Synthetic Strategies Directed to the Antitumour Alkaloids Sesbanimide A and Manzamine A

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Synthons derived from nature's chiral pool have been utilized in developing strategies aimed at the syntheses of the alkaloids sesbanimide A and manzamine A. The route designed for sesbanimide A has provided the naturally occurring alkaloid and a facile access to several analogues for structure-activity relationship studies. The approach to the synthesis of manzamine A has led to a strategically functionalized chiral tricyclic intermediate possessing the absolute stereochemistry of the natural product. Recent results on the synthesis of sesbanimide analogues and the progress towards the total synthesis of manzamine A is described.

Studies directed to the synthesis of complex natural products constitute an area of research which serves a number of objectives. As a primary goal such studies provide the target molecules themselves. In addition, they lead to related systems for biological and physico-chemical investigations and, as a further bonus, they result in the evolution of synthetic methodologies, which can find broader general application.

to camptothecin [1], bleomycin analogues [2], aspidosperma alkaloids [3] and ellipticines [4a-c].

This paper presents our studies on the synthesis of the plant alkaloid sesbanimide A (1) [Scheme 1] and its analogues and discusses the strategy developed in our laboratory which aims at the total synthesis of manzamine A (2), an alkaloid obtained from sea sponges.

Sesbanimides.

The sesbanimides are a group of structurally related alkaloids which have been isolated from the seeds of *Sesbania drummondii* [5a,b] and *Sesbania punicea* [6]. In 1983, the structure of the most active antitumour principle of *S. drummondii* was announced [5a], without defining its absolute stereochemistry. The X-ray data, on which the structure was based, while revealing the relative stereochemistry of the molecule, could not distinguish between the two possible antipodes. Initially, the alkaloid was called sesbanimide [5a]; when several related compounds were obtained from the same source, it was termed sesbanimide A [5,6]. Sesbanimide A possesses an unusual tricyclic system, comprising a glutarimide ring (A), a six-membered methylene acetal (B) and a five-membered cyclic hemiketal (C), which are linked together *via*
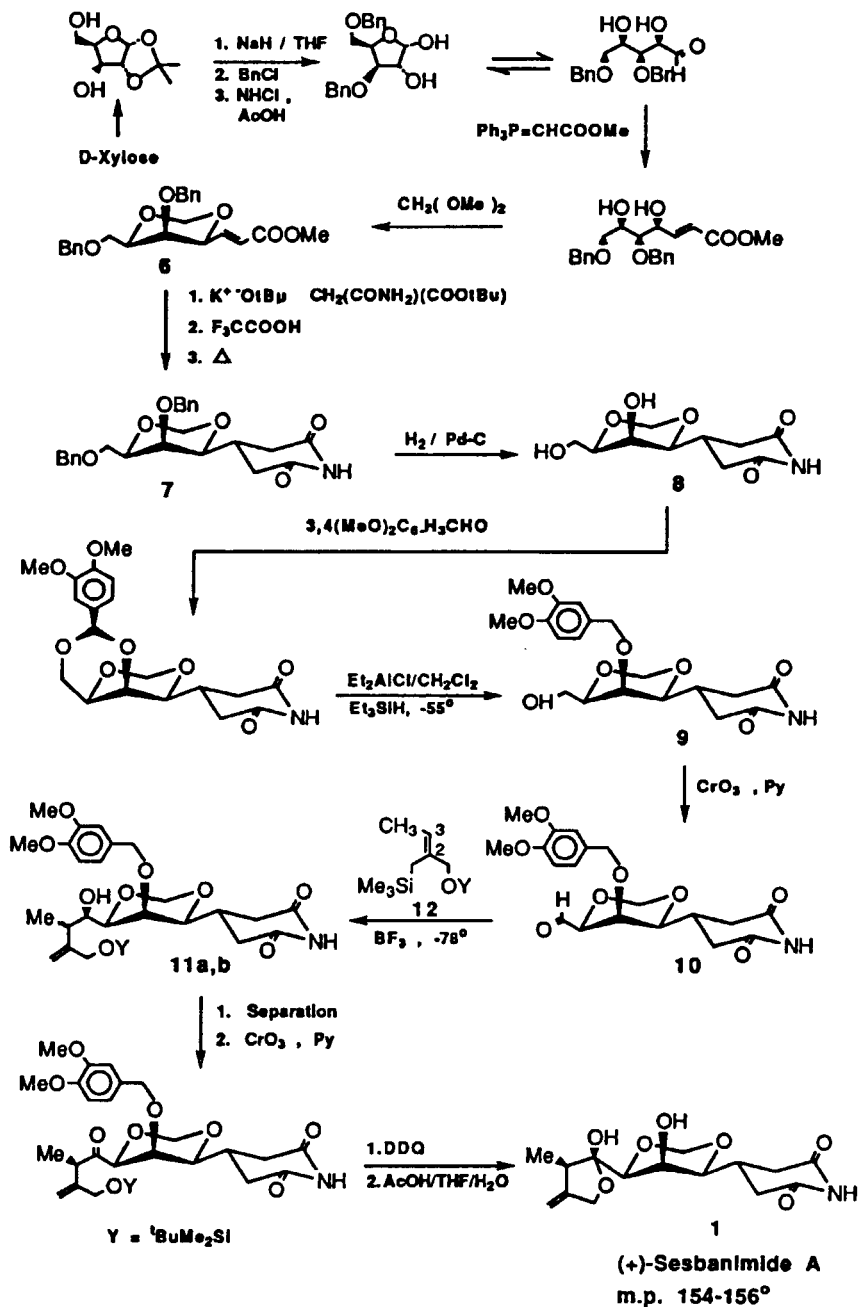

