Carbohydrate Research, 188 (1989) 228–238
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Improved synthesis of the 2-, 3-, and 4-deoxy derivatives from methyl β-D-galactopyranoside*

TSU-HSING LIN, PAVOL KOVÁČ†, AND CORNELIS P. J. GLAUDEMANS
NIDDK, National Institutes of Health, Bethesda, Maryland 20892 (U.S.A.)
(Received July 29th, 1988; accepted for publication, January 18th, 1989))

A number of forces may play roles in the binding of carbohydrate antigens to immunoglobulins. We have previously shown[1] that the major part of the binding energy of the interaction between several anti-galactan monoclonal antibodies and their homologous carbohydrates may arise from hydrogen bonding. This is indicated by the binding pattern shown by a great number of derivatives of methyl β-D-galactopyranoside (mono- and oligo-saccharides), many of them having fluorine substituted for hydroxyl groups at certain positions. To refine this investigation, we will examine the binding pattern of these immunoglobulins with deoxygenated ligands related to β-D-galactan. Here, we describe the syntheses of a series of deoxy analogs of methyl β-D-galactopyranoside.

The preparation of the title compounds by the previously described methods involves tedious, multistep procedures giving only moderate yields of the desired products. In view of new chemistry and blocking strategies developed since the last of any of these compounds was reported[2], we decided to develop a general approach to the synthesis of 2-, 3-, and 4-deoxy derivatives of methyl β-D-galactopyranoside (**1**). The most conventional approach to deoxygenation of a carbohydrate, *i.e.*, the hydrogenolysis of a corresponding halogeno derivative[3–6], was considered first. To prepare the 4-deoxy derivative **9**, an approach was chosen similar to that described for preparation of the corresponding α anomer[7]. In anticipation that side reactions[6,8] might be minimized, methyl 2,3,6-tri-*O*-benzoyl-β-D-galactopyranoside[9] (**2**), rather than the corresponding D-*gluco* derivative[6], was converted into the 4-*O*-(*p*-bromophenylsulfonyl) derivative **3**, which was then treated with potassium iodide in Me_2SO. Several products were formed, and the desired compound **4** was obtained in a yield of only 45%. A small proportion of the corresponding D-*galacto* derivative[6] (**5**) was also obtained. The physical constants of **4**

*Presented at the XIVth International Carbohydrate Symposium, Stockholm, Sweden, 14–19 August, 1988.
†To whom correspondence should be addressed.

TABLE I

^{1}H-N.M.R. CHEMICAL SHIFTS

Compound	*Chemical shift (δ)*[a,b]										
	H-1	*H-2a*	*H-2b*	*H-3a*	*H-3b*	*H-4a*	*H-4b*	*H-5*	*H-6a*	*H-6b*	OCH_3
3	4.668d	5.666dd		5.390dd		5.531d		4.222dd	4.323dd	4.635dd	3.529s
4	4.700d	5.347dd		5.840t		4.297t		4.181ddd	4.792dd	4.961dd	3.505s
5	4.733d	5.809dd		4.846dd		4.897dd		3.493m	4.707dd	4.452dd	3.559s
6	4.744d	5.752dd		5.579dd		5.551bs		4.39	4.28m	4.86–4.76m	3.566s
7[c]	5.209d	5.845dd		6.369dd		6.225bd		4.85		4.50m	3.598s
8	4.615d	5.543		5.407m		1.95–1.70m	2.55–2.45m	4.11–4.04m	4.455	4.497m	3.529s
9[d]	4.306d	3.165t		[e]		1.981dd	1.406dd	[e]	[e]	[e]	3.568s
13	4.676d	5.747dd		5.241dd		6.054d		4.222t	4.411dd	4.668dd	3.560s
14	4.966d	4.768dd		[f]		5.674dd		[f]	4.494dd	4.652dd	3.595s
15	4.684d	5.343dd		2.682dd	2.039ddd	5.542bs		4.256bt	4.632dd	4.485dd	3.584s
16[d]	4.327d	[g]		1.78–1.69m	2.25–2.17m	3.96–4.10m		[g]	[g]	[g]	3.580s
17	4.811d	5.851dd		6.078dd		6.112bd		4.344t	4.455dd	4.767dd	3.612s
18	4.384dd	1.79–1.67m	2.14–2.05m	3.83		3.74m		3.722t	4.531dd	4.653dd	3.503s
19[d]	4.562dd	1.71–1.62m	2.06–1.97m	[h]		[h]		[h]	[h]	[h]	3.545s
20	[i]	2.33–2.25m		5.49–5.44m		5.873bd		4.204t	4.500dd	[i]	3.649s
22	4.127d	3.580t		[j]		4.240dd		[j]	4.70	4.58m	3.550s
23	4.451d	5.266t		4.485dd		4.322dd		4.220ddd	4.74	4.62m	3.481s
24	4.473d	5.886t		4.419dd		4.352dd		4.239ddd	4.72	4.67m	3.486s
25	4.355dd	2.218m	1.697m	4.330m		4.058m		4.058m	4.621m	4.621m	3.494s

