one-pot cyclization sequence gives the tosylated bicyclic guanidines **18** in 87% yield. When crystalline they are fairly stable, but deteriorate rapidly to apparently ring-opened products in the presence of basic hydroxylic solvents.

Thus the final detosylation step had to take place under essentially neutral conditions, because acidic media affect the silyl protection whereas basic conditions would harm the bicycle itself. Our first choice was the electrochemical reductive detosylation conducted at a mercury cathode in buffered methanol. As in the case of sulfonamides,[12] we observed the ready cleavage of the sulfonyl–nitrogen bond of **18** provided care was taken to readjust the H^+ ion concentration by admission of acetic acid. Besides the desired target compounds **3** or **4**, respectively, toluolsulfinate was formed as the only other detectable product. Although in principle quite satisfactory, the fragile and sometimes tricky experimental conditions of electrochemical reductions made us look for some chemical means to bring about guanidine deprotection. Recently Kemp[22] demonstrated the utility of aluminum amalgam[27] as a convenient reagent to cleave the 9-anthracene sulfonylamido-protection of arginine. Following his recipe, our tosylated guanidines were cleanly deprotected under neutral conditions within a few hours. The stereochemical reliability of this new strategy to chiral guanidinium receptor functions was checked by HPLC (Nucleosil RP18, 15000 theor. plates). The compounds **3c** and **4** are diastereomeric and as such are separable by achiral chromatography.

Neither of them contained any contamination of the other, the detection limit being at 1%. We conclude that the diastereomeric excess de is >98% and, in consequence, no stereochemical scrambling at either site had happened at any stage of the entire synthesis.

This synthesis opens an easy access road to chiral guanidines characterized by cheap commercial starting material of either configuration, high overall yields (>50%), configurational reliability, rapidity, adaptability to large scale, and experimental simplicity. We consider this to be a firm basis for widespread applications of these anchor groups in molecular hosts.

Experimental Section

Tetrahydrofuran (THF) was dried and purified by distillation from benzophenone ketyl. The other solvents were bought in p.a. quality or distilled before use. Hydride reagents were analyzed by gas volumetric measurements. Reactions in organic solvents were kept under N_2 and analyzed by HPLC. Instrument: Merck-Hitachi, Model 655 A-11 pump equipped with a Model 655-66/71 low pressure gradient mixing device, a Knauer 97.00 UV detector, and a Kipp-Zonen two-channel recorder. HPLC analyses were run on 250 × 4 Nucleosil RP-18 columns using methanol/water mixtures containing 30 mM $NaClO_4$ and formic acid each. Melting points were determined on a Fisher-Jones apparatus. Elemental analyses were made by the microanalytical laboratory of the TU München. ^1H and ^{13}C NMR spectra were obtained on the Bruker instruments AM 360 or WP 200. Chemical shifts [ppm] refer to internal TMS in organic solvents or DSS in D_2O unless otherwise noted. The assignment of resonances designated with asterisk (*) may be interchanged. IR and MS spectra (EI = 70 eV) were measured on Perkin-Elmer 157G and Varian CH5 instruments, respectively. Electrolysis were conducted in homemade thermostated cells taking a mercury layer as cathode, a Pt-net anode separated from the cathode compartment by a D4 frit, and a Ag/0.1 N $AgNO_3$ in CH_3CN reference electrode connected to the cathodic compartment by a salt bridge.

(2*S*)-2-Amino-5-thiahexan-1-ol (11) (L-Methioninol). To a well-stirred suspension of 29.8 g (0.2 mol) of L-methionine in 500 mL of THF was added 40 mL (0.4 mol) of borane dimethyl sulfide complex cautiously. Stirring was continued for another hour at 25 °C followed by a reflux period of 16 h. The mixture was clear, and HPLC analysis (a sample was hydrolyzed in formic acid, 30 mM HCOOH/30 mM $NaClO_4$ in H_2O: R_v **10** = 5.4 mL, R_v 11 = 8.2 mL, RI detection) indicated complete conversion to

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(27) Keck, G. E.; Flemming, S.; Nickel, D.; Weider, P. *Synth. Commun.* **1979**, *9*, 281–286.

the amino alcohol 11. After cooling, 150 mL of 10% HCl in CH_3OH were added (caution! vigorous gas evolution!), and the mixture was refluxed for 30 min.

Evaporation of the solvent in vacuo left an oily residue, which was taken up in 100 mL of water and made basic by addition of 70 mL of 4 N NaOH. An emulsion formed which was transferred to a continuous extractor and extracted with 300 mL of ether for 16 h. The two-phase etheral extract was evaporated, and the residue refluxed with 100 mL of toluene using a Dean–Stark trap to collect the water, which was removed by azeotropic distillation. When no more water formed, the toluene solution was concentrated and distilled at 100 °C/13 Pa to give 23.0 g (0.17 mol, 85%) of a colorless oil that slowly solidified: ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 65.9 (C-1), 51.9 (C-2), 32.9 (C-4*), 31.0 (C-3*), 15.4 (C-6).

