ACYL MIGRATIONS IN THE SYNTHESIS OF ETHYL 4-*O*-METHYL-β-D-GLUCOPYRANOSIDE

R. M. ROWELL

Forest Products Laboratory, Forest Service, U.S. Department of Agriculture, Madison, Wisconsin 53705 (U. S. A.)*

(Received March 6th, 1972; accepted in revised form April 3rd, 1972)

ABSTRACT

During the methylation of ethyl 2,3,4,-tri-*O*-acetyl-β-D-glucopyranoside with methyl iodide and silver oxide in *N*,*N*-dimethylformamide, an O-4→O-6 acyl migration occurs to give ethyl 2,3,6-tri-*O*-acetyl-4-*O*-methyl-β-D-glucopyranoside; a concomitant O-3→O-4 migration gives rise to a 3-*O*-methyl derivative.

INTRODUCTION

Ethyl 4-*O*-methyl-β-D-glucopyranoside has been synthesized, as a simple model system to represent a single, inner D-glucopyranose unit in a cellulose molecule, as part of an investigation of the mechanism of the alkaline cleavage of internal glycosidic bonds in cellulose. It was necessary for the model compound to be substituted at O-4, have a β-glycosidic bond, and have dissimilar groups at C-1 and C-4 to permit distinction between the points of elimination when the molecule is degraded in an alkaline medium.

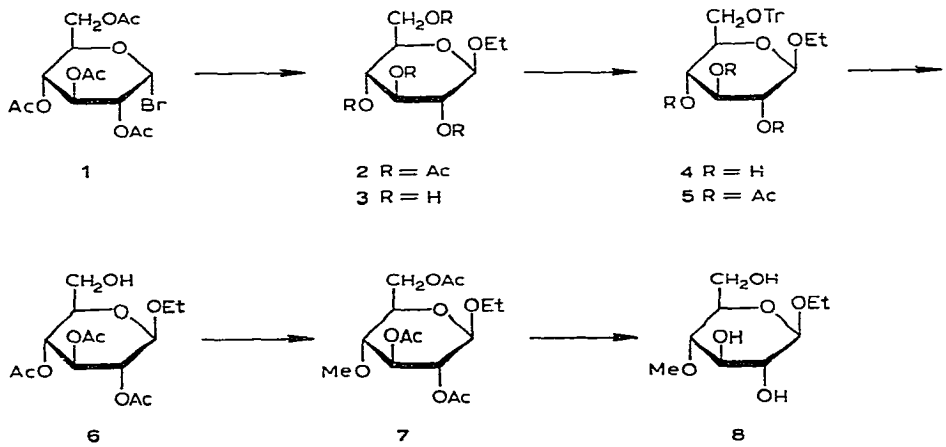
The starting material was 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[1] **1**, which was converted into the ethyl β-glucoside **2** by the Koenigs–Knorr reaction. Helferich and Wedemeyer[2] prepared compound **2**, but reported a yield of only 48%. The product is sparingly soluble in ethyl alcohol, and crystallized from the reaction solution. Filtration through Celite to remove the silver oxide and calcium sulfate also removed about half of the crystalline product, but washing the filter pad with acetone allowed isolation of **2** in a yield of 88%.

Deacetylating **2** with sodium ethoxide gave the syrupy glycoside **3**, which crystallized as a hygroscopic solid after several days in the cold.

Tritylating **3** with chlorotriphenylmethane in refluxing pyridine, followed by acetylation, gave ethyl 2,3,4-tri-*O*-acetyl-6-*O*-trityl-β-D-glucopyranoside (**5**). The tritylation reaction did not go to completion, and it was necessary to isolate the 6-*O*-

*The Laboratory is maintained at Madison, Wisconsin, in cooperation with the University of Wisconsin.

trityl intermediate **4** before acetylation, because the unreacted **3** on acetylation gave **2**, which hindered the crystallization of **5**. T.l.c. in ethyl acetate–hexane (1:1, *v/v*) of the reaction mixture from **5**, after treatment with hydrogen bromide in acetic acid, showed minor products having R_F 0.92, 0.79, 0.61, 0.38, and a major product having 0.28. The spots having R_F 0.92, 0.79, and 0.61 were bromotriphenylmethane, unreacted starting material **5**, and **2**, respectively. The compounds having R_F 0.38 and 0.28 gave correct carbon and hydrogen analyses for a triacetate, and deacetylation of each gave **3**. Retritylation of a mixture of the R_F 0.28 and 0.38 components showed that the R_F 0.28 component decreased as that having R_F 0.79 (**5**) increased, and the R_F 0.38 component did not seem to react. These data show that the major product (R_F 0.28) was ethyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranoside (**6**), and that the minor triacetate (R_F 0.38) was ethyl 2,3,6-tri-*O*-acetyl-β-D-glucopyranoside, indicating some acetyl migration from O-4 to O-6.



