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A Biomimetic Approach to the Manzamine Alkaloids; Model Studies

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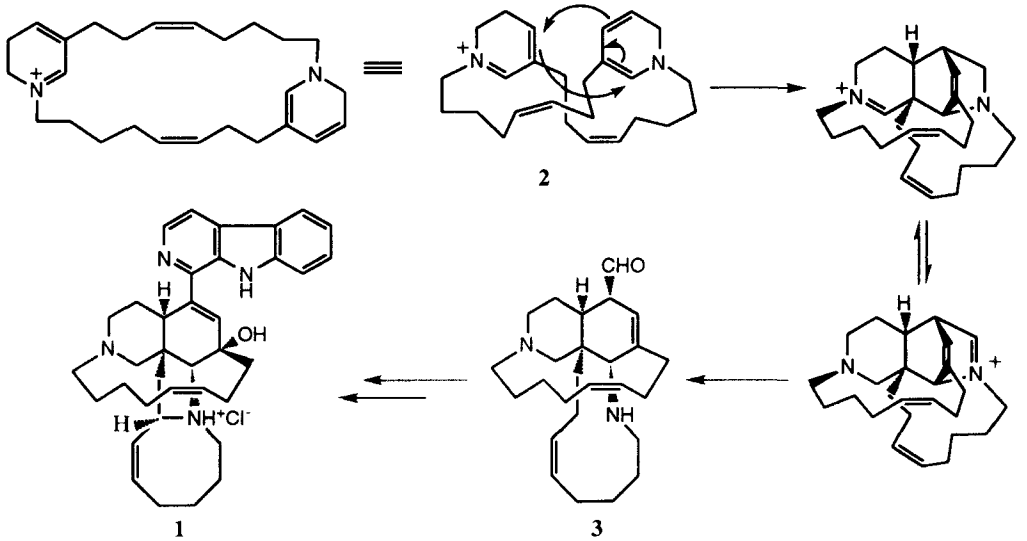
Abstract: *An approach to the manzamine alkaloids based on a biogenetic theory has been investigated using a simple model system and the key cycloaddition step has been accomplished in moderate yield.*

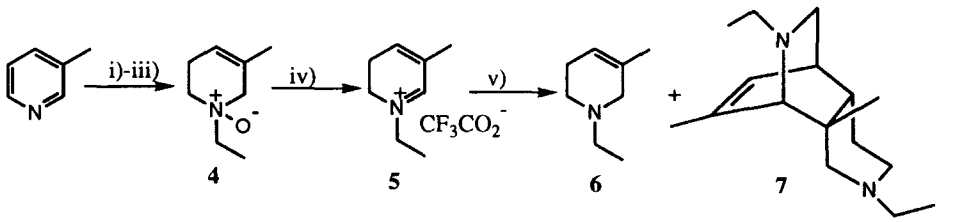
The manzamine alkaloids constitute a small family of unusual β–carboline alkaloids which have been isolated from three different genera of marine sponges.[1-3] The unprecedented structure of manzamine A **1** led the discoverers to conclude that there was "no obvious biogenetic path" for this compound.[1] However, the structural complexity of the alkaloids, coupled with their potent antileukaemic and cytotoxic properties has made them challenging targets for organic synthesis.[4]

Recently, we have proposed that the central tetracyclic ring system of the more complex manzamines is biosynthesised *via* an intramolecular Diels-Alder reaction of the tri-cycle **2** wherein the diene component is a dihydropyridine and the dienophile a conjugated iminium ion.[5] Subsequently, disproportionation followed by hydrolysis of the intermediate iminium ion gives a tetracyclic aldehyde **3** which is finally transformed to the manzamines *via* reaction with tryptophan.



1 **2** **3**

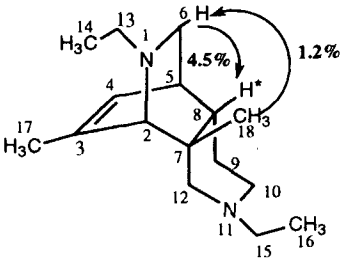
To our knowledge, there is little literature precedent for cycloadditions of the kind implicated in this proposal, although a similar reaction pathway was recently invoked to explain the decomposition of the N-methyl-4-phenyl-5,6-dihydropyridinium ion (MPDP+).[6] We have therefore initiated an investigation into this reaction type and now report our findings using a simple model system.



Reagents i) CH_3CH_2Br, acetone, reflux, 86%. ii) $NaBH_4$, H_2O, CH_3OH, 55%.iii) *m*CPBA, CH_2Cl_2, 87%. iv) $(CF_3CO)_2O$, CH_2Cl_2. v) pH 8.3 TRIS/HCl buffer, RT, 18hrs, then $NaBH_4$, H_2O, CH_3OH; 10% yield of **7** from **4**.

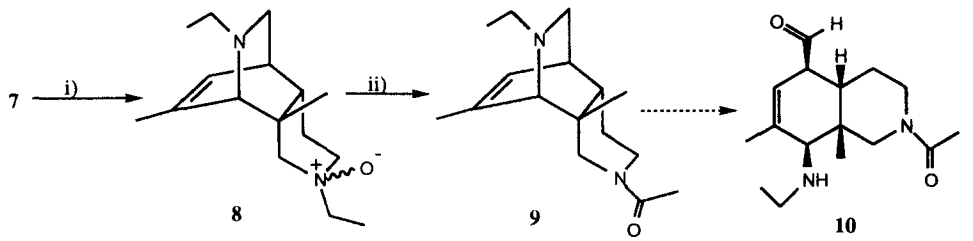
The 3-substituted 5,6-dihydropyridinium ion **5** was prepared using standard chemistry.[7] Subsequent treatment of **5** in pH 8.3 buffer for 18 hours followed by reduction with excess sodium borohydride furnished the tetrahydropyridine **6** as the major product, together with another component which was isolated by preparative chromatography. Extensive NMR analysis of this material has shown it to be the *endo* cycloadduct **7**[8] which is presumed to arise from cycloaddition of a 1,6-dihydropyridine onto the conjugated iminium ion **5**.

