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Benzylated Orthoesters in Glycoside Synthesis

The Synthesis of α-D-Glucopyranosides and β-D-Mannopyranosides

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3,4,6-Tri-*O*-benzyl-1,2-*O*-(methoxyethylidene)-α-D-glucopyranose and the corresponding β-D-mannopyranose are easily prepared from the corresponding 3,4,6-tri-*O*-acetyl-1,2-*O*-(methoxyethylidene) compounds by deacetylation followed by benzylation with benzyl bromide and silver oxide in dimethyl formamide. Glycoside syntheses using the Kochetkov orthoester method and the 3,4,6-tri-*O*-benzyl orthoesters, is followed by removal of the acetyl group in the 2-position. Oxidation and reduction produces inversion at C-2 and thereby new methods for the syntheses of α-D-glucopyranosides and β-D-mannopyranosides.

One of the classical topics of carbohydrate chemistry is the search for stereospecific, high-yield syntheses of glycosides and oligosaccharides. Access to such syntheses would be of considerable interest in both synthetic natural products chemistry and in biological chemistry. The topic can be divided into two separate problems, the synthesis of glycosides with 1,2-*trans*-configuration and those with 1,2-*cis*-configuration. The former of these is by far the easiest one, and therefore the one for which relatively satisfactory solutions have been found. The traditional way of preparing 1,2-*trans*-glycosides is the Koenigs-Knorr synthesis in which an acetoxy group in the 2-position exerts steric control in the reaction.[1] An important improvement has been described by Kochetkov and co-workers who developed the orthoester glycoside synthesis in which a 3,4,6-tri-*O*-acyl-1,2-(alkoxyethylidene)-hexose (or the corresponding pentose) is allowed to react with an alcohol or a suitably protected sugar in the presence of an acidic catalyst such as *p*-toluenesulphonic acid or mercuric bromide.[2] The steric outcome of the reaction normally is a 1,2-*trans*-glycoside, although exceptions have been noted.[3,4] Of the various attempts made in order to obtain 1,2-*cis*-glycosides [5–7] two recent approaches are particularly noteworthy. In the first of these, due to Lemieux and co-workers, nitrosyl chloride adducts of protected glycals are used in glycoside syntheses.[8] The reaction product of an alcohol (or a suitably protected monosaccharide)

with the nitrosyl chloride adduct of a 3,4,6-tri-*O*-acetyl-glycal normally is an α-D-glycoside with an oximino function in the 2-position. This is converted into a keto function by treatment with levulinic acid. Borohydride reduction affords the 1,2-*cis*-glycoside. The method works well in the *gluco*, *galacto*, and *talo* series and produces 1,2-*cis*-configuration,[9] although one exeption has been noted.[10] Another promising approach is that due to Ferrier and co-workers in which an acylated 2-hydroxyglycal is allowed to react with an alcohol or a suitably protected monosaccharide under catalysis with boron trifluoride.[11] The products are 3-deoxy-hex-2-enopyranosyl glycosides, with the α-anomers predominating. Here, the problem lies in the subsequent stereospecific conversion of the 3-deoxy-2-hexenopyranose unit (or a 2,3,-dideoxy-2-hexenopyranose unit, produced as above, but from acylated glycals instead of 2-hydroxyglycals) into a saturated pyranoside. The subject of *O*-glycoside synthesis has recently been reviewed by Ferrier.[12]

