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SYNTHESIS OF SUBSTITUTED 2,7-DIOXABICYCLO[4.1.0]HEPTANES: 1,2-ANHYDRO-3,4,6-TRI-*O*-BENZYL- AND 1,2-ANHYDRO-3,4,6-TRI-*O*-(*p*-BROMOBENZYL)-α-D-GALACTOPYRANOSE*

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ABSTRACT

The title compounds were synthesized from D-galactose *via* 9 steps. For obtaining stable, 1,2-blocked D-galactopyranose ethers, the 1,2-hydroxyl groups were protected with an ethylidene group instead of a 1-ethoxyethylidene group. The key intermediates for the synthesis were 2-*O*-acetyl-3,4,6-tri-*O*-benzyl- and 2-*O*-acetyl-3,4,6-tri-*O*-(*p*-bromobenzyl)-β-D-galactopyranosyl fluoride that were prepared from the corresponding, substituted α-D-galactopyranosyl chlorides with silver fluoride. Ring closure of the β-D-galactopyranosyl fluorides was quantitative with potassium *tert*-butoxide in oxolane under reflux, and crystalline target compounds were obtained. Most of the reactions involved in the synthesis were carried out readily in high yield.

INTRODUCTION

The synthesis of 1,2-anhydro-3,4,6-tri-*O*-benzyl- (**14**) and 1,2-anhydro-3,4,6-tri-*O*-(*p*-bromobenzyl)-α-D-galactopyranose (**15**) is of interest, as not only do they have potential utility as synthetic intermediates, but also their stereoregular polymerization may afford β-(1→2)-linked D-galactopyranan. The synthesis of 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-mannopyranose[1] and 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose[2] by an intramolecular, SN2 reaction of a free hydroxyl group on C-2 with C-1 bearing a leaving group has been reported. We now report the synthesis of **14** and **15** by an improved, intramolecular reaction of an oxyanion on C-2, obtained from the corresponding 2-acetate under strongly basic condition, with C-1 bearing a β-fluorine atom.

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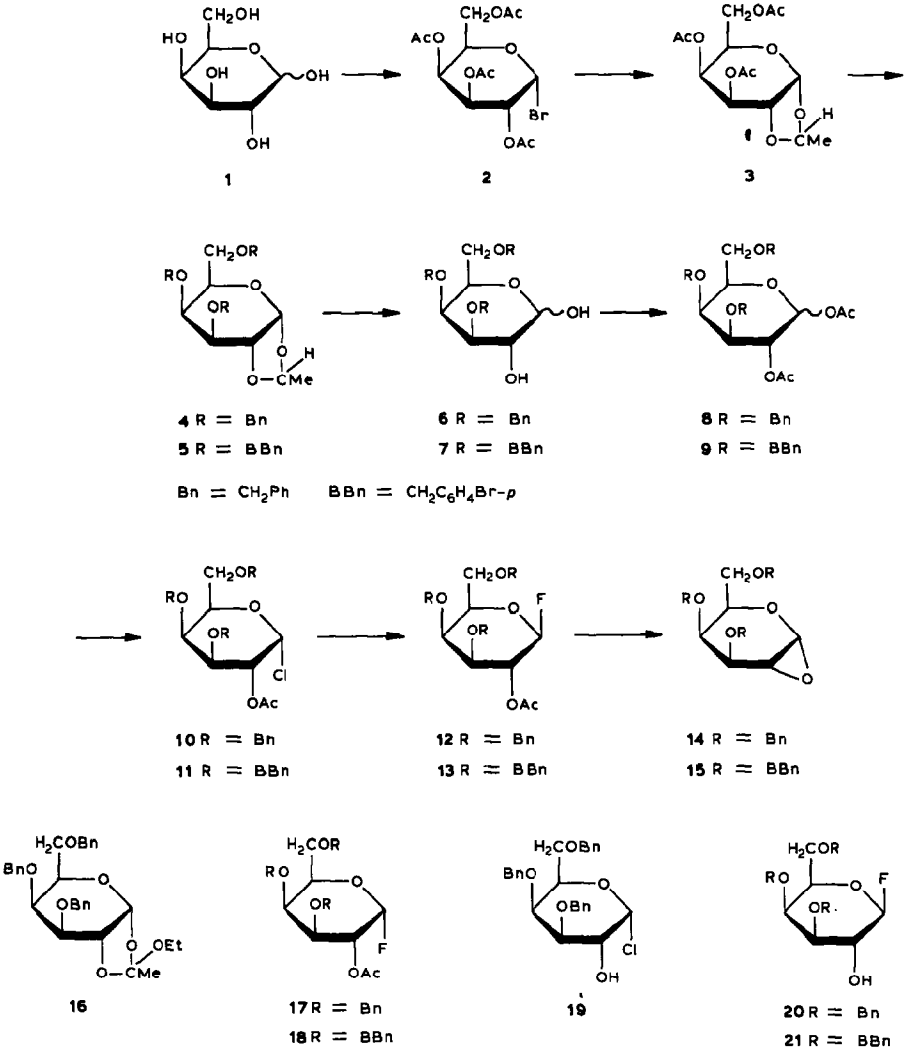
RESULTS AND DISCUSSION

