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CHAIN ELONGATION BY USE OF AN IRON CARBONYL REAGENT: A FACILE SYNTHESIS OF 6-DEOXYHEPTOSIDURONIC ACIDS

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ABSTRACT

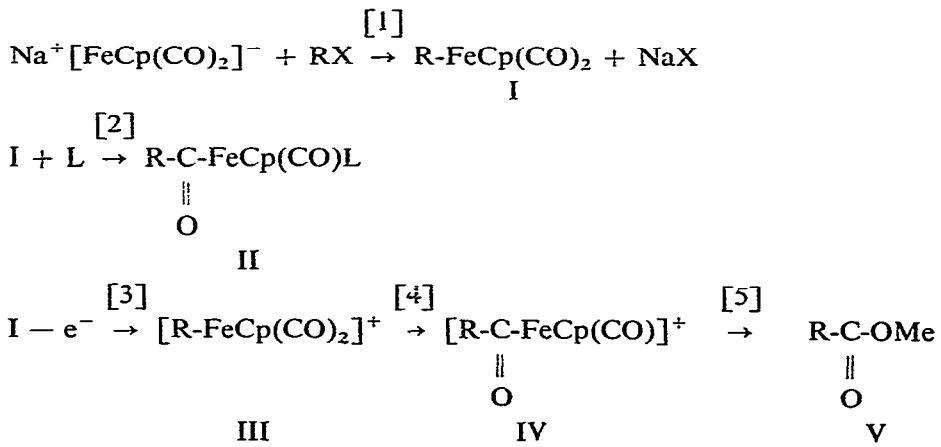
A method of chain elongation at the nonreducing terminal of 6-deoxy-6-halo- and 6-*O*-tosyl-hexopyranosides, to give methyl (methyl 6-deoxyheptopyranosid)uronates was developed on the basis of organo-iron chemistry. Thus, methyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-β-D-glucopyranoside reacted almost instantly under mild conditions with sodium dicarbonyl-η^5-cyclopentadienyliron (NaFp) in oxolane, to form an isolable, well-characterized iron derivative (**2**) in which the tosyloxy group was replaced by the Fp group. Oxidative carbonyl insertion in **2** could be induced by a variety of oxidants, but was best accomplished by bromine in the presence of methanol, at low temperatures. The process caused removal of the iron moiety, and led, in 80% overall yield, to the methyl ester of the corresponding, 6-deoxyheptosiduronic acid. Similarly, the methyl 4-*O*-benzoyl-6-bromo-6-deoxy-α- and -β-D-glucopyranosides, their 2,3-diacetates, and 2,3-dimethyl ethers, as well as the methyl 6-bromo-6-deoxy-α-D-glucopyranoside and 6-deoxy-6-iodo-α-D-mannopyranoside 2,3,4-tribenzoates furnished high yields of 6-deoxyheptosiduronic esters by application of this reaction sequence, although the intermediate sugar–iron compounds were not normally isolated.

INTRODUCTION

In continuation of our studies[1] on the utility of transition-metal, organometallic reagents in carbohydrate synthesis, we turned our attention to metal-carbonyl complexes as aids of considerable promise. A. Rosenthal and his co-workers were the first to realize the great potential of such complexes in sugar synthesis when, during the 1960s, they performed pioneering investigations on the "oxo reaction", *i.e.*, the hydroformylation or hydro(hydroxymethyl)ation of alkenes and oxiranes promoted by cobalt carbonyls, as applied to appropriate sugar derivatives[2]. Among the numerous transformations elaborated were chain-lengthening processes at the nonreducing terminal of aldose derivatives[3,4]. Thus, 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose reacted with carbon monoxide and hydrogen, in the presence of dicobalt octacarbonyl, to give[3] 6-deoxy-1,2-*O*-isopropylidene-α-D-*gluco*-heptodialdo-1,4-furanose-7,3-pyranose; alternatively, it reacted[4] with carbon monoxide and sodium

cobalt tetracarbonyl, followed by methanol and iodine, to afford methyl 6-deoxy-1,2-*O*-isopropylidene-α-D-*gluco*-heptofuranuronate. Yields were high (~80%), but both reactions needed to be performed in an autoclave under pressure, one[3] requiring an elevated temperature (100–105°), and the other[4], an extended period of time (60 h). These somewhat inconvenient conditions, and also the limitation in scope that is inherent in a method predicated on the use of terminal epoxides, are avoided in a new synthesis of 6-deoxyhepturonic acid derivatives from readily available 6-bromo-6-deoxy(or 6-*O*-tosyl)-hexopyranosides, reported in this article.

The method makes use of oxidatively-induced carbonyl insertion by ligand transfer in a σ-bonded, sugar–dicarbonylcyclopentadienyliron intermediate, the latter being produced by substitution of the bromo (or tosyloxy) substituent with sodium dicarbonyl-*pentahapto*-cyclopentadienyliron [$NaFe(CO)_2Cp$, NaFp]. Well established in general organic chemistry[5,6], the process may be represented as shown in Scheme 1. After alkylation of the Fp^- anion (an extremely powerful nucleophile[7]) by RX, to produce an alkyliron complex I (reaction [1]), a ligand-transfer reaction (carbonyl insertion) gives an acyliron complex II (reaction [2]) in which one carbonyl ligand is replaced by a new ligand L. This transfer may be induced thermally, or photochemically, or by reaction with other ligands or solvent. Frequently, L represents triphenylphosphine, or a fresh carbon monoxide molecule supplied from an external source[6]. However, under conditions of *oxidative* insertion as applied here, using an oxidant in the presence of an alcohol[8,9], I is presumed to be oxidized (reaction [3]) to III, which undergoes insertion (reaction [4]) at a greatly increased rate. The resulting, cationic acyliron complex IV is rapidly attacked by methanol to give the ester V (reaction [5]).



