Synthetic Studies towards Ptilomycalin A using a Biomimetic Approach

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Two model compounds, the tetracycle **2** and the tricycle **9** are prepared using a biomimetic synthetic approach to the guanidine-containing natural product ptilomycalin A **1**.

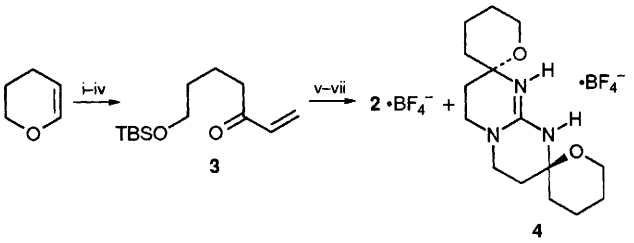
Molecules containing guanidine subunits are of considerable biological interest, owing to the hydrogen-bond mediated interaction of guanidinium ions with phosphate-containing biomolecules[1] and hypotensive and adrenergic neuron blocking effects.[2] Additionally, cyclic marine-derived guanidines, saxitoxin, ptilocaulin and tetrodotoxin, are potent ion-channel blockers with neuroscientific and synthesis interest.[3] Ptilomycalin A has been isolated from the sponge *Ptilocaulis spiculifer* and shown to have antifungal, antiviral and antitumour activity.[4] Structural elucidation has shown that it possesses the unique pentacyclic guanidine structure **1**.

Prompted by recent reports[5] detailing the synthesis of tricyclic BCD and CDE models of **1**, we now present the preparation of a tetracyclic ABDE model **2** and tricyclic BCD model **9**. Retrosynthesis illustrates the possibility of the rapid biomimetic[5a] construction of **2** (and **1**) *via* a double Michael addition of guanidine with two α, β unsaturated ketones with subsequent bis-spirocyclisation, Scheme 1.

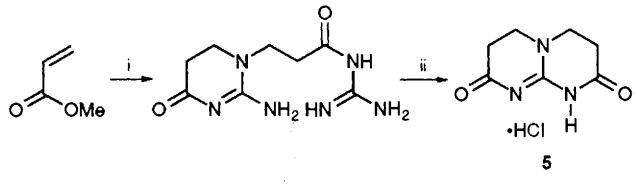
To test this hypothesis we prepared the vinyl ketone **3** *via* a four-step route from 2,3-dihydropyran (hydrolysis, vinyl magnesium bromide, selective silylation and oxidation). Reaction of **3** with 0.5 equiv. of guanidine in DMF for 4 h followed by removal of solvent, deprotection/cyclisation with methanolic HCl and counter ion exchange, led to the formation, in 80% yield, of a 1 : 1 mixture of **2** our desired *syn*-spirocyclic compound and **4**, the corresponding *anti* isomer, Scheme 2. The *syn* product **2** was separated from the mixture by crystallisation ($CHCl_3/CCl_4$; 1 : 2) and the structures of both **2** and **4** were confirmed by X-ray crystallography.†

The X-ray result showed that **2** crystallized as a CCl_4 solvate and that the $[C_{15}H_{26}N_3O_2]^+$ cation in this product has a crystallographic mirror plane passing through the N(2) and C(8) atoms (Fig. 1) while the cation in **4** has an approximate two-fold axis. The bond lengths and angles in the two cations are very similar and the two N–H groups in both forms are hydrogen bonded to two F atoms of the BF_4^- anions.

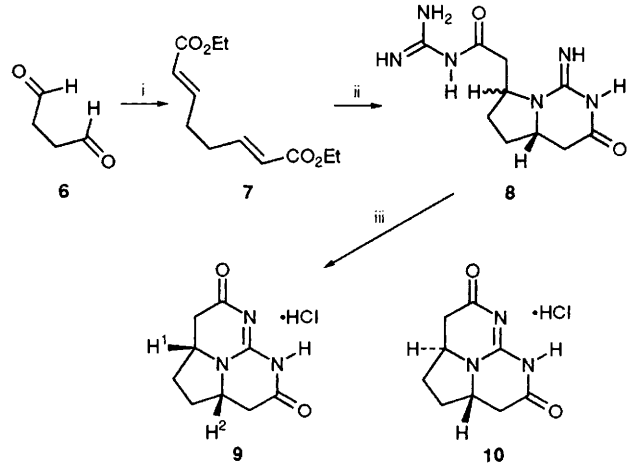
We have also investigated the preparation of a tricyclic BCD model based upon the observation[7] that free guanidine undergoes a double Michael addition and subsequent cyclisation with methyl acrylate to give a pyrimido[1,2-a]pyrimidinedione **5** (Scheme 3). Preparation of a suitable substrate for our model reaction was straightforward, treatment of succinaldehyde **6** with 2 equiv. of carboethoxymethylenetriphenylphosphorane gave the requisite unsaturated diester **7**. Reaction of **7** with guanidine gave the intermediate bicycle **8** as a 2 : 1 mixture of stereoisomers in 25% yield;‡ this mixture was converted to the tricyclic model compounds **9** and **10** in a 2 : 1 ratio by treatment with conc. hydrochloric acid (Scheme 4). The structure of the major isomer **9** was confirmed by the observation of reciprocal NOE between protons H^1 and H^2,



