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Studies on the total synthesis of manzamine A

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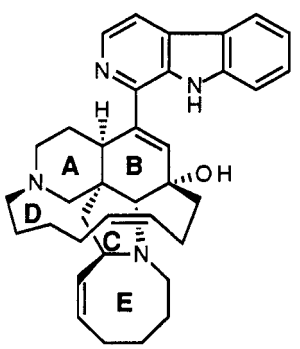
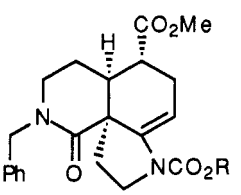
Abstract - Progress towards the synthesis of the marine alkaloid manzamine A is described. The synthesis of the ABCD ring system has been achieved, with the macrocyclic D ring being formed by an olefin metathesis cyclization. Additionally, a chiral ABC tricyclic intermediate has been converted into the ring D-*nor* manzamine A skeleton.

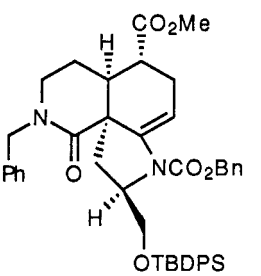
The alkaloid manzamine A (**1**), isolated from the sea sponges *Haliclona sp.*,[1a,b] *Xestopongia sp.*[1c] and *Pellina sp.*,[2] found in the waters of the Okinawa Sea, exhibits significant antileukemic and antimicrobial activity. The compound possesses an unusual nitrogen-containing pentacyclic fused ring system (ABCDE), bearing a pendant β-carboline moiety. An ingenious hypothetical scheme for the biosynthesis of manzamine A has been proposed by Baldwin and Whitehead.[3] According to this scheme, the β-carboline nucleus is completed on the ABCDE template in the last stages of the biosynthesis. The latter aspect has recently received support from the finding that an ABCDE aldehyde, called ircinal A, a constituent of *Ircinia sp.*, is chemically convertible into manzamine A.[4]



Manzamine A (1)

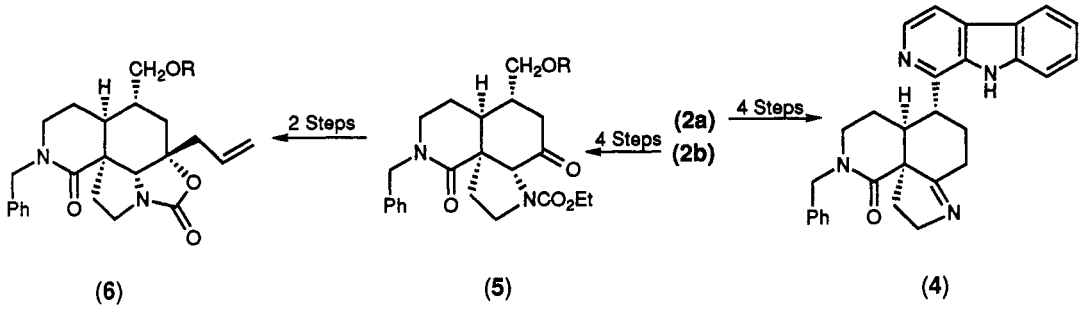


(2a) R = Bn
(2b) R = Et

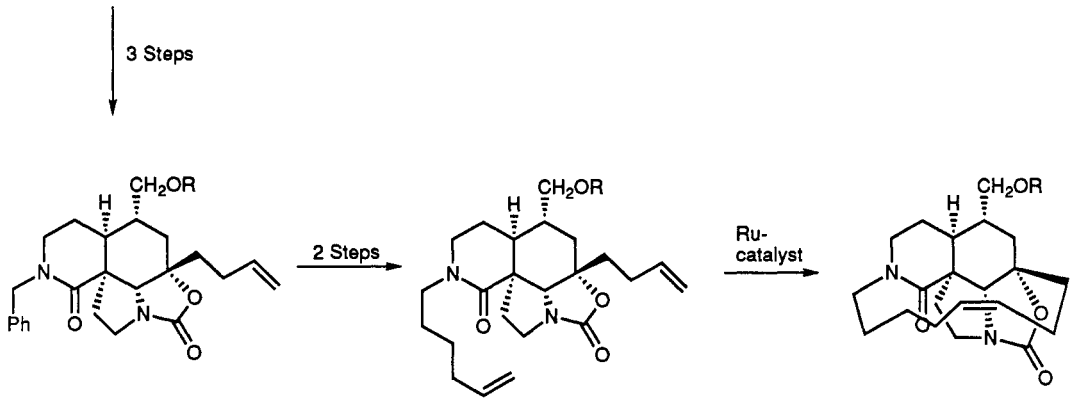


Tricyclic precursor (3)

The novel structure of manzamine A (**1**) coupled with its biological properties makes the alkaloid a highly attractive, though formidable target for chemical synthesis. Several synthetic studies aimed at this goal have been reported in the last few years.[5a-n] A common feature of the strategy projected by most groups, including our own, is the construction of an ABC ring system upon which rings D and E and finally the β-carboline nucleus can be elaborated. This communication presents an account of the progress towards the total synthesis of manzamine A (**1**) in our laboratory.