Sesbanimide A (1)

Manzamine A (2)
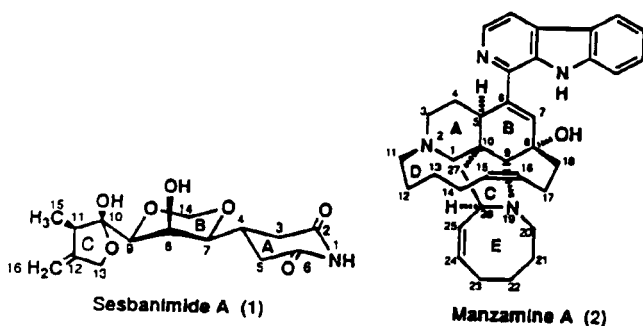
Scheme 1

The theme of anti-tumour natural products has been the subject of study in our laboratory for a number of years. We have previously reported on synthetic studies directed
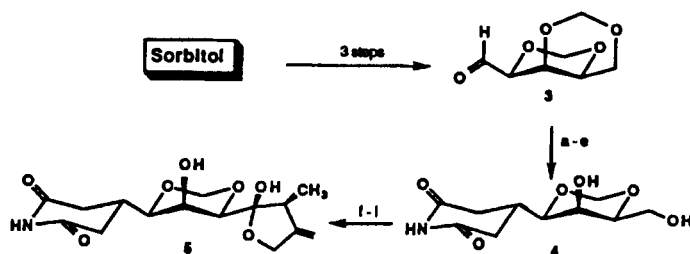
(a) Ph₃P=CHCOOMe/tol. (b) CH₂(CONH₂)COOtBu/tBuOK (c) TFA, RT; DMF, Δ (d) Ac₂O/AcOH, H₂SO₄, 0°
(e) NaOMe/MeOH (f) ArCHO/tol., p-TsOH (g) Et₂AlCl/CH₂Cl₂, Et₃SiH, -60° (h) CrO₃/pyr., CH₂Cl₂/DMF, 0°
(i) CH₂CH=C(CH₂OSiMe₃)CH₂OSiᵗBuMe₂/BF₃. CH₂Cl₂, -90° (j) separate, CrO₃/pyr.CH₂Cl₂/DMF, 0°
(k) DDQ/CH₂Cl₂/THF/H₂O (l) AcOH/THF/H₂O

Scheme 2

Scheme 3

carbon-carbon single bonds; this gives the rings a high degree of relative rotational flexibility within the molecule.

In connection with the development of a synthetic strategy for sesbanimide A, inspection of the contiguous three hydroxy groups in ring B led us to visualize its potential derivation from the carbohydrate xylose, as an appropriate chiral precursor. The functionalities at the terminal ends of a suitable xylose derivative could serve as convenient starting points for the construction of rings A and C. It

was envisaged that the sequence of elaboration should involve the construction of the functionally sensitive ring C in the final stages of the synthesis. Thus, in an overview, the strategy would involve the assembly of rings in the order: B → BA → CBA. In embarking upon the synthesis however, one was confronted with the choice of L-xylose or D-xylose as potential starting carbohydrate synthons; since, as mentioned earlier, information on the absolute stereochemistry of sesbanimide A was unavailable at the time [5a,b].
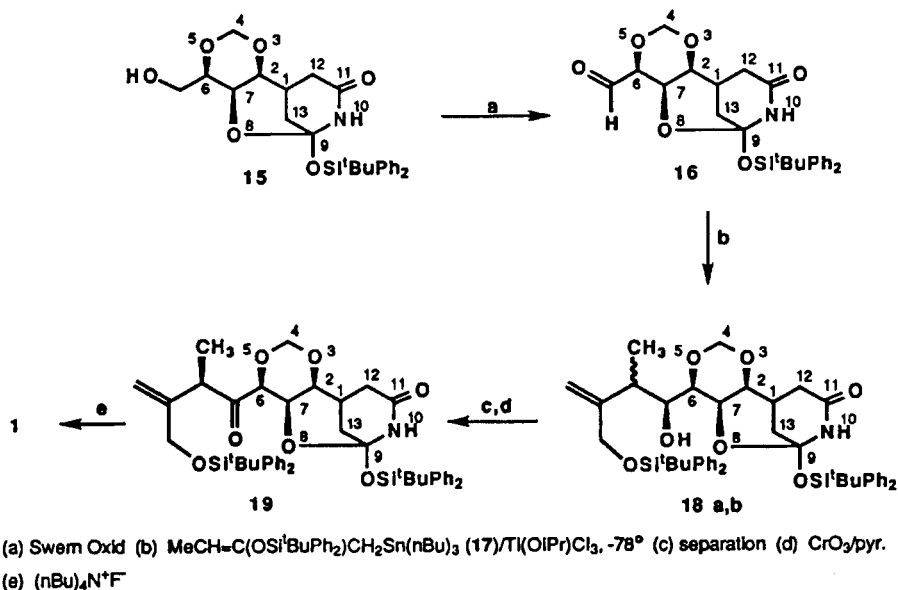
8 R = H, **13** R = Bz