Scheme 1

These reactions resemble, in principle, the cobalt-promoted carbonylations[2–4], but have the advantage of proceeding very rapidly at ordinary pressure and at room temperature or below. Within the broader context of examining the potential of

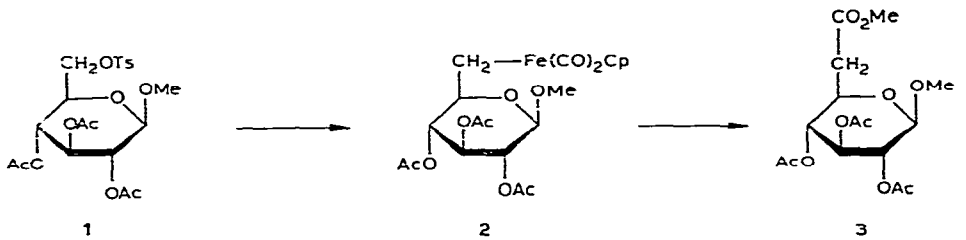
organometallic processes in carbohydrate synthesis, the more immediate aim of the present study was to develop a general route to 6-deoxyhepturonic acid derivatives. To the best of our knowledge, such homologs of the familiar alduronic acids have not as yet been discovered in Nature, and their synthesis seems to have received very little attention. Apart from the aforementioned instance[4], we were unable to find more than one other example of synthesis. The latter involved a sulfonate displacement by potassium cyanide, in 1,2-*O*-isopropylidene-α-D-glucofuranose, which was followed by total hydrolysis of the resulting nitrile[10].

Other work employing organo-iron chemistry in carbohydrates, with different reagents and objectives, has recently been reported[11,12].

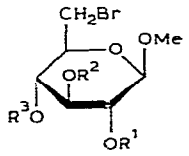
RESULTS

Methyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-β-D-glucopyranoside (**1**) was chosen as the subject of initial trials that were intended to establish the most appropriate reaction-conditions. The tosylate reacted with NaFp in dry oxolane, at room temperature, to give the covalently linked, sugar–iron compound **2**. The reaction was complete almost instantaneously, as evidenced by thin-layer chromatography performed shortly after the mixing of the reactants; **1** had disappeared completely, and the formation of **2** was indicated by a yellow spot (that was visible directly, prior to spraying the plates with sulfuric acid followed by heating). Isolated as a chromatographically purified, yellow syrup, **2** tended to decompose slowly, but its structure could, nevertheless, be ascertained by spectroscopy. It showed light absorption in the visible region (λ_{max}^{MeOH} 412 nm), and displayed strong infrared bands for ligand carbonyl (2015 and 1940 cm^{-1}), as well as for ester carbonyl groups (1745 cm^{-1}). The ^{1}H-n.m.r. spectrum (see the Experimental section) showed all the signals expected of **2**, of special significance being a 5-proton singlet at δ 4.80 for the *pentahapto*-cyclopentadienyl group (Cp), and the multiplets for H-6 and H-6′, which had incurred a strong, upfield shift (to δ 1.62 and 1.24, respectively) from their resonance position (δ 4.12) in **1**. The ^{13}C-n.m.r. data (see Experimental section) also confirmed the structure, with signals occurring at δ 217.4 and 216.8 (ligand CO), 170.4, 169.9, and 169.5 (ester CO), and 85.4 (Cp), in addition to the signals expected from the remaining carbon atoms. An extensive collection of spectral data for alkyl-Fp derivatives has been provided by Rosenblum *et al.*[13], and may be perused for comparison. Compound **2** was even amenable to mass spectrometry using the electron-impact mode, at a probe temperature of 110° (A.E.I. MS 902 instrument with direct-inlet probe). It gave a molecular ion peak at *m/z* 480, fragments signifying the progressive loss of CO and Cp ligands, and a fragment indicating loss of the entire iron moiety Fp (see Experimental).

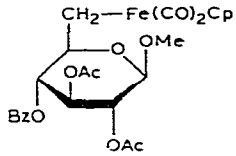
When **2** was dissolved, at room temperature, in methanol containing a sevenfold, molar excess of anhydrous cupric chloride[14], to effect oxidative carbonyl insertion, the heptosiduronic methyl ester **3** was formed within ~1 h, and was subsequently isolated crystalline. In preparative experiments performed on a larger



1 2 3



4 $R^1 = R^2 = R^3 = Ac$
5 $R^1 = R^2 = Ac, R^3 = Bz$
6 $R^1 = R^2 = H, R^3 = Bz$
7 $R^1 = R^2 = Me, R^3 = Bz$



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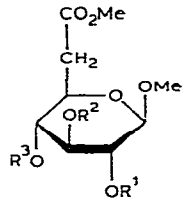
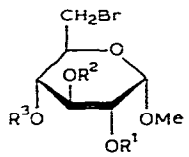
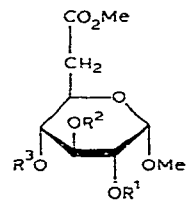


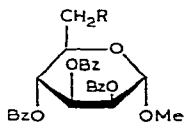
9 $R^1 = R^2 = Ac, R^3 = Bz$
10 $R^1 = R^2 = H, R^3 = Bz$
11 $R^1 = R^2 = R^3 = H$
12 $R^1 = R^2 = Me, R^3 = Bz$



13 $R^1 = R^2 = R^3 = Bz$
14 $R^1 = R^2 = Ac, R^3 = Bz$
15 $R^1 = R^2 = H, R^3 = Bz$
16 $R^1 = R^2 = Me, R^3 = Bz$



17 $R^1 = R^2 = R^3 = Bz$
18 $R^1 = R^2 = R^3 = H$
19 $R^1 = R^2 = Ac, R^3 = Bz$
20 $R^1 = R^2 = H, R^3 = Bz$
21 $R^1 = R^2 = Me, R^3 = Bz$



22 R = I
23 R = CO_2Me
24 R = Br

scale, isolation of **2** was dispensed with, as it proved both unnecessary and detrimental to the overall yield. Instead, methanol and oxidant were added to the reaction mixture of **1** and NaFp. The yields of crystalline **3** were ~60% (based on **1**) when ~7 molar equiv. of cupric chloride, or 4 molar equiv. of ferric chloride[5b], were employed as oxidants, with reaction times of 0.5 and 6 h, respectively, being required. Yields were markedly higher (~80%) with iodine[4,8] or bromine[15]. The latter halogen became our reagent of choice for all subsequent experiments because, in these trials with **1**, it effected complete consumption of the intermediate **2** at a higher rate (within a few minutes) than did iodine (30 min or more, depending on the amount added). The desired product **3** was, however, accompanied by a by-product which was isolated chromatographically, and revealed to be the long-known methyl 6-bromo-6-deoxy-β-D-glucopyranoside triacetate (**4**). It has previously been observed that, in aprotic solvents, alkyliron carbonyls are cleaved by molecular halogen to form alkyl hal-