The first problem involved in the synthesis of 1,2-anhydro-α-D-galactopyranose derivatives was to prepare 1,2-blocked D-galactopyranose ethers that are important intermediates for obtaining the target compounds. An initial attempt was focussed on the synthesis of 3,4,6-tri-*O*-benzyl-1,2-*O*-(1-ethoxyethylidene)-α-D-galactopyranose[3] (**16**). It was found, however, that compound **16**, prepared from 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide in low yield, is not stable. For obtaining stable, 1,2-protected D-galactopyranose ethers, 3,4,6-tri-*O*-acetyl-1,2-*O*-ethylidene-α-D-galactopyranose (**3**) was prepared in high yield according to a reported method[4]. Then, compound **3** was directly converted into 3,4,6-tri-*O*-benzyl- (**4**) and 3,4,6-tri-*O*-(*p*-bromobenzyl)-1,2-*O*-ethylidene-α-D-galactopyranose (**5**) in satisfactory yields under the same conditions used for benzylation and (*p*-bromobenzyl)ation of methyl 2,3-*O*-isopropylidene-α-D-mannopyranoside[5]. Compounds **4** and **5** are very stable when stored below 10°, and thus they constituted suitable intermediates for the present research. Hydrolysis of **4** and **5** in 1,4-dioxane with dilute sulfuric acid under reflux gave 3,4,6-tri-*O*-benzyl- (**6**) and 3,4,6-tri-*O*-(*p*-bromobenzyl)-D-galactopyranose (**7**).

An attempt to prepare 3,4,6-tri-*O*-benzyl-α-D-galactopyranosyl chloride (**19**) from **6** under conditions similar to those used for the preparation of 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl chloride[2] was not successful, as substantial proportions of byproducts were formed, and the chloride thus obtained was very labile, even when stored in a refrigerator. Therefore, compounds **6** and **7** were acetylated, and 1,2-di-*O*-acetyl-3,4,6-tri-*O*-benzyl- (**8**) and 1,2-di-*O*-acetyl-3,4,6-tri-*O*-(*p*-bromobenzyl)-D-galactopyranose (**9**) were obtained in quantitative yield. Conversion of **8** and **9** into the corresponding 2-*O*-acetyl-3,4,6-tri-*O*-benzyl- (**10**) and 2-*O*-acetyl-3,4,6-tri-*O*-(*p*-bromobenzyl)-α-D-galactopyranosyl chlorides (**11**) was successfully achieved under the conditions used for the conversion of 1,3-di-*O*-acetyl-2,4,6-tri-*O*-benzyl-D-mannopyranose into the corresponding D-mannopyranosyl chloride[5]. Chlorination of **9** was faster than chlorination of **8**, and the chlorination product **11** was more stable than **10**.

