Building Blocks for Artificial Anion Receptors: Derivatives of Chiral Bicyclic Guanidines

Wolfgang Peschke,† Petra Schiessl,† Franz P. Schmidtchen,*,† Peter Bissinger,‡ and Annette Schier‡

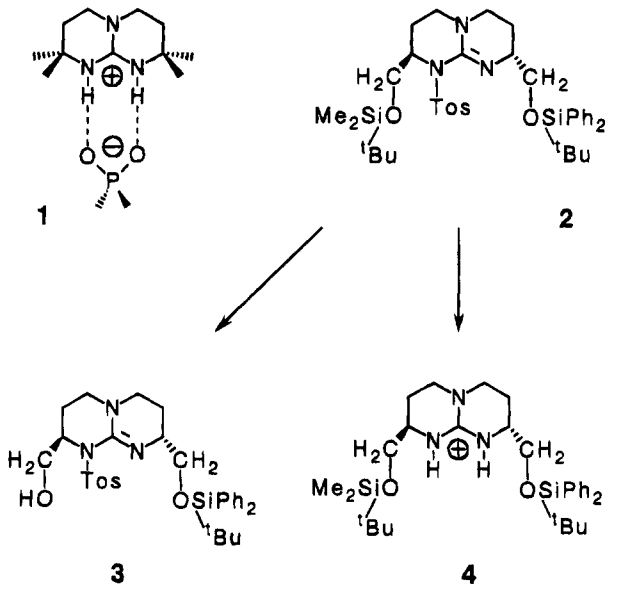
Institut für Organische Chemie und Biochemie and Institut für Anorganische Chemie, Technische Universität München, D-85747 Garching, Germany

Received October 12, 1994®

Bicyclic guanidinium salts are versatile anchor groups for oxoanions. Their incorporation into modular artificial hosts calls for the reliable accessibility of chiral, regioselectively functionalized derivatives. Here the preparation of an ensemble **6**–**14** of suitable building blocks is described, which meets these requirements and may be introduced into polytopic receptors by various nucleophilic displacement reactions. The individual members of this class were conveniently prepared in satisfactory yield by functional group manipulation starting from the known differentially protected parent compound **4**.

Introduction

Bicyclic guanidines **1** are of proven utility in the construction of dedicated molecular hosts for oxoanions.[1] Chiral members of this class of compounds have been synthesized starting from amino acids[2] or by means of the Schöllkopf–Hartwig methodology.[3] An easy access route which can furnish multigram quantities of these versatile anchor groups for anionic species was published by us[4] and paved the way for the elaboration of even more specific polytopic receptors. Thus, simple organic acids,[5] amino acids,[6] and nucleotides[7] have been demonstrated to form defined host–guest complexes with suitably designed derivatives of the parent artificial receptor. Even the exceedingly well hydrated phosphate dianion was bound with unprecedented stability by a ditopic guanidinium host in water,[8] emphasizing the extraordinary strength of guanidinium-phosphate interactions.[9] Any further improvement of receptor design now depends vitally on the availability of functionalized derivatives that may be incorporated with high chemical and regiospecific fidelity into the artificial hosts. Here we describe the preparation of an ensemble of differentially functionalized chiral bicyclic guanidines, which constitute a basic construction set to serve this purpose.



Results and Discussion

The first bicyclic guanidine in our synthesis of disubstituted chiral derivatives[4] is the *N*-tosyl-protected compound **2**. Controlled acidic hydrolysis of **2** readily gave the monodesilylated compound **3** which could be characterized and eventually transformed under acidic conditions but proved rather base sensitive. Even attempts to purify **3** by multilayer-coil-countercurrent distribution (MLCC) using moderately acidic conditions (acetic acid) resulted in a degradation reaction that appeared to involve an attack on the guanidine moiety. This could be prevented by employing formic acid for acidification, but only at the expense of slow deprotection of the second silyl ether function. In view of these difficulties we decided to remove the tosyl protecting group which seemingly caused the chemical lability of this system. The free bicyclic guanidine **4** generated by aluminum amalgam reduction[4] is extremely basic[10] and would remain protonated under most conditions of functional group

† Institut für Organische Chemie und Biochemie.
‡ Institut für Anorganische Chemie.
® Abstract published in *Advance ACS Abstracts,* February 1, 1995.

