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The Orthoester Glycosylation Method. Variations in the Anomeric Composition of the Product with Aglycone Basicity in the Two-Step Procedure

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The steric outcome of the Kochetkov orthoester two-step glycosylation procedure, in which the 1,2-orthoester contains the same alcohol as that used for glycosidation, has been shown to depend on the basicity of the alcohol involved. Thus, whereas monochloroethanol gives mainly the β-D-glucopyranoside upon reaction with the appropriate 3,4,6-tri-*O*-acetyl-1,2-*O*-alkoxyethylidene-α-D-glucopyranose, dichloroethanol gives equal amounts of α-D- and β-D-glucopyranosides and trichloroethanol yields a preponderance of the α-D-glucopyranoside.

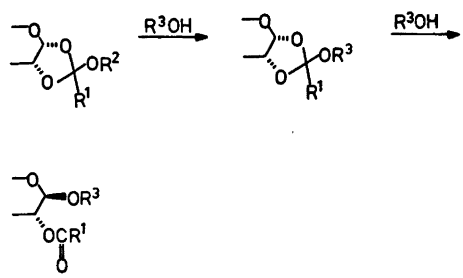


Fig. 1. R^1 = Me or Ph, R^2 = alkyl, R^3 = carbohydrate or other residue.

The potential use of sugar orthoesters for *trans*-1,2-glycoside synthesis was indicated in a study by Perlin who, in 1963, reported methyl 3,4,6-tri-*O*-acetyl-β-D-glucopyranoside as one of the major products on treatment of 3,4,6-tri-*O*-acetyl-1,2-*O*-(ethoxyethylidene)-α-D-glucopyranoside in methanol containing 1 % hydrogen chloride at room temperature for a few minutes.[1] Lemieux and Morgan [2,3] have used sugar orthoesters for *cis*-1,2-glycoside synthesis. It was, however, Kochetkov and co-workers who in a series of papers described the development of the orthoester glycosylation method into a versatile method for the synthesis of *trans*-1,2-glycosides.[4–7] The subject of *O*-glycoside synthesis has recently been reviewed.[8]

In the orthoester glycosylation method, the usual procedure is to first convert a simple alkyl orthoester into the orthoester of the alcohol to be used in the glycosylation step. The new orthoester is treated with more of the same alcohol in the presence of mercury(II) bromide or 2,6-lutidinium perchlorate. The usual solvents are nitromethane or chlorobenzene. Recent improvements include the use of molecular sieves in the synthesis of more complex orthoesters from simple ones.[9] The usual product is a 1,2-*trans*-glycoside, frequently produced in good yields. Exceptions to the expected steric outcome of the reaction have, however, been noted. Thus, in condensations of 3,4,6-tri-*O*-acetyl-1,2-*O*-(methoxyethylidene)-α-D-glucopyranose with benzyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside in nitromethane using mercury(II) bromide as promotor, the 3-*O*-α-D-glucopyranosyl-D-mannose derivative was formed in appreciable amounts, together with the expected corresponding β-linked disaccharide derivative.[10] Similar results were obtained by Kochetkov and co-workers who showed that treatment of 3,4,6-tri-*O*-acetyl-1,2-*O*-(methoxy-