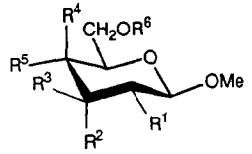
[a]Peak multiplicities: b, broad, d, doublet, m, multiplet, s, singlet, t, triplet. [b]Measured in chloroform-*d*, unless otherwise indicated. [c]Measured in acetone-d_6. [d]Measured in D_2O. [e]4-Proton multiplet, δ 3.793–3.609. [f]2-Proton multiplet, δ 5.05–4.85. [g]4-Proton multiplet, δ 3.736–3.662. [h]5-Proton multiplet, δ 3.912–3.603. [i]2-Proton multiplet, δ 4.774–4.700. [j]2-Proton multiplet, δ 4.161–4.110.

TABLE II

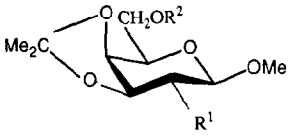
^{1}H-N.M.R. COUPLING CONSTANTS (Hz)

Constant	*Compound*																		
	3	**4**	**5**	**6**	**7**	**8**	**9**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**22**	**23**	**24**	**25**
$J_{1,2}$	7.9	7.8	7.9	7.9	8.0	7.5	7.9	7.9	6.9	7.8	8.0	7.9	[a]	[b]	[c]	7.9	8.0	7.8	[d]
$J_{2,3}$	10.5	9.5	9.6	10.1	10.2	[c]	8.9	10.3	4.3	[e]	[c]	10.0	[c]	[c]	[c]	7.9	8.0	7.8	[f]
$J_{3,4}$	3.2	10.4	4.3	2.9	3.2	[c]	[c]	3.5	4.1	[g]	[c]	3.4	[c]	[c]	2.3	5.4	5.6	5.4	[c]
$J_{4,5}$	<1	10.8	1.0	0	0	[c]	[c]	<1	1.9	<1	[c]	<1	[c]	[c]	[c]	2.2	2.0	2.1	[c]
$J_{5,6a}$	7.3	4.6	5.9	[c]	[c]	[c]	[c]	6.6	6.3	6.8	[c]	6.3	6.6	[c]	6.4	[c]	7.1	7.3	[c]
$J_{5,6b}$	6.0	2.0	6.6	[c]	[c]	[c]	[c]	5.6	6.5	6.1	[c]	6.3	6.6	[c]	6.4	[c]	5.1	5.4	[c]
$J_{6a,6b}$	11.2	12.1	11.4	[c]	[c]	[c]	[c]	11.3	11.4	11.1	[c]	11.4	11.3	[c]	11.3	[c]	[c]	[c]	[c]

[a] $J_{1,2a}$ 2.2; $J_{1,2b}$ 9.8. [b] $J_{1,2a}$ 2.9; $J_{1,2b}$ 9.7. [c] Undetermined due to overlap of signals. [d] $J_{1,2a}$ 9.5; $J_{1,2b}$ 6.9. [e] $J_{2,3a}$ 5.1; $J_{2,3b}$ 11.2. [f] $J_{2a,2b}$ 13.1; $J_{2a,3}$ 9.5; $J_{2b,3}$ 2.2. [g] $J_{3a,3b}$ 14.0; $J_{3a,4}$ 4.7, $J_{3b,4}$ 3.2.



	R1	R2	R3	R4	R5	R6
1	OH	H	OH	OH	H	H
2	OBz	H	OBz	OH	H	Bz
3	OBz	H	OBz	OBs	H	Bz
4	OBz	H	OBz	H	I	Bz
5	OBz	H	OBz	I	H	Bz
6	OBz	H	OBz	OTf	H	Bz
7	OBz	H	OBz	OItc	H	Bz
8	OBz	H	OBz	H	H	Bz
9	OH	H	OH	H	H	H
10	OH	H	OBn	OH	H	H
11	OBz	H	OBn	OBz	H	Bz
12	OBz	H	OH	OBz	H	Bz
13	OBz	H	OTf	OBz	H	Bz
14	OBz	I	H	OBz	H	Bz
15	OBz	H	H	OBz	H	Bz
16	OH	H	H	OH	H	H
17	OBz	H	OItc	OBz	H	Bz
18	H	H	OH	OH	H	Bz
19	H	H	OH	OH	H	H
20	H	H	OPab	OPab	H	OPab



	R1	R2
21	OH	H
22	OH	Bz
23	OBz	Bz
24	OItc	Bz
25	H	Bz

Bn = benzyl
Bz = benzoyl
Bs = 4-bromophenylsulfonyl
Itc = imidazol-1-ylthiocarbonyl
Pab = 4-(phenylazo)benzoyl
Tf = F_3CSO_2

and **5** agreed essentially with the reported values[6], and the structures were fully supported by the ^{1}H-n.m.r. data (see Tables I and II). In another approach, the 4-*O*-(trifluoromethylsulfonyl) derivative **6** was treated with iodide ion under much milder conditions. In this case, compound **4**, the only product (t.l.c.), was isolated crystalline in 78% yield. The iodo derivative **4** was hydrogenolyzed in the presence of 20% palladium-on-charcoal catalyst, to give the fully protected deoxy derivative **8**. *O*-Debenzoylation (Zemplén) of **8** afforded the target glycoside **9**, the physical constants of which agreed well with the literature values[6].

