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PREPARATION OF SOME BROMODEOXYALDONIC ACIDS*†

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ABSTRACT

Reaction of L-ascorbic acid with hydrogen bromide in acetic acid gave 6-bromo-6-deoxy-L-ascorbic acid, which was converted into 5,6-dideoxy-D-*glycero*-hex-2,3-enono-1,4-lactone. Hexonic acids or their lactones also gave bromo compounds on treatment with HBr–AcOH. From D-galactono-1,4-lactone a 6- bromo derivative was obtained. Calcium D-gluconate yielded 2,6-dibromo-2,6-dideoxy-D-mannono-1,4-lactone, whereas D-mannono-1,4-lactone gave 2,6-dibromo-2,6-dideoxy-D-glucono-1,4-lactone.

INTRODUCTION

The formation of a 6-bromo-6-deoxy-D-mannofuranose derivative by treatment of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose with hydrogen bromide in acetic acid and a similar preparation of a 6-bromo-6-deoxy-D-galactofuranose derivative have been described previously[1,2]. These results indicate that other cyclic compounds having an exocyclic, vicinal diol-group may react with HBr–AcOH to give bromodeoxy compounds. This has been tried on a number of compounds, and in the present paper the reaction of L-ascorbic acid and of some hexonic acids with HBr–AcOH is described.

RESULTS AND DISCUSSION

L-Ascorbic acid (**1**) has an exocyclic diol-group, and on treatment with HBr–AcOH it gave 5-*O*-acetyl-6-bromo-6-deoxy-L-ascorbic acid (**2**) as a syrup. After deacetylation, crystalline 6-bromo-6-deoxy-L-ascorbic acid (**3**) was isolated in ~80% yield. No other products could be detected. The preparation of **3** by treatment of ascorbic acid with hydrogen bromide in formic acid has been described recently in a patent[3]. Treatment of the 5-acetate (**2**) with zinc dust and acetic acid gave the 5,6-unsaturated product **4** which, on catalytic hydrogenation, yielded 5,6-dideoxy-D-*glycero*-hex-2,3-enono-1,4-lactone (**5**).

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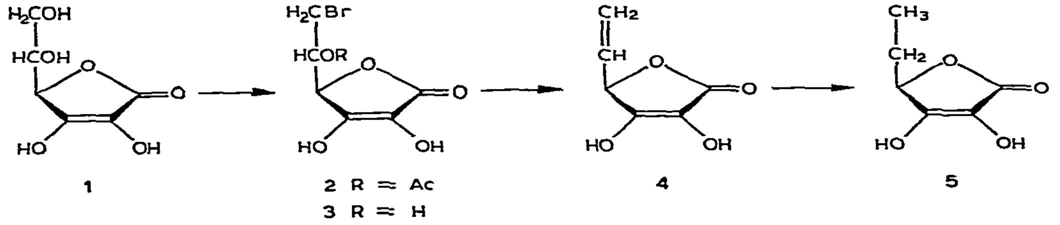
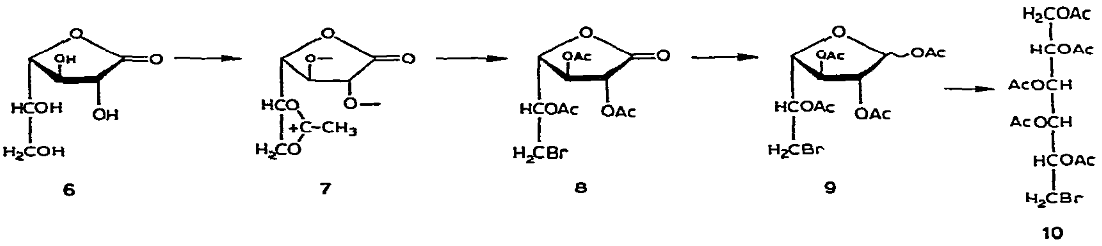
*Dedicated to Professor Kurt Heyns on the occasion of his 70th birthday.

†Reaction of aldonic acids with hydrogen bromide I.