Ring closure of **11** with base in the presence or absence of the phase-transfer reagent tetrabutylammonium iodide[4] or bromide at room temperature, or under reflux, did not afford the 1,2-anhydro sugar ether. Instead, decomposition byproducts, namely, *p*-bromobenzyl alcohol, *p*-bromobenzyl acetate, and some oligomers (identified by ^{1}H-n.m.r. spectroscopy) were formed, with a substantial proportion of the starting material left unchanged. It seemed that side reactions occurred more easily than halide anomerization. Thus, it is necessary to prepare β-halides suitable for an intramolecular SN2 reaction from back-side attack. Fluorination with silver fluoride is a suitable way for achieving this. Thus, 2-*O*-acetyl-3,4,6-tri-*O*-benzyl- (**12**) and 2-*O*-acetyl-3,4,6-tri-*O*-(*p*-bromobenzyl)-β-D-galactopyranosyl fluoride (**13**) were obtained as crystals in good yields after separating the fluorination product by analytical t.l.c. on silica gel. Fluorination of **11** was much



slower than fluorination of **10**, as the former was the more stable. Crystalline α-fluorides **17** and **18** were also obtained as minor products that would have potential use for β-glycosation.

Ring closure of **12** and **13** with potassium *tert*-butoxide in benzene or oxolane for several hours or overnight at room temperature was not successful, as substantial proportions of 3,4,6-tri-*O*-benzyl- (**20**) and 3,4,6-tri-*O*-(*p*-bromobenzyl)-β-D-galactopyranosyl fluoride (**21**), identified by ^{1}H-n.m.r. spectroscopy, were formed, and it was difficult to purify the target compounds. In contrast, ring closure of **12** and **13** with potassium *tert*-butoxide in boiling oxolane quantitatively afforded crystalline 1,2-anhydro-3,4,6-tri-*O*-benzyl- (**14**) and 1,2-anhydro-3,4,6-tri-*O*-(*p*-bromobenzyl)-α-D-galactopyranose (**15**) in a very short time.

Monitoring the ring closure of **12** and **13** by t.l.c. was difficult, because the 1,2-anhydro sugar ethers completely decompose when spotted on a t.l.c. plate. However, disappearence of starting material **12** or **13**, and of **20** or **21**, could be indicated by t.l.c. Thus, the ring closure was judged to be complete by the disappearence of the known compounds. As the 1,2-anhydro sugar ethers were found sensitive to acid and hydroxylic solvents, the reaction mixture was not washed with water. Instead, it was evaporated to dryness and the residue was repeatedly extract with 1:3 ethyl acetate–petroleum ether and, on evaporation of the extracts, compounds **14** and **15** crystallized spontaneously. Analytical l.c. (Lichrosorb-NH_2) showed a single peak for **14** and **15** with a shorter retention time than that of the corresponding precursors **12** and **13**. Extension of the reaction time for the ring closure tended to decrease the yield of epoxides, because of formation of oligomers.

The target compounds **14** and **15** were characterized by ^{1}H-n.m.r. spectroscopy, optical rotation, and elemental analysis, and **14** by mass and i.r. spectra also, with good agreement with the designated structure. The ^{1}H-n.m.r. spectra showed H-2 of **14** and **15** upfield, characteristic of the epoxide ring[6]. The mass spectrum of **14** gave a clear, molecular-ion peak (432) and fragment peaks from breaking of ether linkages. The i.r. spectrum of **14** showed strong absorption for ether linkages, and no absorption for a C=C or a C=O bond. The key intermediates, the β-fluorides **12** and **13**, were characterized by ^{1}H-n.m.r. spectra showing the anomeric H upfield, in contrast to the α-fluoride spectra giving the anomeric H downfield. All of the new compounds involved in the synthesis were characterized by ^{1}H-n.m.r. spectra, optical rotation, and elemental analysis.

EXPERIMENTAL

General methods and materials. — Melting points were determined in a "Mel-Temp" apparatus with a 76-mm immersion thermometer. Optical rotations were determined with a Perkin–Elmer Model 241-MC polarimeter using a 1-dm, jacketed cell. Infrared spectra were recorded with a Perkin–Elmer 125 spectrometer. ^{1}H-N.m.r. spectra were recorded with a Varian XL-200 spectrometer, with chloroform-*d* as the solvent and tetramethylsilane (Me_4Si) as the internal standard; chemical shifts are given in p.p.m. Mass spectra were recorded with a JMS-D 3005 mass spectrometer by using a direct-insertion technique to introduce the samples. Analytical l.c. was carried out by use of a pump (Model YSB-2, made in China), stainless-steel columns (4.6 × 250 mm) packed with silica gel (10 × 150 mm) or Lichrosorb-NH_2, a differential refractometer (Model 1107L, made by LDC, Division of Milton Roy Company, Florida, U.S.A.), and ethyl acetate–petroleum ether (b.p. 60–90°) as the eluant at a flow rate of 1 to 4 mL/min. Thin-layer chromatography (t.l.c.) was performed on precoated plates of silica gel G with detection by 30% sulfuric acid solution in methanol. Column chromatography was conducted with columns (16 × 240, 18 × 300, 35 × 400, and 40 × 600 mm) packed with silica gel (100–200 mesh). Silver fluoride was prepared by reaction of silver carbonate

