Preparation of 3-Methoxycarbonylpropyl α-D- and 7-Methoxycarbonylhexyl β-D-Galactopyranosides: Spacer-arm Glycosides for Branched Oligosaccharide Synthesis

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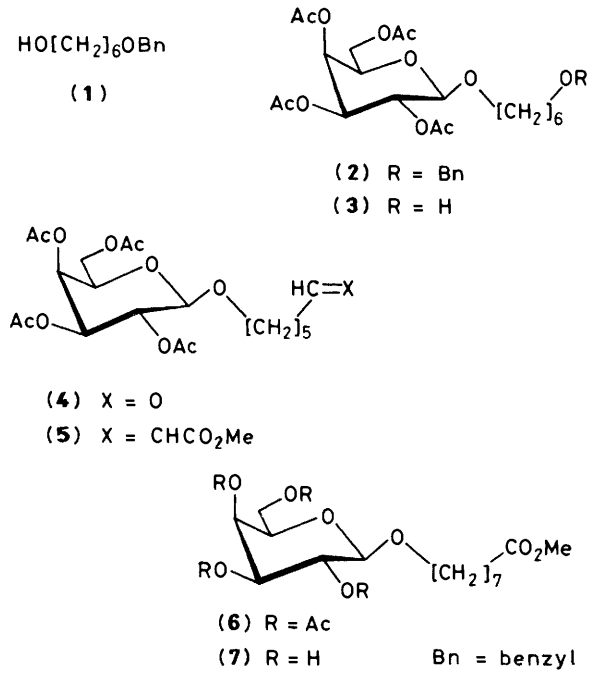
7-Methoxycarbonylheptyl β-D-galactopyranoside (**7**), 3-methoxycarbonylpropyl α-D-galactopyranoside (**18**), and its 6-*O*-pivaloloyl derivative (**20**), suitable for coupling to proteins or functionalised solid supports, have been synthesised from galactopyranosyloxyalkanals (**4**), (**9**), and (**11**) by sequential application of Wittig condensations, hydrogenations and, for the first example, deacetylation. Glycoside (**2**), prepared by galactosylation of the abundant ω-functionalised alcohol (**1**), was readily transformed into aldehyde (**4**) by chlorochromate oxidation of the ω-hydroxyglycoside (**3**) obtained upon debenzylation of (**2**). Aldehydes (**9**) and (**11**), obtained by ozonolysis of the allyl galactosides (**8**) and (**10**), were readily converted into enoates (**12**) and (**13**) respectively.

To increase the value of photolabile *ortho*-nitrobenzylidenated sugar derivatives as intermediates in the synthesis of branched trisaccharides of biological interest,[1] glycosides were required which possessed aglycones stable to u.v. light that would serve as spacer-arms suitable for subsequent coupling to proteins,[2] lipids,[3] or stationary phases.[4] These glycosides would be valuable synthons for the preparation of synthetic glycoconjugates and affinity chromatographic adsorbents.

There have been several syntheses of glycosides with ω-substituted aglycones suitable for such couplings. Notable is Lemieux's[5] synthesis of 8-methoxycarbonyloctyl n-acetyl glucosaminide in which the full aglycone chain was prepared directly from the hydroxy ester. Others have employed this[6,7] direct approach, whereas indirect routes, in which the aglycone chain has been built up from shorter terminally functionalised aglycones, have been developed by other groups. For example allyl,[8–11] 2-bromoethyl,[12] and 2-benzylideneaminoethyl[13] glycosides are all being investigated.

We report here use of the second approach to synthesise three methoxycarbonylalkyl galactosides which are suitable for preparing oligosaccharides branched at galactose and can be subsequently coupled at the ester group.[5,14]



Discussion

The inexpensive hexane-1,6-diol is of potential value in the preparation of terminally functionalised aglycones. Temporary blocking of one hydroxy function affords alcohols which may be glycosylated and subsequently modified at the terminal position. This route has been explored with 6-benzyloxyhexan-1-ol (**1**) which was readily prepared on a large scale from the diol. Condensation of (**1**) with penta-*O*-acetyl-β-D-galactopyranose catalysed by tin(IV) chloride[15] or with acetobromogalactose in the presence of mercury(II) cyanide[16] each gave after chromatography a similar yield of the galactose (**2**). The β-configuration was indicated by the anomeric proton doublet split by 7.0 Hz and the ^{13}C n.m.r. spectrum shown in Table 1 which exhibited resonances for the hexose carbons similar to those for methyl tetra-*O*-acetyl-β-D-galactopyranoside.[17]

Hydrogenolysis of the benzyl group gave a quantitative yield of the hydroxy glycoside (**3**), the ^1H and ^{13}C n.m.r. spectra of which showed that cleavage had occurred, with the resonance for the ω-carbon atom of the aglycone exhibiting the upfield shift of 7.9 p.p.m. expected upon de-etherification[18] (see Table 1.)

Oxidation of the alcohol with pyridinium chlorochromate[19] gave in good yield the aldehyde (**4**) as indicated by two signals at δ_H 10.44 and δ_C 202.6 p.p.m. in the ^1H and ^{13}C n.m.r. spectra (see Table 1). The aldehyde is stable, having been stored at 0 °C for 2 years, and could be of value for forming a bovine serum albumin (BSA) conjugate by the reductive amination coupling method.[20] It was quantitatively converted into the enoate (**5**) using the Horner–Emmons modified Wittig reaction[21] with trimethyl phosphonoacetate. This method was selected because it gave the water-soluble dimethylphosphate by-product which was readily separated from the fully protected glycoside. The conjugated unsaturated methyl ester function gave rise to resonances at δ_C 149.4, 121.2, 167.3, and 51.3 p.p.m. ($CH{=}CHCO_2Me$, see Table 1) and two doublets of triplets at δ_H 7.24 (16.8, 7.0, and 7.0 Hz) and 6.05 (16.8, 1.5, and 1.5 Hz). The large coupling of 16.8 Hz indicated a *trans*-configuration at the double bond. Hydrogenation of compound (**5**) gave the saturated ester glycoside (**6**) which was fully characterised by elemental analysis and ^1H and ^{13}C n.m.r. spectroscopy. Deacetylation of (**6**) in anhydrous methanol with sodium methoxide gave the desired 7-methoxycarbonylheptyl β-D-galactopyranoside (**7**), the ^{13}C n.m.r. spectrum of which