(2*S*)-2-Amino-1-[(*tert*-butyldiphenylsilyl)oxy]-5-thiahexane (12). A solution of 60.8 g (0.22 mol) of *tert*-butyldiphenylchlorosilane in 30 mL of CH_3CN was added to a solution of 23.0 g (0.17 mol) of methioninol 11 and 23 g (0.34 mol) of imidazole in 190 mL of acetonitrile under nitrogen, while the temperature was kept at 20 °C. After standing over night, the conversion to the silyl ether 12 was complete as judged by HPLC (11, H_2O, R_v = 8.2 mL; 12, 75% MeOH, R_v = 4.1 mL; *tert*-butyldiphenylsilanol, R_v = 9.5 mL). The solvent was evaporated, and the residue was distributed at 50 °C between 600 mL of 1 N NaOH and 500 mL of hexane. The aqueous phase was extracted again with 200 mL of hexane, and the combined organic phases were washed with water (3 × 200 mL).

Separation from the silanol byproduct was achieved by extraction of the hexane layer with $CH_3CN/H_2O/CH_3COOH$ = 40:60:2 vol (400 mL, 3 × 100 mL). The aqueous phase was reextracted with hexane (6 × 150 mL) to remove residual silanol, made basic by addition of 25 g anhydrous Na_2CO_3, and concentrated to half its volume in vacuo. The emulsion was taken up in ether (2 × 250 mL) followed by drying of the organic phase (Na_2SO_4). Evaporation in vacuo left an almost colorless viscous oil (63 g), which could not be distilled without deterioration: ^1H NMR (360 MHz, $CDCl_3$) δ 7.65 (m_c, 4 H, arom H), 7.40 (m_c, 6 H, arom H), 3.61 (dd, J = 9.8/4.3 Hz, 1 H, H-1), 3.46 (dd, J = 9.9/6.7 Hz, 1 H, H-1), 3.01 (m_c, 1 H, H-2), 2.52 (m_c, 2 H, H-4), 2.07 (s, 3 H, H-6), 1.70 (m_c, 1 H, H-3), 1.55 (m_c, 1 H, H-3), 1.07 (s, 9 H, *tert*-butyl); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 135.5, 133.4, 129.8, 127.9 (arom C), 68.8 (C-1), 52.0 (C-2), 33.0 (C-4*), 31.0 (C-3*), 26.9 (*tert*-butyl CH_3), 19.2 (CSi), 15.4 (C-6); the assignment is backed by a θ = 135° DEPT spectrum; MS (*m/z*, %) 373 (7.6, M^+), 316 (89, M − C_4H_9), 268 (12, 316 − CH_3SH), 238 (16, $SiC_{16}H_{18}$), 135 (35, $M^+ - SiC_{16}H_{18}$), 117 (41, $CH_3SCH_2CH_2CH(NH_2)CH$), 104 (100, $CH_3SCH_2CH_2CHNH_2$); $[\alpha]^{20}_D$ = −20.7° (*c* = 2.2, CH_3CN).

(2*S*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-5-thiahex-2-yl Isothiocyanate (13). The crude compound 12 (63 g) was dissolved in 300 mL of CH_2Cl_2. Under vigorous mechanical stirring a solution of 94 g of Na_2CO_3 in 500 mL of water and then 14.7 mL (22.2 g, 0.19 mol) of thiophosgene in 180 mL of CH_2Cl_2 were added. The mixture was stirred for another 2 h at room temperature. The layers were separated, the organic phase was washed with water (4 × 200 mL) and brine and dried (Na_2SO_4), and the solvent was evaporated in vacuo, finally at 13 Pa to leave 61.7 g of a light yellow gum, which was >95% pure by HPLC (87% based on 11): HPLC (90% methanol) R_v = 8.4 mL; $[\alpha]_D$ = −29.3 ± 1.2° ($CHCl_3$, *c* = 2.0); ^1H NMR (360 MHz, $CDCl_3$) δ 7.65 (m_c, 4 H, arom H), 7.42 (m_c, 6 H, arom H), 3.94 (m_c, 1 H, H-2), 3.71 (m_c, 2 H, H-1), 2.67–2.48 (m, 2 H, H-4), 2.08 (s, 3 H, H-6), 2.0–1.8 (m, 2 H, H-3), 1.08 (s, 9 H, *tert*-butyl CH_3); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 135.4, 132.5, 129.8, 127.7 (arom C), 135.0 (NCS*), 65.5 (C-1), 58.4 ((C-2), 31.1 (C-4*), 30.3 (C-3*), 26.6 (*tert*-butyl CH_3), 19.0 (SiC), 15.4 (C-6); IR (CCl_4) 3170, 2960, 2930, 2860, 2075 cm^{-1} (–NCS).