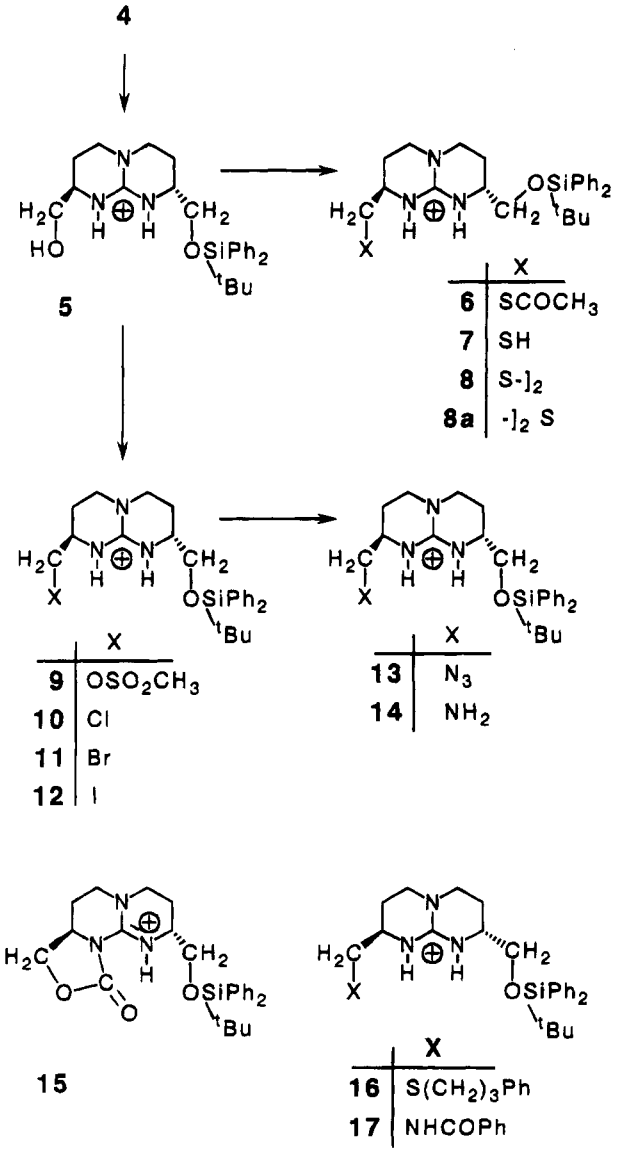
(1) (a) Schmidtchen, F. P.; Gleich, A.; Schummer, A. *Pure Appl. Chem.* **1989**, *61*, 1535–1546. (b) Müller, G.; Riede, J.; Schmidtchen, F. P. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1516–1518. (c) Schmidtchen, F. P. *Nachr. Chem. Tech. Lab.* **1988**, *36*, 8–17.
(2) (a) Echavarren, A. M.; Galán, A.; de Mendoza, J.; Salmerón, A.; Lehn, J.-M. *Helv. Chim. Acta* **1988**, *71*, 685. (b) Gleich, A.; Schmidtchen, F. P. *Chem. Ber.* **1990**, *123*, 907–915.
(3) Schmidtchen, F. P.; Oswald, H.; Schummer, A. *Liebigs Ann. Chem.* **1991**, 539–543.
(4) Kurzmeier, H.; Schmidtchen, F. P. *J. Org. Chem.* **1990**, *55*, 3749–3755.
(5) (a) Gleich, A.; Schmidtchen, F. P.; Mikulcik, P.; Müller, G. *J. Chem. Soc., Chem. Commun.* **1990**, 55–57. (b) Schiessl, P.; Schmidtchen, F. P. *Tetrahedron Lett.* **1993**, *34*, 2449–2452. (c) Echavarren, A.; Galán, A.; Lehn, J.-M.; de Mendoza, J. *J. Am. Chem. Soc.* **1989**, *111*, 4994–4995.
(6) Galán, A.; Andreu, D.; Echavarren, A. M.; Prados, P.; de Mendoza, J. *J. Am. Chem. Soc.* **1992**, *114*, 1511–1512.
(7) (a) Schmidtchen, F. P. *Tetrahedron Lett.* **1989**, *30*, 4493–4496. (b) Deslongchamps, G.; Galán, A.; de Mendoza, J.; Rebek, J., Jr. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 61.
(8) Schiessl, P.; Schmidtchen, F. P. *J. Org. Chem.* **1994**, *59*, 509–511.
(9) (a) Hannon, C.; Anslyn, E. V. The Guanidinium Group: Its Biological Role and Synthetic Analogs. In *Bioorganic Chemistry Frontiers*; Dugas, H., Schmidtchen, F. P., Eds.; Springer: Heidelberg, 1993, Vol. 3, pp 193–255. (b) Rebek, J., Jr.; Kato, Y.; Conn, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 3279–3284.
(10) Schwesinger, R. *Nachr. Chem. Tech. Lab.* **1990**, *38*, 1214–1222.

0022-3263/95/1960-1039$09.00/0

interconversions. Thus, we planned to convert the known detosylated guanidine **4**[4] into the monodeprotected hydroxymethyl derivative **5**, which was to function as the root compound for two synthetic targets.

The first contained functionalities amenable to nucleophilic displacements. The other aim, instead, was to lead to stronger nucleophiles in the side chain. The concept was set up to furnish a basic arsenal of building blocks to be used in very simple covalent junctions with each other or with spacer elements, reporting or catalytically active functions. By virtue of permutative combinations of this basic set of building blocks which also included the enantiomeric series of chiral guanidines, a vast variety of artificial receptors could conveniently be produced to find out optimal arrangements for a given host–guest binding or catalysis task.

Two issues were considered essential for the success of the strategy outlined above: All reaction conditions must be compatible with the base sensitivity of the parent guanidine system which *a priori* eliminated the use of the majority of organometallic and condensation reactions. Furthermore, the silyl protection of one ring substituent must be preserved at all times in order to avoid regiochemical scrambling.



Our initial choice for the introduction of a leaving group moiety in **5** was the conversion into the corresponding chloride, because of its versatility for further transformations and its putative chemical stability. On using $SOCl_2$ under standard conditions, however, rapid degradation of the starting material was observed. This could be prevented by the presence of excess pyridine, and careful optimization of the reaction conditions (reagent stoichiometry, solvent, base, and temperature) finally gave 95% yields of the chloro derivative **10**, reproducibly. The more reactive bromo and iodo analogues **11** and **12** could not be obtained so readily. Especially all the modern methods that most likely involve the formation of cationic intermediates[11–13] failed to yield the halides from the starting alcohol. Very mild methods like the use of carbonyldiimidazole/ allyl bromide[14] stopped at some intermediate stage (in this case the cyclic urethane **15**) whereas more rigorous treatment generally led to silyl ether cleavage before the desired conversion took place. The best method to prepare **11** appears to employ thionyl bromide/2,6-lutidine in trichloroethylene under reflux though the yields were somewhat variable and did not exceed 60%. Similar difficulties were encountered when the iodo derivative **12** was to be prepared directly from the (hydroxymethyl)guanidine **5**. P_2I_4,[15] iodotrimethylsilane,[16] diphenylchlorophosphane/iodine,[17] or triphenylphosphane, imidazole/iodine[18] failed to give the desired target compound. However, Finkelstejn halide exchange under forcing conditions (acetonylacetone, 100 °C) produced **12** from the chloro derivative **10**. **12** could be crystallized from toluene as the ClO_4^- salt in suitable quality for X-ray crystal structure determination. (Figure 1). As already seen in analogous bicycles[19] the guanidinium substructure is almost ideally planar and the hydrogens were located in bonding distance to the two respective nitrogens. In spite of the notoriously poor hydrogen bonding ability of perchlorate