All NMR experiments were performed on a 1.5mg sample in CD_3OD on a 500MHz spectrometer. ^1H correlations were obtained from a double-quantum filtered COSY (DQF-COSY) experiment and the structural fragments identified were consistent with **7**. ^{13}C multiplicities were obtained from DEPT experiments and were also consistent with **7**. Further analysis utilised nOe difference experiments which enabled placement of the ethyl groups identified in the DQF-COSY experiment, assignment of the diastereotopic methylene ring protons and identification of the cycloadduct as being the *endo* isomer. NOe's that assign the product as being the *endo* cycloadduct are shown below.



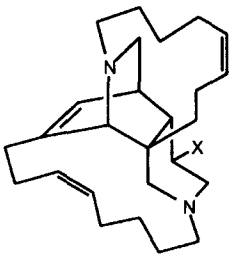
The proton marked with an asterisk was unsuitable for selective irradiation as its multiplet was coincident with part of a neighbouring resonance. NOe's onto this proton however, were distinct. ^{13}C assignments were obtained from a BIRD-HMQC experiment.[9]

Oxidative cleavage of the N1-C6 bond, in a manner analogous to that involved in the proposed biosynthesis of the manzamines, requires differentiation of the two nitrogen atoms in the cycloadduct **7**. This has been accomplished synthetically by treatment of **7** with one equivalent of *m*CPBA in dichloromethane which furnished the N-oxide **8** as a mixture of diastereoisomers in 75% yield. Subsequent exposure of **8** to acetic anhydride in dichloromethane gave the acetamide **9** as the major product. It is envisaged that subsequent oxidative cleavage of the N1-C6 bond will furnish the amino-aldehyde **10** possessing the hydroisoquinoline framework present in the ircinals[10] and the manzamines.

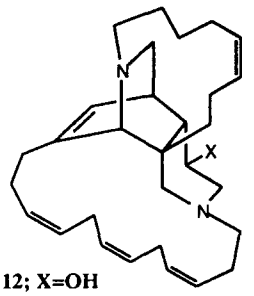


i) *m*CPBA, CH_2Cl_2, 75% ii) $(CH_3CO)_2O$, CH_2Cl_2, -78°C to RT 50%

In summary, we have accomplished the synthesis of the tri-cycle **7** in a manner pertinent to the proposed biosynthesis of the manzamines and made progress towards the oxidative ring-opening of this compound to give a hydroisoquinoline possessing the same functionality as the central core of manzamines A and B. It is noteworthy that the cycloadduct **7** bears a clear resemblance to the central core of ingenamine **11**[11], the ingamines A **12** and B **13** [12] and keramaphidin B **14**.[13] We are currently investigating methods for introducing oxygen functionality at C9 on the *exo* face of **7**, thus providing a simpler congener of the cytotoxic alkaloids **11**, **12** and **13**.



11; X=OH
14; X=H



12; X=OH
13; X=H

Investigations into an intramolecular variant of the cycloaddition reported herein are in progress with the aim of accomplishing the total 'biomimetic' syntheses of the manzamines and ingenamine *via* keramaphidin B. Results of our efforts directed at these goals will be reported in due course.

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δ_H(500 MHz; CD_3OD) 5.90 (1H, br d, *J* 6.3Hz, H4), 2.99 (1H, dd, *J* 9.5, 2.1Hz, H6), 2.74 (1H, m, H10), 2.67 (1H, d, *J* 1.8Hz, H2), 2.59 (2H, m, H15), 2.58 (1H, m, H10') 2.47 (1H, dq, *J* 11.8, 7.3Hz, H13), 2.35 (1H, d, *J* 11.8Hz, H12), 2.25 (1H, m, H5), 2.22 (1H, m, H13'), 2.22 (1H, d, *J* 11.8Hz, H12'), 1.82 (3H, d, *J* 1.8Hz, H17), 1.79 (1H, dd, *J* 9.5, 2.8Hz, H6'), 1.57 (1H, m, H9), 1.34 (3H, s, H18), 1.30 (1H, m, H9'), 1.26 (1H, m, H8), 1.09 (3H, t, *J* 7.2Hz, H16), 1.03 (3H, t, *J* 7.3Hz, H14); δ_C(125.7 MHz; CD_3OD) 141.05 (C3), 122.65 (C4), 67.54 (C2), 57.28 (C12), 56.14 (C6), 54.00 (C15), 52.77 (C13), 49.87 (C10), 42.93 (C7), 42.86 (C8), 39.44 (C5), 29.08 (C18), 27.73 (C9), 23.48 (C17), 14.00 (C14), 12.28 (C16); ν_{max}/cm^{-1} 2965 s, 2928 s, 2872 s, 1652 w, 1445 m, 1382 m, 1343 m, 1224 m, 1131 m, 1092 m, 807 m, 670 m; *m/z* (CI) 249 (MH^+, 100%), 192 (10), 126 (33), 122 (63), (Found: MH^+ 249.2331. $C_{16}H_{29}N_2$ requires 249.2331).
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