Bouveng, Lindberg, and Theander[3] prepared methyl 4-*O*-methyl-β-D-glucopyranoside by methylating methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranoside, with subsequent deacetylation. In this reaction, an acetyl group migrates from O-4 to O-6. Under similar reaction conditions, **6** was converted into ethyl 2,3,6-tri-*O*-acetyl-4-*O*-methyl-β-D-glucopyranoside (**7**, R_F 0.57), and another monomethyl triacetate (R_F 0.46) was also produced (approximately 10%). Deacetylating **7** with sodium ethoxide in ethanol gave crystalline ethyl 4-*O*-methyl-β-D-glucopyranoside **8**.

Proof of the position of the methoxyl group was provided by examining the trimethylsilyl ethers prepared from **8** after hydrolysis with dilute hydrochloric acid. By the technique* of Dick, Baker, and Hodge[4], the two mono-*O*-methylglucose trimethylsilyl ethers were compared with standards of 2-*O*-, 3-*O*-, 4-*O*-, and 6-*O*-methylglucose trimethylsilyl ethers (Table I).

*Work done in the laboratories of the Northern Utilization Research and Development Division, Agricultural Research Service, USDA, Peoria, Illinois, with the cooperation of W. E. Dick and J. E. Hodge.

As seen in Table I, the major mono-O-methyl triacetate was the 4-*O*-methyl derivative (7); however, the minor monomethyl triacetate was the 3-*O*-methyl derivative, and not the expected 6-*O*-methyl derivative. During the methylation of **6** with silver oxide and methyl iodide in *N*,*N*-dimethylformamide, an acetyl migration must have taken place.

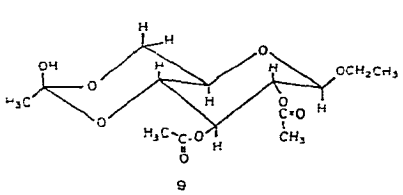
TABLE I

G.L.C. OF TRIMETHYLSILYL ETHERS OF MONO-*O*-METHYL-D-GLUCOSE[a]

Sample (*before trimethylsilylation*)	*Relative retention times*[b]
3-*O*-Methyl-α-D-glucose	1.0
4-*O*-Methyl-α-D-glucose	1.2
α-D-Glucose	1.3
2-*O*-Methyl-α-D-glucose	1.4
3-*O*-Methyl-β-D-glucose	1.6
2-*O*-Methyl-β-D-glucose	1.9
6-*O*-Methyl-α-D-glucose	2.0
4-*O*-Methyl-β-D-glucose	2.1
β-D-Glucose	2.3
6-*O*-Methyl-β-D-glucose	2.4
Sample A[c]	1.2, 2.1
Sample B[d]	1.0, 1.6

[a]Column of 19.5% Carbowax 20M on Chromosorb W at 150°. [b]All values are given relative to 3-*O*-methyl-α-D-glucose. [c]From deacetylation, hydrolysis, and trimethyl silylation of the major triacetate **7** having R_F 0.57. [d]From deacetylation, hydrolysis, and silylation of the minor triacetate having R_F 0.46.

Acyl migrations were first reported in 1920 by Fischer[5] in acylated esters of glycerol. These migrations were first observed in the carbohydrate series by Ohle[6], who converted 3-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose into the 6-*O*-benzoyl isomer under the influence of mild alkali. Several brief reviews on migration have been written[7–9]. The most commonly reported reaction is a 4→6 acetyl migration in the glucopyranose series[3,9–17], presumably through a strainless, cyclic, ortho ester[5,18–19] **9**. Under similar conditions, an O-benzoyl group did not migrate from



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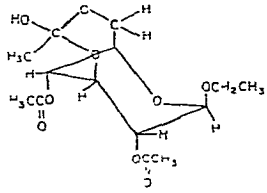

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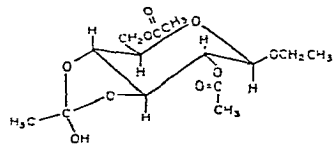

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O-4 to O-6 on methylation[20]. It is also interesting that Haworth, Hirst, and Teece[21] treated methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside with methyl iodide and silver

oxide, and isolated not the 4-*O*-methyl derivative, as did Bouveng *et al.*[3], but the 2-*O*-methyl derivative. Their results show that these acyl migrations are not always predictable.