Table 1. ^{13}C N.m.r. chemical shifts (p.p.m.) of some β-D-galactopyranosides in $CDCl_3$ relative to tetramethylsilane (15 MHz)

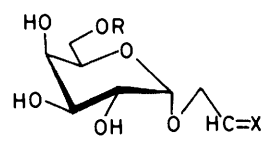
	β-D-Galactopyranosyl residue						Aglycone				
Compound	C-1	C-2	C-3	C-4	C-5	C-6	OCH_2	$[CH_2]_4$		R	
(22)[a]	101.5	68.5	70.2	66.8	70.6	61.0					
(2)[a,b]	101.5	69.1	70.2	67.2	70.4	61.4	71.1	(29.7)	(26.0)	70.7	
								(29.4)	(25.7)		
(3)[a]	101.6	69.1	70.2	67.2	70.7	61.4	71.1	(32.7)	(25.7)	62.8	
								(29.4)	(25.5)		
(4)[a]	101.4	69.0	69.7	67.1	70.7	61.3	71.0	(29.1)	(21.6)	202.6	
								(25.4)	(43.7)		
(5)[a]	101.4	69.0	69.9	67.2	70.7	61.3	71.0	(29.2)	(27.7)	149.4	167.3
								(25.3)	(32.0)	121.2	51.3
(6)[a]	101.4	69.0	70.1	67.1	70.7	61.3	71.0	(29.3)	(28.9)	24.8	174.7
								(28.9)	(25.5)	33.9	51.4
(21)[c]	104.5	71.7	73.9	69.7	76.0	62.0					
(7)[c,d]	103.7	71.6	73.8	69.4	75.8	61.6	71.2	(29.6)	(29.1)	25.2	177.7
								(29.2)	(25.6)	34.5	52.8

(21) Methyl β-D-galactopyranoside, (22) the tetra-acetate of (21).

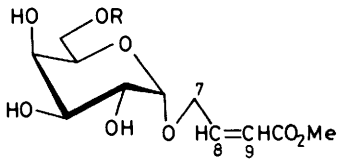
[a] Four acetyl groups at δ_C 169.7 ± 0.1 (× 1), 170.6 ± 0.2 (× 3), and 20.6 ± 0.1 (× 4) p.p.m. [b] $PhCH_2O$ signals at δ_C 127.8 (*m* and *p*), 128.6 (*o*), 138.9, and 73.0 p.p.m. [c] In D_2O with dioxane as internal standard. [d] Measured at 50 MHz.

exhibited six hexose resonances similar to those of methyl β-D-galactopyranoside[17] as shown in Table 1.

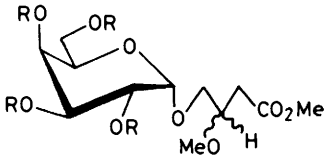
Allyl α-D-galactopyranoside[9] (**8**) is an abundant compound that offers scope for constructing spacer-arms with the α-configuration.[8–11] Ozonolysis[22] of a methanolic solution of the glycoside (**8**) gave the aldehyde (**9**), which Bernstein and Hall[10] have recently coupled to BSA. Aldehyde (**9**) was not fully characterised but was directly treated on this occasion with methyl triphenylphosphoranediylacetate. This phosphorane was employed since it yielded triphenylphosphine oxide as a by-product, which was separated from the hydrophilic glycoside (**12**) with ease. The enoate glycoside (**12**), which was unstable (see below), was immediately hydrogenated to give, after chromatography, the desired methoxycarbonylpropyl α-D-galactopyranoside (**18**) in 75% overall yield, which although analytically pure gave a rather uninformative ^1H n.m.r. spectrum exhibiting a doublet for 1-H (δ_H 4.77, $J_{1,2}$ 0.8 Hz), two multiplets at δ_H 1.71 and 2.25 for CH_2CH_2CO, and a singlet at δ_H 3.30 for the methoxy group. The ^{13}C n.m.r. spectrum on the other hand was highly diagnostic; it gave the expected eleven signals, six of which agreed closely with those of methyl α-D-galactopyranoside[17] as shown in Table 2. The structure was confirmed by conversion of compound (**18**) into the tetra-acetate (**19**) which gave informative ^1H and ^{13}C (see Table 2) n.m.r. spectra.



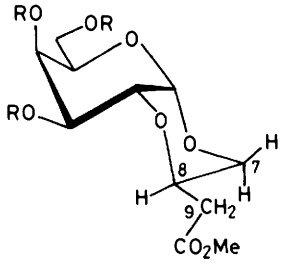
(**8**) R = H, X = CH_2
(**9**) R = H, X = O
(**10**) R = Pv, X = CH_2
(**11**) R = Pv, X = O



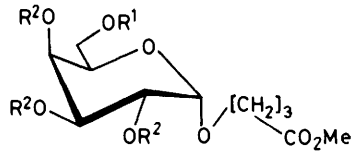
(**12**) R = H
(**13**) R = Pv



(**14**) R = H
(**15**) R = Ac



(**16**) R = H
(**17**) R = Ac



Pv = pivaloyl

(**18**) R^1 = R^2 = H
(**19**) R^1 = R^2 = Ac
(**20**) R^1 = Pv, R^2 = H

The enoate (**12**) was found to be susceptible to Michael-type additions. In an experiment in which this Wittig reaction product (**12**) was stored prior to hydrogenation the saturated ester (**18**) proved difficult to isolate pure, because two other products, each present to the extent of *ca.* 10—15%, were also formed. One of these was separated by chromatography and since it gave only the triacetate (**17**) upon acetylation it was assigned structure (**16**).