Easy access[10] to methyl 2,4,6-tri-*O*-benzoyl-β-D-galactopyranoside (**12**) made it possible to synthesize the 3-deoxy derivative **16**, *via* the 3-*O*-triflyl derivative **13**, in a way analogous to that just described for the preparation of **9**. The resulting **16** showed physical constants in accord with the published data[3], and its n.m.r. characteristics (not previously recorded), as well as those of its intermediates, fully supported the anticipated structures.

A suitable starting-material for the synthesis of the 2-deoxyglycoside **19** appeared to be methyl 6-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranoside (**22**). This compound was used by Flowers[11] in disaccharide syntheses, but details of its preparation or characterization had not been reported. We obtained compound **22** by selective benzoylation of methyl 3,4-*O*-isopropylidene-β-D-galactopyranoside (**21**; see ref. 12). A small proportion of the 2,6-di-*O*-benzoyl derivative[13] **23**, formed along with **22** during benzoylation of **21**, was also isolated. Both compounds **22** and **23** were obtained crystalline, and fully characterized. Treatment of **22** with trifluoromethanesulfonic anhydride, as described for the preparation of **6** and **13**, yielded a sharp-melting, crystalline material, m.p. 105° (dec.), which was homogeneous by t.l.c. and gave correct analytical data required for methyl 6-*O*-benzoyl-3,4-*O*-isopropylidene-2-*O*-(trifluoromethylsulfonyl)-β-D-galactopyranoside. The n.m.r. spectra of the substance showed, however, that it was a mixture of two compounds. Because isolation of the desired compound by recrystallization was unsuccessful, this approach was not pursued further, and we turned our attention to the possibility of deoxygenating carbon atom 2 in **22** *via* the corresponding imidazol-1-ylthiocarbonyl derivative[14–16]. Compound **22** showed poor reactivity towards thiocarbonyldiimidazole (TCDI), as shown by t.l.c., but imidazolethiocarbonylation preceded by butylstannylation was successful. In this way, the crystalline thiocarbonyl derivative **24** was obtained in a yield of 86%. Reduction of **24** with tributyltin hydride gave the crystalline deoxy sugar **25** in 73% yield. Treatment of **25** with dilute acetic acid produced crystalline **18**, and *O*-debenzoylation of **18** yielded material which crystallized readily. The compound shows a negative specific optical rotation ($[\alpha]_D$ −16°), whereas methyl 2-deoxy-α-D-*lyxo*-hexopyranoside has been reported[17,18] to show $[\alpha]_D$ +169 to +181°. A direct comparison of physical constants with literature data could not be made, as methyl 2-deoxy-β-D-*lyxo*-hexopyranoside was previously obtained in amorphous state only[3,18], and n.m.r. data for the compound have not been published. The corresponding tri-*O*-[4-(phenylazo)benzoyl] derivative **20** shows a m.p. close to that reported[18] for a compound derived from amorphous, putative **19**. However, the reported assignment of the (incomplete) ^{1}H-n.m.r. data is at some variance with our more-complete data reported here. Based on the analytical data found for this material and a comparison of the splitting pattern observed for H-1 and H-2 in its ^{1}H-n.m.r. spectrum (see Tables I and II) with that observed in the spectra of α- and β-linked 2,6-dideoxy-D-*lyxo*-hexopyranose[19,20], we assigned to it structure **19**.

Prompted by the ease of preparation of **19** *via* **24**, we applied the same method of deoxygenation to the synthesis of 3- and 4-deoxy derivatives **9** and **16**. Preparation of the intermediate compounds **8** and **15** *via* **7** and **17**, respectively, was uneventful. Thus, judging by the yields obtained and the simplicity of the operations involved, we find that the deoxygenation *via* imidazol-1-ylthiocarbonyl derivatives definitely superior to the conversions developed earlier. A high-yielding deoxygenation in the D-galactose series involving a dithiocarbonate derivative has recently been described by Kihlberg *et al.*[21].

