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Synthesis of 2-(α-D-glucopyranosyl)benzoic acid by an intramolecular Friedel–Crafts reaction

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Abstract

6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl chloride reacted with silver tetrafluoroborate to give the internal *C*-glycoside, 1,2″-anhydro-2′-(6″-*O*-acetyl-3″,4″-di-*O*-benzyl-α-D-glucopyranosyl)phenylmethanol (**2**) with complete α-stereoselectivity and good yield. Oxidation of **2** by ruthenium (VIII) oxide gave the lactone, 3,4-dihydro-(6-*O*-acetyl-3,4-di-*O*-benzoyl-1,2-dideoxy-α-D-glucopyranoso)[2,1-*c*]-2-benzopyran-1-one the structure of which was analysed by X-ray diffraction. Alternatively, treatment of **2** by ozone followed by methanolysis gave the title product in 60% yield. © 1996 Elsevier Science Ltd.

Keywords: *C*-Glycoside; Friedel–Crafts reaction; Intramolecular reaction; Silver tetrafluoroborate

1. Introduction

C-Glycosylarenes form a class of natural products derived from plants or microorganisms which are characterized by the presence of a carbon–carbon linkage between the anomeric centre of a carbohydrate moiety and an aryl component. Their stability towards chemical or enzymatic hydrolysis can be used in biochemical studies and may

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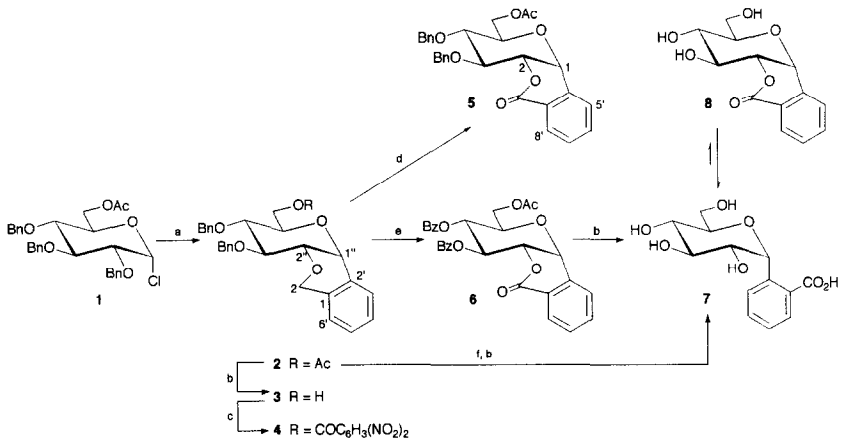
contribute in some cases to their activity as antibiotics [1]. Their synthesis has received considerable attention in the last few years [2] and has been mostly achieved by the stereoselective *C*-glycosylation of aromatic systems. The most popular approach consists in a Friedel–Crafts reaction between a glycosyl donor (anomeric halide, acetate, trichloroacetimidate, or even glycoside) and an aryl compound which usually needs to be activated by electron-donating substituents. Various Lewis acid promoters have been used according to the nature of the donor leaving group and the nucleophilicity of the aromatic compound. As a rule, a much lower reactivity has always been observed with pyranoses, which usually give the thermodynamically more stable 1,2-*trans* anomer, whereas more flexible furanoses afford mixtures of anomers. Silver (I) activation of pyridyl thioglucopyranosides was the first reported [3] method giving acceptable yields of *C*-aryl α-D-glucopyranosides. The most important breakthrough in the stereoselective preparation of 1,2-*cis* *C*-aryl glycosides came from the use of an internal *C*-glycosylation by Friedel–Crafts reaction between a 2-*O*-benzyl substituent and the anomeric centre [4,5]. When applied to benzylated furanoses this process, followed by oxidative cleavage of the auxiliary carbon–oxygen linkage, gave a convenient access to 1,2-*cis* *C*-aryl glycofuranosides. The internal *C*-arylation procedure has been successfully applied to D-mannopyranose derivatives, but required a reactive 2-*O*-benzyl substituent and rather drastic conditions (acetic acid–3 M sulfuric acid at 80–90 °C); besides, no further transformation has been reported [5]. There are, however, a few indications in the literature [3,6,7] that activation of a thioglycopyranoside or a pyranosyl fluoride by silver (I) salts could lead to an internal *C*-glycosylation without the need for electron-donating groups in the benzyl reacting moiety.