The other product had the same chromatographic mobility as (**18**) and so it could not be isolated. However, the mixture obtained after acetylation was amenable to chromatographic separation and this gave, in addition to (**19**), a compound that was shown by n.m.r. spectroscopy to be the tetra-acetate (**15**). The most salient spectral features were the absences of vinylic ^{13}C and ^1H signals and the presence of signals for another methoxy group at δ_C 58.0 p.p.m. (see Table 2) and two singlets in the ratio of 1:2, δ_H 3.98 and 4.02. This indicates that methanol competes with O-2 in attack at the double bond, with the intermolecular addition giving rise to two isomers (**14**).

In much of our work[23] galactosides blocked at O-6 will be required. Consequently we conducted a similar series of transformations on allyl 6-*O*-pivaloylgalactoside (**10**). This crystalline compound was sequentially ozonolysed and treated with methyl triphenylphosphoranediylacetate to give the crude

Table 2. ^{13}C N.m.r. chemical shifts (*p.p.m.*) of some α-D-galactopyranosides in $CDCl_3$ relative to tetramethylsilane (15 MHz)

	α-D-Galactopyranosyl residue						Aglycone				
Compound	C-1	C-2	C-3	C-4	C-5	C-6					
(**24**)	96.5	67.6	67.6	67.0	65.7	61.2					
(**15**)[a]	96.9	68.3	68.2	67.8	66.7	61.9	69.6	36.7 (58.0 MeO)	76.6	171.8	51.8
(**19**)[a,b]	96.3	68.2	68.1	67.6	66.3	61.8[c]	67.5[c]	24.8[c]	30.6[c]	173.7	51.6
(**23**)[d]	100.1	69.2	70.5	70.2	71.6	62.2					
(**18**)[d]	99.2	69.1	70.4	70.1	71.7	61.9	67.8	25.0	31.5	177.8	53.0
(**20**)[d,e]	98.4	70.4	69.9	68.4	66.9	63.5	68.4	24.6	30.8	174.1	51.4

(**23**) Methyl α-D-galactopyranoside, (**24**) the tetra-acetate of (**23**).

[a] Four acetyl groups at δ_C 20.6 (× 4) and four signals in the region δ_C 169.9—170.63 p.p.m. [b] Measured at 50 MHz. [c] Shown to be methylene carbons from an INEPT experiment. [d] Measured in D_2O with dioxane as reference. [e] Pivaoloyl signals at δ_C 26.8, 38.4, and 178.5 p.p.m.

enoate (**13**) which was hydrogenated without delay. This gave, after chromatography, crystalline, analytically pure, 3-methoxycarbonylpropyl 6-*O*-pivaolyl-α-D-galactopyranoside (**20**) with diagnostic ^1H n.m.r. singlets at δ_H 1.16 and 3.58 for the CMe_3 and OMe groups and a doublet at δ_H 4.64 for the anomeric proton with $J_{1,2}$ 3.5 Hz. The ^{13}C n.m.r. spectrum exhibited resonances for all the carbons in structure (**20**). Further verification of structure was obtained when compound (**20**) was converted with methanolic sodium methoxide into the deblocked galactose (**18**) and when selective pivaloylation achieved the reverse process, transforming (**18**) into (**20**).

Of the two routes to compound (**20**), that starting from (**10**) is preferable and it has been used[23] in the synthesis of 2,3-di-*O*-galactopyranosyl galactopyranoside.

Experimental

General Methods.—^1H N.m.r. spectra were usually measured on $CDCl_3$ solutions with tetramethylsilane (TMS) as internal standard, either with a Jeol FX 200 FT instrument or a Jeol M100 CW instrument. Natural-abundance ^{13}C n.m.r. spectra were determined usually at 15 MHz with a Jeol FX60 spectrometer and occasionally at 50 MHz with a Jeol FX 200 instrument. TMS was the internal standard for $CDCl_3$ solutions and dioxane for D_2O solutions. All δ_C values are recorded with reference to TMS.

Optical rotations were measured on 1.0 ± 0.3% chloroform solutions at 21 ± 2 °C with an Optical Activity polarimeter model A100. I.r. spectra were recorded for solids dispersed in KBr discs and for gums smeared on KBr discs with a Perkin-Elmer model 597 spectrophotometer.

T.l.c. was carried out on silica gel GF_{254} (Merck) and materials were located either visually under u.v. light or with a sulphuric acid–ethanol spray reagent. Column chromatography was carried out on silica gel 70—230 mesh (Merck 7734) at atmospheric pressure. Non-alcoholic organic solvents were dried with molecular sieves 4 Å.

1-O-*Benzylhexane*-1,6-*diol* (**1**).—To a stirred solution of hexane-1,6-diol (40 g, 0.34 mol) in anhydrous dimethyl sulphoxide (DMSO) (300 ml) at 22 °C was added portionwise sodium hydride (80%) (9 g, 0.3 mol) and then the mixture was heated to 120 °C until the evolution of hydrogen ceased. The suspension was cooled to 60 °C and benzyl bromide (37 ml, 0.31 mol) was added during 30 min. The white solid dissolved and after a further 30 min at 60 °C the reaction was complete. The DMSO (220 ml) was evaporated under reduced pressure and the white residue was partitioned between diethyl ether (300 ml) and water (100 ml). The aqueous phase was separated and extracted with diethyl ether (50 ml × 2). The combined ethereal solution was washed with water (100 ml × 3), dried, and evaporated to give a liquid containing compound (**1**) and the dibenzyl ether. This mixture was fractionated on silica gel with Et_2O–light petroleum (b.p. 60—80 °C) (4:1) as eluant to give the pure *mono-ether* (**1**) (27.4 g, 44%), b.p. 120 °C at 0.1 mmHg; $\nu_{max.}$ 3 380 cm^{-1} (OH); δ_H 7.38 (5 H, s, Ph), 4.54 (2 H, s, $PhCH_2O$), 3.44—3.82 (4 H, m, 2 CH_2O), 1.87 (1 H, s, OH), and 1.28—1.85 (8 H, br m, 4 CH_2); δ_C 138.80, 128.18 (× 2), and 127.4 (× 3) (Ph), 72.82 ($PhCH_2O$), 70.05 (OCH_2), and 61.71, 32.42, 29.55, 25.84, and 25.52 p.p.m. (5 × CH_2) (Found: C, 74.85; H, 9.9. $C_{13}H_{20}O_2$ requires C, 74.94; H, 9.70%).

