Asymmetric Synthesis. Part 6.[1] Copper Salt promoted Grignard Reagent Additions to Ethyl 2,3-Dideoxy-4,5:6,7-di-*O*-isopropylidene-D-*arabino*-*trans*-hept-2-enonate and subsequent Formation of Optically Active 2-Alkyl (or Aryl) Butane-1,4-dioic Acids and Butyro-1,4-lactones

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The copper-salt promoted 1,4-additions of aryl and t-butyl Grignard reagents to ethyl 2,3-dideoxy-4,5:6,7-di-*O*-isopropylidene-D-*arabino*-*trans*-hept-2-enonate are highly stereoselective yielding products with the D-*manno*-configuration. In contrast isopropyl and ethyl Grignard reagents give products preponderantly with the D-*gluco*-configuration. Cyclohexylmagnesium bromide does not react stereoselectively but gives a 55 : 45 mixture of the D-*gluco*- and D-*manno*-isomers. Controlled degradation of the carbohydrate molecule affords 2-aryl (alkyl) butane-1,4-dioic acids and 3-aryl (alkyl)-butyro-1,4-lactones. The enantiomeric purity of these products is established by reference to known products or by use of optically active n.m.r. shift reagents.

The use of carbohydrates for the synthesis of optically active, non-carbohydrate compounds, first reviewed[2] in 1972 and subsequently,[3] has generated much recent interest in the stereochemistry of carbon–carbon bond-forming reactions on carbohydrates. In the course of many studies well recognised, but poorly explained, stereochemical anomalies have been described. For example, alkyl-lithiums react with keto-sugars to give products epimeric to those obtained with the corresponding Grignard reagent, and methylmagnesium iodide reacts with 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose to give a preponderance of the product with the D-*gluco* configuration, whereas phenylmagnesium iodide affords the product with the D-*manno* configuration.[4]

In this paper is reported another difference between alkyl and aryl Grignard reagents in the 1,4-addition reaction with αβ-unsaturated esters, catalysed by cuprous salts. Such 1,4-addition reactions, and similar reactions of alkyl-lithiums, have been reported to be highly stereoselective.[5]

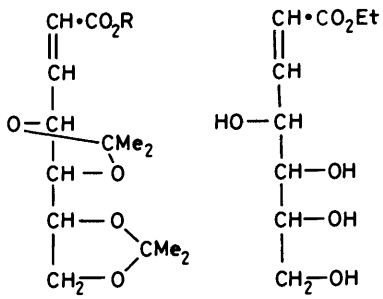
The αβ-unsaturated ester used as substrate was ethyl 2,3-dideoxy-4,5:6,7-di-*O*-isopropylidene-D-*arabino*-*trans*-hept-2-enonate (1), prepared by reaction of 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose with sodium hydride and triethyl phosphonacetate in benzene at 25 °C. This procedure usually afforded a single isomer on the evidence of chromatographic and ^1H and ^{13}C n.m.r. data although in some preparations and particularly when the methyl ester (2) was used, the n.m.r. spectrum indicated the presence of small amounts of a second product. Pure (1) had $[\alpha]_D^{22}$ +3.2° (*cf.* lit.,[6] −2.2°). [The methyl ester (2) had $[\alpha]_D^{19}$ −1.1° and an ^1H n.m.r. spectrum which was consistent with that reported[6] for a product with $[\alpha]_D^{24}$ +6.6°.]

To confirm that epimerization[7] at C-2 in the *aldehydo*-arabinose had not occurred during the addition reaction and that (1) had the *arabino*-configuration, (1) was hydrolysed to ethyl 2,3-dideoxy-D-*arabino*-*trans*-hept-2-enonate (3), $[\alpha]_D^{21}$ +12.1° (*cf.* lit.,[8] $[\alpha]_D^{19}$ +14.45° for the D-*arabino*-isomer and $[\alpha]_D^{21}$ −21.0° for the D-*ribo*-isomer).

As a preliminary to studies of the 1,4-addition reactions with different Grignard reagents the effect of the copper salt on the yield of the 1,4-addition reaction was investigated for the reaction of (1) with 4-chlorophenylmagnesium iodide. The results are summarized in Table 1. The identity of the copper salt had no effect on the stereochemical outcome of the reaction. In all other reactions cuprous iodide was used as catalyst.

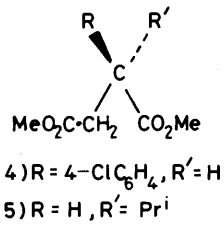
Arylmagnesium halides, with the exception of *ortho*-substituted derivatives with (1), in the presence of cuprous iodide (5 mol %), afforded 1,4-addition products as single isomers with the D-*manno*-configuration in high yield. The high stereoselectivity of the reaction was confirmed and the configuration of the products was established by their degradation to optically pure 2-arylbutane-1,4-dioic acids and 3-arylbutyro-1,4-lactones according to the Scheme.

For example ethyl 2,3-dideoxy-4,5:6,7-di-*O*-isopropylidene-3*C*-phenyl-D-*manno*-heptonate (14) was formed in 89% yield by addition of (1) to phenylmagnesium bromide containing cuprous iodide (5 mol %). Acid hydrolysis of (14) resulted in removal of the isopropylidene groups and spon-

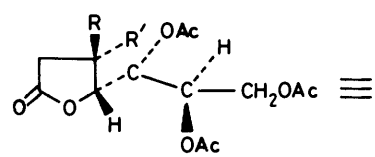


(1) R = Et
(2) R = Me

(3)



(4) R = 4-ClC$_6$H$_4$, R′ = H
(5) R = H, R′ = Pr^i
(6) R = Bu^t, R′ = H



(7) R = H, R′ = c-C$_6$H$_{11}$
(8) R = H, R′ = Pr^i
(9) R = c-C$_6$H$_{11}$, R′ = H
(10) R = Ph, R′ = H
(11) R = 4-ClC$_6$H$_4$, R′ = H
(12) R = H, R′ = Et
(13) R = Bu^t, R′ = H

Table 1. Effect of the copper salt on the yield of ethyl 3*C*-(4-chlorophenyl)-2,3-dideoxy-4,5:6,7-di-*O*-isopropylidene-D-*manno*-heptonate (10)

Copper salt [a]	CuCl	CuBr	CuI	CuCN	$Cu(OAc)_2 \cdot H_2O$ [c]
% Yield	61	87	91	53	37

[a] 5 Mol % copper salt was used. [b] 4 Mol equiv. of Grignard in tetrahydrofuran was used.

