Pure & Appl. Chem., Vol. 61, No. 3, pp. 423–426, 1989.
Printed in Great Britain.

Synthetic studies on sesbanimides

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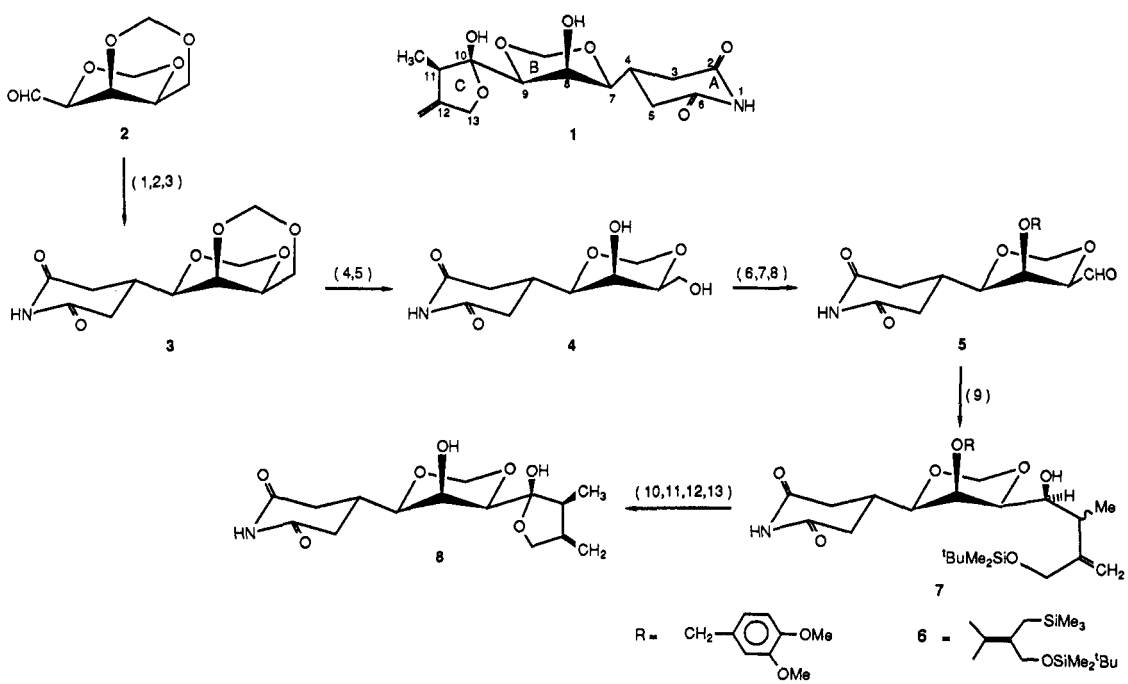
Abstract - The alkaloid (+)-sesbanimide A, first isolated from the seeds of Sesbania drummondii, possesses potent antileukemic properties. A strategy for the total synthesis of the alkaloid has been developed which has led to both, the naturally occurring product, and its antipode, namely, (-)-7R,8S,9R,10S,11S-sesbanimide A. The first synthesis of this compound established the absolute stereochemistry of the natural alkaloid. The synthetic strategy is being further developed for the synthesis of new "sesbanimides" for structure-activity relationship studies.

Powell et al. (ref. 1) have shown that the seeds of Sesbania drummondii contain a number of antileukemic alkaloids of which (+)-sesbanimide A (1) is the most potent compound (ref. 2). The structure of (+)-sesbanimide A, without defining its absolute stereochemistry, was first reported in 1983 (ref. 3).

A programme directed at the synthesis of sesbanimides was initiated in our laboratory, with the aim of developing structure-activity relationship within this class of alkaloids and ultimately designing a clinically useful anti-cancer drug. In an initial approach to 1, but without knowledge of its absolute stereochemistry, we selected the derivative 2 of L-xylose (Scheme I), which is readily available from D-sorbitol, as the starting material. The protected L-xylose (2) represented the ring B precursor on which ring A was constructed via steps involving (i) a Wittig two carbon extension, (ii) a one-pot sequential Michael addition of $CH_2(CONH_2)COOtBu$ and subsequent Thorpe-Dieckmann cyclization and (iii) acid catalyzed removal of the t-butoxycarbonyl group (2 → 3). Although the regiospecific opening of one of

