The Total Synthesis of (−)-Litsenolides C-1 and C-2

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The total synthesis of (−)-litsenolides C_1 and C_2 from D-glucose in 12% overall yield is described in which the α-alkylidene double-bond is formed by a Wittig reaction of a C-2 oxocarbohydrate derivative.

The α-alkylidene-γ-butyrolactone function is found in many different natural products and is responsible for a number of different biological activities.[1] These compounds react *in vivo* by way of a Michael reaction with biological nucleophiles such as L-cysteine or thiol containing enzymes.[2] It would appear that the compounds inhibit metabolism within cells, but do not alkylate DNA.[3]

The presence of an α-alkylidene-γ-butyrolactone function in a compound normally leads to that compound causing allergic contact dermatitis (ACD).[4] The widespread occurrence of ACD due to contact with industrial or naturally occurring compounds is a growing problem. Many different industries are affected by the problem including agriculture, printing, lumber, and perfumery.

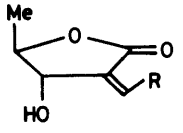
In addition to causing ACD, the α-alkylidene-γ-butyrolactone function can have useful activities. Several compounds with the functional group show tumour-inhibiting activity, while other compounds show phytotoxic and antimicrobial activities.[5]

Although many of the naturally occurring α-alkylidene-γ-butyrolactones are found in complex sesquiterpenes, there are a number of natural products in which the α-alkylidene-γ-butyrolactone is the principal functional group. The litsenolides, a group of three pairs of geometrical isomers [(**1**) and (**2**), Scheme 1], were isolated from *Litsea japonica*,[6] which grows by the shores of the southern part of Japan. A second group of structurally related compounds have been isolated from the trunk wood of the 'Mahuba' tree (*Clinsostemon mahuba*) which grows in the estuary of the river Amazon.[7] These are the mahuba lactones (**3**)—(**6**).

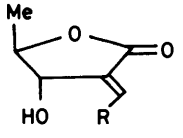
There have been a number of syntheses of compounds in this series, leading both to the natural products themselves and to the corresponding racemic modifications. Two strategies have been invoked to prepare the compounds: the butyrolactone ring is either present at the beginning of the synthesis and the necessary functional group interconversions are applied to convert this into the target,[8] or, alternatively, the necessary functionality is introduced to an open chain intermediate which is cyclized at a late stage in the synthesis.[9]

Of the approaches reported in the former class, Joullie and Chen prepared (−)-litsenolides C_1 (**1c**) and C_2 (**2c**) from D-ribonolactone,[8a] while Wollenberg prepared (±)-litsenolide C_1 (**1c**) from α-bromo-γ-valerolactone.[8b] More syntheses have been achieved using the latter of the two strategies, including one of (−)-dihydromahubanolide B (**3c**) and (−)-isodihydromahubanolide B (**4c**) using L-tartaric acid as a starting material.[9a].

We sought a general route by which to prepare all these compounds in their optically active forms, using 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (**7**) as a starting material. The strategy adopted involved the use of simple functional group manipulations to prepare the C-3 hydroxy and C-4 methyl groups in their correct stereochemistries, leading to an intermediate of type (**8**). This would then be converted into the ketone (**9**). The crucial steps in the synthesis would then be the formation of the α-alkylidene subunit, by a Wittig reaction, and the de-protection and oxidation of C-1. The appeal of this strategy lay in the fact that the ketone (**9**) could be used as an advanced precursor for all the litsenolides by changing

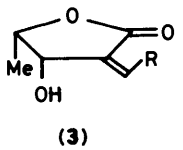


(**1**)

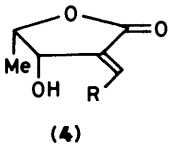


(**2**)

a; R = $(CH_2)_9CH{=}CH_2$
b; R = $(CH_2)_9C{\equiv}CH$
c; R = $(CH_2)_{11}CH_2Me$

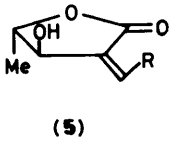


(**3**)

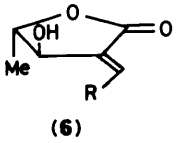


(**4**)

a; R = $(CH_2)_{13}CH{=}CH_2$
b; R = $(CH_2)_{13}C{\equiv}CH$
c; R = $(CH_2)_{13}CH_2Me$