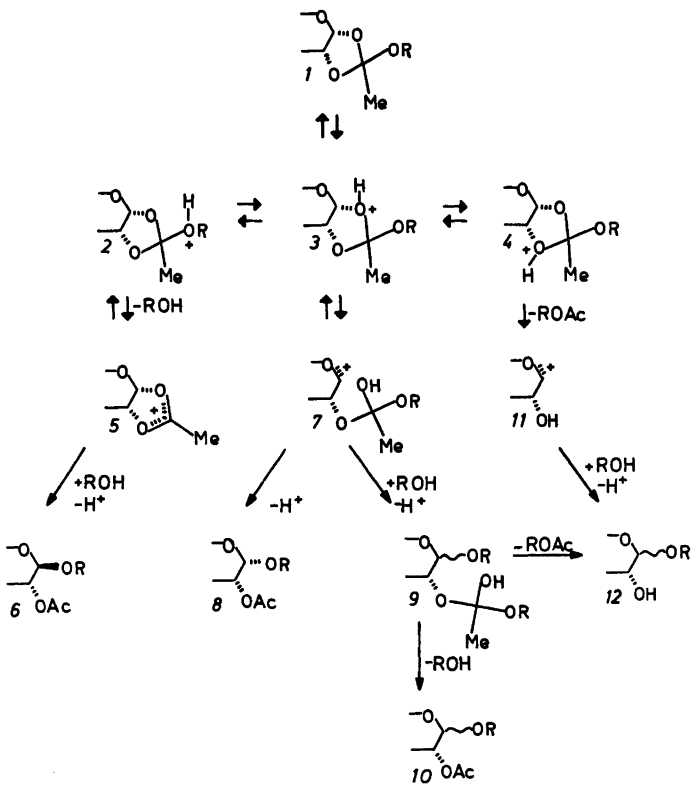


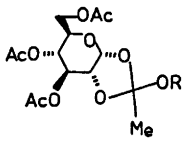
Fig. 2.

ethylidene)-α-D-glucopyranose or the corresponding orthoester of cyclohexanol with 2,6-lutidinium perchlorate in chlorobenzene containing the appropriate alcohol afforded 1,2-*cis*- as well as 1,2-*trans*-glycosides. The loss of acetyl in the 2-position was also observed.[11]

In the present paper, the variation in the proportion of *cis*-1,2- and *trans*-1,2-glycosides with the basicity of the alcohol used in the orthoester glycosylation procedure is discussed.

The various reactions which are possible in the orthoester glycosylation method are outlined in Fig. 2. For the sake of simplicity, the catalysis is represented as that of protonation. Depending on the site of the initial attack (by Lewis acid or proton) various products may be formed. The stable ion *5*, formed from *2*, with the positive charge on the alkoxyl oxygen, gives rise to the usual product, the 1,2-*trans*-glycoside. Attack at O-1 of the pyranose ring (*3*), however, may lead to the glycosyl cation (*7*) which reacts intramolecularly to give the *cis*-1,2-glycoside (*8*) or intermolecularly *via 9* to give an anomeric mixture of glycosides, retaining the acetyl as in 10 or with loss of acetyl at O-2 as in *12*. Attack at O-2 (4) would lead to the glycosyl cation *11* and, subsequently, to the anomeric mixture *12* with loss of acetyl at O-2.

The steric outcome of the orthoester glycosylation thus would seem to depend upon the initial site of Lewis acid attack or protonation. Varying the electron density at the alkoxyl oxygen in the orthoester starting material, *i.e.* the basicity of the alcohol ROH used in making the orthoester *1*, thus should influence the product distribution. In order to ascertain this, we have carried out glycosylations by the method described by Kochetkov and co-workers [4–7] using 2-chloro-, 2,2-dichloro- and 2,2,2-trichloroethanol as the alcohol component. The monochloro-, dichloro- and tri-



14, 15, 16

Fig. 3. 14: R = OCH_2CH_2Cl; *15*: R = OCH_2CHCl_2; *16:* R = OCH_2CCl_3.

chloro-orthoesters *14 – 16* (Fig. 3) were treated with 2 molar equivalents of the appropriate alcohol and 1/3 molar equivalent of mercury(II) bromide in refluxing nitromethane. The products were separated by chromatography and characterized. The composition of each reaction mixture was determined by GLC. Only traces of products other than the above pyranosides were observed. The following ratios of α:β glucopyranoside 2,3,4,6-tetraacetates were obtained: from the monochloroethyl orthoester *14* 16:84, from the dichloroethyl orthoester *15* 50:50 and from the trichloroethyl orthoester *16* 67:33. A clear correlation between the anomeric composition and the electron density at the oxygen atom of the alcohol to be glycosylated was thus established; for trichloroethanol, the α-D-glucoside predominates and for monochloroethanol, the β-D-glucoside. Ethanol yields the β-anomer exclusively.[5] The results indicate the need for careful consideration of the basicity of the free hydroxyl group in protected sugar moieties used in the synthesis of di- and oligosaccharides by the orthoester glycosylation procedure.

In the present work, products corresponding to glucosides deacetylated at O-2 (*13* in Fig. 2) were not observed. In studies where loss of acetyl from O-2 occurred, the reactions were proton catalyzed [1,11] and not Hg(II) catalyzed as in the present work.

