STUDIES IN THE STEREOSPECIFIC SYNTHESIS OF SESBANIMIDE. APPROACHES TO RING C

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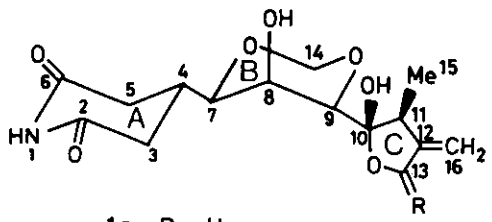
Abstract - Starting from 2-methylpropenol-2 and dimethyl 2,3-dimethylmaleate model approaches for the syntheses of ring C of sesbanimide and 13-oxo-sesbanimide have been developed.

The alkaloid sesbanimide (1a) isolated from the seeds of Sesbania drummondii[1] and Sesbania punicea[2] constitutes a synthetic target of considerable interest in view of both, its novel structure and its potent antitumour activity. The development of a general approach to the synthesis of sesbanimide and its analogs has been undertaken in our laboratory. In this connection we have recently reported the stereospecific synthesis of the AB ring moiety[3] of the alkaloid which bears a suitable functionalization for elaboration of ring C. A similar intermediate using a different route has been reported by Koga et al[4a] and by Fleet et al[4b]. In this communication we describe approaches to ring C synthons for 15-nor-sesbanimide and its C_{13} oxo analogs.

At the very outset it was recognized that the C_{13}-oxo derivative of sesbanimide, namely compound 1b, would be a valuable analog for biological evaluation. The rationale for this lies in the known cytostatic activity of natural products bearing the α-methylenebutyrolactone moiety and the possible role of 1b as an active metabolite of sesbanimide itself. It was consequently planned to develop synthetic strategies for ring C synthons corresponding to both 1a and 1b.

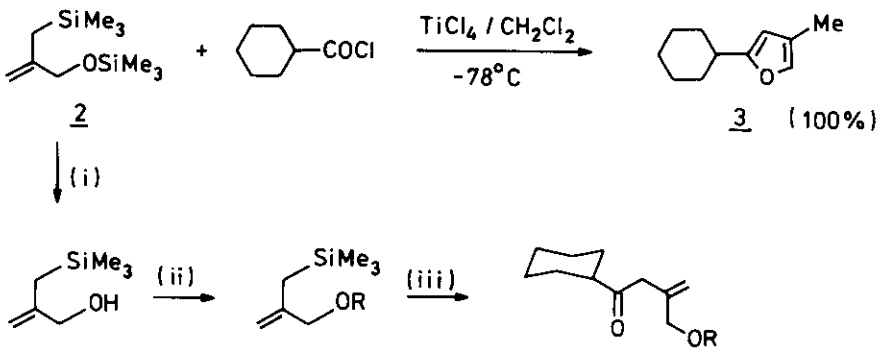
An approach to 15-demethyl ring C, which could be conveniently extended to the C_{11}-methyl moiety, was visualized via the Lewis acid catalyzed reaction of acid chlorides with a suitably protected 2-(hydroxymethyl)-allylsilane. In a model study, allylsilane derivative 2[5] was allowed to react with cyclohexanecarbonyl chloride at -78° C, with $TiCl_4$ as catalyst (Scheme A). The product of this reaction was, however, not the expected β,γ-unsaturated ketone, but the furan derivative 3[6], which was formed in quantitative yield. The formation of 3 can be rationalized in terms of the mechanistic steps described in Scheme B. It is visualized that the first product of the reaction between 2 and cyclohexanecarbonyl chloride (in the presence of $TiCl_4$) is indeed the anticipated ketone a (R^1=c-C_6H_{11}, R^2=$SiMe_3$, Scheme B). A subsequent $TiCl_4$ catalyzed cyclization of a leads to intermediate b which is converted into 3 in two steps, namely, elimination of elements of EOH (from b) followed by rearrangement of the generated dihydrofuran c. While the facile formation of furan derivative 3 suggests that the reaction could find application as a general synthetic pro-



1a R = H_2

1b R = O

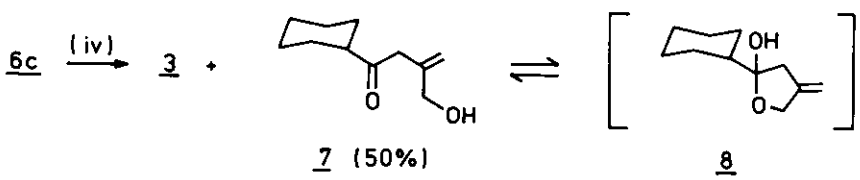
Scheme A



2 (i) 4 (ii) 5a (66%) 5b (94%) 5c (96%) (iii) 6a (95%) 6b (95%) 6c (95%)