TABLE I

YIELDS OF GLYCURONATES AND BY-PRODUCTS

Starting compound	*Glycuronate*	*Isolated yield (%)*	*By-product*		
			Compound	*Yield (%)*	*Identification method*
1	**3**	~80[a], ~60[b]	**4**	15[c]	[d]
5	**9**	71	**5**	23	[d]
6	**10**	80	**6**	<9	[e]
	11[f]	92			
7	**12**	90	**7**	<10	[e]
13	**17**	79	**13**	13	[d]
	18[g]	97			
14	**19**	88	**14**	trace	[h]
15	**20**	70	[i]		
16	**21**	85	[i]		
22	**23**	75	**24**	12	[d]

[a]With Br_2 or I_2. [b]With $CuCl_2$ or $FeCl_3$. [c]Observed in the case of Br_2 oxidation only. [d]By physical and spectral data for isolated compound. [e]By t.l.c., and proton-n.m.r. spectrum, of impure, syrupy material. [f]From **10** by debenzoylation. [g]From **17** by debenzoylation. [h]By t.l.c. only. [i]Although the crude product contained impurities, the presence of regenerated starting-compound could not be established.

ides[5b,9,15]; although oxidative, carbonyl insertion dominates in methanolic solution[9,15], brominolysis of **2** can evidently compete to some extent in that medium, too. A lowered reaction temperature (0 to −50°) did not seem to make any difference in this regard. However, as it was found that the reactions with bromine were still very fast, even at low temperatures, cooling was, in subsequent experiments, employed as a precaution against secondary reactions that could involve other functionalities in the sugar molecule. (In fact, it was noticed on some occasions that partial deacylation may take place slowly at room temperature.)

Analogous (methoxycarbonyl)ations, all using NaFp in oxolane followed by bromine in methanol, were performed with the 6-bromo-6-deoxy glycosides **5**–**7**, and **13**–**16**. The corresponding heptopyranosiduronates **9**, **10**, **12**, **17**, and **19**–**21** were obtained in high yields, together with various proportions of the respective, starting bromo sugars (see Table I). The latter were present, not as a result of incomplete conversion in the first stage (as could be demonstrated by t.l.c.), but owing to partial brominolysis in the second stage, just as **4** had arisen from **2**. Reaction of methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-α-D-mannopyranoside (**22**) led to the 6-deoxy-D-*manno*-hepturonic ester **23**, demonstrating that iodo sugars may also be used as substrates. The by-product observed in this case was the 6-bromo analog (**24**) of **22**.

In one experiment with **5**, the alkyliron intermediate (**8**) was isolated for characterization by ^{1}H-n.m.r. spectroscopy. Like **2**, it was a rather unstable syrup.

TABLE II

PROTON MAGNETIC RESONANCE DATA FOR METHYL (METHYL 6-DEOXYHEPTOPYRANOSID)URONATES[a]

Compound	*Chemical shifts (δ)*								*Coupling constants (Hz)*					
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6,6'*	*OMe*[b]	*OAc*[b]	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$
3	4.43d	4.95dd	5.22t	4.91t	3.97o	2.57d (2 H)	3.71, 3.46	2.05, 2.01, 1.99	7.7	9.2	9.5	9.5	7	5
9	4.51d	5.02dd	5.42t	5.17t	4.12o	2.65d, 2.63d	3.59, 3.49	2.06, 1.89	7.8	9.2	9.2	9.5	7.3	4.8
10	4.25d	~3.5[c]	3.77t	4.99t	4.00dt	2.57d (2 H)	3.57, 3.50		7.5	9.0	9.0	9.0	6.5	6.5
11[d]	4.15d		~3.8–3.1m (4 H)			2.90dd, 2.42dd	3.69, 3.45		7.5				3.1	9.3[e]
12	4.32d	3.15dd	3.46t	5.06dd	3.99o	2.59d, 2.58d	3.59, 3.57, 3.53, 3.48		7.5	9.0	8.7	9.7	7	5.5
17	~5.2m (2 H)		6.16t	5.42t	4.59dt	2.67d (2 H)	3.70, 3.55			9.5	9.5	9.5	6.7	6.7
18	4.68d		~4.2–3.3m (4 H)			2.95dd, 2.46dd	3.71, 3.44		3				2.5	10[f]
19	~4.9m (2 H)		5.70t[g]	5.14t	4.44dt	2.59d (2 H)	3.65, 3.49	2.09, 1.90			10	10	7	7
20	4.73d	~3.6m	3.96sx[h]	4.96dd	4.33dt	2.55d (2 H)	3.62, 3.46		3.5	9.5	9.5	10.5	6.3	6.3
21	4.85d	3.35dd	3.75t	5.03dd	4.33dt	2.55d (2 H)	3.63, 3.55, 3.51, 3.48		3.5	9.5	9.2	10.1	6.5	6.5
23	4.92d		5.9–5.6m (3 H)		4.6m	2.73d, 2.72d	3.66, 3.59		1.8				7	5

[a]From 100-MHz spectra, measured at 250-Hz sweep-width, for solutions in $CDCl_3$ (unless specified otherwise) containing tetramethylsilane as the internal standard. Signal multiplicities: d, doublet; m, multiplet; o, octet; sx, sextet; and t, triplet. All compounds containing benzoate groups showed the characteristic, multiplet pattern for OBz, centered near δ 7.7. [b]Three-proton singlets. [c]Obscured by OMe signals. [d]In CD_3OD solution, because of poor solubility in $CDCl_3$. [e]$J_{6,6'}$ 15.6 Hz. [f]$J_{6,6'}$ 15.5 Hz. [g]Each line showed an additional, small splitting. [h]Collapsing to t after D_2O exchange; OH-2 and OH-3 gave doublets at δ 2.90 and 3.28.

