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A Biomimetic Approach to the Manzamine Alkaloids

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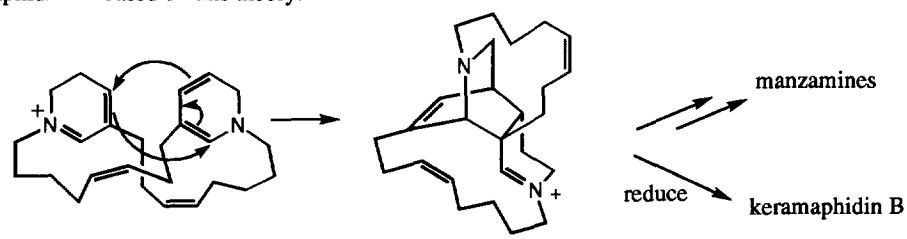
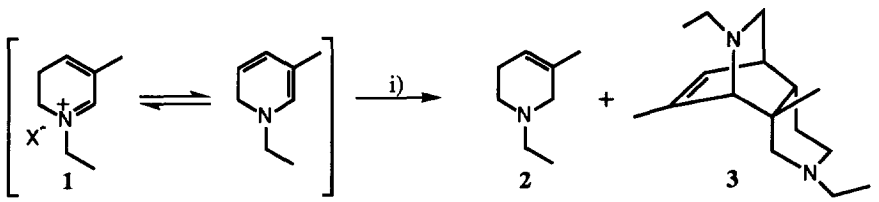
Abstract: *Results from model studies of a synthetic approach to the manzamine alkaloids based on a biogenetic theory are reported together with the synthesis of a plausible biogenetic precursor to these alkaloids.* Copyright © 1996 Elsevier Science Ltd

In 1992 we proposed[1] a plausible biosynthetic pathway (Scheme 1) to the structurally complex family of marine alkaloids, the manzamines, and we have recently reported[2] the results of model studies directed towards the biomimetic synthesis of these compounds. We now disclose further results arising from the model studies and outline the synthesis of the biogenetic precursor to manzamines A[3] and B[4] and keramaphidin B[5] based on this theory.



Scheme 1

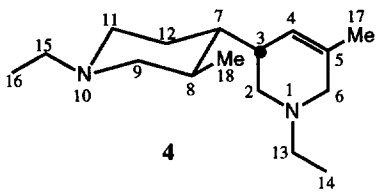
Previously,[2] we reported that treatment of the simple dihydropyridinium salt **1** (X=CF_3CO_2) with pH 8.3 buffer followed by reduction with sodium borohydride at the same pH yielded the tetrahydropyridine **2** as the major product together with the cycloadduct **3** in up to 10% yield (Scheme 2).



Reagents/Conditions; i) pH 8.3 TRIS/HCl buffer, RT, 18h, then $NaBH_4$, H_2O, CH_3OH; 10% yield of **3**.

Scheme 2

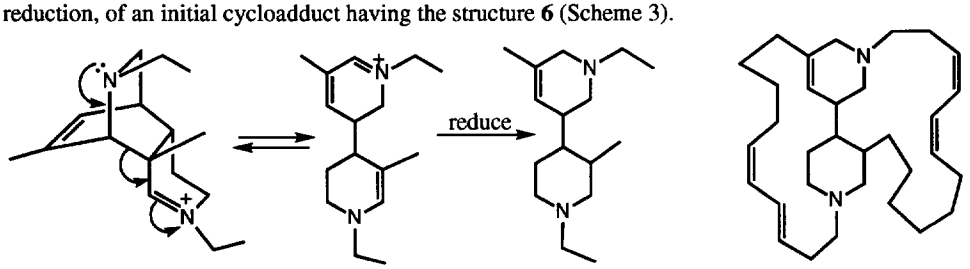
Further chromatographic analysis and purification of the crude product arising from this reaction has resulted in the isolation of a new, minor component (<4% yield) which has been assigned the partially reduced bi-pyridyl structure **4**.[6] This structure was confirmed by comprehensive NMR analysis.[7] In particular, homonuclear nOe difference experiments were performed to prove the connectivity between the rings and to establish their relative conformations. The results of these experiments were consistent with a structure having the relative stereochemistry shown below, in which the two rings are approximately orthogonal and the dihedral angle between H3 and H7 is almost 90°. This is consistent with the absence of observable coupling between these protons.