14 OSI^tBuPh₂

X-Ray structure (15)   (a) ^tBuPh₂SiTrf/collidine (b) DIBALH
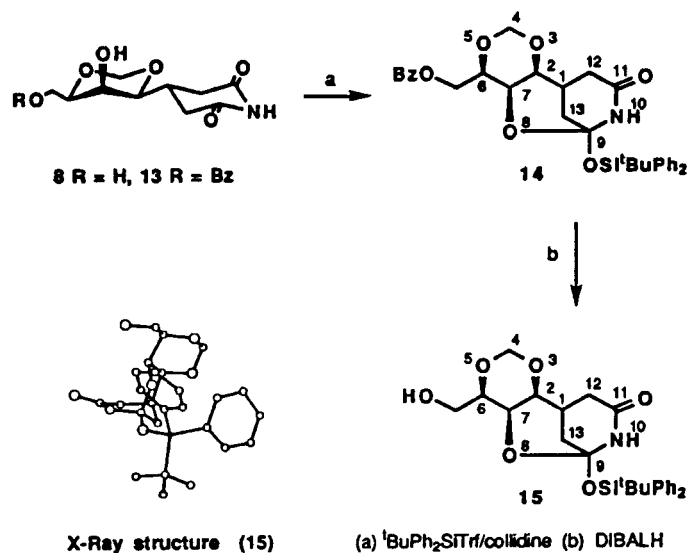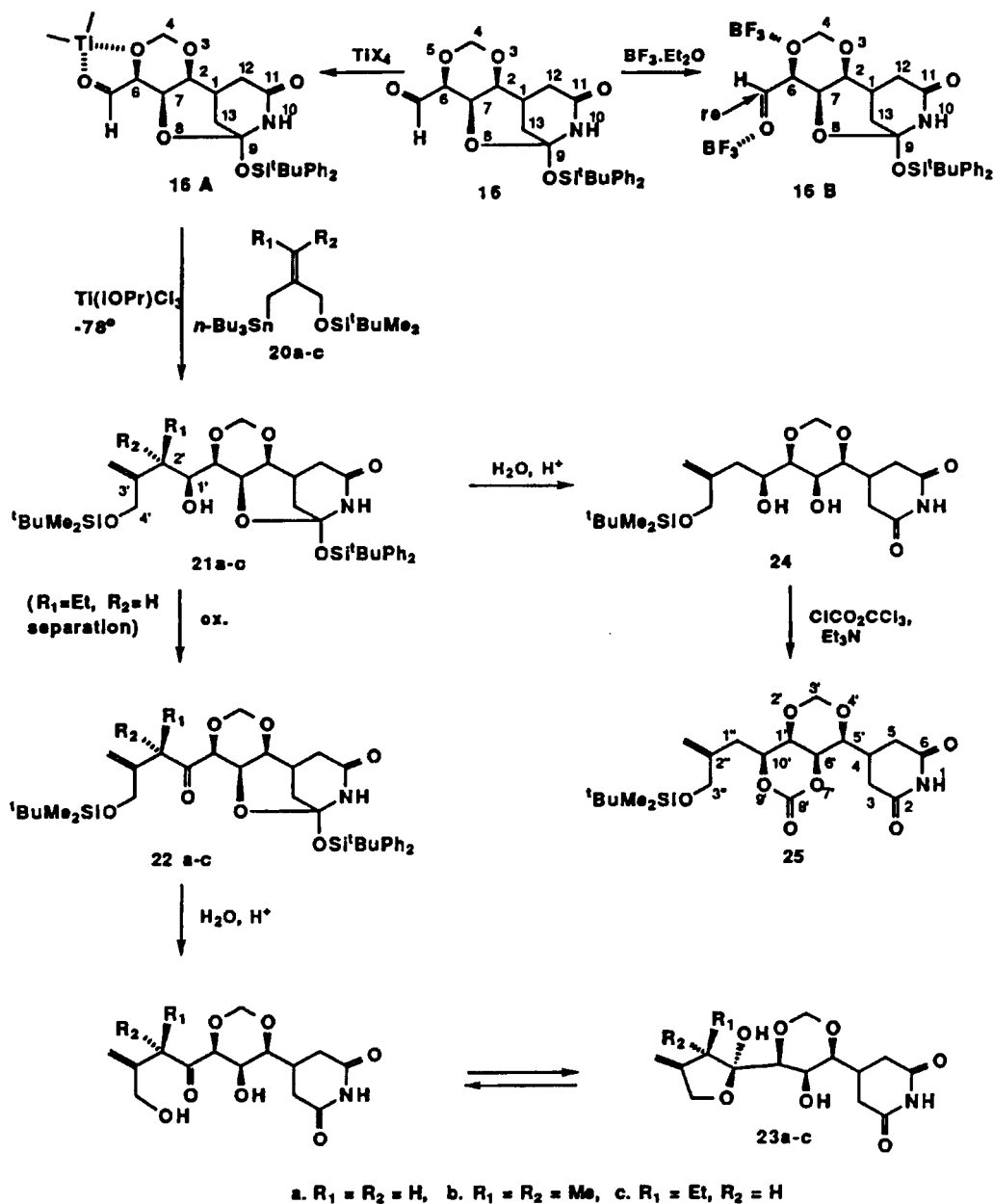
Scheme 4