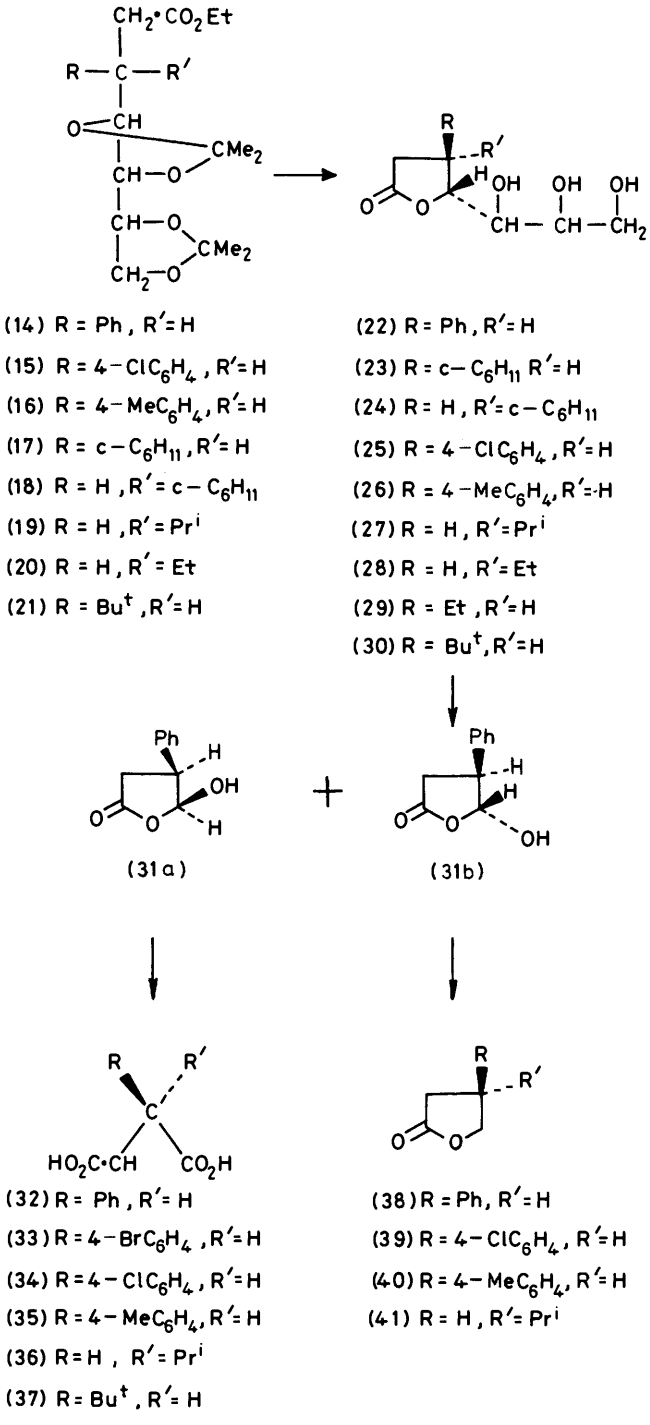
taneous lactonization to afford 2,3-dideoxy-3*C*-phenyl-D-*manno*-heptono-1,4-lactone (22) in 77% yield. Ring opening of (22) with sodium hydroxide, followed by diol cleavage with sodium metaperiodate and subsequent acidification led to racemization at the benzylic carbon atom. This was avoided by buffering to pH 6.5 with potassium dihydrogen phosphate after ring opening but prior to diol cleavage. Under these conditions (22) afforded 4-hydroxy-3-phenylbutyro-1,4-lactone (31) as a 4 : 1 mixture of diastereoisomers (31a) and (31b) in 80% yield. Oxidation of (31) with Jones reagent [9] afforded (+)-(*S*)-2-phenylbutane-1,4-dioic acid (32) [10] in 90% yield. Oxidation of (31) could also be achieved with bromine water but resulted in bromination of the aromatic ring to afford (33). Reduction of (31) with sodium borohydride in ethanol afforded optically pure (+)-(*S*)-3-phenylbutyro-1,4-lactone [11] (38) in 92% yield. The *S*-configuration for (32) and (38) implies a D-*manno*-configuration for (14) and (22).

Similarly the 4-chlorophenyl derivative (15) and the 4-methylphenyl derivative (16) afforded the corresponding optically active acids (34) and (35) and 1,4-butyrolactones (39) and (40) when degraded according to the Scheme. These were assigned the *S*-configuration by analogy with (14) and (22). In the case of (39) oxidation was carried out with bromine water and the resultant acid was converted into its dimethyl ester (4) with diazomethane. Comparison of the methyl ester resonances in the ^1H n.m.r. spectrum of (4) and the corresponding racemate in the presence of the optically active shift reagent tris(D-3-heptafluorobutyrylcamphoratoeuropium [$Eu^{III}(hfc)_3$] demonstrated that (4) was essentially optically pure.

In contrast to the reaction of (1) with arylmagnesium halides, the reaction of (1) with cyclohexylmagnesium bromide required inverse addition and a prolonged reaction time at low temperature to achieve a moderate yield of the 1,4-addition product. Further, the ^{13}C n.m.r. spectrum implied the presence of both the D-*manno*- (17) and D-*gluco*- (18) isomers. This was confirmed by acidic hydrolysis of the mixture to afford a 45 : 55 mixture (D-*manno*) (23) and (D-*gluco*) (24) lactones which were separated over silica. That the minor isomer (23) had the D-*manno*-configuration was established by its unequivocal synthesis by hydrogenation of (14) over 5% rhodium on carbon and subsequent hydrolysis of the product to (23).

The reaction of (1) with isopropylmagnesium bromide under similar conditions also afforded preponderantly the D-*gluco*-isomer (19) as shown by its degradation by sequential hydrolysis, diol cleavage, and oxidation or reduction to (−)-(*R*)-2-isopropylbutane-1,4-dioic acid (36) and (+)-(*R*)-3-isopropylbutyro-1,4-lactone (41) respectively of previously established configurations.[10,12,13] The optical rotations observed for these compounds compared with recorded values [12,13] implied optical purities of greater than 90%.

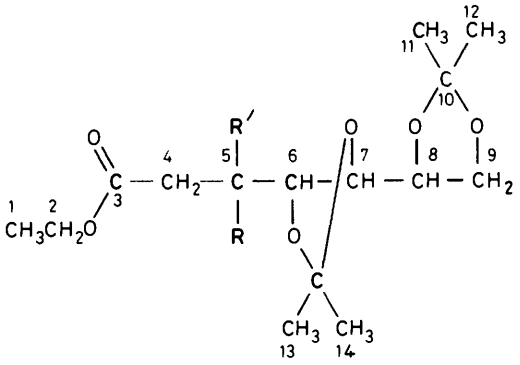
This was confirmed when the dimethyl ester (5) formed by treating (36) with diazomethane was shown by ^1H n.m.r. spectroscopy in the presence of the shift reagent [$Eu^{III}(hfc)_3$] to be a 9 : 1 mixture of isomers. Thus the ratio of the D-*gluco*- and D-*manno*-isomers formed during the reaction of (1) with isopropylmagnesium bromide reaction may be estimated as 9 : 1.



Scheme.