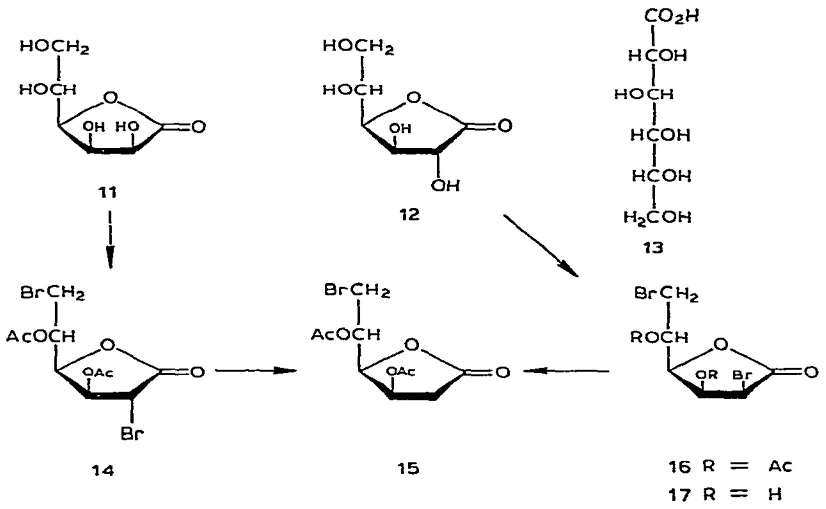
The smooth reaction of ascorbic acid with HBr–AcOH indicated that other lactones might behave similarly, and it has indeed been found that hexonolactones react to give acetylated mono- or di-bromolactones. Treatment of D-galactono-1,4-lactone (**6**) with HBr–AcOH for a few hours at room temperature gave a 63% yield of the acetylated 6-bromo-6-deoxy-D-galactono-1,4-lactone (**8**). The reaction probably proceeds *via* the acetoxonium ion **7**; acetylation of O-2 and O-3 may take place before or after formation of **7** and **8**. Anhydrous calcium D-galactonate also gave **8** in the same yield when treated with HBr–AcOH. On more prolonged treatment of **6**, the yield of **8** decreased and a mixture of dibromolactones was formed. The latter products have not been studied in detail; however, the dibromolactone (**16**), also obtained from D-gluconic acid (see later), was isolated in low yield.



Reduction of **8** with bis(1,2-dimethylethyl)borane[4], followed by acetylation, gave a low yield of the anomeric 1,2,3,5-tetra-*O*-acetyl-6-bromo-6-deoxy-D-galactofuranoses (**9**). Reduction with excess sodium borohydride yielded 6-bromo-6-deoxy-D-galactitol, isolated as the acetate **10**.

Reaction of D-mannono-1,4-lactone (**11**) with HBr–AcOH for 2–3 h gave a high yield of the dibromolactone **14**. The introduction of a bromide group at C-2 with inversion of configuration indicates that a 2,3-acetoxonium, as well as a 5,6-ion, have been involved in the formation of **14**. Thus, acetoxonium ions fused to 1,4-lactones can apparently be formed in HBr–AcOH solution, whereas benzoxonium ions fused to furanose or pyranose rings do not appear to arise with this reagent[2].

D-Glucono-1,4- or -1,5-lactone, or calcium D-gluconate, all gave the dibromolactone **16** when treated for 18 h with HBr–AcOH. Again, inversion had taken place at C-2, indicating that a 2,3-acetoxonium ion had been an intermediate. Since O-2 and O-3 are *trans* oriented, this ion could not be formed from the lactone **12**. The bromo residue at C-2 is therefore more likely to be introduced *via* D-gluconic acid (**13**), which after partial acetylation could form a 2,3-acetoxonium ion and then undergo substitution with a bromide group at C-2. The bromide group at C-6 is probably introduced *via* a 5,6-acetoxonium ion, which could arise from the 1,4-lactone or from the acid.



The diacetate (**16**) was formed in ~75% yield from calcium D-gluconate, as seen from n.m.r. spectra, but it was difficult to crystallize it from the crude product. When the reaction mixture was treated with methanol, the deacetylated product **17** was formed, and it could be readily isolated in 40–50% yield. On acetylation it gave **16** in high yield.

Treatment of the acetylated lactones **14** and **16** with sodium iodide in acetone in the presence of trifluoroacetic acid led to hydrogenolysis of the bromide group at C-2 and gave good yields of the 6-bromo-2-deoxylactone **15**. This result shows that **14** and **16** are epimeric at C-2. The debromination with sodium iodide was first described by Paulsen and Eberstein[5] and, as expected from their results, the bromide group at C-6 was not reduced. The configuration at C-2 in **14** and **16** may be deduced from the p.m.r. data. The $J_{2,3}$ value of **14** is 0 Hz, whereas those of **16** and **17** are ~5 Hz, indicating that H-2 and H-3 are *trans* oriented in **14** and *cis* in **16**. These structures were further confirmed by reduction to dibromodideoxy-D-glucose and -D-mannose derivatives[6].