(**5**)

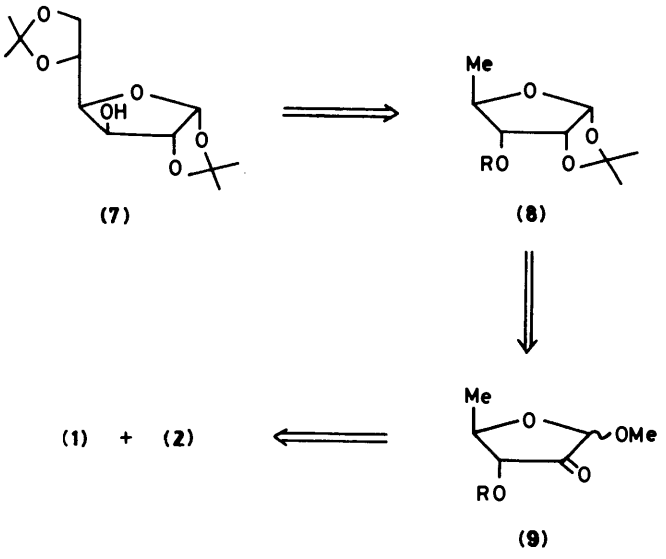


(**6**)

a; R = $(CH_2)_{13}CH{=}CH_2$
b; R = $(CH_2)_{13}C{\equiv}CH$
c; R = $(CH_2)_{13}CH_2Me$

Scheme 1.

the Wittig reagent. Literature precedence suggested that deprotection at C-1 might prove difficult, but the successful synthesis of (−)-litsenolides C_1 (**1c**) and C_2 (**2c**) described in full herein demonstrates the success of the strategy.[10]



Scheme 2.

Results and Discussion

The first stage in the synthesis (Scheme 3) required the inversion of stereochemistry at the 3-hydroxy group of (**7**). The procedure reported by Sowa and Thomas[11]—oxidation with DMSO–acetic anhydride followed by sodium borohydride reduction—gave the crystalline allose derivative (**10**) in 60% yield, but chromatography was required to purify the product. A much cleaner preparation was achieved using catalytic ruthenium tetraoxide oxidation[12] and subsequent reduction. This gave compound (**10**) in the same yield as before, but without recourse to chromatography.

In the early work on this synthesis, the methoxyethoxymethyl (MEM)[13] group was used to protect the 3-hydroxy group. Thus, compound (**11a**) was prepared by treating the allose derivative (**10**) with MEMCl and sodium hydride in THF. The next stage in the synthesis required the reduction of the 5,6-diol moiety to give a methyl group. Selective hydrolysis of the 5,6-isopropylidene (0.8% H_2SO_4) led to compound (**12a**),[14] which was oxidatively cleaved and reduced in a one-pot procedure ($NaIO_4$, MeOH; $NaBH_4$) to give compound (**13a**), in 93% yield from (**10**).

Initial attempts to tosylate the ribofuranose derivative (**13a**) in pyridine led only to the corresponding 5-chloro derivative,[15] but mesylation, however, was easily achieved (CH_3SO_2Cl, pyr.). The resulting mesylate was reduced with lithium aluminium hydride to give compound (**14a**) in 88% yield from (**13a**). Hydrolysis of the 1,2-isopropylidene group proved more difficult, since, although the ribofuranoside (**15a**) could be isolated in good yield (*ca.* 65%), it was always contaminated with another compound.

This compound was separated by flash chromatography and examined by ^1H and ^{13}C n.m.r. spectroscopy. It was immediately clear from the simplicity of the ^1H n.m.r. spectrum, and in particular from the absence of peaks due to the MEM-ethyl group, that the MEM protection had been removed. Resonances at 1.50 and 1.31 p.p.m. in the ^1H spectrum and 25.2 and 26.7 p.p.m. in the ^{13}C spectrum indicated the presence of an isopropylidene group, while a methyl singlet at 3.33 p.p.m. with a corresponding carbon resonance at 54.2 showed the presence of an anomeric methoxyl group. This evidence suggested structure (**16**) for the compound, with the assigned stereochemistry at C-1. This latter point was indicated by the lack of coupling between 1-H and 2-H (*cf.* other compounds in this series with α-anomeric substituents where $J_{1,2}$ *ca.* 3.5 Hz).