The preparation and configuration of compounds (14)—(17) and (19) having been achieved, it was pertinent to find whether their ^1H or ^{13}C n.m.r. spectra, or their derivatives, had distinctive features which could be used for configurational assignment of other aryl or alkyl adducts. The ^1H n.m.r. spectra were too complex and ^{13}C n.m.r. spectra (see Table 2) showed no definitive resonances. The ^{13}C n.m.r. spectra of the derived lactones (22)—(27) (see Table 3) showed small differences between isomers but these were masked by larger differences

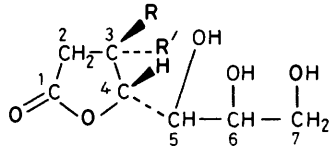
Table 2. ^{13}C N.m.r. spectra of 3*C*-substituted ethyl 2,3-dideoxy-4,5:6,7-di-*O*-isopropylidene-D-*gluco*/*manno*-heptonates



Compd.	R	R′	1	2	3	4	5	6, 7, 8	9	10	11, 12, 13, 14	15
(14) (*manno*)	Ph	H	14.0	66.3	172	36.9	45.5	76.3, 79.6, 82.7	60.0	109.3	25.1, 26.1, 27.8	109.8
(15) (*manno*)	4-ClC_6H_4	H	14.1	66.9	172	36.5	44.5	76.7, 79.7, 82.9	60.1	109.3	26.2, 26.7, 27.7	109.8
(16) (*manno*)	4-MeC_6H_4	H	14.0	66.2	172	37.1	45.3	76.4, 79.9, 82.8	60.1	109.3	25.1, 26.1, 27.8	109.8
(17) (*manno*)	c-C_6H_{11}	H	14.2	67.5	174	31.8	42.0	77.5, 79.7, 80.3	60.1	109.1	25.3, 26.6, 27.2	109.6
(18) [a] (*gluco*)	H	c-C_6H_{11}	14.2	67.5	174	32.3	42.7	77.7, 80.1, 81.7	60.0	109.0	25.3, 26.6, 27.2	109.4
(19) (*gluco*)	H	Pr^i	14.2	67.7	174	31.4	42.9	77.2, 80.4, 82.0	60.3	109.2	25.4, 26.5, 27.3 27.7	109.6
(20) (*gluco*)	H	Et	14.3	67.7	173	35.7	38.8	77.4, 79.3, 82.2	60.1	109.0	25.4, 26.6, 27.3 27.4	109.6
(21) (*manno*)	Bu^t	H	14.1	67.6	175	30.1	45.0	77.7, 78.8, 79.4	60.3	108.9	25.4, 26.6, 26.8 27.9	109.6

[a] A mixture with (17), data obtained by subtraction.

Table 3. 4-H Resonance and ^{13}C n.m.r. spectra of 3*C*-substituted 2,3-dideoxy-D-*gluco*/*manno*-heptono-1,4-lactones



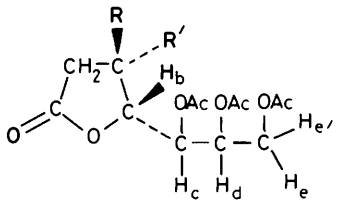
Compd.	R	R′	1	2	3	4	5, 6	7	4-H resonances δ	J
(22) (*manno*)	Ph	H	176.5	37.6	42.9	86.1	71.4, 71.9	64.8	4.90	6.5
(23) (*manno*)	c-C_6H_{11}	H	179.9	33.3	45.9	83.6	72.2, 73.6	64.6	4.85	5.0
(24) (*gluco*)	H	c-C_6H_{11}	180.3	34.0	42.7	81.7	70.9, 71.6	64.4	4.95	6.5
(25) (*manno*)	4-ClC_6H_4	H	178.2	37.9	42.9	86.8	70.7, 72.3	64.7	4.85	8.0
(26) (*manno*)	4-MeC_6H_4	H	176.3	37.6	42.5	86.0	71.4, 71.7	64.7	4.83	7.5
(27) (*gluco*)	H	Pr^i	180	33.9	46.4	80.9	70.6	64.0	4.91	7.0
(28) (*gluco*)	H	Et	180	35.5	41.3	82.4	71.3, 71.7	64.5	4.94	6.0
(30) (*manno*)	Bu^t	H	180	31.6	47.3	81.8	71.6, 74.5	64.2	4.85	4.0

induced by the different R groups. In the ^1H n.m.r. spectrum of (23) the lactonic 4-H resonance occurred at δ 4.95 whereas it occurred at δ 4.85 in the spectrum of (24). Although the lactonic proton tended to resonate at lower field in the ^1H n.m.r. spectrum of the D-*gluco*-lactones (24) and (27) compared to its position in the spectrum of the D-*manno*-lactones (22), (23), (25), and (26) (see Table 4),[14] variation of the position of the 4-H resonance with the R group made assignment uncertain.

The ^1H n.m.r. spectra of the D-*gluco*-lactone triacetates (7) and (8) were clearly defined. The 4-H, 5-H, 6-H, and 7-H resonances were separate and a clear first-order splitting pattern was observed. In contrast, in the ^1H n.m.r. spectra of the D-*manno*-lactone triacetates (9)—(11), 5-H and 6-H resonated together; the splitting pattern was more complex and of different general shape and the position of the 4-H resonance was shifted to higher field (see Table 4).[14] Thus, observation of the position of the lactonic proton resonance in the spectra of the lactone and its derived triacetate, together with consideration of the overall splitting pattern of the 4-H to 7-H resonances, suggested that tentative configurational assignments could be made for other substituents and were used for the ethyl and t-butyl derivatives (see below).

The reaction of (1) with ethylmagnesium bromide afforded preponderantly the D-*gluco*-derivative (20) in very low yield. The ^{13}C n.m.r. spectrum of (20) suggested that it was a pure isomer but the spectrum of the derived lactone (28) suggested a trace of the D-*manno*-isomer (29) was present. The D-*gluco*-configuration was assigned to (20) on the basis of the ^1H n.m.r. spectra of (28) and its triacetate (12). In the spectrum of (28) the 4-H resonance was observed at δ 4.95, and in the spectrum of (12) the position of the 4-H resonance at δ 4.73 and the

Table 4. ^{1}H N.m.r. spectra of 3*C*-substituted 5,6,7-triacetyl-2,3-dideoxy-D-*manno*/*gluco*-heptono-1,4-lactones



Compd.	R	R′	H_b	H_c	H_d	H_e	$H_{e'}$	J_{ab}	J_{bc}	J_{cd}	J_{ed}	$J_{e'd}$	$J_{ee'}$
(7) (*gluco*)	H_a	c-C_6H_{11}	4.78	5.43	5.20	4.40	4.12	6.5	1.5	6.0	3.0	6.0	13.5
(8) (*gluco*)	H_a	Pr^i	4.76	5.44	5.16	4.43	4.10	6.6	0.8	5.6	3.0	6.3	24
(9) (*manno*)	c-C_6H_{11}	H_a	4.48	5.20	5.20	4.24	*a*	5.0	1.2	*a*	*a*	*a*	*a*
(10) (*manno*)	Ph	H_a	4.70	5.15	5.15	4.31	4.16	7.2	2.0	*a*	2.8	4.2	12.4
(11) (*manno*)	4-ClC_6H_4	H_a	4.60	5.15	5.15	4.35	4.12	7.0	2.0	*a*	2.4	4.3	12.0
(12) (*gluco*)	H_a	Et	4.73	5.37	5.20	4.44	4.12	6.5	2.0	5.7	3.0	6.0	12.0
(13) (*manno*)	Bu^t	H_a	4.58	5.11	5.11	4.40	4.15	3.2	1.0	*a*	2.0	4.8	12.0

[a] Unobtainable, first order pattern destroyed.

overall splitting pattern was consistent with a D-*gluco*-configuration.