Whereas several of the uronates (**3**, **9**, **19**, **20**, and **23**) were obtained crystalline, compounds **10**, **12**, **17**, and **21** failed to crystallize. Zemplén deacylation of **10** and **17**, however, furnished the corresponding, crystalline triols, namely, methyl (methyl 6-deoxy-β-D-*gluco*-heptopyranosid)uronate (**11**) and its α anomer **18**, respectively. The ^{1}H-n.m.r. data for the new compounds are given in Table II.

One further observation may be worth mentioning. We have routinely provided an atmosphere of carbon monoxide (at ambient pressure) for the carbonyl-insertion reaction, a measure that is not strictly indispensable, but has been recommended[14] for achieving improved yields. Substituting nitrogen gas for the carbon monoxide in one experiment with **1**, we found a diminution in yield to 69%, from 80% (for bromine oxidation), whereas no marked effect was noticed in a similar experiment with **13**.

In summary, (methoxycarbonyl)ation by use of NaFp has been demonstrated to be a simple and efficient method for chain-elongation in 6-halogeno (or 6-*O*-tosyl) hexopyranosides, leading to homologous, 6-deoxyheptopyranosiduronic methyl esters. The method is compatible with the presence of free hydroxyl groups, or their acetic or benzoic esters, or methyl ethers, on the sugar ring.

EXPERIMENTAL

General methods. — General, preparative, and chromatographic procedures, as well as instrumental techniques, were the same as those previously employed[1]. Optical rotations were measured at 25°, and refer to chloroform solutions, unless otherwise specified. In addition to chromatographic solvents especially mentioned, the following solvent combinations (v/v) were used: (*A*) 1:1 ethyl acetate–hexane; (*B*) 1:2 ethyl acetate–hexane; (*C*) 1:1 ether–petroleum ether; (*D*) the same solvents, but 1:2; (*E*) the same, but 1:10; (*F*) the same, but 10:1; and (*G*) 9:1 methanol–ether. Petroleum ether refers to the fraction having b.p. 30–60°. The technique of iron-promoted (methoxycarbonyl)ation is detailed in the description of the preparation of **2**, **3**, and **9**, and the variant using bromine for the oxidative insertion step was used in the same way for all the other examples. Air and moisture were rigorously excluded in these procedures.

Preparation of the starting glycosides. — *A. Methyl 2,3,4-tri-*O*-acetyl-6-*O*-p-tolylsulfonyl-β-*D*-glucopyranoside* (**1**). For an improved yield and a simpler mode of processing, the procedure of Compton[16] was modified as follows. To a chilled (−20°) solution of methyl β-D-glucopyranoside (10.0 g) in dry pyridine (50 mL) was added dropwise a solution of *p*-toluenesulfonyl chloride (17.7 g, 1.8 mol. equiv.) in dry dichloromethane (18 mL). The mixture was kept overnight at room temperature, and acetic anhydride (15 mL) was then added and allowed to react for 24 h. The mixture was processed with crushed ice and water, to give a crystalline solid which was isolated and then dissolved in ethyl acetate. The solution was successively washed with water, aqueous sodium hydrogencarbonate, and water, dried ($MgSO_4$), and evaporated. The solid residue was recrystallized once from hot ethyl acetate, to

give pure **1** (12 g, 50%), m.p. 170–171°, $[\alpha]_D$ +5.7° (*c* 3); lit.[16] m.p. 169–170° (after 3 recrystallizations from ethanol), $[\alpha]_D$ +7.4° (*c* 3.7). The mother liquor of recrystallization contained additional **1**, together with a (very slightly) faster-moving, second product (t.l.c. by triple irrigation with 1:3 ethyl acetate–hexane) which presumably was a ditosylate. N.m.r. data (100 MHz) for **1** in $CDCl_3$: δ 7.3 (q, 4 H, arom.), 5.19 (t, $J_{2,3} = J_{3,4}$ = 9 Hz, H-3), 4.92 (~t, $J_{3,4}$ 9, $J_{4,5}$ 10 Hz, H-4), 4.89 (dd, $J_{1,2}$ 7.8, $J_{3,4}$ 9 Hz, H-2), 4.38 (d, $J_{1,2}$ 7.8 Hz, H-1), 4.12 (d, 2 H, *J* 4.2 Hz, H-6,6'), 3.75 (m, *J* 4.2 and 10 Hz, H-5), 3.44 (s, 3 H, OMe), 2.46 (s, 3 H, tosyl-Me), and 2.04 (s, 3 H) and 2.00 (s, 6 H) for 3 OAc.

*B. Methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-bromo-6-deoxy-β-*D*-glucopyranoside* (**5**). Compound **5** was obtained in 74% yield from methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranoside[17,18] by application of the Hanessian–Hullar reaction[19]. Recrystallized from ethyl acetate–ether, **5** had m.p. 169–170°, $[\alpha]_D$ −57° (*c* 0.65); ^{1}H-n.m.r. data (100 MHz) in $CDCl_3$: δ 7.7 (m, 5 H, OBz), 5.43 and 5.20 (two symmetrical, one-proton triplets, *J* 9.3 Hz, H-3,4), 5.05 (dd, $J_{1,2}$ 7.8, $J_{2,3}$ 9.3 Hz, H-2), 4.54 (d, $J_{1,2}$ 7.8 Hz, H-1), 3.84 (o, H-5), 3.58 (s, 3 H, OMe), 3.5 (m, 2 H, H-6,6'), and 2.07 and 2.00 (s, 3 H each, 2 OAc).

C. The glycosides **6**, **13**, *and* **15**. Prepared according to the literature[19,20], compound **6** had m.p. 123–124.5° and $[\alpha]_D$ −11.4° (*c* 3); lit.[20] m.p. 120–121°, $[\alpha]_D$ −9°. Compound[21] **13** had m.p. 126.5–128°, $[\alpha]_D$ +45.7° (*c* 2.6, chloroform) and +91.8° (*c* 2, pyridine); lit.[21] m.p. 125–126° and[22] $[\alpha]_D$ +90.9° (pyridine). Compound[20] **15** had m.p. 129–130° and $[\alpha]_D$ +116° (*c* 0.5); lit.[20] m.p. 130–131°, $[\alpha]_D$ +118°.

