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THE PREPARATION AND STUDY OF SOME NOVEL GLYCOSIDES OF D-GALACTOSE*

PRABHAKAR A. RISBOOD, LAWRENCE A. REED, III, AND LEON GOODMAN†
Department of Chemistry, University of Rhode Island, Kingston, Rhode Island 02881 (U.S.A.)
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ABSTRACT

The *tert*-butyl- and the 2,2,2-trichloroethyl α- and β-D-galactopyranosides were prepared and both α-D-glycosides were selectively benzoylated to give the 2,3,6-tri-*O*-benzoyl-D-galactopyranosides. Cleaving of the glycosidic groups is described. The glycosides are useful intermediates for oligosaccharide synthesis where generation of a reducing sugar terminus under mild conditions is necessary.

INTRODUCTION

As part of a program to synthesize potential enzyme inducers, we were concerned with the preparation of certain thiodisaccharides. The only literature reports of such compounds that contain a reducing sugar are those of Hutson[1], who prepared thiogentiobiose, and of Boos *et al.*[2], who prepared the D-galactopyranosyl analog of gentiobiose. Recently, a number of methyl glycosides of related thiodisaccharides have been reported[3]. In the final step of Hutson's synthesis[1], conversion of the methyl glycoside to the free thiogentiobiose gave a low yield (28%) as a result of extensive cleavage of the intersugar linkage; sulfuric acid-catalyzed acetolysis completely cleaved that linkage. Accordingly, we thought it would be of interest to investigate more labile glycosides as blocking groups for the reducing sugar termini.

RESULTS AND DISCUSSION

The *tert*-butyl- and 2,2,2-trichloroethyl groups appeared to be removable under conditions compatible with the stability of the intersugar bonds. Our contemplated route required D-galactopyranose sugars as the ultimate source of the reducing end of some of the thiodisaccharides, and so a study of the preparation of these two glycosides of D-galactose, heretofore unreported, was initiated. As a source of the α-D anomers of the two glycosides, 3,4,6-tri-*O*-acetyl-β-D-galactopyranosyl chloride[4]

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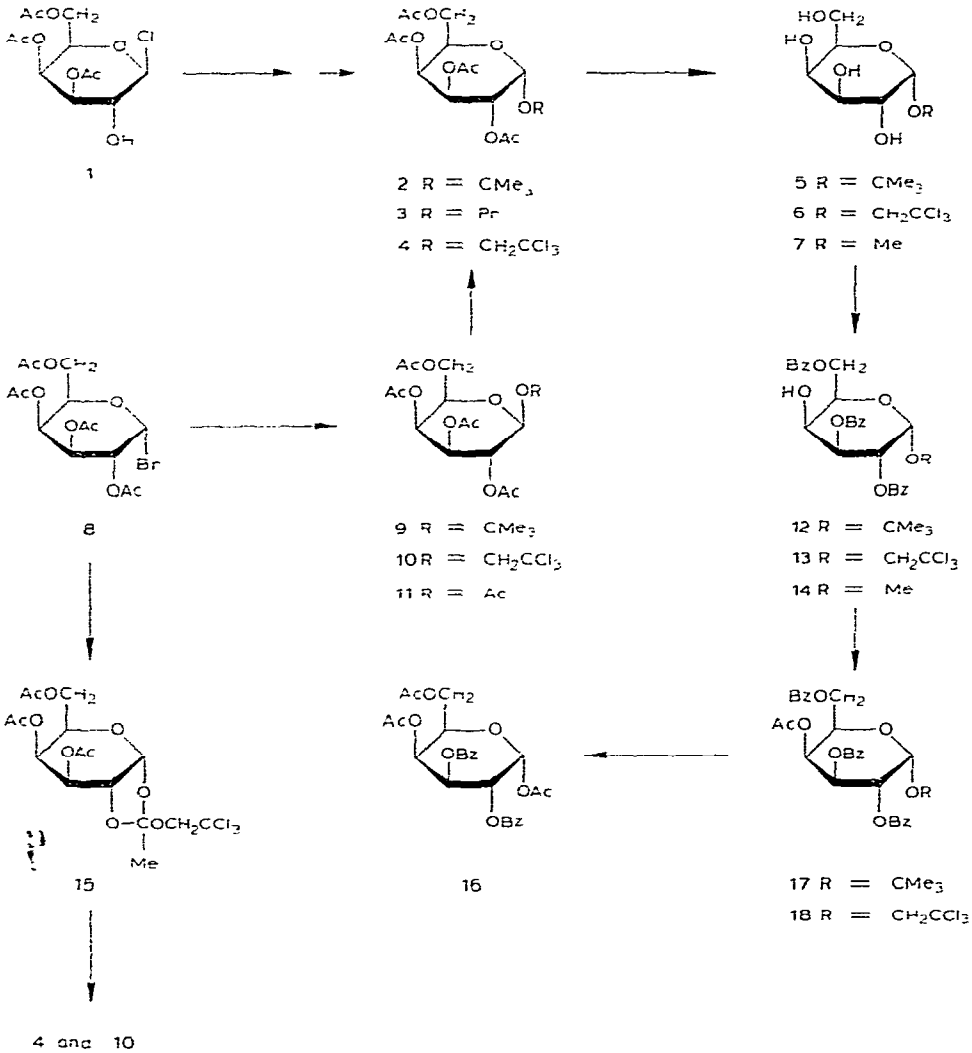
†To whom reprint requests should be addressed.