Compound (**16**) is presumably formed by migration of the 1,2-isopropylidene group. The fact that no other compounds could be detected in the reaction mixture, and in particular that no products arising from a straightforward removal of the MEM group, suggests that the migration either takes part in the displacement of the MEM, or occurs immediately the MEM is hydrolysed.

At this stage in the synthesis it became apparent that the MEM group was a considerable liability and would have to be replaced. This was even more apparent when the Wittig reaction was attempted to introduce the necessary side-chains for the target molecules. Although the necessary ketone (**17a**) could be prepared by DMSO–acetic anhydride oxidation, the Wittig reaction of the ketone gave very low yields of olefins.

It was clear from the results described above that a less acid sensitive protecting group was required. However the group would have to be removed in the presence of the α,β-unsaturated lactone moiety of the final products. This restriction excluded the simple benzyl group, but the discovery of the *p*-methoxybenzyl group by Yonemitsu,[16] which can be removed oxidatively by dichlorodicyanobenzoquinone (DDQ), seemed to provide the necessary solution.

Thus the *p*-methoxybenzyl ether (**11b**) was prepared (*p*-$MeOC_6H_4CH_2Cl$, NaH, THF) from the allose derivative (**10**) and converted into compound (**14b**) in 82% overall yield. Methanolysis of (**14b**) proceeded smoothly to give (**15b**) as a 10:1 (β:α) mixture of anomers. This was oxidized with DMSO–acetic anhydride to give first the hydrate of (**17b**) and then the ketone itself [94% from (**14b**)] after dehydration (3 Å molecular sieves, CH_2Cl_2) and the first chromatography of this part of the synthesis.

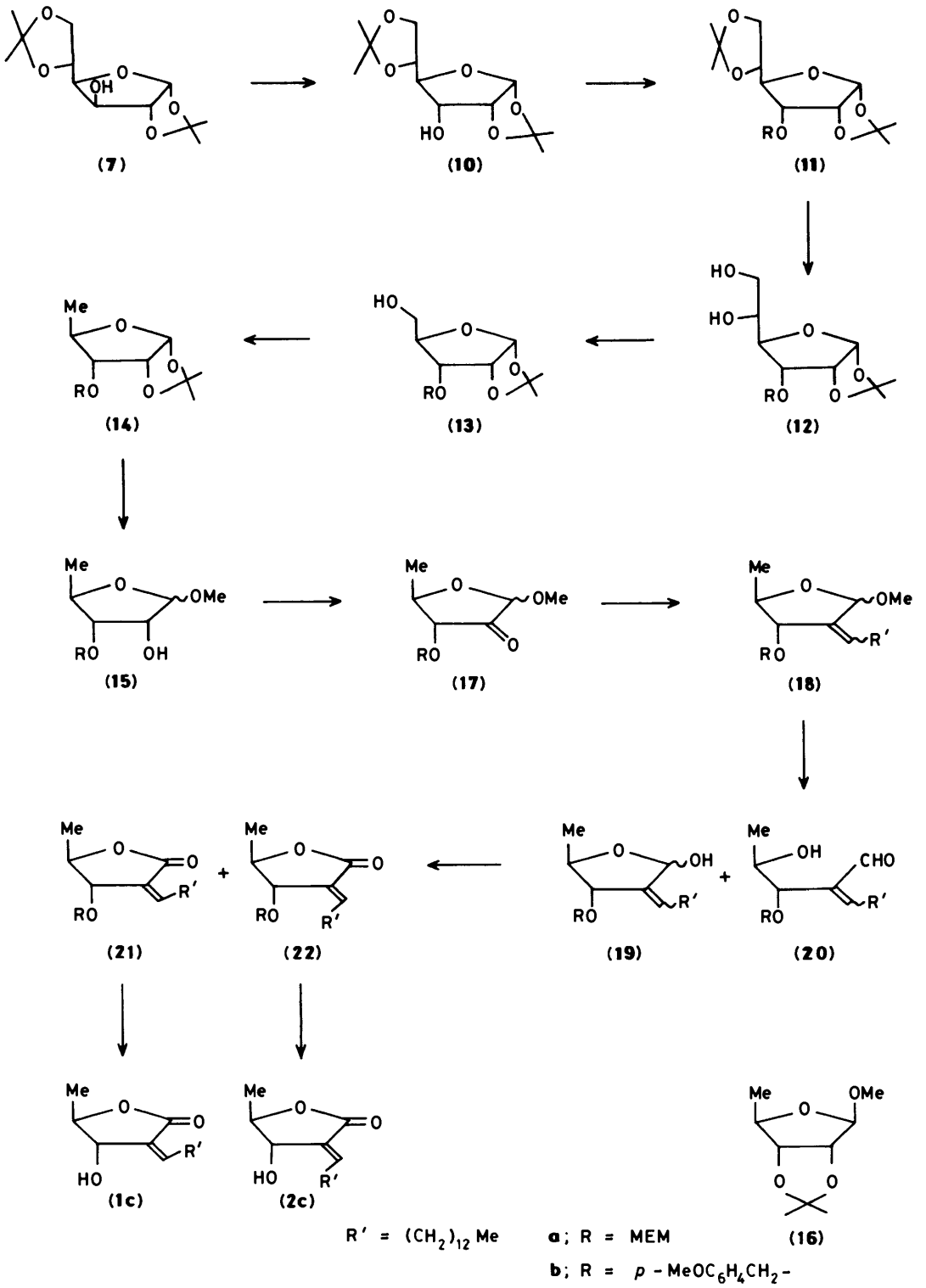
Having produced an efficient synthesis of a suitable ketone precursor, we were able to address the crucial Wittig reaction. Treatment of (**17b**) with tetradecyltriphenylphosphonium bromide (BuLi, THF, −78 °C) gave the mixture of geometric isomers (**18b**) in 69% yield. In spite of literature precedence which suggested that hydrolysis of the anomeric protection of (**18b**) could result in low yields and the formation of furans,[17] a 1:1 mixture of (**19b**) and (**20b**) was obtained (THF–H_2O, HCl) in quantitative yield. Oxidation of these compounds with Fetizon's reagent (Ag_2CO_3–Celite, PhH) gave a 3:1 mixture of compounds (**21b**) and (**22b**) in 92% yield.[18]