Doerschuk[22] showed that acyl migration is intramolecular and not intermolecular; rearrangement of 2-monopalmitin in alkali in the presence of glycerol-*1*-^{14}C, gave 1-monopalmitin containing no ^{14}C. His results show that mechanisms involved with hydrolysis and re-esterification are not important in the migration reaction.

Another acyl migration common in the D-glucose series is a 3→6 migration in 3-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose[23–26]. In this reaction, the intermediate, cyclic, ortho ester is a seven-membered ring; the benzoyl group is also known to migrate[25–27]. If O-6 is blocked in the 3-*O*-acetyl derivative, migration proceeds from O-3 to O-5. Thus, methylation of 3-*O*-acetyl-1,2-*O*-isopropylidene-6-*O*-trityl-α-D-glucofuranose gives 5-*O*-acetyl-1,2-*O*-isopropylidene-3-*O*-methyl-6-*O*-trityl-α-D-glucofuranose[28].

Other migrations have been reported in the D-glucose series. Arita and Matsushima[17] treated 2,3,2′,3′,4′-penta-*O*-acetyl-1,6-anhydro-β-maltose with methyl iodide and silver oxide, and isolated 2′-, 3′-, and 4′-monomethyl ethers in the ratio of 2:1:4. The migrations were 2′→6′, 3′→6′, and 4′→6′, respectively. Helferich and Klein[29] methylated (silver oxide and methyl iodide) 1,2,3,6-tetra-*O*-acetyl-β-D-glucopyranose and obtained methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside by 1→4 migration. Haworth, Hirst, and Teece[30] explained the formation of methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside from 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose as an involvement of a cyclic ortho ester with the hydroxyl groups at C-1 and C-6.

Migration of acyl groups between hydroxyl groups on contiguous carbon atoms has also been observed in the D-glucose series. Bonner[9] found that 1,3,4,6-tetra-*O*-acetyl-α- or β-D-glucopyranose gave methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside, by 1→2 migration, on Purdie methylation. Bourne, Huggard, and Tatlow[31] observed 2→3 benzoyl group migration in the preparation of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside from methyl 2-*O*-benzoyl-4,6-*O*-benzylidene α-D-glucopyranoside. Finally, Wood and Fletcher[32] observed 1→2 migration of a mesitoyl group on deacetylation of 2,3,4,6-tetra-*O*-acetyl-1-*O*-mesitoyl-α-D-glucopyranose with ammonia in cold methanol. In these migrations between adjacent hydroxyl groups, the cyclic ortho ester must form a five-membered ring.

Migrations under alkaline conditions usually proceed away from the reducing end, although Garegg[33] observed, on methylating benzyl 3-*O*-acetyl-4-*O*-methyl-β-D-xylopyranoside with silver oxide and methyl iodide in *N,N*-dimethylformamide, that the major product (65%) was the 2,4-dimethyl ether no migration) together with a lower yield (35%) of the 3,4-dimethyl ethers, which must have arisen by 3→2 acetyl migration.

Garegg[33] also studied the effects of each of the components in the methylating system. With silver oxide and methyl iodide in *N,N*-dimethylformamide at room temperature, he observed migration and methylation. With silver oxide in *N,N*-dimethylformamide at room temperature, some migration occurred, but no deacetyla-

tion. With *N,N*-dimethylformamide alone at 100°, no migration or deacetylation was observed.

In the present investigation, the major acetyl migration is from O-4 to O-6. With the D-glucopyranoside in the *C1*(D) conformation, the six-membered, cyclic ortho ester (**9**) can form readily and have both rings in stable chair forms.

The 3-methyl ether could arise by 3→6 acetyl migration, a process sterically possible if the D-glucose ring adopts the *1C*(D) conformation with the formation of a seven-membered, cyclic ortho ester (**10**).