We now report on the use of silver tetrafluoroborate for an intramolecular Friedel–Crafts reaction of a benzylated glucopyranosyl chloride and on oxidative procedures for the cleavage of the connecting carbon–oxygen bond.

2. Results and discussion

We have recently reported [8–10] that silver tetrafluoroborate efficiently promotes the addition of alkynyltributylstannanes to hexopyranosyl halides. A transient oxonium species, stabilized by its counter-anion BF_4^-, reacts smoothly at 0 °C with the weakly nucleophilic alkyne π system. It is known that tetrafluoroborate ions can release fluoride ions to an electron-deficient carbon centre [11]; glycosyl fluorides have thus been obtained [12] by treatment of the corresponding chlorides with silver tetrafluoroborate. This will certainly contribute to the stabilization of an oxonium intermediate which could also be generated by complexation of an α-fluoride with BF_3. As a matter of fact, a 2-azido-2-deoxy-α-D-glucopyranosyl chloride reacting with an alkynylstannane in the presence of silver tetrafluoroborate led to the corresponding α-fluoride when the reaction was quenched with a base before completion [8,9]. Olah and Kuhn [13] have shown that σ-complexes, stable at low temperatures, could be isolated from the reaction of an aromatic compound and an alkyl or acyl chloride or bromide in the presence of $AgBF_4$. On heating, these complexes led to the products of Friedel–Crafts alkylation or acylation.



Scheme 1. (a) $AgBF_4$, $(CH_2Cl)_2$; (b) NaOMe, MeOH; (c) $3,5(NO_2)_2C_6H_3COCl$–NEt_3–DMAP, CH_2Cl_2; (d) PCC, $(CH_2Cl)_2$; (e) $RuCl_3 \cdot xH_2O$–KIO_4, MeCN–CCl_4–H_2O; (f) O_3, CH_2Cl_2.

When 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl chloride **1** [10] was treated with 1.2 equiv of silver tetrafluoroborate in 1,2-dichloroethane at 0 °C under rigorously anhydrous conditions, no fluoride formation could be detected, but the crystalline internal *C*-glycoside **2** was isolated in 74% yield instead (Scheme 1). Its ^1H NMR spectrum in deuterated benzene revealed a large geminal coupling constant (J 15.8 Hz) for the benzylic methylene group which is incorporated in a cycle and two well differentiated signals in the aromatic region, corresponding to the ortho protons H-6′ (δ 6.61) and H-3′ (δ 7.56). The coupling constant (J 6.1 Hz) between H-1″ and H-2″ has a higher value than expected for an α-*C*-glucopyranoside (J 3–5.5 Hz) and the other coupling constants of the pyranose protons ($J_{2'',3''} = J_{3'',4''} = 8.7$ and $J_{4'',5''}$ 9.7 Hz) indicate a slight distorsion of the $^4C_1$ chair conformation.

Deacetylation of compound **2** with sodium methoxide in methanol gave the crystalline alcohol **3**, which could be converted into a crystalline 3,5-dinitrobenzoate **4**. Both compounds showed again a high value for their $J_{1'',2''}$ coupling constant (6.4 and 6.1 Hz in **3** and **4**, respectively). Unfortunately, none of compounds **2**–**4** could afford suitable crystals for X-ray diffraction analysis.

Cleavage of the auxiliary bond between C-2 and O-1 was next investigated. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has been recently reported [14] to convert isochromans to cationic species which can be trapped by water or alcohols to give lactols or acetals. Treatment of **2** with DDQ in moist dichloromethane gave a mixture of partially debenzylated products [15] where oxidation of the intracyclic methylene group has not occurred.

Pyridinium chlorochromate (PCC) has been used [16] to oxidize 5,6-dihydropyrans to the corresponding α,β-unsaturated δ-lactones; by this means isochroman has been converted into dihydroisocoumarin in 80% yield. Treatment of compound **2** with 5 equiv of PCC in refluxing 1,2-dichloroethane for 17 h gave only 25% of the expected lactone **5** together with unreacted **2** (40%). The ^1H NMR spectrum of **5** in deuterated benzene showed that the two benzyl ethers have not been oxidized and that the H-2″ and H-6′

signals have been shifted downfield ($\Delta\delta$ +0.19 and +1.59, respectively) by the carbonyl function.