EXPERIMENTAL

General methods. — The solution of hydrogen bromide in acetic acid (HBr–AcOH) was prepared by saturating glacial acetic acid with anhydrous hydrogen bromide at 0°. It contained ~35% of hydrogen bromide. Optical rotations were measured with a Perkin–Elmer 141 instrument. ^{1}H-N.m.r. and ^{13}C-n.m.r. spectra were obtained on Bruker HX-90, WH-90, and HX-270 instruments. Melting points are uncorrected.

*6-Bromo-6-deoxy-*L*-ascorbic acid* (**3**). — To L-ascorbic acid (**1**) (10 g) was added 50 ml of HBr–AcOH, and the mixture was stirred for 20 h at room temperature. Water (200 ml) was then added, and the solution was kept for 2 h in order to hydrolyze the 5-acetate **2** to **3**. Evaporation and co-evaporation with ethanol and ethyl acetate gave a semicrystalline residue, which was triturated with chloroform (~75 ml) and allowed to crystallize overnight. Filtration under nitrogen gave 11.5 g (85%) of **3**, m.p. 165–168°. Recrystallization from ethyl acetate–chloroform gave 10.2 g (75%), m.p. 170–172°. Further recrystallization from ethyl acetate gave a product with m.p. 170–172°, $[\alpha]_D^{20}$ −6.3° (*c* 1.2, water) (lit.[3] m.p. 175–176°, $[\alpha]_D^{25}$ −7.5°); ^{1}H-n.m.r. (D_2O): δ 5.06 (1 H, $J_{4,5}$ 2.0 Hz, H-4); 4.20 (1 H, $J_{5,6}$ 5.8 Hz, H-5), 3.64 (1 H, $J_{6,6'}$ 10.8 Hz, H-6), and 3.57 (1 H, $J_{6',5}$ 7.6 Hz, H-6'); ^{13}C-n.m.r. (D_2O): 173.8 (C-1), 156.1 (C-3), 118.81 (C-2), 77.4 (C-4), 69.7 (C-5), and 33.5 p.p.m. (C-6).

Anal. Calc. for $C_6H_7BrO_5$: C, 30.15; H, 2.95; Br, 33.43. Found: C, 30.14; H, 3.04; Br, 32.86.

*5,6-Dideoxy-*D-glycero*-hex-2,3:5,6-dienono-1,4-lactone* (**4**). — L-Ascorbic acid (10 g) was treated with HBr–AcOH (50 ml) for 20 h as just described. The solution was then evaporated, and toluene was added twice and again evaporated. The residue thus obtained consisted of the crude, syrupy acetate **3**, which was only characterized through its ^{13}C-n.m.r. spectrum (D_2O): 170.3 (C-1), 151.2 (C-3), 118.7 (C-2), 74.5 (C-4), 69.5 (C-5), and 28.0 p.p.m. (C-6).

The product was dissolved in a mixture of water (50 ml) and acetic acid (50 ml). The solution was stirred at room temp. while zinc dust (30 g) was added in portions during 1 h. The mixture was stirred for an additional hour and filtered, and the filtrate evaporated. The residue was dissolved in water and poured through a column of Amberlite IR-120 (OH^-) ion-exchange resin to remove cations. Evaporation and co-evaporation with ethanol and ethyl acetate, and crystallization from ethyl acetate–chloroform gave 7.1 g (88%) of **4**, m.p. 140–145°. One recrystallization from the same solvent gave 5.5 g (68%), m.p. 147–150°. A sample was recrystallized from ethyl acetate, m.p 151–153°, $[\alpha]_D^{20}$ −94 3° (*c* 1 5, ethanol); ^{1}H-n.m.r. (D_2O): δ 5.75 (1 H, $J_{5,6}$ 16.8 Hz, H-5), 5.58 (1 H, $J_{6,6'}$ 1 Hz, H-6), 5.49 (1 H, $J_{6',5}$ 10.0 Hz, H-6'), and 5.22 (1 H, $J_{4,5}$ 7.2 Hz, H-4); ^{13}C-n.m.r. (D_2O): 173.7 (C-1), 157.4 (C-3), 131.8 (C-5), 127.7 (C-6), 117.7 (C-2), and 78.3 p.p.m. (C-4).