3 (100%)

a. R = CCH_3 (=O) b. R = $CO-C_6H_4-NO_2$ c. R = $CO-CH_2CCl_3$



6c (iv) 3 + 7 (50%) ⇌ 8

(i) 1N H_2SO_4 / THF, r.t. ; (ii) RCl, pyr., r.t. ; (iii) $C_6H_{11}COCl$, $TiCl_4$, CH_2Cl_2 -78°C ; (iv) Zn/MeOH, Δ.

cedure for 2-substituted 4-methylfurans, the inability to isolate the target compound a required an analysis of the driving force for the cyclization step. Since, in the latter process, nucleophilicity of the ether oxygen is expected to play a dominant role, it was projected that a more electronegative R^2 group (than $SiMe_3$) should suppress the ring-formation reaction. The desired change in the substrate system was achieved by hydrolyzing 2 to alcohol 4 and protecting the hydroxy group via acylation with three different acyl chlorides. The resulting esters 5a-c were formed in good to excellent yields (Scheme A). When 5a-c were subjected to a $TiCl_4$-catalyzed reaction with cyclohexanecarbonyl chloride the desired keto esters 6a-c were formed in high yields. Structures of 5a-c and 6a-c are based upon their spectral data, which are presented (in part) in the Table. The conversion of 5a-c to 6a-c vindicates the argument that an increase in electronegativity of the ether oxygen in intermediate a (Scheme B) suppresses the tendency for the process a → b. As a consequence, the initial reaction products, viz. 6a-c, can be isolated as stable compounds.

Table

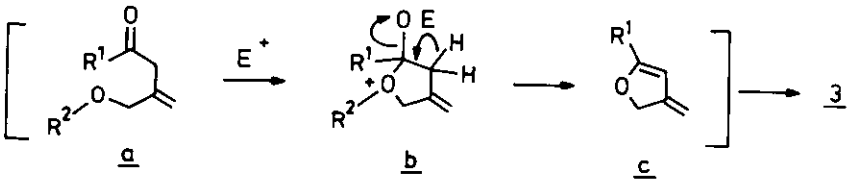
Characteristic ^{1}H NMR (partial) spectral data of 5a-c, 6a-c and 7.

(Solvent = $CDCl_3$, TMS)

	CH_2Si	CH_2O	$=CH_2$	CH_2CO	OCH_2	$=CH_2$
5a	1.55 s	4.45 d J=1	4.7, 4.2 2m			
5b	1.65 s	4.68 d J=1	4.87, 5.03 2m			
5c	1.55 s	4.55 d J=1	4.8, 4.95 2m			
6a				3.28 s	4.6 s	5.1, 5.3 2m
6b				3.3 s	4.8 s	5.2, 5.4 2m
6c				3.3 s	4.7 s	4.75, 5.1 2 m
7				3.26 s	4.05 s	4.90, 5.15 2 d

The following critical step involved the deblocking of the alcohol function in the unsaturated keto esters 6a-c. Attempts to hydrolyze the ester function under acidic or basic conditions led to rearrangement of the double bond in the product alcohol or formation of furan derivative 3. The ester 6c could, however, be cleaved under neutral conditions (Zn/MeOH,Δ) to give alcohol 7 (50%) and spectrally detectible amounts of 3. The formation of 3 can once again be accounted for by the sequence of reactions a→b→c→3 (Scheme B, R^1=c-C_6H_{11}, R^2=H), whereby $ZnCl_2$, generated in the course of the reaction, plays the role of the electrophile. The structure of 7 in solution was established by its IR and PMR spectra (see Table). The hydroxy ketone 7 can exist in equilibrium with its