Internal *C*-aryl glycofuranosides have been oxidized [5] by ruthenium (VIII) oxide into the corresponding lactones with a remarkable selectivity for the benzylic methylene group as compared to the methine one. It is of course expected [17] that a similar oxidation of compound **2** will also affect the two *O*-benzyl groups at C-3″ and C-4″. Indeed, treatment of compound **2** with a catalytic amount of ruthenium (III) chloride hydrate and 12 equiv of potassium periodate in 2:2:3 acetonitrile–carbon tetrachloride–water for 24 h at room temperature gave the crystalline lactone **6** together with a mixture of incompletely oxidized products. After isolation and further oxidation of the reaction mixture, an overall 47% yield of **6** could be obtained (Scheme 1). Its ^{1}H NMR spectrum in deuterated chloroform showed the disappearance of all benzylic methylene signals and the shift of H-2″ and H-6′ signals ($\Delta\delta$ +0.70 and +1.28, respectively) due to the vicinity of the carbonyl function. The $J_{1,2}$ coupling constant kept the same value (6.1 Hz) as in **2**, the pyranose ring showing a conformation close to the $^4C_1$ chair ($J_{2,3} = J_{3,4} = 9.2$ and $J_{4,5}$ 8.6 Hz). The presence of a lactone ring was also ascertained by a ^{13}C signal of the carbonyl function (δ 161.51), distinct from C=O signals of the benzoyl (δ 165.15 and 165.59) and acetyl (δ 170.60) groups.

The structure of **6** was confirmed by an X-ray diffraction analysis [1] (Fig. 1). Table 1 shows a comparison between the torsion angles of the pyranose ring for compound **6**, α-D-glucopyranose [18] and penta-*O*-acetyl bergenine [19], an analogous tricyclic lactone with a *S* configuration at C-1. It appears that both lactones have a slightly distorted $^4C_1$ chair geometry of their pyranose ring. Dihedral angles H-1–C-1–C-2–H-2 of 38° (*J* 6.1 Hz) and −174.8° (*J* 10 Hz) are found for **6** and bergenine derivative respectively. Torsion angles C-2–O–C=O and H-2–C-2–O–C for **6** are −165.8° and −158.7°, respectively, showing that the dihydropyran ring has a $^OH_3$ half-chair conformation. Their respective values of 160.8° and −63.3° in the bergenine derivative fit with a ^3H_O geometry, accounting for [19] the anisotropic effect of the carbonyl group upon H-2 (δ 4.29 instead of 4.94 in **6**).

Treatment of lactone **6** with 4 equiv of sodium methoxide in methanol for 24 h at room temperature gave 2-(α-D-glucopyranosyl)benzoic acid **7** in 87% yield. Its ^{1}H NMR spectrum in deuterium oxide showed the H-1 signal as a doublet at δ 5.34 ($J_{1,2}$ 4.6 Hz) and coupling constants for the pyranose protons ($J_{2,3} = J_{3,4} = 7.6$, $J_{4,5}$ 8.1 Hz) reflecting a mixture of conformers or a distorted chair conformation.

The formation of carboxylic acid **7** can be explained by the reaction of an intermediate methyl ester with methoxide ions according to the known [20,21], but infrequent, $B_{Al}2$ mechanism of methyl–oxygen cleavage. Methyl benzoate, produced by transesterification of benzoyl groups, undergoes the same cleavage to give sodium benzoate.

When a sample of **7** in deuterium oxide was left for 48 h at room temperature, TLC indicated the formation of a faster-migrating compound which was shown to be the

[1] Tables of atomic coordinates, bond lengths, and bond angles have been deposited with the Cambridge Crystallographic Data Centre. These tables may be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