EXPERIMENTAL

General methods. Melting points are corrected. Concentrations were performed at reduced pressure and a bath temperature below 40 °C. Optical rotations were recorded at room temperature (22 – 24 °C) using a Perkin-Elmer 141 instrument. NMR spectra were recorded on a JEOL JNM-PS-100 instrument. Analytical TLC was performed on precoated silica gel F_{254} plates (Merck). Sulfuric acid was used as spray reagent. Preparative separations were carried out on silica gel (particle size 0.040 – 0.063 mm) columns (Merck). GLC was performed on a Perkin-Elmer 900 instrument and an OV-225 column (silicone phase) at 250 °C. The relative molar response for anomeric pairs of glycosides were assumed to be 1:1. MS was performed on a Varian MAT-311-SS 111 MS-computer system. Spectra were recorded at 70 eV with an ionization current of 1000 mA and an ion source temperature of 135 °C. Mass spectra, recorded for all the compounds, gave the expected mass fragmentations.[12] Anomeric pairs gave identical fragmentation patterns, with the expected minor differences in peak intensities.

Preparation of orthoesters. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (4.11 g, 10 mmol) in nitromethane (10 ml) was treated with the appropriate chloroethanol (20 mmol) in the presence of 2,6-lutidine (2.33 ml, 20 mmol) at 37 °C for 20 h. Aqueous silver nitrate (7.5 ml 2 M), water (12.5 ml) and acetone (25 ml) were added with stirring. The mixture was filtered and the filtrate extracted with chloroform. The combined chloroform extracts were washed with water, dried over magnesium sulfate, filtered and concentrated. The crystals obtained were recrystallized from ethanol. *3,4,6-Tri*-O-*acetyl-1,2*-O-*(2'chloroethoxyethylidene*-α-D-*glucopyranose (14)* was obtained in a 69 % yield, m.p. 121.5 – 122.5 °C, $[\alpha]_D$ + 25° (*c* 1.0, $CHCl_3$). NMR ($CDCl_3$): δ 5.76 (d, H-1), 4.42 (dd, H-2), 5.20 (t, H-3), 4.92 (dd, H-4), 3.94 (m, H-5), 4.20 and 4.24 (H-6 and H-6'), 2.12 (s, OAc), 1.73 (s, CCH_3), 3.55 – 3.85 (CH_2CH_2). First-order coupling constants (Hz): $J_{1,2}$ 5, $J_{2,3}$ 3, $J_{3,4}$ 3, $J_{4,5}$ 9. *3,4,6-Tri*-O-*acetyl-1,2*-O-*(2',2'-dichloroethoxyethylidene)*-α-D-*glucopyranose* (*15*) was obtained in a 67 % yield, m.p. 110.5 – 111.5 °C, $[\alpha]_D$ + 23° (*c* 1.1, $CHCl_3$). NMR ($CDCl_3$): δ 5.75 (d, H-1), 4.39 (dd, H-2), 5.16 (t, H-3), 4.90 (dd, H-4), 3.92 (m, H-5), 4.17 and 4.21 (H-6 and H-6'), 2.09 (s, OAc), 1.75 (s, CCH_3), 5.70 (d, $CHCl_2$), 3.89 (d, $CHCl_2$-CH_2O). First-order coupling constants (Hz): $J_{1,2}$ 5, $J_{2,3}$ 3, $J_{3,4}$ 3, $J_{4,5}$ 10, $J_{H-1',H-2'}$ of Cl_2CHCH_2O 6. *3,4,6-Tri*-O-*acetyl-1,2*-O-*(2',2',2'-trichloroethoxyethylidene)*-α-D-*glucopyranose (16)* was obtained in a 54 % yield, m.p. 79 – 80 °C, $[\alpha]_D$ + 22° (*c* 1.0, $CHCl_3$). NMR ($CDCl_3$): δ 5.82 (d, H-1), 4.49 (dd, H-2), 5.20 (t, H-3), 4.93 (dd, H-4), 3.97 (m, H-5), 4.19 and 4.23 (H-6 and H-6'), 2.11 (s, OAc), 1.80 (s, CCH_3), 4.14 (s, Cl_3CCH_2O). First-order coupling constants (Hz): $J_{1,2}$ 5, $J_{2,3}$ 3, $J_{3,4}$ 3, $J_{4,5}$ 9.