Scheme I

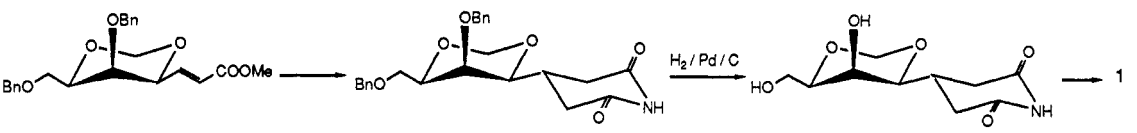


1. $Ph_3\overset{+}{P}\overset{-}{C}HCOOMe$; 2. $CH_2(CONH_2)COO^tBu$, OH^- ; 3. TFA , Δ ; 4. Ac_2O / AcOH ; 5. MeONa , MeOH ; 6. 3,4,- $(MeO)_2$ - C_6H_3CHO ; 7. Et_2AlCl , Et_3SiH ; 8. CrO_3 , pyr. ; 9. BF_3 . Et_2O , -90° C ; 10. separation ; 11. CrO_3 , pyr. ; 12. DDQ ; 13. AcOH / H_2O / THF.

the two methylene acetal groups in 3, namely 3 → 4, was easily achieved, suitable protection of the secondary hydroxyl group in diol 4 did not prove to be straightforward. Reacetalization of the diol function in 4 with 3,4-dimethoxybenzaldehyde and subsequent diethylaluminium chloride mediated reductive ring-opening yielded the desired primary alcohol, which was oxidized to the crucial intermediate 5. In the final carbon-carbon bond formation step, the ring C precursor was attached to the aldehydic carbon of intermediate 5 in the form of allylsilane derivative 6 ($BF_3.Et_2O$, -90°C). This reaction, not unexpectedly, exhibited partial stereochemical control, and a mixture of diastereomeric alcohols 7a,b was produced. Subsequently, the mixture (7a,b) was separated, the correct diastereomer oxidized and the protecting groups removed, whereupon, hemiacetal 8 was obtained as a crystalline product. The latter compound was identical to the natural alkaloid in all respects, except its optical rotation. Consequently, this sequence of reactions (Scheme I), which lead to (-)-7R,8S,9R,10S,11S-sesbanimide A (12), constituted the first total synthesis (ref. 4) of the mirror image of the alkaloid (1). The completion of the synthesis had two further implications. First, it established the absolute stereochemistry of the naturally occurring alkaloid as the 7S,8R,9S,10R,11R-compound, and second, it represented the formal synthesis of (+)-sesbanimide A (1), as well, since the intermediate diol 6 possessing the opposite 7S,8R,9S-configuration is described in the literature (ref. 5).

In view of the aforementioned results, we undertook the application of the strategy developed in our laboratory to the synthesis of (+)-sesbanimide A (Scheme II). Starting from commercially available D-xylose, ester 9 was prepared essentially following the procedure of Terashima (ref. 5) but involving considerable modification of the individual steps (ref. 6). Construction of the glutarimide ring on 9 followed the steps (2, 3) shown in Scheme I. The resulting product 10 was debenzylated to diol 11, which is chemically identical to diol 4. The diol 11 was then subjected to the sequence of transformations described in Scheme I. All steps proceeded in the expected manner, to yield crystalline (+)-sesbanimide A (1) (ref. 7), which was completely identical with the natural product (ref. 8).

Scheme II



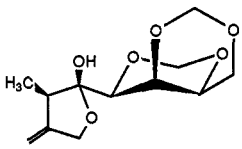
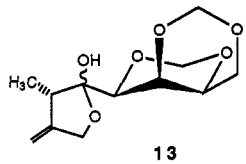
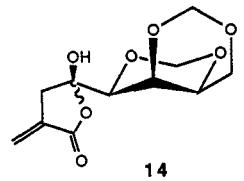
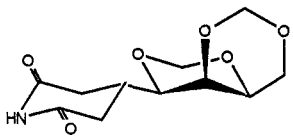
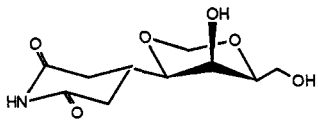
9 10 11

The mode of action of sesbanimide is not known at present. Also, except for limited data on the various congeners of sesbanimides and their transformation products (ref. 2), no information is available on structure-activity relationship. With the availability of (+)- and (-)-sesbanimides A and several partial structures involving AB and BC ring systems, a structure-activity study has been initiated. The results of the in vivo tests using P-388 murine leukemia are presented in Table I. The difference in the behaviour of (+)- and (-)-sesbanimides in this test, points to the striking role of stereochemistry of the molecule in the expression of its biological activity. The total lack of activity of compounds 12-16, suggests that all three rings are a necessary minimum structural requirement for activity; although in case of 15 and 16 this conclusion should be tempered, since the stereochemistry of the sugar moiety corresponds to (-)-sesbanimide, which is itself inactive. It is noteworthy that the α-methylene lactone derivative 14 is inactive, even at a high dose level. However, this result need not have implications for the suggestion (ref. 9) that sesbanimides might function via a C(13)-oxo metabolite. It is apparent that ideas on the mechanism of action and structure activity relationship shall have to await further work.