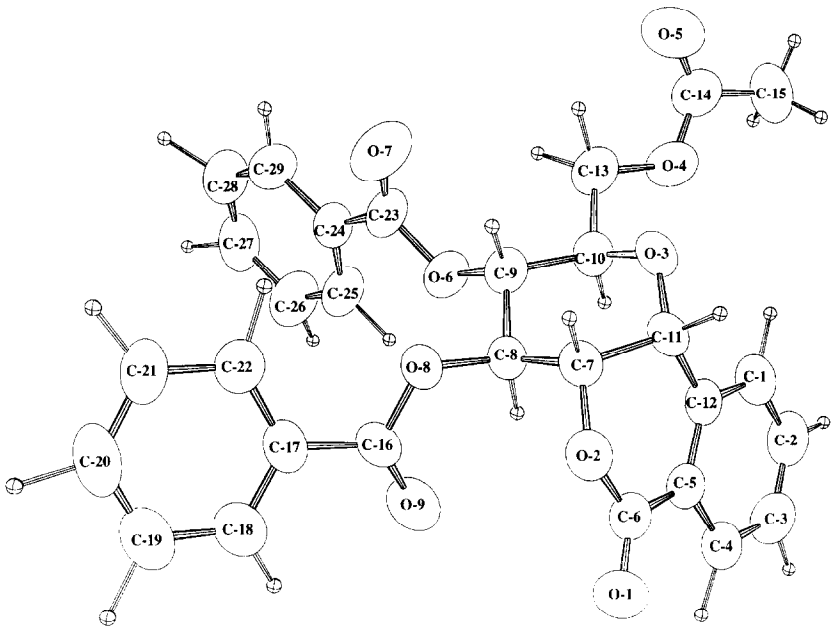


Fig. 1. X-Ray crystal structure of 3,4-dihydro-(6-*O*-acetyl-3,4-di-*O*-benzoyl-1,2-dideoxy-α-D-glucopyranoso) [2.1-*c*]-2-benzopyran-1-one (**6**).

lactone **8** (~ 20% in a mixture with **7**) by ^{1}H and ^{13}C NMR analysis. The signal of H-1 appeared at δ 5.40 ($J_{1,2}$ 6.6 Hz), not far from the corresponding signal in **7**; but the signal of H-2 was shifted downfield (Δδ +0.68) by the carbonyl function. A signal at low field (δ 7.81) in the aromatic region was found for H-8′, more shifted by the vicinal lactone than it was by the carboxylic acid. The ^{13}C signal of the lactone carbonyl group appeared at δ 165.0, whereas the corresponding signal in the carboxylic acid **7** was found at δ 178.4.

Ozone has been used [22] to oxidize benzyl ethers and, in the case of polybenzylated compounds such as carbohydrate derivatives, mixtures of partially benzoylated products have been obtained because of the two possible pathways for insertion of ozone into methylene groups. Nevertheless, ozonisation followed by deacylation offers a mild and

Table 1
Ring torsion angles for **6**, (i) α-D-glucopyranose and (ii) penta-*O*-acetyl bergenine [a]

	6	(i) [18]	(ii) [19]
O-5–C-1–C-2–C-3	51.3	54.1	63.7
C-1–C-2–C-3–C-4	−51.7	−51.3	−62.3
C-2–C-3–C-4–C-5	56.0	53.3	58.3
C-3–C-4–C-5–O-5	−60.4	−57.5	−56.0
C-4–C-5–O-5–C-1	62.9	62.2	–
C-5–O-5–C-1–C-2	−58.0	−60.9	−61.9

[a] Carbohydrate numbering for the pyranose rings.

non-acidic method for deprotection of benzylated carbohydrates. According to the results obtained above with ruthenium (VIII) tetraoxide, we expected that prolonged treatment of **2** with ozone would oxidize both benzyl ethers and the isochroman methylene group. When compound **2** in dichloromethane was treated at 0 °C by a stream of oxygen containing 2% of ozone for 8 h, then with 4 equiv of sodium methoxide in methanol at room temperature for 24 h, the acid **7** identical to the product described above was obtained in 60% yield (Scheme 1).

3. Experimental

General methods.—Melting points were recorded with an electrothermal apparatus and are uncorrected. Optical rotations were measured at 20 °C on a Polartronic-D polarimeter. ^{1}H NMR spectra were recorded on a Bruker ARX 400 (400.13 MHz) spectrometer. Chemical shifts are reported in δ values relative to tetramethylsilane. ^{13}C NMR spectra were recorded on a Bruker ARX 400 spectrometer operating at 100.62 MHz. Thin layer chromatography was conducted on precoated Silica Gel 60 F 254 (Art. 5554; E. Merck) with detection by UV fluorescence and charring with 1:10 H_2SO_4–EtOH. Flash chromatography was performed using Silica Gel 60 (E. Merck, 40–63 μm). Ether and petroleum ether refer to diethyl ether and light petroleum (bp 40–65 °C), respectively. All solvents were dried and distilled using standard methods [23]. Elemental analyses were performed by the Service Central de Microanalyse du Centre National de la Recherche Scientifique (Gif-sur-Yvette, France).