Preparation of glycosides. The appropriate orthoester (3 mmol), mono-, di- or trichloroethanol (6 mmol) and mercury(II) bromide (1 mmol) in dry nitromethane (12 ml) was refluxed for 15 min. The reaction mixtures were examined by GLC. The glycosides were separated by chromatography on dimethyl sulfoxide impregnated silica gel using diethyl

ether saturated with dimethyl sulfoxide containing 4 % water as solvent.[13] The individual substances were obtained by freeze-drying fractions containing the same substance. Monochloroethyl glucosides were recrystallized from ethanol, the others from diethyl ether–light petroleum. *2'-Chloroethyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside* was obtained in a 7 % yield, m.p. 77–78 °C, $[\alpha]_D$ +86° (*c* 1.2, $CHCl_3$). NMR ($CDCl_3$): δ 5.15 (d, H-1), 4.87 (dd, H-2), 5.49 (t, H-3), 5.05 (t, H-4), 3.5–3.9 (m, H-5), 4.2 (m, H-6 and H-6'), 2.02, 2.04, and 2.10 (s, OAc), 3.5–3.9 (m, $ClCH_2CH_2O$). First-order coupling constants (Hz): $J_{1,2}$ 4, $J_{2,3}$ 10, $J_{3,4}$ 10, $J_{4,5}$ 9.5. *2'-Chloroethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside* was obtained in a 65 % yield, m.p. 118.5–119.5 °C, $[\alpha]_D$ −14° (*c* 1.1, $CHCl_3$) (Lit. values [14]m.p. 118.5–119.5 °C, $[\alpha]_D$ −13.7°). NMR ($CDCl_3$): δ 4.60 (d, H-1), 4.90–5.35 (m, H-2, H-3 and H-4), 4.0–4.4 (m, H-5, H-6 and H-6'), 2.02, 2.03, 2.06, 2.07 (s, OAc), 3.5–3.9 (m, $ClCH_2CH_2O$). First-order coupling constant (Hz): $J_{1,2}$ 8. MS: B_1 fragment – 60:[11] Found: m/e 248.0439 and 250.0420. Calc. for $C_{10}H_{13}{}^{35}ClO_5$: 248.0448, for $C_{10}H_{13}{}^{37}ClO_5$: 250.0418. In addition to the pure anomeric 2'-chloroethyl 2,3,4,6-tetra-*O*-acetyl-D-glucosides above, a 15 % yield of a mixed fraction was also obtained. *2',2'-Dichloroethyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside* was obtained in a 37 % yield, m.p. 86–87 °C, $[\alpha]_D$ +125° (*c* 1.2,$CHCl_3$). NMR ($CDCl_3$): δ 5.22 (d, H-1), 4.84 (dd, H-2), 5.47 (t, H-3), 5.04 (t, H-4), 3.9–4.3 (m, H-5, H-6 and H-6'), 2.05, 2.06, 2.10 (s, OAc), 3.9–4.3 (m, OCH_2CHCl_2), 5.84 (t, OCH_2CHCl_2). First-order coupling constants (Hz): $J_{1,2}$ 4, $J_{2,3}$ 10, $J_{3,4}$ 10, $J_{4,5}$ 9.5. MS: B_1 fragment – 60:[11] Found: *m/e* 282.0093, 284.0055. Calc. for $C_{10}H_{12}{}^{35}Cl_2O_5$: 282.0059, for $C_{10}H_{12}{}^{35}Cl^{37}ClO_5$: 284.0029. *2',2'-Dichloroethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside* was obtained in a 38 % yield, m.p. 135.5–136.5 °C, $[\alpha]_D$ −12° (*c* 1.1, $CHCl_3$). NMR ($CDCl_3$): δ 4.66 (d, H-1), 4.8–5.3 (m, H-2, H-3 and H-4), 3.73 (m, H-5), 3.9–4.3 (m, H-6 and H6-'), 2.00, 2.03, 2.05 and 2.09 (s, OAc), 3.9–4.3 (m, OCH_2CHCl_2), 5.70 (dd, OCH_2CHCl_2). First-order coupling constant (Hz): $J_{1,2}$ 8. In addition to the pure anomeric 2',2'-dichloroethyl 2,3,4,6-tetra-*O*-acetyl-D-glucosides above, an 8 % yield of a mixed fraction was also obtained. *2',2',2'-Trichloroethyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside* was obtained in a 58 % yield, m.p. 99–100 °C, $[\alpha]_D$ +136° (*c* 1.0, $CHCl_3$). NMR ($CDCl_3$): δ 5.41 (d, H-1), 4.87 (dd, H-2), 5.53 (t, H-3), 5.07 (t, H-4), 4.0–4.4 (m, H-5, H-6, H-6' and OCH_2CCl_3), 2.03, 2.05 and 2.08 (s, OAc). First-order coupling constants (Hz): $J_{1,2}$ 4, $J_{2,3}$ 9.5, $J_{3,4}$ 9.5, $J_{4,5}$ 9.5. MS: B_1 fragment – 60:[11] Found: *m/e* 315.9716, 317.9703. Calc. for $C_{10}H_{11}{}^{35}Cl_3O_5$: 315.9670, for $C_{10}H_{11}{}^{35}Cl_2{}^{37}ClO_5$: 317.9640. *2',2',2'-Trichloroethyl 2,3,4,6-tri-O-acetyl-β-D-glucopyranoside* was obtained in a 17 % yield, m.p. 143–144 °C, $[\alpha]_D$ −24° (*c* 0.8, $CHCl_3$). NMR ($CDCl_3$): δ 4.84 (d, H-1), 4.9–5.3 (m, H-2, H-3 and H-4), 3.74 (m, H-5), 4.0–4.5 (m, H-6, H-6' and OCH_2CCl_3), 2.01, 2.04, 2.06 and 2.10 (s, OAc). $J_{1,2}$ 7 Hz. In addition to the pure anomeric 2',2',2'-trichloroethyl 2,3,4,6-tetra-*O*-acetyl-D-glucosides above, a 3 % yield of a mixed fraction was also obtained.

