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Note

Synthesis of aryl β-D-mannopyranosides

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The preparation of β-D-mannopyranosides has attracted a great deal of interest, because of the importance of this linkage in oligo- and poly-saccharide sequences of natural origin[1–4]. Although several routes to these compounds have been developed, few if any have the virtues of practicality and efficiency to be considered general methods[5]. Aryl β-D-mannopyranosides form a more specific class of compounds; their utility in provinding linking groups to proteins and in serving as substrates in assays of β-D-mannopyranosidases has been well documented[6,7]. Despite the biochemical importance of these compounds, only four aryl β-D-mannopyranosides have been reported in the literature[8], one of these being a 1-thio-β-D-mannopyranoside[9]. The difficulty in preparing β-D-mannopyranosides is evident when the large number of aryl β-D-galacto-[10] and -gluco-pyranosides known[11] is considered, a reflection of the ease in preparing 1,2-*trans*-glycosides relative to their 1,2-*cis*-glycoside counterparts[12].

Our solution to the problem of synthesis of aryl β-D-mannosides involves the use of 4,6-di-*O*-acetyl-2,3-*O*-carbonyl-α-D-mannopyranosyl bromide (**1**) as the starting material. This choice was predicated on the following considerations: (*a*) the bromide **1** is available in large quantities by the method of Bebault and Dutton[13], recently modified by Tewson and Soderlind[14]; (*b*) **1** contains a nonparticipating group on O-2, thereby favoring displacement reactions with inversion[15]; and (*c*) the fused 5-membered carbonate ring modifies the conformation of the pyranose ring, such as to resist formation of a planar carbonium ion at C-1, thereby suppressing SN1 reactions in favor of SN2 reactions[16].

With these criteria in mind, we determined that reaction of **1** with the anhydrous potassium salt of the appropriate phenol **2**, in the presence of dicyclohexyl-18-

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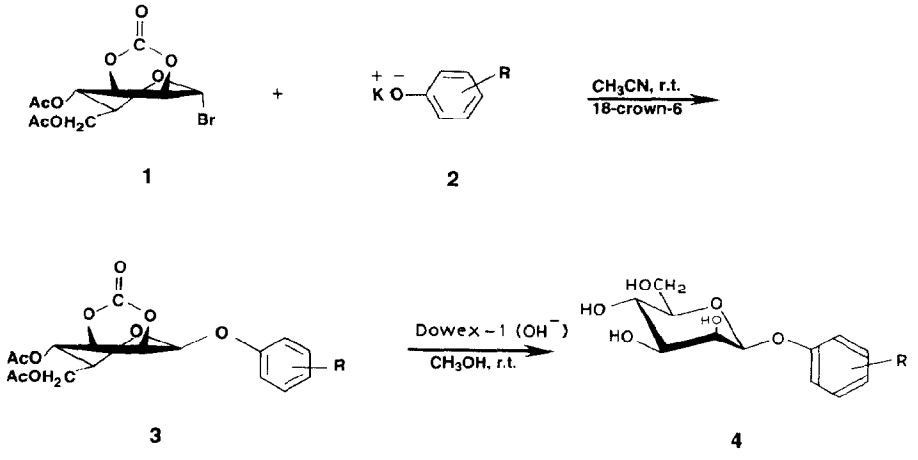

Scheme 1

crown-6, gave the expected aryl 4,6-di-*O*-acetyl-2,3-*O*-carbonyl-β-D-mannopyranoside **3** (see Scheme 1).

With one exception, compounds corresponding to **3** were purified by normal aqueous work-up followed by crystallization from ethanol, and fully characterized by analytical and spectral techniques (see Table I). Treatment of **3** with Dowex (basic) resin in methanol gave the deprotected aryl β-D-mannopyranosides (**4**), which were purified by crystallization (see Table II).

The β-D-configuration of compounds **3** and **4** was established as follows. *(i)* Members of both series gave high, negative specific rotations, indicative of the

TABLE I

ARYL 4,6-DI-*O*-ACETYL-2,3-*O*-CARBONYL-β-D-MANNOPYRANOSIDES

Compound	*Aryl substituent*	*Yield (%)*	*M.p. (°C)*	$[\alpha]_D^{22}$ *(degrees)*[a]	*Elemental analyses (%)*					
					Calculated			*Found*		
					C	*H*	*X*	*C*	*H*	*X*
3a	4-OMe	64	155–157	−82.9	54.55	5.09		54.55	5.09	
b	4-Br	56	127–129	−90.7	45.86	3.85		46.01	3.69	
c	4-Ph	40	200	−96.4	62.44	5.01		62.45	5.05	
d	4-SMe	46	166–170	−95.7	52.42	4.89	7.77[b]	52.71	4.87	7.14[b]
e	4-OEt	47	106–108	−80.0	55.61	5.40		55.85	5.38	
f	4-Cl	71	127–129	−95.4	50.94	4.27	8.84[c]	50.81	4.26	8.86[c]
g	4-NO_2	74	123–126[d]	−141.5[e]			known	(ref. 9)		
h	3-CN	60	113–116	−116.5	55.25	4.38	3.58[f]	55.29	4.42	3.55[f]
i	3-NO_3	55	141–142	−124.3	49.64	4.17	3.41[f]	49.63	4.19	3.36[f]
j	2,4-di-Cl	64[g]	154–156	−97.0	46.92	3.71	16.29[c]	46.79	3.78	15.88[c]
k	H	57	130–134	−75.0	55.74	4.95		55.15	5.07	

[a] *c* 1, chloroform. [b] X = S. [c] X = Cl. [d] Reported 124–126°. [e] Reported[9] −140° (*c* 1, $CHCl_3$). [f] X = N. [g] Purified by chromatography.