EXPERIMENTAL

General methods. — Melting points were determined on a Kofler hot stage. Unless otherwise stated, optical rotations were measured at 25° for solutions in chloroform, using a Perkin–Elmer automatic polarimeter, Model 241 MC. Preparative chromatography was performed by gradient elution from columns of Silica Gel 60 (Merck, Cat. No. 9385). All reactions were monitored by thin-layer chromatography (t.l.c.) on glass slides coated with silica gel (Analtech or Whatman). Elutions were conducted with solvent mixtures of appropriately adjusted polarity, consisting of: *A*, carbon tetrachloride–ethyl acetate; *B*, carbon tetrachloride–ethyl acetate–acetone; *C*, toluene–ethyl acetate; *D*, dichloromethane–methanol; and *E*, carbon tetrachloride–acetone. ^{13}C-N.m.r. and ^{1}H-n.m.r. spectra were routinely recorded at 25° with a Varian XL 300 spectrometer. Proton-signal assignments were made by first-order analysis of the spectra, supported by selective homonuclear decoupling experiments, and carbon-signal assignments were made by mutual comparison of the spectra. Unambiguous assignment of lines in the ^{13}C-n.m.r. spectrum of **19** was achieved by a heteronuclear ^{1}H–^{13}C correlation 2D n.m.r. experiment (HETCOR), using a GE 300 WB (NT Series) spectrometer. Solvents for compounds used in measurements are reported in Tables I and II, as required. ^{13}C-N.m.r. chemical shifts found in the spectra recorded for solutions in $CDCl_3$ and D_2O are reported using Me_4Si and methanol as internal standards (δ_{MeOH} *vs.* δ_{Me_4Si} 49.0). Desorptive c.i. mass spectra were recorded using ammonia as the reagent gas and a Finnigan 4500 spectrometer. Palladium-on-charcoal (20%) catalyst was a product of Engelhardt Industries. *N,N'*-Thiocarbonyldiimidazole (TCDI, 97% purity) was purchased from Fluka Chemical Company, and used as supplied. Solutions in organic solvents were dried with anhydrous sodium sulfate, and concentrated or evaporated at <40°/2 kPa.

*Methyl 2,3,6-tri-*O*-benzoyl-4-*O*-(*p*-bromophenylsulfonyl)-β-*D*-galactopyranoside* (**3**). — A mixture of **2** (lit.[9], 5.06 g, 10 mmol), pyridine (25 mL), and *p*-bromobenzenesulfonyl chloride (5.11 g, 20 mmol) was stirred overnight at 50°. Conventional processing gave the product **3** (6.10 g, 85%), which crystallized from ethanol. Recrystallization of a portion from the same solvent gave material having m.p. 178–179°, $[\alpha]_D$ +65° (*c* 0.5); ^{13}C-n.m.r. data: δ 102.2 (C-1), 69.0 (C-2), 71.6 (C-3), 75.7 (C-4), 70.9 (C-5), 61.8 (C-6), and 57.0 (OCH_3).

Anal. Calc. for $C_{34}H_{29}BrO_{11}S$: C, 56.28; H, 4.03; Br, 11.01; S, 4.42. Found: C, 56.34; H, 4.03; Br, 11.10; S, 4.41.

*Methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-iodo-β-*D*-glucopyranoside* (**4**) *and methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-iodo-β-*D*-galactopyranoside* (**5**). — (*a*) A mixture of compound **3** (0.363 g, 0.5 mmol) and potassium iodide (1.66 g, 10 mmol) in Me_2SO (5 mL) was heated overnight at 110° (bath). T.l.c. (solvent *B*) then showed that all of the **3** had been consumed, and that one major and several minor products had been formed. The mixture was partitioned between water and dichloromethane, the organic layer was washed with an aqueous solution of sodium thio-

sulfate, dried, and concentrated, and the residue was chromatographed (solvent *B*), to give, first, a small amount of **5**; m.p. 166° (lit.[6] 163–164°); ^{13}C-n.m.r. data: δ 102.7 (C-1), 67.7 (C-2), 72.1, 71.2, 71.0 (C-3,5,6), 33.5 (C-4), and 56.8 (O*C*H$_3$).

Eluted next was the major product **4** (0.145 g, 45%); m.p. 144.5–145° (from methanol), $[\alpha]_D$ +49° (*c* 0.2), (lit.[6] m.p. 131–133°, $[\alpha]_D$ +19.9°); ^{13}C-n.m.r. data: δ 102.2 (C-1), 75.8, 75.3, 72.8 (C-2,3,5), 24.0 (C-4), 65.5 (C-6), and 57.0 (O*C*H$_3$).

Anal. Calc. for $C_{28}H_{25}IO_8$: C, 54.56; H, 4.11; I, 20.59. Found: C, 54.67; H, 4.11; I, 20.67.

Both compounds **4** and **5** produced a peak at *m/z* 634 $(M + 18)^+$ in their c.i.m.spectra.

(*b*) Potassium iodide (0.996 g, 6 mmol) was added to a solution of **6** (1.277 g, 2.0 mmol) in acetonitrile (15 mL). The mixture was heated for 3 h at 50°; t.l.c. then showed that the reaction was complete and that only one product had been formed. After concentration, the concentrate was partitioned between dichloromethane and water, and the organic layer was dried and concentrated. Chromatography (solvent *A*), and crystallization from methanol, yielded **4** (0.957 g, 78%); m.p. 144.5–145°.

