Synthesis of a Novel C_2-Symmetric Guanidine Base

Andrew Howard-Jones, Patrick J. Murphy,* and Dafydd A. Thomas

Department of Chemistry, University of Wales, Bangor, Gwynedd LL57 2UW, U.K.

Peter W. R. Caulkett

CM and M Department, Zeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, U.K.

Received September 9, 1998

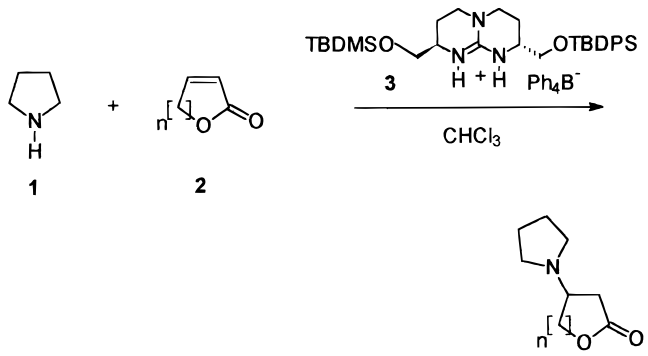
The hydrogen-bond-mediated interaction of guanidinium ions with phosphate- and carboxylate-containing biomolecules is of considerable interest in bioorganic chemistry.[1] Not least of these are the key interactions of the guanidine-containing side chain of arginine residues involved in substrate recognition at enzyme active sites.[1] In addition, the guanidinium motif has also been utilized in synthetic host receptors for phosphate- and carboxylate-containing host molecules which, together with bicyclic amidine systems, are of considerable current interest.[2]

Synthetic applications are also known; for example, tetrasubstituted guanidines have been used in an asymmetric variant of the base-catalyzed nitro-aldol (Henry) reaction, with enantiomeric excesses as high as 54% having been reported,[3] and the Michael addition of pyrrolidine **1** to unsaturated lactones **2** (n = 1, 2) has been reported to undergo an 8.4-fold increase in reaction rate when catalyzed by C_2-symmetric guanidinium salts such as **3** (Scheme 1).[4] The key interaction involved in both these reactions is a two-point hydrogen-bonding interaction of the guanidinium motif with the nitronolate in the Henry reaction and an interaction such as in **4** for the Michael addition (Figure 1).

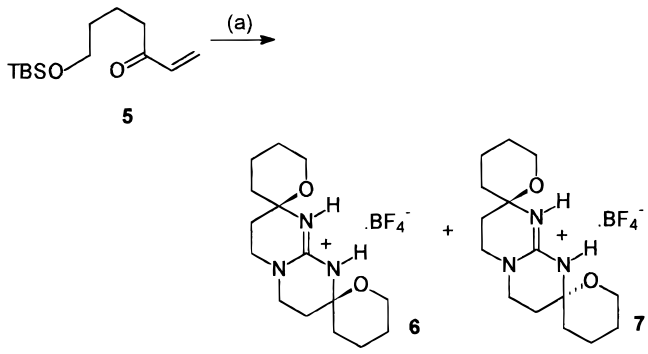
With these considerations in mind, it is not surprising that considerable synthetic effort has been directed toward the synthesis of guanidine- and amidine-containing bases of this general type.[2] To access these homochiral bicyclic guanidines, several groups have employed amino acids or their derivatives as starting points in multistep syntheses.[2]

During a synthetic project directed toward the total synthesis of the marine natural products,[5] we investigated the conjugate addition of guanidine to the vinyl ketone **5** (prepared in a high yielding sequence from 2,3-dihydropyran) and found that, after acid-catalyzed deprotection and subsequent cyclization, the isomeric tetracyclic guanidinium salts **6** and **7** were formed as a 1:1 mixture in an 80% yield (Scheme 2). This distribution of isomers was found to be the equilibrium mixture, as isolation of either isomer and treatment with a catalytic amount of acid resulted in the regeneration of this mixture. On inspection of **7**, it is apparent that if it were available as a single enantiomer and that the propensity for equilibrium could be suppressed, this system could represent a new type of C_2-symmetric guanidine base. Further encouragement of the suitability of this system for this application is illustrated on inspection of the X-ray crystallographic structure of **7** (Figure 2), which confirms that the fluoroborate ion associates with the guanidine in a manner similar to that known in the nitronolate case. It was apparent that if substituents were present on the pyran rings of **7** they would act as conformational "locks" for the system and drive any equilibrium to favor an overall trans arrangement, thus offering the potential for a new route to enantiomerically pure C_2-symmetric guanidine bases.

