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Note

Use of the 2,6-dimethoxybenzoyl group to prevent acyl migration during Purdie methylation· a synthesis of 2-*O*-methyl-D-mannose

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That acyl migration can occur during Purdie methylation (and in the modified procedure of Kuhn[1]) of partially acylated carbohydrates has long been recognised[2] Such rearrangements can sometimes be synthetically useful[3,4], but their often unpredictable nature[3], resulting from a close dependence on reaction conditions, reduces the general utility of these alkylations Acyl migration during methylation may be averted by the use of the diazomethane–boron trifluoride procedure[5], but the reagent is unpleasant to handle If acyl migration could be suppressed during Purdie methylation, then this simple method would be the one of choice

Benzoyl groups migrate less readily than acetyl groups[6–8] and *p*-nitrobenzoyl[9] and *p*-methoxybenzoyl[6,10] groups migrate more and less readily, respectively, than benzoyl groups, as expected from the resonance interactions of the para-substituents with the aromatic system The 2,6-dimethoxybenzoyl group should therefore not migrate readily, as the electrophilic nature of the carbonyl function is reduced by mesomeric interaction with the *o*-methoxyl groups which, additionally, offer steric hindrance to nucleophilic attack at the carbonyl function, the resistance of 2,4,6-trimethylbenzoic esters towards hydrolysis and their reluctance to undergo migration noted below illustrate the steric control that *o*-substituents can have on the reactivity at the carbonyl function of the ester group

The test of this supposition was combined with a synthetically useful goal, namely, the synthesis of 2-*O*-methyl-D-mannose, previously obtained unambiguously *via* methyl 4,6-*O*-ethylidene-3-*O*-tosyl-α-D-mannoside[11], and by methylation of 1,3,4,6-tetra-*O*-acetyl-β-D-mannopyranose using diazomethane–boron trifluoride[12]. The present synthesis is similar to the former route, but the 2,6-dimethoxybenzoyl group is used in place of the tosyl function as a blocking group Tosyl is a non-migrating, blocking group, but its removal is not as simple as the transesterification used for removing acyl residues, and complications (*e g*, epoxide formation) may sometimes arise

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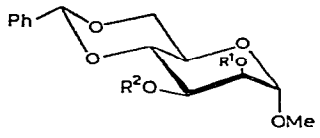
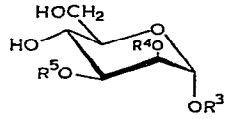
Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**1**), when treated with one mol of 2,6-dimethoxybenzoyl chloride in pyridine, gave, as a major product after chromatography, the 3-(2,6-dimethoxybenzoate) **2** (63%), some starting diol was recovered In contrast to the 3-benzoate **3**, **2** did not isomerise under the conditions of Purdie methylation Thus, although stirring **3** in chloroform containing a trace of methyl iodide in the presence of silver oxide led to rapid establishment of an equilibrium of 2- and 3-esters, **2** was unchanged after prolonged treatment It is noteworthy that acyl migration was very much slower when methyl iodide was omitted, **3** was virtually unchanged after 10 h, but with a trace of the iodide present, migration was immediately apparent and equilibrium was established after ~6 h The 3-(4-methoxybenzoate) **4**, although more stable than the 3-benzoate **3**, underwent slow isomerisation, but the 3-(2,4,6-trimethylbenzoate) **5** was stable Similar, relative stabilities were observed on boiling chloroform solutions of the esters in the presence of imidazole However, isomerisation of **2** and **5** occurred in strong, aqueous base The 3-(2,6-dimethoxybenzoate) **2** was selected for further synthetic transformation



1 $R^1 = R^2 = H$
2 $R^1 = H$, $R^2 = 2,6\text{-}(MeO)_2 \cdot C_6H_3 \cdot CO-$
3 $R^1 = H$ $R^2 = Bz$
4 $R^1 = H$ $R^2 = MeO\ C_6H_4\ CO-$
5 $R^1 = H$ $R^2 = 2\ 4\ 6\text{-}(Me)_3 \cdot C_6H_2 \cdot CO-$
6 $R^1 = Me$ $R^2 = 2\ 6\text{-}(MeO)_2\ C_6H_3 \cdot CO-$



