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A new stereoselective approach to the manzamine alkaloids

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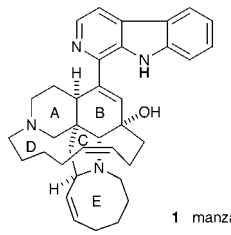
The key step in a new, stereoselective approach to the manzamine alkaloids involves an intramolecular azomethine ylide cycloaddition reaction, which forms rings B and C simultaneously, together with three new chiral centres; this has allowed a rapid access to the core ABC ring system of manzamine A.

The manzamine and related alkaloids consist of a structurally complex polycyclic ring system, typified by manzamine A **1**.[1]

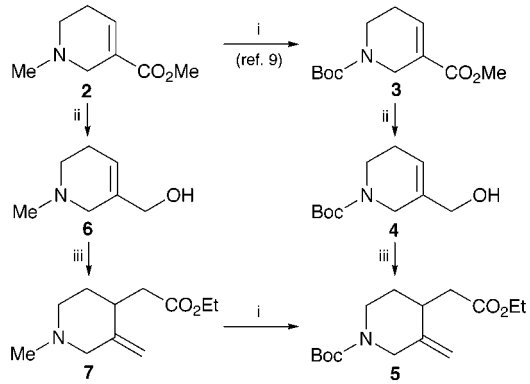


1 manzamine A

Manzamine A was the first of the family to be isolated in 1986 and, together with other manzamine alkaloids isolated from various marine sponges, has been shown to possess significant antileukemic and antibacterial properties.[1,2] The fascinating molecular structure and the promising biological activity of manzamine A has led to a number of synthetic endeavors in this area.[3] Recently the groups of Winkler[4] and Martin[5] have reported the synthesis of manzamine A, ircinol A and ircinal A. The key step in these syntheses makes use of a [2 + 2] (followed by ring expansion) or [4 + 2] cycloaddition reaction to set up ring B. Other [4 + 2] cycloaddition or cyclization strategies have been reported.[6] Our own efforts have centred on a [3 + 2] azomethine ylide cycloaddition reaction[7] to set up ring C. This approach seems ideally suited to access the manzamine alkaloids as an intramolecular cycloaddition reaction would allow, in a single step, the simultaneous formation of not only ring C but also ring B, together with all three chiral centres within ring C. Literature precedent[7,8] suggested that the azomethine ylide cycloaddition reaction would proceed to give the desired stereochemical arrangement found within the manzamine alkaloids. Herein we report a successful model study using this strategy.

The conversion of commercially-available arecoline **2** (Scheme 1) to the corresponding *N*-Boc derivative **3** has been reported by Olofson and co-workers.[9] Reduction of the ester **3** with $LiAlH_4$ gave the alcohol **4**. Use of the Johnson–Claisen rearrangement[10] with triethyl orthoacetate gave a rapid access to the piperidine **5**, containing the *exo*-methylene unit required for the key cycloaddition reaction. As an alternative route, reduction of arecoline and Johnson–Claisen rearrangement gave the corresponding *N*-methyl derivative **7**. Replacement of the *N*-Me for the *N*-Boc group in derivative **7** provided the desired compound **5**, although the yields in each step were more variable using this latter route.

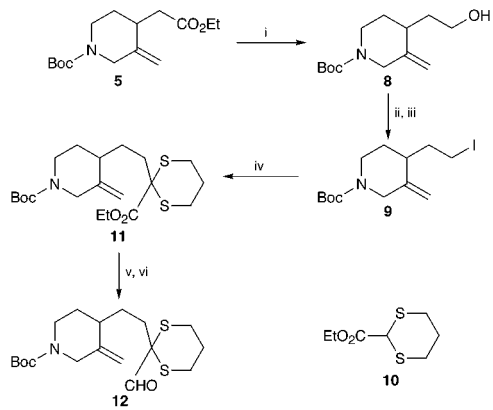
The ester **5** was reduced to the corresponding alcohol **8** using $LiAlH_4$ (Scheme 2). Conversion of the alcohol **8** to the iodide



Scheme 1 *Reagents and conditions*: i, MeCH(Cl)OCOCl, PhMe, heat, then MeOH, heat, then Boc_2O, CH_2Cl_2, Et_3N, 81% from **2**, 79% from **7**; ii, $LiAlH_4$, THF, 0 °C, 95% from **3**, 99% from **2**; iii, $MeC(OEt)_3$, xylene, 2,4-dinitrophenol, heat, 71% from **4**, 39–87% from **6**.

