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A concise enantioselective synthesis of the AB ring system of the manzamine alkaloids by ring-closing enyne metathesis

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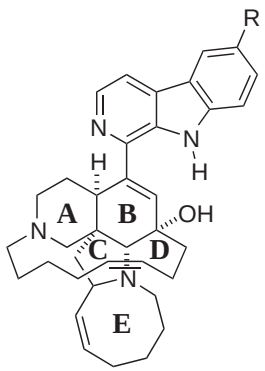
Abstract—The AB ring system found in the manzamine A and related alkaloids has been prepared from (–)-quinine by a short enantioselective route. The key step in the sequence is a ruthenium-catalysed ring-closing enyne metathesis re action which delivers a bicyclic diene in good yield. The functionality required for further elaboration of the AB system has been installed by sequential regioselective hydroboration and stereoselective catalytic aminohydroxylation. © 2001 Elsevier Science Ltd. All rights reserved.

Over the past 15 years, members of the manzamine family of alkaloids have been the focus of an unprecedented level of synthetic interest.[1] Since the discovery of manzamine A in 1986[2] and the subsequent isolation of structurally related alkaloids from marine sponges of the *Haliclona*, *Pellina* and *Xestospongia* genera,[3] the unique structures of these compounds coupled with their potent anti-tumour and anti-microbial activities has made them alluring synthetic targets.[2–4] The complex pentacyclic core found in most of the manzamines, ircinals and ircinols contains interlocking 5-, 6-, 8- and 13-membered rings and is one of the most challenging naturally occurring ring systems known. In recent years an ever increasing number of new strategies and reactions have been developed for the assembly of sub-units found in the pentacyclic core of these alkaloids.[5] This intense synthetic activity has culminated in two recent landmark syntheses of members of the manzamine family of natural products, completed by the groups of Winkler and Martin.[6,7]

In previous studies, we have prepared the CE ring system of manzamine A in enantiomerically pure form.[8] Simultaneous construction of both rings was accom-



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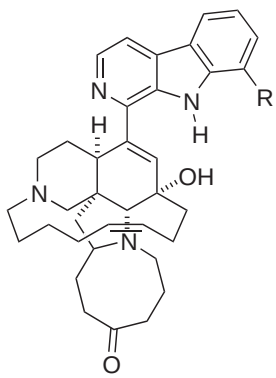
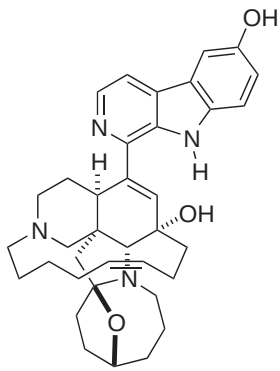
manzamine Y R = OH



manzamine E R = H
manzamine F R = OH



manzamine X

Keywords: manzamine; alkaloids; ring-closing; enyne; metathesis.
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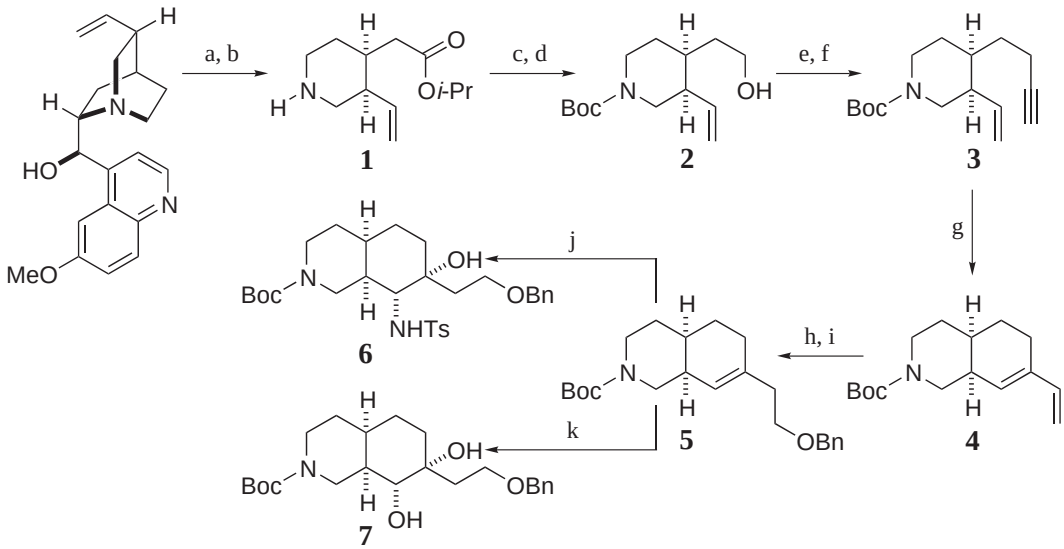