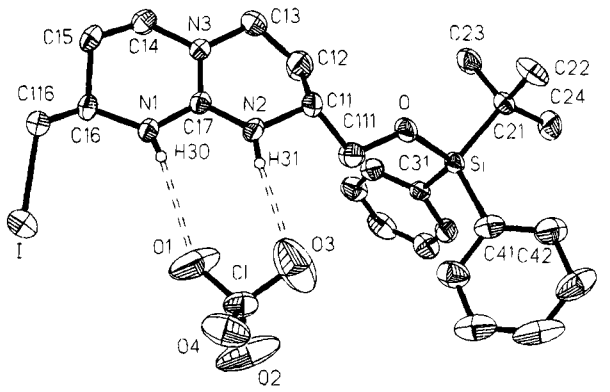


Figure 1. ORTEP drawing of 12·ClO_4. The dedicated host–guest binding interaction between the guanidinium moiety and the anion is visible even though perchlorate is an extremely poor hydrogen bond acceptor.

(11) Hodge, P.; Khoshdel, E. *J. Chem. Soc., Perkin. Trans. 1* **1984**, 195–198.
(12) (a) Manna, S.; Falck, J. R.; Mioskowski, C. *Synth. Commun.* **1985**, *15*, 663–668. (b) Ho, P.-T.; Davies, N. *J. Org. Chem.* **1984**, *49*, 3027–3029.
(13) (a) Olah, G. A.; Gupta, B. G. B.; Malhotra, R.; Narang, S. C. *J. Org. Chem.* **1980**, *45*, 1638–1639. (b) **1979**, *44*, 1247–1251.
(14) Kamijo, T.; Harada, H.; Iizuka, K. *Chem. Pharm. Bull.* **1983**, *31*, 4189.
(15) Lauwers, M.; Regnier, B.; Van Eenoo, M.; Denis, J. N.; Krief, A. *Tetrahedron Lett.* **1979**, 1801–1804.
(16) Jung, M. E.; Ornstein, P. L. *Tetrahedron Lett.* **1977**, 2659–2662.
(17) Classon, B.; Lin, Z.; Samuelson, B. *J. Org. Chem.* **1988**, *53*, 6126–6130.
(18) Marshall, J. A.; Grote, J.; Audia, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 1186–1194.
(19) Gleich, A.; Schmidtchen, F. P.; Mikulcik, P.; Müller, G. *J. Chem. Soc. Chem. Comm.* **1990**, 55–57.

this anion forms two weak (N−H···O = 3.085 Å, 3.190 Å) but nonlinear hydrogen bonds (<159.2 and 147.6°) to the guanidinium moiety emphasizing the extraordinary oxoanion binding power of the parent host system. The 6-membered rings adopt pseudochairlike conformations, in which the bulky substituents both occupy equatorial positions. Overall, a cleft is formed which hosts the hydrogen-bonded anion.[29]

The most convenient access to the iodo derivative **12** involved the conversion of **5** to the mesylate **9** using a mildly alkaline medium followed by nucleophilic displacement of the mesylate for iodide. The iodo derivative **12** opened routes to introduce more nucleophilic amino- or thiol groups into the side chain. Initial attempts for a direct process using Gabriel chemistry[20] or a seemingly gentle substitution/elimination procedure[21] were unsuccessful or gave unsatisfactory yields. Instead we chose to go a roundabout way via the azide **13**, which was obtained both from **12** or **9** with equal efficiency. Unfortunately, the direct preparation of **13** from the hydroxymethyl compound **5** using the well established DPPA method[22] did not work out. Reduction of **13** to the amine **14** was brought about by catalytic hydrogenation using palladium catalyst as well as by Staudinger reaction (triphenylphosphine/H_2O/THF)[23] in high yields. The aminoguanidine **14** is easy to purify, and the monoamino function exhibited the expected nucleophilic reactivity and was readily converted into the corresponding benzamide **16**.

For the preparation of strongly nucleophilic thiol compounds like our target **7** the classical methods[24] call for hydrolysis of some intermediates (e.g., Bunte salts) under rather harsh acidic or alkaline conditions which would very likely harm at least the silyl protection. Some of the more gentle procedures like the Mitsunobu coupling[25] of **5** with thioacetate failed to give the corresponding thioester **6**.

This intermediate, however, was readily obtained by reaction of thioacetate on the (iodomethyl)guanidine **12**. The cleavage of **6** could be effected by aqueous ammonia or hydroxylamine solutions but invariably furnished mixtures of the thiol **7** and its oxidation product **8**. The latter proved to be the compound of choice for storage, because the very sensitive thiol **7** was easily generated therefrom in an almost instantaneous reaction by addition of a small excess of tributylphosphine.[27] Surprisingly, the disulfide **8** also was obtained directly from the chloro compound **10** by reaction with thiophosphate in refluxing methanol[26] without any sign of the obligatory thiophosphate ester intermediate appearing. This reaction circumvents the unpleasant manipulation of thioacetate and represents the quickest and most convenient access to the desired thiol target **7**. The high and unperturbed nucleophilicity of **7** was apparent from the occurrence of a byproduct. When only a slight excess (120 mol %) of thiophosphate over iodo compound **12** was used the symmetrical sulfide **8a** was isolated. Undoubtedly this arose from the attack of thiol on **12** that was still present in the reaction mix due to a too slow initial nucleophilic displacement. Thiol **7** generated by an *in situ* reduction from **8** and tributylphosphine[27] in methanol readily reacted with 3-phenylpropyl mesylate in the presence of tetramethylguanidine as a base forming the corresponding 3-phenylpropyl ether.