(2*S*)-*N*-[(4-Methylphenyl)sulfonyl]asparagine (6). A solution of 63.3 g (0.33 mol) of (4-methylphenyl)sulfonyl chloride in 150 mL of acetone was added over 5 h at 40–50 °C to a solution of 37.5 g (0.25 mol) of L-asparagine in 280 mL of 1 N NaOH, while the pH was kept at 9–10 by addition of 1 N NaOH. A small amount of precipitated sulfonyl chloride was removed by filtration, and the filtrate was concentrated to ≈200 mL in vacuo. Acidification with concentrated hydrochloric acid to pH <2 and cooling yielded a white precipitate, which was collected, recrystallized from 45% aqueous ethanol, and dried (80 °C/13 Pa) to give 75.5 g (80%) of crystals: mp 188 °C (lit.[23] mp 185–188 °C); ^{13}C NMR (90.5 MHz, DMSO-d_6) δ 171.8, 170.4, 142.3, 138.3, 129.2, 126.4, 52.2, 37.8, 20.8.

(2*S*)-4-Amino-2-[[(4-methylphenyl)sulfonyl]amino]butan-1-ol (7). $LiBH_4$ (10.9 g, 0.5 mol) was dissolved in 360 mL of absolute THF under nitrogen, and 126 mL (1 mol) of trimethylchlorosilane was added cautiously with stirring. The mixture was chilled in an ice bath when 44.3 g (0.155 mol) of powdered carboxylic acid 6 was added in small portions over a period of 30 min. Stirring was continued for 30 min at T < 10 °C and another hour at room temperature. Heating under reflux for 2 h led to complete and clean conversion to the amino alcohol 7, as shown by a sample after hydrolysis (HPLC analysis). The reaction mixture was cooled again and solvolyzed by addition of 200 mL of methanol. Evaporation in vacuo left an oily residue, which was taken up in 200 mL of water and concentrated again in vacuo. Redissolution in 150 mL of water and adjustment of the pH to 10.5–11.0 with 5 N NaOH gave a thick white precipitate, which was filtered after standing overnight at 4 °C. Recrystallization from 120 mL of water and drying in the desiccator gave 31.7 g of tan crystals. Another crop of 3.0 g could be isolated from the combined mother liquors by continuous extraction with ethyl acetate: yield 34.7 g (86%); mp 146–148 °C (acetonitrile); HPLC (35% methanol) R_v = 5, 2 mL; ^1H NMR (360 MHz, DMSO-d_6) δ 7.69 (d, J = 8.2 Hz, 2 H, arom H), 7.37 (d, J = 8.2 Hz, 2 H, arom H), ≈3.5 (br, OH, NH_2, NHTos), 3.22 (m, 1 H, H-1), 3.10 (m, 2 H, H-1, H-2), 2.41 (m), 2.39 (s, together 5 H, H-4 and $ArCH_3$), 1.52 (m, 1 H, H-3), 1.30 (m, 1 H, H-3); ^{13}C NMR (90.5 MHz, DMSO-d_6 = 39.5 ppm) δ 142.3, 139.0, (ArC-1, C-4), 129.5, 126.4 (ArC-2/6; C-3/5), 63.6 (C-1), 53.6 (C-2), 37.8 (C-4), 34.8 (C-3), 21.0 ($ArCH_3$). Anal. Calcd for $C_{11}H_{18}N_2SO_3$ (258.3): C, 51.14; H, 7.02; N, 10.84. Found: C, 51.16; H, 6.72; N, 10.94.

(3*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-[[(4-methylphenyl)sulfonyl]amino]butylamine (8). The compound was prepared by standard silylation ($ClSi(CH_3)_2tC_4H_9$/imidazole) in acetonitrile. 8·CH_3COOH: ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 177.0 (acetate CO), 143.4, 137.8, 129.7, 126.9 (arom C), 64.1 (C-4), 52.7 (C-3), 36.8 (C-1), 29.7 (C-2), 25.6 (*tert*-butyl CH_3), 22.1 (acetate CH_3), 21.4 ($ArCH_3$), 18.1 (Si-C quat), −5.78, −5.82 ($SiCH_3$).