Scheme 1. *Reagents:* (a) *t*-BuOK, Ph_2CO, PhMe, reflux, 6 h (100%); (b) *t*-BuOK, O_2, *i*-PrOH, THF, 0→20°C, 3 h (89%); (c) $(t\text{-BuOCO})_2O$, Et_3N, DMAP, CH_2Cl_2, 0°C→rt, 18 h (77%); (d) $LiAlH_4$, THF, 0°C→rt, 1.5 h (95%); (e) TsCl, Et_3N, CH_2Cl_2, rt, 16 h; (f) $HCCLi{\cdot}(NH_2CH_2)_2$, DMSO, THF, rt (55%, 2 steps); (g) $Cl_2(PCy_3)_2RuCHPh$ (10 mol%), CH_2CH_2, CH_2Cl_2, rt (96%); (h) (i) Sia_2BH, THF, −10→4°C, 6 h, (ii) NaOH aq., 30% H_2O_2, THF, −10°C→rt, 18 h (70%); (i) NaH, BnBr, *n*-Bu_4NI, 18-c-6, THF, 0°C→rt, 19 h (92%); (j) $K_2OsO_2(OH)_4$ (8 mol%), $(DHQD)_2PHAL$ (10 mol%), TsNClNa (6 equiv.), MeCN, H_2O, rt, 72 h (76%); (k) $K_2OsO_2(OH)_4$ (8 mol%), $(DHQD)_2PHAL$ (10 mol%), MsNClNa (6 equiv.), *n*-PrOH, H_2O, rt, 17 h (83%).

plished by treatment of a diazo-substituted vinyl pyrrolidine with copper(II) acetylacetonate. During this key reaction, cyclisation of the intermediate copper carbenoid generated a spirocyclic ammonium ylide which underwent immediate [2,3] rearrangement to deliver the required ring system. We now disclose a short enantioselective synthesis of the AB ring system present in manzamine A and other alkaloids of the manzamine family.

In most published syntheses of sub-units containing the AB ring system, Diels–Alder reactions have been used to construct the reduced isoquinoline core.[9] In our synthesis of this system, sequential ruthenium-catalysed ring-closing enyne metathesis and catalytic aminohydroxylation reactions are employed to construct the functionalised B ring. Although ring-closing diene metathesis reactions have been used by others to prepare the 13-membered D ring and the 8-membered E ring,[7,9n,o,10] preparation of the AB ring system using a ring-closing enyne metathesis reaction has not been explored.

The synthesis commenced with the efficient conversion of (−)-quinine into the meroquinene ester **1** following the procedure of Martinelli et al.[11] Thus, oxidation of (−)-quinine to quininone and subsequent ring cleavage afforded the ester **1**. Protection of the amine as the *t*-butyl carbamate and subsequent ester reduction with lithium aluminium hydride afforded the alcohol **2** in good yield. Conversion of the primary alcohol into the tosylate and subsequent displacement with lithium acetylide ethylene diamine complex delivered the alkyne **3** in 55% yield over two steps. The enyne **3** was then treated with a sub-stoichiometric amount of the Grubbs ruthenium catalyst $[Cl_2(PCy_3)_2RuCHPh]$ which resulted in efficient ring-closing enyne metathesis and delivered the diene **4** in 96% yield.[12] Regioselective hydroboration at the terminal position of the diene was accomplished using disiamylborane, and the resulting homoallylic alcohol was alkylated to provide the benzylic ether **5**. The required amino and hydroxyl groups were then introduced simultaneously by employing a highly diastereoselective and regioselective Sharpless aminohydroxylation reaction.[13,14] The highest yield (76%) of the required amino alcohol **6** was obtained by using a large excess of Chloramine-T and sub-stoichiometric amounts of potassium osmate(VI) dihydrate and the phthalazine ligand $(DHQD)_2PHAL$ in degassed aqueous acetonitrile at room temperature.[13a,d] The phthalazine was required to accelerate the reaction, but even in the presence of this ligand the reaction was rather sluggish and took 3 days to proceed to completion. The diastereoselective aminohydroxylation reaction is noteworthy because there are relatively few