A variety of practical considerations led us to initiate the synthesis from L-xylose as the ring B synthon. In doing so, we were aware that there was only a 50% chance of arriving at the correct naturally occurring product. The over-all synthetic approach starting from sorbitol, a convenient source of L-xylose derivative **3**, led, *via* 12 steps [Scheme 2], to compound **5**. The latter, while exhibiting identical melting point and ir and nmr spectra to those of sesbanimide A, possessed a negative rotation, in contrast to the known positive rotation for the natural compound. This fact revealed the identity of **5** as the antipode of the naturally occurring alkaloid [7].

This *first* synthesis of the sesbanimide molecule was significant for two reasons. Firstly, since the stereochemistry of **5**, namely, 7*R*, 8*S*, 9*R*, 10*S*, 11*S*, followed from the starting carbohydrate L-xylose, the absolute stereochemistry of naturally occurring sesbanimide A could now be established as 7*S*, 8*R*, 9*S*, 10*R*, 11*R*. Secondly, it was obvious that the synthesis of natural sesbanimide A (**1**) could be achieved with facility *via* the strategy worked out for **5**, by starting with a suitable D-xylose derivative. It being implicit that the chemistry of the reaction steps and the nature of the intermediates involved in the synthetic sequence beginning with D-xylose would be familiar from the sequence for **5**, since one would be dealing with antipodes. The synthesis of natural (+)-sesbanimide

(a) Swern Oxid (b) MeCH=C(OSi^tBuPh₂)CH₂Sn(nBu)₃ (**17**)/Ti(OiPr)Cl₃, -78° (c) separation (d) CrO₃/pyr.

(e) (nBu)₄N⁺F^{−}

Scheme 5

Scheme 6

A starting from D-xylose and following the previously employed strategy is described in Scheme 3 [8]. Three steps in this synthetic scheme require comment. (i) The sequence involving the conversion of α,β-unsaturated ester **6** to the corresponding glutarimide derivative **7** constitutes a three step general approach to glutarimide ring synthesis from α,β-unsaturated esters. (ii) It is essential that the secondary hydroxyl function at C(8) in diol **8**, be selectively protected with an electron-donating substituent (e.g. 3,4-dimethoxybenzyl), in order to achieve a practically useful oxidation of the primary hydroxy group of intermediate **9**. Attempts to protect the C(8)-hydroxyl as

an ester [OOCR] interfered with the oxidation step **9** → **10**, due to an accompanying elimination of elements of the corresponding acid [RCOOH]. This elimination involves the *trans* axial proton located at the α-position to the aldehyde function. (iii) Finally, the attachment of the allylsilane 5-carbon synthon **12** to aldehyde **10**, under influence of boron trifluoride, results in a mixture of diastereomeric diols **11a,b,** which differ in the stereochemistry of the C(11)-methyl substituent.