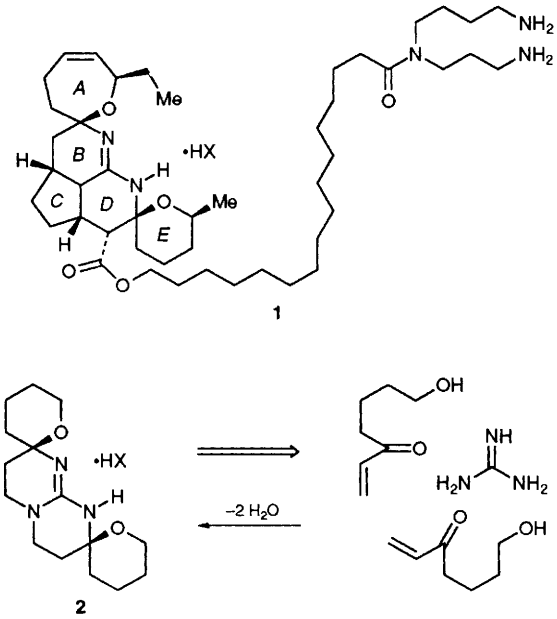
Scheme 2 *Reagents and conditions*: i, 0.1 mol dm^{-3} HCl, 5 min; 75%; ii, CH_2=CHMgBr, THF; 70%; iii, TBDMSCl, imidazole, DMF; 98%; iv, PCC, CH_2Cl_2, celite; 78%; v, guanidine, DMF; vi, MeOH, HCl, 0 °C; vii saturated aq. HBF_4, 80% overall, **2**:**4**, 1 : 1



Scheme 3 *Reagents*: i, guanidine, DMF; ii, conc. HCl



Scheme 4 *Reagents*: i, 2 equiv. EtO_2CCH=PPh_3; 78%; ii, guanidine, DMF; 25%; iii, conc. HCl; 100%, **9**:**10**, 2 : 1