Anal. Calc. for $C_6H_6O_4$: C, 50.71; H, 4.26. Found: C, 50.61; H, 4.23.

*5,6-Dideoxy-*D-glycero-*hex-2,3-enono-1,4-lactone* (**5**). — A solution of **4** (3.0 g) in ethanol (30 ml) was hydrogenated for 3 h at room temp. and 1 atm. pressure in the presence of 5% palladium-on-barium sulfate (300 mg) as catalyst. Filtration and evaporation, followed by crystallization from ethyl acetate–pentane, gave 2.6 g (87%) of **5**, m.p. 111–113°. Recrystallization from the same solvent gave **5**, m.p. 117–119°, $[\alpha]_D^{20}$ +27.1° (*c* 2.2, ethanol); ^{13}C-n.m.r. (D_2O): 174.1 (C-1), 158.8 (C-3), 117.8 (C-2), 78.4 (C-4), 24.7 (C-5), and 7.5 p.p.m. (C-6).

Anal. Calc. for $C_6H_8O_4$: C, 50.00; H, 5.59. Found: C, 49.84; H, 5.53.

*2,3,5-Tri-*O*-acetyl-6-bromo-6-deoxy-*D*-galactono-1,4-lactone* (**8**). — D-Galactono-1,4-lactone (**6**) (10.0 g) was dissolved in HBr–AcOH (75 ml) and kept for 4 h at room temp. Acetic anhydride (25 ml) was then added, and the mixture was kept for 1 h. It was then poured on ice and stirred, and after 2 h the crystalline material was filtered off, washed with water, and dried. The product (15 g) was recrystallized from ethanol to give 13.0 g (63%) of **8**, m.p. 98–100°. Recrystallization from ethanol gave pure **8**, m.p. 100–101°, $[\alpha]_D^{20}$ −10.1° (*c* 2.5, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 5.65 (1 H, $J_{2,3}$ 7.0 Hz, H-2), 5.39, (1 H, $J_{3,4}$ 7.0 Hz, H-3), 5.23 (1 H, $J_{5,6} = J_{5,6'} = 7.0$ Hz, H-5), 4.85 (1 H, $J_{4,5}$ 2.2 Hz, H-4), and 3.53 (2 H, H-6, H-6′); ^{13}C-n.m.r. ($CDCl_3$): 168.1 (C-1), 77.5 (C-4), 72.4 (C-3), 72.1 (C-2), 70.3 (C-5), and 27.6 p.p.m. (C-6).

Anal. Calc. for $C_{12}H_{15}BrO_8$: C, 39.26; H, 4.12; Br, 21.77. Found: C, 39.28; H, 4.10; Br, 21.75.

*1,2,3,5-Tetra-*O*-acetyl-6-bromo-6-deoxy-β-*D*-galactofuranose* (*β anomer of* **9**). — A solution of bis(1,2-dimethylpropyl)borane was prepared from borane–dimethyl sulfide (1.0 ml) in tetrahydrofuran (5 ml) and 2-methyl-2-butene[7] (2.17 ml). The solution was cooled in ice and a solution of lactone **8** (0.92 g) in oxolane ("tetrahydrofuran") (5 ml) was added with stirring during 10 min. The mixture was kept overnight at room temperature. Water (4 ml) was added, and the solution was boiled for 30 min. It was then cooled in ice, mixed with an excess of solid sodium hydrogencarbonate, stirred while 40% hydrogen peroxide (3.4 ml) was added dropwise in the course of 15 min, and stirring continued for 1 h. Most of the solvent was then evaporated, and the residue was extracted with dichloromethane. The extract was dried and evaporated, and the residue was acetylated with acetic anhydride in pyridine. The product thus obtained (500 mg) crystallized from ether–pentane to give 250 mg (25%) of the *β* anomer of **9**, m.p. 140–143°; recrystallization from ether–pentane or from ethanol gave pure **7**, m.p. 144–146°, $[\alpha]_D^{20}$ −36.8° (*c* 2.8, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 6.19 (1 H, $J_{1,2}$ ~0 Hz, H-1), 5.30 (1 H, $J_{5,6}$ 6.5 Hz, H-5), 5.20 (1 H, $J_{2,3}$ 1.5 Hz, H-2), 5.04 (1 H, $J_{3,4}$ 5 Hz, H-3), 4.36 (1 H, $J_{4,5}$ 3.5 Hz, H-4), 3.56 (1 H, $J_{6,6'}$ 6.5 Hz, H-6), and 3.48 (1 H, $J_{6,6'}$ 11.0 Hz, H-6′).