*Methyl 2,3,6-tri-O-benzoyl-4-O-(trifluoromethylsulfonyl)-β-*D*-galactopyranoside* (**6**). — Trifluoromethanesulfonic anhydride (0.42 mL, 2.5 mmol) was slowly added at −10° to a solution of **2** (0.506 g, 1 mmol) in pyridine (5 mL), the mixture was stirred for 1 h at 0°, ice–water (20 mL) was added, and the mixture was extracted with dichloromethane. The extract was dried and concentrated, and the residue was chromatographed (solvent *A*). Crystallization from ethanol gave **6** (0.524 g, 83%); m.p. 142–143°, $[\alpha]_D$ +22° (*c* 0.8); ^{13}C-n.m.r. data: δ 102.4 (C-1), 68.7 (C-2), 70.8, 70.4 (C-3,5), 81.0 (C-4), 61.0 (C-6), and 57.3 (O*C*H$_3$): c.i.m.s.: *m/z* 656 $(M + 18)^+$.

Anal. Calc. for $C_{29}H_{25}F_3O_{11}S$: C, 54.55; H, 3.95; F, 8.93; S, 5.02. Found: C, 54.23; H, 4.17; F, 8.63; S, 5.19.

*Methyl 2,3,6-tri-O-benzoyl-4-O-(imidazol-1-ylthiocarbonyl)-β-*D*-galactopyranoside* (**7**). — A mixture of **2** (0.506 g, 1 mmol) and TCDI (0.3 g, 1.6 mmol) in toluene (15 mL) was boiled for 3 h under reflux, cooled, and concentrated, the residue was chromatographed (solvent *A*), and the product crystallized from ethanol, to give **7** (0.45 g, 75%); m.p. 150.5–151°, $[\alpha]_D$ +112° (*c* 0.6); ^{13}C-n.m.r. data: δ 102.4 (C-1), 69.7 (C-2), 71.1, 71.4 (C-3,5), 76.3 (C-4), 61.5 (C-6), and 57.2 (O*C*H$_3$); c.i.m.s.: *m/z* 617 $(M + 1)^+$.

Anal. Calc. for $C_{32}H_{28}N_2O_9S$: C, 62.33; H, 4.58; N, 4.54; S, 5.20. Found: C, 62.39; H, 4.61; N, 4.48; S, 5.16.

*Methyl 2,3,6-tri-O-benzoyl-4-deoxy-β-*D*-xylo-hexopyranoside* (**8**). — (*a*) A mixture of **4** (0.924 g, 1.5 mmol), 20% palladium-on-charcoal catalyst (0.46 g), and $NaHCO_3$ (0.252 g, 3 mmol) in DMF (20 mL) was stirred overnight in a hydrogen atmosphere. After conventional processing, the crude product was chromatographed (solvent *C*) to give 0.56 g (76%) of amorphous, major product **8**; $[\alpha]_D$ +53° (*c* 0.8); ^{13}C-n.m.r. data: δ 102.2 (C-1), 72.6, 71.6, 69.7 (C-2,3,5), 33.3 (C-4), 65.9 (C-6), and 56.9 (O*C*H$_3$); c.i.m.s.: *m/z* 508 $(M + 18)^+$.

Anal. Calc. for $C_{28}H_{26}O_8$: C, 68.56; H, 5.34. Found: C, 68.60; H, 5.38.

Under the same conditions, compound **5** did not react, as shown by t.l.c.

(*b*) A solution of compound **7** (0.616 g, 1 mmol) in toluene (20 mL) was added to a refixing solution of tributyltin hydride (0.5 mL, 1.5 mmol) in toluene (50 mL). The mixture was boiled under reflux until t.l.c. (solvent *C*) showed that the reaction was complete (~0.5 h). After concentration, the residue was chromatographed (solvent *C*), to give **8** in almost theoretical yield.

*Methyl 4-deoxy-β-*D-xylo-*hexopyranoside* (**9**). — M Methanolic sodium methoxide (1 mL) was added to a solution of **8** (0.54 g, 1.1 mmol) in methanol (50 mL), and the solution was kept overnight at room temperature. One product was formed, as shown by t.l.c. (solvent *D*). After neutralization of the base with Amberlite IR-120 (H^+) ion-exchange resin, the solution was concentrated with addition of toluene, to remove methyl benzoate, and crystallization of the residue from methanol–ethyl acetate gave **9** (0.124 g, 63%); m.p. 148–148.5°, $[\alpha]_D$ −38° (*c* 0.4, water), (lit.[6] m.p. 146–147°, $[\alpha]_D$ not reported; lit.[3] m.p. 143°, $[\alpha]_D$ −35.5°); ^{13}C-n.m.r. data: δ 103.7 (C-1), 75.1, 72.7, 70.6 (C-2,3,5), 35.1 (C-4), 63.7 (C-6), and 57.2 (OCH_3); c.i.m.s.: *m/z* 179 $(M + 1)^+$.

Anal. Calc. for $C_7H_{14}O_5$: C, 47.19; H, 7.92. Found: C, 47.29; H, 7.96.