The stereochemistry of the C(10)-hydroxyl is assigned on the basis of analogy with the known stereochemical course of such condensations [9]. Model experiments in
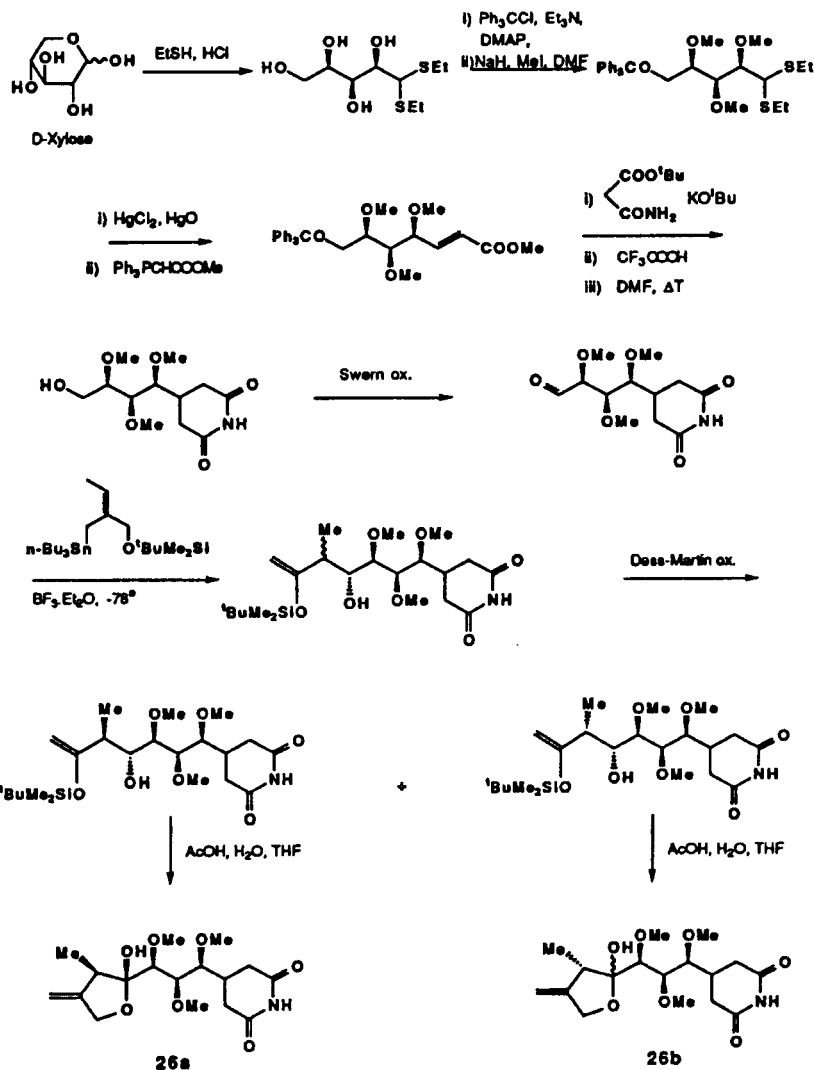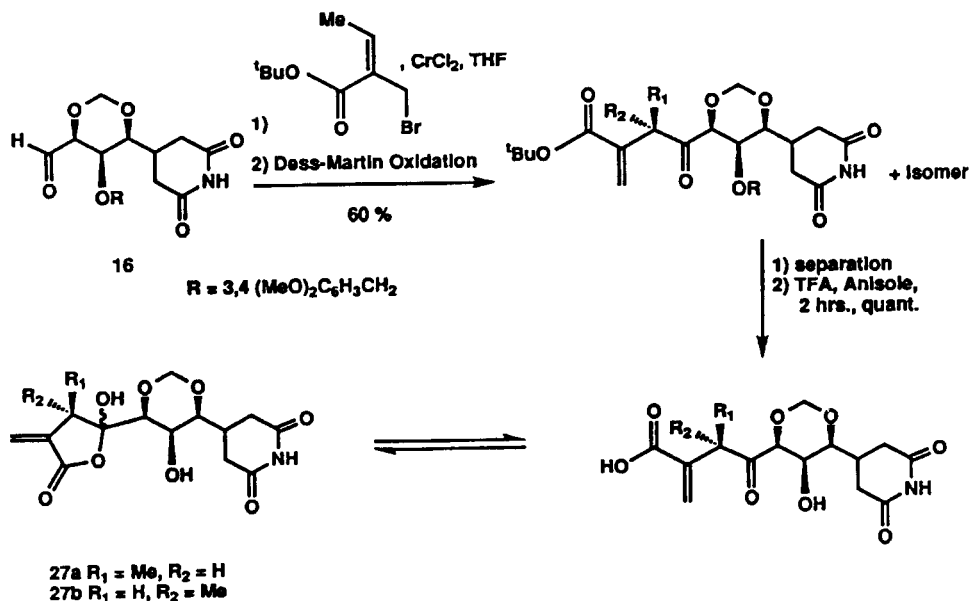
Scheme 7

our laboratory [10] involving boron trifluoride and titanium tetrachloride as catalysts have, as expected, established that the condensations with these two types of catalysts lead to products with opposite configurations of the C(10)-OH. Furthermore, these experiments reveal that the major diastereomer in model experiments [10] is that which is produced by an attack *via* the 2si-3re face of reagent **12**.

Several groups [11a-d] have synthesized (-)-sesbanimide A and (+)-sesbanimide A following a strategy analogous to the one described in Scheme 3. Differences in these synthetic sequences (compared to Scheme 3) centre around the method of constructing the glutarimide ring A and especially in the procedure for selective protection of the C(8)-hydroxyl function in intermediate **8**. In all cases, a derivative of **8** - with the protected primary hydroxyl function - is allowed to react with a silylating reagent, to

provide what has been regarded as the corresponding C(8)-silyl derivative [11a-d]. In our laboratory, a similar reaction of **13** (Scheme 4) with *t*-BuPh$_2$SiTrf led to the tricyclic compound **14**, whose structure was unambiguously established by cleavage of the ester group and determining the X-Ray structure of the resulting alcohol **15** [12a]. The detailed nmr analysis of **14** was in agreement with its assigned structure [12a]. This structure has recently received further support [12b].

The unexpected formation of **14** (from **13**) can be rationalized as follows: an initial reaction of the silyl reagent with a carbonyl of the glutarimide moiety, yields a silyl imino ether; subsequently, an intramolecular addition of the C(8)-OH group to the C=N bond of the imino ether function completes the formation of **14**. A model of diol **8** reveals that the C(8)-OH group is sterically shielded to an approach by bulky molecules like the *t*-BuPh$_2$SiTrf

Scheme 8

reagent. Not withstanding the unexpected structure of **14**, it was realised that the corresponding alcohol **15** does represent a derivative of **8** in which the C(8)-hydroxyl function is protected, albeit in a somewhat bizarre fashion. Oxidation of the primary hydroxy group of **15** provides an aldehyde intermediate **16** [Scheme 5] that readily condenses with the tin analogue **17** of the 5-carbon allylsilane synthon **12**, to yield a diastereomeric mixture of alcohols **18a,b**. The sequence of standard steps involving separation of the alcohols (**18a,b**), followed by oxidation of **18a** (11-Me R diastereomer) to **19** and deprotection by fluoride ions constitute in an alternate synthesis of sesbanimide A [13].