(**1**) was prepared and utilized according to the procedure described for the preparation of some α-D-glucopyranosides[5]. Good yields of the *tert*-butyl **2** (after acetylation of the intermediate) and of the propyl glycoside (**3**) could be obtained, but attempts to prepare **4** led to an intractable mixture that showed no evidence for glycoside formation. In any event, the preparation of **1** in sufficient purity for glycosidation was



difficult and gave low yields. In the presence of mercuric succinate, 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**8**) gave a fair yield of the *tert*-butyl β-D-glycoside **9** in a reaction similar to that described by Lindberg[6] for the analogous D-glucoside and, in the presence of silver carbonate, gave a low yield of the 2,2,2-trichloroethyl glycoside **10**. Following the procedure described by Garegg and Kwarnström[7] for the D-glucose compounds, we converted **8** to the orthoester **15** and rearranged it with

mercuric bromide to give, after chromatographic separation, a fair yield of the mixture of anomers **4** and **10** (2.42:1), in excellent agreement with the ratio found in the D-glucose series.

By far the most convenient preparation of the desired glycosides utilized β-D-galactose pentaacetate (**11**) with the appropriate alcohols in the presence of boron fluoride etherate in a reaction patterned after that of Prystaš *et al.*[8], for the preparation of 2,2,2-trichloroethyl 2,3,5-tri-*O*-acetyl-β-D-ribofuranoside. Thus, the reaction of **11** with trichloroethanol for 12 h gave a 90% yield of the β-D anomer (**10**) while reaction for 60 h caused such substantial anomerization that the α-D anomer (**4**) could be directly crystallized from the α,β mixture in 41% yield. The *tert*-butyl glycoside **2** was the direct product of the reaction of **11** and *tert*-butyl alcohol in the presence of the Lewis acid; the β-D anomer **9** was present after the separation of **2**, and it can be assumed that substantial β to α anomerization occurred during the reaction; the method suffers from a slow cleavage of the *tert*-butyl group during the reaction. The pure β-D anomer **9** could be isomerized to the α-D anomer (**2**) in 80% yield by use of boron fluoride under conditions similar to those used previously by Lindberg[9] in the β-to-α anomerization of the *tert*-butyl D-glucopyranosides. *O*-Deacylation with sodium methoxide yielded the deblocked glycosides **5** and **6**.

To explore further the utility of glycosides **5** and **6** for our projected syntheses, they were subjected to the conditions of selective benzoylation that had given good yields[10] of methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside (**14**) from **7**. Useful yields of the tri-*O*-benzoyl derivatives (**12** and **13**, respectively) were obtained; the reactions were run on a small scale and have not been optimized. To verify the positions of the benzoyl groups and to investigate the conditions required to cleave the glycoside groups, **12** and **13** were converted into product **16** that was also obtained from the known glycoside **14**. Thus, after acetylation to **17**, the *tert*-butyl glycoside **12** was treated with 90% aqueous trifluoroacetic acid, then acetylated to give a good yield of the α-D diacetate **16**, as shown by its n.m.r. spectrum. The trichloroethyl glycoside **13**, after acetylation to **18**, was treated with zinc in hot acetic anhydride to give a high yield of **16**. Conventional acetolysis[11] of the methyl glycoside[10] (**14**) furnished an authentic sample of **16**, thus verifying the positions of the benzoyl groups in **12** and **13** at O-2, -3, and -6.