Although it was possible to deprotect the mixture of (**21b**) and (**22b**) prior to removal of the *p*-methoxybenzyl group, it proved more convenient to separate the geometric isomers at this stage and to carry out the deprotection reactions separately. Deprotection then gave litsenolides C_1 (**1c**) and C_2 (**2c**), which had identical physical and spectroscopic properties to those reported for the naturally occurring compounds. The overall yield of this sequence [starting from (**7**)] was 12%.

The successful synthesis of these two litsenolides demonstrates the power of the approach to the synthesis of this class of compound. Work is currently in hand to prepare suitable Wittig reagents for the synthesis of the other litsenolides and to bring about inversion of stereochemistry at C-4, thus gaining entry into the mahuba lactone series.

Experimental

M.p.s were recorded with Kofler hot-stage melting point apparatus and are uncorrected. Optical rotations were determined on a Perkin-Elmer 141 polarimeter. Low resolution mass spectra were recorded with a Kratos MS25 mass spectrometer



Scheme 3.

and DS55 data system. High resolution mass spectra were recorded with a Kratos MS80 spectrometer and DS55 data system. I.r. spectra were recorded with a Perkin-Elmer 157G spectrometer, and ^{1}H n.m.r. spectra were recorded on a Bruker AM250 (250 MHz) spectrometer in $CDCl_3$ with TMS as internal standard, at room temperature; J in Hz. $^N\delta_H$ Refers to the ^{1}H n.m.r. spectrum after the addition of trichloroacetyl isocyanate. ^{13}C N.m.r. spectra were recorded with a Bruker AM250 (62.9 MHz) spectrometer in $CDCl_3$ with TMS as internal standard.

1,2;5,6-*Di*-O-*isopropylidene*-α-D-*allofuranose* (**10**).—(*a*) *Using ruthenium tetraoxide.* To a solution of 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (**7**) (40.0 g, 154 mmol) in alcohol-free chloroform (prepared by washing six times with distilled water, distilling and passing through a neutral alumina column)