with hydrogen fluoride[7]. *p*-Bromobenzyl bromide was prepared from *p*-bromotoluene and bromine by a photochemical reaction[8]. Other reagents used in the syntheses were obtained from commercial sources.

3,4,6-Tri-O-*acetyl-1,2*-O-*ethylidene*-α-D-*galactopyranose* (**3**). — A mixture of crystalline 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**2**) (12.3 g, 30 mmol, m.p. 80°, prepared by a standard method[9] from **1**), sodium borohydride (5.7 g, 150 mmol), tetrabutylammonium iodide (5.12 g, 15 mmol), and anhydrous acetonitrile (60 mL) was stirred for 24 h at room temperature. T.l.c. (1:1 ethyl acetate–petroleum ether) then indicated the reaction to be complete. The mixture was diluted with dichloromethane (300 mL), washed with water (3 × 200 mL), filtered through glass wool, and evaporated to dryness. The residue was subjected to chromatography on a column (40 × 600 mm) of silica gel with 1:1 ethyl acetate–petroleum ether as eluant, and isomeric mixture **3** was obtained as a colorless syrup, yield 82%, $[\alpha]_D^{20}$ +91.3° (*c* 1.1, chloroform); lit.[3] $[\alpha]_D^{20}$ +93° (*c* 2.6, chloroform).

3,4,6-Tri-O-*benzyl-1,2*-O-*ethylidene*-α-D-*galactopyranose* (**4**). — To a solution of compound **3** (3.8 g, 11.4 mmol) in toluene (15 mL) was added finely powdered potassium hydroxide (12.3 g) under vigorous stirring. The mixture was heated to boiling, and benzyl chloride (18 g, 142 mmol) was added dropwise during 30 min under reflux. The reaction was continued under reflux and vigorous stirring for 2 h or more, until t.l.c. (1:3 ethyl acetate–petroleum ether) indicated that benzylation was complete. The mixture was cooled, and partitioned between dichloromethane (100 mL) and water (30 mL), and the organic layer was concentrated. Toluene (10 mL) and solid sodium hydrogencarbonate (1 g) were added to the concentrate, and this mixture was subjected to steam distillation to remove the excess of benzyl chloride and the benzyl ether formed in the reaction. The mixture was repeatedly extracted with dichloromethane and the extracts were combined, dried, and evaporated to a syrup that was purified by chromatography on a column (35 × 400 mm) of silca gel with 1:3 ethyl acetate–petroleum ether as the eluant, giving pure **4**, yield 89%; $[\alpha]_D^{20}$ +24.7° (*c* 1.1, chloroform); ^{1}H-n.m.r.: δ 7.32–7.15 (m, 15 H, Ph–H), 5.60–3.37 (m, 14 H, H-1–5, 2 H-6, 3 CH_2Ph, and C*H*Me), and 1.40–1.28 (m, 3 H, CCH_3).

Anal. Calc. for $C_{29}H_{32}O_6$: C, 73.10; H, 6.72. Found: C, 73.38; H, 6.67.

An alternative method for the preparation of **4** was that, without chromatographic purification, the crude product **3** obtained after working up the reaction mixture was subjected to direct benzylation, and the benzylation mixture was purified by the procedure just described; yield (from compound **2**) 75%.

