

STUDIES IN THE STEREOSPECIFIC SYNTHESIS OF SESBANIMIDE. SYNTHESIS OF 4-SACCHARIDALGLUTARIMIDES

Martin J. Wanner, Gerrit-Jan Koomen and Upendra K. Pandit*

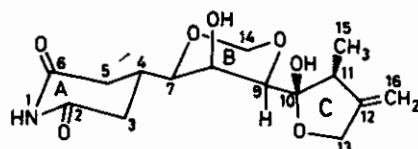
Organic Chemistry Laboratory, University of Amsterdam,

Nieuwe Achtergracht 129 1018 WS Amsterdam, The Netherlands

Abstract - Suitably protected saccharidyl aldehydes are converted into the corresponding glutarimide derivatives via a two-step sequence involving reactions with (a) $\text{Ph}_3\text{P}=\text{CHCOOMe}$ and (b) $\text{CH}_2(\text{CONH}_2)\text{COOR}$.

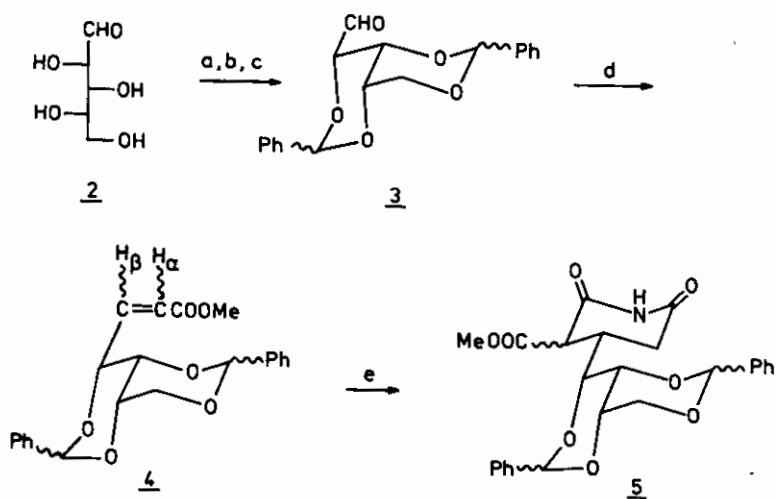
The alkaloid sesbanimide (1), recently isolated from the seeds of *Sesbania drummondii*, has been shown to display potent antitumour activity¹. In view of our interest in the synthesis of the cytostatic components of *Sesbania drummondii* extracts², we have undertaken the development of a general approach to the stereospecific synthesis of sesbanimide and its analogs. The strategy of this approach visualizes the preparation of two synthons corresponding to (i) a functionalized glutarimide-sugar moiety and (ii) the six carbon fragment ($\text{C}_{10}\text{-C}_{16}$) of ring C, and their subsequent coupling to provide the tricyclic alkaloid. In this communication we present a convenient procedure for construction of the AB (saccharidalglutarimide) synthon bearing suitable functionalization for coupling with the ring C precursor.

In a model study L-xylose (2) was converted into the bis-benzylidene acetal 3, mp 179-182°C, in three conventional steps (Scheme A). Coupling of 3 with the ylid $\text{Ph}_3\text{P}=\text{CHCOOCH}_3$ yielded the unsaturated ester 4 (85%) as a mixture of the Z/E isomers (Z/E = 3/2; Z-isomer, mp 161-162°C, $J_{\text{H}_\alpha\text{H}_\beta} = 12 \text{ Hz}$, E-isomer, mp 203-206°C, $J_{\text{H}_\alpha\text{H}_\beta} = 15.5 \text{ Hz}$). For the following step, the mixture was employed directly. The formation of the glutarimide ring was achieved by a base-catalyzed reaction with the half amide of malonic ester ($\text{H}_2\text{NCOCH}_2\text{COOMe}$), whereupon the Michael addition and the subsequent cyclization took place in one practical step. The resulting product consisted of a mixture of two stereoisomeric esters 5 (2/1, via NMR), from which the major isomer could be isolated in crystalline form, mp 182-185°C. The structure of the tricyclic ester followed from its spectral data⁴.



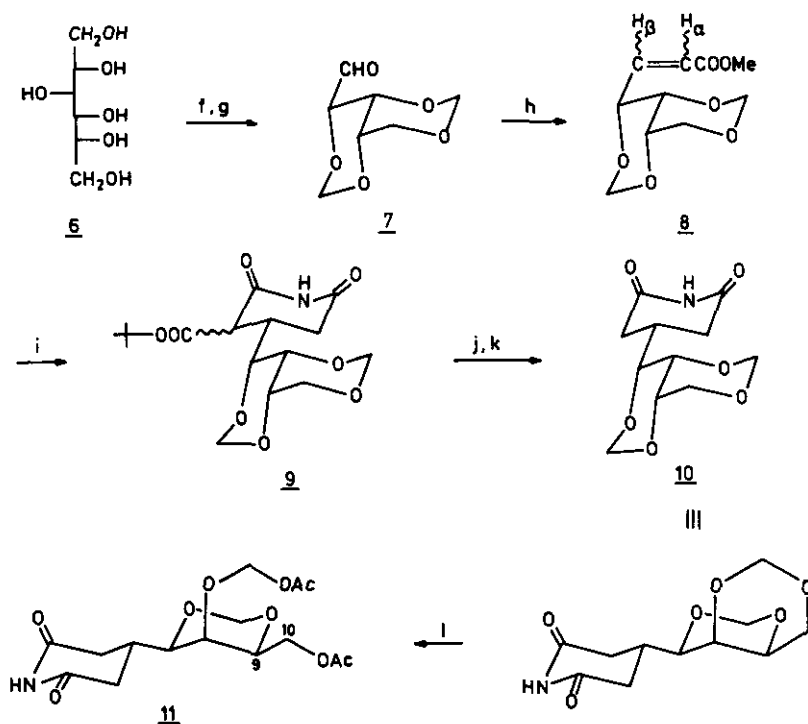
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Scheme A