*D. Methyl 4-*O*-benzoyl-6-bromo-6-deoxy-2,3-di-*O*-methyl-β-*D*-glucopyranoside* (**7**) *and its α anomer* (**16**). Methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-β-D-glucopyranoside[23] and its α anomer[24] were conveniently prepared by Kuhn methylation[25] of the corresponding diols, with the procedure following a recent example[26], and then subjected to the Hanessian–Hullar reaction[19].

The β-anomeric acetal gave **7** as a syrup in 79% yield after flash chromatography on a short column of silica gel (eluant, petroleum ether followed by solvent *E*); $[\alpha]_D$ −47° (*c* 2.5); ^{1}H-n.m.r. data (100 MHz) in $CDCl_3$: δ 7.7 (m, 5 H, OBz), 5.06 (t, $J_{3,4} = J_{4,5}$ = 9.3 Hz, H-4), 4.31 (d, $J_{1,2}$ 7.5 Hz, H-1), 3.69 (o, H-5), and 3.60 (s, 6 H) and 3.48 (s, 3 H) for 3 OMe groups. The H-2, -3, -6, and -6' atoms gave ill-resolved multiplets, partially overlapped by the OMe signals, in the δ 3.6–3.1 region.

The α-anomeric acetal gave syrupy **16** in 88% yield after column-chromatographic purification; $[\alpha]_D$ +56.1°, $[\alpha]_{578}$ +58.3° (*c* 4.1); lit.[27] $[\alpha]_{578}$ +68 and +71°; ^{1}H-n.m.r. data (100 MHz) in $CDCl_3$: δ 7.7 (center of m, 5 H, OBz), 5.07 (dd, $J_{3,4}$ 9, $J_{4,5}$ 10 Hz, H-4), 4.93 (d, $J_{1,2}$ 3.7 Hz, H-1), 4.03 (m, H-5), 3.75 (t, *J* 9.3 Hz, H-3), and 3.6–3.3 (unresolved multiplets for H-2, -6, and -6', superposed by 3 singlets for OMe). Assignment[27] of the H-4 signal as an 8-Hz doublet at δ 5.13 (60-MHz spectrum) appears to be in error.

*E. Methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-bromo-6-deoxy-α-*D*-glucopyranoside* (**14**). Compound **14** was prepared from methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-

α-D-glucopyranoside[18,23a,28] by application of the Hanessian–Hullar reaction[19,27]. It was obtained in 95% yield as a slightly impure syrup which crystallized from ether–petroleum ether after purification by flash chromatography (eluant, petroleum ether followed by solvent *E*); m.p. 106–107°, $[\alpha]_D$ +57.2°, $[\alpha]_{578}$ +59.0° (*c* 2.5); lit.[27] oil, $[\alpha]_{578}$ +61°; ^{1}H-n.m.r. data (100 MHz) in $CDCl_3$: δ 7.7 (center of 2 m, 5 H, OBz), 5.69 (t, $J_{2,3} = J_{3,4} = 9.2$ Hz, H-3), 5.19 (t, $J_{3,4} \approx J_{4,5} \approx 9.5$ Hz, H-4), 5.04 (d, $J_{1,2} \sim 3.6$ Hz, H-1), 4.95 (dd, $J_{1,2} \sim 3.6$, $J_{2,3}$ 9.2 Hz, H-2), 4.13 (sp, H-5), 3.50 (s for OMe superposed on m for H-6 and -6′; total intensity, 5 H), and 2.09 and 1.90 (s, 3 H each, 2 OAc). Reported[27] 60-MHz data were incomplete, and contained some obvious errors in assignments.

F. Methyl 2,3,4-tri-O-benzoyl-6-deoxy-6-iodo-α-D-mannopyranoside (**22**). Methyl α-D-mannopyranoside (3.0 g) was converted into its 6-deoxy-6-iodo derivative by treatment with triphenylphosphine, iodine, and imidazole, essentially as described by Garegg and Samuelsson[29], except that the reaction was performed in oxolane solution at 70° (oil-bath temperature) for 4 h, rather than in boiling toluene for 5 h. The crude product was benzoylated by treatment with benzoyl chloride and pyridine for 90 min at room temperature After the customary processing, the material crystallized on trituration with ether, and was recrystallized from ethyl acetate–petroleum ether, to give pure **22** (4.2 g, 44%; the isolated yield was low, because of losses incurred during an unsuccessful attempt at purifying, by column chromatography, the crude iodination product prior to benzoylation). Compound **22** showed m.p. 207–208.5°, $[\alpha]_D$ −110° (*c* 0.65); lit.[30] m.p. 202–203°, $[\alpha]_D$ −101.6°, and[31] m.p. 199–201°, $[\alpha]_D$ −106°; ^{1}H-n.m.r. data (100 MHz) in $CDCl_3$: δ 7.7 (m, 15 H, 3 OBz), 5.65–6.0 (overlapping m, 3 H, H-2,3,4), 5.00 (d, W_H 3 Hz, H-1), 4.06 (sx, H-5), 3.60 (s, 3 H, OMe), and 3.30–3.55 (m, 2 H, H-6,6′); *m/z* 616 (M^+), 585 (M^+ − OMe), and 495 (M^+ − OBz).

