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An Enantioselective Synthesis of the CE Ring System of the Alkaloids Manzamine A, E and F, and Ircinal A

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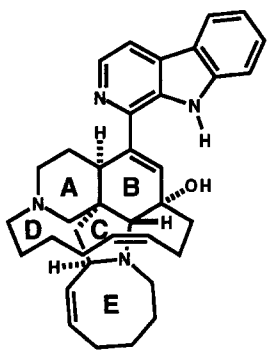
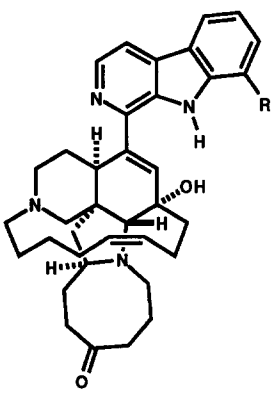
Abstract: An efficient enantioselective synthesis of the azabicyclo[6.3.0]-undecane **6**, corresponding to the CE ring system found in the manzamines A, E, and F, and ircinal A, from (*S*)-prolinol is described. The key step in the route to **6** was the intramolecular generation and rearrangement of the spiro-fused bicyclic ylide **5** from a copper carbenoid.

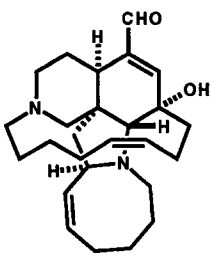
The manzamines and ircinals are a group of structurally complex polycyclic alkaloids of marine origin, which are cytotoxic and have been shown to possess antileukemic and antibacterial activity (**Figure 1**).[1] The formidable synthetic challenges posed by the manzamines and ircinals, coupled with their significant biological activity, has stimulated many synthetic studies, culminating in the synthesis of several fragments and sub-units of these alkaloids.[2,3] In spite of these synthetic endeavours, however, the only member of this family of natural products which has been synthesised is manzamine C,[4] a congener which is much less complex than the other manzamines.



Manzamine A



R = H **Manzamine E**
R = OH **Manzamine F**



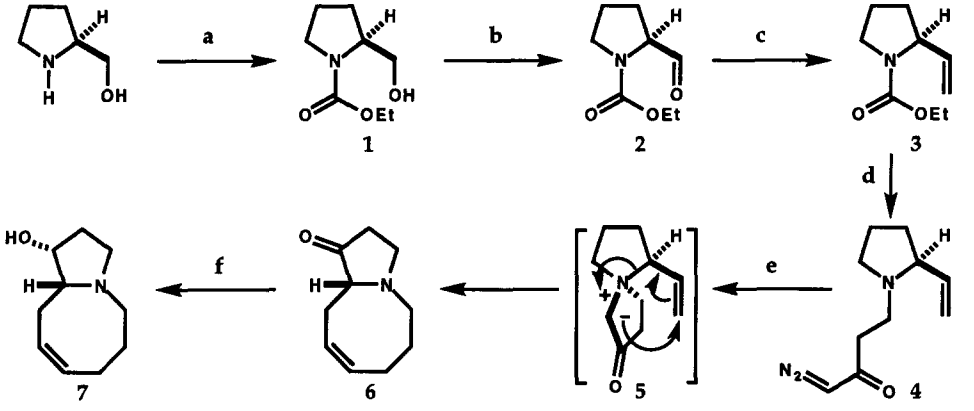
Ircinal A

Figure 1

Manzamines A, E, and F, and ircinal A possess complex pentacyclic cores containing 5-, 6-, 8-, and 13-membered rings. Most of the previous studies towards the synthesis of the manzamines have focused on the preparation of the octahydroisoquinoline AB ring system by Diels-Alder reactions;[2] few of these studies have been directed towards the *enantioselective* synthesis of sub-units which are suitable for elaboration to the natural products.[2c,g,n,3d]

Herein, we describe a very efficient enantioselective route to the CE ring system of manzamines A, E, and F, and ircinal A from (*S*)-prolinol (**Scheme 1**). The key step in our route is the sequential catalytic generation and rearrangement of a spiro-fused ammonium ylide from a copper carbenoid, using our recently developed procedure.[5]

The key intermediate in our synthetic route, the diazo ketone **4**, was prepared from vinyl pyrrolidine **3**, which in turn was synthesised from (*S*)-prolinol by an analogous route to that described by Ikeda.[6] Thus, protection of the secondary amine of (*S*)-prolinol as the carbamate afforded the alcohol **1**, which was oxidised to the aldehyde **2** and subsequently methylenated to furnish the vinyl pyrrolidine **3**. This compound was then deprotected using hydrazine, and the resulting amine immediately treated with 4-bromo-1-diazobutan-2-one in the presence of triethylamine to afford the cyclisation precursor **4** in 55% yield over two steps.[5] Treatment of **4** with $Cu(acac)_2$ (2 mol%) in benzene at reflux afforded the fused bicyclic system **6** as the sole isolable product in 56% yield.[7,8] The reaction is presumed to have occurred by [2,3]-sigmatropic rearrangement of the spiro-fused bicyclic ammonium ylide intermediate **5**,[5] resulting in three-carbon ring-expansion of the pyrrolidine. Remarkably, there was efficient transfer of stereochemical information from **4** to **6** during rearrangement, even though the original stereogenic centre was lost in the process. Reduction of unpurified ketone **6** with L-Selectride® afforded **7**, and this alcohol was judged to have an optical purity of >98% ee on the basis of ^{19}F nmr analysis of the ester formed by reaction of **7** with the acid chloride prepared from (*R*)-Mosher's acid. Thus, the bicyclic compound **6** corresponding to the CE ring system manzamines A, E, and F, and ircinal A, was prepared with high enantiomeric purity from (*S*)-prolinol in six steps and with an overall yield of 17%.