EXPERIMENTAL

General methods. — Organic solutions were dried over magnesium sulfate and were evaporated *in vacuo*, generally <40°. N.m.r. spectra were recorded at 60 MHz with a Varian EM-360 spectrometer usually for solutions in chloroform-*d* with tetramethylsilane as internal standard. Optical rotations were measured at ambient temperature (20–22°), for solutions in chloroform, unless otherwise noted, with a Perkin–Elmer Model 141 automatic polarimeter. I.r. spectra were recorded with a Beckman Aculab 4 spectrometer for chloroform or carbon tetrachloride solutions. Column chromatography employed SilicAR CC-7 (Mallinckrodt) silica gel at

atmospheric pressure and t.l.c. was performed on Brinkmann Polygram Sil G/UV_{254} plates with u.v. light or sulfuric acid spray for detection and solvent systems of ethyl acetate–hexane varying from 20 to 50% of ethyl acetate. Melting points were determined on a Mel-Temp apparatus and are uncorrected.

*Propyl 2,3,4,6-tetra-*O*-acetyl-α-*D*-galactopyranoside* (**3**). — A mixture of 3,4,6-tri-*O*-acetyl-β-D-galactopyranosyl chloride[4] (**1**; 0.13 g, 0.04 mmol) purified by silica gel chromatography, 1-propanol (0.20 g, 3.3 mmol), dry mercuric succinate (0.09 g), and dry benzene (10 mL), protected from moisture, was stirred for 18 h at room temperature, and then filtered through a Celite pad. The residue was washed with ether (3 × 25 mL), which was added to the filtrate. The ether solution was washed with ice–water (2 × 100 mL), 5% aq. potassium bromide (2 × 100 mL), and ice–water (2 × 100 mL), dried, and evaporated. The residue was acetylated with acetic anhydride (0.5 mL) and dry pyridine (3 mL). The customary processing *via* dilution with water, extraction into dichloromethane, and removal of pyridine by washing with cold, dilute aq. hydrochloric acid afforded a solid (0.08 g, 53%), which was recrystallized from ether–hexane, m.p. 98°, $[\alpha]_D^{20}$ +150.8° (*c* 1.0, chloroform): n.m.r. (CCl_4): δ 5.30 (s, 1 H), 5.10 (m, 3 H), 4.03 (m, 3 H), 3.50 (q, 2 H, *J* 6 Hz), 2.13, 2.03, 2.00, and 1.93 (s, 3 H, each), and 1.53–1.00 (m, 5 H).

Anal. Calc. for $C_{17}H_{26}O_{10}$: C, 52.30; H, 6.71. Found: C, 52.38; H, 6.67.

tert-*Butyl 2,3,4,6-tetra-*O*-acetyl-α-*D*-galactopyranoside* (**2**). — *Method A*. The procedure using **1**, described earlier for the preparation of **3**, afforded a 64% yield of **2** which, after crystallization from ether–hexane, had m.p. 134°, $[\alpha]_D^{20}$ +141.4° (*c* 1.0, chloroform); n.m.r. δ 5.30 (m, 2 H), 5.10 (d, 1 H, *J* 3 Hz), 4.90 (m, 1 H), 4.10 (m, 3 H), 2.10, 2.00, 1.96, and 1.90 (s, 3 H each), and 1.30 (s, 9 H).

Anal. Calc. for $C_{18}H_{28}O_{10}$: C, 53.49; H, 6.98. Found: C, 53.67; H, 6.97.

Method B. A mixture of the β-D-glycoside **9** (1.0 g), boron trifluoride etherate (1 mL), and dry benzene (10 mL) was stirred for 24 h at room temperature, at which time t.l.c. showed that only ~5% of **9** had not been converted. The solution was washed with aqueous sodium hydrogencarbonate, dried, and evaporated to give, after crystallization, **2** (0.80 g) having melting point and n.m.r. spectra identical to those of the product from Method A.

Method C. A mixture of β-D-galactopyranose 1,2,3,4,6-pentaacetate (**11**) (5.0 g), (50 mL) was stirred for 24 h at room temperature. Neutralization and evaporation afforded a residue from which **2** (1.3 g) could be obtained by direct crystallization from ether–hexane. Chromatography on silica gel afforded 1.8 g more for a total yield of 3.1 g (60%) of material identical with that described above. No attempt was made to recover the β-D anomer **9** that was also a product of the reaction.

