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Synthetic studies on manzamine A

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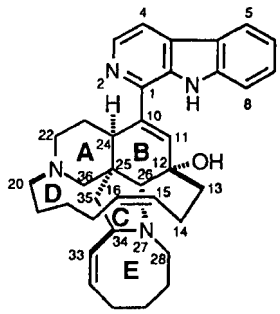
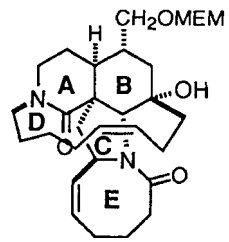
Abstract - The total synthesis of the ABCDE ring system of manzamine A, with the correct absolute stereochemistry at the chiral centers, is described. Key steps in the synthetic route are the formation of both the eight- and the thirteen-membered rings by an olefin metathesis cyclization reaction.

The sponge alkaloid manzamine A (**1**) is a challenging synthetic target in view of its antileukemic and antibacterial activities and particularly due to its unique structure. It consists of a novel pentacyclic heterocyclic nucleus onto which a β-carboline ring system is attached as a pendant substituent. In this communication we wish to present a total synthesis of the chiral ABCDE ring system of the alkaloid (**2**) bearing a suitable substituent for elaboration of the β-carboline heterocycle, for the final stages of the synthesis.



1 (Manzamine A)



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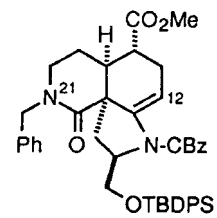
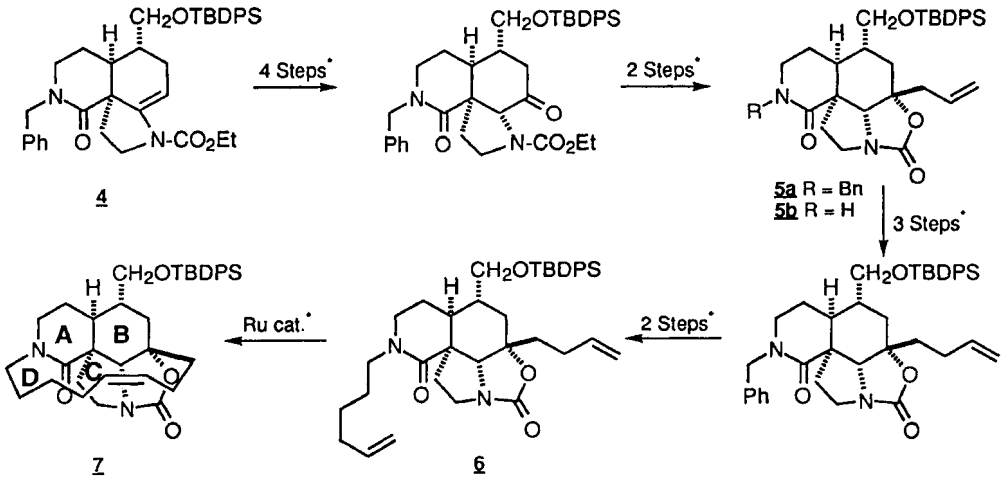


3

A route for the synthesis of the strategically functionalized chiral pyrrolo[2,3-*i*]isoquinoline derivative **3**, *via* a highly selective intramolecular [4+2] cyclization, was first reported from this laboratory (1). It was recognized by us and by others (2a-s) that **3** represented the 'heart' of the manzamine nucleus that could serve as a core intermediate upon which the other ring systems could be constructed.

In the second phase of the strategy towards the total synthesis of the alkaloid, it was realized that the challenge of constructing the macrocyclic thirteen-membered ring, in which an eight-carbon unit spans the C(12)-N(21) positions, would have to be addressed. In principle, starting from precursor **3**, there are three potential approaches to attain this goal: (i) to link the appropriate (eight carbon) chain to C(12) and complete the macrocycle by ring closure at N(21) (manzamine numbering); (ii) to alkylate N(21) with the eight-carbon fragment and make a C-C bond at C(12) in the terminal step and (iii) to attach suitably functionalized three-carbon and five-carbon arms at C(12) and N(21) respectively, and to generate the macrocyclic ring by a C=C bond formation in the strategic step. Orientation experiments designed to examine the first two approaches did not, however, prove promising. This led us to concentrate on the feasibility of the third

strategy. A particularly attractive route to cyclic olefins is *via* an intramolecular metathesis cyclization of terminal olefins, for which suitable catalysts have been developed (3). In a recent report (4) Grubbs has described a ruthenium catalyst [$(Cy_3P)_2Cl_2Ru{=}CHCH{=}CPh_2$] which can be employed under standard laboratory conditions and, moreover, can cause the ring closure of terminal olefins incorporating functionalities such as the amide moieties.