Experimental Section

All chemicals were reagent grade and used as obtained. Solvents were dried by standard laboratory procedures but freshly distilled before use. The reactions generally were monitored by gradient HPLC using commercial reversed phase columns. Column I: 250 × 4 mm Nucleosil RP-18, 5 μm (Macherey-Nagel). Column II: 250 × 4 mm Purospher RP-18, 5 μm (Merck). In addition to the organic modifier given with the individual preparations, all eluents contained 30 mM phosphoric acid and 30 mM sodium perchlorate. Multilayer-coil-countercurrent distribution (MLCC) used an Ito machine (Zinsser Analytic) and a preparative coil (370 mL). MS spectra were obtained using EI or CI (isobutane) ionization or preferably FAB technique. Elemental microanalyses were obtained from the Microanalytical Laboratory, Institut für Organische Chemie, TU München.

The entire synthesis has been completed with either enantiomer of the starting guanidinium salt **4**.

(2*R*,8*R*)-8-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2-(hydroxymethyl)-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]-pyrimidine Hydrobromide (5). A solution of bis-silyl ether **4** (50.3 g, 79.5 mmol) in 100 mL of methanol was treated with 60 mL of 1.5 M HBr at rt. After 45 min when HPLC indicated complete disappearance of the starting material, 4 g of powdered Na_2CO_3 was added cautiously followed by evaporation of the solvent in vacuo. The residue was distributed between $CH_2Cl_2$and H_2O (100 mL each), the organic layer was extracted twice with aqueous saturated NaBr solution (20 mL) and dried (Na_2SO_4), and the solvent was evaporated in vacuo. The remaining highly viscous oil was redissolved in hot toluene and filtered through Celite. On cooling the solution to −20 °C, white crystals separated to give 35.3 g (85%) of **5**, mp 133−134 °C. HPLC (column I, gradient, 1.0 mL/min: 65% to 90% methanol in 10 min): R_v = 10.6 mL. Anal. Calcd for $C_{25}H_{36}BrN_3O_2Si$ (518.6): C, 57.90; H, 6.99; N, 8.10. Found: C, 57.65; H, 6.94; N, 8.00. $[\alpha]^{25}_D$ = −36.5 (*c* = 0.85, $CHCl_3$). IR (KBr) 3350 br, 1650,1630, s (guanidine). MS (CI) *m*/*z* 438 (100, M − Br); 200 (40), 182 (4),168 (6). ^{1}H-NMR ($CDCl_3$): δ 8.15 (s, 1H ,NH); 7.66−7.62 (m, 4H); 7.59 (s, 1H, NH); 7.45−7.36 (m, 6H); 4.47−4.44 (t, *J* = 5.9 Hz, 1H); 3.76−3.71 (m, 2H); 3.59.3.53 (m, 4H); 3.37−3.18 (m, 4H); 2.03, 1.96−1.84 (2m, 4H); 1.06 (s, 9H). ^{13}C-NMR ($CDCl_3$): δ 151.3 (q), 135.6, 132.7, 129.9, 127.9, 65.5, 63.7, 50.7, 49.5, 45.7, 44.7, 26.9, 22.8, 22.7, 19.1.

(2*R*,8*R*)-8-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2-(chloromethyl)-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine Hydrochloride (10). To a chilled mixture of 900 μL of dry pyridine and 7.5 mL of freshly distilled $CHCl_3$ was added 300 μL of $SOCl_2$ under N_2. This solution was heated to reflux, and a solution of 500 mg (960 μmol) of (hydroxymethyl)-guanidine **5** in 5 mL of $CHCl_3$ was introduced via syringe pump over 1 h. Refluxing was continued for another 2 h, and then the mixture was chilled and quenched by addition of 4 mL of water and the solvent was removed in vacuo. Redissolution of the residue in 5 mL of $CHCl_3$ was followed by extractions (3 × 10 mL of 1M HCl, 10 mL of 0.5 M soda solution, 5 mL of brine) and drying of the organic phase with $MgSO_4$. Evaporation of the solvent at 0.01 mmHg gave 451 mg (95%) of tan glassy solid that appeared >98% pure by HPLC. A small sample was converted into the perchlorate salt using anion exchange with Serdolit AS-6 (ClO_4) in methanol. HPLC (column I, gradient 65% to 90% MeOH in 10 min, 1.0 mL/min): R_v = 12.4 mL. Anal. Calcd for $C_{25}H_{35}ClN_3OSi{\cdot}ClO_4$ (556.6): C, 53.95; H, 6.33; N, 7.55. Found: C 54.04; H 6.27;

(20) (a) Ragnarsson, U.; Grehn, L. *Acc. Chem. Res.* **1991**, *24*, 285−289. (b) Ragnarsson, U.; Grehn, L. *Synthesis* **1987**, 275−276.
(21) Hendrickson, J. B.; Bergeron, R.; Sternbach, D. D. *Tetrahedron* **1975**, *31*, 2517−2521.
(22) Thompson, A. S.; Humphrey, G. R.; De Marco, A. M.; Mathre, D. J.; Grabowski, E.J. J. *J. Org. Chem.* **1993**, *58*, 5886−5888.
(23) Knouzi, N.; Vaultier, M.; Carrie, R. *Bull. Soc. Chim. Fr.* **1985**, 815−819.
(24) Kice, J. L. *J. Org. Chem.* **1963**, *28*, 957.
(25) (a) Breslow, R.; Czarnik, A. W.; Lauer, M.; Leppkes, R.; Winkler, J.; Zimmerman, S.; *J. Am. Chem. Soc.* **1986**, *108*, 1969−1979. (b) Mitsunobu, O. *Synthesis* **1981**, 1−27.
(26) Bieniarz, C.; Cornwell, M. J. *Tetrahedron Lett.* **1993**, *34*, 939−942.
(27) Rüegg, U. T.; Rudinger, J. *Methods Enzymol.* **1977**, *47*, 111−116.