7 $R^3 = R^4 = Me$, $R^5 = 2,6\text{-}(MeO)_2\ C_6H_3\ CO$
8 $R^3 = R^4 = Me$, $R^5 = H$
9 $R^3 = R^5 = H$, $R^4 = Me$

Methylation of **2** gave the crystalline 2-methyl ether **6** (85%), with no sign (t l c) of other reaction products Hydrogenolysis of the benzylidene group in **6** yielded methyl 3-*O*-(2,6-dimethoxybenzoyl)-2-*O*-methyl-α-D-mannopyranoside (**7**) Deacylation of **7** with methanolic sodium methoxide afforded syrupy methyl 2-*O*-methyl-α-D-mannopyranoside (**8**), which gave a crystalline tris(2,6-dimethoxybenzoate) Acid hydrolysis of **8** yielded crystalline 2-*O*-methyl-α-D-mannose (**9**), which was further characterised by conversion into D-*arabino*-hexose phenylosazone

Since there is considerable evidence that acyl migration occurs more readily between vicinal *cis*- than vicinal *trans*-disposed oxygen functions[13–18], the stability of the 2,6-dimethoxybenzoyl group implies that it may find considerable use as a blocking group during methylation in carbohydrate syntheses However, isomerisation between the mono-acyl derivatives of a vicinal *cis*-diol occurs much more readily in furanoid than in pyranoid derivatives, and a further modified benzoyl group is required to suppress acyl migration in such cases We are currently investigating this aspect

EXPERIMENTAL

Preparative layer chromatography (p l c) was carried out on Kieselgel PF_{254}, and dry-column chromatography on Kieselgel 60–Merck 7734 (70–230 mesh) The following solvent combinations were used *A*, toluene–ethyl acetate (5 1), *B*, benzene–ethyl acetate (4 1), *C*, chloroform–methanol (10 1), *D*, chloroform–methanol (8 1).

N m r spectra were measured with a Varian HA-100 instrument, with Me_4Si as internal standard, chemical shifts are accurate to ±0 02 Hz Rotations were measured for solutions in chloroform, unless stated otherwise, at ambient temperature with a Perkin–Elmer 141 polarimeter Organic solutions were dried over anhydrous sodium sulphate Routine identifications were based on mixture m p 's and i r. spectra Silver oxide was prepared by the method of Helferich and Klein[19]

*Methyl 4,6-*O*-benzylidene-3-*O*-(2,6-dimethoxybenzoyl)-α-*D*-mannopyranoside* (**2**) — To a solution of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside[20] (**1**, 2 g) in pyridine (50 ml) was added a solution of 2,6-dimethoxybenzoyl chloride[21] (2 g) in pyridine (20 ml), and the mixture was stored at room temperature for 12 h Water (70 ml) was added and the mixture was extracted with chloroform (100 ml). The extract was washed with saturated, aqueous sodium hydrogen carbonate and water, then dried, and concentrated The residue was freed from pyridine by evaporation of toluene therefrom, and then subjected to dry-column chromatography (Kieselgel, 70 g, solvent *A*) The main fraction, on recrystallisation from toluene–light petroleum, gave **2** (1 2 g, 63% based on utilised diol), m p 160–161°, $[\alpha]_D$ −69° (*c* 0 1), ν_{max}^{Nujol} 3530 (OH), 1735 cm^{-1} N m r data (C_6D_6) δ 2 94 (s, OMe), 3 14 (s, 2 ArOMe), 4 82 (d, $J_{1\ 2}$ 2 Hz, H-1), 5 34 (s, benzylic H), 5 85 (dd, $J_{2\ 3}$ 4, $J_{3,4}$ 10 Hz, H-3)