General Procedure To Prepare the Thioureas 15. Finely ground tosylamide 7 (18.6 g, 72 mmol) was added all at once to a solution of 28.7 g (69 mmol) of isothiocyanate 13 in 140 mL of dry acetonitrile. On stirring at 35 °C, the mixture became clear within 3 h, and HPLC analysis after standing over night confirmed the complete conversion of the starting material 13 to product 14 (85% CH_3OH; R_v (7) = 2.4 mL; R_v (13) = 28.4 mL; R_v (14) = 8.8 mL). Product 14S was isolated by preparative HPLC from a pilot run: ^{13}C NMR (CH_3CN-d_3 = 1.30 ppm) δ 183.4 (C=S), 144.4, 139.3, 136.44, 136.40, 134.25, 134.19, 130.85, 130.82, 130.62, 128.8, 127.7 (arom C), 66.0, 64.4 (CO), 55.5, 54.3, 41.3 (CN), 32.1, 31.55, 31.17 (CH_2), 27.25 (*tert*-butyl CH_3), 21.5 ($ArCH_3$), 19.8 (SiC), 15.47 (SCH_3).

The solvent was evaporated in vacuo, the residue was taken up in 250 mL of CH_2Cl_2, and 100 mL of the solvent was distilled off to remove any water. Then 9.6 g (142 mmol) of imidazole and 13.5 g (90 mmol) of *tert*-butyldimethylchlorosilane were added to the mixture. After two more hours at room temperature, the bissilyl ether 15 had formed from alcohol 14.

The solvent was stripped off in vacuo, and the residue was redissolved in ether (300 mL), extracted with 0.5 M succinate buffer pH 4.5 (3 × 150 mL) and 1 M soda solution (200 mL), dried ($MgSO_4$), and concentrated in vacuo to give 49.5 g (91%) of a yellowish oil, which did not crystallize though it was >96% pure as read from the HPLC analysis (UV and RI detection).

***N*-[(3*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-[[(4-methylphenyl)sulfonyl]amino]butyl]-*N'*-[(2*R*)-1-[(*tert*-butyldiphenylsilyl)oxy]-5-thiahex-2-yl]thiourea (15R)**: HPLC (90% methanol) R_v = 11.0 mL; ^1H NMR (360 MHz, $CDCl_3$) δ 7.73 (d, J = 8.3 Hz, 2 H, TosH-2,6), 7.67 (m_c, 4 H, arom H), 7.41 (m_c, 6 H, arom H), 7.32 (d, J = 8.1 Hz, 2 H, Tosyl-H-3/5), 6.45 (br, 1 H, NH), 6.29 (d, J = 7.9 Hz, 1 H, N'-H), 5.72 (d, J = 7.6 Hz, 1 H, TosNH), 3.9–3.15 (several poorly resolved multiplets, ≈8 H), 2.48 (m_c, 2 H, H-4'), 2.36 (s, 3 H, $ArCH_3$), 2.04 (s, 3 H, SCH_3), 1.85, 1.55 (m_c, 4 H, H-2, H-3'), 1.03 (s, 9 H, *tert*-butyl), 0.80 (s, 9 H, *tert*-butyl), −0.07, −0.08 ($SiCH_3$); ^{13}C NMR (90.5 MHz, CH_3CN-d_3) δ 183.5 (C=S), 144.2, 139.4, 136.3, 134.1, 130.71, 130.67, 128.7, 127.7 (arom C), 66.0, 65.4 (CO), 55.3, 41.3 (CN), 54.0

(CNTos), 32.2, 31.5, 31.1 (CH_2), 27.2, 26.2 (*tert*-butyl CH_3), 21.5 ($ArCH_3$), 19.8, 18.8 (*tert*-butyl CSi), 15.4 (SCH_3), -5.3 ($SiCH_3$); MS *m/z* (% I) M^+ not observable; 359 (28), 358 (100), 357 (24), 316 (52), 299 (23), 240 (82), 199 (32), 198 (28), 135 (20), 104 (50), 101 (27), 61 (55); IR 3340 (NH), 1540 (C=S), 1430 (CH_3) cm^{-1}.