6-*Benzyloxyhexyl* 2,3,4,6-*Tetra*-O-*acetyl*-β-D-*galactopyranoside* (**2**).—*Method* (*a*). Tin tetrachloride (0.18 ml, 1.5 mmol) was added[15] in one portion to a stirred solution of penta-*O*-acetyl-β-D-galactopyranose (390 mg, 1 mmol) in anhydrous methylene dichloride (10 ml) at −5 °C. A white precipitate formed after 20 min and then the hydroxy benzyl ether (**1**) (624 mg, 3 mmol) dissolved in methylene dichloride (1 ml) was added in one portion to the cold solution. The white solid dissolved during 15 min and the solution was analysed by t.l.c. (EtOAc–C_6H_6) (1:2) which showed that, after 2.5 h, all of the penta-acetate, R_F 0.45, and most of the hydroxybenzyl ether (**1**), R_F 0.36, had reacted to give a glycoside (**2**), R_F 0.54. The reaction mixture was stirred at 0 °C with aqueous sodium hydrogen carbonate and the product was extracted into methylene dichloride (10 ml × 3). The organic phase was worked up in the usual way to give a syrup (887 mg) which was purified by column chromatography on silica gel with EtOAc–C_6H_6 (1:2) as eluant to give the pure glycoside (**2**) (275 mg, 51%).

Method (*b*). A solution of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (1 g, 2.4 mmol) in nitromethane (1 ml) and benzene (1 ml) containing mercury(II) cyanide (410 mg) was treated[16] at 21 °C with the hydroxy benzyl ether (**1**) for 20 h. At this stage t.l.c. [Et_2O–light petroleum (b.p. 40—60 °C) (3:1)] revealed that the bromo-sugar (R_F 0.29) had reacted and that the *glycoside* (**2**), R_F 0.24, had been formed. The product was extracted into benzene, worked up in the usual way, and purified by column chromatography on silica gel with Et_2O–light petroleum (b.p. 40—60 °C) (3:1) as eluant to give a mixed fraction (80 mg), R_F 0.44 and 0.45 (*ca.* 1:1), $\nu_{max.}$ 2 250 cm^{-1} (C≡N); δ_H 6.40 (d) and 4.48 (d), and a pure fraction which was the glycoside (**2**) (438 mg, 51%), R_F 0.44; $[\alpha]_D^{24}$ −8.2° (*c* 1.0 in

$CHCl_3$); *m/z* 43 (CH_3CO^+, parent peak), 331 (8%) (tetra-acetylgalactosyl cation); δ_H (200 MHz) 2.16, 2.07, 2.05, and 1.98 (4 × 3 H, 4 s, 4 Ac), 7.32 (5 H, s, Ph), 4.51 (2 H, s, $PhCH_2O$), 1.24—1.40 and 1.45—1.60 (2 × 4 H, 2 m, 4 CH_2), 3.38—3.48 (3 H, m), 3.80—3.92 (2 H, m), 4.08—4.18 (2 H, m) [OCH_2, $BnOCH_2$, and 5-, 6-, and 6′-H], 4.42 (1 H, d, $J_{1,2}$ 8.0 Hz, 1-H), 5.18 (1 H, dd, $J_{2,1}$ 8.0, $J_{2,3}$ 10.5 Hz, 2-H), 4.98 (1 H, dd, $J_{3,2}$ 10.5, $J_{3,4}$ 3.5 Hz, 3-H), and 5.38 (1 H, br, dd, $J_{4,3}$ 3.5, $J_{4,5}$ 0.7 Hz, 4-H); ^{13}C n.m.r. data are recorded in Table 1 (Found: C, 59.85; H, 7.05. $C_{27}H_{38}O_{11}$ requires C, 60.21; H, 7.11%).

6-*Hydroxyhexyl* 2,3,4,6-*Tetra*-O-*acetyl*-β-D-*galactopyranoside* (**3**).—The benzyloxyhexyl glycoside (**2**) (7.36 g, 13.7 mmol) in ethanol (40 ml) was catalytically hydrogenolysed [10% palladium–charcoal (1.7 g)] under hydrogen at 3 atm during 4.5 h. The usual work-up, followed by column chromatography on silica gel with diethyl ether as eluant, gave the syrupy *hydroxyhexyl glycoside* (**3**) (5.95 g, 97%), R_F 0.29; $[\alpha]_D^{22}$ −12.2° (*c* 1.06 in $CHCl_3$); δ_H (100 MHz) 2.23, 2.10, 2.11, and 2.06 (4 × 3 H, 4 s, 4 Ac), 1.2—1.9 (8 H, br m, 4 CH_2), 2.74 (1 H, s, HO), 4.73 (1 H, d, $J_{1,2}$ 7.5 Hz, 1-H), 5.40 (1 H, dd, $J_{2,1}$ 7.5, $J_{2,3}$ 10.5 Hz, 2-H), 5.28 (1 H, dd, $J_{3,2}$ 10.5, $J_{3,4}$ 3.5 Hz, 3-H), 5.67 (1 H, dd, $J_{4,3}$ 3.5, $J_{4,5}$ 0.7 Hz, 4-H), 3.5—4.5 (7 H, br m, 5-, 6-, and 6′-H and 2 CH_2O); ^{13}C n.m.r. data are recorded in Table 1 (Found: C, 53.25; H, 7.15. $C_{20}H_{32}O_{11}$ requires C, 53.56; H, 7.19%).