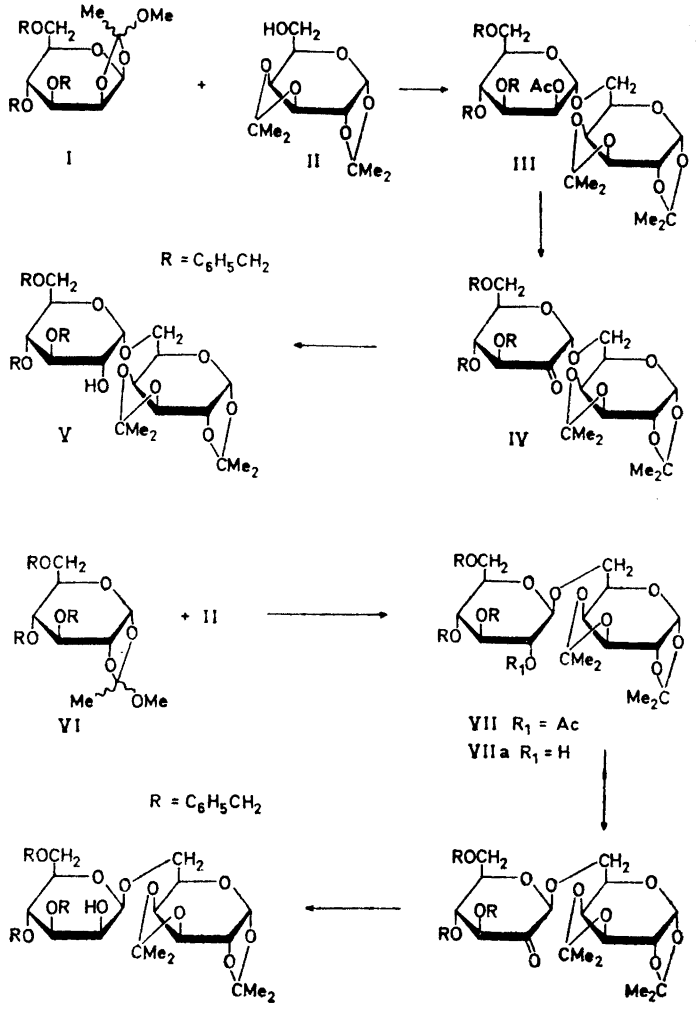
Of these various glycoside syntheses, the one with the generally highest yield and stereoselectivity is the orthoester synthesis, which leads to 1,2-*trans*-glycosides. One possible approach to the synthesis of 1,2-*cis*-glycosides would seem to be the use of this reaction, followed by the stereospecific inversion at the 2-position. This approach will be discussed in the present paper, as applied to the synthesis of α-D-glucopyranosides and of β-D-mannopyranosides. The work follows from the application of the principle of stereoselective 1,2-*trans*-glycoside synthesis followed by C-2 inversion in the synthesis of β-D-mannopyranosides previously communicated from this Department.[13] In that work, the key step consisted in the Koenigs-Knorr synthesis applied to 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl bromide, the product of which was converted into the corresponding β-D-mannoside by debenzoylation, oxidation and reduction.

3,4,6-Tri-*O*-acetyl-1,2-*O*-(methoxyethylidene)-α-D-glucopyranose [2] and the corresponding β-D-mannopyranose [14] are easily made from the appropriate 2,3,4,6-tetra-*O*-acetyl-α-D-hexosyl bromides. The orthoesters were deacetylated in the 3,4,6-positions by treatment with methanolic ammonia. The products were benzylated in the same positions by treatment with benzyl bromide and silver oxide in dimethyl formamide.[15] The yields from the orthoester starting materials were about 50 %. Each of the two tri-*O*-benzyl orthoesters underwent normal orthoester glycoside syntheses and produced the expected 1,2-*trans*-glycosides. Since the protecting group in the 2-position now was an acetyl group and those in the 3,4,6-positions were benzyl groups, the 2-hydroxyl group could be specifically generated with protecting groups in all other positions, offering an opportunity for inversion at the 2-position by oxidation followed by reduction. The result of this sequence of reactions therefore was an α-D-glucopyranoside (from the tribenzylmannose orthoester) or a β-D-mannopyranoside (from the tribenzylglucose orthoester).

The 1,2-*cis*-glycoside synthesis is illustrated by the syntheses of 6-*O*-α-D-glucopyranosyl-D-galactose and 6-*O*-β-D-mannopyranosyl-D-galactose.