N 7.54. ^{1}H-NMR (250 MHz, CD_3CN) δ 9.27, 8.86 (2s, ~2H, NH); 7.72–7.69 (m, 4H); 7.47–7.39 (m, 6H); 3.66–3.52 (m, 6H); 3.27–3.22 (m, 4H); 2.21–2.12 and 2.03–1.78 (2m, 4H); 1.04 (s, 9H). ^{13}C-NMR (90 MHz, CD_3CN) δ 152.6 (q), 136.6, 134.0, 130.9, 128.9, 66.8, 50.6, 50.3, 47.2, 45.7, 45.3, 27.0, 24.2, 23.5, 19.7 (q).

(2*R*,8*R*)-8-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2-(bromomethyl)-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-a]pyrimidine Hydrobromide (11). A mixture of 260 mg (0.50 mmol) of (hydroxymethyl)guanidine **5** and 0.4 mL of 2,6-lutidine in 15 mL of trichloroethylene was heated to reflux (bath 110 °C). A solution of 250 μL of freshly distilled $SOBr_2$ in 2 mL of trichloroethylene was then added slowly by syringe pump over 1 h with efficient stirring to agitate the dark precipitate that separated in this period. The mixture was refluxed for an additional hour, cooled, and extracted with 0.2 M HBr (2 × 20 mL), 0.5 M $NaHCO_3$ solution (2 × 20 mL), and saturated aqueous NaBr solution. Evaporation of the solvent left a sticky oil that was dissolved in 5 mL of CCl_4. Slow addition of hexane precipitated the product which was dried in vacuo after decantation of the mother liquor to give 173 mg (59%) of brown powder. Anal. $C_{25}H_{35}Br_2N_3OSi$ (581.5). HPLC (column I, gradient 65% to 90% MeOH in 20 min, 1.0 mL/min): R_v = 12.8 mL. ^{1}H-NMR (360 MHz, $CDCl_3$): δ 9.09, 8.32 (2s, ~2H, NH); 7.66–7.61 (m, 4H); 7.46–7.37 (m, 6H); 3.80 (dd, ^3J = 7.6 Hz, ^2J = 13.5 Hz, 1H); 3.71 (br m, 1H); 3.64–3.55 (m, 3H); 3.36–3.15 (m, 5H); 2.2–2.1, 2.1–2.0, 2.0–1.9 (3m, 4H); 1.07 (s, 9H). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 151.3 (q), 135.7, 135.6, 132.72, 132.67, 130.1, 128.06, 128.01, 65.35, 49.39, 49.12, 44.89, 44.74, 33.0, 27.0, 24.39, 22.81, 19.3 (q). The assignment is backed by a 135° DEPT-spectrum.

(2*R*,8*R*)-8-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2-(iodomethyl)-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine Hydroiodide (12). Sodium iodide (5 g) was dissolved in 15 mL of carefully deaerated acetonylacetone and heated to 100 °C under N_2 when a solution of 472 mg (0.96 mmol) of the chloromethyl compound **10,** dissolved in 5 mL of air-free acetonylacetone, was introduced. Heating at 100 °C was continued for 5 h, and the progress of the reaction was occasionally checked by HPLC. The solvent was distilled off (Kugelrohr, 80 °C, 0.1 mmHg), and the dark brown residue was taken up in 5 mL of CH_2Cl_2. Extraction with dilute aqueous ascorbic acid (5 × 10 mL) gave a yellow organic phase, which was concentrated in vacuo. The iodide salt could be precipitated form a THF solution with ether to yield tan flakes, but was better converted into the perchlorate salt (Serdolit AS-6 anion exchange in methanol). Crystallization from toluene yielded 460 mg (74%) of off-white coarse prisms. Impure iodomethyl derivative **12** (e.g., from the mother liquors) could conveniently be purified by MLCC using $CCl_4/CH_2Cl_2/CH_3OH$/0.1 M NaCl in H_2O = 2:2:3:1 vol as the distribution system employing the lower layer as the stationary phase. The product **12** eluted after 2 coil volumes of mobile phase, mp 146 °C; $[\alpha]^{25}_D$ = −17.4 (*c* = 0.86,$CHCl_3$). HPLC (column I, gradient 65% to 90% MeOH in 20 min, 1.0 mL/min): R_v = 13.0 mL. Anal. Calcd for $C_{25}H_{35}IN_3OSi{\cdot}ClO_4$ (648.0): C, 46.33; H, 5.44; N, 6.48. Found: C, 46.71; H, 5.64; N, 6.45. ^{1}H-NMR (iodide salt, 360 MHz, $CDCl_3$): δ 8.5, 7.8 (2s, ~2H, NH); 7.66–7.62 (m, 4H); 7.47–7.38 (m, 6H); 3.78 (m, 1H); 3.66–3.55 (br m, 3H); 3.49 (dd, ^2J = 10.3 Hz, ^3J = 3.9 Hz, 1H); 3.36–3.25 (br m, 4H); 3.19 (dd, ^2J = 10.3 Hz, ^3J = 9.3 Hz, 1H); 2.19, 2.1–1.9 (2br m, 4H); 1.07 (s, 9H). The assignment was confirmed by a DQF-COSY spectrum. ^{13}C-NMR (iodide salt, 90 MHz,$CDCl_3$) δ 151.0 (q), 135.65, 135.54, 132.57, 132.48, 130.03, 128.02, 127.96, 65.3, 49.4 , 44.9, 26.9, 26.1, 22.7, 19.2 (q), 6.81. This assignment is backed by a 135° DEPT spectrum.