6-*Oxohexyl* 2,3,4,6-*Tetra*-O-*acetyl*-β-D-*galactopyranoside* (**4**).—To a stirred solution of the hydroxyhexyl galactose (**3**) (7.6 g, 17 mmol) in distilled methylene dichloride (100 ml) was added pyridinium chlorochromate (8 g, 37 mmol).[19] T.l.c. (Et_2O) indicated, after 20 min, unchanged (**3**) and products (R_F 0.29 and 0.5). More oxidant (2 g, 9 mmol) was added and after 30 min the reaction mixture was diluted with diethyl ether (400 ml), and then filtered through a 1 inch layer of silica gel covered by an equal thickness of Celite. The brown tar which remained in the flask was triturated with diethyl ether (100 ml × 4) and the combined extracts were filtered as described. Evaporation of the ethereal solution and column chromatography of the residue on silica gel with diethyl ether as eluant gave pure syrupy *aldehyde* (**4**) (6.2 g, 82%), R_F 0.5; $[\alpha]_D^{20}$ −9.0° (*c* 1.04 in $CHCl_3$); $\nu_{max.}$ 1 750 cm^{-1} (C=O); δ_H (100 MHz) 2.26, 2.13, 2.11, and 2.06 (4 × 3 H, 4 s, 4 Ac), 1.3—1.9 (6 H, br m, 3 CH_2), 2.5—2.8 (2 H, br t, CH_2CHO), 4.71 (1 H, d, $J_{1,2}$ 7.5 Hz, 1-H), 5.52 (1 H, dd, $J_{2,1}$ 7.5, $J_{2,3}$ 10.5 Hz, 2-H), 5.30 (1 H, dd, $J_{3,2}$ 10.5, $J_{3,4}$ 3.5 Hz, 3-H), 5.70 (1 H, dd, $J_{4,3}$ 3.5, $J_{4,5}$ 0.7 Hz, 4-H), 3.5—4.5 (5 H, br m, 5-, 6′-, and 6′-H and CH_2O), and 10.44 (1 H, t, *J* 1.5 and 1.5 Hz, CHO); ^{13}C n.m.r. data are recorded in Table 1 (Found: C, 53.7; H, 6.7. $C_{20}H_{30}O_{11}$ requires C, 53.81; H, 6.77%).

[(E)-7-*Methylcarbonylhept*-6-*enyl*] 2,3,4,6-*Tetra*-O-*acetyl*-β-D-*galactopyranoside* (**5**).—Trimethyl phosphonoacetate (2.5 g, 13.7 mmol) was added to a stirred suspension of sodium hydride (415 mg, 13.7 mmol) in tetrahydrofuran (THF) (100 ml). After 10 min, when hydrogen evolution ceased, a solution of the aldehyde (**4**) (5.6 g, 12.5 mmol) in THF (5 ml) was added.[23] The mixture was stirred for 5 min and then filtered through Celite. The filtrate was evaporated, the residue was dissolved in diethyl ether, and the solution was washed with water and worked up in the usual manner to give chromatographically pure *enoate glycoside* (**5**) (6.0 g, 95%). A portion (500 mg) of this material was chromatographed on a column of silica gel to give material with R_F 0.64 (Et_2O) and 0.55 [Et_2O–light petroleum (b.p. 40—60 °C) (5:1)], $[\alpha]_D^{20}$ −11.4° (*c* 1.04 in $CHCl_3$); $\nu_{max.}$ 1 750 cm^{-1} (C=O), 1 720, and 1 660 cm^{-1} (C=C–C=O); δ_H (100 MHz) 2.08, 2.14, 2.16, and 2.25 (4 × 3 H, 4 s, 4 Ac), 1.3—1.9 (8 H, m, 4 CH_2), 7.24 (1 H, dt, $J_{6',7'}$ 16.8, $J_{6',5'}$ 7.0, and $J_{6',5'}$ 7.0 Hz, vinylic 6′-H), 6.05 (1 H, dt, $J_{7',6'}$ 16.8, $J_{7',5'}$ 1.5, and $J_{7',5'}$ 1.5 Hz, 7′-H vinylic), 3.86 (3 H, s, OMe), 4.65 (1 H, d, $J_{1,2}$ 7.8 Hz, 1-H), 5.38 (1 H, dd, $J_{2,1}$ 7.8, $J_{2,3}$ 10.5 Hz, 2-H), 5.20 (1 H, dd, $J_{3,2}$ 10.5, $J_{3,4}$ 3.5 Hz, 3-H), 5.58 (1 H, dd, $J_{4,3}$ 3.5, $J_{4,5}$ 0.7 Hz, 4-H), and 3.6—4.6 (5 H, m, 5-, 6-, and 6′-H and aglycone OCH_2); ^{13}C n.m.r. data are recorded in Table 1 (Found: C, 55.25; H, 6.8. $C_{23}H_{34}O_{12}$ requires C, 54.97; H, 6.82%).

7-*Methoxycarbonylheptyl* 2,3,4,6-*Tetra*-O-*acetyl*-β-D-*galactopyranoside* (**6**).—The unsaturated glycoside (**5**) (5.5 g, 11 mmol) was hydrogenated in ethanol (50 ml) containing 10% palladium–carbon (1 g) under 1 atm of hydrogen during 1 h. The usual work-up afforded the syrupy *methoxycarbonylheptyl glycoside* (**6**) (5.3 g, 95%), R_F 0.5 [Et_2O–light petroleum (b.p. 40—60 °C) (5:1)]; $[\alpha]_D^{21}$ −11.5° (*c* 1.1 in $CHCl_3$); δ_H (100 MHz) 2.08, 2.15, 2.17, and 2.22 (4 × 3 H, 4 s, 4 Ac), 1.02—2.00 (10 H, br m, 5 CH_2), 2.44 (2 H, br t, ^3J 6.5 and 6.5 Hz, CH_2O), 3.82 (3 H, s, OMe), 4.70 (1 H, d, $J_{1,2}$ 7.8 Hz, 1-H), 5.44 (1 H, dd, $J_{2,1}$ 7.8, $J_{2,3}$ 10.5 Hz, 2-H), 5.27 (1 H, dd, $J_{3,2}$ 10.5, $J_{3,4}$ 3.5 Hz, 3-H), 5.61 (1 H, dd, $J_{4,3}$ 3.5, $J_{4,5}$ 0.7 Hz, 4-H), and 3.5—4.5 (5 H, br m, 5-, 6-, and 6′-H and aglycone OCH_2); ^{13}C n.m.r. data are recorded in Table 1 (Found: C, 54.55; H, 7.1. $C_{23}H_{36}O_{12}$ requires C, 54.75; H, 7.20%).