2,3,4-Tri-*O*-benzyl-1,2,-*O*-(methyoxyethylidene)-β-D-mannopyranose (I) [16] was allowed to react with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (II) [17] in nitromethane containing mercuric bromide under the general glycosylation conditions described by Kochetkov and co-workers.[2] The product III

was deacetylated in methanolic ammonia and the product, with a free hydroxyl group in the 2-position of the mannose residue was oxidized to the corresponding 2-hexosulose residue with dimethyl sulphoxide-acetic anhydride [18] yielding IV. The 2-hexosulose-containing disaccharide IV was reduced with diborane in tetrahydrofuran [19] to yield the glucosylgalactose derivative V. In the reduction of the 2-hexosulose moiety of IV to the glucose residue of V the ratio of glucose-mannose residue formed was 88:12. Reduction with sodium borohydride gave a ratio of 60:40 for the same sugars. The yield of the glucosylgalactose derivative V from I was 25 %. Removal of blocking groups from V afforded 6-*O*-α-D-glucopyranosyl-D-galactose with $[\alpha]_D + 126°$ (lit.[20,21] $[\alpha]_D + 125°$).



2,3,4-Tri-*O*-benzyl-1,2-*O*-(methoxyethylidene)-α-D-glucopyranose (VI) was condensed with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (II) as described above for the corresponding mannose orthoester, to produce the glucosylgalactose derivative VII in 77 % yield. The deacetylated product (VIIa) was found to be identical to that previously synthesized in this Department by an alternative route.[13] Since the deacetylation of VII, the oxidation of the product VII and the highly stereoselective reduction with H_2/Pt has previously been demonstrated,[13] the synthesis of VII constitutes a synthesis of a β-D-mannopyranosyl disaccharide.

The stereoselectivity of the above sequence of reactions depends on two key steps, the orthoester glycoside synthesis [2] and on the reduction of the intermediate 2-hexosulose derivatives (IV and VIII). Despite occasional exceptions [3,4] the glycoside synthesis generally proceeds with a high degree of stereoselectivity. The problems associated with the stereochemical outcome of the reduction step are also encountered in the α-D-glycoside synthesis described by Lemieux and co-workers.[8,9] In instance where sodium borohydride offers poor selectivity, improved results may be obtained with diborane as described above. Even higher degrees of selectivity may be attainable with more sterically hindered boranes.

Some extensions from the above synthetic scheme are obvious. Since glycosides and disaccharides containing a 2-hexosulose residue are produced as intermediates, the conversion of these into the corresponding oximes and the reduction of the latter should lead to useful syntheses of 2-amino-2-deoxy-α-D-glucopyranosides and 2-amino-2-deoxy-β-D-mannopyranosides. Work on this particular aspect of the use of benzylated orthoesters in glycoside synthesis is in progress in this Department. A less general extension would be the synthesis, from the intermediates with a single hydroxyl group free in the hexose unit, of (1 → 2) linked oligosaccharides.

EXPERIMENTAL

General methods. Melting points are corrected. Concentrations were performed at reduced pressure. Optical rotations were recorded at room temperature (20 – 22°) at *c* 0.05 – 1.0 using a Perkin-Elmer 141 instrument. NMR spectra (in deuteriochloroform unless otherwise stated) were recorded with a Varian A60-A instrument, using tetramethylsilane as internal reference. The NMR spectra, determined for all new compounds were invariably in agreement with the postulated structures. TLC was performed on silica gel F_{254} (Merck) plates. When necessary, sulphuric acid was used as spray reagent. Silica gel column chromatography was performed using Mallinckrodt 100 mesh silicic acid. GLC was performed on a Perkin-Elmer F 11 instrument using XE-60 (3 % on Gas Chrom Q, 100 – 120 mesh) for disaccharide derivatives or ECNSS-M (3 % on Gas Chrom Q, 100 – 120 mesh), for monosaccharide analysis.