(200 ml) in a 1 l Morton flask fitted with an overhead stirrer were added water (200 ml), potassium periodate (52.8 g, 230 mmol), potassium carbonate (2.8 g, 42 mmol), and ruthenium dioxide (0.35 g, 2.6 mmol). The biphasic solution was stirred rapidly until the reaction was complete by t.l.c. (1:1, chloroform–diethyl ether). Isopropyl alcohol (15 ml) was added to quench the reaction and the solids were removed by filtration through Celite. The resulting solution was separated and the aqueous layers were extracted with chloroform. The combined organic extracts were then dried (Na_2SO_4) and concentrated under reduced pressure to give a white solid. The solid was taken up in methanol (300 ml), cooled to 0 °C, and sodium borohydride (2.3 g, 60.5 mmol) was added portionwise over 20 min. The solution was then allowed to warm to room temperature and stirred for a further 2 h. Ammonium chloride solution (300 ml) was added and the mixture was stirred for 20 min. The solution was then extracted with dichloromethane, and the extract dried (Na_2SO_4), and concentrated under reduced pressure to give a clear viscous oil, which was recrystallized from light petroleum to give a white solid (25.0 g, 62.5%), m.p. 75—76 °C, $[\alpha]_D^{20}$ +37.2° (*c* 1.2, $CHCl_3$) [lit.,[11] m.p. 77—78 °C, $[\alpha]_D$ +36.0° (*c* 0.5 in water)]; $\nu_{max.}$(Nujol) 3 480 cm^{-1} (OH); δ_H 1.34, 1.37, 1.47, and 1.59 (4 × 3 H, d, *J* 0.7 Hz, 4 × Me, acetonides), 2.6 (1 H, d, *J* 8.5 Hz, OH), 3.83 (1 H, dd, *J* 8.5 and 4.5 Hz, 4-H), 4.05 (3 H, m, 3-H and 2 × 6-H), 4.32 (1 H, dt, *J* 7.0 and 4.5 Hz, 5-H), 4.63 (1 H, dd, *J* 5.5 and 3.5 Hz, 2-H), and 5.83 (1 H, d, *J* 3.5 Hz, 1-H); δ_C 25.2, 26.2, 26.4, and 26.5 (4 × Me, acetonides), 65.7 (C-6), 72.4, 75.5, 78.9, and 79.5 (C-2, C-3, C-4, and C-5), 103.8 (C-1), and 109.6 and 112.6 (2 × CMe_2); *m/z* (c.i. reagent NH_4^+) 261 (M + H) and 245 (M^+ + CH_3).

(*b*) *Using ruthenium trichloride.* An identical oxidation was carried out as above except that ruthenium trichloride was used in place of ruthenium dioxide. The product was identical in every respect with the 1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose described above; yield 28 g (70%).

1,2;5,6-*Di*-O-*isopropylidene*-3-O-(*methoxyethoxymethyl*)-α-D-*allofuranose* (**11a**).—To sodium hydride (50% dispersion in oil, pre-washed with hexane; 4.6 g, 0.1 mmol) suspended in dry THF (500 ml) was added 1,2;5,6-di-*O*-isopropylidene-α-D-allofuranose (**10**) (10 g, 0.04 mol), dissolved in a minimum of dry THF. Methoxyethoxymethyl chloride (7.3 g, 0.06 mol) was added and the mixture was boiled under reflux for 48 h. The reaction mixture was quenched with methanol and diluted with water. The product was extracted into dichloromethane, and the extract dried (Na_2SO_4), and concentrated under reduced pressure to give the title compound (**11a**) as an oil, yield 14.5 g (quantitative). A small sample of the product was purified by flash column chromatography [2:3, light petroleum (40—60 °C)–ethyl acetate], $[\alpha]_D^{20}$ +41.85° (*c* 0.92, $CHCl_3$) (Found: C, 54.85; H, 7.9. $C_{16}H_{28}O_8$ requires C, 55.16; H, 8.10%); δ_H 5.76 (1 H, d, *J* 3.8, 1-H), 4.90 and 4.84 (2 H, AB, *J* 7.0, OCH_2O), 4.71 (1 H, t, *J* 3.8 2-H), 4.38 (1 H, td, *J* 6.5, 3.0, 5-H), 4.15—3.70 (8 H, m, 3-, 4-, 6-, and 6′-H, OCH_2CH_2O), 3.58 (3 H, s, OMe), and 1.61, 1.48, 1.36, and 1.35 (4 × 3 H, s, 2 × CMe_2); δ_C 24.9, 26.2, 26.4, and 26.8 (all q, 4 × C*Me*), 58.9 (q, OMe), 65.2 (t, C-6), 67.2 and 71.6 (both t, OCH_2CH_2O), 74.9, 76.9, 77.8, and 78.8 (all d, C-2, C-3, C-4, and C-5), 95.4 (t, OCH_2O), 103.6 (d, C-1), and 109.5 and 112.6 (both s, CMe_2); *m/z* (e.i.) 333 (M^+ − Me), (c.i., NH_4^+), 336 (M^+ + NH_4^+, and 333 (M^+ − Me).