7-*Methoxycarbonylheptyl* β-D-*Galactopyranoside* (**7**).—The tetra-acetate (**6**) (0.86 g) was treated with a catalytic quantity of sodium methoxide in methanol (10 ml). The usual work-up gave the *deblocked glycoside* (**7**) (0.52 g, 91%), m.p. 93—95 °C; $[\alpha]_D^{22}$ −10.7° [*c* 1.0 in MeOH–H_2O (1:1)]; δ_H (200 MHz; D_2O) 3.48 (3 H, s, OMe), 2.18 (2 H, t, ^3J 6.5 and 6.5 Hz, CH_2CO), 1.02—1.20 and 1.29—1.52 (6 H and 4 H respectively, 2 m, 5 CH_2), 4.16 (1 H, d, $J_{1,2}$ 8.0 Hz, 1-H), and 3.2—3.8 (8 H, m, 2-, 3-, 4-, 5-, 6-, and 6′-H and aglycone OCH_2); ^{13}C n.m.r. data are recorded in Table 1 (Found: C, 534.4; H, 8.5. $C_{15}H_{28}O_8$ requires C, 53,6; H, 8.4%).

Allyl α-D-*Galactopyranoside* (**8**).—D-Galactose (200 g), allyl alcohol (2 l), and Amberlite IR-120(H) resin (120 g) were stirred and heated under reflux for 2.5 h. The cooled solution was filtered and stirred for 15 min with Amberlite IR-45(OH) resin (40 g) and then filtered and evaporated to give an oil which was triturated with diethyl ether (800 ml × 3). The residue was crystallised from ethanol (500 ml) to give a solid (66.5 g, 27%), m.p. 137—139 °C, which was recrystallised from ethanol to give compound (**8**) (45 g), m.p. 139—142 °C; $[\alpha]_D^{23}$ +178.6° (*c* 1.0 in H_2O) [lit.,[9] m.p. 143—145 °C; $[\alpha]_D^{25}$ +181° (H_2O)].

3-*Methoxycarbonylpropyl* α-D-*Galactopyranoside* (**18**).—The allyl galactose (**8**) (14.6 g, 66.5 mmol) in methanol (200 ml) was maintained at −70 °C and ozonated oxygen was bubbled into the solution for 150 min at a rate of 0.5 mmol min^{-1} as described by Pappas *et al.*[22] The cold, blue solution was flushed with nitrogen for 10 min, dimethyl sulphide (7 ml, 0.1 mol) was added, and after 3 h at room temperature t.l.c. [EtOAc–MeOH (4:1)] showed that compound (**8**) (R_F 0.44) had been converted into the oxidised product (**9**) (R_F 0.25). Methoxycarbonylmethylene(triphenyl)phosphorane (50 g, 155 mmol) was added to the stirred mixture and the solution was heated under reflux. Initially, t.l.c. analysis of the reaction showed the presence of the aldehyde (R_F 0.25), the product (R_F 0.4), and triphenylphosphine oxide (R_F 0.9) [EtOAc–MeOH (4:1)] and subsequently indicated that the reaction was complete after 0.5 h. The methanol was evaporated, water (200 ml) was added to the residue, the mixture was shaken, and the phosphine oxide was filtered off. The solid was washed with two portions of water (50 ml) and the combined aqueous fractions were extracted four times with benzene (100 ml) to remove the yellow colour. The aqueous phase was evaporated to yield a yellow syrup from which the last traces of water were removed by azeotropic evaporation with ethanol.

The crude yellow syrupy enoate (**12**) was immediately

dissolved in ethanol (200 ml) and hydrogenated during 4 h in the presence of 10% palladium–charcoal (3 g) under hydrogen at 3 atm pressure. After filtration and evaporation the yellow syrup (21.7 g) obtained was triturated with diethyl ether (100 ml). It was dissolved in chloroform (50 ml) and then precipitated as an oil by addition of diethyl ether (400 ml). The oil was separated and the traces of solvents it retained were removed by evaporation to give a syrup (17.7 g), R_F 0.34 [EtOAc–MeOH (4:1)].

This material was chromatographed on silica gel with EtOAc–MeOH (4:1) as eluant to give the glycoside (**18**) (13.7 g, 75%), $[\alpha]_D$ +120° (*c* 1 in $CHCl_3$); δ_H (200 MHz; D_2O with CF_3CO_2H), 4.77 (1 H, d, $J_{1,2}$ 0.8 Hz, 1-H), 2.25 (2 H, m, CH_2CO), and 1.71 (2 H, m, CH_2); ^{13}C n.m.r. data: see Table 2.

