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Simple Large-Scale Synthesis of Methyl 2,3:4,6-Di-0-Benzylidene-α-D-Mannopyranoside

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SIMPLE LARGE-SCALE SYNTHESIS OF METHYL 2,3:4,6-DI-*O*-BENZYLIDENE-α-D-MANNOPYRANOSIDE

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Abstract: An extremely simple and efficient large-scale synthesis of the *exo*-dioxolane epimer of methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyrannoside is described.

In recent years, carbohydrate-based synthesis has established itself as one of the more important methods for asymmetric synthesis.[1] Of the many cheap and readily-available sugars, D-mannose, in the form of methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside (**I**), is a frequently-used starting material and has been applied to the synthesis of such targets as daunosamine,[2] as well as finding considerable application in the field of carbohydrate-based synthetic research.[3]

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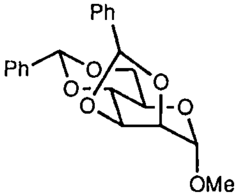

(I)

As part of our studies towards the synthesis of naturally-occurring terpene γ-lactones,[4] we required large quantities of (I) and although a number of syntheses of this material had already been described in the literature,[2,5,6] none of these methods was found to be suitable. An alternative preparation was therefore needed.

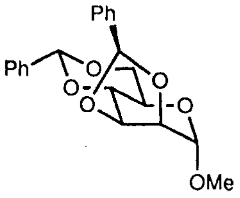
Results and Discussion

The literature syntheses of methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside (I) all involve an acid-catalysed condensation reaction between methyl α-D-mannopyranoside and benzaldehyde or its dimethyl acetal. Of the three procedures tried in our laboratories,[2,5,6] none was particularly reliable and only modest (30 - 40 %) yields were ever obtained. The method of Horton and Weckerle[2] was the most successful but was difficult to control since it requires a water aspirator to be connected to the system (boiling DMF) in order to drive the reaction to completion.

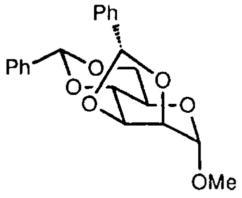
An alternative procedure was developed whereby an acetal exchange reaction between methyl α-D-mannopyranoside and benzaldehyde dimethylacetal is run in acetonitrile, using camphor sulphonic acid as the catalyst. The reaction is driven to completion by distilling the acetonitrile-methanol azeotrope from the reaction mixture until no more methanol remains in the distillate. After neutralising the catalyst, the product crystallises from the mixture in 90 % yield.

The spectral data of the product formed by this method showed it to be a single diastereomer, in which the phenyl group at the dioxolane centre is *exo-* to the molecule (Ia). This is in contrast to the other syntheses of

(I),[2,5,6] all of which produce a mixture of the two epimers (**Ia** and **Ib**). One possible explanation for the exclusive formation of (**Ia**) is that by using a significantly lower boiling solvent (MeCN b.p. 81 °C; DMF b.p. 153 °C [7]), energetics favour only the formation of (**Ia**), the kinetic and thermodynamic product.



(**Ia**)



(**Ib**)

This method provides a simple and convenient preparation of methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside on an 86 g scale from readily available starting materials.

Experimental

General: All reagents were used as supplied by the manufacturers. Acetonitrile was distilled from calcium hydride under nitrogen.

Methyl 2,3:4,6-di-O-benzylidene-α-D-mannopyranoside (I): α,α-Dimethoxytoluene (83 g, 545 mmol) was added to a solution of methyl α-D-mannopyranoside (50 g, 258 mmol) and β-(±)-camphor-10-sulphonic acid (0.5 g, 2.15 mmol) in anhydrous acetonitrile (500 ml), and the mixture heated to reflux under an atmosphere of dry nitrogen for 2 hours. The apparatus was then altered to remove the solvent by distillation, protected by a calcium chloride guard tube. After around 300 ml of distillate had been removed and the liquids were condensing at 81 °C, the mixture was neutralised with triethylamine (0.3 ml; 0.22 g, 2.16 mmol) and allowed to cool whereupon the product crystallised as white needles (34 g). The mother liquors were concentrated under reduced pressure to leave a colourless syrup which was crystallised from 95 % ethanol to yield a second crop of white crystals. Both crops were dried *in vacuo* to give a total yield of 86 g, 90 %, m.p. 184 °C (from acetone), $[\alpha]_D$ +0.0° (*c* 1.0 in chloroform) (lit.,[2] m.p. 180-182 °C, $[\alpha]_D$ +0°, *c* 1 in chloroform) (Found: C, 67.8; H, 6.0. Calculated for $C_{21}H_{22}O_6$: C, 68.1; H, 5.9 %); δ_H (250 MHz, $CDCl_3$) 3.40 (3 H, s, CH_3O), 3.80-3.94 (3 H, m, 4-H, 5-H and 6-Hax.), 4.14 (1 H, dd, *J* 5.5 and 1 Hz, 2-H), 4.33-4.38 (1 H, m, 6-Heq.), 4.63 (1 H, dd, *J* 7.5 and 5.5 Hz, 3-H), 5.01 (1 H, s, 1-H), 5.64 (1 H, s, PhC*H* dioxane), 6.29 (1 H, s, PhC*H* dioxolane), 7.33-7.56 (10 H, m, 2 x Ph); δ_C (62.9 MHz, $CDCl_3$) 55.09 (CH_3O), 60.21, 68.79, 75.21, 75.44, 77.36, 98.69, 101.86, 102.89, 125.93-138.48; *m/z* 370 (M^+, 8.3 %), 105 (100).

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