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Synthesis of a Chiral Di(hydroxyalkyl) Substituted Bicyclic Guanidine

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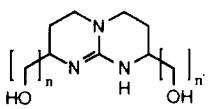
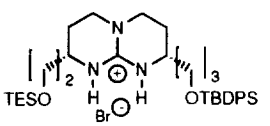
Abstract: Schmidtchen's methodology is used successfully for the synthesis of the chiral disubstituted bicyclic guanidinium salt **2**. The two therefore required primary amine compounds **6** and **9** are obtained from L-methionine and L-glutamic acid, respectively.

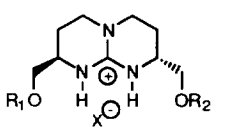
It is known that the esterification of alcohols by (reactive) amides such as acetylimidazole can be accelerated via general base catalysis when a correctly located basic nitrogen is present in the alcohol (cf. first step in the mechanism of serine proteases). Pursuing our interest in developing structural moieties containing suitable functional arrays for that purpose we wished to study the reactivity of bicyclic guanidines carrying primary hydroxyalkyl chains such as in **1** (n, n' = 1, 2 and/or 3).[1] Herein we wish to report the synthesis of the chiral regioselectively functionalized bicyclic guanidinium salt **2**.



1



2

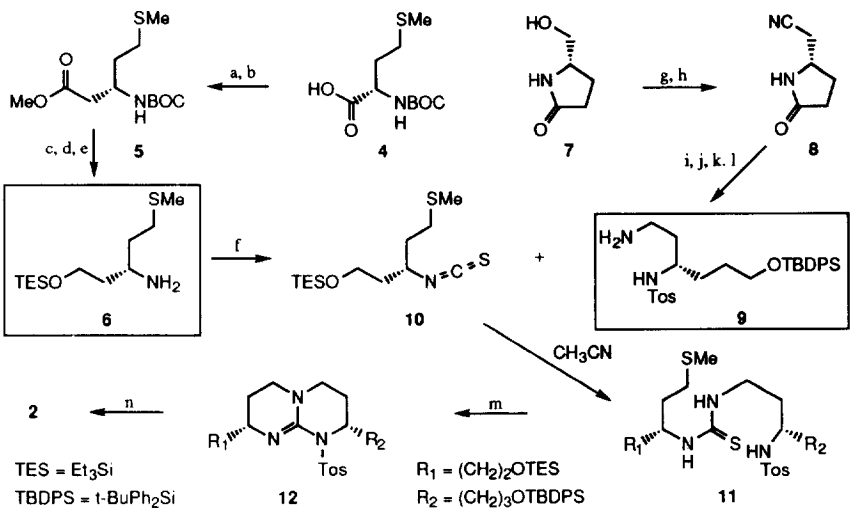


3 R_1, R_2 = H or R_3Si

Interest in the synthesis of bicyclic guanidines rose with the recognition of their capacity to bind oxoanions.[2] Particularly attractive is Schmidtchen's convergent methodology that led to **3** and rests on the bicyclization of a suitably fuctionalized thiourea derivative (cf. **11** -> **12**), the latter being obtained by the formal condensation of two primary amine compounds with thiophosgene.[3] Since the amine compounds are likely to be available from commercial amino acids the method is also configurationally reliable. We further describe the synthesis of the required amines **6** and **9** from L-methionine and L-glutamic acid, respectively, and their further conversion to **2**.

Synthesis of the amine component **6** is based on the homologation of N-BOC protected L-methionine (**4**)[4] via the Arndt-Eistert procedure. Therefore, the mixed anhydride obtained from acid **4** and ethyl chloroformate - triethylamine is directly treated with diazomethane leading to the expected diazoketone (66%). The latter is converted to methyl ester **5** via treatment with silver benzoate (0.02 eq) - triethylamine in methanol (95%).[5] The eventual conversion of ester **5** into amine **6** further involved reduction ($NaBH_4$, THF - 5% MeOH), acidic deprotection of the BOC-amine and silylation of the primary alcohol (95% overall).

The second amine component **9** is obtained via homologation of commercially available (S)-(+)-5-hydroxymethyl-2-pyrrolidinone **7** . This is performed via tosylation, followed by displacement with potassium cyanide (80%). The required amine **9** is obtained from lactam **8** after N-tosylation, lactam opening with NaOMe,[6] reduction (LAH, DME) and silylation of the primary alcohol (45%).



(a) EtOCOCl (1 eq), Et3N (1 eq), THF, 0°C, 2 h, followed by CH_2N_2 (66%); (b) AgOBz (0.02 eq), Et3N (1.2 eq), MeOH, r.t., 3 h (95%); (c) $NaBH_4$ (1.7 eq), THF/5% MeOH (100%); (d) conc. HCl, Me_2S (10 eq) (100%); (e) TESCl, Et3N, DMAP, CH_2Cl_2, r.t. (94%); (f) Cl_2CS, Na_2CO_3, CH_2Cl_2, H_2O (84%); (g) TosCl (1.5 eq), Et3N (2.0 eq), CH_2Cl_2, r.t., 24 h (92%); (h) KCN (3 eq), CH_3CN, Δ, 16 h (86%); (i) TosCl (1.5 eq), NaH (1.4 eq) (87%); (j) NaOMe, MeOH, r.t. (100%); (k) LAH, DME, r.t. (65%); (l) TBDPSCl, imidazole, CH_3CN (79%); (m) MeOTf (2 eq), EtN^iPr_2, CH_2Cl_2, followed by a large excess of EtN^iPr_2 (10 eq); (n) Al/Hg, THF-H_2O, followed by NH_4Br.

The thiourea cyclization precursor **11** is readily synthesized by treatment of isothiocyanate **10** with amine **9** in acetonitrile (84% yield). The isothiocyanate is readily formed from amine **6** via standard thiophosgene / base treatment in a two-phase mixture (84% yield). The final sequence to **2** involves first reaction with two equivalents of methyl triflate. Subsequent heating with a large excess of Hünig's base leads to the N-tosylated bicyclic guanidine **12**. Due to its high sensitivity towards nucleophilic species,[3] **12** is directly detosylated using aluminum amalgam and the resulting guanidine converted to its stable guanidinium salt form **2** (NH_4Br; 80% overall yield).[7, 8]

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References and notes

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4. From L-methionine via treatment with $(BOC)_2O$ / NaOH in H_2O-dioxane, r.t. (92%).
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7. All described compounds gave satisfactory physical and spectral data. ^1H NMR (500 MHz, $CDCl_3$) of **2**: δ 8.30 (1H, br s), 7.96 (1H, br s), 7.63 (4H, m), 7.43-7.36 (6H, m), 3.95 (1H, ddd: 12.2, 8.4, 4.2 Hz), 3.79-3.64 (5H, m), 3.42-3.34 (2H, m), 3.25-3.19 (2H, m), 2.09 (1H, dq: 13.7, 4.6 Hz), 2.00 (1H, dq: 13.7, 4.6 Hz), 1.86-1.60 (8H, m), 1.03 (9H, s), 0.96 (9H, t: 8.0 Hz), 0.60 (6H, q: 8.0 Hz) ppm.
8. The *cis*-derivative **2** is contaminated (^1H NMR) with the corresponding *trans*-derivative. The latter results from the coupling between amino components **6** and **9** that are less than 95% enantiomerically pure (chiral column HPLC). This issue will be delt with in detail in the full account.

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