3,4,6-Tri-O-benzyl-1,2-O-(methoxyethylidene)-β-D-mannopyranose (I).[16] 3,4,6-Tri-*O*-acetyl-1,2-*O*-(methoxyethylidene)-β-D-mannopyranose was obtained in a 63 % yield from 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide by treatment with methanol and lutidine according to the general method described by Kochetkov and coworkers.[2] The material had m.p. 111 – 113° which corresponds to the major stereoisomer of this compound, obtained by another route.[14] NMR ($CDCl_3$) confirmed the presence of one stereoisomer only. The triacetyl orthoester (3.0 g) was deacetylated in methanol (25 ml) by the addition of ammonia-saturated methanol (5 ml) at room temperature overnight. The solution was concentrated to a chromatographically pure suryp (2.21 g). The product (1.15 g) was

dissolved in dimethyl formamide (8.6 ml) and benzylated with benzyl bromide (4.6 ml) and silver oxide (5 g) with stirring at room temperature in the dark for 20 h. Methanol (3.5 ml) was added and the mixture stirred for another 2 h. The mixture was filtered through kiselguhr. The filtrate was concentrated and the product purified by chromatography on silica gel (ethyl ether-hexane 2:1) to yield pure I (1.19 g) which crystallized from ethyl ether-light petroleum (40 – 60°) m.p. 75 – 77°, $[\alpha]_D$ +29° (chloroform) (Found: C 71.1; H 6.90. Calc. for $C_{30}H_{34}O_7$: C 71.1; H 6.77).

6-O-(2-O-Acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (III). The above orthoester I (1.45 g) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (II) (800 mg) were dissolved in nitromethane (20 ml). Solvent (*ca.* 200 ml) was removed by distillation with the continuous addition of nitromethane at constant volume. The trans-esterification was completed after 5.5 h (TLC, ethyl ether-hexane 2:1). Mercuric bromide (70 mg) was added and the mixture was refluxed overnight. The solution was concentrated and the product purified by TLC (ethyl ether-hexane 2:1) to yield pure III (800 mg), $[\alpha]_D$ −6° (chloroform). (Found: C 67.1; H 6.85. Calc. for $C_{41}H_{50}O_{12}$: C 67.0; H 6.85).

6-O-(3,4,6-Tri-O-benzyl-α-D-arabino-2-hexulopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (IV). The above disaccharide derivative III (760 mg) in methanol (25 ml) was deacetylated by the addition of ammonia-saturated methanol (25 ml) for 24 h at room temperature. The solution was concentrated to a syrup (680 mg) $[\alpha]_D$ +9° (chloroform). The product (680 mg) was oxidized in dimethyl sulphoxide (68 ml) and acetic anhydride (3.4 ml) at room temperature for 96 h. The solution was lyophilized to yield a residue which was purified by TLC (ethyl ether-hexane 2:1) to give IV (555 mg), $[\alpha]_D$ +1° (chloroform), which was used directly in the next step.

6-O-(3,4,6-Tri-O-benzyl-α-D-glucopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (V). The above disaccharide derivate IV (330 mg) in tetrahydrofuran (30 ml) in a serum bottle under nitrogen was reduced by the injection of a solution of diborane in tetrahydrofuran (0.75 M, 30 ml). The solution was kept at room temperature for 2.5 h, water was then added and the product concentrated. Boric acid was removed by repeated co-distillations with methanol. TLC (ethyl ether-hexane 3:1) showed the presence of a major component and a minor one, with lower R_F value (see below). The main component V was obtained by TLC in the same solvent as a chromatographically pure syrup (276 mg), $[\alpha]_D$ +31° (chloroform) (Found: C 67.4; H 6.86; O 25.6. Calc. for $C_{39}H_{48}O_{11}$: C 67.6; H 6.98; O 25.4).