(2*R*,8*R*)-8-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2-[[(methylsulfonyl)oxy]methyl]-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine Hydrochloride (9). A solution of (hydroxymethyl)guanidine **5** (1.0 g, 1.93 mmol) and 0.1 mL of triethylamine in 10 mL of CH_2Cl_2 was chilled in an ice bath under N_2. With stirring, freshly prepared 1 M solutions of mesylchloride and triethylamine in CH_2Cl_2, respectively, were added alternately in 1 mL portions. The progress of the reaction was monitored by HPLC (column I, 75% acetonitrile, isocratic, R_v(**5**) = 5.0 mL; R_v (**9**) = 5.7 mL). When the fast and clean reaction was found to be complete (usually 300 mol % reagent required), the mixture was extracted with 0.1 M HCl (3 × 10 mL), brine (2 × 5 mL) and dried ($MgSO_4$). Concentration at rt at 0.1 mmHg left an almost colorless oil (yield nearly quantitative), which was >98% pure by gradient HPLC (column I, gradient 50% to 90% CH_3CN in 20 min, 0.8 mL/min) R_v(**9**) = 14.1 mL. ^{1}H-NMR (250 MHz, CD_3CN): δ 9.0, 8.5 (2s, ~2H, NH); 7.62–7.59 (m, 4H); 7.39–7.29 (m, 6H); 4.17 (dd, ^2J = 10.2 Hz, ^3J = 4.3 Hz, 1H); 4.03 (dd, ^2J = 10.2 Hz, ^3J = 7.0 Hz, 1H); 3.65 (m, 1H); 3.55 (m, 2H); 3.47 (m, 1H); 3.19–3.14 (m, 4H); 3.14 (s,~3H); 1.95–1.69 (m, 4H); 0.94 (s, 9H). ^{13}C-NMR (62 MHz, CD_3CN): δ 152.6 (q), 136.5, 133.9, 130.9, 128.9, 71.4, 66.8, 50.7, 48.2 , 45.8, 45.5, 38.0, 27.3, 23.4, 22.8, 19.8 (q).

(2*R*,8*R*)-8-[[(*tert*-Butyldiphenylsilyl)oxy)methyl]-2-(azidomethyl)-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]-pyrimidine Hydroperchlorate (13). The honey-like mesyl ester **9** (553 mg, 1.0 mmol) was dissolved in 3 mL of dry DMF, and 390 mg of powdered NaN_3 was added. The mixture was heated with stirring to 85 °C for 1 h. After cooling and dilution with 10 mL of 0.5 M $NaClO_4$ in water the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was washed with 0.1 M $HClO_4$ (3 × 10 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue could be crystallized from toluene to give 505 mg (90%) of white prisms. Less pure samples could conveniently be purified by MLCC using $CCl_4/CHCl_3/CH_3OH$/0.1 M aqueous $NaClO_4$ = 5:4:7:1 vol for distribution. Taking the lower layer as the stationary phase in a preparative coil the product eluted between 450 and 550 mL, mp 100 °C. Anal. Calcd for $C_{25}H_{34}N_6OSi{\cdot}ClO_4$ (563.1): C, 53.32; H, 6.26; N, 14.92. Found: C, 53.53; H, 6.63; N, 14.34. IR (KBr): 2100 cm^{-1} (N_3). ^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.65–7.62 (m, 4H); 7.46–7.38 (m, 6H); 7.05, 6.77 (2s, ~2H, NH); 3.69 (dd, ^2J = 10.4 Hz, ^3J = 5.2 Hz, 1H); 3.62 (dd, ^2J = 10.3 Hz, ^3J = 5.8 Hz, 1H); 3.58–3.48 (m, 4H). ^{13}C-NMR (90 MHz, $CDCl_3$) δ 150.8 (q), 135.6, 132.6, 130.0, 127.9, 65.4, 53.6, 50.0, 48.1, 45.30, 45.25, 26.8 , 23.5, 22.7, 19.2 (q). The assignment is backed by a 135° DEPT spectrum.

(2*R*,8*R*-8-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2-(aminomethyl)-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]-pyrimidine Hydrochloride (14). Staudinger reaction. Azidomethyl derivative **13** (225 mg, 0.4 mmol) was dissolved in 2 mL of THF and 200 μL of water. On addition of 300 mg of triphenylphosphane-on-polymer (Fluka, ~0.9 mmol phosphane) some gas evolution commenced. The suspension was stirred at rt overnight after which an HPLC analysis indicated complete conversion of **13**. The polymer was filtered off, the filtrate was concentrated, and the product **14** was isolated by MLCC using $CCl_4/CHCl_3/CH_3OH$/50mM citrate, pH 5.0 + 50 mM NaCl in H_2O = 1:4:6:3 vol as the distribution system. The product **14** was eluted after 200 mL taking the upper layer as the mobile phase in a preparative coil (380 mL). The product-containing fractions were concentrated, the residue was distributed between CH_2Cl_2 and water, the organic phase was extracted with 0.5 M HCl (2 mL), and the solvent was evaporated in vacuo. Crystallization from 25% CH_2Cl_2 in acetonitrile (−20 °C) gave 158 mg (77%) of off-white crystals, mp > 139 °C dec. **Hydrogenation.** Azido compound **13** (390 mg, 0.69 mmol) was dissolved in 5 mL of methanol and hydrogenated at atmospheric pressure and rt using 50 mg of 10% Pd on charcoal as a catalyst. A sample taken after 2.5 h indicated complete conversion. The suspension was filtered first through Celite followed by anion exchange (Serdolit AS-6, chloride) to obtain the chloride salt. The eluate was acidified with HCl and evaporated by a stream of N_2, and the product was crystallized from CH_2Cl_2/CH_3CN. Reduction of **13** to **14** was also achieved in transfer hydrogenations employing ammonium formate/formic acid (2:1 per weight) in methanol as hydrogen source and 10% Pd on charcoal as the catalyst.[28] (Aminomethyl)guanidine **14** was isolated by ion exchange chromatography on Sephadex SP C-25 using a gradient of

(28) Gartiser, T.; Selve, C.; Delpuech, J.-J. *Tetrahedron Lett.* **1983**, 1609–1610.