Anal Calc for $C_{23}H_{26}O_9$ C, 61 9, H, 5 9 Found C, 61 5, H, 5 7

Tosylation of **2** gave methyl 4,6-*O*-benzylidene-3-*O*-(2,6-dimethoxybenzoyl)-2-*O*-tosyl-α-D-mannopyranoside (62%), m p 163–164°, $[\alpha]_D$ −97° (*c* 0 15), identical to the compound obtained on esterification of methyl 4,6-*O*-benzylidene-2-*O*-tosyl-α-D-mannopyranoside with 2,6-dimethoxybenzoyl chloride in pyridine

The structure of non-crystalline methyl 4,6-*O*-benzylidene-2-*O*-tosyl-α-D-mannopyranoside, the minor product of the monotosylation of **1**, is secure since, on benzoylation, it yields known[22] methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-2-*O*-tosyl-α-D-mannopyranoside

*Methyl 4,6-*O*-benzylidene-3-*O*-(2,6-dimethoxybenzoyl)-2-*O*-methyl-α-*D*-mannopyranoside* (**6**) — A solution of **2** (3 g) in methyl iodide (40 ml) was stirred in the presence of silver oxide (5 g) and boiled under reflux T l c (solvent *B*) after 12 h showed the reaction to be incomplete To the filtered mixture, fresh silver oxide (5 g) was added, and stirring and heating were continued until the starting material had disappeared (~18 h) The mixture was diluted with chloroform (200 ml), filtered through Kieselguhr and then filter paper, and concentrated at <30° (higher temperatures caused debenzylidenation of the crude product) More chloroform (50 ml) was added, and the solution was washed successively with aqueous solutions of sodium thiosulphate and sodium hydrogen carbonate, then dried, and concentrated.

The residue was crystallised from ethyl acetate–hexane to yield **6** (2 65 g, 85%), m p. 155–157°, $[\alpha]_D$ −40° (*c* 0 22), ν_{max}^{Nujol} 1730 cm^{-1} (C=O), no absorption near 3600 cm^{-1}.

Anal Calc for $C_{24}H_{28}O_9$ C, 62 6, H, 6 1. Found C, 62 6; H, 6 2

Methyl 3-O-(2,6-dimethoxybenzoyl)-2-O-methyl-α-D-mannopyranoside (**7**) — The ether **6** (0 63 g) partly dissolved in methanol (20 ml) was stirred under a slight overpressure of hydrogen in the presence of 10% palladium-on-charcoal (0 06 g), and the reaction was monitored by t l c (solvent *C*), as reaction proceeded, the starting material went into solution On disappearance of **6**, the filtered solution was concentrated and the residue was crystallised from ethyl acetate–light petroleum to yield **7** (0 46 g, 90%), m p 122–124°, $[\alpha]_D$ +51° (*c* 0 3)

Anal Calc for $C_{17}H_{24}O_9$ C, 54 8, H, 6 5 Found C, 54 4, H, 6 4

Methyl 2-O-methyl-α-D-mannopyranoside (**8**) — To a solution of **7** (1 6 g) in methanol (45 ml), sodium (0 02 g) was added and the solution was heated under reflux for 45 h, t l c (solvent *C*) then indicated the disappearance of starting material The triol **8**, separated from methyl 2,6-dimethoxybenzoate by dry-column chromatography (Kieselgel 70 g, solvent *D*), was obtained as a chromatographically homogeneous syrup (0 82 g, 93%), $[\alpha]_D$ +51° (*c* 0 15), ν_{max}^{Nujol} 3400 cm^{-1} (broad OH), no absorption near 1730 cm^{-1}

The triol was characterised as its 3,4,6-tris(2,6-dimethoxybenzoate), m p 239 5–241° (from chloroform–ethyl acetate–hexane), $[\alpha]_D$ +77° (*c* 0 1)