9 was accomplished *via* the corresponding bromide. The iodide **9** was found to be a better electrophile than the bromide towards the deprotonated dithiane **10**. Addition of the dithiane gave the ester **11**, which contained the required carbon framework for rings A and B of manzamine A. Reduction of the ester **11** and oxidation gave the aldehyde **12** needed for the key cycloaddition reaction.

Our initial studies towards the formation of the ABC ring system of manzamine A have centred on the condensation of the secondary amine sarcosine ethyl ester **13** with the aldehyde **12**. Formation of the azomethine ylide (Fig. 1) and intramolecular cycloaddition leads to the generation of the pyrrolidine ring C, together with simultaneous formation of ring B. A single diastereomeric product **14** was obtained† which consisted of the



Scheme 2 *Reagents and conditions*: i, $LiAlH_4$, THF, 0 °C, 85%; ii, CBr_4, Ph_3P, CH_2Cl_2; iii, NaI, acetone, 96% over two steps; iv, BuLi, THF, HMPA, **10** followed by addition of **9**, −78 °C to room temp., 82%; v, $LiAlH_4$, THF, 0 °C, 92%; vi, $(COCl)_2$ (2.2 equiv.), DMSO, CH_2Cl_2, −60 °C then Et_3N, 70%.

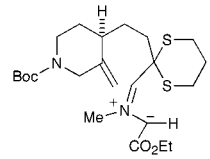
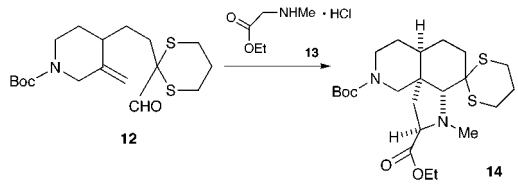


Fig. 1 Azomethine ylide formed from the condensation of **12** and **13**.



Scheme 3 *Reagents and conditions*: i, Pr^i_2NEt, PhMe, heat, 24 h, 45%.

desired ABC ring system of the manzamine alkaloids (Scheme 3). The stereochemical assignment could not be verified by NMR spectroscopy due to overlapping signals. Hydrolysis of the *N*-Boc group (TFA, CH_2Cl_2) gave rise to the corresponding secondary amine in which the peaks in the ^1H NMR spectrum were better resolved, but not to the extent required for NOE studies. The problem was solved by single crystal X-ray spectroscopic studies (Fig. 2)‡ of the *N*-Boc derivative **14**, which confirmed the structure and the relative stereochemistry of the cycloaddition product. The *cis* ring junction is favoured between rings A and B and between rings B and C. A possible ylide stereochemistry and orientation for cycloaddition is shown in Fig. 1.

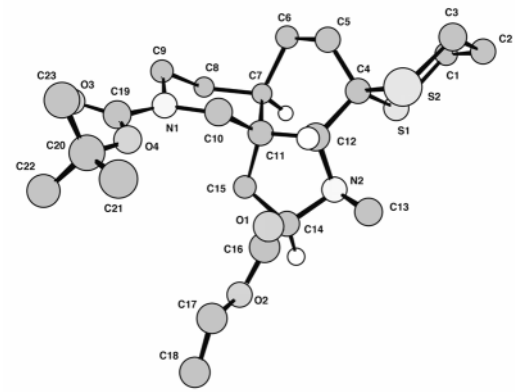


Fig. 2 X-Ray structure of the cycloadduct **14**.

In conclusion, we have demonstrated a short and efficient route to the core ABC ring system of the manzamine alkaloids. The key step is a stereocontrolled intramolecular azomethine ylide cycloaddition reaction, which sets up two new rings (rings B and C) and three new chiral centres (controlled by the existing chiral centre) in a single transformation. Further work to extend this chemistry to the preparation of more advanced intermediates of the manzamine alkaloids and to complete the total synthesis is in progress.