Anal. Calc. for $C_{14}H_{19}BrO_9$: C, 40.89; H, 4.66; Br, 19.43. Found: C, 40.91; H, 4.62; Br, 19.65.

The material in the mother liquor contained smaller amounts of the *α* anomer of **9**, as seen from n.m.r. spectra. It was not further purified.

*1,2,3,4,5-Penta-O-acetyl-6-bromo-6-deoxy-*D*-galactitol* (**10**). — To a solution of the lactone **8** (1.0 g) in ethanol (20 ml) was added Amberlite IR-120 ion-exchange resin (~10 g). The mixture was stirred at 0°, sodium borohydride (500 mg) was added during 20 min, and the mixture was stirred for an additional 30 min. The residue was filtered off, the filtrate was evaporated, and the residue was acetylated with acetic anhydride–pyridine. Processing in the usual way gave 1.0 g of a product that crystallized from ether–pentane to give 650 mg (52%) of **10**, m.p. 132–135°; recrystallization from the same solvent gave pure **10**, m.p. 136–138°, $[\alpha]_D^{20}$ −10.3° (*c* 2.2, chloroform); ^{13}C-n.m.r. ($CDCl_3$): 69.5, 68.1, 67.7 (C-2, C-3, C-4, and C-5), 62.3 (C-1), and 29.1 p.p.m. (C-6).

Anal. Calc. for $C_{16}H_{23}BrO_{10}$: C, 42.21; H, 5.09; Br, 17.55. Found: C, 42.62; H, 5.30; Br, 17.43.

*3,5-Di-O-acetyl-2,6-dibromo-2,6-dideoxy-*D*-glucono-1,4-lactone* (**14**). — D-Mannono-1,4-lactone (2.0 g) was dissolved in HBr–AcOH (15 ml) and kept at room temp. for 3 h. Acetic anhydride (10 ml) was then added and after 1 h the solution was poured into ice–water and stirred. The crystalline precipitate was filtered off, washed with water, and dried to give 3.12 g (72%) of **13**, m.p. 86–89°. Recrystallization from ether gave the pure product, m.p. 93–95°, $[\alpha]_D^{20}$ +51.4° (*c* 2.3, chloroform); ^{1}H-n.m.r. ($CDCl_3$); δ 5.52 (1 H, $J_{3,4}$ 3.4 Hz, H-3), 5.31 (1 H, $J_{5,6}$ 3.0 Hz, H-5), 5.09 (1 H, $J_{4,5}$ 9.6 Hz, H-4), 4.16 (1 H, $J_{2,3}$ ≃0 Hz, H-2), 3.79 (1 H, $J_{6,6'}$ 12 Hz, H-6), and 3.67 (1 H, $J_{6',5}$ 4.2 Hz, H-6'); ^{13}C-n.m.r. ($CDCl_3$): 168.8 (C-1),77.9 (C-4), 73.5 (C-3), 66.7 (C-5), 38.0 (C-2), and 32.3 p.p.m. (C-6).

Anal. Calc. for $C_{10}H_{12}Br_2O_6$: C, 30.95; H, 3.12; Br, 41.19. Found: C, 30.96; H, 3.11; Br, 40.98.

*2,6-Dibromo-2,6-dideoxy-*D*-mannono-1,4-lactone* (**17**). — To calcium D-gluconate monohydrate (50 g) was added HBr–AcOH (300 ml) and the mixture was stirred at room temp. for 18 h Methanol (500 ml) was then added and the solution was kept overnight. It was then evaporated at 50°, and water (200 ml) was twice added and evaporated. The residue was dissolved in water (100 ml) and extracted 8 times with 50-ml portions of ether. The combined ether extract was dried ($MgSO_4$) and evaporated, leaving 40 g of a semicrystalline residue. Crystallization from water (~100 ml) gave 30 g (44%) of crude **17**, m.p. ~125°. Recrystallization from ethyl acetate–pentane gave 26 g (38%), m.p. 130–132°. Additional recrystallizations gave pure **17**, m.p. 131–133°, $[\alpha]_D^{20}$ +52.2° (*c* 0.7, ethyl acetate); ^{1}H-n.m.r. (D_2O): δ 5.22 (1 H, $J_{2,3}$ 4.4 Hz, H-2), 4.67 (1 H, $J_{3,4}$ 3.2 Hz, H-3), 4.64 (1 H, $J_{4,5}$ 8.5 Hz, H-4), 4.21 (1 H, $J_{5,6}$ 2.6 Hz, H-5), 3.80 (1 H, $J_{6,6'}$ 11.6 Hz, H-6), and 3.67 (1 H, $J_{5,6'}$ 5.0 Hz, H-6'); ^{13}C-n.m.r. (D_2O): 174.8 (C-1), 82.6 (C-4), 70.0 (C-3), 67.1 (C-5), 48.5 (C-2), and 37.5 p.p.m. (C-6).