***N*-[(3*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-[[(4-methylphenyl)sulfonyl]amino]butyl]-*N'*-[(2*S*)-1-[(*tert*-butyldiphenylsilyl)oxy]-5-thiahex-2-yl]thiourea (15S)**: HPLC (85% CH_3OH) R_v = 28.2 mL; ^1H NMR (360 MHz, $CDCl_3$) δ 7.66 (m_c, 6 H, TosH-2,6 and arom H), 7.42 (m_c, 6 H, arom H), 7.21 (d, *J* = 7 Hz, TosH-3,5), 6.59 (br, ≈1 H, NH), 6.07 (br, ≈1 H, N'-H), 4.98 (d, *J* = 8.3 Hz, 1 H, TosNH), 3.95 (m, 1 H, H-3), 3.81 (dd, *J* = 10.4/3.5 Hz, 1 H, H-1'), 3.73 (dd, *J* = 10.4/2.9 Hz, 1 H, H-1'), 3.47 (m_c, 1 H, H-1), 3.20 (dd, *J* = 10.1/2.1 Hz, 1 H, H-4), 3.14 (m_c, 1 H, H-2'), 2.99 (dd, *J* = 10.1/3.0 Hz, 1 H, H-4), 2.53 (m_c, 2 H, H-4'), 2.41 (s, 3 H, $ArCH_3$), 2.12 (s, 3 H, SCH_3), 1.97 (m_c, 2 H, H-3'), 1.88 (m_c, 1 H, H-2), 1.67 (m_c, 1 H, H-2), 1.07 (s, 9 H, *tert*-butyl CH_3), 0.81 (s, 9 H, *tert*-butyl CH_3), -0.07 (s, 3 H, $SiCH_3$), -0.1 (s, 3 H, $SiCH_3$); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 181.7 (C=S), 143.8, 137.6, 135.7, 132.9, 130.0, 129.9, 128.0, 126.9 (arom C), 65.1 (C-1'), 63.9 (C-4), 52.9 (C-2'), 52.3 (C-3), 41.0 (C-1), 31.4 (C-2), 30.9 (C-3'), 30.7 (C-4'), 27.0 (*tert*-butyl CH_3 at C-1'), 25.9 (*tert*-butyl CH_3 at C-4), 21.6 (CH_3Ar), 19.4, 18.3 (*tert*-butyl CSi), 15.6 (SCH_3), -5.5, -5.6 ($SiCH_3$). The assignments are backed by θ = 135° DEPT and 2D CH shift correlation spectra.

General Procedure for the Cyclization of the Thioureas (15). Thiourea **15R** (5.7 g, 7.5 mmol) was dissolved in 100 mL of CH_2Cl_2, and 50 mL solvent was distilled from the mixture. After cooling to 0–10 °C, 0.5 mL of ethyldiisopropylamine and then 2.12 mL (3.07 g, 250 mol %) of methyl trifluoromethanesulfonate was added. The formation of the isothiuronium–sulfonium salt was monitored by HPLC (90% CH_3OH, R_v (**16**) = 4.4 mL), and, after completion (ca. 2 h), 13 mL (75 mmol) of ethyldiisopropylamine was added. The mixture was now refluxed gently over night after which the HPLC analysis indicated the clean conversion to guanidine **18**. The solvent was evaporated in vacuo and the honeylike oil was distributed between ether (100 mL) and 1 N NaOH (50 mL) in the cold. The etheral layer was washed with another 50 mL of 1 N NaOH and water (50 mL), dried ($MgSO_4$), and evaporated finally under 13 Pa to give an off-white solid, which was crystallized from a small amount of hexane (4.7 g, 87%).

(2*S*,8*R*)-2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-8-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1-[(4-methylphenyl)sulfonyl]-1,5,9-triazabicyclo[4.4.0]dec-9-ene (18R): mp 113 °C (hexane); HPLC (90% CH_3OH) R_v = 6.2 mL; (85% CH_3OH) R_v = 18.2 mL; ^1H NMR (360 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2 H, Tos H-2/6), 7.63 (m_c, 4 H, arom H), 7.38 (m_c, 6 H, arom H), 6.98 (d, *J* = 8.2 Hz, 2 H, Tos H3/5), 4.63 (m_c, 1 H, H-8*), 3.74 (m, 2 H, one CHO at C-2 and C-8), 3.54 (dd, *J* = 9.4/9.4 Hz, 1 H, CHO at C-8), 3.30 (m, 1 H, H-2), 3.11 (dd, *J* = 9.7/9.5 Hz, ≈1 H, CHO at C-2), 3.04 (m_c, ≈4 H, H-4 and H-6), 2.28 (s, 3 H, $ArCH_3$), 2.14 (m, 1 H, H-7), 2.06 (m, 2 H, H-3 and H-7), 1.42 (m, 1 H, H-3), 1.03 (s, 9 H, *tert*-butyl CH_3), 0.85 (s, 9 H, *tert*-butyl CH_3), 0.04 (s, ≈3 H, $SiCH_3$), 0.02 (s, ≈3 H, $SiCH_3$). The assignment is backed by a 2D double-quantum COSY spectrum: ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 143.6, 142.6, 138.9, 135.6, 134.0, 129.6, 129.5, 128.8, 128.3, 127.6 (C-10 and arom C), 68.3, 62.9 (CO), 54.3, 53.3 (C-2, C-8), 46.8, 44.6 (C-4, C-6), 26.9, 25.8 (*tert*-butyl CH_3), 24.9, 24.2 (C-3, C-7), 21.4 ($ArCH_3$), 19.3, 18.1 (*tert*-butyl CSi), -5.37, -5.49 ($SiCH_3$); this assignment is backed by a DEPT spectrum (θ = 135°); IR (KBr) 1640 cm^{-1} (C=N—); MS (chemical ionization with isobutane) *m/z* 706 (100%, M^+ + 1); EI mode (70 eV) *m/z* (I %) 705 (0.59, M^+), 641 (23), 498 (35), 497 (100), 436 (28), 372 (12), 348 (18), 224 (14). Anal. Calcd for $C_{38}H_{55}N_3O_4SSi_2$ (706.1): C, 64.63; H, 7.85; N, 5.95. Found: C, 64.74; H, 7.90; N, 5.90.