3,4,6-Tri-O-(p-*bromobenzyl*)-*1,2*-O-*ethylidene*-α-D-*galactopyranose* (**5**). — To a vigorously stirred solution of compound **3** (4.8 g, 14.5 mmol) in toluene (20 mL) was added finely powdered potassium hydroxide (15 g), and the mixture was heated to boiling. A solution of *p*-bromobenzyl bromide (20 g, 80 mmol) in toluene (9 mL) was added dropwise within 40 min to the boiling solution under vigorous stirring, and the reaction was continued for a further 1 h under boiling and agitation. T.l.c. (1:3 ethyl acetate–petroleum ether) then indicated the reaction to be com-

plete. After cooling the mixture, water (10 mL) and toluene (10 mL) were added, the mixture shaken, and the organic layer dried (sodium sulfate), and evaporated to dryness under vacuum. The residue thus obtained was separated by chromatography on a column (35 × 400 mm) of silica gel with benzene and then benzene–ether (50:3 to 50:10) as eluant. Syrupy **5** was obtained from the main fraction; yield 84%; $[\alpha]_D^{20}$ +29° (*c* 1.3, chloroform); ^{1}H-n.m.r.: δ 7.49–7.05 (m, 12 H, Ph–H), 5.56–3.46 (m, 14 H, H-1–5, 3 C*H*$_2$Ph, 2 H-6, and C*H*Me), and 1.35 (d, 3 H, CC*H*$_3$).

Anal. Calc. for $C_{29}H_{29}Br_3O_6$: C, 48.81; H, 4.01. Found: C, 49.05; H, 4.02.

*3,4,6-Tri-*O*-(*p*-bromobenzyl)-*D*-galactopyranose* (**7**). — Compound **5** (2.9 g, 4.07 mmol) was converted into **7** by the procedure used for the conversion of **4** into **6**, and compound **7** was obtained crystalline; yield 91%; m.p. 51°, $[\alpha]_D^{20}$ +18.7° (*c* 1.0, chloroform); ^{1}H-n.m.r.: δ 7.47–7.04 (m, 12 H, Ph–H), 5.27 (d, 0.6 H, $J_{1,2}$ 3.5 Hz, H-1 of α anomer), and 4.80–3.24 (m, 14.4 H, 0.4 H-1 of β anomer, H-2–5, 3 C*H*$_2$Ph, 2 H-6, and 2 O*H*).

Anal. Calc. for $C_{27}H_{27}Br_3O_6$: C, 47.16; H, 3.93. Found: C, 47.24; H, 4.01.

*1,2-Di-*O*-acetyl-3,4,6-tri-*O*-benzyl- (**8**) and 1,2-di-*O*-acetyl-3,4,6-tri-*O*-(*p*-bromobenzyl)-*D*-galactopyranose* (**9**). — To a solution of compound **4** (2.0 g) in 1,4-dioxane (30 mL) was added M sulfuric acid (6 mL), and the mixture was boiled under reflux for 4 h. The mixture was cooled, made neutral with solid sodium hydrogencarbonate, and evaporated to dryness. The residue was partitioned between water and dichloromethane, and the organic layer dried (sodium sulfate), and evaporated to a syrup. Pure **6** was obtained as a colorless syrup after column-chromatographic separation of the syrupy mixture with 1:2 ethyl acetate–petroleum ether as eluant; yield 74%; $[\alpha]_D^{20}$ +44.3–52.2° (*c* 1.05, chloroform); lit.[10] +48.5–53.0° (*c* 1, chloroform).

Compound **6** was acetylated with acetic anhydride in pyridine by the standard method. The reaction was quantitative, as indicated by t.l.c. (ethyl acetate), and pure syrupy **8** was obtained after working up the reaction mixture; $[\alpha]_D^{20}$ +45.1° (*c* 2, chloroform); ^{1}H-n.m.r.: δ 7.26–7.22 (m, 15 H, Ph–H), 6.33 (d, 0.55 H, $J_{1,2}$ 3.5 Hz, H-1 of α anomer), 5.51 (m, 1.45 H, 0.45 H-1 of β anomer, and 1 H for H-2), 5.02–3.50 (m, 11 H, 3 C*H*$_2$Ph, H-3,4,5, and 2 H-6), 2.11, 2.09 (s, s, 3 H, C*H*$_3$CO-1, 1.35 H for β and 1.65 H for α anomer), and 2.04 (s, 3 H, C*H*$_3$CO-2).