1,2″-Anhydro-2′-(6″-O-acetyl-3″,4″-di-O-benzyl-α-D-glucopyranosyl)phenylmethanol (**2**).—A mixture of chloride **1** ([10], 1.53 g, 3 mmol), and 3 Å molecular sieves (3 g) in dry 1,2-dichloroethane (40 mL), was stirred at room temperature under nitrogen for 1 h, then was cooled to −30 °C. Dry silver tetrafluoroborate (701 mg, 3.6 mmol) was rapidly added and the temperature was allowed to rise slowly to 0 °C. The mixture was stirred under nitrogen at 0 °C for 2 h, then was diluted with dichloromethane (100 mL) and filtered over Celite. The filtrate was washed successively with saturated aq $NaHCO_3$ and water, dried, and concentrated. Flash chromatography (4:1 petroleum ether–EtOAc) gave compound **2** (1.05 g, 74%), mp 75–76 °C (from petroleum ether); $[\alpha]_D$ +123° (*c* 0.98, $CHCl_3$); R_f 0.35 (4:1 petroleum ether–EtOAc); ^{1}H NMR (C_6D_6): δ 7.56 (d, 1 H, H-3′), 7.41–7.12 (m, 10 H, 2 × Ph), 7.08 (dd, 1 H, $J_{3',4'}$ 7.6 Hz, H-4′), 7.00 (dd, 1 H, $J_{4',5'}$ 7.6 Hz, H-5′), 6.61 (d, 1 H, $J_{5',6'}$ 7.6 Hz, H-6′), 5.02 (d, 1 H, $J_{1'',2''}$ 6.1 Hz, H-1″), 4.81, 4.76, 4.62 and 4.45 (4 d, 4 H, *J* 11.2 Hz, 2 × PhCH_2), 4.51 and 4.41 (2 d, 2 H, *J* 15.8 Hz, H-2), 4.44 (dd, 1 H, $J_{5'',6''a}$ 2, $J_{6''a,6''b}$ 11.7 Hz, H-6″a), 4.31 (dd, 1 H, $J_{5'',6''b}$ 5.6 Hz, H-6″b), 4.21 (dd, 1 H, $J_{2'',3''}$ 8.7 Hz, H-2″), 3.80 (dd, 1 H, $J_{3'',4''}$ 8.7 Hz, H-3″), 3.64 (ddd, 1 H, $J_{4'',5''}$ 9.7 Hz, H-5″), 3.52 (dd, 1 H, H-4″) and 1.70 (s, 3 H, OAc); ^{1}H NMR ($CDCl_3$): δ 7.48–7.21 (m, 13 H, H-3′,4′,5′, 2 × Ph), 6.99 (d, 1 H, $J_{5',6'}$ 7.1 Hz, H-6′), 5.11 (d, 1 H, $J_{1'',2''}$ 6.1 Hz, H-1″), 4.94, 4.83 and 4.55 (3 d, 4 H, *J* 11.2 Hz, 2 × PhCH_2), 4.77 and 4.70 (2 d, 2 H, *J* 15.8 Hz, H-2), 4.31 (m, 2 H, H-6″), 4.24 (dd, 1 H, $J_{2'',3''}$ 8.7 Hz, H-2″), 3.87 (dd, 1 H, $J_{3'',4''}$ 8 Hz, H-3″), 3.65–3.56 (m, 2 H, H-4″,5″) and 2.10 (s, 3 H, OAc). Anal. Calcd for $C_{29}H_{30}O_6$: C, 73.40; H, 6.37. Found: C, 73.64; H, 6.41.

*1,2″-Anhydro-2′-(3″,4″-di-*O*-benzyl-α-*D*-glucopyranosyl)phenylmethanol* (**3**).—Sodium (16 mg, 0.7 mmol) was added to a solution of **2** (475 mg, 1 mmol) in dry MeOH (30 mL). The solution was stirred for 90 min at room temperature, then neutralized with acetic acid and concentrated. The residue was chromatographed with 7:3 petroleum ether–EtOAc as eluent to give **3** (428 mg, 99%), mp 97–98 °C (from EtOH); $[\alpha]_D$ +99° (*c* 1, MeOH); R_f 0.32 (7:3 petroleum ether–EtOAc); ^{1}H NMR (C_6D_6): δ 7.57–7.16 (m, 12 H, H-3′,4′, 2 × Ph), 7.10 (dd, 1 H, $J_{4',5'}$ 7.3 Hz, H-5′), 6.72 (d, 1 H, $J_{5',6'}$ 7.6 Hz, H-6′), 5.14 (d, 1 H, $J_{1'',2''}$ 6.4 Hz, H-1″), 4.92, 4.89, 4.78 and 4.68 (4 d, 4 H, *J* 11 Hz, 2 × PhCH_2), 4.63 and 4.56 (2 d, 2 H, *J* 16.2 Hz, H-2), 4.36 (dd, 1 H, $J_{2'',3''}$ 8.9 Hz, H-2″), 3.90 (dd, 1 H, $J_{3'',4''}$ 8.6 Hz, H-3″), 3.86 (ddd, 1 H, $J_{5'',6''a}$ 2.7, $J_{6''a,6''b}$ 11.9, $J_{6''a,OH}$ 5.5 Hz, H-6″a), 3.78 (ddd, 1 H, $J_{5'',6''b}$ 4, $J_{6''b,OH}$ 7.9 Hz, H-6″b), 3.72 (dd, 1 H, $J_{4'',5''}$ 9.8 Hz, H-4″), 3.52 (ddd, 1 H, H-5″) and 1.96 (dd, 1 H, OH). Anal. Calcd for $C_{27}H_{28}O_5 \cdot 0.33\ H_2O$: C, 73.96; H, 6.59. Found: C, 73.96, H, 6.54.

