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A NOVEL SYNTHESIS OF CHIRAL GUANIDINIUM MOLECULAR HOSTS

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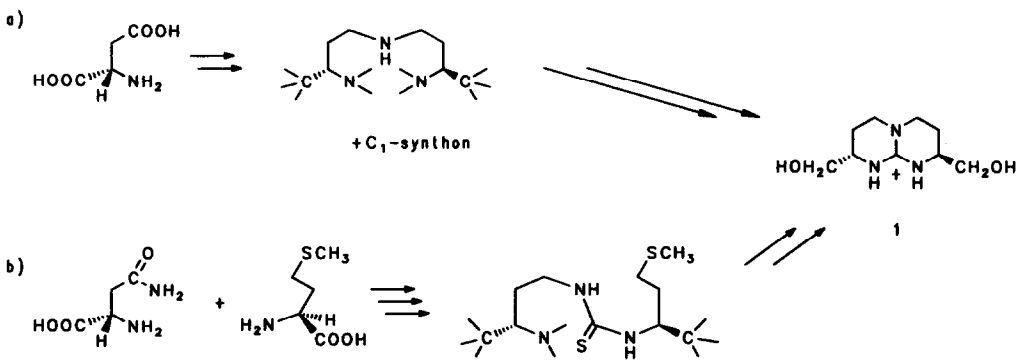
Abstract: Chiral bicyclic guanidinium salts (e.g. 1) were readily prepared from asparagine and methionine via alkylative cyclisation of an open chain thiourea.

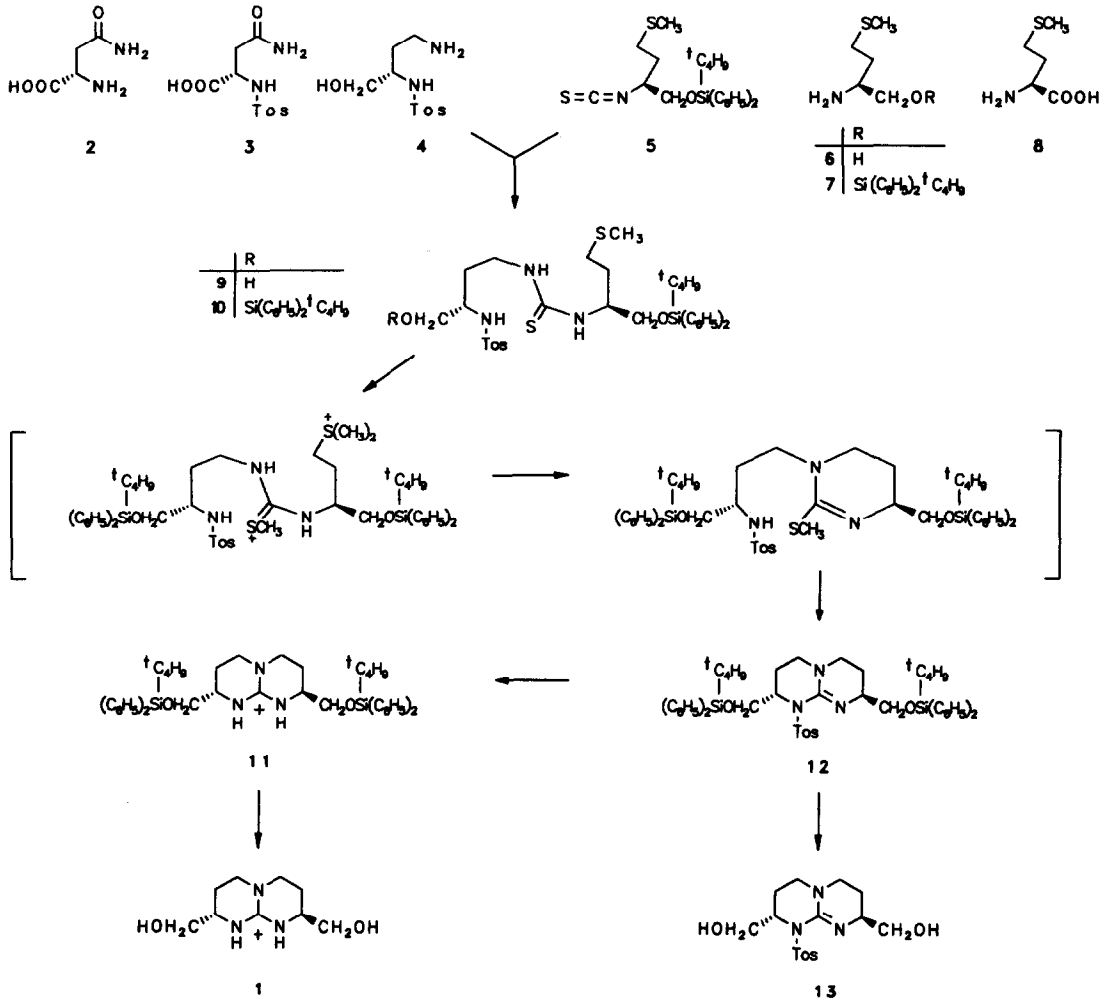
Bicyclic guanidinium compounds mimic anion binding (carboxylates, phosphates) in proteins [1] and have therefore been utilized recently as anchor groups in artificial molecular hosts [2]. Though strategies for the preparation of the chiral analogue 1 have been published [3], their usefulness is hampered by long access pathways, mediocre yields and insecure configurational integrity [4].