(2*S*,8*S*)-2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-8-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1-[(4-methylphenyl)sulfonyl]-1,5,9-triazabicyclo[4.4.0]dec-9-ene (18S): HPLC (85% CH_3OH) R_v = 15.8 mL; ^1H NMR (360 MHz, $CDCl_3$) δ 7.53 (m, arom H), 7.33 (m, 8 H, arom H), 6.89 (d, *J* = 7.9 Hz, 2 H, Tos-H-3/5), 4.66 (m, 1 H, H-8), 3.82 (dd, *J* = 4.9/9.7 Hz, 1 H, CHO), 3.59 (m, 2 H, CH-O), 3.51 (m, 1 H, H-2), 3.16 (m, 2 H, H-4*), 2.95 (m, 2 H, H-6*), 2.66 (dd, *J* = 9.6/9.6 Hz, 1 H, CHO), 2.15 (s, ≈3 H, $ArCH_3$), 2.22–2.0 (m, ≈3 H, H-3*, H-7*), 1.38 (m, 1 H, H-3*), 1.01 (s, 9 H, *tert*-butyl CH_3), 0.88 (s, 9 H, *tert*-butyl CH_3), 0.07 (s, ≈3 H, $SiCH_3$), 0.05 (s, ≈3 H, $SiCH_3$); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 143.9, 142.7, 138.3, 135.5, 134.0, 133.85, 129.6, 128.5, 128.2, 127.6 (arom C and C=N), 67.7, 63.4 (CO), 54.7, 53.2 (C-2, C-8), 46.8, 45.0 (C-4, C-6), 26.9, 25.8 (*tert*-butyl CH_3), 25.4, 24.0 (C-3, C-7), 21.3 ($ArCH_3$), 19.2, 18.2 (*tert*-butyl CSi), 1.0 (SiC). Anal. Calcd for $C_{38}H_{55}N_3O_4SSi_2$ (706.1): C, 64.63; H, 7.85; N, 5.95. Found: C, 64.70; H, 8.09; N, 5.82.

(3'*S*,6*S*)-3-[4'-[(*tert*-Butyldiphenylsilyl)oxy]-3'-[[(4-methylphenyl)sulfonyl]amino]butyl]-6-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-2-(methylthio)-3,4,5,6-tetrahydropyrimidine Hydroperchlorate (17). This product was isolated as an oil from a preparative HPLC separation of the cyclization reaction mixture: ^1H NMR (360 MHz, $CDCl_3$) δ 7.68 (br s, 1 H, NH), 7.63–7.56 (m, 6 H, arom H), 7.50–7.32 (m, 16 H, arom H), 7.18 (d, *J* = 8.2 Hz, 2 H, Tos H-3,5), 5.10 (d, *J* = 8 Hz, 1 H, TosNH), 4.07 (m, 1 H, H-6), 3.91–3.80 (m, 2 H, CHO at C-6), 3.71 (m, 1 H, H-4), 3.57–3.42 (m, 3 H, H-4 and H-1'), 3.36 (m, 1 H, H-4'), 3.27–3.18 (m, 2 H, H-4' and H-3'), 2.61 (s, 3 H, SCH_3), 2.38 (s, 3 H, $ArCH_3$), 2.06 (m, 2 H, H-2'), 1.88 (m, 2 H, H-5), 1.05 (s, 9 H, *tert*-butyl CH_3), 0.99 (s, 9 H, *tert*-butyl CH_3); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 144.0, 135.5, 132.4, 130.2, 129.9, 128.1, 128.0, 126.9 (arom C), 65.0 (CO at C-6), 64.6 (C-4'), 52.8 (C-3'), 51.7 (C-6), 50.3 (C-4), 46.6 (C-1'), 29.8 (C-5), 26.9 (*tert*-butyl CH_3), 21.62 (C-2'), 21.58 ($ArCH_3$), 19.2 (*tert*-butyl CSi), 13.8 (SCH_3). The assignments are based on 1D DEPT- and 2D double-quantum COSY, TOCSY,[28] and CH correlation spectra.

