Registry No. 1, 95-94-3; 2, 2142-31-6; 3, 134757-85-0; 4, 134757-86-1; 5, 134757-87-2; 6, 134757-88-3; 7, 79839-44-4; 8, 2136-95-0; 9, 134757-89-4; 10, 608-93-5; 11, 134781-06-9; 12, 134757-90-7; 13, 134757-91-8.

A Stereospecific Route to 2-Deoxy-β-glycosides

Jacquelyn Gervay and Samuel Danishefsky*

Department of Chemistry, Yale University, New Haven, Connecticut 06511-8118

Received February 22, 1991

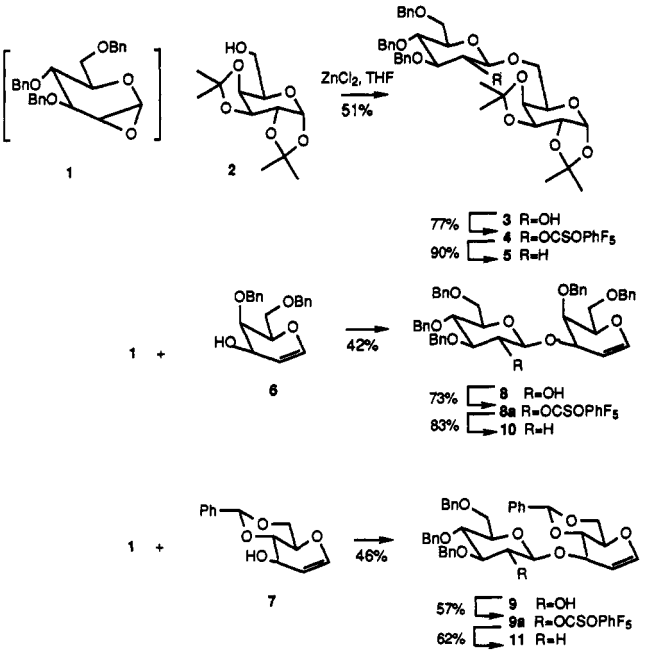
The 2-deoxy-β-glycoside unit is found in a variety of important antibiotics.[1-3] The stereospecific synthesis of such a linkage from various 2-deoxyglycosyl donors is complicated at several levels. First, the stereospecific installation of an anomeric activating group, with stereocontrol, in a system that lacks a directing influence at C_2 is beset with difficulties. Furthermore, lack of guidance from C_2 may erode the selectivity in the glycosylation reaction, if even a single C_1 anomer is available.

An ingenious solution to the problem was provided by Nicolaou, who used guidance from a C_2 α-phenylthio, C_1 β-fluoro arrangement (in turn generated by migration of a phenylthio group from $C_1 \rightarrow C_2$).[4] An alternative strategy involves activation of a glycal with an electrophile disposed to attack the double bond in an α sense. The α "onium" species, so generated, directs the glycosyl acceptor to the β-face of the C_1 of the donor. A particularly promising version of this method, utilizing thiosulfonium activation, was recently disclosed by Franck[5] with favorable stereoselectivity. In both the Nicolaou and Franck sequences, a C_2 phenylthio substituent is reductively cleaved to generate the 2-deoxy-β-glycoside system. The Franck method was applied to the synthesis of phenyl β-glycosides.

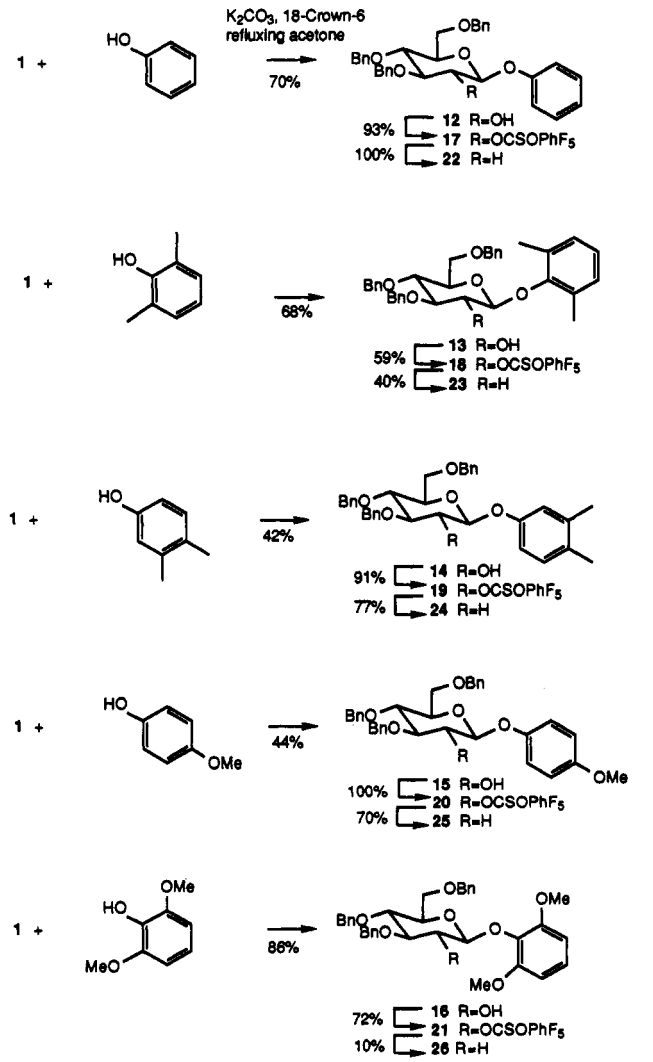
Recently the synthesis of 1α,2α oxiranes by direct epoxidation of D-glucal and D-galactal derivatives with 3,3-dimethyldioxirane was reported.[6] Under appropriate circumstances these epoxides function as stereospecific glycosyl donors, favoring β-face attack by the nucleophile by inversion at the anomeric carbon.[6,7] The deoxygenation of the C_2 hydroxyl group, generated from the glycosylation reaction, would be required to reach the title series. In this paper, we describe such deoxygenations. Applications to the synthesis of phenyl 2-deoxy-β-glycosides have been accomplished.

