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SYNTHESIS OF THE "TRICYCLIC HEART" OF MANZAMINES

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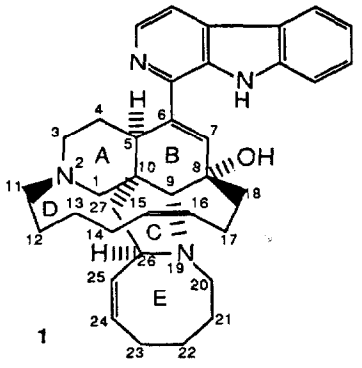
ABSTRACT: The synthesis of a strategic tricyclic intermediate for the construction of manzamine is described.

The alkaloid manzamine-A (**1**), isolated by Sakai et al.[2] from Okinawan marine sponge Haliclona sp., exhibits potent antitumour activity (P 388, IC_{50} = 0.07 μ/ml). In an independent study Nakamura and coworkers[3] have isolated the same compound from the marine sponge Pellina sp. and named it Keramamine-A. Both groups have established the structure and absolute configuration of the alkaloid, via X-ray analysis.

As a part of an ongoing programme on the synthesis and the structure-activity relationship study of antitumour natural products[4], we have undertaken the total synthesis of manzamine-A. The recent announcement[5] dealing with this subject prompts us to report our own results on the stereoselective synthesis of a functionalized tricyclic intermediate which can be potentially elaborated to the alkaloid.

In considering possible approaches for the construction of the complex skeleton of manzamine - consisting of an array of five, six, eight and thirteen membered rings, in addition to the β-carboline unit - it was recognized that the pyrroloisoquinoline ABC ring system of **1**, bearing four of the five chiral centres of the molecule, could serve as the "*architectural heart*" of the alkaloid. In view of this, the judiciously substituted tricyclic system **2a** was seen as the model ABC intermediate and, therefore, selected as the initial synthetic target. The functionalization in **2a** is well-suited for (*a*) a facile introduction of the β-carboline unit at C_6, (*b*) construction of the C_8 - N_2 bridge of the 13-membered ring and (*c*) elaboration of the azocine moiety, via a suitable C_{26}-substituent, as in **2b**; manzamine numbering[3]. The stereoselective synthesis of **2a** was visualized by the cyclization of triene **3a** in an



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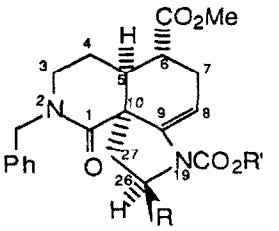
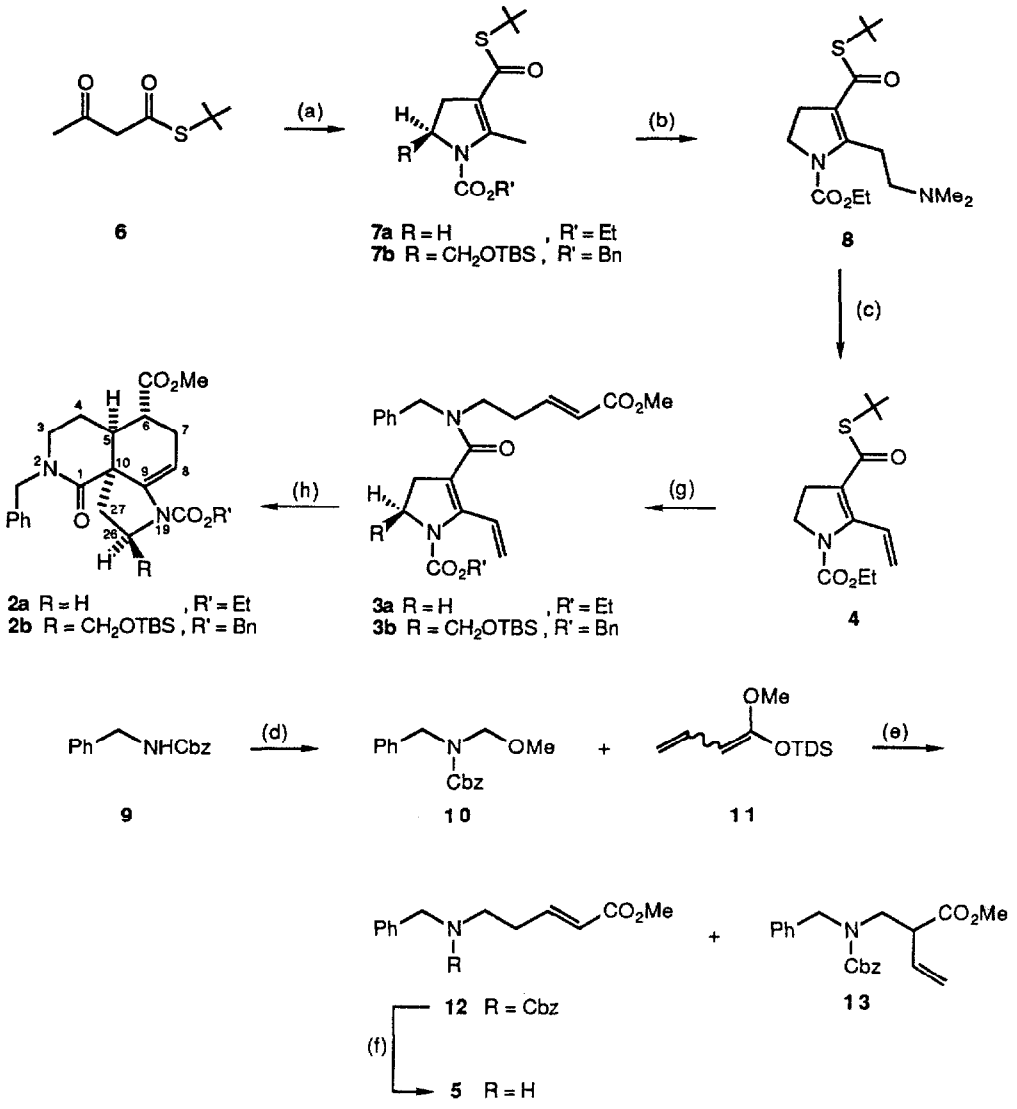