*Methyl 2,4,6-tri-*O*-benzoyl-3-*O*-(trifluoromethylsulfonyl)-β-*D*-galactopyranoside* (**13**). — Compound **12** (1.013 g, 2 mmol) was dissolved in pyridine (10 mL), and trifluoromethanesulfonic anhydride (1 mL, 1.667 g, 5.8 mmol) was slowly added at −10°. The solution was kept for 1 h at −10° and then for 2 h at room temperature. The yellow solution was poured into ice–water (50 mL), and the mixture was extracted with dichloromethane (3 × 40 mL); the extracts were combined, dried, and concentrated, and the concentrate was subject to chromatography (solvent *A*), giving **13** (0.95 g, 75%) as a colorless glass; $[\alpha]_D$ +41° (*c* 0.5); ^{13}C-n.m.r. data: δ 102.1 (C-1), 70.9, 69.1, 68.1 (C-2,4,5), 83.2 (C-3), 61.9 (C-6), and 57.2 (OCH_3); c.i.m.s.: *m/z* 656 $(M + 18)^+$.

Anal. Calc. for $C_{29}H_{25}F_3O_{11}S$: C, 54.55; H, 3.95; F, 8.93; S, 5.02. Found: C, 54.87; H, 3.81; F, 8.94; S, 5.21.

*Methyl 2,4,6-tri-*O*-benzoyl-3-deoxy-3-iodo-β-*D*-gulopyranoside* (**14**). — A mixture of compound **13** (3.31 g, 5.18 mmol) and potassium iodide (1.72 g, 10.3 mmol) in acetonitrile (50 mL) was heated overnight at 60° (bath), cooled, and concentrated; the residue was extracted with toluene (300 mL), the extract concentrated, and the concentrate chromatographed (solvent *A*), to give the major product **14** (2.47 g, 77%) as a colorless glass; $[\alpha]_D$ +61° (*c* 0.6); ^{13}C-n.m.r. data: δ 101.2 (C-1), 72.3, 70.3, 68.6 (C-2,4,5), 27.9 (C-3), 63.1 (C-6), and 57.1 (OCH_3); c.i.m.s.: *m/z* 634 $(M + 18)^+$.

Anal. Calc. for $C_{28}H_{25}IO_8$: C, 54.56; H, 4.09; I, 20.59. Found: C, 54.41; H, 4.11; I, 20.49.

*Methyl 2,4,6-tri-*O*-benzoyl-3-*O*-(imidazol-1-ylthiocarbonyl)-β-*D*-galactopyranoside* (**17**). — TCDI (0.3 g, 1.6 mmol) was added to a solution of **12** (0.506 g, 1 mmol) in toluene (15 mL), and the mixture was refluxed for 4 h. After processing

as described for the preparation of **7**, compound **17** (0.54 g, 88%) was obtained as a colorless glass; $[\alpha]_D$ +67° (*c* 0.5); ^{13}C-n.m.r. data: δ 102.1 (C-1), 71.1, 69.4, 67.1 (C-2,4,5), 79.4 (C-3), 61.9 (C-6), and 57.2 (OCH_3); c.i.m.s.: *m/z* 617 $(M + 1)^+$.

*Methyl 2,4,6-tri-O-benzoyl-3-deoxy-β-*D-xylo-*hexopyranoside* (**15**). — (*a*) To a solution of **14** (2.28 g, 3.7 mmol) in DMF (50 mL) were added 20% palladium-on-charcoal catalyst (1.0 g) and sodium hydrogencarbonate (0.62 g, 7.4 mmol), and the mixture was stirred in a hydrogen atmosphere overnight. After conventional processing, the crude product was chromatographed (solvent *C*) to give 1.346 g (74%) of the major product **15** as a colorless glass: $[\alpha]_D$ −17° (*c* 0.4); ^{13}C-n.m.r.: δ 103.3 (C-1), 68.2, 67.6 (C-2,4), 32.6 (C-3), 74.1 (C-5), 62.8 (C-6), and 56.6 (OCH_3); c.i.m.s.: *m/z* 508 $(M + 18)^+$.

Anal. Calc. for $C_{28}H_{26}O_8$: C, 68.56; H, 5.34. Found: C, 68.67; H, 5.35.

(*b*) A solution of **17** (0.616 g, 1 mmol) in dry toluene (20 mL) was treated as described for preparation (*b*) of **8**. When the reaction was complete (~1 h), the mixture was concentrated, and the residue was chromatographed (solvent *C*), to give **15** in a virtually theoretical yield.

*Methyl 3-deoxy-β-*D-xylo-*hexopyranoside* (**16**). — A solution of **15** (0.62 g, 1.26 mmol) in methanol (40 mL) was treated as described for the preparation of **9**. Chromatography (solvent *D*), and crystallization yielded **16** (0.161 g, 73%); m.p. 177.5–179°, $[\alpha]_D$ −67° (*c* 0.5, water), (lit.[3] 173–174°, $[\alpha]_D$ −69.4°); ^{13}C-n.m.r. data: δ 106.0 (C-1), 65.9, 65.6 (C-2,4), 37.3 (C-3), 78.4 (C-5), 61.4 (C-6), and 56.9 (OCH_3).

