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SELECTIVE FUNCTIONALIZATION OF THE C2 HYDROXYL GROUP OF N-CARBOBENZYLOXY-4,6-O-BENZYLIDENE-1-DEOXYNOJIRIMYCIN

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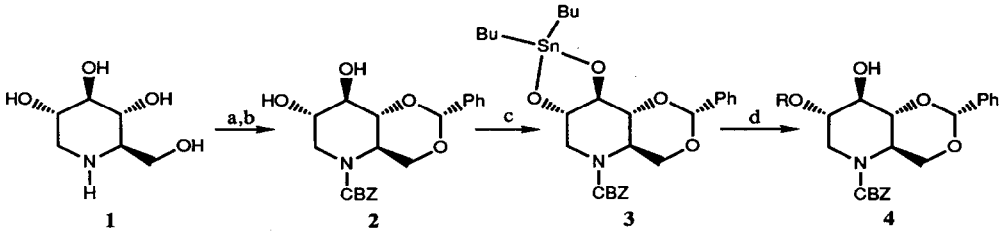
Abstract: 1-Deoxynojirimycin was converted into its N-CBZ-4,6-O-benzylidene derivative **2** in two steps in 51% yield. Compound **2** could be regioselectively functionalized at the C2 hydroxyl group by activation with di-n-butyltin oxide, followed by reaction of the resulting stannylene with electrophiles. In this manner, the 2-O-benzoyl and 2-O-tosyl analogs could be obtained in yields of 73% and 94%, respectively.

There has been considerable interest in analogs of 1-deoxynojirimycin[1] and castanospermine[2] as potential anti-AIDS drugs. However, few synthetic methods exist for the replacement of the individual hydroxyl groups[3,4,5] by other functional groups. No method has been reported for the selective functionalization of the C2 and C3 hydroxyls of **1**. As part of a program to prepare analogs of 1-deoxynojirimycin **1**, where the C2, C3 and C4 hydroxyls are systematically replaced by other functional groups, we sought to differentiate the C2 and C3 hydroxyl groups of N-carbobenzyloxy-4,6-O-benzylidene-1-deoxynojirimycin **2**.

Compound **2**, m.p. 147-148°C, was prepared in two steps from 1-deoxynojirimycin in 51% overall yield. The reaction of **1** with benzyl chloroformate in saturated aqueous bicarbonate afforded N-carbobenzyloxy-1-deoxynojirimycin after multiple extractions with ethyl acetate. After drying in vacuo over P_2O_5, the crude product was directly converted into **2** using benzaldehyde and anhydrous zinc chloride in the presence of 4A° molecular sieves.[6]

Our early attempts to differentiate the two hydroxyls of **2** using one equivalent of a variety of electrophilic reagents led to complex mixtures of unreacted **2**, 2-O-acyl, 3-O-acyl and 2,3-di-O-acyl products with little, if any, selectivity for either the C2 or C3 hydroxyl group. Since both hydroxyls are secondary and occupy equatorial positions, these results were not unexpected. However, when **2** was converted into its 2,3-O-di-n-butylstannylene derivative **3** using di-n-butyltin oxide[7] and then reacted with electrophiles, regioselective functionalization of the C2 hydroxyl group occurred and compounds of structure **4** were obtained. In certain cases, **4A** (mp 120-121°C, 73%) and **4D** (mp 115-117°C, 94%), the reactions were regiospecific and none of the isomeric C3 products were observed by either ^{1}H NMR or thin layer chromatography.[8] In contrast, the acylations with either acetyl chloride or n-butyryl chloride were less selective and provided a 90:10 and 85:15 mixtures of the C2 and C3 products, respectively. Following chromatographic purification, the 2-O-acetyl **4B** and 2-O-butyryl **4C** esters were obtained in yields of 44% and 28%, respectively. The structural assignments for **4A-4D** were based primarily on the characteristic downfield shift of H2 in their ^{1}H NMR spectra. Since the coupling patterns of H2 (ddd) and H3 (dd) are distinctly different, they are readily distinguishable.



(a) CBZCl, $NaHCO_3$; (b) PhCHO, $ZnCl_2$; (c) n-Bu_2SnO; and (d) RCl, Et_3N

4A: R = $C_6H_5C(O)$
4B: R = $CH_3C(O)$
4C: R = $CH_3(CH_2)_2C(O)$
4D: R = p-$CH_3C_6H_4SO_2$

The reason for the selective functionalization of the C2 hydroxyl is currently unknown. However, it is consistent with the results recently reported on the selective acylation of the C6 hydroxyl group of castanospermine using di-n-butyltin oxide.[4] Similarly, methyl 4,6-O-benzylidene-2,3-O-dibutylstannylene-α-D-glucopyranoside has been selectively benzoylated at the C2 hydroxyl group.[9] In contrast, the β isomer showed little selectivity. These results were attributed to the ability of the α isomer to coordinate to the tin of the stannylene. Since stannylene **3** contains no coordinating group at C1, one cannot explain our results in this manner.

Our current efforts involve the utilization of intermediates **4** for the preparation of analogs of 1-deoxynojirmycin.[10] The results of that work will be reported in due course.[11]

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7) For a review, see S. David and S. Hanessian, Tetrahedron, **1985**, 41(4), 643-663.
8) Compounds **4A** and **4D** could be readily prepared on 20g scale. Compound **4A** was isolated by simple crystallization, whereas **4D** required chromatography to remove the tin salts prior to crystallization.
9) R.M. Munavu and H.H. Szmant, J. Org. Chem., **1976**, 41, 1832.
10) For the analog work, the 4,6-O-benzylidene was removed with 50% aqueous trifluoroacetic acid and the N-CBZ group removed by hydrogenolysis.
11) All new compounds gave satisfactory ^1H, ^{13}C NMR and mass spectra, as well as correct elemental analysis or high resolution mass spectra.

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