Aldehyde **16** can serve as a general precursor of ring C modified sesbanimides. For example, by allowing it to react with tin reagents **20a-c**, new sesbanimide analogues can be synthesized by following the sequence **21a-c** → **22a-c** → **23a-c** [14] [Scheme 6]. It should be noted that the use of TiCl₃-i-OPr as the Lewis acid catalyst in the condensation with the tin reagents [Schemes 5 and 6], involves a change in the stereochemistry of the new sp³ centre generated at C(1') [**21a-c**, Scheme 6], in comparison with the boron trifluoride-catalyzed reaction. However, it is recognized that the stereochemistry of this hydroxyl group is inconsequential to the synthesis, since it is destroyed in the subsequent oxidation step.

The nature and conformation of the aldehyde function in **16** in the complexes with TiCl₃-i-OPr and boron trifluoride are represented by complexes **16A** and **16B**, respectively [Scheme 6]. The stereochemistry of the reaction product of **16A** with the tin reagents was rigorously investigated in the case of the reaction with **20a**. The product

alcohol **21a** [14] was converted, *via* **24**, to **25**, in which the C(1')-OH was bound in the form of a cyclic carbonate. Detailed nmr analysis of **25** established its structure and thereby the configuration of the C(1')-OH in **21a**. Particularly relevant to the structural analysis of **25** was the establishment of the 1,3-diaxial configuration of the protons at C(6') and C(10) in the molecule [14].

It is interesting to comment on the hydroxy ketone-hemiketal equilibrium in the series of sesbanimides **23a-c**. The nmr studies in various solvents show that while **23b** is in the hemiketal form in all the solvents studied; the equilibrium shifts in favour of the hydroxy ketone form especially in polar solvents, in case of the other sesbanimides. The product **23a**, which has no alkyl substituent, shows the highest concentration of the hydroxy ketone form. These facts are consistent with the well-known effect of alkyl substituents on open chain-ring equilibria. This effect can be of influence in the biological properties of the sesbanimides.

The general strategy for the synthesis of sesbanimides has also been applied to ring B analogues **26a,b** [Scheme 7] [15] in which the acetal ring is replaced by the corresponding (protected) trihydroxyalkyl chain. Special attention has been recently directed to the synthesis of analogues, **27a,b** in which ring C constitutes a five ring α-methylene lactone moiety, a structural element, which has been commonly associated with a biologically active template. In fact, it is projected that sesbanimide A might be biotransformed into **27a** as the active metabolite of the alkaloid. The synthesis of **27a** and **27b** - which are in equilibrium with their hydroxy ketone forms - has been achieved *via* the sequence of reactions outlined in Scheme 8 [16].

Manzamine A (2)   Tricyclic precursor (29)   Triene (28)