Similar acetylation of **7** gave compound **9** quantitatively, as white needles; m.p. 138°, $[\alpha]_D^{20}$ +45.1° (*c* 2.07, chloroform); ^{1}H-n.m.r.: δ 7.51–7.07 (m, 12 H, Ph-H), 6.29 (d, 0.4 H, $J_{1,2}$ 3.6 Hz, H-1 of α anomer), 5.54–3.46 (m, 12.6 H, 0.6 H-1 for β anomer, H-2–5, 3 C*H*$_2$Ph, and 2 H-6), 2.10, 2.07 (s, s, 3 H, C*H*$_3$CO-1 for β and α anomer, respectively), and 2.00 (s, 3 H, C*H*$_3$CO-2).

Anal. Calc. for $C_{31}H_{31}Br_3O_8$: C, 48.25; H, 4.02. Found: C, 48.25; H, 3.89.

*2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-*D*-galactopyranosyl chloride* (**10**). — Compound **8** (2 g, 3.75 mmol) was dissolved in anhydrous ether (50 mL), and anhydrous hydrogen chloride was bubbled in at 0°, under nitrogen, to saturation. The solution was kept overnight in a refrigerator (−5°), and t.l.c. (1:3 ethyl acetate–petroleum ether) then indicated that the reaction was complete. The solution was evaporated

under diminished pressure to a syrup which was dissolved in dichloromethane, and the solvent evaporated; this procedure was repeated several times, to lower the content of hydrogen chloride to the minimum. The syrup was then purified by analytical l.c. on silica gel with 1:2 ethyl acetate–petroleum ether as the eluant. Pure compound **10** was obtained as a colorless syrup; yield 91%; $[\alpha]_D^{20}$ +126.5° (*c* 0.82, chloroform); ^{1}H-n.m.r.: δ 7.38–7.25 (m, 15 H, Ph–H), 6.38 (d, 1 H, $J_{1,2}$ 4.2 Hz, H-1), 5.41 (m, 1 H, $J_{1,2}$ 4.2, $J_{2,3}$ 11 Hz, H-2), 5.01–3.53 (m, 11 H, H-3,4,5, 3 C*H*$_2$Ph, and 2 H-6), and 2.04 (s, 3 H, C*H*$_3$CO).

Anal. Calc. for $C_{29}H_{31}ClO_6$: C, 68.17; H, 6.07. Found: C, 68.05; H, 6.11.

2-O-Acetyl-3,4,6-tri-O-(p-bromobenzyl)-α-D-galactopyranosyl chloride (**11**). — Compound **9** (1.3 g, 1.69 mmol) was dissolved in ether (25 mL), and at 0° anhydrous hydrogen chloride was bubbled in to saturation under a nitrogen atmosphere. Then, the reaction was continued for 5 h at room temperature. T.l.c. (1:2 ethyl acetate–petroleum ether) then indicated the chlorination to be complete. The reaction mixture was worked up as for the conversion of **8** into **10**. The crude, crystalline **11** obtained was purified by analytical l.c. on silica gel with 1:2 ethyl acetate–petroleum ether as the eluant; pure **11** was obtained as white needles after evaporation; yield 87%; m.p. 85°, $[\alpha]_D^{20}$ +73.7° (*c* 0.9, chloroform); ^{1}H-n.m.r.: δ 7.50–7.10 (m, 12 H, Ph–H), 6.47 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.47 (m, 1 H, $J_{1,2}$ 4, $J_{2,3}$ 10 Hz, H-2), 4.91–3.69 (m, 11 H, H-3,4,5, 3 C*H*$_2$Ph, and 2 H-6), and 2.22 (s, 3 H, C*H*$_3$CO).

Anal. Calc. for $C_{29}H_{28}Br_3ClO_6$: C, 46.56; H, 3.75. Found: C, 46.74; H, 3.68.