Deprotection of Tosylguanidines 18. Example A. In a thermostated (20 °C) electrochemical cell (50 mL) which was divided into two compartments by a D4-frit to separate anodic and cathodic solutions was introduced 30 mL of 0.2 M NH_4Br in methanol as the catholyte and electrolyzed between a mercury cathode and a Pt-net anode at -2.5 V against a Ag/0.1 N $AgNO_3$ in CH_3CN reference electrode connected by a salt bridge close to the cathode surface. When cell voltage and current had reached a plateau (ca. 15 min), 6.8 g (10 mmol) of the tosylguanidine **18S** dissolved in 5 mL of 0.2 M NH_4Br in methanol was added. The detosylation commenced at once as was indicated by the rise of the cell current and confirmed by HPLC analysis of samples drawn at regular intervals. At the end (after 5 h), the catholyte was concentrated in vacuo and the residue was extracted with water (50 mL) to remove inorganic salts. The viscous oil remaining was dissolved in a mixture of methanol (70 mL) and 0.8 M soda solution (70 mL) and extracted with hexane/ether, 4:1 vol (150, 2 × 50 mL). The almost colorless and clear organic layer was washed with soda solution and water, and a mixture of 30 mL of 1 M aqueous NH_4Br and 100 mL of acetonitrile was added. After shaking, three layers were obtained, the middle one containing all of the product. This phase was washed with hexane (2 × 50 mL) and brought to dryness in vacuo. Recrystallization of the residue from toluene gave 5.1 g of **3c**·Br^- (80%) as white nonhygroscopic crystals.

(2*S*,8*S*)-2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-8-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine Hydrobromide (3c·Br⁻): mp 163–165 °C; HPLC (80% CH_3OH) R_v = 14.6 mL; ^1H NMR (360 MHz, $CDCl_3$) δ 8.58 (s, 1 H, NH), 8.43 (s, 1 H, NH), 7.63 (m_c, 4 H, arom H), 7.41 (m_c, 6 H, arom H), 3.83 (dd, *J* = 7.2/13.0 Hz, 1 H, CHO), 3.78 (dd, *J* = 3.9/9.7 Hz, 1 H, CHO), 3.61–3.51 (m, 3 H, 2 CHO and H-2*), 3.47 (m_c, 1 H, H-8*), 3.36 (m, 1 H, H-6), 3.19 (m, 3 H, H-6 and 2 H-4), 2.03 (m, 2 H, H-3, H-7), 1.91 (m, 2 H, H-3, H-7), 1.07 (s, 9 H, *tert*-butyl CH_3), 0.88 (s, 9 H, *tert*-butyl CH_3), 0.07 (s, 6 H, $SiCH_3$); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 151.5 (C-10), 135.6, 135.5, 132.7, 130.0, 128.2 (arom C), 65.2, 64.8 (CO), 49.4, 49.2 (C-2, C-8), 45.1, 44.7 (C-4, C-6), 26.9, 25.9 (*tert*-butyl CH_3), 23.0, 22.8 (C-3, C-7), 19.2, 18.2 (*tert*-butyl CSi), -5.5 ($SiCH_3$); the assignments are backed by 2D TOCSY,[28] CH correlation, and 1D DEPT spectra; IR (KBr) 3230, 3160, 3120 (NH), 2940, 2840 (CH), 1630, 1615 cm^{-1} (guanidine). Anal. Calcd for $C_{31}H_{50}N_3O_2Si_2Br$ (632.8): C, 58.83; H, 7.96; N, 6.64. Found: C, 59.07; H, 8.08; N, 6.62.

Example B. Minced heavy-duty aluminum foil (3 g) was etched on a D-4 frit with 1 N KOH for 1 min, washed with water, and amalgamated by soaking in 0.5% $Hg(OAc)_2$ solution for 2

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min. The metal shreds were thoroughly washed with water and then transferred to a stirred solution of 15.1 g (21.4 mmol) of **18R** in 200 mL of THF and 50 mL of water. Detosylation took place at ambient temperature, the progress being monitored by HPLC analysis. After complete conversion (usually requiring 2–4 h), the gray suspension was filtered through Celite and concentrated in vacuo. The residue was distributed between ice-cold ether/THF (100 mL, 30 mL) and 4 N NaOH (25 mL), and the organic layer was extracted again with 1 N NaOH (30 mL) and water (30 mL) and finally was shaken with 50 mL of 1 N aqueous NH_4I. Evaporation of the etheral phase left a residue, which was crystallized from toluene/ether at low temperature to give 12.3 g (85%) of $4{\cdot}I^-$.

