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An Enantioselective Approach to the Synthesis of Manzamine A.

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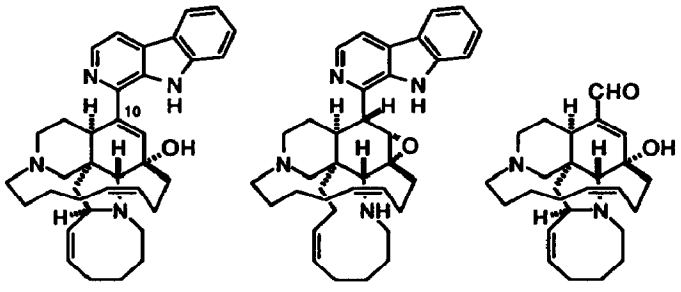
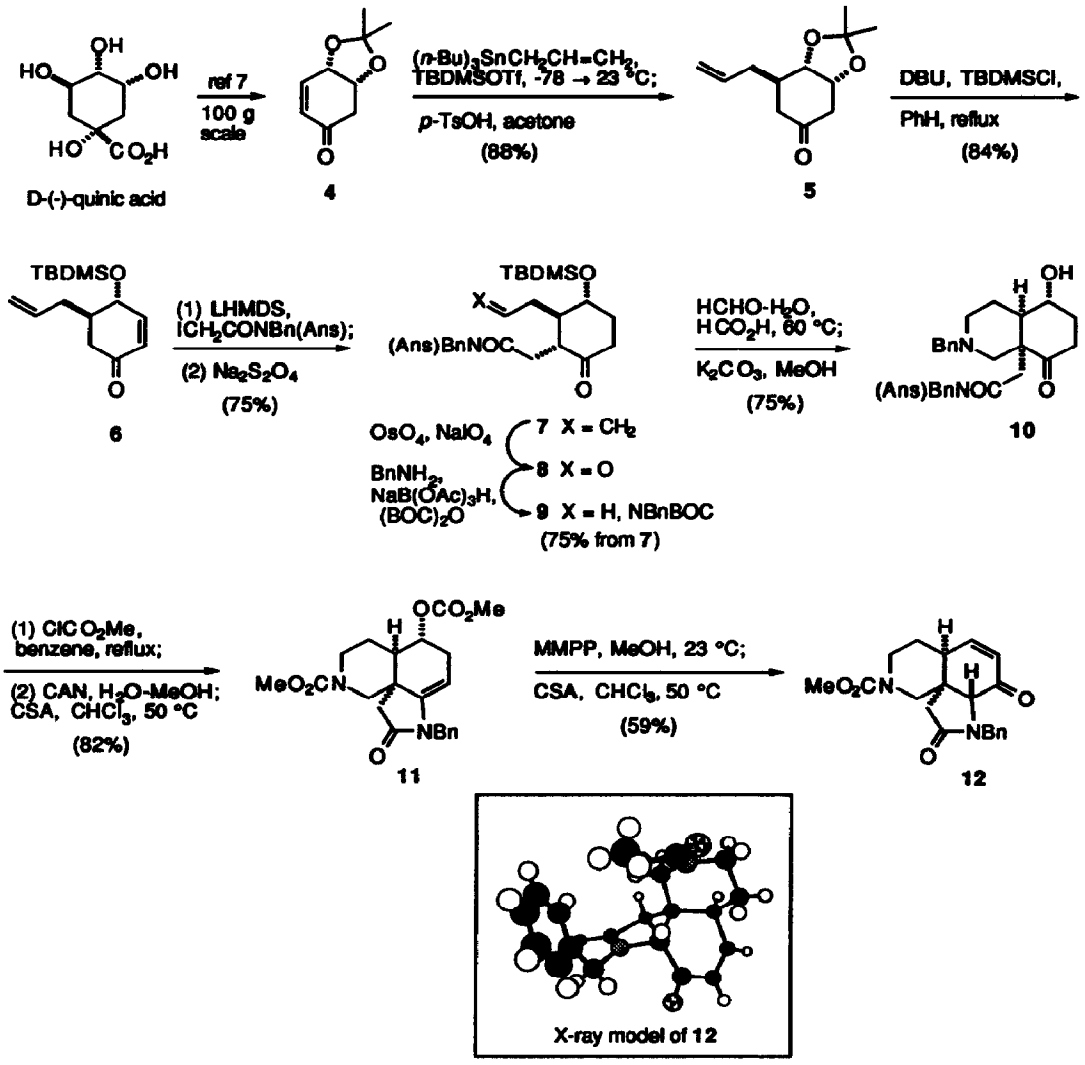
Abstract. A new approach for asymmetric construction of the pyrrolo[2,3-i]-isoquinoline core of manzamine A is described. The synthesis starts with D-(-)-quinic acid and features an intramolecular Mannich reaction as the central step.