In contrast to the other alkyl Grignard reagents, which gave D-*gluco*-products, t-butylmagnesium chloride was allowed to react with compound (1), in the presence of cuprous iodide to give a good yield of the D-*manno*-derivative (21). No trace of the corresponding D-*gluco*-isomer was detected. In the ^{1}H n.m.r. spectrum of (30) the 4-H resonance occurred at δ 4.85 and in the ^{1}H n.m.r. spectrum of (13) the 4-H resonated at δ 4.58 and the first-order spectrum was lost. In support of this assignment degradation of (21) according to the Scheme afforded (+)-2-t-butylbutane-1,4-dioic acid (37). In comparison all other (*S*)-2-alkyl and (*S*)-2-arylbutane-1,4-dioic acids have a positive rotation,[10] which implies that (37) has the *S*-configuration and hence that (30) has the D-*manno*-configuration.*

Comparison of the ^{1}H n.m.r. spectrum of dimethyl (+)-2-t-butylbutane-1,4-dioate (6) in the presence of [Eu^{III} (hfc)$_3$] with that of the racemate showed that (6) was essentially optically pure.

Attempts to prepare methyl derivatives were unsuccessful. Methylmagnesium iodide, methyl-lithium and lithium dimethylcuprate, each under a variety of conditions, failed to add to compound (1). Unchanged (1) was recovered as the only carbohydrate product in each case. Whilst this was surprising, similar results have been reported previously.[16]

The above results show that with certain Grignard reagents the high yields and high stereoselectivity of 1,4-additions to (1) and the straightforward degradation sequence provides a practically convenient synthesis of optically active butane-1,4-dioic acid derivatives. The results however do not offer any obvious clues as to the mechanism of the copper-catalysed reactions [17] or to the nature of the transition states [2] which determine the stereochemical outcome. With so many sites for complex formation in the carbohydrate molecule it is easy to draw a transition intermediate which leads to the product obtained but it is not possible to explain why that transition intermediate is the preferred one for a particular Grignard reagent. Certainly the presence of copper salts is essential for without them, at the reaction temperatures used, no reaction (not even 1,2-addition) of the Grignard reagents occurs. For reactions which go slowly or in poor yield, higher temperatures favour neither 1,4- nor 1,2-additions but merely cause a multiplicity of products perhaps by removal of the isopropylidene groups.

* (*S*)-(+)-Dimethyl 2-t-butylbutane-1,4-dioate has been prepared and has $[\alpha]_D$ +12.3° (*c* 1.108, ethanol).[15]

Experimental

I.r. spectra, as KBr discs unless otherwise stated, were recorded with a Perkin-Elmer 157 spectrophotometer. ^{1}H N.m.r. spectra were measured at 100 MHz in deuteriochloroform unless otherwise stated. ^{13}C N.m.r. spectra were measured at 15 MHz. Optical rotations were measured using a 1 dm path length cell. All solutions were dried over magnesium sulphate. All melting and boiling points are uncorrected. For small scale (bulb-to-bulb) distillations the temperature quoted refers to the oven temperature at which distillation commenced.

Ethyl 2,3-*Dideoxy*-4,5:6,7-*di*-O-*isopropylidene*-D-arabino-trans-*hept*-2-*enonate* (1).—Triethyl phosphonoacetate (36 g) was added dropwise to a stirred suspension of sodium hydride (5 g, 80% dispersion in mineral oil) in dry benzene (250 ml) under dry nitrogen at 20—25 °C and the mixture was stirred at 20 °C for 1 h. A solution of 2,3:4,5-di-*O*-isopropylidene-*aldehyde*-D-arabinose [18] (37 g) in benzene (50 ml) was added dropwise with stirring at 20—25 °C and the mixture was stirred for 5 min. Water (250 ml) was added and the organic layer was separated, washed with saturated aqueous sodium chloride, dried, and distilled to afford (1) (27.5 g, 62%), b.p. 99—101/0.35 mmHg, n_D^{23} 1.4540, $[\alpha]_D^{25}$ +3.2° (*c* 2.5, ethanol) {lit.,[6] $[\alpha]_D^{22}$ −2.2° (*c* 2.5, ethanol)}, $\nu_{max.}$ (liquid film) 1 730 cm^{-1} (αβ unsaturated ester) and 1 670 cm^{-1} (conjugated C=C); δ_H 1.20—1.45 (15 H, 4s, Me), 3.60—4.35 (6 H, m, O-CH and O-CH$_2$), 4.45—4.65 (1 H, m, OCHC=C), 6.15 (1 H, dd, *J* 1.6 and 16 Hz, HC=C*H*CO$_2$), 7.05 (1 H, dd, *J* 4.5 and 16 Hz, C*H*=CH-CO$_2$); δ_C 14.2 (ester Me), 25.1, 26.7, and 26.9 (acetal Me), 60.3 (ester CH$_2$), 67.4 (CH$_2$O), 77.0, 78.9, and 81.2 (CH-O), 109 and 110 (acetal C), 121 (C=*C*HCO$_2$), 145 (*C*=CHCO$_2$), and 166 (CO).

Methyl 2,3-*Dideoxy*-4,5:6,7-*di*-O-*isopropylidene*-D-arabino-trans-*hept*-2-*enonate* (2).—This compound was prepared in a similar fashion to (1) but using trimethyl phosphonoacetate; yield 55%, b.p. 95—97 °C/0.2 mmHg, $[\alpha]_D^{19}$ −1.1° (*c* 3.0, ethanol) {lit.,[6] $[\alpha]_D^{24}$ +6.6° (*c* 3.0, ethanol)}, $\nu_{max.}$ (liquid film 1 735 (αβ unsaturated ester) and 1 665 cm^{-1} (conjugated C=C); δ_H 1.35 and 1.41 (3 H and 9 H, 2 s respectively; acetal Me), 3.60—4.20 (6 H, m, OCH and OCH$_2$), 3.73 (3 H, s, OMe), 4.45—4.60 (1 H, m, O-CH-C=C), 6.14 (1 H, dd, *J* 1.5 and

16.4 Hz, CH=C*H*CO_2), and 7.00 (1 H, dd, *J* 4.0 and 16.4 Hz, C*H*=CH-CO_2); δ_C 25.1, 26.7, and 26.9 (acetal Me); 51.6 (O-Me), 67.5 (CH_2O), 76.9, 78.9, and 81.1 (CH-O), 109.8, 110.2 (acetal C), 121 (C=*C*HCO_2), 145 (*C*=CH-CO_2), and 167 (CO).

Hydrolysis of (1).—A mixture of (1) (3.0 g), ethanol (25 ml), and concentrated hydrochloric acid (5 ml) was heated with stirring at 40 °C for 5 h. The mixture was concentrated and the residue was recrystallized twice from ethyl acetate to afford ethyl 2,3-dideoxy-D-*arabino-trans*-hept-2-enonate (3) (1.6 g, 73%), m.p. 137—139 °C (lit.,[8] m.p. 133—135 °C), $[\alpha]_D^{16}$ +12.1° (*c* 2.98, water) {lit.,[8] $[\alpha]_D^{20}$ +14.45° (*c* 2.97, water)}.