Scheme 9

L-(+)-Ser
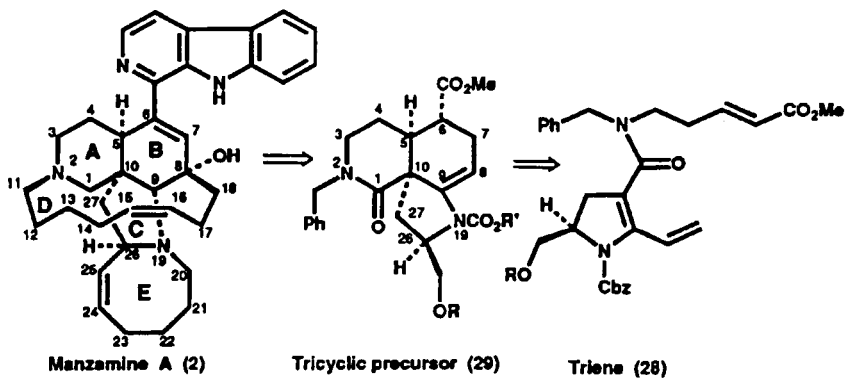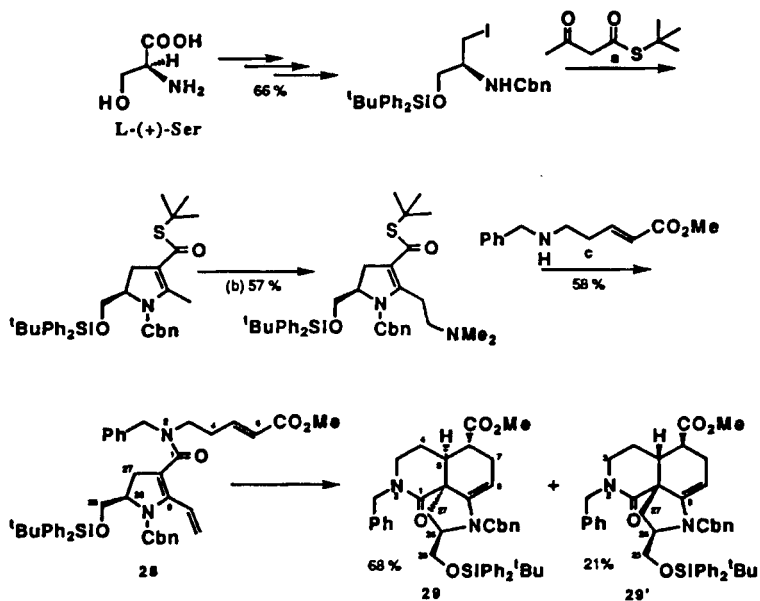
(a) i NaH, DME, RT, 7d; ii TsOH, PhCH₃, reflux; (b) TMSOTf, Et₃N, Eschenmoser's salt,
RT, 1h; (c) i MeI, MeCN, RT, 1h; ii DBU, MeCN, RT, 1h; iii AgOTf, DIPEA, MeCN, RT, 16h;
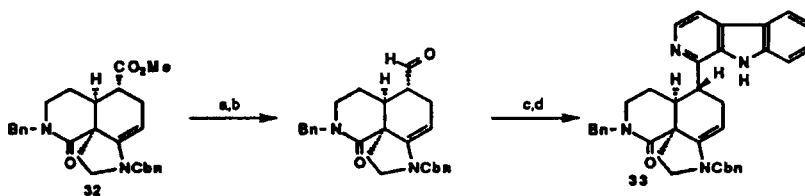(d) xylenes, reflux , 4h.
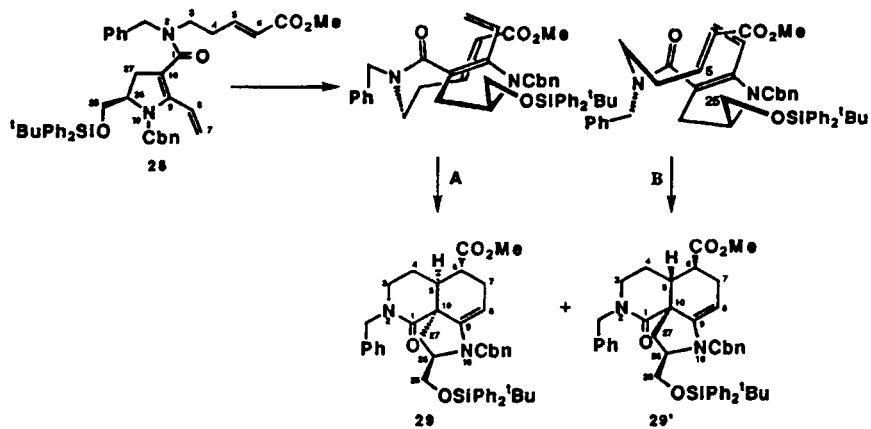
Scheme 10

Manzamine A.

Several structurally related alkaloids containing a β-carboline unit and a complex array of 5, 6, 8 and 13 membered rings have been isolated from marine sponges (*Haliclona sp.* [17ab], *xestospongia sp.* [17c] and *Pellina sp.*) found in the waters of the Okinawa Sea. Biological screening has shown that the alkaloid manzamine A (2) [Scheme 9] possesses significant antileukemic and antimicrobial activity. The unusual structures of the manzamines has prompted much interest in their biogenetic origin and a speculative biosynthetic pathway, leading to manzamine A, has been recently suggested [19,20].
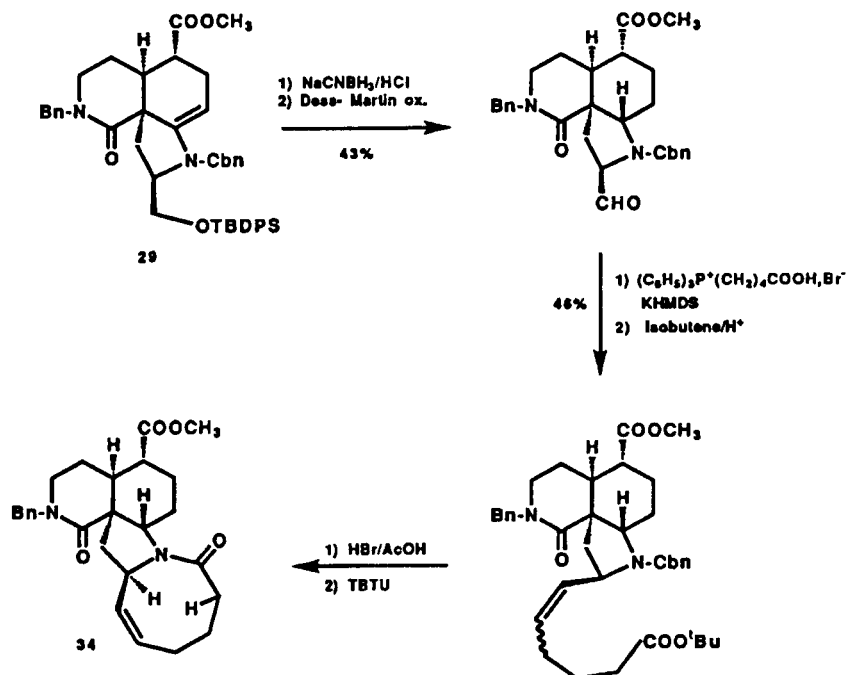