Anal. Calc. for $C_6H_8Br_2O_4$: C, 23.71; H, 2.65; Br, 52.58. Found: C, 23.76; H, 2.66; Br, 52.68.

*3,5-Di-O-acetyl-2,6-dibromo-2,6-dideoxy-*D*-mannono-1,4-lactone* (**16**). — To the dibromolactone **17** (10.0 g) in acetic anhydride (25 ml) was added 60% aqueous perchloric acid (1 ml). The solution was kept for 2 h at room temp., and it was then poured into ice–water and stirred until the acetic anhydride was hydrolyzed. The crystalline precipitate was filtered off, washed with water, and dried to give 12.5 g (98%) of **16**, m.p. 98–103°. One recrystallization from ether–pentane gave 11.0 g (86%), m.p. 103–105°. Further recrystallization did not change the m.p., $[\alpha]_D^{20}$ +11.7° (*c* 3.2, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 5.87 (1 H, $J_{3,4}$ 3.5 Hz, H-3), 5.28 (1 H, $J_{5,6}$ 3.0 Hz, H-5), 4.90 (1 H, $J_{2,3}$ 5.0 Hz, H-2), 4.86 (1 H, $J_{4,5}$ 9.5 Hz, H-4), 3.73 (1 H, $J_{6,6'}$ 12.0 Hz, H-6), and 3.68 (1 H, $J_{5,6'}$ 3.7 Hz, H-6'); ^{13}C-n.m.r. ($CDCl_3$): 169.0 (C-1), 77.6 (C-4), 68.7 (C-3), 66.8 (C-5), 42.9 (C-2), and 32.3 p.p.m. (C-6).

Anal. Calc. for $C_{10}H_{12}Br_2O_6$: C, 30.95; H, 3.12; Br, 41.19. Found: C, 30.96; H, 3.09; Br, 41.40.

*3,5-Di-O-acetyl-6-bromo-2,6-dideoxy-*D-arabino-*1,4-lactone* (**15**). — A solution of **16** (1.0 g) in acetone (18 ml) and trifluoroacetic acid (2 ml) was stirred with sodium iodide (5 g) for 20 h at room temp. The mixture was then diluted with chloroform, washed with water and with aqueous sodium hydrogensulfite, dried, and evaporated. The residue was crystallized from ether–pentane to give 697 mg (87%) of **15**, m.p. 94–97°. Two recrystallizations from ether–pentane gave the pure product, m.p. 99–100°, $[\alpha]_D^{20}$ −2.9° (*c* 1.3, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 5.63 (1 H, $J_{3,4}$ 3.5 Hz, H-3), 5.28 (1 H, $J_{5,6}$ 3.0 Hz, H-5), 4.75 (1 H, $J_{4,5}$ 9.5 Hz, H-4), 3.79 (1 H, $J_{6,6'}$ 12.0 Hz, H-6), 3.68 (1 H, $J_{5,6'}$ 4.0 Hz, H-6'), and 2.93 (1 H, $J_{2,2'}$ 18, $J_{2,3}$ 6.0, $J_{2',3} \simeq 0$ Hz, H-2); ^{13}C-n.m.r. ($CDCl_3$): 172.8 (C-1), 79.5 (C-4), 68.3 (C-3), 67.2 (C-5), 36.9 (C-2), and 32.9 p.p.m. (C-6).

Anal. Calc. for $C_{10}H_{13}BrO_6$: C, 38.85; H, 4.24; Br, 25.85. Found: C, 38.91; H, 4.21; Br, 25.86.

By the same procedure **14** was converted into **15** in 72% yield. The reaction was faster in this case, only a 2-h treatment with sodium iodide being required.

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