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A FACILE SELECTIVE ACYLATION OF CASTANOSPERMINE

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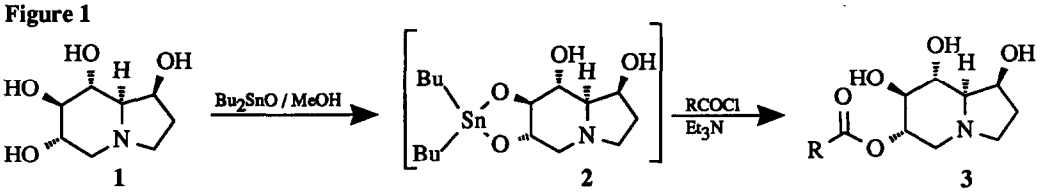
Summary: *A facile selective acylation on the 6-hydroxyl group of the polyhydroxylated indolizidine alkaloid castanospermine, (1), has been achieved by the in situ use of a preformed dibutyl organotin derivative.*

The Indolizidine alkaloid castanospermine (**1**)[1] has attracted considerable attention due to its ability to inhibit the enzymes *α-glucosidase I* and *α-glucosidase II*.[2] These are of key importance in the production of glycoproteins gp120 and gp41 which are both contained within the envelope of the HIV virus and required for the spread of the virus to uninfected cells. Inhibition of glycoprotein synthesis is therefore an important target for the development of anti-AIDS drugs.

Inspection of the structure of castanospermine (**1**) shows it to have three equatorial hydroxyl groups on the piperidine ring. Synthetic modification of castanospermine by manipulation of these similar secondary hydroxyl groups therefore constitutes a formidable challenge. We wish to report a simple one-pot procedure for the acylation of the 6-hydroxyl group, to our knowledge the only currently available method for ready preparation of a 6-acylcastanospermine derivative.[3]

The reaction of 1,2-diols with dibutyltin oxide results in a readily formed cyclic 5-membered dibutylstannyl derivative. These have been successfully used in nucleoside chemistry[4] as both protecting groups and activating groups for subsequent alkylations and acylations. Based on this strategy, it was anticipated that two of the vicinal hydroxyl groups (6 and 7, or 7 and 8) of castanospermine might be protected as dibutylstannyl derivatives. Acylation of the stannyl derivative *in situ* then would lead to the isolation of monoacylated castanospermine or a mixture of monoacylated derivatives. When castanospermine was subjected to the reaction conditions, the 6-acylcastanospermine (**3**) was the only isolable product.[5] Further 6-acylated derivatives were prepared in moderate yields as detailed below. The formation of the 6-acylated product was evident from the significant downfield shift of the C6 proton (from δ 3.4 to δ 4.7 in the case of acetyl). This was corroborated by 2D correlation spectroscopy which clearly shows the connectivity of the shifted C6 proton with the C5 and C7 protons. It is probable that attack at the sterically less crowded 6-hydroxyl group leads to preferential formation of a 6,7-stannylidene[6] (**2**) which in turn affords a 6-acylcastanospermine.[7]

Figure 1



In a typical procedure, castanospermine (0.189 g, 1 mmol) and dibutyl tin oxide (0.248 g, 1.1 mmol) were heated under reflux in dry methanol until the reaction mixture was clear (*ca.* 45 min). The mixture was allowed to cool to room temperature then triethylamine (0.51 g, 5 mmol) and an acid chloride (5 mmol) were added. The mixture was stirred for *ca.* 2 h at room temperature during which a white precipitate of triethylamine hydrochloride formed. This was filtered and the filtrate was concentrated *in vacuo* to give an immobile clear liquid. After one or more purifications by flash chromatography over silica (acetone, acetone:ethyl acetate 3:1, or dichloromethane:methanol 9:1) the 6-acylated product was isolated as a white crystalline solid.[8] The compounds prepared were **3a** [R = CH_3; 40 %, mp 182 °C (dec)], **3b** [R = $CH_3(CH_2)_2$; 38 %, mp 65 °C], **3c** [R = $(CH_3)_2CHCH_2$; 18 %, mp 67 °C], **3d** [R = $CH_3(CH_2)_6$; 35 %, mp 134 °C]; **3e** [R = $CH_3(CH_2)_8$; 39 %; mp 96 °C], **3f** [R = $CH_3(CH_2)_{12}$; 23 %, mp 104 °C], and **3g** [R = C_6H_5; 44 %, mp 234 °C (dec)].

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References and Notes

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3. The anti-HIV activities of **3b** and **3g** were reported but the syntheses were not: Sunkara, P. S.; Taylor, D. L.; Kang, M. S.; Bowlin, T. L.; Liu, P. S.; Tyms, A. S.; Sjoerdsma, A. *Lancet* **1989**, 1206.
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5. A significant amount of unreacted **1** was recovered in each case, and, in the case of **3b**, analysis of the crude product showed the presence of a trace amount of an isomeric product that was not characterized.
6. The ^{1}H-NMR of **2** showed significant line broadening even at temperatures as low as -70°, presumably because of facile intermolecular exchange.[4] The ^{13}C-NMR spectrum of **2** gave sharp signals for the butyl carbons (δ 14.37, 28.38, 29.04, 29.13) but the remainder of the spectrum was less well resolved.
7. A control experiment carried out with acetyl chloride under identical conditions in the absence of dibutyltin oxide led to quantitative recovery of castanospermine.
8. All new compounds were characterized by mass spectrometry and 1D and 2D 300MHz or 400MHz ^{1}H NMR, and gave satisfactory (±0.4%) combustion analysis (C,H,N).

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