Scheme 1



The key step in these syntheses involved the double cyclisation reaction of a C_1-synthon acting on an open chain triamine (scheme 1, route a), itself being obtained from L-aspartic acid. Here a novel route is described (route b) which avoids the low yield bimolecular cyclisation, but still relies on readily available building blocks from the chiral pool. This strategy makes use of two different polyfunctional amino acids to construct the monocyclic halves of the bicyclic skeleton, by virtue of a four-step one-pot double cyclisation reaction of an open chain thiourea compound containing all of the

Scheme 2



requisite atoms of the target already. In addition, the stereochemical configurations and the protecting functions of the ring substituents can be manipulated independently.

Since two of the nitrogen atoms of the guanidinium substructure are contributed by one building block, their differential reaction mode must be warranted. Thus, the initial step (see scheme 2) of the sequence consisted in the tosylation of L-asparagine 2 which after hydride reduction afforded the chiral diaminoalcohol 4 (86%). The partner to react with the terminal prim. amino group of 4 was prepared by reduction of L-methionine 8, protection of the resulting hydroxy group as the diphenyl-t-butylsilylether and transformation of the amino function into the isothiocyanate 5 by thiophosgene in aqueous base (74% for 3 steps). Stirring 4 and 5 in acetonitrile solution at

25°C resulted in the clean formation of the thioruea addition product 9 without any sign of a competing attack of the hydroxy function of 4. However, elaboration of this unsymmetrical thiourea into the guanidinium target structure required the prior conversion into the bissilylether 10. Now the crucial cyclisation sequence could be initiated by methylation of the sulfur atoms. The intermediate sulfonium-isothiuronium compound ring-closed on treatment with tert. amine base in refluxing CH_2Cl_2 in a step wise manner. The product 12 was obtained in 75% yield and proved identical in every respect to the material prepared according to route a (scheme 1) [3b] followed by tosylation. No trace of the diastereomeric compound obtained from D-asparagine and L-methionine could be detected in 12 by HPLC which puts the lower limit of its stereochemical purity to de >98%.

The different protecting groups in 12 could be cleaved selectively. While mild acid treatment removed the silylether functions one after another to produce the hydrolytically sensitive tosylated bishydroxy guanidine 13, electrochemical (Hg-cathode, -2.20 V vs SCE, NH_4Br/CH_3OH) or chemical reduction [6] (Al/Hg, THF/H_2O) resulted in clean deprotection of the guanidine moiety to give 11. Acidic hydrolysis gave the chiral target compound in almost quantitative yield.

This novel strategy marks a considerable improvement with respect to experimental ease, rapidity, stereochemical reliability and yield over the known synthesis of these valuable anchor modules for oxoanionic guests.

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References

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2)a) Echavarren, A., Galán, A., Lehn, J.-M., de Mendoza, J., J. Am. Chem. Soc. 1989, 111, 4994; b) Schmidtchen, F. P., Tetrahedron Lett. 1989, 30, 4493.

3)a) Echavarren, A., Galán, A., de Mendoza, J., Lehn, J.-M., Helv. Chim. Acta 1988, 71, 685; b) Gleich, A., Schmidtchen, F. P., Chem. Ber., in press.

4) The configurational purity of 1 has been claimed [2a], but was not demonstrated and has been questioned [3b].

5) (2S,8S)2,8-Bis(t-butyldiphenylsilyloxymethyl)-1-(4-methylphenylsulfonyl)-1,5,9-triazabicyclo[4.4.0]dec-9-ene12:
To 7.5 mmol of thiourea 10 dissolved in 50 ml dry dichloromethane 500 µl of ethyldiisopropylamine and then 2.12 ml (250 mol%) methyltrifluoromethanesulfonate was added below 10°C. Following a period of 2h at 20°C, the reaction mixture was refluxed with 13 ml ethyldiisopropylamine over night. Product isolation by distribution between ice cold ether and 1 N NaOH yielded a honey like oil on evaporation of the solvent.
360 MHz ^{1}H-NMR ($CDCl_3$) δ = 7.7-7.55 (m, 8H, ArSi), 7.50 (d, J = 8.2 Hz, 2H, H2/6 in Tos), 7.47-7.30 (m, 12H, ArSi), 6.83 (d, J = 8.2 Hz, 2H, H3/5 in Tos), 4.78 (m, 1H, H8), 3.85 (dd, J = 10/4.9 Hz, 1H, CHO at C8), 3.62-3.56 (m, 2H, CHO at C8 and C2), 3.45 (m, 1H, H2), 3.01 (m, 1H, H4), 2.83-2.90 (m, 3H, H4, H6), 2.75 (dd, J = 10/≈10 Hz, 1H, CHO at C2), 2.15 (s, 3H, $TosCH_3$), 2.25-1.95 (m, ≈3H, H3, H7), 1.38 (m, 1H, H3), 1.06, 1.01 (2s, 9H each, tert.butyl); 90.5 MHz ^{13}C-NMR ($CDCl_3$) δ = 144.0, 142.6, 138.3, 135.6, 135.5, 134.0, 133.9, 133.1, 132.9, 129.8, 129.6, 128.5, 128.3, 127.8, 127.6, 127.1 (arom. C), 67.64, 63.7 (C-O), 54.7, 53.1 (C2, C8), 46.7, 44.8 (C4, C6), 26.87 (tert.butyl-CH_3), 25.3 (C3), 24.0 (C7), 21.33 ($TosCH_3$), 19.24 (tert.butyl).
These assignments are based on DQF-Cosy, Tocsy, CH-shift correlation and DEPT spectra.

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