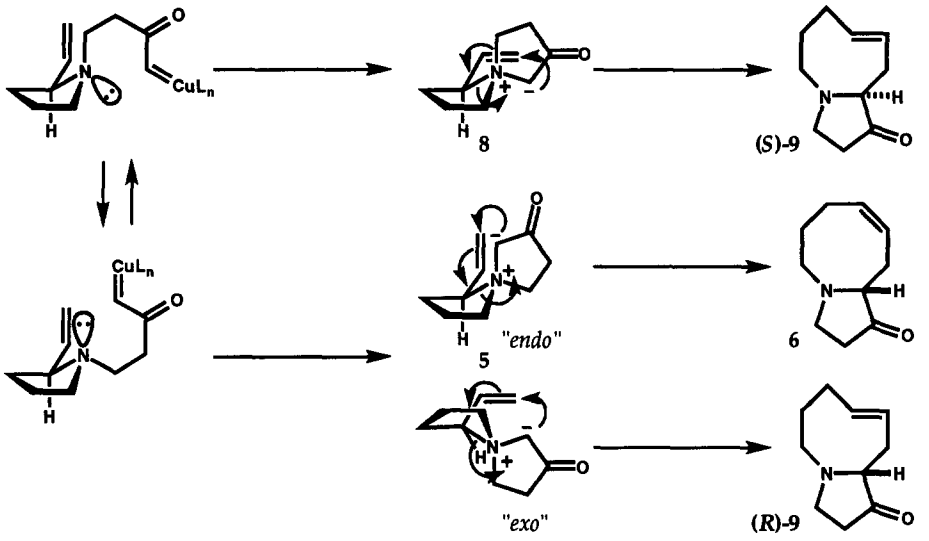


Reagents: **a** EtO_2CCl, NaOH aq., 0 °C→RT (88%); **b** SO_3-pyr., Et_3N, DMSO–CH_2Cl_2, 0 °C (81%); **c** $(Ph_3PMe)^+ Br^-$, NaH, DMSO, 0 °C→RT (78%); **d** (i) $(H_2N)_2.H_2O$, KOH, $HO(CH_2)_2OH$, reflux, (ii) $Br(CH_2)_2COCHN_2$, Et_3N, EtOAc, 60 °C (55%); **e** $Cu(acac)_2$ (2 mol%), C_6H_6, reflux (56%); **f** L-Selectride®, THF, 0 °C (75%) (**4** →**7**, 47% over two steps)

Scheme 1

Transfer of stereochemical information during the [2,3]-rearrangement of ylides is well known,[9] and there are many examples of efficient "chirality transfer" during rearrangement of ylides which have an adjacent stereogenic centre or possess a stereogenic heteroatom.[10,11] Our reaction was complicated however, because two diastereomeric ylides, **5** and **8**, could be produced by reaction of each invertomer with the carbenoid (**Scheme 2**). Ylide **5** could undergo rearrangement to give the bicycle **6** *via* a transition state in which the vinyl group is *endo* to the newly formed ring, or **(*R*)-9** by way of a transition state in which the vinyl group is *exo* to

the new ring. Ylide **8** would rearrange to (*S*)-**9** because the transition state required for the formation of the enantiomer of **6** cannot be achieved due to geometric constraints.



Scheme 2

In practice, compound **9** was not isolated, although analysis of the crude reaction product by ^{1}H nmr revealed the presence of a small amount of another olefinic product prior to purification. It is possible that **9** is produced during the reaction but that this compound does not survive work-up and purification. The isolation of the Z-alkene **6** as the sole product from our cyclisation reactions is consistent with results reported by Vedejs for the ring expansion of related ammonium ylides derived from vinyl pyrrolidines.[12]

Our results suggest that the product **6** arises by *endo* rearrangement of the ylide produced by reaction of the carbenoid with the amine from the face of the pyrrolidine which presents the vinyl group. An analogous result has been reported by West during the sequential formation and [1,2]-rearrangement of spiro-fused bicyclic ammonium ylides from carbenoids.[13]

The enantioselective route from (*S*)-proline to the azabicyclo[6.3.0]undecane is short and efficient, and we are currently developing this route in order to prepare more highly functionalised precursors to the manzamines and ircinals. The results of these studies will be reported in due course.

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7. Data for **6**: IR ($CHCl_3$) $\nu_{max.}$ 2930, 2850, 2800, 1750, 1600, 1460 cm^{-1}; ^1H nmr (250 MHz, $CDCl_3$) δ 5.78-5.64 (m, 2H), 3.34-3.27 (m, 1H), 2.82 (ddd, J = 14.1, 5.5, 2.2 Hz, 1H), 2.75-2.64 (m, 1H), 2.62-2.32 (m, 6H), 2.27-2.16 (m, 1H), 2.08-1.97 (m, 1H), 1.91-1.75 (m, 1H), 1.47-1.32 (m, 1H); ^{13}C nmr (67.8 MHz, $CDCl_3$) δ 215.7(s), 131.8(d), 127.3(d), 72.6(d), 53.8(t), 52.1(t), 37.4(t), 29.0(t), 28.5(t), 24.2(t); HRMS (EI) calcd for $C_{10}H_{15}NO$ m/z 165.1154 (M^+), found 165.1154 (M^+).

8. The *cis* alkene geometry of **6** was verified by ^1H nmr analysis of **7** in C_6D_6, which gave separate signals for the vinylic protons (5.58 and 5.74 ppm) with J = 10 Hz.

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