Reaction of tribenzyl-D-glucal with 3,3-dimethyldioxirane affords epoxide 1, which, on coupling with 1

Scheme I



Scheme II



(1) (a) Thiem, J.; Meyer, B. *J. Chem. Soc., Perkin Trans.* **1979**, *2*, 1331. (b) Thiem, J.; Meyer, B. *Tetrahedron* **1981**, *37*, 551.

(2) Koenuma, M.; Uchicha, N.; Yamaguchi, K.; Kawamura, Y. *J. Antibiot.* **1988**, *41*, 45.

(3) For a recent collection of natural products bearing this substructure, see ref 5.

(4) Nicolaou, K. C.; Ladduwahetty, T.; Randall, J. L.; Chucholowski, A. *J. Am. Chem. Soc.* **1986**, *108*, 2466.

(5) Franck, R. W.; Ramesh, S.; Kaila, N.; Grewal, G. *J. Org. Chem.* **1990**, *55*, 5.

(6) Danishefsky, S. J.; Halcolm, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 6661. For the first instance of epoxidation of a cyclic enol ether by the dioxirane method see: Baertschi, S. W.; Raney, K. D.; Stone, M. T.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7929. For the preparation of the dioxirane reagent, see: Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847.

(7) Prior to our work,[6] there had been extensive studies of the use of 1,2-anhydro sugars (cf. Brigl's anhydride) as glycosylating agents. While inversion of C_1 had been observed with primary alcohols, related reactions with less reactive secondary alcohols, including saccharides, had afforded anomeric mixtures of glycosides in disappointing yield. The key to the success of the method lies in the use of nonparticipatory protecting groups. A thorough accounting of the prior art is provided in our previous paper[6] under citations 1–5 and 14.

0022-3263/91/1956-5448$02.50/0

equiv of glycosyl acceptor 2 in the presence of zinc chloride/THF, gave a 51% yield of 3 (Scheme I). This compound was converted to thiocarbonate 4. Treatment of 4 with triphenyltin hydride–AIBN in toluene, by the protocol of Barton,[8] provided 2-deoxy-β-glycoside 5.

In anticipation of reiterative syntheses, it was important to determine whether deoxygenation of a C_2-alcohol could be carried out in the presence of a glycal in the "reducing" terminal sugar. Epoxide 1 was coupled with glycosyl acceptors 6[9] and 7[10] to afford 8 and 9, respectively. These compounds were deoxygenated by the same protocol to produce disaccharide glycals 10 and 11 in the indicated yields. In principle, it should be possible to synthesize oligomeric units containing 2-deoxy-β-glycoside repeating units by reiteration of the epoxidation–glycosidation–deoxygenation sequence.

We have also addressed the applicability of the method to the synthesis of phenyl 2-deoxy-β-glycosides. Such substructures are found in aureolic acids and other antibiotics.[5] Glycosides 12–16 were prepared in a stereospecific fashion by coupling of the appropriate phenoxides with epoxide 1 using potassium carbonate/18-crown-6 via a protocol recently developed in our laboratory (Scheme II).[11] The thionocarbonates 17–21 prepared from the C_2-hydroxyl compounds by standard means[8] were examined as substrates for the deoxygenation reaction. With substrates 17, 19, and 20, deoxygenation occurred quite smoothly. It is interesting to note that in two 2,6-disubstituted cases (18 and 21), deoxygenation could be carried out in only low yield. There was considerable competition via elimination of the anomeric function with formation of 3,4,6-tribenzyl-D-glucal. The particularly low yield of 26 obtained from 21 apparently reflects the ease of ejecting the stable 2,6-dimethoxyphenoxy radical equivalent from the anomeric position upon formation of radicaloid character at C_2. Barring this limitation, which does not pertain to the major target systems,[1-3] a stereospecifc route to aryl 2-deoxy-β-glycosides is now in hand.

In summary, the Barton-type deoxygenation of C_2-hydroxyl groups via their pentafluorophenyl thiocarbonates[8] has been shown to be applicable to the synthesis of aryl glycosides and to disaccharides containing potentially sensitive glycals. The amenability of the glycal function to the de-oxygenation sequence augurs well for application of the method in reiterative oligosaccharide synthesis.

Experimental Section

General Procedure for Preparation of β-Glycosides.[6] Tri-*O*-benzyl-D-glucal (200 mg, 0.5 mmol) was diluted in 2 mL of dichloromethane and cooled to 0 °C in a nitrogen atmosphere. Dioxirane[6] reagent (20 mL of a 0.03 M solution, 0.6 mmol) was added dropwise and stirring continued at 0 °C for 15 min. The anhydro sugar was concentrated to dryness by passing a stream of nitrogen over the reaction mixture and placing it under vacuum for 1 h. A solution of the acceptor sugar (1.5 equiv) in dry tetrahydrofuran (1.5 mL) was added to the 1,2 anhydro sugar and the temperature reduced to −78 °C. Zinc chloride (1.5 equiv of a 1 M solution in diethyl ether) was added to the reaction mixture dropwise. The reaction was allowed to slowly warm to 25 °C and stirred overnight. The reaction was quenched by evaporation of the solvent and the resulting residue placed onto a bed of silica gel and eluted with a 30% ethyl acetate in hexanes solvent mixture.