*1,2″-Anhydro-2′-[3″,4″-di-*O*-benzyl-6″-*O*-(m,m′-dinitrobenzoyl)-α-*D*-glucopyranosyl]phenylmethanol* (**4**).—A mixture of **3** (87 mg, 0.2 mmol), 3,5-dinitrobenzoyl chloride (60 mg, 0.26 mmol), Et_3N (84 μL, 0.6 mmol) and 4-dimethylaminopyridine (6.1 mg, 50 μmol) in CH_2Cl_2 (5 mL) was stirred at room temperature under nitrogen for 4 h. The solution was washed with brine, dried, and concentrated. Flash chromatography (4:1 petroleum ether–EtOAc) gave **4** (89 mg, 71%), mp 185–186 °C (from EtOH); $[\alpha]_D$ +78° (*c* 0.45, $CHCl_3$); R_f 0.61 (7:3 petroleum ether–EtOAc); ^{1}H NMR (C_6D_6): δ 8.68 [d, 2 H, *J* 2 Hz, $(NO_2)_2C_6H$-*oH-o′*)], 8.47 [t, 1 H, $(NO_2)_2C_6H_2$-*p*], 7.69 (d, 1 H, $J_{3',4'}$ 7.6 Hz, H-3′), 7.49–7.02 (m, 12 H, H-4′,5′, 2 × Ph), 6.65 (d, 1 H, $J_{5',6'}$ 7.6 Hz, H-6′), 5.01 (d, 1 H, $J_{1'',2''}$ 6.1 Hz, H-1″), 4.84, 4.79, 4.61 and 4.40 (4 d, 4 H, *J* 11.2 Hz, 2 × PhCH_2), 4.55 and 4.42 (2 d, 2 H, *J* 15.8 Hz, H-2), 4.52 (dd, 1 H, $J_{5'',6''a}$ 3, $J_{6''a,6''b}$ 11.7 Hz, H-6″a), 4.47 (dd, 1 H, $J_{5'',6''b}$ 7.1 Hz, H-6″b), 4.22 (dd, 1 H, $J_{2'',3''}$ 8.1 Hz, H-2″), 3.88 (dd, 1 H, $J_{3'',4''}$ 7.6 Hz, H-3″), 3.84 (ddd, 1 H, $J_{4'',5''}$ 9.7 Hz, H-5″) and 3.42 (dd, 1 H, H-4″).

*3,4-Dihydro-(6-*O*-acetyl-3,4-di-*O*-benzyl-1,2-dideoxy-α-*D*-glucopyranoso)[2,1-c]-2-benzopyran-1-one* (**5**).—Pyridinium chlorochromate (539 mg, 2.5 mmol) was added portionwise within 4 h to a solution of **2** (237 mg, 0.5 mmol) in refluxing 1,2-dichloroethane (10 mL). The mixture was refluxed for 17 h, then was cooled and directly chromatographed with 4:1 petroleum ether–EtOAc as eluent. Starting material (95 mg, 40%) was eluted first, R_f 0.64 (3:2 petroleum ether–EtOAc). The lactone **5** (62 mg, 25%) was eluted next, R_f 0.44 (3:2 petroleum ether–EtOAc); ^{1}H NMR (C_6D_6): δ 8.20 (d, 1 H, $J_{7',8'}$ 7.6 Hz, H-8′), 7.35–6.90 (m, 13 H, H-5′,6′,7′, 2 × Ph), 4.94, 4.72, 4.47 and 4.37 (4 d, 4 H, *J* 11.2 Hz, 2 × PhCH_2), 4.84 (d, 1 H, $J_{1,2}$ 6.6 Hz, H-1), 4.40 (dd, 1 H, $J_{2,3}$ 9.2 Hz, H-2), 4.35 (dd, 1 H, $J_{5,6a}$ 2, $J_{6a,6b}$ 12.2 Hz, H-6a), 4.23 (dd, 1 H, $J_{5,6b}$ 5.6 Hz, H-6b), 3.61 (dd, 1 H, $J_{3,4}$ 8.7 Hz, H-3), 3.54 (ddd, 1 H, $J_{4,5}$ 9.2 Hz, H-5), 3.32 (dd, 1 H, H-4) and 1.68 (s, 3 H, OAc).