*2,2,2-Trichloroethyl 2,3,4,6-tetra-*O*-acetyl-α-*D*-galactopyranoside* (**4**). — A mixture of β-D-galactopyranose 1,2,3,4,6-pentaacetate (**11**), (9.75 g), 2,2,2-trichloroethanol (6.0 g), boron trifluoride etherate (20 mL), and dichloromethane (20 mL) was stirred for 60 h at room temperature, then pyridine (15 mL) was added to neutralize the catalyst. The usual processing afforded a residue that was crystallized from dichloromethane–hexane to give **4** (4.9 g, 41%), m.p. 127°, $[\alpha]_D^{20}$ +125.2° (*c* 1.0,

chloroform); n.m.r.: δ 5.46 (m, 2 H), 5.26 (m, 2 H), 4.16 (m, 5 H), 2.16, 2.10, 2.03, and 1.96 (s, 3 H, each).

Anal. Calc. for $C_{16}H_{21}Cl_3O_{10}$: C, 40.06; H, 4.41; Cl, 22.17. Found: C, 40.61; H, 4.37; Cl, 22.03.

The mother liquors showed, according to t.l.c., more **4**, the β-D anomer **10**, and starting material **11**.

tert-*Butyl* α-D-*galactopyranoside* (**5**). — A mixture of **2** (2.0 g) and of 10mM methanolic sodium methoxide (25 mL) was stirred for 16 h at room temperature. The base was neutralized with Amberlite IRC-50 (H^+) cation-exchange resin, and the solution evaporated to leave 1.1 g (95%) of a residue that resisted crystallization but had spectral properties in accord with structure **5**. $[\alpha]_D^{20}$ +131.3° (*c* 1.0, chloroform).

2,2,2-Trichloroethyl α-D-*galactopyranoside* (**6**). — This compound was prepared as described for **5**, and the noncrystalline product was obtained in a yield of 92%, $[\alpha]_D^{20}$ +130.0° (*c* 1.0, chloroform).

tert-*Butyl 2,3,4,6-tetra*-O-*acetyl*-β-D-*galactopyranoside* (**9**). — A mixture of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**8**) (3.0 g), dry mercuric succinate (1.0 g), *tert*-butyl alcohol (5.0 g), and dry benzene (15 mL) was stirred for 16 h at room temperature, then diluted with ether (200 mL), and the solution was washed with water (2 × 100 mL), 5% aqueous potassium bromide (2 × 100 mL), and water (100 mL), dried, and evaporated. The residue was chromatographed on silica gel to give 1.5 g (52%) of **9** which was crystallized from ether–hexane, m.p. 70°, $[\alpha]_D^{20}$ −20.8° (c 1.0, chloroform); n.m.r.: δ 5.23 (s, 1 H), 4.93 (m, 2 H), 4.60 (m, 1 H), 4.00 (m, 3 H), 2.26, and 1.90 (s, 3 H each), 1.96 (s, 6 H), and 1.20 (s, 9 H).

Anal. Calc. for $C_{18}H_{28}O_{10}$: C, 53.49; H, 6.98. Found: C, 53.66; H, 6.96.

2,2,2-Trichloroethyl 2,3,4,6-tetra-O-*acetyl*-β-D-*galactopyranoside* (**10**). — *Method A*. When a mixture of **11** (1.0 g), 2,2,2-trichloroethanol (1.4 g), boron trifluoride etherate (1.5 mL) and dichloromethane (10 mL) was stirred for only 12 h and processed as described for the preparation of **4**, 1.1 g (90% yield) of **10** was obtained after crystallization from ether–hexane, m.p. 109°, $[\alpha]_D^{20}$ −23.4° (*c* 1.0, chloroform); n.m.r.: δ 5.23 (m, 1 H), 5.00 (m, 2 H), 4.81 (s, 1 H), 4.56 (d, 1 H), 4.10 (m, 4 H), 2.20 and 1.90 (s, 3 H each), and 2.03 (s, 6 H).

Anal. Calc. for $C_{16}H_{21}Cl_3O_{10}$: C, 40.06; H, 4.41. Found: C, 40.50; H, 4.45.