(29) The authors have deposited atomic coordinates for **12** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambrigde, CB2 1 EZ, UK.

NaCl in 40% methanol (0.05–1.0 M) for elution, mp > 154 °C dec. ^{1}H-NMR (360 MHz, $CDCl_3$): δ 8.51 (br, 2H), 8.46 (s, 1H), 7.69 (s, 1H), 7.60–7.65 (m, 4H), 7.35–7.45 (m, 6H), 4.13 (m, 1H), 3.75–3.6, 3.58–3.48, 3.40–3.25, 3.20–3.05 (4m, ~9H), 2.2–2.0, 1.90–1.80 (2m, ~4H), 1.03 (s, 9H). ^{13}C-NMR (62 MHz, $CDCl_3$): δ 150.9 (q), 135.6, 132.8, 129.9, 127.9, 65.4, 49.4, 45.7, 44.7, 44.4, 42.7, 26.9, 23.1, 22.4, 19.2 (q). The signals at 49.4 and 45.7 ppm show a fine structure (splitting 7 Hz).

(2*R*, 8*R*)-8-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2-[(acetylthio)methyl]-3,4,5,6,7,8,9-hexahydro-2*H*-pyrimido-[1,2-*a*]pyrimidine Hydrochloride (6). A solution of iodomethyl compound **12** (34 mg, 50 μmol) dissolved in 400 μL of deaerated DMF was reacted with 38 μL of tetramethylguanidine and 18 μL (250 μmol) of thioacetic acid under argon at 25 °C. The black solution was stirred for 16 h followed by distribution between CH_2Cl_2 and water (3 mL each). The organic layer was washed with acetate buffer (3 × 1 mL, pH 4.5) and 0.1 M Na–ascorbate solution (3 mL) and concentrated by a jet of N_2. The residue was taken up in methanol (2 mL) and filtered over Serdolit AS-6 (Cl^-) anion exchange resin. Evaporation of the eluate left a residue of the chloride salt that was 90% pure by gradient HPLC.

HPLC (column II, gradient 50 to 90% CH_3CN in 20 min (0.8 mL/min)) R_v(**6**) = 10.9 mL; R_v(**12**) 11.2 mL. ^{1}H-NMR (360 MHz, $CDCl_3$): δ 9.21 (s, 1H), 8.75 (s, 1H), 7.6–7.65 (m, 4H), 7.45–7.35 (m, 6H), 3.82 (m, 1H), 3.62–3.46 (m, 3H), 3.43–3.35 (m, 1H), 3.30–3.16 (m, 3H), 3.12–3.08 (m, 2H), 2.37 (s, 3H), 2.1–1.75 (4m, 4H), 1.06 (s, 9H). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 194.9, 151.0, 135.4, 132.5, 129.8, 127.7, 65.1, 49.0, 48.2, 44.7, 44.5, 32.5, 30.5, 26.7, 24.3, 22.6 , 19.0.

Bis[[(2*R*,8*R*)-8-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3,4,5,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidinyl]-2-methyl]disulfide Bis(hydroiodide) (8). Via cleavage of 6. A solution of thioester **6** (20 mg) in CH_3OH (500 μL) was treated with 100 μL of concd aqueous ammonia at rt. The reaction was completed after 30 min as indicated by the disappeareance of starting thioester (HPLC monitoring). On standing, the primarily formed thiol **7**, having a slightly smaller R_v than the ester (R_v(**6**) = 11.2 mL, R_v(**7**) = 11.0 mL), was rapidly transformed into the disulfide **8** (R_v(**8**) = 15.1 mL) which was isolated by preparative HPLC. **Via nucleophilic Displacement with Thiophosphate.** In a refluxing solution of 100 mg (148 μmol) of iodo compound **12** in 4 mL of CH_3OH was dissolved 117 mg of $Na_3SPO_4{\cdot}12H_2O$ (200 mol %). The white suspension that formed rapidly was stirred under reflux for 20 h followed by evaporation of the solvent. The residue was distributed between H_2O and CH_2Cl_2 (3 mL each), the aqueous phase was extracted by another portion of CH_2Cl_2 (2 mL), and the combined organic layers were washed with 1 M NaI in H_2O (2 × 3 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a reddish-brown crude product (82 mg) that was chromatographed on neutral Al_2O_3 (activity II) using a stepwise elution: 100 mL of 1% MeOH/$CHCl_3$ wash; 100 mL of MeOH/$CHCl_3$ 1:1 vol. Evaporation of the fraction containing the product gave 50 mg (59%) of brownish powder. HPLC column I, gradient 65% to 90% (10 min) to 90% (10 min) MeOH): R_v(**8**) = 10.4 mL. ^{1}H-NMR (360 MHz, $CDCl_3$): δ 8.27 (s, 2H), 8.00 (s, 2H), 7.65–7.6 (m, ~8H), 7.41–7.33 (m, ~12H), 3.94–3.85 (m, 2H), 3.74 (dd, ^2J = 10.0 Hz, ^3J = 4.6 Hz, 2H), 3.62–3.50 (m, ~4H), 3.40–3.20 (m, ~8H), 3.12 (dd, ^2J = 14.2 Hz, ^3J = 6.6 Hz, 2H), 3.00 (dd, ^2J = 14.2, ^3J = 5.6 Hz, 2H), 2.18–2.0, 2.0–1.85 (2m, ~8H), 1.07 (s, ~18H). ^{13}C-NMR (62 MHz, $CDCl_3$): δ 150.9, 135.3, 132.5, 132.4, 129.7, 127.6, 65.1, 49.2, 47.9, 45.2, 44.6, 43.4, 26.7, 24.9, 22.5, 18.9.