1,2-O-*Isopropylidene*-3-O-(*methoxyethoxymethyl*)-α-D-*allofuranose* (**12a**).—Sulphuric acid (0.8%; 50 ml) was added dropwise to 1,2;5,6-*O*-isopropylidene-3-*O*-(methoxyethoxymethyl)-α-D-allofuranose (**11a**) (13.6 g, 0.039 mol) dissolved in methanol (300 ml) with cooling. The mixture was stirred for 48 h and then neutralized by adding barium carbonate and stirring overnight. Sodium hydrogen carbonate was added to ensure neutralization, and the mixture was filtered and concentrated under reduced pressure. The residue was taken up in dichloromethane, dried (Na_2SO_4), and concentrated under reduced pressure to give the title compound (**12a**) as an oil, (11.2 g, 93%), $[\alpha]_D^{20}$ +74.8° (*c* 1.1, $CHCl_3$) (Found: C, 50.35; H, 7.7. $C_{13}H_{24}O_8$ requires C, 50.54; H, 7.85%); $\nu_{max.}$(film) 3 450br cm^{-1} (OH); δ_H 5.75 (1 H, d, *J* 3.8, 1-H), 4.85 and 4.82 (2 H, AB, *J* 7.5, OCH_2O), 4.71 (1 H, t, *J* 3.8, 2-H), 4.08 (1 H, d, *J* 3.8, 3-H), 3.97 (1 H, br m, 5-H), 3.90—3.60 (7 H, m, 4-, 6-, and 6′-H, OCH_2CH_2O), 3.38 (3 H, s, OMe), 2.42 (1 H, br t, *J* 6.0, 6-OH), 2.97 (1 H, br d, *J* 5.0, 5-OH), and 1.57 and 1.33 (both 3 H, s, CMe_2); $^N\delta_H$ 8.63 (1 H, s, NH), 8.50 (1 H, s, NH), 5.73 (1 H, d, *J* 3.5, 1-H), 5.46 (1 H, ddd, *J* 3.0, 4.5, 7.0, 5-H), 4.75 (1 H, t, *J* 3.5, 2-H), and 4.59 and 4.46 (2 H, ABd, *J* 12.5, 3.0, 7.0, 6- and 6′-H), and 4.22 and 4.06 (2 H, ABd, *J* 9.0, 4.5, $MeOCH_2CH_2O$–), 3.86 and 3.71 (both 1 H, m, 3- and 4-H), 3.57 (2 H, m, $MeOCH_2CH_2O$–), 3.37 (3 H, s, OMe), and 1.58 and 1.33 (both 3 H, s, CMe_2); δ_C 26.4 and 26.8 (both q, 2 × C*Me*), 58.7 (q, OMe), 66.7 (t, C-6), 67.3 and 71.6 (both t, OCH_2CH_2O), 71.6, 76.2, 78.5, and 78.9 (all d, C-2, C-3, C-4, and C-5), 95.3 (t, OCH_2O), 103.8 (d, C-1), and 112.6 (s, *C*Me).