Anal. Calc. for $C_7H_{14}O_5$: C, 47.19; H, 7.92. Found: C, 46.96; H, 7.86.

Methyl 6-O-benzoyl- (**22**) *and 2,6-di-O-benzoyl-3,4-O-isopropylidene-β-*D-*galactopyranoside* (**23**). — Benzoyl chloride (0.64 mL, 5.5 mmol) was slowly added at −20° to a solution of compound **21** (lit.[18]; 1.17 g, 5 mmol) and dry pyridine (0.53 mL, 6.5 mmol) in dichloromethane (30 mL). When addition was complete, the mixture was allowed to warm to −10° and, after 15 min, it was processed in the usual way. The crude product was chromatographed (solvent *E*), to give, first, the minor product **23** (0.45 g, 21%); m.p. 123.5–125°, $[\alpha]_D$ +30° (*c* 0.8), (lit.[13] 121–122°, $[\alpha]_D$ +31°); ^{13}C-n.m.r. data: δ 101.5 (C-1), 77.1, 73.7, 73.4, 71.1 (C-2,3,4,5), 63.8 (C-6), and 56.6 (OCH_3); c.i.m.s.: *m/z* 460 $(M + 18)^+$.

Eluted next was the major product **22** (0.935 g, 55%); m.p. 168–168.5°, $[\alpha]_D$ +11° (*c* 0.5); ^{13}C-n.m.r. data: δ 103.2 (C-1), 73.7, 73.5 (C-2,4), 78.8 (C-3), 71.3 (C-5), 63.8 (C-6), and 56.9 (OCH_3); c.i.m.s.: *m/z* 356 $(M + 18)^+$.

Anal. Calc. for $C_{17}H_{22}O_7$: C, 60.35; H, 6.55. Found: C, 60.27; H, 6.60.

*Methyl 6-O-benzoyl-3,4-O-isopropylidene-2-O-(imidazol-1-ylthiocarbonyl)-β-*D-*galactopyranoside* (**24**). — A mixture of **22** (3.38 g, 10 mmol) and bis(tributyltin) oxide (3.0 g, 2.82 mL, 5 mmol) in dry toluene (100 mL) was refluxed for 3 h with continuous azeotropic removal of water, cooled to room temperature, TCDI (2.7 g, 15 mmol) added, and the mixture heated almost at reflux for 1 h. The mixture was concentrated to a yellow oil which was dissolved in dichloromethane (100 mL), and the solution was washed successively with M HCl (100 mL), 5% aqueous

sodium hydrogencarbonate solution (100 mL), and water (100 mL), dried, concentrated, and the residue crystallized from ether, to give **24** (3.82 g, 86%); m.p. 130.5°, $[\alpha]_D$ +8° (*c* 0.2); ^{13}C-n.m.r. data: δ 100.8 (C-1), 81.1 (C-2), 76.7, 73.8, 71.2 (C-3,4,5), 63.5 (C-6), and 56.8 (OCH_3); c.i.m.s.: *m/z* 449 $(M + 1)^+$.

Anal. Calc. for $C_{21}H_{24}N_2O_7S$: C, 56.23; H, 5.39; N, 6.24; S, 7.15. Found: C, 56.32; H, 5.43; N, 6.25; S, 7.08.

*Methyl 6-O-benzoyl-2-deoxy-3,4-O-isopropylidene-β-*D*-lyxo-hexopyranoside* (**25**). — Compound **24** (2.69 g, 6 mmol) was treated with tributyltin hydride (2.9 g, 2.8 mL, 10 mmol) as described for preparation (*b*) of **8**. When the reaction was complete (~2 h), the mixture was processed as described for the preparation of **8**, and the product crystallized from hexane to afford pure **25**; m.p. 62.5–63°, $[\alpha]_D$ −18° (*c* 0.8). Chromatography (solvent *C*) of the material in the mother liquor gave a further crop of **25** (total yield 1.4 g, 73%); ^{13}C-n.m.r. data: δ 100.6 (C-1), 35.5 (C-2), 72.2, 71.3, 71.1 (C-3,4,5), 64.3 (C-6), and 56.3 (OCH_3); c.i.m.s.: *m/z* 340 $(M + 18)^+$.

Anal. Calc. for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.13; H, 6.89.

*Methyl 6-O-benzoyl-2-deoxy-β-*D*-lyxo-hexopyranoside* (**18**). — A solution of compound **25** (0.71 g, 1.45 mmol) in a mixture of 1,2-dimethoxyethane (5 mL) and 10% aqueous acetic acid (4 mL) was heated for 18 h at 60°, cooled, concentrated, and the concentrate subjected to column chromatography (solvent *D*). Compound **18** (0.59 g, 88%) crystallized from acetone; m.p. 149–151°, $[\alpha]_D$ −27° (*c* 0.4, methanol); ^{13}C-n.m.r. data: δ 101.3 (C-1), 35.1 (C-2), 68.4 (C-3), 67.2 (C-4), 72.5 (C-5), 63.1 (C-6), and 56.5 (OCH_3); c.i.m.s.: *m/z* 300 $(M + 18)^+$.