(8) Barton, D. H. R.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1989**, *30*, 2619.
(9) Kessler, H.; Kling, A.; Kottenhahn, M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 425.
(10) Terui, Y.; Tori, K.; Tsuji, N. *Tetrahedron Lett.* **1976**, 621.
(11) Dushin, R. D., Yale University, unpublished results.

***O*-(3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl)-(1→3)-1,5-anhydro-4,6-di-*O*-benzyl-2-deoxy-D-*lyxo*-hex-1-enitol (8):** 42% yield as a colorless liquid; $[\alpha]^{25}_D$ −26.0° (*c* 0.50, $CHCl_3$); ^1H NMR (250 MHz, CD_2Cl_2) δ 7.12–7.46 (25 H, m), 6.42 (1 H, dd, *J* = 6.3, 1.5 Hz), 4.99 (1 H, d, *J* = 11.3 Hz), 4.93 (1 H, d, *J* = 12.1 Hz), 4.83 (1 H, d, *J* = 11.3 Hz), 4.79 (1 H, m), 4.66 (1 H, d, *J* = 12.1 Hz), 4.62–4.56 (4 H, m), 4.52 (1 H, d, *J* = 9.6 Hz), 4.41 (2 H, AB q, *J* = 12.0 Hz), 4.17 (1 H, dd, *J* = 6.4, 5.3 Hz), 4.01 (1 H, m), 3.79–3.48 (6 H, m), 2.47 (1 H, d, *J* = 1.7 Hz); HRFAB M + Na 781.3354.

***O*-(3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl)-(1→3)-1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-D-*arabino*-hex-1-enitol (9):** 46% yield as a colorless liquid; $[\alpha]^{25}_D$ −26.6° (*c* 0.65, $CHCl_3$); FTIR (neat) 3487, 3054, 3030, 2866, 1626, 1443, 1370, 1091, 1061, 745, 690 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.54–7.18 (20 H, m), 6.43 (1 H, d, *J* = 6.2 Hz), 5.60 (1 H, s), 4.97–4.82 (4 H, m), 4.71 (1 H, d, *J* = 7.5 Hz), 4.62–4.52 (4 H, m), 4.40 (1 H, dd, *J* = 10.2, 4.8 Hz), 4.14–3.40 (9 H, m), 2.63 (1 H, br s); HRFAB M + Na 689.2780.

General Procedure for the Preparation of Phenyl Glycosides.[11] Tri-*O*-benzyl-D-glucal (200 mg, 0.5 mmol) was diluted in 2 mL of dichloromethane and cooled to 0 °C in a nitrogen atmosphere. Murray reagent[6] (20 mL of a 0.03 M solution, 0.6 mmol) was added dropwise and stirring continued at 0 °C for 15 min. Meanwhile, the desired phenol (2.5 mmol), potassium carbonate (691 mg, 5.0 mmol), and a catalytic amount of 18-crown-6 were refluxed in acetone for 2.5 h. The anhydro sugar was concentrated to dryness by passing a stream of nitrogen over the reaction mixture and placing it under vacuum for 1 h. Acetone (3 mL) was then added to the sugar and the solution added to the refluxing phenoxide. Refluxing was continued for 8 h after which time the reaction mixture was cooled. Ethyl acetate (50 mL) was added and the solution extracted with 5 × 25 mL portions of saturated sodium carbonate. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was subjected to flash column chromatography using 85:15 hexanes/ethyl acetate to afford the phenyl glycoside.

Phenyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (12):[11] 70% yield as a white solid; mp 99–100 °C; $[\alpha]^{25}_D$ −26.0° (*c* 0.33, $CHCl_3$); FTIR (neat) 3426, 3025, 2905, 2862, 1582, 1482, 1231, 1099, 1055, 748, 729, 692 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.50–7.00 (20 H, m), 4.92 (2 H, q, *J* = 8.0 Hz), 4.91 (1 H, d, *J* = 7.6 Hz), 4.85 (1 H, d, *J* = 12.5 Hz), 4.60 (1 H, d, *J* = 12.5 Hz), 4.58 (1 H, d, *J* = 12.3 Hz), 4.50 (1 H, d, *J* = 12.3 Hz), 3.78–3.66 (6 H, m), 2.54 (1 H, d, *J* = 2.6 Hz); HRFAB M + Na 549.2272.

2,6-Dimethylphenyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (13): 68% yield as a white solid; $[\alpha]^{25}_D$ + 4.9° (*c* 0.59, $CHCl_3$); FTIR (neat) 3455, 3021, 2911, 2856, 1446, 1366, 1195, 1091, 1061, 737, 689 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.41–7.19 (15 H, m), 7.04–6.93 (3 H, m), 4.93, 4.88 (2 H, AB q, *J* = 11.4 Hz), 4.83 (1 H, d, *J* = 10.9 Hz), 4.68 (1 H, d, *J* = 7.7 Hz), 4.59 (1 H, d, *J* = 10.9 Hz), 4.48, 4.47 (2 H, AB q, *J* = 12.0 Hz), 3.80 (1 H, m), 3.65–3.58 (4 H, m), 3.38–3.33 (1 H, m), 2.64 (1 H, d, *J* = 2.7 Hz), 2.33 (6 H, s). Anal. Calcd for $C_{35}H_{38}O_6$: C, 75.79; H, 6.91. Found: C, 75.94; H, 6.93.