It is possible that this migration is not a simple, single-step reaction, but proceeds by two successive migrations[10] toward C-6. The first step might be a 4→6 migration, followed by a 3→4 migration. It is also possible that the first ortho ester may undergo displacement with formation of the second ester.

In the favored *C1* conformation of D-glucopyranose, all of the contiguous, secondary hydroxyl groups are equatorial. Five-membered, cyclic ortho esters can be formed between adjacent hydroxyl groups having an equatorial–equatorial or an axial–equatorial disposition without major bond distortion (Formula **11**). In the D-glucopyranose series there is thus no steric restriction to migration of acyl groups; this factor may explain why many researchers have isolated different products under a variety of reaction conditions. It is also possible that some of the migrations earlier described, such as 1→6, 2→6, and 1→4 in the pyranose ring, and 3→6 in the furanose ring, actually are the result of a series of adjacent migrations toward carbon 6; namely 1→2, 2→3, 3→4, and 4→6.

In work of this type, minor isomers are no doubt formed. Other monomethyl or dimethyl ethers or products of acetyl or benzoyl migration may also be formed, but they are probably separated as contaminant, and are seldom characterized or reported.

EXPERIMENTAL

Analytical methods. — Purity of crystalline products was determined by t.l.c. at 24° on silica gel H-coated glass plates irrigated with (*A*) ethyl acetate–hexane (1:1 v/v) or (*B*) chloroform–ethanol (4:1 *v/v*). Components were located by spraying with 10% sulfuric acid in ethanol, and heating. Chromatographic separations were performed in columns (2.5 × 50 cm) packed with Mallinckrodt* SilicAR cc-4 (100–200 mesh) and were developed in one of the two solvent systems noted. All melting points are corrected values.

Ethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**2**). — Abs. ethyl alcohol (200 ml), silver oxide (12 g), and anhydrous calcium sulfate (35 g) were added to 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (20 g). The mixture was stirred for 18 h at 25°, and then filtered through a Celite pad. The filtrate was concentrated

*Mention of specific instruments or trade names is made for identification purposes only, and does not imply endorsement by the USDA.

to a thick syrup that crystallized from ethanol in the cold to give 6.2 g. of product. The Celite filter pad was washed with acetone (200 ml), and evaporation of the acetone gave a further 9.8 g; combined yield, 16 g (87.9%), m.p. 106–107°, lit.[2] m.p. 105–107° R_F, solvent *A*, 0.61 ±0.04.

Ethyl β-D-glucopyranoside (**3**). — A small piece of metallic sodium was added to **2** (30 g) in abs. ethanol (200 ml). The solution was kept overnight at 25° and then passed through an ethanol-washed column (4 × 15 cm resin bed) of Bio-Rad AG 50W-X8 (H^+ form, 20–50 mesh). Concentration of the effluent gave a thick, clear syrup; yield 16.8 g (82.1%) that crystallized in the cold, after several days, to a hygroscopic solid; R_F (solvent *A*) 0.0; R_F (solvent *B*) 0.28 ±0.02.

Ethyl 6-O-trityl-β-D-glucopyranoside (**4**). — Chlorotriphenylmethane (8 g) in dry pyridine (100 ml) was added to **3** (6 g). The solution was refluxed for 2.5 h, cooled, and stirred with ice–water (4 liters). The resulting fine white precipitate was filtered off, washed with water, and air-dried; yield, 9.4 g (72.3%); R_F (solvent *A*) 0.087 ±0.005.

Ethyl 2,3,4-tri-O-acetyl-6-O-trityl-β-D-glucopyranoside (**5**). — Compound **4** (10 g) and then acetic anhydride (75 ml) was added to dry pyridine (100 ml). The mixture was kept for 2.5 h at 25° and then poured, with stirring, into ice–water (4 liters). The fine white precipitate that formed was filtered off, washed, and air-dried. Crystallization from ethanol gave 11.1 g of **5**. Recrystallization from hot ethanol gave 10.6 g (82.8%), m.p. 156°; $[\alpha]_D^{20}$ +23.8° (*c* 0.67, chloroform); R_F (solvent *A*) 0.79 ±0.04.

Anal. Calc. for $C_{33}H_{36}O_9$: C, 68.74; H, 6.29. Found: C, 68.69, H, 6.16.