Anal Calc for $C_{34}H_{40}O_{15}$ C, 59 3, H, 5 85 Found C, 58 9, H, 5 6

2-O-Methyl-α-D-mannose (**9**) — Methyl 2-*O*-methyl-α-D-mannopyranoside (**8**, 0 6 g) was hydrolysed with 0 5M hydrochloric acid (10 ml) at 100° for 8 h Water (10 ml) was added, and the solution was neutralized with silver carbonate, filtered, saturated with hydrogen sulphide, and then concentrated to dryness *in vacuo* The resulting, black residue was extracted with boiling ethanol (3 × 50 ml), and the combined extracts were filtered through Keiselguhr and again through filter paper Concentration yielded a chromatographically homogeneous, foamy solid (0 465 g) which, on crystallisation from ethanol, yielded **9** (0 24 g, 44%), m p 136–138°, $[\alpha]_D$ +11 (initial) → +4 5° (36 h, *c* 0 1, water), lit [12] m p 138–139°, $[\alpha]_D^{23}$ +6 6 → +4 8° (24 h, *c* 1 1, water), lit [23] m p 136–137°, $[\alpha]_D$ +7 → +4 5° (24 h, *c* 2 88, water), lit [11] m p. 137°, $[\alpha]_D^{19}$ +15 → +5° (24 h, *c* 1 3, water), lit [24] $[\alpha]_D$ +4 2° (*c* 1 21, water) On p c in 1-butanol–ethanol–water (4 1 5, organic phase), it had R_F 0 33 and R_{Glc} 2 23

The 2-*O*-methyl-D-mannose was characterised by conversion into D-*arabino*-hexose phenylosazone, m p 202–205°, $[\alpha]_D$ −67 (initial) → −42 (12 h) → −38° (24 h, *c* 0 045, ethanol–pyridine, 6 4), lit.[24] m p 198–200°, $[\alpha]_D^{27\,5}$ −55 → −35° (*c* 1, ethanol–pyridine, 6 4), lit [23] m p 204–206°, $[\alpha]_D$ −65 → −34° (24 h, *c* 0 6, ethanol–pyridine, 6 4)

Methyl 4,6-O-benzylidene-3-O-(4-methoxybenzoyl)-α-D-mannopyranoside (**4**) — To a frozen (~ −70°) solution of **1** (0 7 g) in pyridine (10 ml) was added a solution of 4-methoxybenzoyl chloride (0 45 g) in pyridine (10 ml). The temperature of the reactants was allowed to rise, and when the reactants became molten, stirring was

commenced and continued until the bath temperature reached 5°. The mixture was then stored for 12 h at 5° and for 7 h at room temperature Water (0 5 ml) was added and, after 0 5 h, the mixture was added to saturated, aqueous sodium hydrogen carbonate, and the combined liquids were extracted with chloroform (3 × 50 ml) The extract was washed with aqueous sodium hydrogen carbonate and water, dried, and concentrated T l c (solvent *B*) of the residue showed four components *W*, *X*, *Y*, and *Z*, in order of increasing R_F values, *W* was starting diol P l c (solvent *B*, which contained ~1 5% of 2M acetic acid in acetone to suppress acyl migration) gave the major component *X* (0 66 g) which, on crystallisation from ether–hexane, gave **4**, m.p 132–134°, $[\alpha]_D$ −37° (*c* 0 4), ν_{max}^{Nujol} 3570 (OH), 1700 cm^{-1} (C=O) N m r data (C_6D_6) δ 2 95 (s, OMe), 3 12 (s, ArOMe), 4 54 (d, $J_{1,2}$ 2 Hz, H-1), 5 43 (s, benzylic-H), 5 85 (dd, $J_{2,3}$ 4, $J_{3,4}$ 10 Hz, H-3)

Anal Calc for $C_{22}H_{24}O_8$ C, 63 45, H, 5 8 Found C, 63 2, H, 5 8

Treatment of **4** with tosyl chloride in pyridine gave the 2-*O*-tosyl derivative, m p. 159–161° (from ethyl acetate–light petroleum), $[\alpha]_D$ −66° (*c* 0 15)

Anal. Calc for $C_{29}H_{30}O_{10}S$ C, 61 0, H, 5 3 Found C, 60 9, H, 5 4

Component *Z* (52 mg) crystallised from ether–hexane to yield the 2,3-di-*O*-(4-methoxybenzoyl) derivative of **1**, m p 161–162°, $[\alpha]_D$ −236° (*c* 0 1)