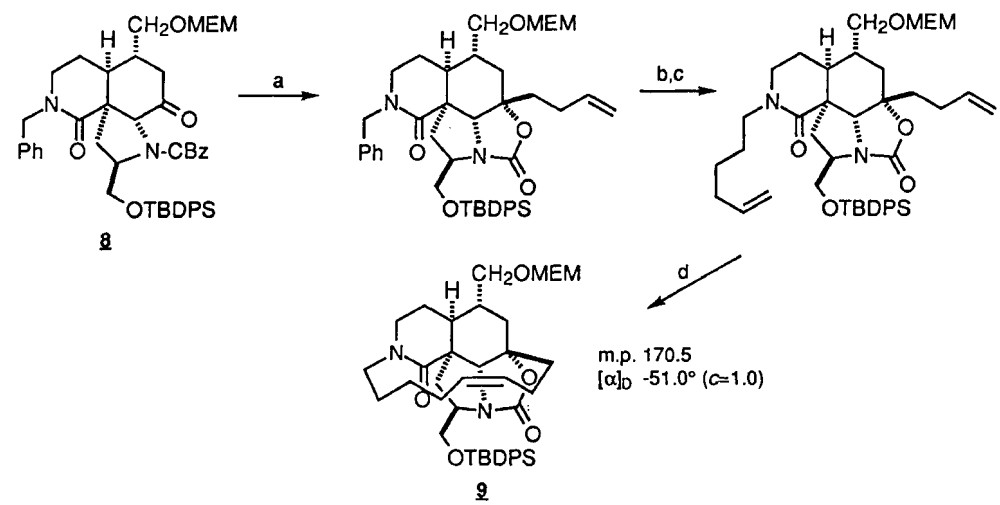


*Ref. 5

Scheme I

Employing non-chiral pyrroloisoquinoline derivative **4**, a sequence (Scheme I) was developed by which the required olefin arms could be attached at C(12) and N(21) (manzamine numbering), to yield the required precursor **6**. The structure and the stereochemistry of **6** were based on the X-ray data for amide **5b**, which itself is derived by debenzylation of the allylmagnesium bromide addition intermediate **5a**. A metathesis cyclization of **6**, mediated by the ruthenium catalyst, led to the formation of the desired ABCD system **7** (5).

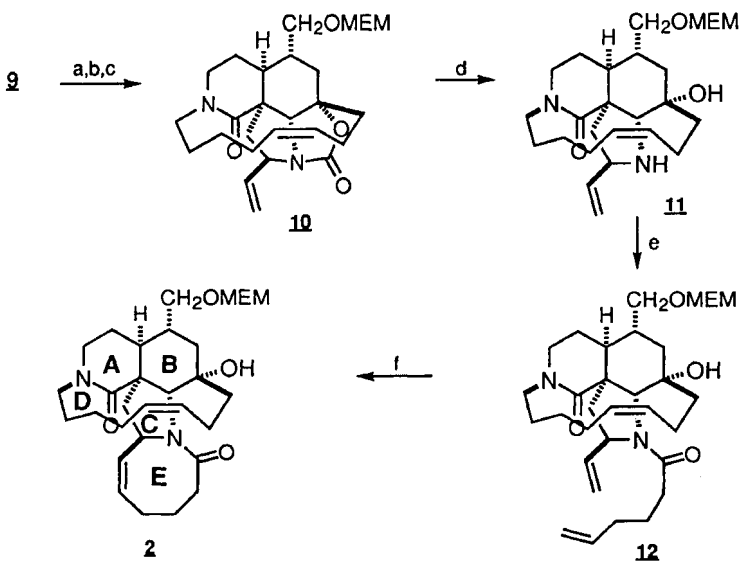
Employing essentially the same sequence (Scheme II), the chiral ketone **8**, obtained from **3**, was converted to crystalline **9**, [m.p. 170.5°], which represents the chiral ABCD ring system of manzamine A. The structure of **9** has been established by spectroscopic data (NMR, MS) and efforts to obtain crystals of **9** which are suitable for X-ray analysis are in progress.



a) $CH_2{=}CHCH_2CH_2MgBr$, THF; b) Li/NH_3, then Bn_2O; c) $I\text{-}CH_2(CH_2)_3CH{=}CH_2$, KOH, DMSO; d) $(Cy_3P)_2Cl_2Ru{=}CHCH{=}CPh_2$, 50 °C, 48 h.

Scheme II

With the success of the metathesis cyclization reaction in the elaboration of ring D, we embarked on the construction of the azocine ring (E) on compound **9**, *via* a similar strategy. Our interest in using this approach was enhanced by the recent report by Martin *et al.* (2p) describing the conversion of an ABC ring intermediate into the corresponding ABCE system, by cyclizing a diolefinic precursor employing a molybdenum catalyst. In order to achieve this transformation in the case of **9**, the hydroxymethyl function at C(34) was liberated and oxidized, and the resulting aldehyde group extended by a methylene moiety (to give **10**) *via* a Wittig reaction (Scheme III).



a) TBAF, THF; b) Dess-Martin periodinane; c) $Ph_3P{=}CH_2$, THF; d) 40% KOH/MeOH; e) $CH_2{=}CH(CH_2)_3CO_2H$, EDC; f) $(Cy_3P)_2Cl_2Ru{=}CHCH{=}CPh_2$.