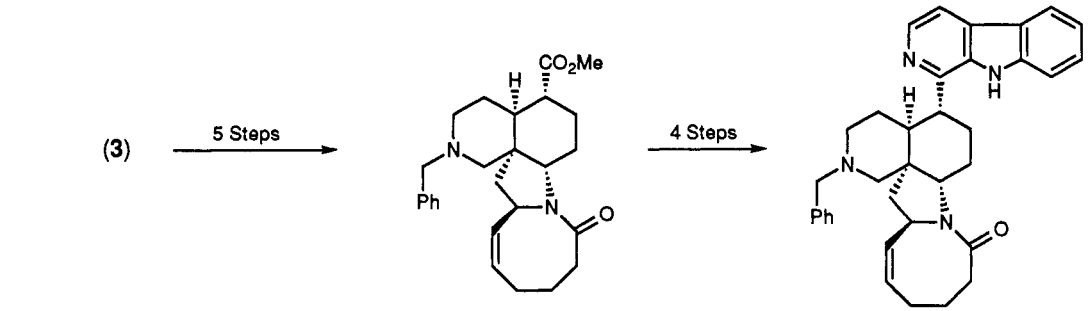


(6) (5) (4)



(7) (8) (9)

R = Si^{t}BuPh$_2$



(10) (11)

In the first phase of our studies we have developed the strategy for the preparation of the required pyrroloisoquinoline intermediate (**2a,b**).[6a] The crucial step in the sequence leading to this system consisted of an intramolecular Diels-Alder (4+2) cycloaddition. This sequence was subsequently applied to construct the strategically functionalized, chiral tricyclic intermediate (**3**) using S-serine as the starting chiral synthon. The intramolecular cyclization step leading to (**3**)[6b,c,d] was regioselective, giving the desired compound as the major product (69%), and a minor amount (21%) of the expected diastereomer. In the second phase of our work, we have directed our attention to the development of methodologies for the construction of the remaining rings. Intermediate (**2a**) could be conveniently elaborated to the β-carboline-bearing pyrrolo[2,3-*i*]isoquinoline (**4**),[7] which represents the upper half of the alkaloid molecule. The route to (**4**) involved the following steps: $-CO_2Me \rightarrow -CH_2OH \rightarrow -CHO$, followed by a Pictet-Spengler cyclization and oxidation (Pd/C). During the last step, the *N*-benzyloxycarbonyl group is cleaved, presumably by the hydrogen generated during the oxidative reaction or adsorbed on the surface of the catalyst. The exocyclic double bond in the resulting product is stabilized by tautomerism to the Δ^1-pyrroline moiety in (**4**).

The challenge of attaching the 13-membered macrocyclic ring D was then addressed. There are several approaches available for the elaboration of this ring on the tricyclic intermediate. Using (**2b**) as a model, its transformation to ketone (**5**) has been achieved by the sequence: $-CO_2Me \rightarrow -CH_2OH \rightarrow -CH_2OTBDPS$, followed by osmium tetroxide oxidation and dehydration. Addition of allyl Grignard to (**5**) resulted in a specific addition from the β-face of the molecular template, to yield the expected alcohol, which could be cyclized (NaH) to the pentacyclic carbamate (**6**). The olefin function in (**6**) was homologated to (**7**) in a three-step sequence: (i) 9-BBN/H_2O_2; (ii) Dess-Martin periodinane oxidation and (iii) Wittig reaction with $Ph_3P{=}CH_2$. The *N*-benzyl group of (**7**) was smoothly cleaved by treatment with Li/NH_3 and the amide nitrogen alkylated with $CH_2{=}CH(CH_2)_4$-I to give (**8**). The transformation of (**8**) to (**9**) has been carried out *via* an olefin metathesis cyclization, employing the ruthenium catalyst [$(Cy_3P)_2Cl_2Ru{=}CH\text{-}CH{=}CPh_2$] recently described by Grubbs.[8] It should be noted that ozonolysis of (**8**) would provide a dialdehyde intermediate which could also be converted to (**9**), using the McMurry cyclization[9] procedure. This route is currently under examination.

The chiral intermediate (**3**) has been utilized for the construction of azocine ring D. In an orientation study, the double bond in (**3**) has been reduced (H^+/$NaCNBH_3$), during which the primary hydroxyl group is deprotected. The $-CH_2OH$ is oxidized (Dess-Martin periodinane) and the thereby generated aldehyde function subjected to chain extension by a Wittig reaction with $Ph_3P{=}CH(CH_2)_3COOK$. Subsequent removal of the *N*-$COOCH_2Ph$ group (HBr/HOAc) and amide cyclization (Py-BOP) led to the tetracyclic compound (**10**).[10] The ester group in (**10**) has been transformed into a β-carboline unit, using the procedure described earlier, to give (**11**), the heptacyclic ring system of manzamine A.

With the strategies for constructing the various rings now in hand, the total synthesis of manzamine A is being vigorously pursued.

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