Scheme 1



Scheme 2[a]



[a] Key: (a) (i) guanidine, DMF, (ii) MeOH, HCl, 0 °C, (iii) saturated aqueous HBF_4; 80% overall, **6**:**7**, 1:1.

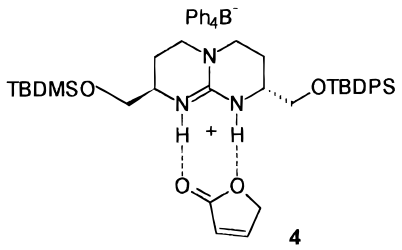


Figure 1.

* To whom correspondence should be addressed. Tel: 01248 382392. Fax: 01248 370528. E-mail: chs027@bangor.ac.uk.

(1) For a comprehensive review of the biological role of the guanidine group see: Hannon, C. L.; Anslyn, E. V. *Bioorganic Chemistry Frontiers*; Springer-Verlag: Berlin, Heidelberg, 1993; Vol. 3, pp 193−255.

(2) For leading references see: Schmidtchen, F. P.; Berger, M. *Chem Rev*. **1997**, *97*, 1609.

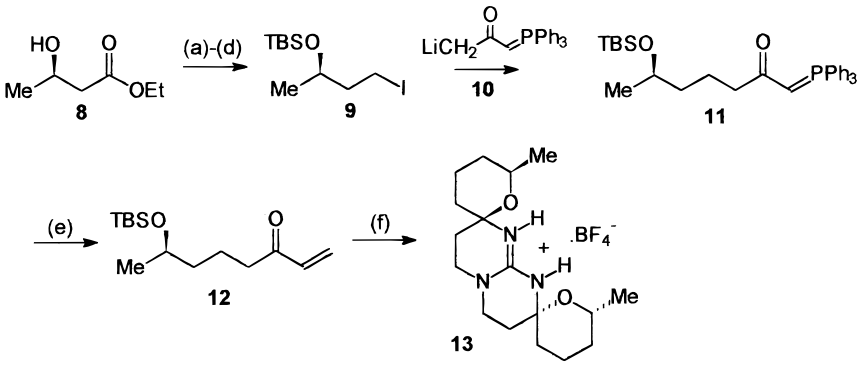
(3) Chinchilla, R.; Najerg, C.; Sanchez-Agullo, P. *Tetrahedron: Asymmetry* **1994**, *5*, 1393.

(4) Alcazar, V.; Moran, J. R.; de Mendoza, J. *Tetrahedron Lett.* **1995**, *36*, 3941.

(5) Murphy, P. J.; Williams, H, L.; Hibbs, D. E.; Hursthouse, M. B.; Abdul Malik, K. M. *Tetrahedron* **1996**, *52*, 8315.

10.1021/jo981841f CCC: $18.00
Published on Web 01/15/1999

Scheme 3[a]



[a] Key: (a) TBDMSCl/Imid/DMF; 99%; (b) DIBAH/hexane/−78 °C; 82%; (c) TosCl/Py; 80%; (d) NaI/acetone; 85%; (e) (i) $CH_3COCHPPh_3$/*n*-BuLi, (ii) H_2O quench, (iii) excess aqueous formaldehyde; 69%; (f) (i) guanidine/DMF/0 °C/16 h, (ii) HCl/MeOH/3 h, (iii) $NaBF_4$/DCM; 44%.

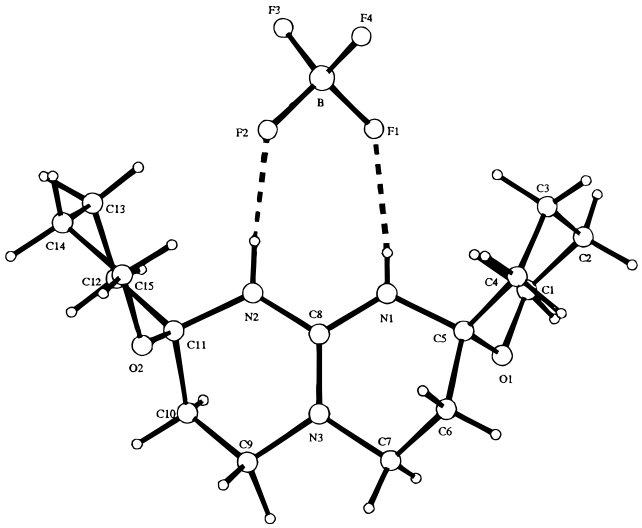


Figure 2.