TABLE II

ARYL β-D-MANNOPYRANOSIDES

Compound	Aryl substituent	Yield (%)	M.p. (°C)	$[\alpha]_D^{22}$ (degrees) (c, solvent)[a]	δ for H-1[b] (Multiplicity, $J_{1,2}$ in Hz)	Elemental analyses(%) Calculated C	H	X	Found C	H	X
4a	4-OMe	66	148-152	−66.4(1.3,A)	5.05(d,1.2)	53.20	6.45		53.25	6.39	
b	4-Br	75	163-4	−57.7(0.9,A)	5.16(d,0.9)	43.59	5.06		43.10	5.12	
c	4-Ph	58	221-4	−62.5(1.4,C)	5.24(bs)	63.01	6.23		62.89	5.94	
d	4-SMe	33	159-165	−62.5(1,A)	5.15(bs)	51.03	6.06	10.48[c]	50.99	5.95	9.70[c]
e	4-OEt	81	185-6	−70.8(1,B)	5.06(bs)	55.99	6.71		55.98	6.63	
f	4-Cl	80	163-5	−68.8(1.3,A)	5.18(bs)	48.09	5.38	11.83[d]	48.21	5.75	11.29[d]
g	4-NO_2	47	198-9[e]	−89.5(1,A)[f]	5.36(bd,1.2)			known	(ref. 8)		
h	3-CN	83	202-4	−72.6(1,A)	5.27(d,1.1)	54.13	5.52	4.86[g]	54.10	5.56	4.52[g]
i	3-NO_2	76	160-1[h]	−83.2(1.9,A)[i]	5.34(bs)			known	(ref. 8)		
j	2,4-di-Cl	66	173-5	−62.5(1.2,A)	5.14(d,1.2)	44.33	4.34	21.81[j]	44.19	4.37	21.78[j]
k	H	54	170-2[k]	−61.7(2.3,B)[l]	5.16(d,1.0)			known	(ref. 19)		

[a]A = MeOH; B = H_2O; C = MeOH + Me_2SO. [b]in CD_3OD solns.; **4c** in CD_3OD + $(CD_3)_2SO$. [c]X = S. [d]X = Cl. [e]Reported 205-207°. [f]Reported −108° (*c* 1, H_2O). [g]X = N. [h]Reported 73.5°. [i]Reported −69° (*c* 0.7, H_2O). [j]X = Cl. [k]Reported 175-176°. [l]Reported −71.6° (H_2O).

β-D-mannosyl configuration (see Tables I and II). In those cases where literature examples were available for comparison (*i.e.*, for **3g**, **4g**, **4i**, and **4k**), specific rotations were found to be in good-to-reasonable agreement with reported values. Two aryl α-D-mannopyranosides (**5a** and **5b**) prepared as comparative examples gave, as expected, high positive specific rotations. *(ii)* The small value of $J^{\beta}_{1,2}$ (~1 Hz) observed in the ^{1}H-n.m.r. spectrum of **4** is suggestive of a 1,2-*cis*-glycoside, although it does not provide unamiguous proof of the β-D-mannopyranosyl configuration. Further information was obtained by comparison with the corrsponding α anomers . Thus, for the α anomers of **4a** and **4b** (*i.e.*, **5a** and **5b**), $J^{\alpha}_{1,2}$ was found to be 1.88 and 1.83 Hz, respectively, suggesting that $J^{\alpha}_{1,2} > J^{\beta}_{1,2}$ can be used as a rule of thumb to distinguish between anomers in the aryl D-mannopyranoside series. (Despite reports of the preparation of simple aryl D-mannopyranosides, there is a remarkable paucity of n.m.r. data concerning these compounds, for some discussion along these lines, see reference 17).

In summary, the susceptibility of **1** toward SN2 type displacements by nucleophilic phenoxides provides facile entry into the aryl β-D-mannopyranoside series.

EXPERIMENTAL

General. — Melting points were determined in a Laboratory Devices Mel-temp apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 MC polarimeter. Preparative chromatography was conducted in a Waters Prep-500A instrument. Elemental analyses were performed by Atlantic Microlabs Inc, Atlanta, GA. ^{1}H-N.m.r. spectra were recorded at 300 MHz with a Varian 300XL spectrometer.