*3,4-Dihydro-(6-*O*-acetyl-3,4-di-*O*-benzoyl-1,2-dideoxy-α-*D*-glucopyranoso)[2,1-c]-2-benzopyran-1-one* (**6**).—Ruthenium (III) chloride hydrate (9.1 mg) and potassium periodate (1.89 g, 8.2 mmol) were added to a mixture of **2** (949 mg, 2 mmol), MeCN (20 mL), CCl_4 (20 mL), and water (30 mL). The biphasic mixture was stirred vigorously for 24 h at room temperature, further additions of ruthenium (III) chloride hydrate (2 × 4.5 mg) and potassium periodate (2 × 943 mg, 8.2 mmol) being made after 3 and 9

h. Dichloromethane (20 mL) was then added, the phases were separated, the aq phase was extracted three times with CH_2Cl_2, and the combined organic extracts were dried and concentrated. The residue was purified by flash chromatography (7:3 petroleum ether–EtOAc) as eluent. Incompletely oxidized products (475 mg) were eluted first and were set apart. The lactone **6** was eluted next and was crystallized from EtOH (310 mg, 30%), mp 220–221 °C; $[\alpha]_D$ +96° (*c* 0.97, $CHCl_3$); R_f 0.38 (7:3 petroleum ether–EtOAc); ^{1}H NMR ($CDCl_3$): δ 8.27 (d, 1 H, $J_{7',8'}$ 7.6 Hz, H-8'), 7.98–7.30 (m, 13 H, H-5',6',7', 2 × Ph), 5.67 (d, 1 H, $J_{1,2}$ 6.1 Hz, H-1), 5.65 (dd, 1 H, $J_{2,3} = J_{3,4} = 9.2$ Hz, H-3), 5.52 (dd, 1 H, $J_{4,5}$ 8.6 Hz, H-4), 4.94 (dd, 1 H, H-2), 4.49 (dd, 1 H, $J_{5,6a}$ 5.6, $J_{6a,6b}$ 12.2 Hz, H-6a), 4.24 (dd, 1 H, $J_{5,6b}$ 3.1 Hz, H-6b), 4.08 (ddd, 1 H, H-5) and 2.13 (s, 3 H, OAc). Anal. Calcd for $C_{29}H_{24}O_9$: C, 67.44; H, 4.68. Found: C, 67.17; H, 4.91.

The mixture of partially oxidized products (475 mg) was treated with ruthenium (III) chloride hydrate (5.5 mg) and potassium periodate (943 mg, 4.1 mmol) in 2:2:3 MeCN–CCl_4–water (35 mL) for 20 h at room temperature as described above to give a further amount of **6** (177 mg, 17%).