Ethyl 2,3,4-tri-O-acetyl-β-D-glucopyranoside (**6**). — Compound **5** (8.3 g, 14.4 mmoles) was added to glacial acetic acid (35 ml), and dissolved by gentle warming. After cooling to 25°, 48% hydrogen bromide (4 ml) in acetic acid was added with stirring. After stirring for 30 sec, the precipitated bromotriphenylmethane was filtered off, and the filter pad was washed with acetic acid (10 ml). The filtrate was poured quickly onto crushed ice and sodium hydrogen carbonate (500 ml). When evolution of carbon dioxide ceased and the solution was neutral, water (250 ml) was added, and the solution was extracted 2 times with 100-ml portions of chloroform. The extract was dried over sodium sulfate, and concentrated to a solid mass. T.l.c. showed five spots. The major spot was **6**, R_F 0.28 ±0.03 (solvent *A*), with minor ones having R_F 0.38 ±0.3, 0.61 ±0.04, 0.79 ±0.04, and 0.92 ±0.02. The solid mass was dissolved in the minimum volume of chloroform, and added to the top of a column previously described. Elution with solvent *A*, followed by combination and concentration of the pure fractions, gave 2.8 g of **6**, which on recrystallization from hot ethanol had m.p. 137–138°, $[\alpha]_D^{20}$ −27.1° (*c* 1.7, chloroform); R_F (solvent *A*) 0.28 ±0.03.

Anal. Calc. for $C_{14}H_{22}O_9$: C, 50.29; H, 6.63. Found: C, 50.23; H, 6.66.

Ethyl 2,3,6-tri-O-acetyl-4-O-methyl-β-D-glucopyranoside (**7**). — Methyl iodide (15 ml) and silver oxide (10 g) were added to **6** (4 g) in *N*,*N*-dimethylformamide (50 ml). The mixture was stirred for 6 h at 25°, and then filtered through a Celite pad. The filtrate was diluted to 300 ml with *n*-butyl alcohol, and then concentrated at 60°,

to give a thin, light-yellow syrup. The syrup was dissolved in a small volume of chloroform, and applied to a column as described previously. Elution with solvent *A*, followed by combination and concentration of the pure fractions, gave 1.6 g of **7** which, on recrystallization from hot ethanol had m.p. 69–70°; $[\alpha]_D^{20}$ −39.4° (*c* 1.85, chloroform); R_F, (solvent *A*), 0.57 ±0.04. This product was used to prepare the sample A described in Table I.

Anal. Calc. for $C_{15}H_{24}O_9$: C, 51.72; H, 6.94. Found: C, 51.59; H, 6.89.

*Ethyl 2,4,6-Tri-*O*-acetyl-3-*O*-methyl-β-*D*-glucopyranoside.* — From the previous column separation there was obtained another crystalline fraction (200 mg), which on recrystallization from ethanol had m.p. 98°, $[\alpha]_D^{20}$ −41.6° (*c* 0.75, chloroform); R_F (solvent *A*) 0.46±0.04. This product was used to prepare Sample B (Table I).

Anal. Calc. for $C_{15}H_{24}O_9$: C, 51.72; H, 6.94. Found: C, 51.80; H, 6.94.

*Ethyl 4-*O*-methyl-β-*D*-glucopyranoside* (**8**). — Compound **7** (2 g) was dissolved in 2M sodium ethoxide (50 ml) in abs. ethanol and kept for 18 h at 25°. The solution was neutralized with cation-exchange resin, as described previously, and concentrated to a solid mass. Two minor compounds, R_F 0.76 ±0.02 and 0.94 ±0.04 (solvent *B*), interfered with the crystallization, and therefore the syrup was dissolved in a small volume of ethanol and purified by column chromatography in solvent *B*, as previously described. Combination and concentration of the pure fraction, followed by recrystallization from hot ethyl acetate, gave 0.9 g (70%) of **8**; m.p. 133°, $[\alpha]_D^{20}$ −29.2° (*c* 0.65 water); R_F (solvent *B*) 0.48 ±0.04.

Anal. Calc. for $C_9H_{18}O_6$: C, 48.64; H, 8.16. Found: C, 48.37; H, 8.19. OCH_3, 13.95; Found, 14.00. OCH_2CH_3, 20.25; Found, 20.32.