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Notes and references

† *Cycloaddition of the aldehyde* **12**: The aldehyde **12** (139 mg, 0.39 mmol), sarcosine ethyl ester hydrochloride **13** (90 mg, 0.59 mmol) and Pr^i_2NEt (0.12 cm^3, 0.7 mmol) in dry toluene (2.0 cm^3) were heated under reflux using a Dean–Stark trap. After 24 h, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with light petroleum (bp 40–60 °C)–EtOAc (5:1) to give the amine **14** (82 mg, 45%) as needles; R_f 0.59 [light petroleum (bp 40–60 °C)–EtOAc (3:1)]; mp 140–142 °C; ν_{max}(neat)/cm^{-1} 1735 (C=O, ester) and 1685 (C=O, carbamate); δ_H(400 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.0), 1.24–2.17 (11H, m), 1.41 (9H, s), 2.57 (2H, br t, *J* 12.5), 2.74–2.91 (1H, m), 2.82 (1H, s), 2.85 (3H, s), 2.95 (1H, t, *J* 12.5), 2.97–3.16 (1H, m), 3.26 (1H, t, *J* 12.5), 3.50–3.76 (3H, m), 4.10–4.16 (2H, m); δ_C(100 MHz, $CDCl_3$, broad) 14.3, 22.0, 25.8, 25.9, 26.5, 27.6, 28.4, 29.8, 33.9, 38.9, 39.1, 47.1, 50.9, 55.9, 60.0, 65.1, 73.5, 79.3, 155.1, 173.9 (Found: M^+ 470.2263. $C_{23}H_{38}N_2O_4S_2$ requires *M*, 470.2273); *m/z* 470 (45%, M^+), 414 (24, M − C_4H_8), 397 (100, M − OBu^t), 369 (20, M − CO_2Bu^t), 341 (98) (Found: C, 58.63; H, 8.17; N, 5.67. $C_{23}H_{38}N_2O_4S_2$ requires C, 58.72; H, 8.08; N, 5.96%).

‡ *Crystal data* for **14**: $C_{23}H_{38}N_2O_4S_2$, M_r = 470.67, triclinic space group *P*, *a* = 9.891(2), *b* = 10.419(3), *c* = 13.574(3) Å, α = 67.91(3), β = 74.89(3), γ = 87.88(3)°, *U* = 1248.4(4) $Å^3$, *Z* = 2, D_c = 1.252 g cm^{-3}, μ = 0.244 mm^{-1}, *F*(000) = 508, crystal size 0.15 × 0.15 × 0.05 mm. Data were collected at 293 K on a Nonius KappaCCD area detector diffractometer, at the window of a Nonius FR591 rotating anode [λ(Mo-Kα) = 0.71073 Å]. Combined φ and ω scans, with a frame increment of 2.0°, gave 100% completeness to θ_{max} = 22.5° (index ranges $-10 \leqslant h \leqslant 10$, $-11 \leqslant k \leqslant 11$, $-14 \leqslant l \leqslant 14$). A correction was applied to account for absorption effects by means of comparing equivalent reflections, using the program SORTAV (ref. 11) (transmission factors = 0.995 / 0.912). A solution was obtained *via* direct methods and refined (ref. 12) by full-matrix least-squares on F^2, with hydrogens included in idealised positions. 3267 unique data were produced from 19877 measured reflections (R_{int} = 0.0968). 285 parameters refined to R_1 = 0.0556 and wR_2 = 0.1348 [$I > 2\sigma(I)$] (R_1 = 0.0931 and wR_2 = 0.1593 for all data), with residual electron densities of 0.342 and −0.308 e $Å^{-3}$. CCDC 182/1358. See http://www.rsc.org.suppdata/cc/1999/1757/ for crystallographic data in .cif format.

1 R. Sakai, T. Higa, C. W. Jefford and G. Bernardinelli, *J. Am. Chem. Soc.*, 1986, **108**, 6404; H. Nakamura, S. Deng, J. Kobayashi, Y. Ohizumi, Y. Tomotake, T. Matsuzaki and Y. Hirata, *Tetrahedron Lett.*, 1987, **28**, 621.