2-(α-D-Glucopyranosyl)benzoic acid (**7**).—*Method A*. Sodium (46 mg, 2 mmol) was added to a solution of lactone **6** (258 mg, 0.5 mmol) in dry MeOH (25 mL). The solution was stirred for 24 h at room temperature, then was neutralized with Amberlite CG-50 (H^+) ion-exchange resin and filtered over Celite. The filtrate was concentrated and the residue was triturated with dry ether (3 × 10 mL) to remove benzoic acid, then was purified by flash chromatography (3:3:1 EtOAc–propan-2-ol–water) to give **7** as an amorphous white solid (124 mg, 87%), $[\alpha]_D$ +101° (*c* 0.28, 0.1 M NaOMe in MeOH); R_f 0.33 (3:3:2 EtOAc–propan-2-ol–water); ^{1}H NMR (D_2O): δ 7.51–7.15 (m, 4 H, Ph), 5.34 (d, 1 H, $J_{1,2}$ 4.6 Hz, H-1), 3.84 (dd, 1 H, $J_{2,3} = J_{3,4} = 7.6$ Hz, H-3), 3.76 (dd, 1 H, H-2), 3.58 (dd, 1 H, $J_{5,6a}$ 6.1, $J_{6a,6b}$ 12.7 Hz, H-6a), 3.46 (dd, 1 H, $J_{5,6b}$ 2.5 Hz, H-6b), 3.37 (dd, 1 H, $J_{4,5}$ 8.1 Hz, H-4) and 3.20 (ddd, 1 H, H-5); ^{13}C NMR (D_2O): δ 178.35 (CO_2H), 139.70–126.76 (4 C Ar), 75.53 (C-5), 73.17 (C-3), 72.24 (C-2), 71.88 (C-1), 69.14 (C-4) and 59.97 (C-6). Anal. Calcd for $C_{13}H_{16}O_7 \cdot H_2O$: C, 51.66; H, 6.00. Found: C, 51.72; H, 5.89.

A sample of **7** in D_2O showed by TLC (3:3:2 EtOAc–propan-2-ol–water) after 48 h at room temperature the formation of 3,4-dihydro-(1,2-dideoxy-α-D-glucopyranoso)[2,1-*c*]-2-benzopyran-1-one **8** (~ 20%), R_f 0.75; ^{1}H NMR (D_2O, mixture of **7** and **8**): δ 7.81 (d, 0.2 H, $J_{7',8'}$ ~ 8 Hz, H-8'), 5.40 (d, 0.2 H, $J_{1,2}$ 6.6 Hz, H-1), 4.44 (dd, 0.2 H, $J_{2,3}$ 9.7 Hz, H-2) and 3.27 (m, 0.4 H, H-3,4); ^{13}C (D_2O): δ 165.02 (C=O), 78.15 (C-2), 74.02 and 69.17 (C-3,4), 67.73 (C-1) and 60.44 (C-6).

Method B. A stream of oxygen containing 2% of ozone was bubbled into a stirred solution of **2** (516 mg, 1 mmol) in CH_2Cl_2 (50 mL) at 0 °C for 8 h. The excess of ozone was removed by bubbling nitrogen for 10 min, then the solution was concentrated. The residue was dissolved into MeOH (50 mL) and sodium (92 mg, 4 mmol) was added. The solution was stirred for 24 h at room temperature, then was treated as described in method A to give **7** (171 mg, 60%).

X-ray structure determination.—Cell dimensions and intensity data were obtained using a CAD4 ENRAF-NONIUS automatic diffractometer with graphite monochromatized Mo K_α radiation (λ = 0.70926 Å). After Lorenz and polarization corrections the structure was solved by direct method [24] and refined by full-matrix least-squares.

Atomic scattering factors were taken from International Tables for X-ray crystallography [25] and all calculations were performed on a Digital Micro VAX 3100 computer with the MOLEN package [26].

Crystal data: $C_{29}H_{24}O_9$, $M_r = 516.51$, monoclinic, space group $P2_1$, $a = 10.866(2)$, $b = 19.374(3)$, $c = 6.101(3)$ Å and $\beta = 98.33(3)°$, $V = 1270.8(6)$ Å^3, $Z = 2$, $D_x = 1.350$ g cm^{-3}, $T = 293$ K, crystal size $0.15 \times 0.20 \times 0.40$ mm^3. The cell parameters were obtained by fitting a set of 25 high-theta reflections. The data collection ($2\Theta_{max} = 50°$, scan $\omega/2\theta = 1$, $t_{max} = 60$ s, range HKL: H -12.12 K 0.23 L 0.7, intensity controls without appreciable decay (0.4%) gave 2533 reflections from which 1498 independant ($R_{int} = 0.016$) with $I > 2\sigma(I)$. After isotropic ($R = 0.090$), then anisotropic refinement ($R = 0.062$), all the hydrogen atoms were found with a Fourier difference between 0.33 and 0.13 e Å^{-3}. Refinement (use of F magnitude; x, y, z, β_{ij} refined for O and C atoms and all H atom parameters kept fixed; 352 parameters and 1498 data; $w = 1/\sigma(F_0)^2 = [\sigma^2(I) + (0.04F_0^2)^2]^{-1/2}$) gave $R = 0.042$, $R_w = 0.040$ and $S_w = 0.682$ (residual $\Delta\rho \leq 0.18$ e Å^{-3}).

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