APPROACHES TO THE SYNTHESIS OF MANZAMINE A. SYNTHESIS OF THE β-CARBOLINE-BEARING ABCE RING SYSTEM

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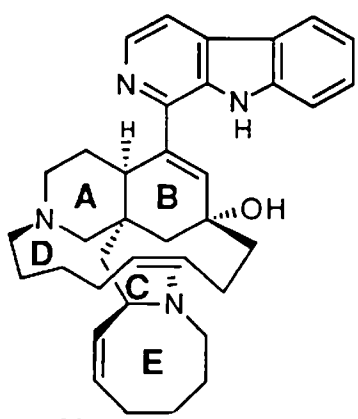
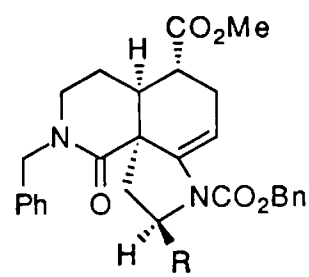
Abstract : The 8-membered ring E has been introduced onto a strategically functionalized chiral pyrrolo[2,3-*i*]isoquinoline derivative by a combination of a Wittig coupling and amide cyclization. The resulting tetracyclic structure has been converted to the ABCE-β-carboline ring system of manzamine A.

The novel structure and significant biological activity of manzamine A **1** - an alkaloid isolated from sea sponges found in the Okinawan waters (1) - has drawn keen attention in connection with its biosynthetic origin (2) and chemical synthesis (3).

In a retrosynthetic analysis of the alkaloid, we, and a number of other groups, have recognized that the ABC ring system of manzamine A constitutes a core structure upon which the remaining rings of the target compound may be elaborated. In this context, we reported the first synthesis of the strategically functionalized chiral pyrrolo[2,3-*i*]isoquinoline intermediate **2** (3d). We now present the elaboration of **2** to the ABCE-β-carboline ring system of manzamine A.