2a R = H , R' = Et
2b R = CH_2OTBS , R' = Bn



(a) *i* NaH , DME , $ICH_2CH_2NHCO_2Et$, R.T. , 4d ; *ii* TsOH / quinoline , Δ , 30 min. ; 58%. (b) LDA , THF , $CH_2NMe_2^{\oplus}\ I^{\ominus}$; 49%. (c) *i* MeI , CH_3CN , R.T. , 16 h ; *ii* DBU ; CH_2Cl_2 , R.T. , 1h ; 76%. (d) NaH , DMF , CH_3OCH_2Cl , R.T. 16h ; 76%. (e) $BF_3 \times Et_2O$, CH_2Cl_2 , R.T. , 2h , 71%. (f) TMSCl , NaI , CH_3CN , Δ , 5h , 81%. (g) **5** , AgOTf , DiPEA , R.T. , 16 h , 77%. (h) $PhCH_3$, Δ , 6h ; 96%.

intramolecular Diels-Alder reaction[6]. It has been shown previously, that intramolecular Diels-Alder cyclizations involving "Z" dienes lead stereoselectively to cis-fused products, exclusively[7]. This strategy has the unique advantage that an analogous cyclization of **3b**, containing a chiral centre at C_{26}, would be expected to result in **2b**, with the simultaneous generation of three new chiral centres with the desired stereochemistry. Since the ABC ring system of **2b** contains three of the five chiral centres of the alkaloid, its construction with the correct absolute stereochemistry should potentially set the stage for the total synthesis of optically active natural manzamine-A.

A retrosynthetic analysis of precursor **3a** identified pyrrole derivative **4** and amino ester **5** as the optimum synthons. The syntheses of the two required compounds was achieved as follows. Commercially available thiol ester **6** was alkylated with $ICH_2CH_2NHCOOEt$ under basic conditions and the resulting product cyclized to pyrrolinethiol ester **7a**. Subsequently, the anion of **7a** was subjected to aminomethylation with the help of Eschenmoser's salt. When the amino group in **8** was further methylated and the quaternary salt induced to undergo a base mediated elimination, the desired product **4** was obtained.

The synthesis of **5** started from urethane derivative **9** [8]. Introduction of a one carbon unit, by methoxymethylation, provided the expected aminal **10**. The latter was coupled with the silyl ketene acetal of methyl crotonate [9] under influence of borontrifluoride etherate. The reaction led to the formation of a 1:1 mixture of esters **12** and **13**, from which the desired isomer **12** could be conveniently separated by chromatography. Deprotection of the amino function of **12** gave ester **5**.

Ammonolysis of the thiolester **4** by **5** was carried out in the presence of silver triflate[10,11] and diisopropylethylamine, whereupon, the triene **3a** was obtained in good yield (77 %). Heating of **3a** in refluxing toluene, for six hours, gave a product which, after silica gel plug filtration, resulted in crystalline **2a**, m.p. 141-142 °C, in 96 % yield. The gross structure of **2a** was consistent with its spectral data[1,2]. The NMR spectrum of **2a** showed the presence of two rotamers due to fixation of rotation about the carbamate bond. At higher temperatures (55 °C, $CDCl_3$ solution, closed tube, or 70 °C, C_6D_6 solution) the spectrum simplified to that of a single molecular species. Further elucidation of the stereochemical details of the structure made use of NMR analysis involving double resonance, COSY, ^{13}C-APT and Nuclear Overhauser experiments[13] . The trans diaxial relationship between H_5 and H_6 was established by a coupling constant of 11.4 Hz. Irradiation of H_5 resulted in enhancement of the signals of the H_{27}-exo and H_7-axial protons, thereby attesting to a cis stereochemistry of the AB ring junction. Dreiding molecular models of **2a** reveal that the C_6-axial proton lies in the vicinity of the C_3-axial proton. In line with this stereochemistry, when the latter proton was irradiated (δ 3.13), only the C_6 proton exhibited a positive signal at δ 2.62.

It can be reported that the synthesis of **7b** starting from L-(+)-serine has been achieved. The synthesis of **2b** from **7b**, which is underway, should allow its elaboration to the total synthesis of natural manzamine-A.

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12. MS observed: 412.1998; Calc. for $C_{23}H_{28}N_2O_5$: 412.2002. IR: 1710, 1665, 1625 cm^{-1}; ^{1}H-NMR (C_6D_6, 70 °C): 7.10 ppm (m, 5H, Ph), 6.28 (br, 1H, H_8), 4.60 (d, 1H, N_2CH_aPh), 4.10 (q, 2H, OCH_2CH_3), 4.07 (d, 1H, N_2CH_bPh), 3.91 (m, 1H, H_{26}), 3.56 (m, 1H, $H_{26'}$), 3.28 (s, 3H, OCH_3), 3.13 (m, 1H, H_3ax), 2.74 (m, 1H, H_3eq), 2.62 (m, 1H, H_6ax), 2.39 (m, 2H, H_7ax, H_7eq), 1.90 (m, 1H, H_5eq), 1.77 (m, 1H, H_{14}endo), 1.58 (m, 2H, H_4ax, H_4eq), 1.22 (m, 1H, H_{14}exo), 1.08 (t, 3H, OCH_2CH_3).
13. Details of the NMR spectra will be published elsewhere.

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