Scheme B

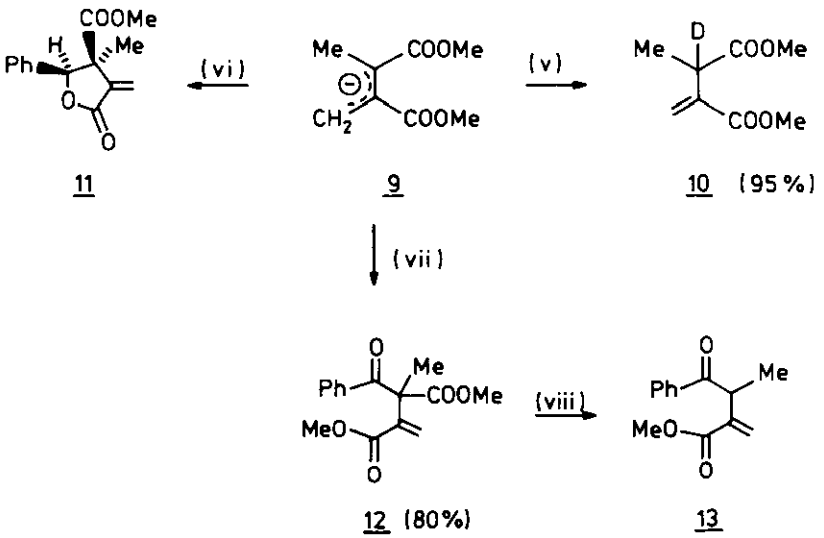


a b c 3

R^1 = c-C_6H_{11}

R^2 = $SiMe_3$, H

Scheme C



11 9 10 (95%)

12 (80%) 13

(v) D_2O ; (vi) PhCHO ; (vii) PhCOCl ; (viii) $MgCl_2 . 6\,H_2O$/DMSO, 150°C

hemiacetal form 8. While no 8 could be detected in solution ($CHCl_3$), it is appreciated that the equilibrium between 7 and 8 will be solvent dependent. In this connection it should be mentioned that sesbanimide (1a) itself is in the hemiacetal form in chloroform[2], but consists of equilibrium mixtures of the hemiacetal and γ-hydroxyketone tautomers in methanol (2:1), pyridine (3:1) and dimethyl sulfoxide (1:1)[2]. The difference in behaviour between 7 and sesbanimide reflects the structural differences between the model and the BC portion of the alkaloid, where, amongst other factors, the C_{11}-methyl group may enhance hemiacetal formation.

For the C-ring synthon corresponding to 1b, reactions of the anion of dimethyl 2,3-dimethylmaleate (9) were investigated (Scheme C). Quenching of the anion with D_2O revealed that it protonates (95%) at position 2 of the diester to give dimethyl 2-deutero-2-methyl-3-methylenesuccinate (10). Reaction of 9 with benzaldehyde did lead to the formation of α-methylenebutyrolactone 11[7], but the low yield (~10%) questions the potential of this route to a 10-deoxy ring C synthon. In a second approach, 9 was allowed to react with benzoyl chloride, whereupon, the acyl derivative 12[8] was conveniently obtained in a practically useful step (80%). Compound 12 carries, in principle, all the functionalities and substituents that are required for the construction of ring C with a C_{13} carbonyl group. Furthermore, the conversion of 9 to 12 constitutes a model reaction for the elaboration of C_{13}-oxo ring C on an AB synthon bearing a carboxyl functionality. It is obvious that the choice of the alkoxy part of diester 9 will have to anticipate the hydrolytic step leading to cleavage of the ester alkyls and decarboxylation, without rearrangement of the double bond. Although the methyl ester is certainly not suited for the aforementioned transformations, it was shown that 12 could be decarboxylated to 13, by $MgCl_2,6H_2O$/DMSO, albeit in low yield.

Further work on the construction of ring C synthons on AB ring precursors of sesbanimide, following the approaches outlined above are actively in progress.

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6. 3; oil: ^{1}H NMR ($CDCl_3$), δ 1.2-1.9(m, 11H, cyclohexyl protons), 2.0(s, 3H, CH_3), 5.8(s, 1H,furan γ-H), 7.1(s, 1H, α-H).

7. 11; oil: IR $CHCl_3$, 1770, 1710. 1660; ^{1}H NMR, δ 1.7(s, 3H, CH_3-$CCOOCH_3$), 3.7(s, 3H, $COOCH_3$), 5.3(s, 1H, PhCH-O), 5.7(s, 1H , C=CH), 6.4(s, 1H, C=CH), 7.3(m, 5H, Ph-H).

8. 12; oil: IR $CHCl_3$, 1730, 1690, 1630, 1600. ^{1}H NMR 1.7(s, 3H, $CH_3(C=O)COOCH_3$), 3.6(s, 6H, 2x $COOCH_3$), 5.7(s, 1H, C=CH), 6.3(s, 1H, C=CH), 7.3, 7.7(m, 3H, m, 2H, Ph-H).

Received, 25th September, 1984