2-O-Acetyl-3,4,6-tri-O-benzyl-β- (**12**) *and 2-O-acetyl-3,4,6-tri-O-benzyl-α-D-galactopyranosyl fluoride* (**17**). — To a solution of compound **10** (2.6 g, 5.06 mmol) in 2:5 acetonitrile–benzene (140 mL) was added solid silver fluoride (1.42 g, 11.1 mmol), and a white precipitate of silver chloride formed. The mixture was stirred vigorously in a dark room for 16 h at room temperature, centrifuged, and the solid washed repeatedly with benzene. The washings and supernatant liquor were combined, and evaporated to a syrup that was subjected to analytical l.c. on silica gel with 1:3 ethyl acetate–petroleum ether as the eluant. The fraction sequence was as follows: chloride **10**, α-fluoride **17**, and β-fluoride **12**. After evaporation, compounds **12** and **17** were obtained as crystals in the ratio of 7:2; total yield for fluorination, 82.5%; m.p. 73° (**12**); 59° (**17**), $[\alpha]_D^{20}$ +17.6° (**12**) (*c* 0.71, chloroform); +48.6° (**17**) (*c* 0.72, chloroform); ^{1}H-n.m.r. (**12**): δ 7.35–7.22 (m, 15 H, Ph–H), 5.12 (m, 1 H, $J_{1,F}$ 52, $J_{1,2}$ 6 Hz, H-1), 5.57–3.46 (m, 12 H, H-2–5, 3 C*H*$_2$Ph, and 2 H-6), and 2.07 (s, 3 H, C*H*$_3$CO); ^{1}H-n.m.r. (**17**): δ 7.36–7.25 (m, 15 H, Ph–H), 5.73 (m, 1 H, $J_{1,F}$ 53, $J_{1,2}$ 4 Hz, H-1), 5.36 (m, 1 H, $J_{1,2}$ 4, $J_{2,3}$ 11, $J_{2,F}$ 26 Hz, H-2), 5.02–3.55 (m, 11 H, H-3,4,5, 3 C*H*$_2$Ph, and 2 H-6), and 2.11 (s, 3 H, C*H*$_3$CO); *m/z* (for both **12** and **17**): 493 (M^+), 432 ($M^+ - F - CH_3CO$), 383 ($M^+ - HF - Bn$), and 107, 91, and 79 (benzyl group).

Anal. Calc. for $C_{29}H_{31}FO_6$: C, 70.59; H, 6.28. Found: C, 70.45; H, 6.25 (**12**); C, 70.32; H, 6.25 (**17**).

2-O-Acetyl-3,4,6-tri-O-(p-bromobenzyl)-β- (**13**) *and 2-O-acetyl-3,4,6-tri-O-(p-bromobenzyl)-α-D-galactopyranosyl fluoride* (**18**). — To a solution of **11** (1.1 g, 1.47 mmol) in 1:2 acetonitrile–benzene (50 mL) was added silver fluoride (430 mg, 3.4 mmol), and the mixture was stirred vigorously for 2 d in the dark at room temperature. The reaction was worked up as for the conversion of **10** into **12**. Crude, crystalline fluorides obtained were subjected to separation by analytical l.c. on silica gel with 1:2 ethyl acetate–petroleum ether as eluant. The sequence of fractions was as follows: unreacted chloride **11**, α-fluoride **18**, and β-fluoride **13**. After evaporation, compounds **13** and **18** were obtained as white crystals in the ratio of 3.4:1; total yield for fluorination, 81.5%; m.p. 107° (**13**); 97° (**18**), $[\alpha]_D^{20}$ +0.8° (**13**) (*c* 0.8, chloroform); +22.7° (**18**) (*c* 0.7, chloroform); ^{1}H-n.m.r. (**13**): δ 7.52–7.14 (m, 12 H, Ph–H), 5.42 (m, 1 H, H-2), 5.15 (dd, 1 H, $J_{1,F}$ 52, $J_{1,2}$ 6 Hz, H-1), 4.80–3.50 (m, 11 H, H-3,4,5, 3 CH_2Ph, and 2 H-6), and 2.03 (s, 3 H, CH_3CO); ^{1}H-n.m.r. (**18**): δ 7.50–7.10 (m, 12 H, Ph–H), 5.74 (dd, 1 H, $J_{1,F}$ 54, $J_{1,2}$ 2.0 Hz, H-1), 5.27 (m, 1 H, $J_{1,2}$ 2.0, $J_{2,F}$ 28, $J_{2,3}$ 10 Hz, H-2), 4.99–3.49 (m, 11 H, H-3,4,5, 3 CH_2Ph, and 2 H-6), and 2.10 (s, 3 H, CH_3CO).