Dicarbonyl-η^5-cyclopentadienyl(methyl 2,3,4-tri-O-acetyl-6-deoxy-β-D-glucopyranosid-6-yl)iron (**2**). — For generation of sodium dicarbonyl-η^5-cyclopentadienyliron[32] (NaFp), the procedure described by Bock and Whitesides[33] for the analogous molybdenum complex was used. Into a flame-dried, 25-mL vessel equipped with a magnetic stirring bar, and nitrogen inlet and outlet was placed mercury (2 mL), and sodium (200 mg) was added to form an amalgam, with rapid stirring under nitrogen. The amalgam was cooled to room temperature, oxolane (20 mL, dried by refluxing over potassium in the presence of benzophenone) was introduced, and nitrogen gas was passed through it for a few minutes. Commercial dicarbonylcyclopentadienyliron dimer (355 mg, 2 mequiv. of Fe) was then added, and the mixture was vigorously stirred for 1 h, during which time the color of the solution turned from dark-red to an orange or olive shade. Stirring was discontinued, the amalgam allowed to settle, and the supernatant liquor transferred, by means of nitrogen pressure through Teflon tubing, into a second reaction-flask (also flame-dried) that contained the crystalline glycoside **1** (0.71 g, 1.5 mmol). The solid dissolved in the reagent on stirring, and, after 10 min, was completely converted into **2** (t.l.c. with solvent *A*; the slow-moving spot of **1**, visible after spraying the plate with 5% ethanolic sulfuric acid followed by

heating, was absent, and a strong, faster-moving, yellow spot of **2** was seen prior to spraying; some unidentified trace-spots were also present). In general, the solution of **2** so obtained was used directly for the preparation of **3**, and similarly, the solutions of analogous iron derivatives made in the same way from other sugars were employed, without isolation of intermediates, for the syntheses of hepturonates described in subsequent sections.

For the isolation of **2**, the aforementioned oxolane solution was evaporated to give a thick, dark syrup which, by means of solvent *B*, was quickly passed through a short column of silica gel. Salts and other contaminants were retained, and the effluent yielded a yellow syrup that was purified further, without delay, by preparative t.l.c. (solvent *A*). The yellow band was extracted with ethyl acetate, furnishing 0.56 g (78%) of **2**. In another experiment, 300 mg of **1** gave 280 mg (92%) of **2**; apparently, the yield of this rather unstable compound is influenced by the speed of the processing operations. Compound **2** showed λ_{max}^{MeOH} 412 nm; ν_{max}^{neat} 2015 and 1940 (strong; ligand CO), and 1745 cm^{-1} (strong; acetyl CO); ^{1}H-n.m.r. data (100 MHz) in $CDCl_3$: δ 5.13 (t, J 9.3, H-3), 4.95 (m, H-4), 4.80 (s, 5 H, for Cp, superposed on m, 1 H, for H-2), 4.35 (d, $J_{1,2}$ 7.5 Hz, H-1), 3.53 (s, 3 H, OMe), 3.27 (o, H-5), 2.07, 2.04, and 2.00 (3 s, 9 H, 3 OAc), 1.62 (dd, $J_{5,6}$ 2.7, $J_{6,6'}$ 11 Hz, H-6), and 1.24 (m, H-6'); ^{13}C-n.m.r. data in $CDCl_3$: δ 217.4 and 216.8 (ligand CO), 170.4, 169.9, and 169.5 (acetyl CO), 101.9 (C-1), 85.4 (Cp), 79.4–71.9 (5 C, C-2–6), 57.1 (OMe), and 20.9 and 20.7 (acetyl Me); *m/z* (relative intensities in parentheses) 480 (10), M^+ for $C_{20}H_{24}O_{10}Fe$; 452 (15), $M^+ - CO$; 424 (70), $M^+ - 2\,CO$; 359 (100), $M^+ - 2\,CO - Cp$; 350 (30), $M^+ - 2\,CO - C_3H_6O_2$; and 304 (50), $M^+ - Fp + H$.

*Methyl (methyl 2,3,4-tri-*O*-acetyl-6-deoxy-β-*D*-gluco-heptopyranosid-uronate* (**3**). — A solution of **2** was prepared, as just described, from **1** (400 mg) and a 1.3-molar excess of NaFp in oxolane (40 mL). The solution was cooled (0 to −5°), a stream of carbon monoxide was passed through, and absolute methanol (20 mL) was added, followed by *bromine* (0.4 mL). By t.l.c. (solvent *A*), the reaction was revealed to be complete after a few minutes: the yellow spot of **2** (R_F 0.4, visible without spraying) was replaced by a strong spot of **3** (R_F 0.3) accompanied by a very weak spot of **4** (R_F 0.4, visible after spraying and heating). The mixture was concentrated to a small volume, diluted with ethyl acetate (or ether), and the solution washed sequentially with sodium thiosulfate solution, sodium hydrogencarbonate solution, and water, dried ($MgSO_4$), and evaporated to a dark syrup which was passed through a short column of silica gel by flash chromatography with solvent *A* or *C*. The effluent furnished a syrup that was subjected to p.t.l.c. (solvent *A*), giving pure **3** (247 mg, 81%). Crystallized from ethyl acetate–petroleum ether, it had m.p. 149–150°, $[\alpha]_D$ −9.6° (*c* 0.7).

Anal. Calc. for $C_{15}H_{22}O_{10}$ (362.3): C, 49.72; H, 6.12. Found: C, 49.52; H, 6.17.

The faster-moving by-product (**4**) was isolated by p.t.l.c. as crystals (~50 mg, 15%), m.p. 124.5–125.5°, $[\alpha]_D$ −2.4° (*c* 0.9); lit.[34] m.p. 125–126°, $[\alpha]_D$ −1.4°. The n.m.r. spectrum was in accord with the structure of methyl 2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy-β-D-glucopyranoside.

In a similar experiment, *iodine* (1.0 g) in methanol (20 mL) was substituted for the bromine, and the reaction was performed at room temperature; it was complete after ~0.5 h (t.l.c. with solvent *A*). Processing as described before, and column chromatography with solvent *E*, yielded crystalline **3** (250 mg from 400 mg of **1**; 82%), identified with the previous product by n.m.r. spectra.

A solution of **2** prepared from **1** (1.00 g) and NaFp (from 0.75 g of dicarbonylcyclopentadienyliron dimer) in oxolane (30 mL) was cooled to +5°, methanol (10 mL) was added, and carbon monoxide was bubbled through the mixture, to which was then added anhydrous *cupric chloride* (2 g). The reaction was almost complete after 20 min; it was allowed to proceed to completion by stirring at room temperature for a further 15 min, with some additional cupric chloride (0.5 g). The mixture was filtered, and the filtrate was evaporated, to give a syrupy product that was dissolved in ethyl acetate, and the solution washed several times with water, and evaporated; purification by flash chromatography, as previously described, gave crystalline **3** (0.45 g, 59%), m.p. 149–150°.