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REFERENCES

1. Perlin, A.S. *Can. J. Chem. 41* (1963) 555.
2. Lemieux, R. U. and Morgan, A. R. *IUPAC Symposium on the Chemistry of Natural Products, Kyoto, Japan.* April 12–18 1964.
3. Lemieux, R. U. and Morgan, A. R. *Can. J. Chem. 43* (1965) 2199.
4. Kochetkov, N. K., Khorlin, A. J. and Bochkov, A. F. *Dokl. Akad. Nauk SSSR 161* (1965) 1342.
5. Kochetkov, N. K., Khorlin, A. J. and Bochkov, A. F. *Tetrahedron 23* (1967) 693.
6. Kochetkov, N. K. and Bochkov, A. R. In Bognár, R., Bruckner, V. and Szántay, Cs. *Recent Developments in the Chemistry of Natural Carbon Compounds*, Akadémiai Kiadó, Budapest 1971, Vol. IV.
7. Kochetkov, N. K. and Bochkov, A. F. *Methods Carbohydr. Chem. 6* (1972) 480.
8. Wulff, G. and Röhle, G. *Angew. Chem. 86* (1974) 173.
9. Bochkov, A. F., Voznyi, Ya. V., Chernetsky, V. N., Dashunyun, V. M. and Rodyonov, A. V. *Izv. Akad. Nauk SSSR,Ser. Khim.* (1975) 420.
10. Alfredsson, G., Borén, H. B. and Garegg, P. J. *Acta Chem. Scand. 26* (1972) 2531, 3431.
11. Bochkov, A. F., Betaneli, V. I. and Kochetkov, N. K. *Carbohydr. Res. 30* (1973) 418: *Bull. Acad. Sci. USSR Chem. Sci 23* (1974) 1299.
12. Kochetkov, N. K. and Chizhov, O. S. *Adv. Carbohydr. Chem. 21* (1968) 39.
13. Wickberg, B. *Methods Carbohydr. Chem. 1* (1962) 31.
14. Jackson, E. L. *J. Am. Chem. Soc. 60* (1938) 722.

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