3,4-Dimethylphenyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (14): 42% yield as a white solid; mp 91–92 °C; $[\alpha]^{25}_D$ −18.2° (*c* 0.49, $CHCl_3$); FTIR (neat) 3467, 3007, 2914, 2865, 1247, 1117, 1061, 731, 694 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.31–7.11 (15 H, m), 6.93 (1 H, d, *J* = 8.3 Hz), 6.77–6.88 (2 H, m), 4.84, 4.80 (2 H, AB q, *J* = 11.3 Hz), 4.78 (1 H, d, *J* = 10.9 Hz), 4.76 (1 H, d, *J* = 8.5 Hz), 4.49 (1 H, d, *J* = 10.9 Hz), 4.47, 4.44 (2 H, AB q, *J* = 11.8 Hz), 3.67–3.51 (6 H, m), 2.40 (1 H, d, *J* = 2.5 Hz), 2.12 (3 H, s), 2.11 (3 H, s). Anal. Calcd for $C_{35}H_{38}O_6$: C, 75.79; H, 6.91. Found: C, 75.49; H, 7.07.

4-Methoxyphenyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (15): 44% yield as a white solid; mp 103.5–105 °C; $[\alpha]^{25}_D$ −16.4° (*c* 0.33, $CHCl_3$); FTIR (neat) 3435, 3007, 2919, 2856, 1507, 1444, 1211, 1054, 739, 720, 688 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.41–7.21 (15 H, m), 7.01 (2 H, dd, *J* = 7.0, 2.3 Hz), 6.80 (2 H, dd, *J* = 7.0, 2.3 Hz), 4.93, 4.88 (2 H, AB, q, *J* = 11.4 Hz), 4.85 (1 H, d, *J* = 10.9 Hz), 4.56, 4.51 (2 H, AB q, *J* = 11.9 Hz), 3.80–3.57 (9 H, m), 2.50 (1 H, d, *J* = 2.4 Hz, OH). Anal. Calcd for $C_{34}H_{36}O_7$: 73.36; H, 6.52. Found: C, 72.94; H, 6.61.

2,6-Dimethoxyphenyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (16):[11] 86% yield as a white solid; ^1H NMR (250

MHz, CD_2Cl_2) δ 7.36–7.13 (15 H, m), 7.01 (1 H, t, J = 8.4 Hz), 6.53 (2 H, d, J = 8.4 Hz), 4.96 (1 H, d, J = 11.4 Hz), 4.79 (1 H, J = 10.9 Hz), 4.75 (1 H, d, J = 11.4 Hz), 4.56–4.45 (4 H, m), 3.76 (6 H, s), 3.73–3.39 (7 H, m).

General Procedure for the Preparation of 3,4,6-Tri-*O*-benzyl-2-*O*-[(pentafluorophenoxy)thiocarbonyl]-β-glycosides.[8] The desired disaccharide (0.1 mmol) was diluted in 1 mL of dry toluene and *N*-hydroxysuccinimide (0.1 mmol) was added. Pentafluorophenyl chlorothionoformate (0.12 mmol) was then added dropwise and finally anhydrous pyridine (0.5 mmol) was added. The yellow reaction mixture was heated to 80 °C until TLC indicated that the reaction was complete, generally about 4 h. The product was purified by placing the entire reaction mixture on a 2 × 16 cm bed of silica and eluting with 4:1 petroleum ether/diethyl ether.

***O*-(3,4,6-Tri-*O*-benzyl-2-*O*-[(pentafluorophenoxy)thiocarbonyl]-β-D-glucosyl)-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (4)**: 77% as a colorless oil; $[\alpha]^{25}_D$ −53.8° (*c* 0.40, $CHCl_3$); FTIR (neat) 2979, 2935, 1519, 1367, 1296, 1154, 1067, 991, 729, 692 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.39–7.20 (15 H, m), 5.48 (1 H, d, J = 5.0 Hz), 5.44 (1 H, t, J = 8.0 Hz), 4.83 (1 H, d, J = 11.0 Hz), 4.78 (2 H, br s), 4.71 (1 H, d, J = 8.0 Hz), 4.86, 4.55 (2 H, AB q, J = 12.1 Hz), 4.57 (1 H, d, J = 11.0 Hz), 4.30 (1 H, dd, J = 5.0, 2.3 Hz), 4.22 (1 H, dd, J = 8.0, 1.4 Hz), 3.99–3.51 (9 H, m), 1.54 (3 H, s), 1.42 (3 H, s), 1.32 (3 H, s), 1.31 (3 H, s); HRFAB M + Na 941.2580.

***O*-(3,4,6-Tri-*O*-benzyl-2-*O*-[(pentafluorophenoxy)thiocarbonyl]-β-D-glucosyl)-(1→3)-1,5-anhydro-4,6-di-*O*-benzyl-2-deoxy-D-*lyxo*-hex-1-enopyranose (8a)**: 73% yield as a colorless oil; $[\alpha]^{25}_D$ −62.8° (*c* 0.32, $CHCl_3$); FTIR (neat) 2924, 2864, 1678, 1648, 1548, 1513, 1153, 1083, 993, 738, 693, 663 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.21–7.38 (25 H, m), 6.34 (1 H, dd, J = 6.2, 1.5 Hz), 5.53 (1 H, dd, J = 9.3, 8.0 Hz), 4.96 (1 H, d, J = 11.5 Hz), 4.83 (1 H, d, J = 10.9 Hz), 4.80 (2 H, s), 4.75 (1 H, d, J = 6.4 Hz), 4.60 (1 H, d, J = 11.5 Hz), 4.55–4.37 (6 H, m), 4.08 (1 H, m), 4.00–3.55 (9 H, m); HRFAB M + Na 1007.2861.