From the data in Table I it follows that modifications of sesbanimide A for development as a potential drug, shall have to be based upon a 7S,8R,9S-configuration of the chiral centres in ring B. With this in mind, we have currently directed our attention to the modification of ring C, which, it is intuitively felt, may somehow be chemically involved in the bio-activity of the alkaloid.

In order to synthesize ring C modified analogs of (+)-sesbanimide A, access to adequate quantities of the AB-aldehyde intermediate 18 is required. The approach described in Scheme I for the synthesis of 5 and its antipode molecule (utilized in Scheme II), is quite effective especially when working with modest amounts of materials. In view of this, we have examined other potential approaches for the synthesis of aldehyde (18), or its immediate precursor 17. Consideration of procedures for the differential protection of the hydroxyl functions in diol 11, led us to examine sequential acylation and silylation of the primary and secondary hydroxyl groups, respectively. Such an approach has been employed by Schlessinger (ref. 10) and Terashima (ref. 11) in connection with the synthesis of sesbanimides. In our hands the best results were obtained when the primary hydroxyl group of 11 was benzoylated to ester 19a, the latter silylated with tertiary butyldiphenylsilyltrifluoromethanesulfonate and the resulting product subsequently treated with diisobutylaluminiumhydride (DIBAH). In accordance with the

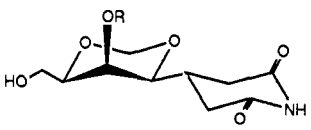
Table I Activity against P388 murine leukemia in vivo

Compound	Dose	Activity
(+) - Sesbanimide A (1)	9 x 64 µg / kg	toxic[a]
(+) - Sesbanimide A (1)	5 x 32 µg / kg	T / C = 181 [ref 2]
(-) - Sesbanimide A (8)	9 x 2 mg / kg	inactive[a]
(-) - Sesbanimide A (8)	9 x 0.2 mg / kg	inactive[a]
 12	400 mg / kg	inactive[b]
 13	400 mg / kg	inactive[b]
 14	240 mg / kg	inactive[b]
 15	240 mg / kg	inactive[b]
 16	100 mg / kg	inactive[b]

[a] Dr. P. Lelieveld, T.N.O. laboratories, Rijswijk, The Netherlands

[b] N.C.I. National Institutes of Health, Bethesda, U.S.A.

anticipated and assumed (refs 10, 11) course of the reactions, the aforementioned two products should possess structures 19b and 19c. However, IR and NMR data of the O-silyl derivatives are not in agreement with the structures previously assigned to them (refs 10, 11). On the basis of COSY, C-H correlation, ^{13}C NMR (APT, DEPT) and Nuclear Overhauser difference experiments, structure 20a is assigned to the silylated benzoate ester. Of particular relevance to this conclusion are the following data. In the ^{13}C NMR spectrum only two carbonyl carbons (δ 165 and 170 ppm) are visible and a tertiary carbon is identified at δ 101 ppm. The latter can be assigned to a carbon bonded to two oxygens and a nitrogen atom [C(2) in 20a]. Nuclear Overhauser difference experiments reveal that the C(8)-proton is proximate to one of the C(5)-protons and the amide N-H. The compound shows one ester (1718 cm^{-1}) and one amide band (1668 cm^{-1}) in the IR spectrum. By analogy, the DIBAH reduction product of 20a is assigned structure 20b. The alcohol 20b constitutes a strategic intermediate for the synthesis of (+)-sesbanimide A and its analogues.



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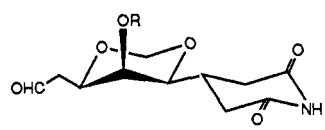

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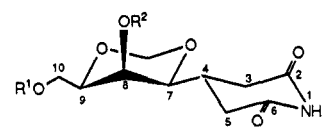
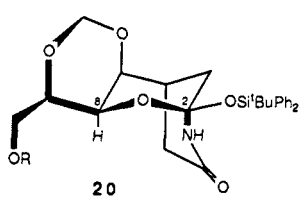


19a $R^1 = \overset{O}{\overset{\|}{C}}Ph$, $R^2 = H$

19b R1 = $\overset{O}{\overset{\|}{C}}Ph$, $R^2 = Si^tBuPh_2$

19c $R^1 = H$, $R^2 = Si^tBuPh_2$



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20a R = $\overset{O}{\overset{\|}{C}}Ph$

20b R = H

Acknowledgement

The financiel support of the Koningin Wilhelmina Fonds (KWF) is gratefully acknowledged.

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