Anal. Calc. for $C_{29}H_{28}Br_3FO_6$: C, 47.67; H, 3.80. Found: C, 47.78; H, 3.68 (**13**); C, 47.70; H, 3.72 (**18**).

1,2-Anhydro-3,4,6-tri-O-benzyl-α-D-galactopyranose (**14**). — To a stirred and preheated solution of compound **12** (150 mg, 0.29 mmol) in oxolane (3 mL) was rapidly added potassium *tert*-butoxide (64 mg, 0.58 mmol), and the mixture was heated in a hot-oil bath to boiling within 1 min. A brown solution formed immediately after adding the base, and the reaction was continued under reflux for 30 min. T.l.c. (1:3 ethyl acetate–petroleum ether) then indicated that the starting material **12** and the intermediate 3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl fluoride (**20**) had disappeared. The mixture was cooled, and evaporated to dryness under vacuum. The residue was repeatedly extracted with 1:3 ethyl acetate–petroleum ether, and the completely colorless extracts were combined and evaporated to dryness. Compound **14** was obtained as needles on standing in a refrigerator; yield 98%; m.p. 32–35°. Recrystallization from ether–petroleum ether gave pure **14**; m.p. 39°, $[\alpha]_D^{20}$ −16.9° (*c* 0.62, chloroform); ^{1}H-n.m.r.: δ 7.34–7.25 (m, 15 H, Ph–H), 4.95 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 4.77–3.48 (m, 11 H, H-3,4,5, 3 CH_2Ph, and 2 H-6), 3.18 (t, 1 H, $J_{1,2}$ 3.0, $J_{2,3}$ 3.0 Hz, H-2); i.r.: 1040, 1080, 1140, 1160 (ether linkages), 1440, 1495 (aromatic ring stretch), 2850, and 2910 cm^{-1} (methylene); *m/z*: 432 (M^+), 341 (M^+ − Bn), 325 (M^+ − OBn), 107, 91, and 79 (benzyl group).

Anal. Calc. for $C_{27}H_{28}O_5$: C, 74.98; H, 6.53. Found: C, 74.88; H, 6.47.

When ring closure was conducted at room temperature, the starting material disappeared immediately after adding the base to the solution of **12**. However, the main product of the reaction was **20**, together with ~30% of the target epoxide. Extension of the reaction time at room temperature did not change the proportion much. Boiling the incomplete-reaction mixture for 2 h afforded the expected **14**. However, the yield was lower than that by direct epoxide formation under reflux, because some oligomers were formed. On separation by analytical l.c. (Lichrosorb-

NH_2) of the incomplete-ring-closure product, compound **20** was obtained as a syrup, and it was characterized by its ^{1}H-n.m.r. spectrum: δ 7.33–7.26 (m, 15 H, Ph–H), 5.03 (m, 1 H, $J_{1,F}$ 53, $J_{1,2}$ 6.8 Hz, H-1), and 4.86–3.35 (m, 13 H, H-2–5, 3 C*H*$_2$Ph, 2 H-6, and O*H*).

*1,2-Anhydro-3,4,6-tri-*O*-(*p*-bromobenzyl)-α-*D*-galactopyranose* (**15**). — To a stirred and preheated solution of compound **13** (150 mg, 0.22 mmol) in oxolane (3 mL) was added potassium *tert*-butoxide (50 mg, 0.44 mmol), and the mixture was heated to boiling within 1 min. The reaction, complete in 10 min, was worked up by the procedure used for the conversion of **12** into **14**. Crystalline **15** was obtained as white needles; yield 92%; m.p. 88–92°. Recrystallization from dichloromethane–petroleum ether gave pure **15**; m.p. 95°, $[\alpha]_D^{20}$ −7.3° (*c* 3, chloroform); ^{1}H-n.m.r.: δ 7.51–7.11 (m, 12 H, Ph–H), 4.99 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 4.83–3.50 (m, 11 H, H-3,4,5, 3 C*H*$_2$Ph, and 2 H-6), and 3.11 (t, 1 H, $J_{1,2}$ 3.0, $J_{2,3}$ 3.0 Hz, H-2).

Anal. Calc. for $C_{27}H_{25}Br_3O_5$: C, 48.43; H, 3.74. Found: C, 48.56; H, 3.81.

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