A solution of **2** (prepared from 500 mg of **1** and 1.3 mol. equiv. of NaFp) in oxolane (40 mL) was treated with methanol as just described, but in the presence of anhydrous *ferric chloride* (720 mg) at an initial temperature of ~ +12°. The reaction was then allowed to proceed at room temperature, and required 6 h for completion (t.l.c. with solvent *A*). Evaporation then gave a syrupy product which was dissolved in ether, the solution washed several times with water, and evaporated, and the residue purified by p.t.l.c. (solvent *A*). The yield of crystalline **3** was 239 mg (62%).

*Methyl (methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-deoxy-β-*D*-gluco-heptopyranosid)-uronate* (**9**). — In a preliminary experiment designed to demonstrate the formation of the sugar–iron intermediate **8**, the bromo sugar **5** (450 mg) was treated with NaFp (1.3 mol. equiv.), exactly as described for the preparation of **2** from **1**. T.l.c. then showed complete consumption of **5** (R_F 0.5 after double irrigation with solvent *C*) and the presence of **8** (seen as a yellow spot, R_F 0.45, prior to spraying; compare **2**) together with traces of slow-moving impurities. The reaction mixture was filtered through a bed of silica gel, the filtrate evaporated, and the syrupy residue dissolved in ether and purified by p.t.l.c. (solvent *C*). Compound **8** was isolated as a yellow syrup (228 mg) that was homogeneous initially, but tended to decompose with time. (Progressive darkening was observed, within a day, on storage in a refrigerator.) The ^{1}H-n.m.r. data (100 MHz) in $CDCl_3$ were: δ 7.7 (center of m, 5 H, OBz), 5.34 and 5.06 (2 t, J ~9 Hz, H-3 and -4, or reverse), 5.03 (dd, $J_{1,2}$ 7.8, $J_{2,3}$ 9 Hz, H-2), 4.74 (s, 5 H, Cp), 4.43 (d, $J_{1,2}$ 7.8 Hz, H-1), 3.55 (s, 3 H, OMe), 3.43 (m, H-5), 2.04 and 1.86 (s, 3 H each, 2 OAc), and 1.68 and 1.34 (centers of two m, 1 H each, H-6,6′).

For the preparation of **9**, the bromo sugar **5** (500 mg) was converted into **8** by the aforedescribed method, except that the reaction temperature was −10°. (Cooling at that stage, also employed in some of the subsequent syntheses, did not appear to have any marked effect; it was probably not essential.) For the following, oxidative insertion (compare the reaction **2**→**3**), the mixture was cooled to −50°, methanol (20 mL) was added, and bromine (0.5 mL) was fairly rapidly administered

dropwise as a solution in methanol (10 mL). After a few minutes, t.l.c. was performed, to ensure that the reaction was complete; it showed **9** (R_F 0.2) as the main product, and **5** (R_F 0.3) as a minor by-product, the yellow spot of **8** having completely disappeared (solvent *D*, double irrigation). Cooling of the reaction mixture was discontinued while the t.l.c. was performed, and the mixture, having attained a temperature near 0° during this period, was immediately thereafter processed as described for **3**, except that the solvents were evaporated completely (bath temperature, 35°), and the residue was dissolved in dichloromethane for performance of the aforementioned (*cf.* **3**) washing operations. It was found advisable to process with the utmost despatch, in order to minimize losses in yield due to secondary reactions. Solvent removal then gave a dark syrup containing **9** and **5**, which were separated by p.t.l.c. (solvent *B*). Compound **9** (340 mg, 71%) crystallized from ether–petroleum ether, and had m.p. 131.5°, $[\alpha]_D$ −69° (*c* 0.75).

Anal. Calc. for $C_{20}H_{24}O_{10}$ (424.4): C, 56.60; H, 5.70. Found: C, 56.36; H, 5.64.

Compound **5** (114 mg, 23%) was identified by its m.p., R_F value, and ^{1}H-n.m.r. spectrum.

*Methyl (methyl 4-O-benzoyl-6-deoxy-β-*D*-gluco-heptopyranosid)uronate* (**10**). — For the preparation of **10**, the procedure just described for **9** was applied to **6** (700 mg), with appropriately adjusted quantities of reagents and solvents. T.l.c. (ether) indicated formation of slow-moving **10** and a small proportion of the faster-moving by-product **6**. The products were separated by p.t.l.c. (solvent *F*), giving **10** (530 mg, 80%) as a syrup, $[\alpha]_D$ −13.2° (*c* 1.5).

Anal. Calc. for $C_{16}H_{20}O_8$ (340.3): C, 55.46; H, 5.92. Found: C, 56.31; H, 5.97.

The faster-moving material was isolated as a slightly impure syrup (63 mg), shown by its ^{1}H-n.m.r. spectrum tc consist mainly of **6**.

*Methyl (methyl 6-deoxy-β-*D*-gluco-heptopyranosid)uronate* (**11**). — The benzoate **10** (400 mg) in absolute methanol (20 mL) was treated with a catalytic amount of sodium methoxide for 16 h at 25°. It was seen by t.l.c. (solvent *G*) that **10** (R_F 0.5) was completely debenzoylated to **11** (R_F 0.2). De-ionization, treatment with activated charcoal, and evaporation of the solution gave **11** (257 mg, 92.5%) as colorless crystals (from methanol–ether), m.p. 186–187°, $[\alpha]_D$ −13.6° (*c* 0.5, methanol).

Anal. Calc. for $C_9H_{16}O_7$ (236.2): C, 45.76; H, 6.83. Found: C, 45.56; H, 6.73.

*Methyl (methyl 4-O-benzoyl-2,3-di-O-methyl-β-*D*-gluco-heptopyranosid)uronate* (**12**). — The procedure detailed for preparation of **3** and **9** was applied to **7** (0.57 g), except that the reaction temperature during the bromine oxidation was −25° initially, and was allowed to rise to +15° in the course of 1 h. Ether was used as the medium for the washing operations. T.l.c. and p.t.l.c. were performed with 1:1:6 ethyl acetate–ether–petroleum ether. Compound **12** (R_F 0.25) was isolated as a syrup (485 mg, 90%) showing $[\alpha]_D$ −48.9° (*c* 1.5).