29 R = CH₂OTBDPS

30a R = CH₂O'BuPh₂Si
30b R = CH₂OH

31
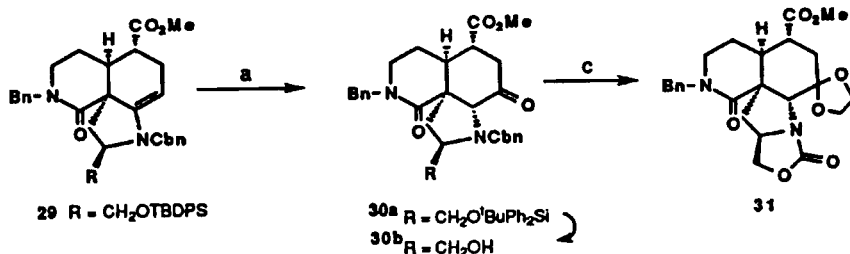
a) i OsO₄ pyr., ii NaHSO₃, iii PTSA, PhH (78%); b) TBAF, THF (90%); c) HOCH₂CH₂OH, PhCH₃ (35%)

Scheme 11

32

33

a) LiBH₄; b) Dess-Martin oxid.; c) tryptamine, HCl,C₆H₆; d) Pd-C/decalins

Scheme 12

29

1) NaCNBH₃/HCl
2) Dess- Martin ox.

43%

1) (C₆H₅)₃P⁺(CH₂)₄COOH,Br⁻
   KHMDS
2) Isobutene/H⁺

46%

34

1) HBr/AcOH
2) TBTU

Scheme 13

In designing a strategy for the total synthesis of manzamine A, it was considered judicious to construct a suitably functionalized core ABC intermediate **29**, with the correct absolute stereochemistry; in the initial phase of the strategy. It was envisaged that, in the subsequent phases, procedures would be developed for the construction of (a) the β-carboline ring, (b) the azocine ring (E) and (c) the macrocyclic system (D), on the ABC ring system **29**. In the final phase, the synthesis of manzamine A would be evolved on the basis of the methodologies worked out for the structural components of the molecule.

Our approach to the synthesis of the required tricyclic precursor **29** visualized an intramolecular cycloaddition of the 1,3-diene moiety in **28** to the α,β-unsaturated

elaboration leading to **33** [Scheme 12] [23].

The synthesis of the azocine ring (E) was initially studied in model experiments employing proline as the starting material [24]. The procedure was thereafter adapted to the synthesis of tetracyclic system **34** [24] [Scheme 13].

In the progress towards the total synthesis of manzamine A, intermediate **34** has been transformed into the D-nor ring skeleton of manzamine A, *viz.* the heptacyclic ring system **35** [Scheme 14] [24], by combining the methodologies worked-out for construction of the various heterocyclic rings. The elaboration of the macrocyclic ring D on the ABC system is currently under investigation. Completion of this work will set the stage for the construction of the complete alkaloid molecule.
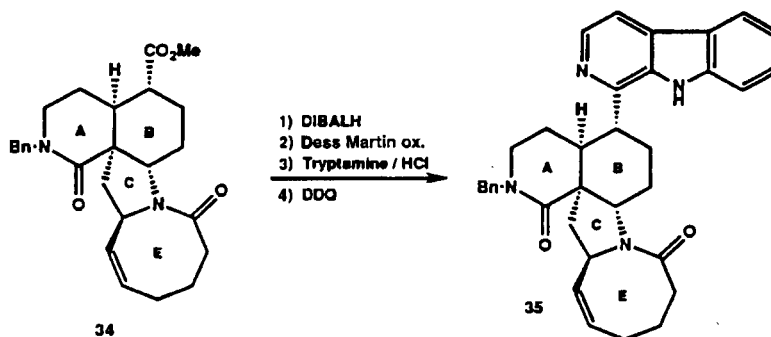
Scheme 14

ester function in the same molecule [Scheme 9]. A synthesis of optically active triene **28** was devised [21a] [Scheme 10] in which the chiral centre at C(26) [manzamine A numbering] was obtained from the readily available amino acid L-serine [21a]. Although, the intramolecular cyclization of **28** can be expected to lead to the two diastereomers **29** and **29'**, [Scheme 10], *via* transition states A and B, respectively, it was reasoned that transition state B would be unfavoured due to steric interaction between the olefin proton at C(5) and the (methylene) hydrogens or the substituent at C(25). Consistent with this expectation it was observed that heating of **28** led to the formation of **29** as the major product (68%); though **29'** was also produced, albeit as the minor cycloadduct (21%) [21b]. The structure and stereochemistry of **29** was unambiguously established by converting it - *via* a reaction sequence, **30a, 30b** in which the chiral centres are unaffected - to the crystalline ketal **31** [Scheme 11] and determining its structure by X-Ray analysis [21b].

In a model study for the construction of the β-carboline on the tricyclic system, the non-chiral pyrroloisoquinoline **32** [22] [Scheme 12] was subjected to the reaction sequence in which the ester function was converted to the aldehyde and subsequently subjected to a Pictet-Spengler

Acknowledgements.

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