*Hydrolysis of ethyl mono-*O*-methyl-β-*D*-glucopyranosides.* — Compound **8** (50 mg), or the deacetylated 3-methyl ether (50 mg), was added to 2M HCl (50 ml), and the solution was heated in sealed glass tubes for 12 h at 95°. After cooling, the solution was concentrated to a light-yellow syrup. Water (5 ml) was added, and the solution was again concentrated. This procedure was repeated three times, followed by final concentration with ethanol–benzene (4:1, *v/v*). The mono-*O*-methyl-D-glucoses each had R_F in solvent *B* of 0.19 ±0.03.

G.l.c. analysis. — Trimethylsilyl ethers of the foregoing mono-*O*-methyl-D-glucoses were analyzed by g.l.c. on a column (1/8 in. × 12 ft) of 19.5% Carbowax 20*M* on Chromosorb W (80-100 mesh) at 150°. The results are given in Table I.

REFERENCES

1 M. Bárczai-Martos and F. Kőrösy, *Nature*, 165 (1950) 369.
2 B. Helferich and K. F. Wedemeyer, *Ber.*, 83B (1950) 538.
3 H. O. Bouveng, B. Lindberg, and O. Theander, *Acta Chem. Scand.*, 11 (1957) 1788.
4 W. E. Dick, B. G. Baker, and J. E. Hodge, *Carbohyd. Res.*, 6 (1968) 52.
5 E. Fischer, *Ber.*, 53B (1920) 1621.
6 H. Ohle, *Ber.*, 57B (1924) 403.
7 E. L. Hirst and S. Peat, *Ann. Rep. Progr. Chem. (Chem. Soc., London)*, 31 (1934) 172.
8 J. M. Sugihara, *Advan. Carbohyd. Chem.*, 8 (1953) 1.
9 W. A. Bonner, *J. Org. Chem.*, 24 (1959) 1388.
10 G. J. Robertson, *J. Chem. Soc.*, (1933) 737.

11 B. HELFERICH, *Ann.*, 453 (1927) 111.
12 B. HELFERICH AND A. MÜLLER, *Ber.*, 63B (1930) 2142.
13 B. HELFERICH AND H. BREDERECK, *Ber.*, 64B (1931) 2411.
14 B. HELFERICH, H. BREDERECK, AND A. SCHNEIDMÜLLER, *Ann.*, 458 (1927) 111.
15 B. HELFERICH AND H. BREDERECK, *Ann.*, 458 (1927) 111.
16 HELFERICH AND W. KLEIN, *Ann.*, 450 (1926) 219.
17 H. ARITA AND Y. MATSUSHIMA, *J. Biochem.* (Tokyo), 68 (1970) 717.
18 E. PACSU, *Advan. Carbohyd. Chem.*, 1 (1945) 77.
19 H. S. ISBELL AND H. L. FRUSH, *J. Res. Nat. Bur. Stand.*, 43 (1949) 161.
20 B. HELFERICH AND E. GÜNTHER, *Ber.*, 64B (1931) 1276.
21 W. N. HAWORTH, E. L. HIRST, AND E. G. TEECE, *J. Chem. Soc.*, (1931) 2858.
22 A. P. DOERSCHUK, *J. Amer. Chem. Soc.*, 74 (1952) 4202.
23 K. JOSEPHSON, *Ber.*, 62B (1929) 1913; 63 (1930) 3089.
24 K. JOSEPHSON, *Svensk. Kem. Tidskr.*, 41 (1929) 99.
25 K. JOSEPHSON, *Ann.*, 472 (1929) 217.
26 H. OHLE, E. EULER, AND R. LICHENSTEIN, *Ber.*, 62B (1929) 2885.
27 H. OHLE AND E. DICKHAÜSER, *Ber.*, 58B (1925) 2593.
28 L. VON VARGHA, *Ber.*, 67B (1934) 1223.
29 B. HELFERICH AND W. KLEIN, *Ann.*, 455 (1927) 173.
30 W. N. HAWORTH, E. L. HIRST, AND E. G. TEECE, *J. Chem. Soc.*, (1930) 1405.
31 E. J. BOURNE, A. J. HUGGARD, AND J. C. TATLOW, *J. Chem. Soc.*, (1953) 735.
32 H. B. WOOD, JR. AND H. G. FLETCHER, JR., *J. Amer. Chem. Soc.*, 78 (1956) 2849.
33 P. J. GAREGG, *Acta Chem. Scand.*, 16 (1962) 1849.

Carbohyd. Res., 23 (1972) 417–424