Anal. Calc. for $C_{18}H_{24}O_8$ (368.4): *C*, 58.69; H, 6.57. Found: C, 58.94; H, 6.53.

The faster-moving band eluted from the p.t.l.c. plates gave a syrup (~0.1 g) that contained **7**, identified by its R_F value of 0.4 and its n.m.r. spectrum, together with some **12** and unidentified impurities.

*Methyl (methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-α-*D*-gluco-heptopyranosid)uronate* (**17**). — Compound **17** was prepared from **13** (600 mg) as described for **9**. In t.l.c. (solvent *D*), **13** had R_F 0.4, and **17**, R_F 0.3. In one experiment, no **13** was detected in the product, and **17** (462 mg, 80%) was obtained as a homogeneous syrup, $[\alpha]_D$ +37.5° (*c* 1.6), after the removal of minor impurities by flash chromatography. In another experiment (which yielded 78% of **17**), the formation of **13** could be observed; it amounted to 13%, and was identified by its n.m.r. spectrum upon isolation by p.t.l.c. (solvent *D*). All attempts at crystallizing **17** failed.

*Methyl (methyl 6-deoxy-α-*D*-gluco-heptopyranosid)uronate* (**18**). — Treatment of **17** (1.00 g) in methanol (25 mL) with a catalytic amount of sodium methoxide effected complete debenzoylation within 3 h at 25° (t.l.c. with solvent *A*). Processing included de-ionization, treatment with charcoal, and passage of the crude material through a short column of silica gel by sequential elutions with petroleum ether and ether (to elute benzoic acid) followed by ethyl acetate (to obtain **18**). Crystallized from ethyl acetate (or warm ether) and petroleum ether, **18** (420 mg, 97%) showed m.p. 92–93°, $[\alpha]_D$ +146° (*c* 0.5).

Anal. Calc. for $C_9H_{16}O_7$ (236.2): C, 45.76; H, 6.83. Found: C, 45.84; H, 6.84.

*Methyl (methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-deoxy-α-*D*-gluco-heptopyranosid)-uronate* (**19**). — Compound **19** was prepared from **14** (700 mg) as described for **9**. The medium for the washing operations was ether. T.l.c. with solvent *C* showed **19** (R_F 0.6) as the major product, and traces of **14** (R_F 0.7), as well as several, slow-moving impurities. Separation by p.t.l.c. was accomplished by double irrigation, first with solvent *C* and then with solvent *A*, giving 590 mg (88%) of **19** after crystallization from 99% ethanol; m.p. 99–101°, $[\alpha]_D$ +56.3° (*c* 0.9).

Anal. Calc. for $C_{20}H_{24}O_{10}$ (424.4): C, 56.60; H, 5.70. Found: C, 56.39; H, 5.75.

Only a very small amount of by-product **14** could be isolated; it was identified by t.l.c. only.

*Methyl (methyl 4-*O*-benzoyl-6-deoxy-α-*D*-gluco-heptopyranosid)uronate* (**20**). — The procedure for preparation of **9** was applied to **15** (700 mg). For processing, the procedure for **3** was first followed, and then a second, identical washing-sequence was applied to the product in dichloromethane solution. The product showed a strong spot of **20** (R_F 0.4), together with traces of more- and less-polar impurities, but little, if any, **15** (R_F 0.5) was seen (t.l.c. with ether). The crude, yellow syrup of processed reaction-product crystallized, in part, from ether–petroleum ether, to give pure **20**, and additional, crystalline **20** was obtained by p.t.l.c. of the mother liquor (solvent *F*), for a total of 461 mg (70%); m.p. 154–155.5°, $[\alpha]_D$ +124.9° (*c* 3.5).

Anal. Calc. for $C_{16}H_{20}O_8$ (340.3): C, 56.46; H, 5.92. Found: C, 56.00; H, 5.87.

*Methyl (methyl 4-*O*-benzoyl-6-deoxy-2,3-di-*O*-methyl-α-*D*-gluco-heptopyrano-sid)uronate* (**21**). — Compound **16** (1.00 g) was converted into **21** at an initial reaction-temperature of −20° (compare the preparation of **12**). Solvent *B* was used to monitor the reaction by t.l.c. and to purify the product by p.t.l.c.; **21** was obtained as a syrup (0.80 g, 84.5%), $[\alpha]_D$ +62.1° (*c* 0.7). No by-product was isolated.

Anal. Calc. for $C_{18}H_{24}O_8$ (368.4): C, 58.69; H, 6.57. Found: C, 58.59; H, 6.83.

*Methyl (methyl 2,3,4-tri-O-benzoyl-6-deoxy-α-*D*-manno-heptopyranosid)uronate* (**23**). — Compound **23** was obtained from the mannoside **22** (0.60 g) as described for **9**. T.l.c. with solvent *B* showed **23** (R_F 0.5) as the main product; also present was a weak spot which migrated slightly faster, like starting **22**, but was due to its bromo analog **24**. P.t.l.c. with solvent *B* gave **23** (0.40 g, 75%), crystallized from ether–petroleum ether; m.p. 136.5–138°, $[\alpha]_D$ −135.6° (*c* 0.7).

Anal. Calc. for $C_{30}H_{28}O_{10}$ (548.5): C, 65.69; H, 5.14. Found: C, 65.74; H, 5.24.

A small amount of crystalline **24** (70 mg) was isolated, and recrystallized from methanol; m.p. 178–180°, lit[20] m.p. 180–182°. The mass spectrum showed the characteristic pattern of twin peaks due to bromine isotopes: *m/z* 570, 568 (M^+ for $C_{28}H_{25}BrO_8$); 539, 537 ($M^+ - OMe$); 510, 508 ($M^+ - HCO_2Me$); 448, 446 ($M^+ - BzOH$); 447, 445 ($M^+ - BzOH - H$); 417, 415 ($M^+ - OMe - BzOH$); 489 ($M^+ - Br$); 458 ($M^+ - OMe - Br$); and 429 ($M^+ - HCO_2Me - Br$).

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