The manzamines, e.g., **1**-**2**, are a new group of complex β-carboline alkaloids that display antitumor and antibacterial activities.[1] Manzamine A (**1**) was isolated from the Okinawan marine sponge *Haliclona sp.* in 1986 by Higa,[2] and independently by Nakamura in 1987 from the marine sponge *Pellina sp.*[3] This complex nitrogen heterocycle, containing 5-, 6-, 8-, and 13-membered rings as well as the β-carboline moiety, is a formidable synthetic target. The majority of published synthetic approaches towards manzamine A rely on the Diels-Alder reaction to prepare the cis-fused decahydroisoquinoline core.[4,5] Only two asymmetric strategies have been described to date.[4c,h,n] Herein, we report an enantioselective strategy for the synthesis of manzamine A that features the use of an intramolecular Mannich reaction to assemble the *cis*-decahydroisoquinoline substructure. The synthesis proceeds by way of a pyrrolo[2,3-i]isoquinoline enone allowing a formyl group, as well as a variety of potential intercalating aromatic residues, to be introduced at C(10).[6]



The synthesis begins with the enantiopure enone **4**, which is conveniently available on a large scale from D-(-)-quinic acid (Scheme I).[7] Stereoselective conjugate addition of tri-*n*-butylallylstannane to **4** in the presence of 1 equiv of TBDMSOTf,[8] followed by cleavage of the resulting enoxysilane during acidic work-up afforded cyclohexanone **5** in high yield.[7c,9] Subjecting this intermediate to DBU

Scheme I. (Ans = *p*-methoxybenzyl)



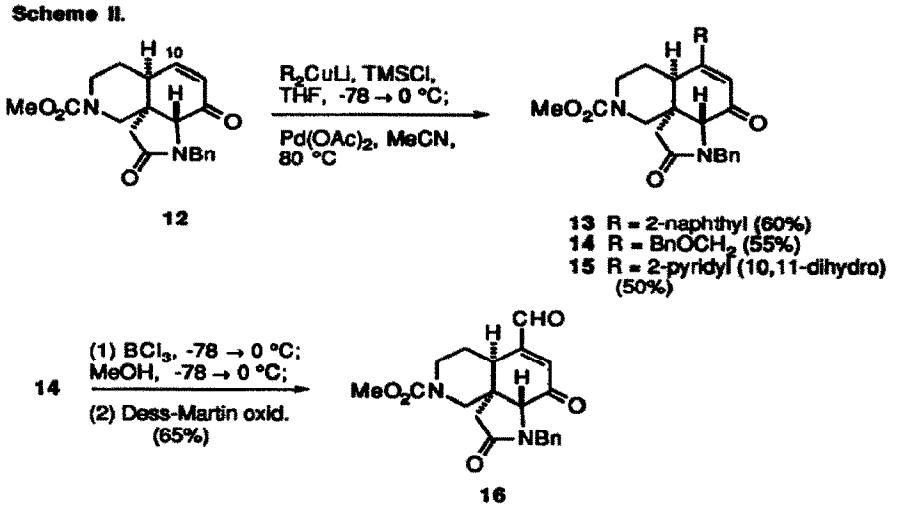
and TBDMSCl in refluxing benzene yielded the γ-siloxy enone **6**.[7c] Alkylation of the kinetic lithium enolate of **6** with *N*-(*p*-methoxybenzyl)-*N*-(benzyl)iodoacetamide,[10,11] followed by direct conjugate reduction of the crude product mixture with sodium hydrosulfite[12] gave the trisubstituted cyclohexanone **7** as single stereoisomer. Oxidative cleavage of the allyl group to an aldehyde, followed by reductive amination with benzylamine and BOC-protection provided **9** in good yield.[13]

The key Mannich cyclization was accomplished under extensively optimized conditions by exposing **9** to 5 equiv of aqueous formaldehyde in 98% formic acid at 60 °C. Concentration of the reaction *in vacuo* followed by a mild basic workup provided decahydroisoquinoline **10** (a single stereoisomer as judged by capillary GLC and ^{13}C NMR analysis) in 75% yield. It is notable that the

intramolecular Mannich reaction occurs more rapidly under these conditions than Eschweiler-Clarke reductive methylation. The cis stereochemistry of **10** was assigned initially based on an expected stereoelectronic preference for axial addition of the iminium ion to the cyclohexanone enol.[14] Debenzylation of **10** by treatment with methyl chloroformate, followed by cleavage of the *p*-methoxybenzyl group and acid-catalyzed dehydration afforded the tricyclic enamide **11** in excellent yield. Oxidation of this intermediate using magnesium monoperoxyperphthalic acid in methanol, followed by acid-promoted rearrangement of the resulting epoxide and subsequent β-elimination, gave the crystalline tricyclic enone **12** in 59 % yield. Single crystal X-ray analysis of this intermediate confirmed the expected stereochemistry (Scheme I).

With enone **12** in hand, we examined the addition of several potential intercalating aromatic substituents at C(10). Although we were not successful in directly adding the β-carboline moiety, addition of the 2-pyridyl, 2-naphthyl and benzyloxymethyl groups could be realized by reaction of enone **12** with the corresponding homocuprate reagent in the presence of TMSCl.[15] In the latter two cases, dehydrogenation of the derived enoxysilane intermediate *in situ* provided the β-substituted enones **13** and **14** in useful yields.[16] Selective cleavage of the benzyl ether protecting group of **14** with BCl_3[17] followed by Dess-Martin oxidation[18] then afforded enal **16** in 65% yield.[19]

Scheme II.



Enone **12**, which comprises the tricyclic core of (+)-manzamine A, has been constructed in enantiopure fashion in 11 steps from the readily available enone **4** (15 steps from commercially available materials). This intermediate serves as a platform for introducing at C(10) the formyl moiety found in ircinal A, as well as other potentially intercalating groups.

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(9) All intermediates were fully characterized by ^{1}H, ^{13}C, IR, and MS analysis. The elemental composition of analytical samples of new compounds was confirmed by combustion analysis or high-resolution mass spectrometry. Yields refer to isolated, purified products.

(10) This iodoacetamide was prepared in 85% overall yield from *p*-methoxybenzylamine by the following sequence: (a) benzaldehyde, $NaBH(OAc)_3$, HOAc;[11a] (b) $ClCH_2COCl$, CH_2Cl_2, 10% NaOH;[11b] (c) NaI, $CaCO_3$, acetone.

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