Method B. Reaction of **8** (3.1 g), 2,2,2-trichloroethanol (9.3 g), and silver carbonate (1.5 g) for 48 h at room temperature gave, after acetylation of the residue from the conventional processing and chromatography on silica gel, 0.7 g (19%) of **10**, identical to the product obtained by Method A.

tert-*Butyl 2,3,6-tri*-O-*benzoyl*-α-D-*galactopyranoside* (**12**). — A solution of **5** (1.18 g, 5 mmol) in dry pyridine (32 mL) was cooled to −10°, and benzoyl chloride (2.19 g, 15.62 mmol) was added dropwise to the stirred solution over a period of 30 min. The solution was stirred for 48 h while it warmed to room temperature, and then the mixture was evaporated to remove most of the pyridine. The residue was dissolved in dichloromethane (100 mL) and the solution was washed with 50 mL each of cold 3M hydrochloric acid, 5% aqueous sodium hydrogencarbonate, and water,

then dried, and evaporated. The residue was chromatographed on silicic acid to give 1.6 g (76%) of an oil (**12**) that could not be crystallized, $[\alpha]_D^{20}$ +131.5° (*c* 1.0, chloroform): n.m.r.: δ 8.0–7.23 (m, 15 H), 5.70 (m, 3 H), 4.83 (m, 4 H), 2.0 (s, 1 H), and 1.23 (s, 9 H).

Reaction of **12** with acetic anhydride in pyridine gave the 4-acetate (**17**) in 89% yield as an oil that was crystalline at ~5°, $[\alpha]_D^{20}$ +121.7° (*c* 1.0, chloroform): n.m.r.: δ 2.20 (CH_3CO). Compounds **12** and **17** were not further characterized.

*2,2,2-Trichloroethyl 4-*O*-acetyl-2,3,6-tri-*O*-benzoyl-α-*D*-galactopyranoside* (**18**). — By use of the procedure described for **12**, **6** (2.0 g, 6.42 mmol) was treated with benzoyl chloride (3.77 g, 26.83 mmol) to give, after chromatography on silica gel, 1.6 g (40%) of **13**, syrup, $[\alpha]_D^{20}$ +133.8° (*c* 1.0, chloroform); n.m.r.: δ 8.3–7.0 (m, 15 H), 5.86 (s, 2 H), 5.63 (s, 1 H), 4.86 (s, 4 H), 4.26 (d, 2 H), and 3.73 (s, 1 H). T.l.c. of the residues of chromatography suggested that a considerable proportion of tetrabenzoate had been formed.

Reaction of **13** with acetic anhydride in pyridine gave the 4-acetate (**18**) in 93% yield after crystallization from carbon tetrachloride–hexane, m.p. 133°, $[\alpha]_D^{20}$ +121.6° (*c* 1.0, chloroform); n.m.r.: δ 8.2–7.1 (m, 15 H), 5.7 (m, 4 H), 4.30 (m, 5 H), and 2.20 (s, 3 H).

Anal. Calc. for $C_{31}H_{27}Cl_3O_{10}$: C, 55.57; H, 4.09; Cl, 15.87. Found: C, 55.81; H, 4.03; Cl, 15.92.

*3,4,6-Tri-*O*-acetyl-1,2-*O*-[1-(2,2,2-trichloroethoxy)ethylidene]-α-*D*-galactopyranose* (**15**). — A mixture of **8** (8.0 g), 2,2,2-trichloroethanol (6.0 g), nitromethane (20 mL), and 2,6-lutidine (5 mL) was stirred for 40 h at 60°. To the mixture was added 2M aqueous silver nitrate (20 mL), water (25 mL), and acetone (50 mL), and the resulting mixture was filtered and the filtrate extracted with chloroform (3 × 75 mL). The extracts were washed with water (100 mL), dried, and evaporated to give, after crystallization from ethanol, 5.4 g (58%) of **15**, m.p. 105°, $[\alpha]_D^{20}$ +337° (*c* 1.0, chloroform); n.m.r.: δ 5.83 (d, 1 H, *J* 5 Hz), 5.26 (m, 1 H, *J* 2 and 3 Hz), 4.93 (dd, 1 H, *J* 3 and 6 Hz), 4.10 (m, 6 H), 2.10, 2.06, and 2.03 (s, 3 H each), and 1.73 (s, 3 H).

Anal. Calc. for $C_{16}H_{21}Cl_3O_{10}$: C, 40.06; H, 4.41; Cl, 22.17. Found: C, 40.31; H, 4.42; Cl, 22.16.