Reaction of (1) *with Arylmagnesium Halides.—Ethyl* 2,3-*dideoxy*-4,5:6,7-*di*-O-*isopropylidene*-3C-*phenyl*-D-manno-*heptenonate* (14). Cuprous iodide (237 mg, 5 mol %) was added in one portion to a solution of phenylmagnesium bromide (26.25 mmol) in ether at −10 °C and the mixture was stirred for 5 min. A solution of (1) (7.5 g, 25 mmol) in diethyl ether (25 ml) was added dropwise with stirring the temperature being maintained between −10 and −15 °C. When addition was complete 10% ammonium chloride (50 ml) was added and the mixture was stirred vigorously. The ether layer was separated, washed with saturated aqueous sodium hydrogencarbonate and water, dried, and concentrated. The residue was recrystallized from light petroleum (b.p. 40—60 °C) to afford (14) (8.4 g, 89%), m.p. 56—58 °C (Found: C, 66.7; H, 8.0. $C_{21}H_{32}O_6$ requires C, 66.65; H, 8.0), $[\alpha]_D^{20}$ +26.9° (*c* 1.3, chloroform), $\nu_{max.}$ 1 735 cm^{-1} (ester); δ_H 1.0—1.6 (15 H, m, Me), 2.50—3.15 (2 H, m, CH_2C=O), 3.30—3.60 (1 H, m, C*H*Ph), 3.70—4.20 (7 H, m, OCH and OCH_2), and 7.25 (5 H, s, Ph).

Ethyl 3C-(4-*chlorophenyl*)-2,3-*dideoxy*-4,5:6,7-*di*-O-*isopropylidene*-D-manno-*heptonate* (15).—This compound was prepared similarly using 4-chlorophenylmagnesium iodide; yield (10.0 g, 94%), m.p. 77—79 °C (light petroleum) (Found: C, 61.25; H, 7.25. $C_{21}H_{31}ClO_6$ requires C, 61.1; H, 7.1), $[\alpha]_D^{22}$ +25.9° (*c* 1.3, chloroform), $\nu_{max.}$ 1 730 cm^{-1} (ester); δ_H 1.0—1.5 (15 H, m, Me), 2.50—3.10 (2 H, m, CH_2CO), 3.35—3.60 (1 H, CH-aryl), 3.65—4.30 (7 H, m, OCH), and 7.25 (4 H, s, aryl).

Ethyl 2,3-*Dideoxy*-4,5:6,7-*di*-O-*isopropylidene*-3C-(p-*tolyl*)-D-manno-*heptonate* (16).—This compound was similarly prepared using 4-methylphenylmagnesium iodide with the modification that stirring was continued for 1 h at −10 °C after the addition of (1) was completed before 10% aqueous ammonium chloride was added to afford (16) (4.9 g, 50%), m.p. 63—65 °C (Found: C, 67.55; H, 8.15. $C_{22}H_{34}O_6$ requires C, 67.3; H, 8.2), $[\alpha]_D^{20}$ +26.1° (*c* 0.75, chloroform), $\nu_{max.}$ 1 735 cm^{-1} (ester); δ_H 1.0—1.6 (15 H, m, Me), 2.30 (3 H, s, Me-aryl), 2.50—3.10 (2 H, m, CH_2C=O), 3.30—3.60 (1 H, m, CH-aryl), 3.65—4.25 (7 H, m, O-CH and OCH_2), and 7.05 (4 H, s, aryl).

2-Chlorophenylmagnesium bromide and 2-methylphenylmagnesium bromide did not react with (1).

Variation of Yield of (15) *with Copper Salt.—Cuprous salts.* Cuprous chloride (25 mg, 5 mol %) was added to aqueous 4-chlorophenylmagnesium iodide (5 mmol) at −10 °C. A solution of (1) (1.5 g, 5 mmol) in ether (5 ml) was added dropwise with stirring whilst the temperature was held between −10 and −15 °C. When the addition was complete 10% aqueous ammonium chloride (10 ml) was added and the ether layer separated, washed with sodium hydrogencarbonate, dried, and concentrated. The residue was purified by column chromatography over silica-gel with dichloromethane–ether (19 : 1) as eluant to afford (15) (1.25 g, 61%). Similarly cuprous bromide (5 mol %) afforded (15) (1.79 g, 87%), cuprous iodide (5 mol %) afforded (15) (1.88 g, 91%) and cuprous cyanide (5 mol %) afforded (15) (1.10 g, 53%).

Cupric acetate monohydrate. 4-Chlorophenylmagnesium iodide (20 mmol) was added to a solution of cupric acetate monohydrate (50 mg, 5 mol %) and (1) (1.5 g, 5 mmol) in tetrahydrofuran (25 ml) at −10 °C. When addition was complete 10% aqueous ammonium chloride (50 ml) was added. The organic layer was separated and the aqueous layer was extracted with ether. The combined extracts were washed with sodium hydrogencarbonate, dried, and concentrated. The residue was purified by column chromatography over silica gel, with dichloromethane–ether (19 : 1) as eluant to afford (15) (0.76 g, 37%).

Reaction of (1) *with Alkyl- and Cycloalkyl-magnesium Bromides.—Cyclohexylmagnesium bromide.* Cyclohexylmagnesium bromide (30 mmol, 20% excess) was added dropwise to a stirred suspension of cuprous iodide (0.475 g, 5 mol %) in a solution of (1) (7.5 g) in ether (25 ml), whilst the internal temperature was maintained below —70 °C. When the addition was complete the mixture was stirred at −70 °C for 5 h. Ammonium chloride (25 ml, 10%) was added and the mixture stirred vigorously. The ether layer was separated, washed with sodium hydrogencarbonate, dried and concentrated. The residue was separated by column chromatography over silica gel, with light petroleum–acetone (19 : 1) as eluant to afford a mixture of *ethyl* 3C-*cyclohexyl*-2,3-*dideoxy*-4,5:6,7-*di*-O-*isopropylidene*-D-manno-*heptonate* (17) *and ethyl* 3C-*cyclohexyl*-2,3-*dideoxy*-4,5:6,7-*di*-O-*isopropylidene*-D-gluco-*heptonate* (18) [2.32 g, 24%, 36% based on (1) consumed], b.p. 200 °C/1.0 mmHg (bulb-to-bulb) (Found: C, 65.4; H, 9.4. $C_{21}H_{36}O_6$ requires C, 65.6; H, 9.45), $[\alpha]_D^{20}$ +15.9° (*c* 2.0, chloroform), n_D^{20} 1.4657, $\nu_{max.}$ (liquid film) 1 745 cm^{-1} (CO); δ_H 0.8—2.5 (29 H, m, Me, cyclohexyl ring protons, CH_2CO, and C*H*-cyclohexyl) and 3.50—4.30 (7 H, m, CH-O); compound (1) (2.5 g) was recovered. Ethyl 3*C*-cyclohexyl-2,3-dideoxy-4,5:6,7-di-*O*-isopropylidene-D-*manno*-heptonate was prepared as a single isomer when (14) (1.6 g) was hydrogenated at room temperature and 1 atm for 4 days over 5% rhodium-on-carbon (0.4 g) and ethanol (10 ml). The mixture was filtered through Celite, concentrated, and the residue separated over silica in light petroleum–acetone (19 : 1) to afford (17) [635 mg, 39% (89% based on (14) consumed)] and unchanged (14) (0.91 g). The i.r. and ^1H n.m.r. spectra of (17) were indistinguishable from those of the mixture of (17) and (18) described above; ^{13}C spectra (Table 2) showed the product to be a single isomer.