***O*-(3,4,6-Tri-*O*-benzyl-2-*O*-[(pentafluorophenoxy)thiocarbonyl]-β-D-glucosyl)-(1→3)-1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-D-*arabino*-hex-1-enopyranose (9a)**: 57% yield as a colorless oil; $[\alpha]^{25}_D$ −16.0° (*c* 0.35, $CHCl_3$); FTIR (neat) 2917, 2855, 1516, 1353, 1300, 1152, 1123, 1090, 1066, 994, 751 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.39–7.04 (20 H, m), 6.38 (1 H, dd, J = 6.1, 1.4 Hz), 5.46 (1 H, t, J = 8.4 Hz), 5.41 (1 H, s), 4.79–4.72 (5 H, m), 4.55–4.47 (4 H, m), 4.29 (1 H, dd, J = 9.7, 4.2 Hz), 4.02 (1 H, dd, J = 9.7, 7.0 Hz), 3.86–3.48 (4 H, m), 3.49 (2 H, m), 3.30 (1 H, m); HRFAB M + Na 915.2220.

Phenyl 3,4,6-tri-*O*-benzyl-2-*O*-[(pentafluorophenoxy)thiocarbonyl]-β-D-glucopyranoside (17): 93% yield as a slightly yellow oil; $[\alpha]^{25}_D$ −6.52° (*c* 0.23, $CHCl_3$); FTIR (neat) 3021, 2909, 2864, 1518, 1290, 1214, 1153, 1062, 991, 743, 693 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.40–7.0 (20 H, m), 5.72 (1 H, t, J = 8.2 Hz), 5.13 (1 H, d, J = 8.2 Hz), 4.86, 4.64 (2 H, AB q, J = 11.0 Hz), 4.81 (2 H, s), 4.61, 4.53 (2 H, AB q, J = 12.0 Hz), 4.02–3.72 (5 H, m); HRFAB M + Na 775.1768.

2,6-Dimethylphenyl 3,4,6-tri-*O*-benzyl-2-*O*-[(pentafluorophenoxy)thiocarbonyl]-β-D-glucopyranoside (18): 59% as a slightly yellow oil; $[\alpha]^{25}_D$ −24.0° (*c* 0.10, $CHCl_3$); FTIR (neat) 3021, 2913, 2854, 1517, 1301, 1150, 1059, 944, 731, 687 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.30–7.14 (15 H, m), 6.98–6.91 (3 H, m), 5.71 (1 H, t, J = 8.0 Hz), 4.87 (1 H, d, J = 8.0 Hz), 4.85–4.74 (3 H, m), 4.55 (1 H, d, J = 11.0 Hz), 4.47, 4.41 (2 H, AB q, J = 12.0 Hz), 3.90 (1 H, app t, J = 9.0 Hz), 3.76 (1 H, app t, J = 9.0 Hz), 3.70–3.61 (2 H, m), 3.39–3.33 (1 H, m), 2.27 (6 H, s); HRFAB M + Na 803.2040.

3,4-Dimethylphenyl 3,4,6-tri-*O*-benzyl-2-*O*-[(pentafluorophenoxy)thiocarbonyl]-β-D-glucopyranoside (19): 91% yield as a slightly yellow oil; $[\alpha]^{25}_D$ +8.0° (*c* 0.40, $CHCl_3$); FTIR (neat) 2908, 2871, 1514, 1297, 1144, 1060, 986, 732, 690 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 6.91–6.46 (18 H, m), 5.43 (1 H, t, J = 9.2 Hz), 4.35 (2 H, d, J = 11.0 Hz), 4.30 (1 H, d, J = 9.2 Hz), 4.22 (1 H, d, J = 11.0 Hz), 4.19 (1 H, d, J = 11.1 Hz), 3.92 (1 H, d, J = 11.1 Hz), 3.87 (2 H, AB q, J = 10.5 Hz), 3.25–3.02 (3 H, m), 2.79–2.77 (1 H, m), 1.60 (3 H, s), 1.50 (3 H, s). Anal. Calcd for $C_{42}H_{37}F_5O_9S$: C, 64.61; H, 4.78. Found: C, 65.61; H, 4.89.

4-Methoxyphenyl 3,4,6-tri-*O*-benzyl-2-*O*-[(pentafluorophenoxy)thiocarbonyl]-β-D-glucopyranoside (20): 100% as a white solid; mp 96–98 °C; $[\alpha]^{25}_D$ +14.0° (*c* 0.15, $CHCl_3$); FTIR (neat) 2906, 2864, 1516, 1290, 1213, 1150, 1065, 996, 752, 695, 667 cm^{-1}; ^1H NMR (250 MHz, toluene-d_8) δ 6.68 (2 H, d, J = 7.8 Hz), 6.55–6.27 (15 H, m), 5.99 (2 H, d, J = 9.0 Hz), 5.19 (1 H, t, J = 9.2 Hz), 4.15 (1 H, d, J = 11.1 Hz), 4.02 (1 H, d, J = 9.2 Hz), 4.00 (1 H, d, J = 11.1 Hz), 3.98 (1 H, d, J = 11.6 Hz), 3.72–3.68 (3 H, m), 3.10–2.81 (4 H, m), 2.63 (3 H, s), 2.60–2.54 (1 H, m); HRFAB M + Na 805.1887.

