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A SIMPLE PROCEDURE FOR THE DEVELOPMENT OF ACID-LABILE PROTECTING GROUPS ON POSITION 2 AND 3 OF METHYL α-D-GLUCOPYRANOSIDE

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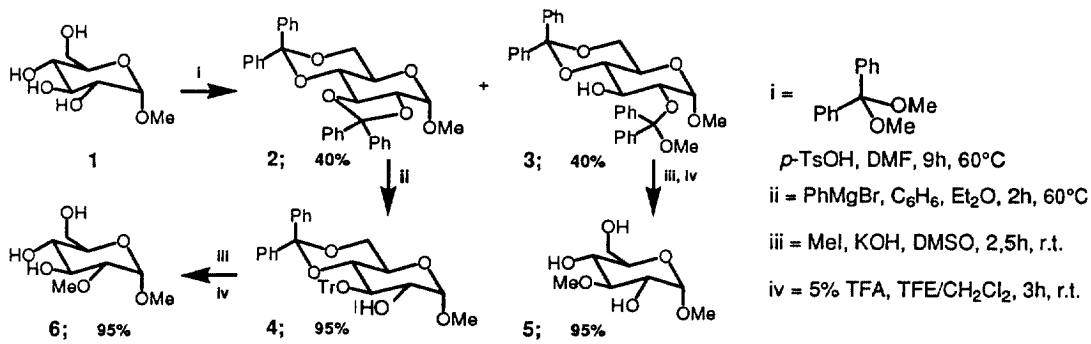
Building blocks of methyl α-D-glucopyranoside possessing free hydroxyl functions in the position 2 or 3 and orthogonal acid-labile protecting groups on the other reacting sites can be conveniently prepared by means of benzophenone dimethyl ketal under very mild experimental conditions. Trityl and diphenylmethoxymethyl groups have been easily built on secondary hydroxyl groups of monosaccharides for the first time.

The treatment of methyl α-D-glucopyranoside with benzophenone dimethyl ketal allows the direct formation of 2,3:4,6-di-*O*-diphenylmethylene-α-D-glucopyranoside (2) and of methyl 2-*O*-diphenylmethoxymethyl-4,6-*O*-diphenylmethylene-α-D-glucopyranoside (3) in equimolar amounts.



The former is easily transformed into the methyl 3-*O*-trityl-4,6-*O*-diphenylmethylene-glucopyranoside (4) in nearly quantitative yields. The uniqueness of the present method is represented by the introduction of triphenylmethyl and diphenyl methoxymethyl groups on the secondary positions of the sugar ring and by their orthogonality to the diphenylmethylene cyclic acetal protection of the positions 4 and 6. The latter, moreover, can be removed under experimental conditions milder than those required by any other cyclic acetal so-far used as a protecting group for the same positions. Moreover, under appropriate conditions benzophenone dimethyl ketal reacts with **1** affording 72% yields of the corresponding 4,6-diphenylmethylene derivative (m.p. 190-191).

The chemistry of carbohydrates has recently been exploited in cancer treatment[1] and gene therapy,[2] in the preparation of drug delivery systems[3, 4] and, among others, in the formation of derivatives with surfactant properties.[5] As a part of our on-going project related to the selective protection of monosaccharides,[6] we have recently exploited the peculiarity of benzophenone dimethyl ketal both as an alternative to the classic benzylidene protection of monosaccharides and, with reference to some recently published results,[7, 8] as a possible source of trityl protecting groups on a secondary hydroxyl function.

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When the glucoside **1** (scheme) reacts with an excess of benzophenone dimethyl ketal in dry DMF, in the presence of 1% of toluene *p*-sulphonic acid and, by continuous removal of methanol under low vacuum at 50 °C, **2** (m.p. 219-221) and **3** (m.p. 196-198) are obtained after chromatographic purification of the crude, each in a 40% isolated yields. The structure of **3** was assigned on the basis of ^{1}H NMR and extensive decoupling experiments. The FABMS spectrum, in *m*-nitrobenzyl alcohol provided low abundant $[M+Na]^+$ and $[M+H]^+$ species since, even under mild conditions, the molecule tends to eliminate methanol. If the diacetal **2**, whose structural characterisation did not pose problems, is added dropwise, in dry benzene, to a solution of a four-fold excess of phenylmagnesium bromide in diethyl ether, more than 95% isolated yield of the ring opened compound **4** (m.p 188-189) is obtained after 3 hours at 60 °C. The regiochemistry of the ring-opening could suggest that participation of the axial α-methoxy group is required. Preliminary results on other systems clearly show that the opening of the five-membered ring does not take place with the β isomer or when methyl 2,3:4,6-*O*-diphenylmethylene-α-D-mannopyranoside reacts under the same conditions. In this case, in fact, the 2,2-diphenyl-1,3-dioxane moiety is stable to Grignard reagents even after prolonging the reaction times. The structures of **3** and **4** were further supported by their transformation into **5** and **6** under mild experimental conditions. Diphenylmethylene cyclic ketals have been previously prepared from dichlorodiphenylmethane under fairly drastic conditions.[9] Benzophenone dimethyl ketal can be prepared in bulk quantities, has an indefinite shelf-life and its reactivity towards monosaccharides can be modulated by controlling both the stoichiometry and the experimental conditions.[10] The formation of **3** and **4** represent an unique strategy for the controlled derivatisation of the position 2 and 3 of monosaccharides in the presence of orthogonal acid-labile protecting groups. Moreover we are unaware of any use of the diphenylmethylene group for the simultaneous protection of the 4 and 6 positions of pyranosides.

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