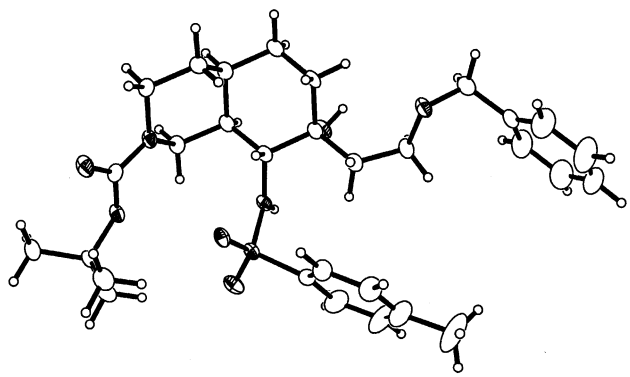
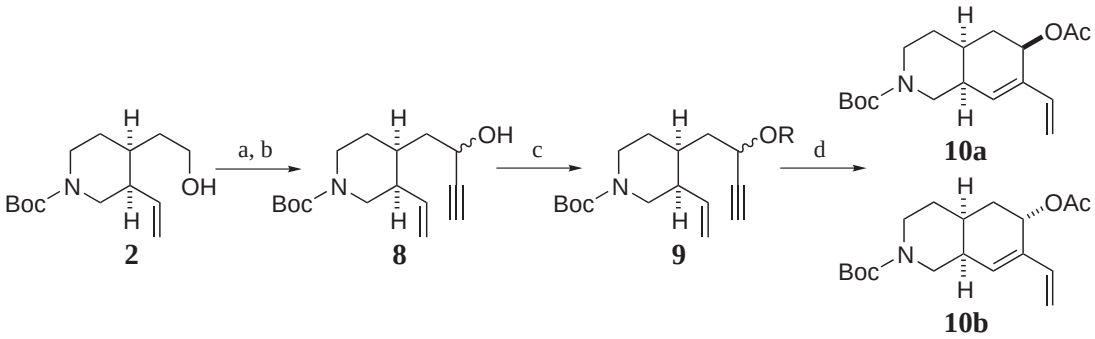


Figure 1. The X-ray crystal structure of amino alcohol **6**.



Scheme 2. *Reagents:* (a) (i) DMSO, $(COCl)_2$, CH_2Cl_2, −78°C, (ii) Et_3N, −78°C→rt (91%); (b) HCCMgBr, THF, 0°C→rt, 26 h (86%); (c) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 1 h (98%); (d) $Cl_2(PCy_3)_2RuCHPh$ (10 mol%), CH_2CH_2, PhMe, 80°C (46%).

published examples in which trisubstituted cyclic alkenes have been used as substrates.[15] Although the highly diastereoselective aminohydroxylation reaction is largely substrate controlled, the $(DHQD)_2PHAL$ ligand was selected with the expectation that reagent control and substrate control would be matched. The choice of $(DHQD)_2PHAL$ was based on results from analogous asymmetric dihydroxylation reactions performed in the presence of this ligand.[16]

The crystalline amino alcohol **6**, which possesses appropriate amino functionality for introduction of ring C and part of the side-chain necessary for construction of the D ring, was obtained in good yield as a single diastereoisomer. Crystals suitable for X-ray crystallography were obtained by recrystallisation of the amino alcohol **6** from diethyl ether. X-ray analysis using synchrotron radiation confirmed both the structure of this compound and the relative configuration of the four contiguous stereogenic centres (Fig. 1).[17]

Further investigation of the aminohydroxylation reaction revealed that the nature of the chloramine reagent is critical to the success of this transformation.[13d] When Chloramine-M was used instead of Chloramine-T,[13b] stereoselective dihydroxylation occurred instead of aminohydroxylation; the 1,2-diol **7** was obtained in good yield and none of the required amino alcohol **6** was isolated (Scheme 1).[16]

In a subsequent study we explored the incorporation of an additional B ring oxygen substituent to facilitate introduction of the β-carboline ring system late in the synthesis (Scheme 2). The alcohol **2** was converted into the corresponding aldehyde by Swern oxidation and subsequent addition of ethynylmagnesium bromide delivered a 1:1 mixture of the diastereoisomeric propargylic alcohols **8**. Acetylation of these alcohols delivered a diastereoisomeric mixture (1:1) of the acetates **9**. Treatment of the mixture of acetates with a sub-stoichiometric amount of the Grubbs ruthenium catalyst $[Cl_2(PCy_3)_2RuCHPh]$ resulted in ring-closing enyne metathesis to give a single diastereoisomer (**a**/**b**) of the diene **10** in 46% yield. Thus, one of the isomeric enynes **9** underwent highly efficient cyclisation whereas the other diastereoisomer did not undergo the required ring closure reaction. Although it was not possible to determine unambiguously which diastereoisomer had undergone cyclisation, it is clear that a highly stereoselective synthesis of one of the diastereoisomeric acetates **9** will be required in order to ensure that the subsequent ring-closing enyne metathesis reaction proceeds in high yield.

In summary, we have prepared the AB ring system of manzamine A in enantiomerically pure form by a short and efficient route which commences from (−)-quinine, an inexpensive and readily available chiral pool starting material. The AB system possesses most of the functionality required for further elaboration to an advanced intermediate in the synthesis of manzamine A, and we are currently exploring the construction of the other rings found in the pentacyclic core of the natural product.

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17. Crystallographic data (excluding structure factors) for the amino alcohol **6** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 155470. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].