Scheme III

Subsequently, the cyclic carbamate system in **10** was opened up by basic hydrolysis to give the tertracyclic pyrrolidine intermediate **11**. Amidation of the pyrrolidine nitrogen in **11** with hex-5-enoic acid resulted in the precursor (**12**) for the cyclization step. In the final step leading to the ABCDE system (**2**), intermediate **12** was subjected to a $[(Cy_3P)_2Cl_2Ru{=}CHCH{=}Ph_2]$ catalyzed ring closure. The structure of **2** is evidenced by its spectral data; a comparison of the NMR spectra of **12** and **2**, which shows the disappearance of the terminal olefin protons and the appearance of the expected (two) vinylic hydrogens being critically informative. This synthesis of **2** represents the first synthesis of the heterocyclic ABCDE nucleus of Manzamine A. The attachment of the β-carboline *via* the primary hydroxymethyl function is currently in progress. The latter transformation would lead to the complete skeleton of manzamine A; a further adjustment in the oxidation states at centres C(10), C(11), C(28) and C(36) being required to form the naturally occurring alkaloid molecule. It should be noted that the attachment of the β-carboline to a chiral ABCE system has already been achieved in our laboratory (6).

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References

1. K. M. J. Brands, A. A. P. Meekel and U. K. Pandit, *Tetrahedron*, **47**, 2005, (1991).

2. (a) K. M. J. Brands and U. K. Pandit, *Tetrahedron Lett.*, **30**, 1423 (1989); (b) D. J. Hart and J. A. McKinney, *Tetrahedron Lett.*, **30**, 2611 (1989); (c) D. de Oliveira Imbroisi and N. S. Simpkins, *Tetrahedron Lett.*, **30**, 1423 (1989); (d) K. M. J. Brands and U. K. Pandit, *Heterocycles*, **30**, 257 (1990); (e) M. Nakagawa, Z. Lai, Y. Torisawa and T. Hino, *Heterocycles*, **31**, 999 (1990); (f) Y. Torisawa, M. Nakagawa, H. Arai, Z. Lai, T. Hino, T. Nakata and T. Oishi, *Tetrahedron Lett.*, **31**, 3195 (1990); (g) D. de Oliveira Imbroisi and N. S. Simpkins, *J. Chem. Soc., Perkin Trans. 1*, 1815 (1991); (h) S. F. Martin, T. Rein and Y. Liao, *Tetrahedron Lett.*, **32**, 6481 (1991); (i) J. Leonard, S. P. Fearnley and D. M. B. Hickey, *Synlett*, 272 (1992); (j) I. E. Markó and A. Chesney, *Synlett*, 275 (1992); (k) Y. Torisawa, M. Nakagawa, T. Hosaka, K. Tanabe, Z. Lai, K. Ogata, T. Nakata, T. Oishi and T. Hino, *J. Org. Chem.*, **57**, 5741 (1992); (l) I. E. Markó, J. M. Southern and H. Adams, *Tetrahedron Lett.*, **33**, 4657 (1992); (m) J. A. Campbell and D. J. Hart, *Tetrahedron Lett.*, **33**, 6247 (1992); (n) M. Nakagawa, Y. Torisawa, T. Hosaka, K. Tanabe, T. Da-te, K. Okamura and T. Hino, *Tetrahedron Lett.*, **34**, 4543 (1993); (o) J. D. Winkler, M. G. Siegel and J. E. Stelmach, *Tetrahedron Lett.*, **34**, 6509 (1993); (p) S. F. Martin, Y. Liao, Y. Wong and T. Rein, *Tetrahedron Lett.*, **35**, 691 (1994); (q) T. M. Kamenecka and L. E. Overman, *Tetrahedron Lett.*, **35**, 4279 (1994); (r) J. Ma, M. Nakagawa, Y. Torisawa and T. Hino, *Heterocycles*, **38**, 1609 (1994); (s) J. Leonard, S. P. Fearnley, M. F. Finlay, J. A. Knight and G. Wong, *J. Chem. Soc., Perkin Trans. 1*, 2359 (1994).
3. O. Fujimura, G. C. Fu and R. H. Grubbs, *J. Org. Chem.*, **59**, 4029 (1994) and references cited therein.
4. G. C. Fu and R. H. Grubbs, *J. Am. Chem. Soc.*, **114**, 7324 (1992); S. T. Nguyen and R. H. Grubbs, *J. Am. Chem. Soc.*, **115**, 9858 (1993).
5. B. C. Borer, S. Deerenberg, H. Bieräugel and U. K. Pandit, *Tetrahedron Lett.*, **35**, 3191 (1994).
6. H. Bieräugel, B. C. Borer and U. K. Pandit, *Heterocyclic Commun.*, (1994) in press.