We embarked upon the synthesis of a suitable substrate for the conjugate addition of guanidine, which was prepared in a straightforward manner using a highly convergent synthetic strategy. Commercially available ethyl (*R*)-3-hydroxybutyrate **8** was converted in four steps (55% overall yield, 7 g scale) to the chiral iodide **9**.[6] This iodide was treated with the readily prepared[7] anion **10** to give the intermediate phosphorane **11**, which on reaction with aqueous formaldehyde gave the α,β-unsaturated ketone **12** in 69% overall yield. Treatment of this substrate with guanidine gave after desilylation and cyclization the required guanidine **13** as a single enantiomer in 44% yield (Scheme 3).

With this material in hand, we decided to investigate its application as a catalyst in the conjugate addition of pyrrolidine **1** to unsaturated lactone **1** ($n = 1$) (Scheme 1).[4] The reaction was carried out under conditions identical to those reported (substrate concentration 0.3 M, 0.1 equiv of catalyst), and it was observed that a 4.3-fold increase in reaction rate was obtained when **13**·HBF_4 was employed as a catalyst. In line with the report of de Mendoza, exchanging the counterion to $HBPh_4$ led to a 16.3-fold increase in reaction rate over the uncatalyzed process, illustrating that **13** is very effective as a catalyst in this process (Table 1). Disappointingly no asymmetric induction was observed in this reaction.

Table 1

base	$t_{1/2q}$/min	rel rate increase
none	115	
13·HBF_4	27	4.3
13·$HBPh_4$	7	16.3
3·$HBPh_4$ (ref 4)		8.4

Despite this, we have demonstrated that our methodology has great potential for the preparation of structurally complex chiral guanidines, and we are currently seeking to extend this chemistry to the preparation of further bases and to investigate their applications in asymmetric processes including catalytic aldol and Michael reactions.

Experimental Section

(*R*)-6-Oxo((*tert*-butyldimethylsilyl)oxy)oct-7-ene (12). Acetylmethylenetriphenylphosphorane (6.53 g, 20.5 mmol) was dissolved in dry THF (120 mL) and cooled (−78 °C), and *n*-BuLi (9.32 mL, 20.5 mmol) was added. The deep red solution of **10** that formed was allowed to stir at −60 °C for 1 h, after which time the reaction was cooled to −78 °C and (*R*)-3-((*tert*-butyldimethylsilyl)oxy)-1-iodobutane **9**[6] (6.95 g, 22.14 mmol) in THF (42 mL) was added. The reaction was then warmed slowly to ambient temperature and stirred overnight. Water (90 mL) was added, the solution was extracted with DCM (3 × 50 mL) and dried ($MgSO_4$), and the solvent was reduced by rotary evaporation to a volume of approximately 50 mL. Formaldehyde solution was prepared by adding aqueous formaldehyde (90 mL) to DCM (50 mL) and the water removed by adding excess $MgSO_4$; this solution was then filtered into the reaction mixture, and stirring was continued overnight. The reaction was then diluted with ether (60 mL), washed with water (2 × 60 mL), and dried ($MgSO_4$), and the solvent was removed by rotary evaporation. Column chromatography (4% ether/petroleum ether) gave the title compound as a clear oil (3.62 g, 69%).

$[\alpha]^{21}_D$: −13.4° ($c = 1.12$ [$CHCl_3$]). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.05 (6H, s, 2 × CH_3), 0.88 (9H, s, 3 × CH_3), 1.14 (3H, d, J = 6.1 Hz), 1.37−1.73 (4H, cm), 2.57 (2H, d, J = 7.3 Hz), 3.79 (1H, app sextet, J = 6.0 Hz), 5.81 (1H, dd, J = 1.5, 10.1 Hz), 6.21 (1H, dd, J = 1.5, 17.6 Hz), 6.36 (1H, dd, J = 10.1, 17.6 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): 200.75 (C=O), 136.48 (CH), 127.8 (CH_2), 68.3 (CH), 39.62 (CH_2), 39.02 (CH_2), 25.84 (3 × CH_3), 23.68 (CH_3), 20.19 (CH_2), 18.06 (C), −4.44 (CH_3), −4.79 (CH_3) ppm. IR ν_{max}: 2942 (CH), 1684 (C=O), 1616 (C=C). *m/z* (CI): 257 (5, $[M + H]^+$), 201 (45, $[M + H - t\text{-Bu}]^+$), 132 (50), 74 (100). HRMS: found, 257.1937 ($[M + H]^+$), $C_{14}H_{29}O_2Si$ requires 257.1937. Anal. Calcd for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.00. Found: C, 65.71; H, 10.81.