Bis[[(2*R*,8*R*)-8-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3,4,5,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidinyl]-2-methyl]sulfide Bis(hydroperchlorate) (8a). $C_{50}H_{70}N_6Cl_2O_8SSi_2$ (1074.3). HPLC (column II, gradient 10% to 65% (10 min) to 90 (10 min) to 90% (10 min) CH_3CN, flow 1.0 mL/min: R_v(**8a**) = 19.9 mL; R_v(**8**) = 20.1 mL. ^{1}H-NMR (250 MHz, CH_3OH-d_4): δ 7.68–7.65 (m, 8H), 7.43–7.41 (m, 12H), 3.69–3.67 (m, 4H), 3.60 (m, 4H), 3.38–3.34 (m, 10H), 2.93–2.86 (dd, ^3J = 5.5Hz, ^2J = 14.0 Hz, 2H), 2.70–2.61 (dd, ^3J = 8.2Hz, ^2J = 14.0 Hz, 2H), 2.16–2.13 (m, 2H), 1.97–1.83 (m, 6H), 1.07 (s, 18H). ^{13}C-NMR (62 MHz, CD_3CN) δ 151.1, 135.8, 135.7, 133.3, 133.2, 130.4, 128.3, 128.2, 66.2, 50.5, 48.3, 45.4, 45.3, 36.2, 26.5, 25.3, 22.5, 19.1. MS (FAB thioglycerol) m/z: 973 (22, M – $HClO_4$), 874 (26), 452 (8), 420 (26), 406 (13).

Reduction of Disulfide 8 to Thiol 7 and Its Subsequent Alkylation To Give 16. To 92 mg (92 μmol) of disulfide **8** dissolved in 2 mL of CH_3OH was added 94 μL (400 mol %) tributylphosphane at 25 °C. Reduction was complete after 5 min as indicated by HPLC: column I, gradient 10% to 65% (10 min) to 90% (10 min) to 90% (10 min) methanol, flow 1.0 mL/min; R_v(**8**) = 26.0 mL, R_v(**7**) = 21.6 mL. The conversion was also checked by NMR. The ^{1}H-signals of the CH_2S group in **8** centered at 3.10 and 2.89 ppm were replaced by resonances with the same splitting pattern, but located at 2.76 and 2.60 ppm, respectively. Likewise, the ^{13}C resonance of the CH_2S group at 43.1 ppm was shifted upfield to 29.6 ppm. The tertiary carbon signals of **8** having identical chemical shift values (51.5 ppm) now differed substantially (52.6, 51.5 ppm) in **7**. To the crude reaction mixture were added 53 mg (250 μmol, 130 mol %) of phenylpropylmesylate and 48 μL (380 μmol) of tetramethylguanidine and another portion (90 μL) of tributylphosphane, and the mixture was heated to reflux. After 30 min HPLC analysis indicated complete alkylation of **7** to the thioether **16** which was isolated by preparative HPLC. ^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.62–7.60 (m, 4H), 7.41–7.36 (m, 6H), 7.27–7.22 (m, 2H), 7.16–7.14 (m, 3H), 6.98 (br s, 1H), 6.76 (br s, 1H), 3.67 (dd, ^3J = 5.2 Hz, ^2J = 10.5 Hz, 1H), 3.59 (dd, ^3J = 4.6 Hz, ^2J = 10.5 Hz, 1H), 3.51–3.43 (2 × m, 2H), 3.30–3.22 (m, 4H), 2.83–2.72 (m, 1H), 2.67 (t, J = 7.4 Hz, ~2H), 2.6–2.5 (br, 1H + H_2O), 2.13–1.82 (3 × m, 6H), 1.10 (s, 9H). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 150.5, 141.3, 135.6, 135.5, 132.6, 132.5, 130.0, 128.5, 128.35, 127.9, 125.9, 65.3, 49.8, 48.7, 45.5, 45.2, 36.1, 34.6, 32.0, 31.1, 26.8, 24.9, 22.7, 19.1.

X-ray Structure Determination. A specimen of suitable quality grown by slow cooling of a solution of **12** in toluene was mounted in a glass capillary and used for measurements of precise cell constants and intensity data collection. Diffraction measurements were made on an Enraf-Nonius CAD-4 diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.710 69 Å) with ω scan mode at −62 °C. During data collection three standard reflections were measured periodically as a general check of crystal and instrument stability. No significant changes were observed. Lp correction was applied, and intensity data were corrected for absorption effects (DIFABS). The structure was solved by direct methods (SHELXS-86) and refined by full-matrix least squares calculations (SHELXTL).

$C_{25}H_{35}N_3O_5SiClI$: M_r = 648.02, orthorhombic, a = 10.674(2) (1) Å, b = 16.340(2) Å, c = 16.391(1) Å, space group $P2_12_12_1$ [No. 19], Z = 4, D_{calc} = 1.505 g cm^{-1}, F(000) = 1320, μ(Mo – K_α) = 12.8 cm^{-1}. 5512 intensity data were measured up to $(\sin\theta/\lambda)_{max}$ = 0.59 Å^{-1}, and 5006 independent structure factors were considered "observed" [$F_o \geq 4\sigma(F_o)$] and used for refinement. Thirty hydrogen atoms could be located, and five were calculated and included with fixed coordinates and isotropic displacement parameters [$U_{iso(fix)}$ = 0.08]. The function minimized was $\Sigma w(|F_o| - |F_c|)^2/\Sigma wF_o^2]^{1/2}$, $w = 1/\sigma^2(F_o)$. The final R and R_w values were 0.036 and 0.037, respectively (0.045 and 0.046 for the inverse model); number of refined parameters: 325. Residual electron density: +1.4/−1.2 eÅ^{-3} (located at I).

Acknowledgment. This work was supported by the German Ministry of Science and Technology (BMFT) and the Fonds der Chemischen Industrie.

Supplementary Material Available: Copies of ^{1}H-NMR and ^{13}C-NMR spectra of compounds **5**, **6**, **8**, **8a**, and **10–16** (24 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO941706C