2,6-Dimethoxyphenyl 3,4,6-tri-*O*-benzyl-2-*O*-[(pentafluorophenoxy)thiocarbonyl]-β-D-glucopyranoside (21): 72% yield as a slightly yellow oil; $[\alpha]^{25}_D$ −13.0° (*c* 1.11, $CHCl_3$); FTIR (neat) 3016, 2939, 2834, 1652, 1600, 1511, 1474, 1297, 1255, 1156, 1104, 994, 728, 691 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.31–7.10 (15 H, m), 6.97 (1 H, t, J = 8.4 Hz), 6.52 (2 H, d, J = 8.4 Hz), 5.64 (1 H, dd, J = 9.1, 7.8 Hz), 5.01 (1 H, d, J = 7.8 Hz), 4.86–4.51 (6 H, m), 3.91–3.75 (2 H, m), 3.72 (6 H, s), 3.62–3.60 (1 H, m), 3.41–3.28 (2 H, m). Anal. Calcd for $C_{42}H_{37}F_5O_9S$: C, 62.06; H, 4.59. Found: C, 61.88; H, 4.48.

General Procedure for the Preparation of 2-Deoxy-β-glycosides.[8] The desired thionocarbonate (0.1 mmol) was diluted in anhydrous toluene and AIBN was added (0.025 mmol, as a standard solution in toluene). The reaction mixture was purged with argon and then heated to 110 °C for 5 min, after which triphenyltin hydride (0.2 mmol) was added dropwise as a solution in toluene. The reaction mixture was heated for 1 h, cooled, and purified, by placing the entire reaction mixture on a 2 × 16 cm column of silica gel. Elution with 85:15 hexanes/ethyl acetate afforded the desired product.

***O*-(3,4,6-Tri-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (5)**: 90% as a clear liquid; $[\alpha]^{25}_D$ −45.1° (*c* 0.57, $CHCl_3$); FTIR (neat) 3021, 2976, 2937, 1450, 1373, 1257, 1205, 1096, 1057, 999, 735, 691 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.37–7.19 (15 H, m), 5.49 (1 H, d, J = 5.1 Hz), 4.88 (1 H, d, J = 11.0 Hz), 4.71–4.48 (7 H, m), 4.30 (1 H, dd, J = 5.0, 2.4 Hz), 4.20 (1 H, dd, J = 7.9, 1.5 Hz), 4.03–3.93 (2 H, m), 3.91–3.35 (6 H, m), 2.40 (1 H, ddd, J = 12.5, 5.2, 1.5 Hz), 1.58 (1 H, 4 broad lines), 1.50 (3 H, s), 1.38 (3, H, s), 1.33 (6 H, s). Anal. Calcd for $C_{39}H_{48}O_{10}$: C, 69.21; H, 7.15. Found: C, 69.26; H, 6.89.

***O*-(3,4,6-Tri-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-1,5-anhydro-4,6-di-*O*-benzyl-2-deoxy-D-*lyxo*-hex-1-enoitol (10)**: 83% yield as a clear liquid; $[\alpha]^{25}_D$ −43.8° (*c* 0.32, $CHCl_3$); FTIR (neat) 3052, 3029, 2924, 2857, 1646, 1624, 1452, 1074, 730, 691 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.38–7.21 (25 H, m), 6.31 (1 H, dd, J = 6.1, 1.5 Hz), 4.94 (1 H, d, J = 11.5 Hz), 4.88 (1 H, d, J = 11.0 Hz), 4.83–4.37 (12 H, m), 4.13–3.96 (2 H, m), 3.75–3.37 (6 H, m), 2.37 (1 H, m), 1.65 (1 H, m); HRFAB M + Na 765.3061.

***O*-(3,4,6-Tri-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-D-*arabino*-hex-1-enopyranose (11)**: 62% yield as a clear liquid; $[\alpha]^{25}_D$ −29.7° (*c* 0.39 $CHCl_3$); FTIR (neat) 3021, 2953, 2912, 2866, 1638, 1441, 1368, 1093, 739, 692 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.42–7.16 (20 H, m), 6.36 (1 H, dd, J = 6.1, 1.2 Hz), 5.49 (1 H, s), 4.84 (1 H, d, J = 10.8 Hz), 4.78 (1 H, dd, J = 6.1, 2.1 Hz), 4.71–4.45 (5 H, m), 4.28 (1 H, dd, J = 9.7, 4.3 Hz), 4.04 (1 H, app t, J = 8.9 Hz), 4.00–3.43 (8 H, m), 3.28 (1 H, m), 2.30 (1 H, ddd, J = 11.9, 4.3, 1.1 Hz), 1.63 (1 H, 4 broad lines); HRFAB M + Na 673.2805.

Phenyl 3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside (22): 100% as a clear liquid; $[\alpha]^{25}_D$ −6.32° (*c* 1.29, $CHCl_3$); FTIR (neam) 3055, 3017, 2914, 2854, 1646, 1592, 1490, 1456, 1218, 1077, 752, 698 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.62–6.92 (20 H, m), 5.02 (1 H, dd, J = 9.7, 2.1 Hz), 4.43–4.90 (6 H, m), 3.51–3.81 (5 H, m), 2.46 (1 H, ddd, J = 12.4, 4.9, 2.1 Hz), 1.90 (1 H, ddd, J = 12.4, 11.7, 9.7 Hz). Anal. Calcd for $C_{33}H_{34}O_5$: C, 77.62; H, 6.71. Found: C, 77.56; H, 6.70.