A portion of this material was acetylated with acetic anhydride in pyridine to give the methoxycarbonylpropyl glycoside tetra-acetate (**19**) (1.52 g), R_F 0.57 [EtOAc–C_6H_6 (1:1)]; $[\alpha]_D^{26}$ +135.5° (*c* 1.0 in $CHCl_3$); ^1H n.m.r. data (200 MHz) 1.99, 2.05, 2.08, and 2.14 (4 × 3 H, 4 s, 4 Ac), 3.69 (3 H, s, OMe), 5.07—5.15 (2 H, m, 1- and 2-H), 5.34 (1 H, d m, $J_{3,2}$ 10 Hz, 3-H: the signal simplifed when 4-H at δ 5.44 was irradiated), 5.44 (1 H, br d, $J_{4,3}$ 10, $J_{4,5}$ 0.7 Hz, 4-H), 4.20 [1 H, br t, $J_{4,5}$ 0.7, $J_{5,6}$ 5.5, and $J_{5,6'}$ 7.5 Hz, 5-H; this signal sharpened to a dd (*J* 5.5 and 7.5 Hz) when 4-H at δ 5.44 was irradiated], 4.08—4.16 (2 H, m, 6- and 6′-H), 3.75 (1 H, dt), and 3.45 (1 H, dt) [both signals have identical ^2J 9.5, ^3J 6.0, ^3J 6.0 Hz; they are resonances of the aglycone OCH_2 and collapsed to doublets (^2J 9.5 Hz) when the quintet at δ 1.94 was irradiated]. 1.94 (2 H, quint, 4 × ^3J 6.0 Hz, aglycone CH_2), and 2.42 [2 H, t, 2 × ^3J 6.0 Hz, aglycone CH_2CO; this signal collapsed to a 2 H (s) when the quintet at δ 1.94 was irradiated]; ^{13}C n.m.r. data are recorded in Table 2.

A similar experiment was carried out in which the crude Wittig reaction mixture was left overnight at room temperature before work-up, and also the syrupy enoate obtained was stored for 12 h prior to hydrogenation.

The crude saturated ester (**18**) (18 g) showed two products on t.l.c. with R_F 0.34 (major) and R_F 0.49 [EtOAc–MeOH (4:1)] and this was subjected twice to chromatography which gave pure (**18**) (9.1 g) and a minor component (**16**) (0.2 g), R_F 0.49, plus a mixture containing both compounds (3.2 g).

The minor component was acetylated with acetic anhydride in pyridine to give the triacetate (**17**) (0.16 g), R_F 0.45 (Et_2O); $[\alpha]_D^{26}$ +76.1° (*c* 0.9 in $CHCl_3$); δ_H (200 MHz) 2.06, 2.08, and 2.13 (3 × 3 H, 3 s, 3 Ac), 3.67 (3 H, s, OMe), 5.07 (1 H, d, $J_{1,2}$ 3.4 Hz, 1-H), 5.75 (1 H, dd, $J_{2,3}$ 10.4, $J_{3,4}$ 3.5 Hz, 3-H), 5.38 (1 H, dd, $J_{4,3}$ 3.5, $J_{4,5}$ 0.7 Hz, 4-H), 4.34 (1 H, br t, $J_{5,4}$ 0.7, $J_{5,6}$ 6.5, and $J_{5,6'}$ 6.5 Hz, 5-H), 3.58 (1 H, t, $J_{7ax,7eq}$ 11.4, $J_{7ax,8}$ 10.5 Hz, 7-H_{ax}), 4.27 (1 H, m, 8-H, collapses to a dd, $J_{8,7ax}$ 10.5, $J_{8,7eq}$ 2.5 Hz, when signals for 9-H and 9′-H are irradiated at δ 2.4), 2.34 (1 H, dd, $J_{9,9'}$ 15.5, $J_{9,8}$ 5.5 Hz, 9-H), 2.42 (1 H, dd, $J_{9',9}$ 15.5, $J_{9',8}$ 7.2 Hz, 9′-H), and 4.00—4.14 (4 H, m, 2-, 6-, and 6′-H, and 7-H_{eq}).

A portion of the major component (1.8 g) was similarly acetylated giving two tetra-acetates which were separated by column chromatography [SiO_2; EtOAc–C_6H_6 (1:1)]. The major one was the glycoside tetra-acetate (**19**) (1.52 g). The minor fraction was the 2-methoxy-3-methoxycarbonylpropyl galactoside tetra-acetate (**15**) (0.42 g), R_F 0.48 [EtOAc–C_6H_6 (1:1)]; $[\alpha]_D^{26}$ +106.9 (*c* 1.1 in $CHCl_3$); δ_H (200 MHz) 2.00, 2.05, 2.07, and 2.14 (4 × 3 H, 4 s, 4 Ac), 3.70 (3 H, s, CO_2Me), 4.02 and 3.98 (2 H and 1 H respectively, 2 s, OMe for two isomers), 5.06—5.20 (2 H, m, 1- and 2-H), 5.36 (1 H, dm, $J_{3,2}$ 10.5 Hz, 3-H), 5.46 (1 H, dd, $J_{4,3}$ 3.5, $J_{4,5}$ 0.7 Hz, 4-H), 4.24 (1 H, br t, $J_{5,4}$ 0.7, $J_{5,6}$ 6.5, and $J_{5,6'}$ 6.5 Hz, 5-H), 4.08—4.16 (2 H, m, 6- and 6′-H), 3.5—3.9 (3 H, m, aglycone OCH_2CH), and 1.56—1.60 (2 H, m, aglycone CH_2CO); ^{13}C n.m.r. data are recorded in Table 2.

3-*Methoxycarbonylpropyl* 6-O-*Pivaloyl*-α-D-*galactopyranoside* (**20**).—The methoxycarbonylpropyl galactoside (**18**) (706 mg, 2.5 mmol) was dissolved in THF (50 ml) containing triethylamine (1 ml, 7.2 mmol) and pivaloyl chloride (0.37 ml, 3 mmol) was added dropwise to the stirred solution during 2 h. The mixture was then refluxed for 16 h when t.l.c. [EtOAc–MeOH (4:1)] showed unchanged (**18**). More pivaloyl chloride was added in three portions (0.13 ml × 3; 3.4 mmol total) at 4 h intervals and the mixture was refluxed for a total of 12 h. The reaction mixture was filtered and aqueous sodium hydrogen carbonate (2 ml) was added to the solution, which was then evaporated. The residue was partitioned between water (20 ml) and ethyl acetate (100 ml). The aqueous phase was extracted further with ethyl acetate (100 ml × 2) and the combined organic phase (300 ml) was dried and evaporated to give a yellow syrup which was triturated with light petroleum (b.p. 60—80 °C). The more polar material which remained was purified by column chromatography. The non-polar products (200 mg) were first eluted with ethyl acetate and then the required monopivaloate (**20**) was eluted with EtOAc–MeOH (4:1) to give upon evaporation a gum (420 mg, 46%), R_F 0.61 [EtOAC–MeOH (4:1)]. The physical constants were identical with those obtained by the other route described below.