6-O-α-D-Glucopyranosyl-D-galactose. The above disaccharide derivative V (35 mg) was hydrolyzed in 90 % aqueous trifluoroacetic acid (10 ml) at room temperature for 10 min and concentrated. The product (30 mg), $[\alpha]_D$ +64° (ethanol) was pure on TLC (ethyl acetate-methanol-water 85:10:5). The material (30 mg) was hydrogenated with 10 % palladium on carbon in ethanol to give a quantitative yield of 6-*O*-α-D-glucopyranosyl-D-galactose as a syrup $[\alpha]_D$ +126° (water). Goldstein and Whelan [20] have reported this disaccharide as a syrup, $[\alpha]_D$ +125° (water). Flowers [21] reports a syrup, $[\alpha]_D$ +123° (water).

The disaccharide on acid hydrolysis (0.25 M aqueous sulphuric acid at 100° overnight), conversion into an alditol acetate mixture (sodium borohydride reduction followed by acetylation with acetic anhydride in pyridine) and examination by GLC (on the ECNSS-M column) gave galactitol and glucitol hexa-acetates in a ratio of 1:1.

The above minor components (38 mg) obtained in the diborane reduction of IV to yield V was obtained pure by TLC as described above for V. An aliquot was subjected to treatment with, in sequence, palladium on carbon, aqueous sulphuric acid, sodium borohydride and finally, acetic anhydride in pyridine. Examination of the product by GLC (ECNSS-M) gave galactitol and mannitol in a ratio of 1:1. Another aliquot of the minor component on acetylation yielded III.

3,4,6-Tri-O-benzyl-1,2-O-(methoxyethylidene)-α-D-glucopyranose (VI). 3,4,6-Tri-*O*-acetyl-1,2-*O*-(methoxyethylidene)-α-D-glucopyranose [2] (6 g) was deacetylated in methanol (50 ml) by the addition of ammonia-saturated methanol (10 ml). After 20 h at room temperature, the solution was concentrated to a syrup (3.6 g). The product (2.0 g) was dissolved in dimethyl formamide (15 ml) and benzylated with benzyl bromide (8 ml) and silver oxide (8 g) with stirring at room temperature in the dark for 20 h. Methanol (6 ml) was added in portions and the stirring continued for another 2 h. The mixture was filtered through kiselguhr. The filtrate was concentrated and the product purified by

chromatography on silica gel (toluene-ethyl acetate 4:1) to yield pure IV (2.25 g) $[\alpha]_D$ +36° (chloroform) (Found: C 71.0; H 6.65. Calc. for $C_{30}H_{34}O_7$: C 71.1; H 6.77).

6-O-(2-O-Acetyl-3,4,6-tri-O-benzyl-β-D-glucopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (VII). The above orthoester VI (1.1 g) and II (0.565 g) were dissolved in nitromethane (13 ml). Solvent was removed by distillation with the continuous addition of nitromethane at constant volume until no more methanol was found in the distillate (GLC). The trans-esterification was complete after 1.5 h (TLC, toluene-ethyl acetate 4:1). Mercuric bromide (42 mg) was added and the mixture was refluxed overnight. After the addition of a few drops of pyridine, the solution was concentrated and the product purified by TLC (toluene-ethyl acetate 4:1) to give pure VII (1.2 g), $[\alpha]_D$ −31° (chloroform) (Found: C 66.8; H 6.71. Calc. for $C_{41}H_{50}O_{12}$: C 67.0; H 6.86).

The disaccharide derivative VII (0.6 g) was deacetylated in methanol (10 ml) by the addition of ammonia-saturated methanol (2 ml) at room temperature overnight to give VIIa in a quantitative yield, $[\alpha]_D$ −42° (chloroform) (Found: C 67.9; H 7.13. Calc. for $C_{39}H_{48}O_{11}$: C 67.6; H 6.98). These values are in agreement with those previously found for this substance, from which 6-*O*-β-D-mannopyranosyl-D-galactose was made.[13]

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