4

Saturated Proton	nOe
H4	H3; 2.3%, H17; 4.3%, $H12_{eq}$; 2.1%, H7; 4.5%
$H2_{ax}$	$H2_{eq}$; 18.9%, $H6_{ax}$; 2.4%, $H12_{ax}$; 5.0%
$H12_{ax}$	$H11_{eq}$; 2.5%, $H2_{ax}$; 5.0%, $H12_{eq}$; 8.8%
H18	$H9_{eq}$; 3.1%, H3 and $H2_{eq}$; 9.1% H8 and $H9_{ax}$; 9.1%, H7; 1.8%

It is informative to note the similarity of the structure **4** to the central core of halicyclamine A **5** recently reported by Crews *et al.*[7] We suspect that **4**, like **5**, arises from fragmentation, followed by reduction, of an initial cycloadduct having the structure **6** (Scheme 3).



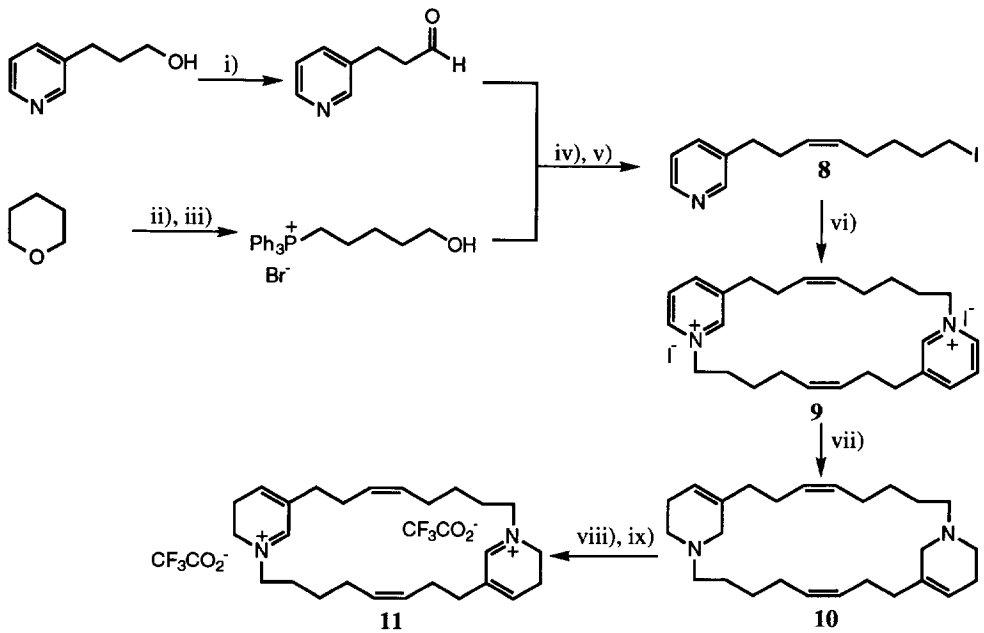
6 **7** **4** **5** halicyclamine A

Scheme 3

Extensive monitoring of the cycloaddition-reduction sequence by ^1H NMR under a variety of reaction conditions has allowed optimisation of the ratio of cycloadduct **3** to fragmentation product **4** with a consequent improvement in the isolated yield of **3**. Thus, in a typical experiment, the dihydropyridinium salt **1** (X=BF_4) was stirred in pH 8.3 TRIS/HCl buffer for 40 hours before the pH of the medium was adjusted to 6.5-7 and an equivalent of $NaBH_4$ was added to the mixture. After 3 hours, analysis of the crude product by ^1H NMR showed the presence of both **3** and **4** in an 8:1 ratio, together with the tetrahydropyridine **2**. Purification by flash chromatography on neutral Al_2O_3 (CH_2Cl_2/MeOH) furnished the cycloadduct **3** in 20-25% yield. The choice of pH at which the reduction step is carried out is crucial; changing to a more basic medium invariably resulted in a poorer ratio of **3** to **4**. We believe that this observation is indicative of a dynamic equilibrium between the initial cycloadduct **6** and fragmentation product **7**, which normally lies substantially in favour of **6**. Indeed, in all experiments, examination of the reaction medium by ^1H NMR prior to reduction indicated only very minor quantities of **7**. The increase in the relative amount of reduction

of **6** compared to **7** at pH 7 is thought to be due to protonation of the bridge nitrogen which disfavours fragmentation.

The success of these early studies has reinforced our proposal that a biomimetic synthesis of keramaphidin B, and subsequently manzamine B, should be feasible using the approach outlined above. To this end we have accomplished the synthesis of the bis-dihydropyridinium species **11**, a plausible biogenetic precursor to these alkaloids, in 9 steps from pyridine-3-propanol and tetrahydropyran.



