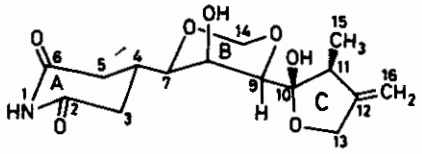
STUDIES IN THE STEREOSPECIFIC SYNTHESIS OF SESBANIMIDE. SYNTHESIS OF 4-SACCHARIDALGLUTARIMIDES

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) Ph_3P=CHCOOMe and (b) $CH_2(CONH_2)COOR$.

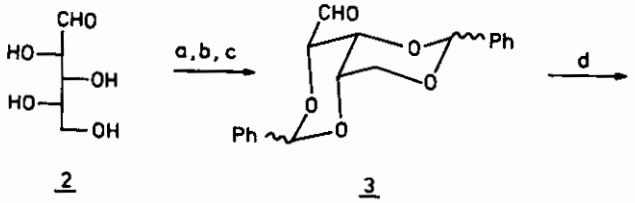
The alkaloid sesbanimide (1), recently isolated from the seeds of Sesbania drummondii, has been shown to display potent antitumour activity[1]. In view of our interest in the synthesis of the cytostatic components of Sesbania drummondii extracts[2], we have undertaken the development of a general approach 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 (C_{10}-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[3], mp 179-182°C, in three conventional steps (Scheme A). Coupling of 3 with the ylid Ph_3P=$CHCOOCH_3$ yielded the unsaturated ester 4 (85%) as a mixture of the Z/E isomers (Z/E = 3/2; Z-isomer, mp 161-162°C, $J_{H_\alpha H_\beta}$ = 12 Hz, E-isomer, mp 203-206°C, $J_{H_\alpha H_\beta}$ = 15.5 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 (H_2NCOCH_2COOMe), 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 data[4].

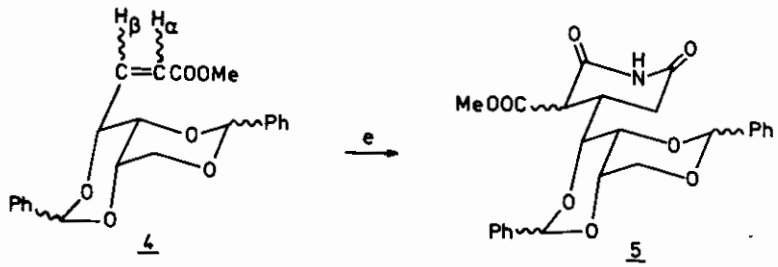


1

Scheme A



2 3

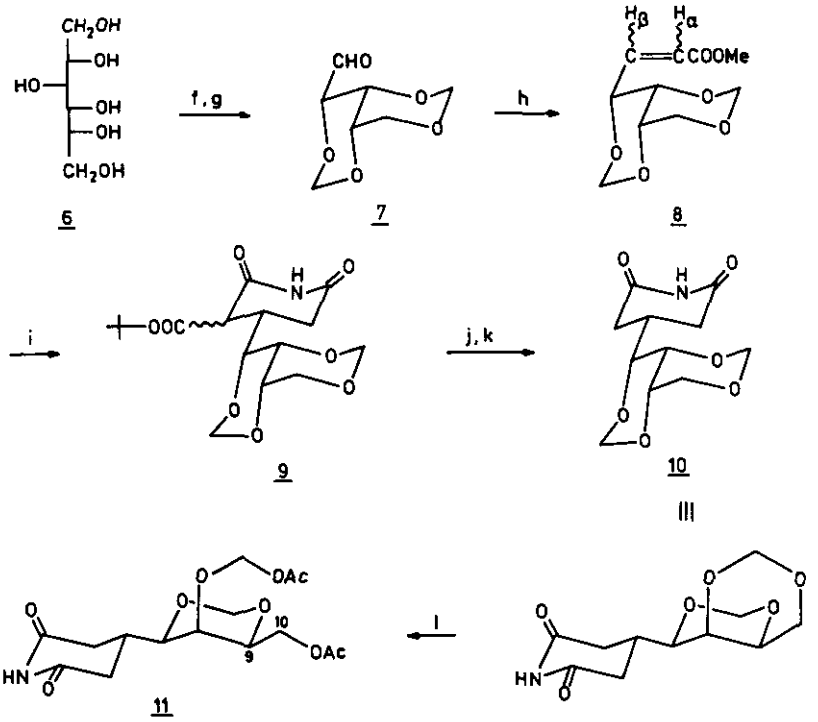


4 5

a. EtSH / HCl , b. PhCHO / p-TsOH / $ClCH_2CH_2Cl$, c. $HgCl_2$ / H_2O

d. $Ph_3P{=}CHCOOMe$ / $PhCH_3$, e. H_2NCOCH_2COOMe / MeONa / THF.

Scheme 8



f. HCHO / HCl , g. HIO_4 , h. $Ph_3P{=}CHCOOMe$ / $PhCH_3$,

i. $H_2NCOCH_2COOBu(t)$ / KOBu(t) , j CF_3COOH / r.t. ,

k. DMF , reflux , l. Ac_2O / 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 7 [5] (Scheme B), via a sequence involving acetal formation (HCHO/HCl), followed by periodate oxidation of the resulting diol. Reaction of 7 with $Ph_3P{=}CHCOOCH_3$, once again yielded a mixture of Z/E isomers, in which the E-compound 8 [6] 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 $C_{16}H_{23}NO_8$ 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 (α = -32.7°, c = 0.291, H_2O; MS: Calcd for $C_{11}H_{15}NO_6$ 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, $-O-CH_2-O$). 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, Ø-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; α = -13.6°, c = 0.273, $CHCl_3$.

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