Isopropylmagnesium bromide. With isopropylmagnesium bromide in 10% excess was prepared *ethyl* 2,3-*dideoxy*-3C-*isopropyl*-4,5:6,7-*di*-O-*isopropylidene*-D-gluco-*heptonate* (19) (6.0 g, 70%), b.p. 110—112/0.08 mmHg, n_D^{22} 1.4465 (Found: C, 62.75; H, 9.6. $C_{18}H_{32}O_6$ requires C, 62.75; H, 9.4), $[\alpha]_D^{21}$ +25.2° (*c* 0.8, chloroform), $\nu_{max.}$ (liquid film) 1 745 cm^{-1} (CO); δ 0.87 and 0.89 (6 H, 2 d, *J* 6.8, CH_3CHCH_3), 1.15—1.50 (15 H, m, Me), 1.80—2.50 (4 H, m, CH_2CO, MeC*H*Me, C*H*Pr^i), and 3.70—4.30 (7 H, m, CH-O and CH_2O).

Ethyl magnesium bromide. With ethylmagnesium bromide was prepared *ethyl* 2,3-*dideoxy*-3C-*ethyl*-4,5:6,7-*di*-O-*isopropylidene*-D-gluco-*heptonate* (20) [0.63 g, 13% (based on (1) consumed)], $[\alpha]_D^{22}$ +17.8 (*c* 0.9, chloroform) $\nu_{max.}$ (liquid film) 1 740 cm^{-1} (ester); δ_H 0.94 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.20—1.60 (17 H, m, acetal Me, ester Me and CH_2Me); 2.10—2.50 (3 H, m, CH_2CO and C*H*Et), 3.60—4.30 (7 H, m, OCH and OCH_2) together with unchanged (1) (3.15 g).

t-Butylmagnesium chloride. With t-butylmagnesium chloride

was prepared at −35 to −40 °C *ethyl* 3C-*t-butyl*-2,3-*dideoxy*-4,5:6,7-*di*-O-*isopropylidene*-D-manno-*heptonate* (21) [3.3 g, 37% (66% based on (1) consumed)], m.p. 54—56 °C (light petroleum) (Found: C, 63.9; H, 9.9. $C_{19}H_{34}O_6$ requires C, 63.65; H, 9.55) $[\alpha]_D^{19}$ +5.1° (*c* 1.3, chloroform), $\nu_{max.}$ 1 745 cm^{-1} (CO); δ_H 0.90 (9 H, s, Bu^t), 1.10—1.60 (15 H, m, Me), 2.20—2.50 (3 H, m, CH_2CO and $CHBu^t$), 3.45—3.70 (1 H, m, CHO), and 3.80—4.30 (6 H, m, CHO); compound (1) (3.3 g) was recovered.

Removal of Isopropylidene Groups and Acetylation of Products.—2,3-*Dideoxy*-3C-*phenyl*-D-manno-*heptono*-1,4-*lactone* (22). A solution of (14) (8.4 g) in ethanol (80 ml) and 2M-hydrochloric acid (40 ml) was heated with stirring at 40 °C for 5 h. The mixture was concentrated and water was removed by azeotropic distillation with toluene. The residue was purified by column chromatography over silica gel with chloroform–ethanol (9 : 1) as eluant to afford (22) (4.3 g, 77%), m.p. 104—106 °C (ethyl acetate) (Found: C, 61.65; H, 6.3. $C_{13}H_{16}O_5$ requires C, 61.9; H, 6.4), $[\alpha]_D^{21}$ −43.1° (*c* 0.6, ethanol), $\nu_{max.}$ 1 790 cm^{-1} (ester); δ_H (CD_3OD) 2.90 (2 H, dd, *J* 6 and 8 Hz, CH_2CO), 3.20 (1 H, s, OH), 3.50—4.30 (5 H, m, $CHPh$ and CH−O), 4.60 (2 H, m, OH), 4.90 (1 H, d, *J* 6.5 Hz, lactonic H), and 7.3 (5 H, s, Ph).

A solution of (22) (100 mg), pyridine (1 ml), and acetic anhydride (1 ml) were stored overnight. The mixture was diluted with toluene (25 ml) and concentrated. The residue was purified by column chromatography over silica gel with light petroleum–acetone as eluant to afford 5,6,7-*tri*-O-*acetyl*-2,3-*dideoxy*-3C-*phenyl*-D-manno-*heptono*-1,4-*lactone* (10) (85 mg) as a colourless oil, $\nu_{max.}$ 1 790 (lactone) and 1 745 cm^{-1} (acetyl).

Similarly (15) afforded 3C-(4-*chlorophenyl*)-2,3-*dideoxy*-D-manno-*heptono*-1,4-*lactone* (25) (72%), m.p. 132—133 °C (chloroform) (Found: C, 54.25; H, 5.25. $C_{13}H_{15}ClO_5$ requires C, 54.45; H, 5.30), $[\alpha]_D^{20}$ −51.1° (*c* 0.5, acetone), $\nu_{max.}$ 1 760 (lactone); δ_H (CD_3OD) 2.60—3.20 (2 H, m, CH_2CO), 3.40—4.20 (7 H, m, CH−O, C*H*-aryl and OH), 4.50 (1 H, d, *J* 7 Hz, OH), 4.85 (1 H, d, *J* 8 Hz, lactonic proton), and 7.50 (4 H, s, aryi); and the triacetate (11), $\nu_{max.}$ 1 790 (lactone) and 1 750 cm^{-1} (acetyl).

Similarly (11) afforded 2,3-*dideoxy*-3C-(4-*methylphenyl*)-D-manno-*heptono*-1,4-*lactone* (26) (90%), m.p. 96—98 °C (ethyl acetate) (Found: C, 63.0; H, 7.1. $C_{14}H_{18}O_5$ requires C, 63.15; H, 6.8), $[\alpha]_D^{20}$ −41.7° (*c* 1.1, ethanol), $\nu_{max.}$ 1 770 cm^{-1} (lactone); δ_H (CD_3OD) 2.30 (3 H, s, aryl Me), 2.50—3.10 (2 H, m, CH_2-CO), 3.40—4.00 (7 H, m, PhCH, CH−O and OH), 4.40 (1 H, d, *J* 6 Hz, OH), 4.82 (1 H, d, *J* 7 Hz, lactonic proton), and 7.10 (4 H, d, *J* 4 Hz, aryl).