(2*S*,8*R*)-2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-8-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine Hydroiodide ($4{\cdot}I^-$): mp 128 °C; HPLC (85% CH_3OH) R_v = 10.4 mL; (80% CH_3OH) R_v = 17.2 mL; ^1H NMR (360 MHz, $CDCl_3$) δ 8.95 (br s, ≈1 H, NH), 8.81 (br s, ≈1 H, NH), 7.56 (m, 4 H, arom H), 7.36 (m, 6 H, arom H), 3.76 (dd, J = 3.8/10.0 Hz, 1 H, CHO), 3.70 (dd, J = 7.8/13.9 Hz 1 H, CHO), 3.55 (m, 1 H, H-2*), 3.45 (m, 3 H, CHO, H-8*), 3.25 (m, 1 H, H-4*), 3.12 (3 H, H-4* and H-6*), 2.02–1.78 (m, 4 H, H-3 and H-7), 1.06 (s, ≈9 H, *tert*-butyl CH_3), 0.85 (s, ≈9 H, *tert*-butyl CH_3), 0.05 (s, ≈3 H, $SiCH_3$), 0.03 (s, ≈3 H, $SiCH_3$); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 151.6 (C-10), 135.6, 135.5, 132.7, 130.0, 127.9 (arom C), 65.2, 64.9 (CO), 49.2, 49.0 (C-2, C-8), 45.1, 44.6 (C-4, C-6), 26.9, 25.8 (*tert*-butyl CH_3), 23.1, 22.8 (C-3, C-7), 19.2, 18.1 (*tert*-butyl CSi), −5.41, −5.47 ($SiCH_3$); MS m/z (% I) 552 (51, guanidine cation, M^+), 406 (82, $M^+ - CH_3OSi(CH_3)_2C_4H_9$), 284 (100, $M^+ - CH_3OSi(C_6H_5)_2C_4H_9$). Anal. Calcd for $C_{31}H_{50}N_3O_2Si_2I$ (679.8): C, 54.77; H, 7.41; N, 6.18. Found: C, 54.90; H, 7.34; N, 6.13.

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Tetrazolo[1,5-*a*]pyridines and Furazano[4,5-*b*]pyridine 1-Oxides

Charlotte K. Lowe-Ma, Robin A. Nissan, and William S. Wilson*

Chemistry Division, Research Department, Naval Weapons Center, China Lake, California 93555

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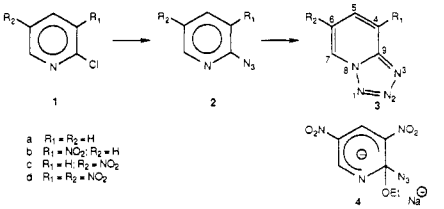
Tetrazolo[1,5-*a*]pyridines may be prepared by the reaction of azide ion with 2-chloropyridines. These tetrazolo[1,5-*a*]pyridines are shown to be in equilibrium with the corresponding 2-azidopyridines. Furazano[4,5-*b*]pyridine 1-oxides may be prepared by thermolysis of the appropriate 4-nitrotetrazolo[1,2-*a*]pyridines, presumably via the corresponding 2-azido-3-nitropyridines. The furazano[4,5-*b*]pyridine 1-oxides are found to be in equilibrium with the 3-oxides. ^1H and ^{13}C NMR are used to examine this equilibrium.

Introduction

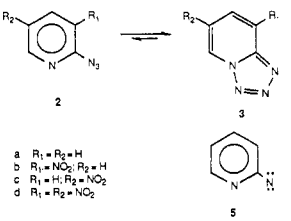
Benzofuroxans (2,1,3-benzoxadiazole 1-oxides) have shown interesting chemistry and wide ranging biological activity.[1] Vasodilatory activity,[2] inhibition of nucleic acid and protein synthesis in leucocytes,[3] and activity against leukemia[4] have all been observed. Benzofuroxan derivatives have also found use as depolarizing agents in dry cell batteries,[5] as polymerization inhibitors,[6] and in pest control.[7] Our interest in these compounds, however, has been as energetic materials, where our goals are improved performance and decreased sensitivity to such environmental stimuli as heat, impact, and friction.

Benzofuroxans have been prepared by oxidation of *o*-quinone dioxime[8] or by oxidation of *o*-nitroanilines with alkaline hypochlorite[9] or (diacetoxyiodo)benzene.[10] Perhaps the most satisfactory method, however, has been the thermolysis of *o*-nitrophenyl azides.[11] A recent report has described a one-pot synthesis of benzofuroxans from *o*-chloronitrobenzenes, involving nucleophilic displacement of the chlorine by azide ion followed by in situ cyclization under solid–liquid phase-transfer catalysis conditions.[12]

Scheme I



Scheme II



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