a. EtSH / HCl , b. PhCHO / p-TsOH / ClCH₂CH₂Cl , c. HgCl₂ / H₂O
 d. Ph₃P=CHCOOMe / PhCH₃ , e. H₂NCOCH₂COOMe / MeONa / THF .

Scheme B



f. HCHO / HCl , g. HIO_4 , h. $\text{Ph}_3\text{P}=\text{CHCOOMe} / \text{PhCH}_3$,

i. $\text{H}_2\text{NCOCH}_2\text{COOBu(t)} / \text{KOBu(t)}$, j. $\text{CF}_3\text{COOH} / \text{r.t.}$,

k. DMF , reflux, l. $\text{Ac}_2\text{O} / \text{AcOH}$.

It should be pointed out that both isomers of 5 can be utilized in the synthetic sequence, since the ester group responsible for asymmetry of C-3 (sesbanimide numbering) shall be removed by hydrolytic decarboxylation, in the subsequent step.

Having shown that the glutarimide unit could be constructed conveniently, in two steps, starting from a protected aldose, attention was directed to the synthesis of the required bis-methylene acetal of L-xylose. However, reaction of the diethyl thioacetal of L-xylose with formaldehyde or dimethoxymethane, did not, under the attempted conditions, lead to the desired bis-acetal. Consequently, use was made of the known procedure for the conversion of D-sorbitol (6) to acetal 7⁵ (Scheme B), via a sequence involving acetal formation (HCHO/HCl), followed by periodate oxidation of the resulting diol. Reaction of 7 with $\text{Ph}_3\text{P}=\text{CHCOOCH}_3$, once again yielded a mixture of Z/E isomers, in which the E-compound 8⁶ represented 90% of the product (yield, 69%). The glutarimide moiety was constructed on the pure isomer 8, by reaction with t-butyl carbamoylacetate. From the resulting isomeric mixture of glutarimides 9, one isomer could be isolated as a crystalline compound, mp 192-197°C (MS: Calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_8$ 357.1446, Found 357.1448). Hydrolysis of the mixture of isomers of 9 (CF_3COOH , R.T.) and decarboxylation (DMF, reflux) yielded a single product 10, mp 248-249°C ($\alpha = -32.7^\circ$, $c = 0.291$, H_2O ; MS: Calcd for $\text{C}_{11}\text{H}_{15}\text{NO}_6$ 257.0893, Found 257.0892; overall yield based on 7, 45%). Upon treatment of 10 with acetic anhydride/acetic acid/ H_2SO_4 mixture, one of the dioxolane rings opened^{5,7} to give the desired diacetate 11 89%; mp 132-134°C (MeOH); IR (CHCl_3): 3380, 1740 and 1710 cm^{-1} ; NMR (CDCl_3): δ 8.15 (s, N-H); 4.90 (AB-system, $J = 6$, $-\text{O}-\text{CH}_2-\text{O}$). Compound 11 represents the synthon containing the A/B rings with the correct absolute configuration of the sugar moiety and possessing a functionalization at C-9, for further elaboration to the sesbanimide molecule. In order to construct ring C, a selective deprotection of the primary alcohol group of 11, followed by transformation of its C-10 to a suitable oxidation state is projected. Model studies directed at the synthesis of ring C on a functional equivalent of C-10 (in 11) are in progress.

REFERENCES

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2. M.J. Wanner, G.J. Koomen and U.K. Pandit, Tetrahedron, **38**, 2741 (1982).
3. While several isomers are possible for this compound, only one isomer (of undefined stereochemistry) was isolated and employed for further reactions.
4. 5, mp 182-185°C (MeOH); MS: Calcd for $C_{25}H_{25}NO_8$ 467.1580, Found 467.1580; IR ($CHCl_3$): 3360, 1730, 1710 cm^{-1} ; NMR ($CDCl_3$): δ 7.95 (s, N-H); 5.65 and 5.55 (2xs, ϕ -C-H); 3.58 (s, 3H, $COOCH_3$); 2.5-3.05 (AB-part of ABX-system, $J_{A,B} = 18$, $J_{A,X} = 4$, $J_{B,X} = 5.5$, $-CH_2-C-N$).
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6. 8, mp 164-164.5°C (MeOH); NMR ($CDCl_3$): $J_{H_\alpha H_\beta} = 16$ Hz; MS: Calcd for $C_{10}H_{14}O_6$ 230.0773, Found 230.0771; $\alpha = -13.6^\circ$, $c = 0.273$, $CHCl_3$.
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