Anal Calc. for $C_{30}H_{30}O_{10}$ C, 65 45, H, 5 5 Found C, 65 1, H, 5 4

The syrupy component *Y* (46 mg) reacted with tosyl chloride in pyridine to give methyl 4,6-*O*-benzylidene-2-*O*-(4-methoxybenzoyl)-3-*O*-tosyl-α-D-mannopyranoside, m p 134–135° (from ethyl acetate–light petroleum), $[\alpha]_D$ −47° (*c* 0 25)

Anal Calc for $C_{29}H_{30}O_{10}S$ C, 61 0, H, 5 3 Found C, 61 0, H, 5 3

Methyl 4,6-O-benzylidene-3-O-(2,4,6-trimethylbenzoyl)-α-D-mannopyranoside (**5**) — A solution of **1** (1 4 g) in pyridine (20 ml) was treated with 2,4,6-trimethylbenzoyl chloride (0.91 g), as described for the preparation of **4**. T l c indicated one major product, which was isolated by p l c (solvent *B*) as an amorphous solid (0 81 g), $[\alpha]_D$ −29° (*c* 0 4), ν_{max}^{Nujol} 3450 (OH), 1750 cm^{-1} (C=O) N m r data (C_6D_6) δ 2 00 (s, 2 ArMe), 2 94 (s, OMe), 4 51 (d, $J_{1,2}$ 2 Hz, H-1), 5 32 (s, benzylic-H), 5 88 (dd, $J_{2,3}$ 4, $J_{3,4}$ 10 Hz, H-3)

Anal Calc for $C_{24}H_{28}O_7$ C, 67 3, H, 6 6 Found: C, 66 85; H, 6 5

Isomerization studies on the 3-benzoate, 3-(4-methoxybenzoate), 3-(2,6-dimethoxybenzoate), and 3-(2,4,6-trimethylbenzoate) esters of methyl 4,6-O-benzylidene-α-D-mannopyranoside. — (*a*) *In chloroform–silver oxide with a trace of methyl iodide* Solutions of each ester (0 03 g) in chloroform (1 ml) containing two drops of methyl iodide were stirred in the presence of silver oxide (0 09 g), and the courses of reactions were monitored by t l c (solvent *B*)

The 3-benzoate isomerized to its 2-isomer at a considerably higher rate than the 3-(4-methoxybenzoate) In each reaction, a very slight preponderance of the 2-isomer was finally observed Neither the 3-(2,6-dimethoxybenzoate) nor the 3-(2,4,6-trimethylbenzoate) underwent isomerization under these conditions

(*b*) *In chloroform with imidazole present.* Solutions of each ester (0 03 g) in chloroform (2 ml) containing imidazole (15 mg) were heated under reflux, and the

reactions were monitored by t l c The 3-benzoate was completely isomerised into an equilibrium mixture of 2- and 3-benzoates after 4 h, the equilibration of the 3-(4-methoxybenzoate) required ~12 h In each reaction, the 2-ester slightly preponderated No isomerization was detected with the 3-(2,6-dimethoxybenzoate) or 3-(2,4,6-trimethylbenzoate) even after prolonged reflux

(*c*) *Sodium hydroxide in acetone–water* Solutions of the 3-(2,6-dimethoxybenzoate) and 3-(2,4,6-trimethylbenzoate) (0 02 g) in acetone (6 ml) were treated with 0 05M sodium hydroxide solution (2 ml) After 1 min, the solutions were neutralized with 2M acetic acid and concentrated, and the residues were dissolved in chloroform (5 ml) Each solution was washed with water (3 × 2 ml), dried, and subjected to t l c, which indicated virtually complete isomerization into a mixture of 2- and 3-esters, in which the latter isomer slightly preponderated

(*d*) *On silica gel* Samples of the 3-benzoate and 3-(4-methoxybenzoate) were placed on a silica gel t l c plate, which was then kept for 10 h at room temperature On development, isomerization of the former derivative was seen to have occurred, in contrast, the latter derivative had isomerised to a much lesser extent

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