Rearrangement of **15** *to the glycosides* **4** *and* **10**. — A mixture of **15** (1.0 g), 2,2,2-trichloroethanol (1.0 g), mercuric bromide (0.36 g), and nitromethane (10 mL) was boiled under reflux for 10 h, and then was evaporated. The residue was dissolved in ether (50 mL), and the solution was washed with water (2 × 100 mL) and 10% aqueous potassium bromide (2 × 100 mL), dried, and evaporated to give 0.93 g of crude product; t.l.c. showed that **4** and **10** were major components.

Analysis by l.c. was performed on a Waters ALC-204 instrument, equipped with a refractive-index detector and a C-18 reversed-phase column, the elution being done with 1:1 (v/v) acetonitrile–water at a flow rate of 1.5 mL.min^{-1}. This showed that the ratio of **4** to **10** was 2.42:1, and that the combined yields of the two compounds were about 40%.

*1,4-Di-*O*-acetyl-2,3,6-tri-*O*-benzoyl-α-*D*-galactopyranose* (**16**). — *From* **14**. The

methyl glycoside **14** (0.5 g) was added to conc. 1:6:13 (v/v) sulfuric acid–glacial acetic acid–acetic anhydride, and the stirred solution (10 mL), was heated on the steam bath for 15 min., and then poured carefully into an ice-cold, saturated solution of sodium hydrogencarbonate in water (200 mL). The resulting mixture was extracted with dichloromethane (2 × 100 mL), and the extracts were dried and evaporated to give a crude residue (0.5 g). Chromatography on silica gel gave 0.3 g of **16** which, after crystallization from carbon tetrachloride–hexane, had m.p. 78–80°, $[\alpha]_D^{20}$ +90.4° (*c* 1.0, chloroform); n.m.r.: δ 8.0–7.5 (m, 15 H), 6.70 (s, 1 H, *J* 2 Hz), 5.86 (s, 2 H), 4.50 (m, 4 H), and 2.20 (s, 6 H).

Anal. Calc. for $C_{31}H_{28}O_{11}$: C, 64.58; H, 4.89. Found: C, 64.20; H, 4.98.

From **17**. A mixture of **17** (0.15 g) and 90% aqueous trifluoroacetic acid (5 mL) was stirred for 4 h at room temperature, and then evaporated. The residue was re-acetylated with acetic anhydride (0.5 mL) and dry pyridine (3 mL) to give, after conventional processing and crystallization from carbon tetrachloride–hexane, 0.115 g of **16**, identical in all respects with the product obtained from **14**.

From **18**. A stirred mixture of **18** (0.07 g), zinc powder (0.5 g), and acetic anhydride (10 mL) was heated for 4 h at 60°, with exclusion of moisture, and then cooled and filtered. The residue was washed with dichloromethane (100 mL) which was added to the filtrate. The solution was evaporated and the residue was dissolved in dichloromethane (100 mL). The solution was washed with water (100 mL), dried, and evaporated to leave a residue that, crystallized as described above, gave 0.06 g (98%) of product, m.p. 80–82°, which showed a t.l.c. behavior identical with, and an n.m.r. spectrum having minor differences from, that of **16** that had been prepared by acetolysis of **14**.

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REFERENCES

1 D. H. Hutson, *J. Chem. Soc., C*, (1967) 442–446.
2 W. Boos, P. Schaedel, and K. Wallenfels, *Eur. J. Biochem.*, 1 (1967) 382–394.
3 M. Blanc-Muesser, J. Defaye, and H. Driguez, *Carbohydr. Res.*, 67 (1978) 305–328.
4 P. M. Collins, W. G. Overend, and B. A. Rayner, *Carbohydr. Res.*, 31 (1973) 1–16.
5 B. Helferich and W. Müller, *Chem. Ber.*, 104 (1971) 671–673.
6 B. Lindberg, *Acta Chem. Scand.*, 3 (1949) 151–156.
7 P. J. Garegg and I. Kvarnström, *Acta Chem. Scand., Ser. B*, 30 (1976) 655–658.
8 M. Prystaš, L. Kalvoda, and F. Šorm, *Collect. Czech. Chem. Commun.*, 41 (1976), 1426–1447.
9 B. Lindberg, *Acta Chem. Scand.*, 2 (1948) 534–535.
10 J. M. Williams and A. C. Richardson, *Tetrahedron*, 23 (1967) 1369–1378; E. J. Reist, R. R. Spencer, D. F. Calkins, B. R. Baker, and L. Goodman, *J. Org. Chem.*, 30 (1965) 2312–2317.
11 K. Takeo, T. Matsunami, and T. Kuge, *Carbohydr. Res.*, 51 (1976) 73–84.