Scheme 1

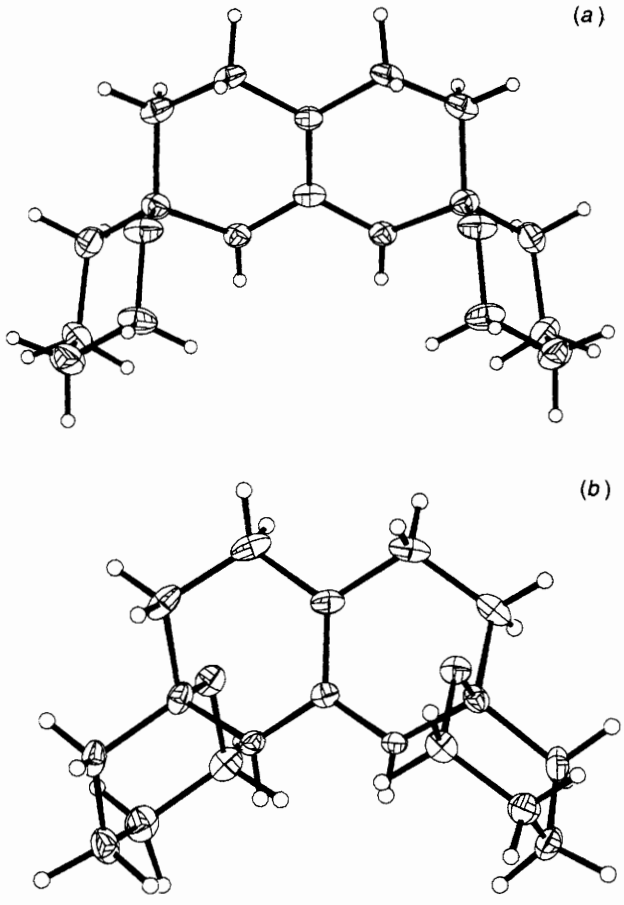


Fig. 1 Structure of the $[C_{15}H_{26}N_3O_2]^+$ cation of **2**(*a*) and of **4**(*b*). Selected bond lengths (Å) in **2** (with the corresponding values in **4** in parentheses) are: N(1)–C(8) 1.344(6) [1.339(4), 1.349(4)]; N(2)–C(8) 1.322(10) [1.321(4)]; N(1)–C(5) 1.459(5) [1.471(4), 1.470(4)]; N(2)–C(7) 1.466(6) [1.472(5), 1.471(5)]; C(5)–O(1) 1.415(6) [1.428(4), 1.425(4)]; C(1)–O(1) 1.439(7) [1.439(4), 1.447(5)]. The two values given in each case for **4** correspond to the two pseudosymmetrical related halves of the ion.

isomer **10** did not show a corresponding NOE.§ This selectivity observed in this reaction is somewhat surprising as molecular mechanical calculations suggest that the preferred reaction conformation should lead to **10** as the major product; we cannot yet rationalise this result.¶

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Footnotes

† *Crystal data* for compound **2**: $[C_{15}H_{26}N_3O_2][BF_4].CCl_4$, M_r = 521.01, orthorhombic, *Pmna*, a = 19.752(6), b = 11.713(4), c = 9.551(4) Å, U = 2209.7 Å^3, Z = 4, D_c = 1.566 g cm^{-3}, $F(000)$ = 1072, T = 150 K.

For **4**: $[C_{15}H_{26}N_3O_2][BF_4]$, M_r = 367.19, monoclinic, $P2_1/c$, a = 11.755(2), b = 8.729(2), c = 16.952(4) Å, β = 94.66(2)° U = 1733.7 Å^3, Z = 4, D_c = 1.407 g cm^{-3}, $F(000)$ = 776, T = 150 K.

All crystallographic measurements were made using a FAST area detector diffractometer and Mo-Kα radiation, following previously described procedures.[6] The structures were solved by direct methods and refined by full matrix least-squares to final conventional R values of 0.066 for 995 observed [$F_o > 4\sigma(F_o)$] data and 168 parameters for **2** and 0.043 for 2130 observed [$F_o > 4\sigma(F_o)$] data and 330 parameters for **4**. Full details of data collection and structure refinement, atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

‡ Considerable decomposition was observed during this reaction, this is attributed to competitive deprotonation and polymerisation of **7** under the reaction conditions; this was not observed during the preparation of **2** and **4**.

§ The central guanidine is not the site of protonation of these structures; this removes the possibility of any symmetry and enables us to perform this experiment. The ^{1}H and ^{13}C spectra of the hydrochloride salt contain individual signals for each nucleus present; in contrast the corresponding hydrogen carbonates of **9** and **10** display protonation at guanidine and an element of symmetry in the corresponding spectra. This is almost certainly due to the nature of the counter ion.

§ The stereochemical outcome of pyrrolidine ring formation in the intermediate **8** is presumbably under kinetic control; our calculations are based on hypothetical precursors to **8**. (Package used: HYPERCHEM on a Silicon Graphics Workstation using MM2 force field parameters.)

References

1 F. A. Cotton, V. W. Day, E. E. Hazen Jr and S. Larsen, *J. Am. Chem. Soc.*, 1973, **95**, 4834.
2 A. G. Gilmour, L. S. Goodman and A. Gilman, *The Pharmacological Basis of Therapeutics*, 6th edn., MacMillan, New York, 1980, p. 198.
3 For leading references see: E. J. Corey and X. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York, 1989, p. 366.
4 Y. Kashman, S. Hirsh, O. J. McConnell, I. Ohtini, T. Kusumi and H. Kakisawa, *J. Am. Chem. Soc.*, 1989, **111**, 892.
5 (*a*) B. Snider and Z. Shi, *Tetrahedron Lett.*, 1993, **34**, 2099; (*b*) L. E. Overman and M. H. Rabinowitz, *J. Org. Chem.*, 1993, **58**, 3235.
6 A. A. Danopoulos, G. Wilkinson, B. Hussain-Bates and M. B. Hursthouse, *J. Chem. Soc., Dalton Trans.*, 1991, 1855.
7 K. Sugino and T. Tanaka, *J. Org. Chem.*, 1968, **33**, 3354.