2,6-Dimethylphenyl 3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside (23): 40% as a clear liquid; $[\alpha]^{25}_D$ −1.64° (*c* 1.10, $CHCl_3$); FTIR (neat) 2948, 2921, 2852, 1523, 1449, 1369, 1080, 728, 691, cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.35–7.10 (15 H, m), 6.97–9.82 (3 H, m), 4.84–4.70 (2 H, m), 4.68 (1 H, dd, J = 9.8, 1.6 Hz), 4.63–4.36 (4 H, m), 3.64–3.58 (4 H, m), 3.46 (1 H, app t, J = 9.4 Hz), 3.24–3.19 (1 H, m), 2.56 (1 H, ddd, J = 12.5, 4.8, 1.6 Hz), 2.24 (6 H, s), 1.77 (1 H, ddd, J = 12.5, 11.7, 9.8 Hz); HRFAB M + Na 561.2646.

3,4-Dimethylphenyl 3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside (24): 77% yield as a clear liquid; $[\alpha]^{25}_D$ −15.0°

(c 1.41, $CHCl_3$); FTIR (neat) 3057, 3017, 2927, 2853, 1600, 1572, 1493, 1453, 1420, 1249, 1085, 723, 689 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.74–7.15 (15 H, m), 6.99 (1 H, d, J = 8.4 Hz), 6.81–6.73 (2 H, m), 5.05 (1 H, dd, J = 9.7, 2.1 Hz), 4.91 (1 H, d, J = 11.0 Hz), 4.70, 4.63 (2 H, AB q, J = 11.7 Hz), 4.58 (1 H, d, M = 11.0 Hz), 4.56, 4.51 (2 H, AB q, J = 11.9 Hz), 3.77–3.53 (5 H, m), 2.50 (1 H, ddd, J = 12.5, 5.0, 2.1 Hz), 2.41 (6 H, s), (1 H, ddd, J = 12.5, 11.5, 9.7 Hz); HRFAB M + Na 561.2646.

4-Methoxyphenyl 3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside (25): 70% yield as a clear liquid; $[\alpha]^{25}_D$ −11.5° (c 0.47, $CHCl_3$); FTIR (neat) 3030, 2954, 2922, 2862, 1491, 1453, 1372, 1220, 1090, 830, 748, 700 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.37–7.27 (15 H, m), 7.00 (2 H, d, J = 9.1 Hz), 6.78 (2 H, d, J = 9.1 Hz), 4.99–4.52 (7 H, m), 3.81–3.56 (5 H, m), 3.77 (3 H, s), 2.51 (1 H, ddd, J = 12.6, 5.1, 1.7 Hz), 1.92 (1 H, ddd, J = 12.6, 10.5, 9.7 Hz); HRFAB M + Na 563.2388.

2,6-Dimethoxyphenyl 3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside (26): 10% yield as a clear liquid; $[\alpha]^{25}_D$ −35.0° (c 0.8); FTIR (neat) 2944, 2917, 2853, 1564, 1351, 1208, 1102, 1127, 789, 752 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 7.38–7.27 (15 H, m), 7.00 (1 H, t, J = 8.3 Hz), 6.54 (2 H, d, J = 8.3 Hz), 4.93 (1 H, d, J = 7.5 Hz), 4.88 (1 H, d, J = 11.0 Hz), 4.65 (2 H, AB q, J = 12.1 Hz), 4.61–4.53 (3 H, m), 3.78 (6 H, s), 3.76–3.51 (5 H, m), 2.65 (1 H, m), 1.96 (1 H, m); HRFAB M + Na 593.2515.

Acknowledgment. This research was supported by PHS Grant AI 16943. An NIH Postdoctoral Fellowship to J.G. (Grant 1 F32 HL08236-01) is gratefully acknowledged. We also wish to thank Dr. Russell Dushin for providing the experimental procedures for the synthesis of phenolic glycosides. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.

Registry No. 1, 74372-90-0; 2, 4064-06-6; 3, 40246-33-1; 4, 135192-35-7; 5, 79384-22-8; 6, 81928-98-5; 7, 63598-36-7; 8, 135192-33-5; 8a, 135192-36-8; 9, 135192-34-6; 9a, 135225-04-6; 10, 135192-37-9; 11, 135192-38-0; 12, 135192-39-1; 13, 135192-40-4; 14, 135192-41-5; 15, 135192-42-6; 16, 135192-43-7; 17, 135192-44-8; 18, 135192-45-9; 19, 135192-46-0; 20, 135192-47-1; 21, 135192-48-2; 22, 124718-81-6; 23, 135192-49-3; 24, 135192-50-6; 25, 135192-51-7; 26, 135192-52-8; tribenzyl-D-glucal, 55628-54-1; 3,3-dimethyldioxirane, 74087-85-7; pentafluorophenyl chlorothionoformate, 135192-53-9; phenol, 108-95-2; 2,6-dimethylphenol, 576-26-1; 3,4-dimethylphenol, 95-65-8; 4-methoxyphenol, 150-76-5; 2,6-dimethoxyphenol, 91-10-1.

Supplementary Material Available: NMR spectra for compounds 4, 5, 8, 8a, 9, 9a, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 23, 24, 25, and 26 (22 pages). Ordering information is given on any current masthead page.