Similarly a mixture of (17) and (18) (448 mg) afforded a mixture of 3C-*cyclohexyl*-2,3-*dideoxy*-D-manno-*heptono*-1,4-*lactone* (23) *and* 3C-*cyclohexyl*-2,3-*dideoxy*-D-gluco-*heptono*-1,4-*lactone* (24) (278 mg, 85%) separated by column chromatography over silica gel with chloroform–ethanol (19 : 1) as eluant to afford (23) (125 mg), m.p. 124—125 °C (chloroform), $[\alpha]_D^{25}$ −40.0° (*c* 0.6, ethanol), $\nu_{max.}$ 1 785 cm^{-1} (lactone); δ_H (CD_3OD) 0.75—2.0 (12 H, m, cyclohexyl protons and C*H*-cyclohexyl), 2.20—2.80 (2 H, m, CH_2CO), 3.30—4.00 (3 H, m, CH−O), 4.60—5.10 and 5.30 (3 H, br m, OH), and 4.85 (1 H, d, *J* 5.0 Hz, lactonic H); and the *triacetate* (9), $\nu_{max.}$ 1 800 cm^{-1} (lactone) and 1 760 cm^{-1} (acetyl) and (24) (153 mg), m.p. 165—166 °C (ethyl acetate) (Found: C, 60.75; H, 8.8. $C_{13}H_{22}O_5$ requires C, 60.45; H, 8.6), $[\alpha]_D^{25}$ −31.1° (*c* 2.9, ethanol), $\nu_{max.}$ 1 760 cm^{-1} (lactone); δ_H (CD_3OD) 0.80—2.0 (12 H, m, cyclohexyl and C*H*-cyclohexyl), 2.10—2.60 (2 H, m, CH_2CO), 3.50—3.90 (3 H, m, CH−O), 4.60—5.20 (3 H, m, OH), 4.95 (1 H, d, *J* 6.5 Hz, lactonic H); and the triacetate (7), $\nu_{max.}$ 1 790 (lactone) and 1 750 cm^{-1} (acetyl).

Pure (17) (300 mg) formed by hydrogenation of (14) afforded (23) (180 mg, 89%), m.p. and mixed m.p. 125—126 °C (chloroform).

Similarly (19) (2.4 g) afforded 2,3-*dideoxy*-3C-*isopropyl*-D-gluco-*heptono*-1,4-*lactone* (27) (1.52 g, 78%), m.p. 97—98 °C (cyclohexane–ethyl acetate) (Found: C, 54.85; H, 8.5. $C_{10}H_{18}O_5$ requires C, 55.05; H, 8.3), $[\alpha]_D^{20}$ −32.5° (*c* 1.3, ethanol), $\nu_{max.}$ 1 760 cm^{-1} (lactone); δ_H (CD_3OD) 0.96 and 1.02 (6 H, 2 d, *J* 2 Hz, CH_3CHCH_3), 1.70—2.10 (1 H, m, CH_3CHCH_3, 2.10—2.65 (3 H, m, CH_2CO and $CHPr^i$), 3.20—3.90 (6 H, m, CH−O and OH), 4.80 (1 H, s, OH), and 4.91 (1 H, d, *J* 7 Hz lactonic proton); and *triacetate* (8), $\nu_{max.}$ 1 790 (lactone) and 1 755 cm^{-1} (acetyl).

Similarly (20) (200 mg) afforded 2,3-*dideoxy*-3C-*ethyl*-D-gluco-*heptono*-1,4-*lactone* (29) (90 mg, 73%) as a colourless oil, $\nu_{max.}$ 1 760 cm^{-1} (lactone); δ_H (CD_3OD) 0.97 (3 H, t, *J* 7 Hz, CH_2Me), 1.61 (2 H, q, *J* 7 Hz, CH_2Me), 2.20—2.90 (3 H, m, CH_2CO and $CHEt$), 3.20—4.20 (5 H, m, CH−O, CH_2O, and OH), *ca.* 4.75 (2 H, s, OH obscured), and 4.94 (1 H, d, *J* 6.5, lactonic proton); and the *triacetate* (12), $\nu_{max.}$ 1 790 (lactone) and 1 750 cm^{-1} (acetyl).

Similarly (21) (6.6 g) afforded 3C-*t-butyl*-2,3-*dideoxy*-D-manno-*heptono*-1,4-*lactone* (30) (3.9 g, 91%), m.p. 150—152 °C (ethanol) (Found: C, 56.7, H, 8.6. $C_{11}H_{20}O_5$ requires C, 56.9; H, 8.7), $[\alpha]_D^{20}$ −30° (*c* 1.7, ethanol), $\nu_{max.}$ 1 740 cm^{-1} (lactone); δ_H (CD_3OD) 0.90 (9 H, s, Bu^t), 2.20—2.90 (3 H, m, CH_2CO and $CHBu^t$), 3.20—390 (4 H, m, CH−O and CH_2O), 4.85 (1 H, d, *J* 4 Hz, lactonic H); and the triacetate (13), $\nu_{max.}$ 1 790 (lactone) and 1 750 cm^{-1} (acetyl).

Removal of Carbohydrate Side-chain.—(+)-(S)-2-*Phenylbutane*-1,4-*dioic acid* (32). Compound (22) (2.52 g, 10 mmol) was dissolved in 1M-sodium hydroxide (25 ml) and 0.5M aqueous potassium dihydrogen phosphate (50 ml) was added to bring the pH to 6.5. A solution of sodium metaperiodate (6.4 g) in water (75 ml) was added dropwise, with stirring and cooling (ice-bath), over a period of 0.5 h. The mixture was stirred at 0 °C for 1 h, acidified to pH 2, and extracted with chloroform (3 × 25 ml). The extract was concentrated to afford 4-hydroxy-3-phenylbutyro-1,4-lactone (31) (1.4 g, 80%), m.p. 90—92 °C (ether–light petroleum), $[\alpha]_D^{20}$ +137° (*c* 0.5, chloroform), $\nu_{max.}$ 1 745 cm^{-1} (lactone) δ_H 2.90 (2 H, d, *J* 7 Hz, CH_2CO), 3.80 (1 H, td, *J* 2 and 7 Hz, $CHPh$), 6.2 (1 H, br s, OH), and 7.2 (5 H, s, Ph). An aliquot (0.7 ml) of a solution of chromium trioxide (2.67 g) in aqueous sulphuric acid (2.3 ml concentrated made up to 10 ml with water) was added dropwise with stirring and cooling (ice-bath) to (31) (0.5 g) in acetone (5 ml). The mixture was filtered, the filtrate concentrated, and the residue recrystallized from water to afford (32) (495 mg, 90%), m.p. 175.5—176.0 °C (lit.,[19] m.p. 173—174 °C), $[\alpha]_D^{22}$ +165.1° (*c* 0.7, acetone) [lit.,[19] $[\alpha]_D^{15.4}$ +171° (*c* 2.0, acetone)].

(+)-(S)-2-(p-*Tolyl*)*butane*-1,4-*dioic Acid* (35).—This compound was similarly prepared from (26) (2.6 g) *via* 4-hydroxy-3-(*p*-tolyl)butyro-1,4-lactone (1.3 g, 69%), m.p. 118—122 °C a portion of which (500 mg) gave (35) (300 mg, 55%), m.p. 204—206 °C (water) [lit.,[20] m.p. 210 °C (racemate)], $[\alpha]_D^{21}$ +160° (*c* 1.4, acetone).

(−)-(R)-2-*Isopropylbutane*-1,4-*dioic acid* (36). This was similarly prepared from (27) (4.0 g) *via* 4-hydroxy-3-(4-isopropyl)butyro-1,4-lactone (1.6 g, 61%), b.p. 105—110 °C/0.1 mmHg (bulb-to-bulb), n^{D}_{18} 1.4568, $[\alpha]_D^{20}$ +17.7° (*c* 0.5, chloroform), +18.0° (*c* 1.2, chloroform), $\nu_{max.}$ 1 760 cm^{-1} (lactone); δ_H 0.95 (6 H, dd, *J* 6 and 7 Hz, CH_3CHCH_3), 1.50—3.00 (4 H, m, CH_2CO, $MeCHMe$ and Pr^iCH), 5.30 (1 H, br s, OH), 5.63 (d, *J* 3.5 Hz), and 5.82 (d, *J* 4.5 Hz) (1 H, ratio 5 : 2, lactonic proton). A portion of the latter (550 mg) afforded (36)

(400 mg, 65%), m.p. 86.5—87.5° (benzene) (lit.,[12] 88—89 °C), $[\alpha]_D^{20}$ −18.8° (*c* 1, water), {lit.,[12] $[\alpha]_D^{25}$ −22.8° (water)].