All phenols were obtained from Aldrich Chemical Co., Milwaukee, WI. These were converted into their potassium salts by dissolving them in an equimolar solution of potassium hydroxide, followed by evaporation *in vacuo*. Exhaustive removal of water was achieved by treatment overnight in a lyophilizer, followed by drying *in vacuo* over phosphorus pentaoxide; this gave the potassium salts of the phenols as free-flowing powders. The D-mannosyl bromide **1** was prepared by the method of Bebault and Dutton[13]. Dowex-1 (basic) resin was obtained from Sigma Chemical Co., St. Louis, and activated by treatment with dilute sodium hydroxide followed by air-drying. All other reagents and solvents were purchased from Fisher Scientific or the Aldrich Chemical Co., and used directly, with the exception of acetonitrile, which was dried over 4A molecular sieves.

Aryl 4,6-di-O-acetyl-2,3-O-carbonyl-β-D-mannopyranosides. (**3a–3k**) — All of these were prepared by the procedure detailed for the 4-methoxy analog **3a**. In a dry flask at room temperature were combined freshly prepared D-mannosyl bromide **1** (5 g, 14 mmol), potassium 4-methoxyphenoxide (2.52 g, 15.5 mmol), dicyclohexyl-18-crown-6 (0.26 g, 0.7 mmol), and acetonitrile (50 mL), with magnetic stirring under a nitrogen atmosphere. After 3 h, the mixture was filtered, and the filtrate evaporated *in vacuo*. A solution of the residue in chloroform was successively washed with water

(2 x 50 mL) and 5% $NaHCO_3$ (1 x 50 mL), dried (magnesium sulfate), and evaporated *in vacuo*; the crude material (5.4 g) was recrystallized from ethanol to provide **3a** as a tan solid (3.6 g; 64% yield); ^{1}H-n.m.r.: δ 7.10–7.00 (m, 2 H, AA′, H-ar.), 6.87–6.79 (m, 2 H, BB′, H-ar.), 5.89 (ddd, 1 H, $J_{4,2}$ 1.29, $J_{4,3}$ 3.87, $J_{4,5}$ 9.68 Hz, H-4), 5.48 (bs, 1 H, H-1), 4.98–4.88 (m, 2 H, H-2,3), 4.23 (dd, 1 H, $J_{6a,5}$ 3.23, $J_{6a,6b}$ 12.5 Hz, H-6[a]), 4.08 (dd, 1 H, $J_{6b,5}$ 3.9, $J_{6a,6b}$ 12.5 Hz, H-6b), 3.99 (dt, 1 H, $J_{5,6a}$ 3.23, $J_{5,6b}$ 3.90, $J_{5,4}$ 9.68 Hz, H-5), 3.77 (s, 3 H, OCH_3), 2.13 (s, 3 H, CH_3CO), and 1.78 (s, 3 H, CH_3CO).

*Aryl β-*D*-mannopyranosides* (**4a–4k**) — Deacetylation of series **3** was accomplished by the following general procedure detailed for **4a**. 4-Methoxyphenyl 4,6-di-*O*-acetyl-2,3-*O*-carbonyl-β-D-mannopyranoside (**3a**; 1.6 g, 4 mmol), was stirred in methanol (50 mL) with Dowex-1 (basic) resin (~1 g), for 3 h at room temperature, filtered, and the filtrate evaporated *in vacuo*. The solid residue was recrystallized from ethanol, to provide **4a** as a white solid (0.75 g, 66% yield); ^{1}H-n.m.r.: δ 7.10–6.95 (m, 2 H, AA′, H-Ar), 6.85–6.77 (m, 2 H, BB′, H-Ar.), 5.05 (d, 1 H, $J_{1,2}$ 1.2 Hz, H-1), 4.03 (dd, 1 H, $J_{2,1}$ 1.2, $J_{2,3}$ 3.42 Hz, H-2), 3.88 (dd, 1 H, $J_{6a,5}$ 2.44, $J_{6a,6b}$ 12.2 Hz, H-6a), 3.73 (dd, 1 H, $J_{6b,5}$ 6.1, $J_{6b,6a}$ 12.2 Hz, H-6b), 3.72 (s, 3 H, OCH_3), 3.64 (t, 1 H, $J_{4,3} = J_{4,5} = 9.76$ Hz, H-4), and 3.54 (dd, 1 H, $J_{3,2}$ 3.42, $J_{3,4}$ 9.76 Hz, H-3).

*Aryl α-*D*-mannopyranosides.* — 4-Methoxyphenyl α-D-mannopyranoside (**5a**) and 4-bromophenyl α-D-mannopyranoside (**5b**) were prepared by reaction of **1** with the appropriate phenol in acetonitrile, with mercuric cyanide as the catalyst, followed by removal of the acetate and carbonate groups with Dowex-1 (basic) resin. Compound **5a** had m.p. 147–149° (lit.[18] 155–156°); $[\alpha]_D^{22}$ +116.6° (*c* 2.2, methanol), lit. +122.6° (*c* 2, methanol)[18]; **5b** had m.p. 198–201° (lit.[18] 207–209°); $[\alpha]_D^{22}$ +112.5° (*c* 0.5, methanol), lit. +117.9° (*c* 0.5, methanol)[18].

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