Anal. Calc. for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.66; H, 6.44.

*Methyl 2-deoxy-β-*D*-lyxo-hexopyranoside* (**19**). — Conventional *O*-debenzoylation of **18** (0.140 g, 0.5 mmol), and crystallization of the product from methanol, gave **19** (0.079 g, 89%); m.p. 125–126°, $[\alpha]_D$ −16° (*c* 0.5, water), (lit.[3] $[\alpha]_D$ 0°, and lit.[18] $[\alpha]_D$ not reported for the amorphous **19**); ^{13}C-n.m.r. data: δ 101.3 (C-1), 33.5 (C-2), 68.0 (C-3), 67.0 (C-4), 75.5 (C-5), 61.5 (C-6), and 56.6 (OCH_3); c.i.m.s.: *m/z* 196 $(M + 18)^+$.

Anal. Calc. for $C_7H_{14}O_5$: C, 47.19; H, 7.92. Found: C, 47.25; H, 7.97.

The corresponding per-*O*-[4-(phenylazo)benzoyl] derivative **20**, prepared as described[18], had m.p. 193–194° (lit.[18] m.p. 187°); ^{13}C-n.m.r. data: δ 101.3 (C-1), 32.5 (C-2), 69.7 (C-3), 66.7 (C-4), 71.4 (C-5), 62.7 (C-6), and 57.0 (OCH_3).

ACKNOWLEDGMENT

The authors thank Dr. Phillip E. Morris, of the University of Alabama in Birmingham, for the heteronuclear 2D ^{1}H–^{13}C-n.m.r. correlation spectroscopy.

REFERENCES

1 C. P. J. Glaudemans and P. Kováč, *Fluorinated Carbohydrate, Chemical and Biochemical Aspects, ACS Symp. Ser.*, 374 (1988) 78–108.
2 J. Jarý and M. Marek, *Collect. Czech. Chem. Commun.*, 45 (1980) 3571–3582.

3 M. DAHLGARD, B. H. CHASTAIN, AND R. L. HAN, *J. Org. Chem.*, 27 (1962) 929–934.
4 E. J. HEDGLEY, W. G. OVEREND, AND R. A. C. RENNIE, *J. Chem. Soc.*, (1963) 4701–4711.
5 H. W. H. SCHMIDT AND H. NEUKOM, *Carbohydr. Res.*, 10 (1969) 361–369.
6 A. MARADUFU AND A. S. PERLIN, *Carbohydr. Res.*, 32 (1974) 261–277.
7 S. K. SINHA AND K. BREW, *Carbohydr. Res.*, 81 (1980) 239–247.
8 C. L. STEVENS, K. G. TAYLOR, AND J. A. VALICENTI, *J. Am. Chem. Soc.*, 87 (1965) 4579–4584.
9 P. J. GAREGG AND S. OSKARSON, *Carbohydr. Res.*, 137 (1985) 270–275.
10 P. KOVÁČ AND C. P. J. GLAUDEMANS, *Carbohydr. Res.*, 142 (1985) 158–164.
11 H. M. FLOWERS, *Carbohydr. Res.*, 74 (1979) 177–185.
12 H. M. FLOWERS, *Carbohydr. Res.*, 39 (1975) 245–251.
13 K. A. WATANABE, R. S. GOODY, AND J. J. FOX, *Tetrahedron*, 26 (1970) 3883–3903.
14 J. B. HENDRICKSON AND K. W. BAIN, *J. Org. Chem.*, 42 (1977) 3875–3878.
15 J. R. RASMUSSEN, *J. Org. Chem.*, 45 (1980) 2725–2727.
16 J. R. RASMUSSEN, C. J. SLINGER, R. J. KORDISH, AND D. NEWMAN-EVANS, *J. Org. Chem.*, 46 (1981) 4843–4846.
17 W. G. OVEREND, F. SHAFIZADEH, AND M. STACEY, *J. Chem. Soc.*, (1950) 671–677.
18 C. KNAPP, J. LEHMANN, AND B. SCHWESINGER, *Chem. Ber.*, 112 (1979) 1147–1152.
19 R. W. BINKLEY AND M. A. ABDULAZIZ, *J. Org. Chem.*, 52 (1987) 4713–4717.
20 R. W. BINKLEY AND D. J. KOHOLIC, *J. Carbohydr. Chem.*, 7 (1988) 487–499.
21 J. KIHLBERG, R. FREJD, K. JANSSON, A. SUNDIN, AND G. MAGNUSSON, *Carbohydr. Res.*, 176 (1988) 271–286.