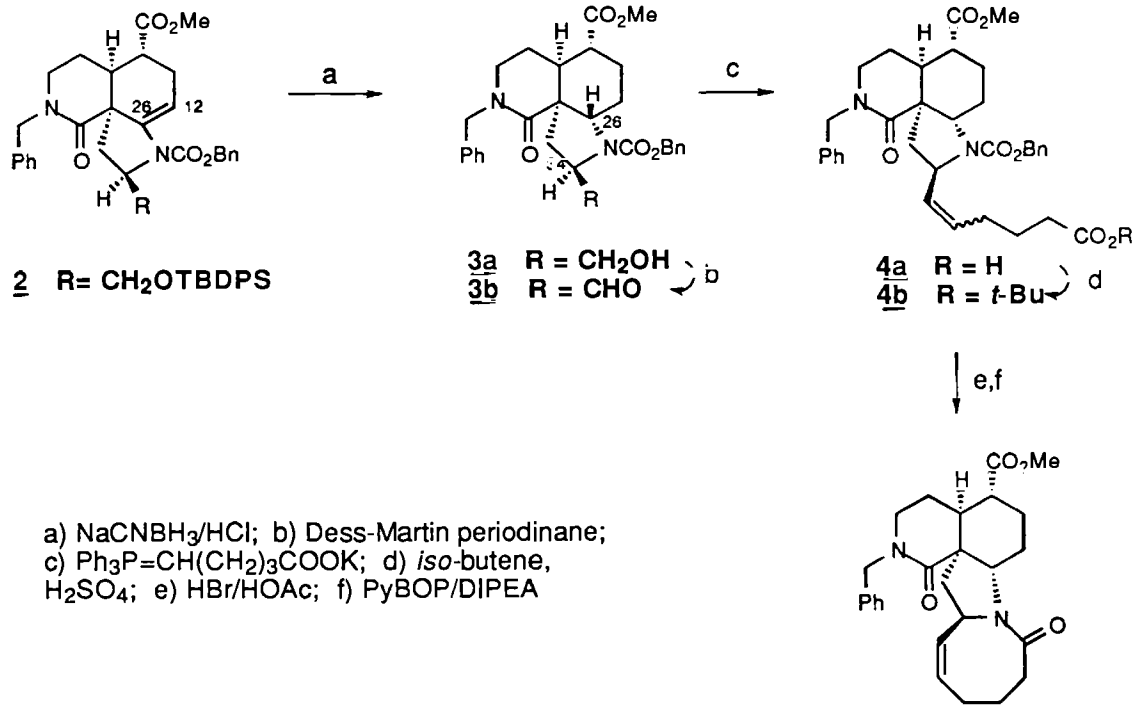


Manzamine A **1**



2 R= $CH_2OTBDPS$

In the present study, the C-(12)-C-(26) double bond of intermediate **2** [manzamine numbering (1b)], was reduced in order to simplify the functional character of the system. During the reduction ($NaCNBH_3$/HCl), the *t*-butyldiphenylsiiyl (TBDPS) group of **2** was cleaved to give alcohol **3a** (80%) (4) (**Scheme 1**). Oxidation of **3a** using the Dess-Martin periodinane (5) provided the corresponding aldehyde **3b**, in good yield (94%). The β-configuration of the C(26)-hydrogen, in **3b**, was derived from an NOE experiment (6). A Wittig coupling of **3b** with $Ph_3P{=}CH(CH_2)_3COOK$, under conditions suited to selectively give the *Z*-olefin, resulted in an isomeric mixture defined by **4a** (46%), containing the *Z*-isomer as the major product (*Z/E*, 4/1). The *E/Z* ratio in the mixture of **4a** was determined by the ^1H NMR spectrum of the corresponding *t*-butyl esters **4b**. The low yield of the Wittig condensation is attributed to steric hindrance by the *N*-benzyl substituent. This feature is convincingly evidenced in the molecular model of **4b** and is further attested by the fact that a similar Wittig reaction of both proline carboxaldehyde (7) and an intermediate analogous to **4b**, but lacking the *N*-benzyl group (3o), proceeds in good yield. The isomeric mixture of **4a** was subjected to removal of the benzyloxycarbonyl protecting group (HBr/HOAc); treatment with the PyBOP peptide coupling reagent (8) gave the homochiral ABCE ring system **5** (45%).

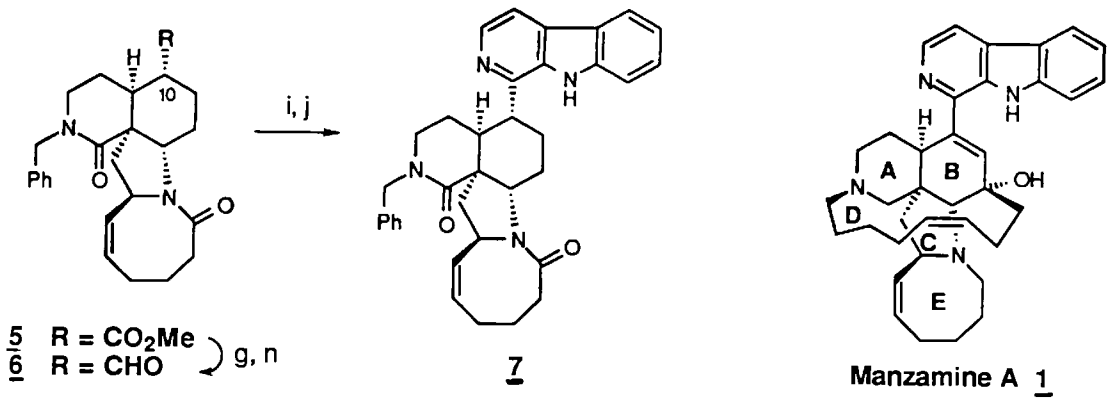


2 R= $CH_2OTBDPS$

5

Scheme 1

The introduction of the β-carboline moiety on the tetracycle **5** was achieved using a standard Pictet-Spengler sequence (**Scheme 2**) (9). To this end, the ester group at C-10 was reduced and subsequently oxidized to afford aldehyde **6**. Condensation of **6** with tryptamine, followed by cyclization using HCl in benzene and a final oxidative aromatization step (Pd/C) yielded the β-carboline derivative **7**, the structure of which was attested by its spectral data (10). The overall yield for this unoptimized five step sequence was 15%.



g) $LiBH_4$; h) Dess-Martin periodinane; i) tryptamine/HCl; j) Pd/C, refluxing decalins

Scheme 2

We have recently developed an efficient strategy for the elaboration of ring D on the tricyclic intermediate **2** (R=H) in our laboratory (3r). The application of the methodologies for constructing rings D, E and the β-carboline nucleus, onto the chiral pyrrolo[2,3-*i*]isoquinoline core, is currently in progress.

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(6) The β-configuration of C(26)-H in **3b** is attested by the absence of an enhancement of the C(26)-H signal upon irradiation of C(34)-H (δ 4.06 ppm, benzene-d_6, 343 K) in an NOE experiment. Based on molecular models, an α-configuration of C(26)-H would have resulted in a positive effect in the NOE experiment

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(10) Selected data for **7**: $[\alpha]_D$ = + 8.9 (*c* = 0.2, $CHCl_3$); MS (FAB) 545 (M^++H, 73%), 448 (61), 279 (80), 250 (41), 91 (100); ^{1}H NMR (400 MHz, $CDCl_3$) 1.30 (m, 2H), 1.64-1.83 (m, 3H), 1.88-2.04 (m, 4H), 2.27-2.40 (m, 2H), 2.55 (dd, 1H, J=7.1, 12.2 Hz), 2.75 (m, 2H), 3.00-3.40 (m, 3H), 3.52 (m, 1H), 3.58 (d, 1H, J=13.9 Hz), 3.67 (m, 1H), 4.86 (m, 1H), 5.50 (m, 1H), 5.65 (m, 1H), 5.73 (d, 1H, J=13.9 Hz), 6.92 (br s, 1H), 7.23-7.30 (m, 2H), 7.34 (d, 1H, J=8.3 Hz), 7.40-7.70 (m, 5H), 7.74 (d, 1H, J=5.3 Hz), 8.03 (d, 1H, J=7.8 Hz), 8.36 (d, 1H, J=5.3 Hz)

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