(6) (a) Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 6187. (b) Garegg, P. J.; Samuelsson, B.; *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866.

(7) Taylor, J. D.; Wolf, J. F. *J. Chem. Soc., Chem. Commun.* **1972**, 876.

(6*R*,6″*R*,2*R*,2″*R*)-6,6″-Dimethyldispiro[tetrahydropyran-2,2′-(2,3,4,6,7,8-Hexahydro-1*H*-pyrimido[1,2-*a*]pyrimidine)-8′,2″-tetrahydropyran]-9′-ium Tetrafluroborate 13. (*R*)-6-Oxo((*tert*-butyldimethylsilyl)oxy)oct-7-ene (**12**) (1.99 g, 7.77 mmol) was dissolved in dry DMF (35 mL) and cooled (0 °C), and a solution of guanidine (0.229 g, 3.89 mmol) in DMF (1 mL) was added dropwise over 5 min. The reaction was stirred for 15 min before being allowed to warm to ambient temperature and then stirred overnight. The reaction was then cooled (0 °C), methanolic HCl (40 mL; prepared by adding acetyl chloride (4 mL) to methanol (36 mL)) was added, and the mixture was allowed to warm to ambient temperature and stirred for 3 h. After dilution with DCM (200 mL), the reaction was washed with saturated LiBr solution (3 × 150 mL) and water (3 × 100 mL); the aqueous washings were back-extracted with DCM, and the combined organic washings were dried over $MgSO_4$. The solvent was removed by rotary evaporation until approximately 30 mL of solution remained, whereupon a saturated solution of $NaBF_4$ (30 mL) was added and the solution stirred vigorously overnight. The organic phase was then separated, washed with water (3 × 30 mL), and dried ($MgSO_4$) and the solvent removed by rotary evaporation. Purification by column chromatography (gradient elution with neat chloroform to 1.5% methanol in chloroform in 0.25% steps of 140 mL each) gave the title compound as a crystalline solid (670 mg, 44%, mp 181−182 °C (Et_2O/petroleum ether)).

$[\alpha]^{21}_D$: +45.2° (c = 0.65 [$CHCl_3$]). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.11 (6H, d, J = 6.1 Hz, 2 × CH_3), 1.18 (2H, m, 2 × CH), 1.50−2.20 (14H, cm), 3.22 (2H, ddd, J = 1.6, 5.8, 12.5 Hz, 2 × CH), 3.68 (2H, apparent dt, J = 5.0, 12.5 Hz, 3.84 (2H, ddq, J = 2.1, 11.8, 6.1 Hz, 2 × CH) 7.50 (2H, br s, 2 × NH) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): 148.41 (C), 78.94 (2 × C), 67.02 (2 × CH), 42.83 (2 × CH_2), 33.63 (2 × CH_2), 33.10 (2 × CH_2), 32.15 (2 × CH_2), 21.81 (2 × CH_3), 17.56 (2 × CH_2) ppm. IR ν_{max}: ($CHCl_3$) 3378 (NH), 3035, 2944 (CH), 1667, 1600 (C═N). ***m/z*** (CI): 308 (100, $[M]^+$). HRMS: found 308.2338 ($[M]^+$), $C_{17}H_{30}N_3O_2$ requires 308.2338. Anal. Calcd for $C_{17}H_{30}N_3O_2BF_4$: C, 51.66; H, 7.65; N, 10.63. Found: C, 51.34; H, 7.53; N, 10.30.

Acknowledgment. Thanks are given to Zeneca Pharmaceuticals and the EPSRC for a CASE studentship to D.A.T. and the ESF and the University of Wales for funding work performed by A.H.J. The support of the EPSRC Mass Spectrometry Centre at Swansea and the EPSRC X-ray crystallography service at Cardiff is also acknowledged.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **12** and **13** (8 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.

JO981841F