Allyl 6-O-*Pivaloyl*-α-D-*galactopyranoside* (**10**).—A solution of the allyl galactose (**8**) (22 g, 0.1 mmol) in THF (1 l) containing triethylamine (32 ml, 0.23 mol) was stirred and heated under reflux while pivaloyl chloride (27.5 ml, 0.23 mol) was added dropwise in portions [15 ml, were added at the outset, 7.5 ml after 4 h, and 5 ml after 21 h]. After the total reflux period of 25 h the reaction mixture was cooled, the white precipitate was filtered off, and aqueous sodium hydrogen carbonate solution (300 ml) was added. The solution was rotary evaporated to leave an aqueous phase which was extracted with ethyl acetate (200 ml × 5). The combined organic phase was dried, filtered, and evaporated to give a pale yellow solid which was suspended in diethyl ether (100 ml) and then filtered off to yield the *title compound* (**10**) as white crystals (14.2 g, 46%), R_F 0.33 (EtOAc) and 0.66 [EtOAc–MeOH (4:1)]; m.p. 143—144 °C [from ethyl acetate–di-isopropyl ether (4:3)]; $[\alpha]_D^{23}$ +133° (*c* 1.0 in MeOH); $\nu_{max.}$ 1 730 cm^{-1} (CO); δ_H (200 MHz; CD_3OD) 1.21 (9 H, s, CMe_3), 5.98 (1 H, sharp m, C*H*=CH_2), 5.33 (1 H, dq, $^3J_{vinyl,E}$ 17.0, $^2J_{vinyl\ gem.}$ 1.5, and $^4J_{allyl}$ 1.5 and 1.5 Hz, CH=C*H*H), 5.18 (1 H, dq, $^3J_{vinyl,Z}$ 10.0, $^2J_{vinyl\ gem.}$ 1.5, and $^4J_{allyl}$ 1.5 and 1.5 Hz, CH=CH*H*), 4.87 (1 H, d, $J_{1,2}$ 2.5 Hz, 1-H), 3.76—3.82 (2 H, m), 3.86—3.91 (1 H, m), 3.96—4.11 (2 H, m), and 4.15—4.29 (3 H, m); δ_C (15 MHz; CD_3OD) 27.6, 39.8, and 180.2 (Me_3CCO), 135.8 and 117.8 ($CH{=}CH_2$), 99.6 (C-1), 65.6 (C-6), and 69.5, 70.0, 70.2, 71.1, and 71.2 p.p.m. (Found: C, 55.55; H, 7.95. $C_{14}H_{24}O_7$ requires C, 55.25; H, 7.95%).

3-*Methoxycarbonylpropyl* 6-O-*Pivaloyl*-α-D-*galactopyranoside* (**20**).—A solution of the allyl galactoside (**10**) (10.1 g, 33.3 mmol) in methanol (200 ml) at −70 °C was treated as described for compound (**8**) with ozonated oxygen for 1 h at a rate of 0.6 mmol min^{-1}. The blue solution was flushed with nitrogen gas for 10 min and then t.l.c. analysis of the solution indicated that the allyl glycoside, R_F 0.68, had been transferred into the oxidised product (**11**), R_F 0.49 [EtOAc–MeOH (4:1)]. Dimethyl sulphide (5 ml, 68 mmol) was added and the solution was left at room temperature for 3 h. Methyl triphenylphosphoranediyl acetate (22 g, 6.6 mmol) was added and the mixture was heated under reflux for 30 min.

The mixture was immediately evaporated to a volume of 50 ml, water (250 ml) was added, the insoluble triphenylphosphine oxide was filtered off, and the yellow coloured material was extracted into benzene (100 ml × 3). The decolourized aqueous phase was evaporated to give a solid residue which was dissolved in ethyl acetate and the solution was dried and evaporated to give the crude enoate (**13**).

The enoate (**13**) (14 g) was dissolved in ethanol (130 ml) and, without delay, hydrogenated in the presence of 10% palladium–charcoal (3 g) for 5 h. After filtration the solution was evaporated to give the *methoxycarbonylpropyl galactoside* (**20**) (13.1 g). Column chromatography on silica gel (280 g) with EtOAc–MeOH (4:1) as eluant gave pure material (8.7 g, 72%), R_F 0.57 [EtOAc–MeOH (4:1)], R_F 0.25 (EtOAc); m.p. 87—90 °C [from EtOAc–Pr^i_2O (3:10)], $[\alpha]_D^{21}$ +95° (*c* 0.95 in $CHCl_3$); δ_H (100 MHz; C_5D_5N) 1.24 (9 H, s, CMe_3), 3.55 (3 H, s, OMe), 1.98—2.16 and 2.40—2.62 (2 × 2 H, 2 m, CH_2CH_2CO), and 5.14 (1 H, d, $J_{1,2}$ 3.5 Hz, 1-H), and 3.55—4.80 (8 H in D_2O-exchanged spectrum, m); δ_H (100 MHz), 1.16 (9 H, s, CMe_3), 3.58 (3 H, s, OMe), 1.74—2.15 and 2.24—2.54 (2 × 2 H, 2 m, CH_2CH_2CO), and 4.64 (1 H, d, $J_{1,2}$ 3.5 Hz, 1-H). ^{13}C N.m.r. data are recorded in Table 2 (Found: C, 52.65; H, 7.9. $C_{16}H_{28}O_9$ requires C, 52.74; H, 7.74%).

Zemplen depivaloylation of a portion (100 mg) of this material gave a tetraol which was acetylated to give tetra-acetate (**19**) (65 mg), with $[\alpha]_D^{26}$ +134° ($CHCl_3$) and ^1H n.m.r. data identical with those obtained earlier for compound (**19**).

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