(+)-(S)-2-*t*-*Butylbutane*-1,4-*dioic acid* (37). This compound was similarly prepared from (30) (1.8 g) *via* 3-t-butyl-4-hydroxybutyro-1,4-lactone (0.98 g, 80%) an unstable yellow oil converted directly into (37) (100 mg), m.p. 127.5—128.5 °C [lit.,[21] m.p. 128 °C (racemate)], $[\alpha]_D^{21}$ +24° (*c* 0.3, acetone).

(+)-(*S*)-2-(4-*Chlorophenyl*)*butane*-1,4-*dioic acid* (34). This compound was prepared similarly from (25) (2.86 g) *via* 3-(4-chlorophenyl)-4-hydroxybutyro-1,4-lactone (1.3 g, 61%), m.p. 62.5—65.0° C (ether–light petroleum), $[\alpha]_D^{19}$ +90° (*c* 0.6, chloroform), $\nu_{max.}$ 1 790 cm^{-1} (acid); δ_H 2.40—3.30 (2 H, m, CH_2CO), 3.60—3.90 (1 H, m, C*H*-Ph), 5.77 (d, *J* 4 Hz), and 6.00 (d, *J* 5 Hz) (1 H, ratio 4 : 1, lactonic proton), 6.80 (1 H, br s, OH), and 7.15 (4 H, q, *J* 7 Hz, aryl). Bromine (0.37 ml) was added to a solution of 3-(4-chlorophenyl)-4-hydroxybutyro-1,4-lactone (1.3 g) in water (50 ml). The mixture was stirred until colourless after which the product was filtered off and recrystallized from water to afford (34) (800 mg, 57%), m.p. 182—185 °C [lit.,[22] m.p. 207.8 °C (racemate)], $[\alpha]_D^{20}$ +154° (*c* 0.5, acetone).

(+)-(S)-2-(4-*Bromophenyl*)*butane*-1,4-*dioic acid* (33). Similarly, compound (31) (800 mg), treated with bromine (0.23 ml) in water (50 ml) afforded (33) (450 mg, 28%), m.p. 198—199 °C (from water) [lit.,[22] m.p. 210—211 °C (racemate)], $[\alpha]_D^{20}$ +114° (*c* 0.7, ethanol).

Dimethyl (+)-(S)-2-(4-*Chlorophenyl*)*butane*-1,4-*dioate* (4).—Compound (12) (800 mg) in diethyl ether (5 ml) was treated with ethereal diazomethane until a yellow colour persisted. The mixture was concentrated and purified by column chromatography over silica gel with chloroform as eluant to afford compound (4) (700 mg, 78%), $[\alpha]_D^{21}$ +116° (*c* 1.5, chloroform), $\nu_{max.}$ 1 750 cm^{-1} (ester); δ_H 2.50—3.30 (2 H, m, CH_2CO), 3.64 (6 H, s, OMe), 4.08 (1 H, dd, *J* 6 and 10 Hz, C*H*-aryl), and 7.26 (4 H, s, aryl). Similarly prepared were (5) (72%), $\nu_{max.}$ 1 740 cm^{-1} (ester); δ_H 0.90 and 0.97 (6 H, 2 s, CH_3-$CHCH_3$), 1.80—1.95 (1 H, m, CH_3CHCH_3), 2.10—2.90, (3 H, m, $CO-CH_2-CH$), and 3.64 and 3.67 (6 H, 2 s, OMe); and compound (6) (65%), $\nu_{max.}$ 1 745 cm^{-1} (ester); δ_H 0.95 (9 H, s, Bu^t), 2.35—2.95 (3 H, m, $COCH_2-CH$), and 3.64 and 3.68 (6 H, 2 s, OMe). The n.m.r. spectra of (4)—(6) were recorded in the presence of the optically active shift reagent [Eu(hfc)$_3$].

(+)-(S)-3-*Phenylbutyro*-1,4-*lactone* (38).—Sodium borohydride (50 mg) was added portionwise to a cooled, stirred solution of (31) (0.45 g) in methanol (5 ml). The mixture was stirred for 0.5 h at 0 °C, acidified, and concentrated. The residue was diluted with water and extracted with chloroform (2 × 25 ml). The extract was washed with sodium hydrogen carbonate, dried, and concentrated to afford (38) (0.38 g, 92%), m.p. 60—62 °C (ether–light petroleum) [lit.,[11] m.p. 61—61.5 °C], $[\alpha]_D^{20}$ +50.4° (*c* 0.5, methanol), +52.0 (*c* 0.4, chloroform) [lit.,[11] $[\alpha]_D^{20}$ +50.4° (*c* 5.0 methanol)].

(+)-(S)-3-(4-*Chlorophenyl*)*butyro*-1,4-*lactone* (39). Similarly, 3-(4-chlorophenyl)-4-hydroxybutyro-1,4-lactone (1.7 g), afforded (39) (1.3 g, 83%), m.p. 71—72 °C (ether–light petroleum) [lit.,[23] m.p. 53.5 °C (racemate)], $[\alpha]_D^{20}$ +46.5 (*c* 0.5, chloroform), $\nu_{max.}$ 1 780 cm^{-1} (lactone); δ_H 2.50—3.10 (2 H, m, CH_2CO), 3.80 (1 H, q, *J* 8.7 Hz, C*H*-aryl), 4.15—4.80 (2 H, m, lactonic protons), and 7.27 (4 H, q, aryl).

(+)-(S)-3-(4-*Methylphenyl*)*butyro*-1,4-*lactone* (40). Similarly, 3-(*p*-tolyl)-4-hydroxybutyro-1,4-lactone (500 mg) afforded (40) (400 mg, 87%), m.p. 63.5—65.0 °C [lit., [24] m.p. 45—46 °C (racemate)], $[\alpha]_D^{21}$ +50° (*c* 1.25, chloroform), $\nu_{max.}$ 1 750 cm^{-1} (lactone); δ_H 2.32 (3 H, s, Me), 2.50—3.00 (2 H, m, CH_2CO), 3.76 (1 H, q, *J* 9 Hz, C*H*-aryl), 4.05—4.70 (2 H, m, lactonic protons), and 7.11 (4 H, s, aryl).

(+)-(S)-3-*Isopropylbutyro*-1,4-*lactone* (41). Similarly, (+)-4-hydroxy-3-isopropylbutyro-1,4-lactone (600 mg) afforded (41) (350 mg, 72%), b.p. 70/0.1 mmHg (bulb-to-bulb), n_D^{19} 1.4413, $[\alpha]_D^{20}$ +11.5° (*c* 0.7, carbon tetrachloride [lit.,[13] $[\alpha]_D^{23}$ −12.4° (carbon tetrachloride) for *R* isomer].

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