Synthesis of 2,3-Dimethoxy-5-iodobenzoic Acid

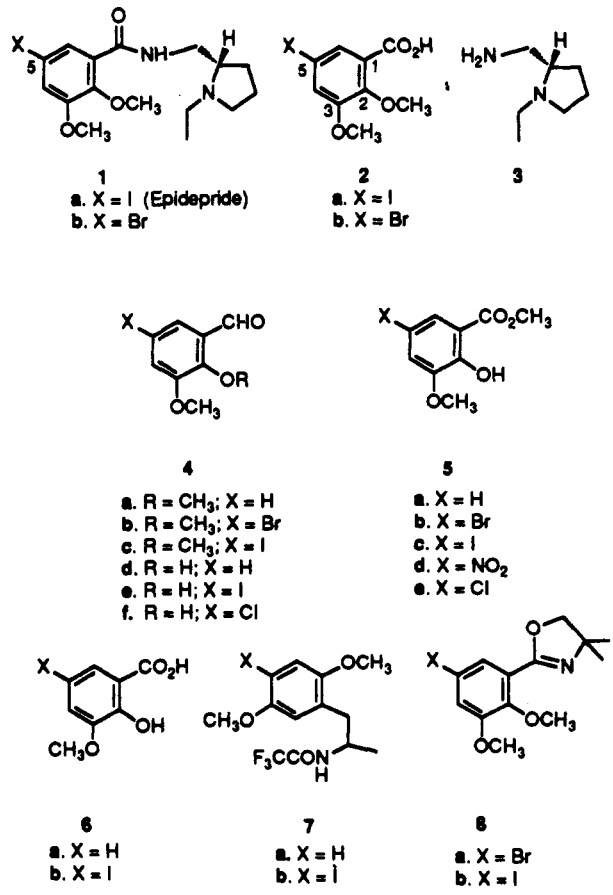
Eddy W. Yue, John M. Gerdes,* and Chester A. Mathis

Research Medicine and Radiation Biophysics Division, Lawrence Berkeley Laboratory, University of California, Berkeley, California 94720

Received January 9, 1991 (Revised Manuscript Received May 6, 1991)

Methoxy-substituted benzamides containing 2-pyrrolidinylmethyl side chains are selective and biologically potent dopamine D_2 receptor antagonists, which when used clinically display minimal deleterious side effects.[1-3] Included in this class of neuroleptics is the 2,3-dimethoxy-5-iodobenzamide 1a (Chart I), also known as epidepride, which has recently been shown to possess high affinity in vitro binding properties.[4] The radioiodinated form of 1a serves as a superior in vivo dopamine D_2 receptor imaging agent.[5] Two syntheses of 1a have been reported, both in low yields (≤25%). The more recent synthesis[2] involved the anion-mediated conversion of the intact 5-bromobenzamide 1b to the 5-iodo 1a (25%). Improvement of this synthetic approach is limited by the unreactive nature of I_2 with the 5-lithio derivative of 1b and the propensity of the pyrrolidine fragment to undergo decomposition. The earlier route[6] to 1a (7%), which was patterned after previous syntheses of related benzamides,[1] employed coupling of the 5-iodobenzoic acid 2a[7] with (*S*)-2-(aminomethyl)-1-ethylpyrrolidine[8] (3). An improved synthesis of 1a by this convergent route is possible if an efficient

Chart I



*To whom correspondence should be addressed at Lawrence Berkeley Laboratory, MS 55-121, 1 Cyclotron Road, Berkeley, CA 94720.

(1) For a review of the chemistry, biochemistry, and pharmacology of benzamide dopamine D_2 agents, see: (a) Högberg, T.; Ramsby, S.; Ögren, S.-O.; Norinder, U. *Acta. Pharm. Suec.* **1987**, *24*, 289. (b) Norinder, U.; Högberg, T. *Acta Pharm. Nordica* **1989**, *2*, 75.

(2) Högberg, T.; Ström, P.; Hakan, H.; Ögren, S.-O. *Helv. Chim. Acta* **1990**, *73*, 417.

(3) Högberg, T.; de Paulis, T.; Johansson, L.; Kumar, Y.; Hall, L.; Ögren, S.-O. *J. Med. Chem.* **1990**, *33*, 2305.

(4) Neve, K. A.; Henningsen, A.; Kinzie, J. M.; de Paulis, T.; Schmidt, D. E.; Kessler, R. M.; Janowsky, A. *J. Pharmacol. Exp Ther.* **1990**, *252*, 1108.

(5) (a) Kessler, R. M.; Votaw, J. R.; de Paulis, T.; Schmidt, D.; Clanton, J. A.; Ansari, M. S.; Holdeman, K. P.; Pfeffer, R.; Manning, R. J. *Nuc. Med.* **1990**, *31*, 779. (b) Kessler, R. M.; Ansari, M. S.; Gillespie, D.; Schmidt, D.; de Paulis, T. Ibid. **1990**, *31*, 882. (c) Kessler, R. M.; de Paulis, T.; Ansari, S.; Gillispie, D.; Clanton, J.; Smith, H. E.; Ebert, M.; Manning, R. Ibid. **1989**, *30*, 803.

(6) de Paulis, T.; Clanton, J. A.; Schmidt, D.; Ansari, S.; Gillespie, D.; Kessler, R. M. 198th American Chemical Society National Meeting, Miami Beach, September 1989; American Chemical Society: Washington, DC, 1989; NUCL12. A two-step conversion of isoveratryl alcohol to 2a (9%) was disclosed during this presentation.

(7) The 2,3-dimethoxy-5-iodobenzoic acid 2a (or a corresponding ester of 2a) has not heretofore been reported in the literature.

(8) For a preparation of 3 in 97.5% enantiomeric excess (ee), see: Högberg, T.; Rämsby, S.; Ström, P. *Acta Chem. Scand.* **1989**, *43*, 660.

0022-3263/91/1956-5451$02.50/0