2 R. Sakai, S. Kohmoto, T. Higa, C. W. Jefford and G. Bernardinelli, *Tetrahedron Lett.*, 1987, **28**, 5493; T. Ichiba, R. Sakai, S. Kohmoto, G. Saucy and T. Higa, *Tetrahedron Lett.*, 1988, **29**, 3083; M. Tsuda, K. Inaba, N. Kawasaki, K. Homna and J. Kobayashi, *Tetrahedron*, 1996, **52**, 2319; I. I. Ohtani, T. Ichiba, M. Isobe, M. Kelly-Borges and P. J. Scheuer, *J. Am. Chem. Soc.*, 1995, **117**, 10 743; F. Kong and R. J. Andersen, *Tetrahedron*, 1995, **51**, 2895; J. Rodríguez, B. M. Peters, L. Kurz, R. C. Schatzman, D. McCarley, L. Lou and P. Crews, *J. Am. Chem. Soc.*, 1993, **115**, 10 436; D. Watanabe, M. Tsuda and J. Kobayashi, *J. Nat. Prod.*, 1998, **61**, 689.

3 For reviews, see M. Tsuda and J. Kobayashi, *Heterocycles*, 1997, **46**, 765; N. Matzanke, R. Gregg and S. Weinreb, *Org. Prep. Proced. Intl.*, 1998, **30**, 1; E. Magnier and Y. Langlois, *Tetrahedron*, 1998, **54**, 6201.

4 J. D. Winkler and J. M. Axten, *J. Am. Chem. Soc.*, 1998, **120**, 6425.

5 S. F. Martin, J. M. Humphrey, A. Ali and M. C. Hillier, *J. Am. Chem. Soc.*, 1999, **121**, 866.

6 For recent studies, see H. Uchida, A. Nishida and M. Nakagawa, *Tetrahedron Lett.*, 1999, **40**, 113; D. I. MaGee, M. L. Lee and A. Decken, *J. Org. Chem.*, 1999, **64**, 2549; S. M. Li and S. Yamamura, *Tetrahedron*, 1998, **54**, 8691; J. E. Baldwin, T. D. W. Claridge, A. J. Culshaw, F. A. Heupel, V. Lee, D. R. Sping, R. C. Whitehead, R. J. Boughtflower, I. M. Mutton and R. J. Upton, *Angew. Chem., Int. Ed.*, 1998, **37**, 2661; A. Kaiser, X. Billot, A. Gateau-Olesker, C. Marazano and B. C. Das, *J. Am. Chem. Soc.*, 1998, **120**, 8026.

7 A. Padwa, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 4, p. 1069; P. A. Wade, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 4, p. 1111.

8 See, for example P. N. Confalone and E. M. Huie, *J. Am. Chem. Soc.*, 1984, **106**, 7175; P. N. Confalone and R. A. Earl, *Tetrahedron Lett.*, 1986, **27**, 2695; L. M. Harwood and I. A. Lilley, *Tetrahedron Lett.*, 1993, **34**, 537; R. Grigg, V. Savic and M. Thornton-Pett, *Tetrahedron*, 1997, **53**, 10 633.

9 R. A. Olofson, J. T. Martz, J.-P. Senet, M. Piteau and T. Malfroot, *J. Org. Chem.*, 1984, **49**, 2081.

10 W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T.-T. Li, D. J. Faulkner and M. R. Petersen, *J. Am. Chem. Soc.*, 1970, **92**, 741; for a Johnson–Claisen rearrangement with a 3-(hydroxyalkyl)tetrahydropyridine derivative, see M. Amat, M.-D. Coll, J. Bosch, E. Espinosa and E. Molins, *Tetrahedron: Asymmetry*, 1997, **8**, 935 and references therein.

11 R. H. Blessing, *Acta Crystallogr., Sect. A*, 1995, **51**, 33; R. H. Blessing, *J. Appl. Crystallogr.*, 1997, **30**, 421.

12 G. M. Sheldrick, SHELXL-97. Program for the refinement of crystal structures. University of Göttingen, 1997.

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