Reagents/Conditions; i) DMSO, $(COCl)_2$, Et_3N, DCM, -65°C to RT, 90% ii) AcBr, Zn dust, Δ, 95% iii) Ph_3P, 100°C, 12h and then K_2CO_3, H_2O, MeOH, 76% iv) $^tBuO^-K^+$, THF, -60°C to RT, 66% v) Ph_3P, I_2, imidazole, CH_3CN, Et_2O, 56-90% vi) 40mM solution in acetone, reflux, 96h, 40-44% vii) $NaBH_4$, H_2O, MeOH, 66% viii) *m*CPBA, DCM, 100% ix) $(CF_3CO)_2O$, DCM, 100%

Scheme 4

The strategic transformation in this sequence was the cyclodimerisation to give the bis-quaternary salt **9**. After investigation into the effects of varying the leaving group, solvent, temperature and concentration, the optimum conditions for this transformation were found (Scheme 4). During the reaction a finely divided white solid precipitated from the reaction mixture which was isolated and characterised as the dimer **9**. This material can now be prepared on a multi-gram scale in 40-44% yield from **8**. It was clearly necessary to prove conclusively the dimeric nature of this product and exclude the possibility that it contained an alternative ring size or a mixture of oligomers. A highly crystalline bis-perchlorate salt was prepared by ion exchange chromatography and crystallisation from acetone/diethyl ether provided a crystal suitable for X-ray crystallographic analysis (Figure 1). Furthermore, the FAB mass spectrum of the diiodide displayed a parent ion at 503 corresponding to $[MI]^+$ and chemical evidence was obtained by reduction of **9** with $NaBH_4$ in H_2O/MeOH which gave the *symmetrical* bis-tetrahydropyridine **10** in 66% yield after separation from an unsymmetrical regioisomer.

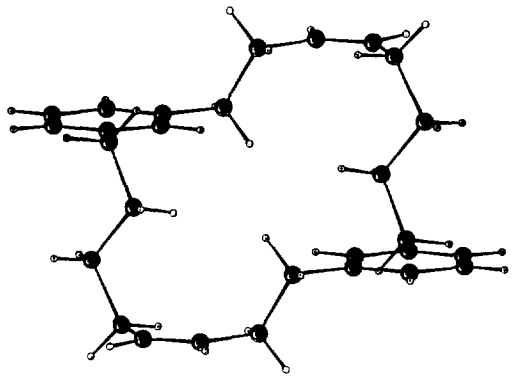


Figure 1

The symmetrical bis-tetrahydropyridine **10** has been readily transformed to the bis-dihydropyridinium salt **11** in quantitative yield[9] and we are currently investigating the behaviour of this compound under the conditions optimised for the model system. We will report our findings arising from this investigation in due course.

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7. Selected spectroscopic data for **4**;
   δ_H(500 MHz; $CDCl_3$) 5.15 (1H, br s, 4-H), 3.01 (1H, br d, *J* 16Hz, 6-H_{eq}), 2.97 (1H, m, 11-H_{eq}), 2.88 (1H, ddd, *J* 10.5, 2.5, 2.5Hz, 9-H_{eq}), 2.75 (1H, m, 3-H_{ax}), 2.71 (1H, m, 2-H_{eq}), 2.52 (1H, br d, *J* 15.5Hz, 6-H_{ax}), 2.51-2.39 (2H, m, 13-H), 2.37 (2H, q, *J* 7.5Hz, 15-H), 1.97 (1H, dd, *J* 10.5, 10.5Hz, 2-H_{ax}), 1.79 (1H, ddd, *J* 12, 12, 3Hz, 11-H_{ax}), 1.65 (3H, s, 17-H), 1.61 (1H, m, 8-H_{ax}), 1.55 (1H, dd, *J* 10.5, 10.5Hz, 9-H_{ax}), 1.52 (1H, dddd, *J* 13, 3, 3, 3Hz, 12-H_{eq}), 1.40 (1H, dddd, *J* 12.5, 12.5, 12.5, 4Hz, 12-H_{ax}), 1.09 (3H, t, *J* 7.5Hz, 14-H), 1.07 (3H, t, *J* 7.5Hz, 16-H), 1.05 (1H, m, 7-H_{ax}), 0.89 (3H, d, *J* 6Hz, 18-H); δ_C(125.7 MHz; $CDCl_3$) 132.4 (C5), 124.7 (C4), 62.2 (C9), 56.5 (C6), 54.2 (C11), 52.5 (C15), 52.2 (C13), 50.2 (C2), 46.3 (C7), 35.8 (C3), 32.7 (C8), 26.2 (C12), 21.0 (C17), 17.0 (C18), 12.0 (C14), 12.0 (C16); *m/z* (CI/NH_3) 251 (MH^+, 100%), 124 (15); (Found: M^+ 250.2409. $C_{16}H_{30}N_2$ requires 250.2409).
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