1,2-O-*Isopropylidene*-3-O-(*methoxyethoxymethyl*)-α-D-*ribofuranose* (**13a**).—To 1,2-*O*-isopropylidene-3-*O*-(methoxyethoxymethyl)-α-D-allofuranose (**12a**) (11.22 g, 0.036 mol) dissolved in water (300 ml) was added in small portions sodium metaperiodate (8.2 g, 0.038 mol) until a starch–iodide test showed that the reaction was complete. Sodium borohydride (1.4 g, 0.037 mol) was added and the reaction mixture was stirred for 15 min. The reaction mixture was poured into aqueous ammonium chloride and the product was extracted into dichloromethane. The resulting solution was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the title compound (**13a**) as an oil, (9.25 g, 92%), $[\alpha]_D^{20}$ +59.37° (*c* 0.48, $CHCl_3$) (Found: C, 51.85; H, 7.8. $C_{12}H_{22}O_7$ requires C, 51.79; H, 8.0%); $\nu_{max.}$ 3 475br cm^{-1} (OH); δ_H 5.78 (1 H, d, *J* 4.0, 1-H), 4.87 and 4.81 (2 H, AB, *J* 7.0, OCH_2O), 4.70 (1 H, t, *J* 4.0, 2-H), 4.10 (2 H, m, 3- and 4-H), 3.94 and 3.72 (2 H, br AB, *J* 12.0, 5- and 5′-H), 3.79 and 3.60 (both 2 H, m, OCH_2CH_2O), 3.41 (3 H, s, OMe), and 1.60 and 1.38 (both 3 H, s, CMe_2); δ_C 26.4 and 26.8 (both q, 2 × C*Me*), 58.7 (q, OMe), 60.0 (t, C-5), 66.7 and 71.6 (both t, OCH_2CH_2O), 75.3, 76.4, and 77.8 (all d, C-2, C-3, and C-4), 95.1 (t, OCH_2O), 103.9 (d, C-1), and 112.5 (s, CMe_2).

1,2-O-*Isopropylidene*-5-O-*methylsulphonyl*-3-O-(*methoxyethoxymethyl*)-α-D-*ribofuranose*.—Methanesulphonyl chloride (5.3 g, 0.046 mol) was added to 1,2-*O*-isopropylidene-3-*O*-(methoxyethoxymethyl)-α-D-ribofuranose (**13a**) (8.25 g, 0.33 mol) dissolved in pyridine (600 ml). After 4 h the reaction mixture was poured into water and the product was extracted into dichloromethane, and the extract dried (Na_2SO_4), and concentrated under reduced pressure to give the title compound as an oil (11.2 g, 95%), $[\alpha]_D^{20}$ +92.71° (*c* 0.96, $CHCl_3$) (Found: C, 44.0; H, 6.75. $C_{13}H_{24}O_9S$ requires C, 43.81; H, 6.79%); $\nu_{max.}$ 1 355 and 1 175 cm^{-1} (OSO_2); δ_H 1.36 and 1.58 (2 × 3 H, both s, CMe_2), 3.07 (3 H, s, $MeOSO_2$), 3.40 (3 H, s, OMe), 3.67 and 3.80 (4 H, both m, OCH_2CH_2O), 3.95 (1 H, dd, *J* 4.0 and 9.0, 3-H), 4.25 (1 H, ddd, *J* 2.0, 4.0, and 9.0, 4-H), 3.98 and 4.54 (2 H, ABd, *J* 2.0, 4.0, and 11.5, CH_2OMs), 4.72 (1 H, br t, *J* 3.5, 2-H), 4.84 (2 H, AB, *J* 7.0, OCH_2O), and 5.76 (1 H, d, *J* 3.5, 1-H); δ_C 26.4 and 26.8 (both q, C-Me_2), 37.4 (q, $MeOSO_2$), 58.8 (q, OMe), 67.1 (t, C-5), 67.5 and 71.7 (both t, OCH_2CH_2O), 76.2, 76.3, and 78.3 (all d, C-2, C-3, and C-4), 95.6 (t, OCH_2O), 104.0 (d, C-1), and 113.1 (s, CMe_2); *m/z* (e.i.) 341 (M^+ − Me), (c.i., reagent NH_4^+) and 374 (M^+ + NH_4^+).

5-*Deoxy*-1,2-*isopropylidene*-3-O-(*methoxyethoxymethyl*)-α-D-ribofuranose (**14a**).—Lithium aluminium hydride (1.7 g, 0.045 mol) was added to 1,2-isopropylidene-5-*O*-methylsulphonyl-3-*O*-(methoxyethoxymethyl)-α-D-ribofuranose (9.7 g, 0.027 mol) in dry diethyl ether (500 ml) and the mixture was heated under reflux for 4 h. The reaction mixture was then quenched with water, filtered through Celite, dried (Na_2SO_4), and concentrated under reduced pressure to give the title compound (**14a**) as an oil (7.0 g, 99%); $[\alpha]_D^{20}$ +83.3° (*c* 2.5, $CHCl_3$), (Found: C, 54.85; H, 8.15. $C_{12}H_{22}O_6$ requires C, 54.95; H, 8.45%); δ_H 5.75 (1 H, d, *J* 4.0, 1-H), 4.88 and 4.82 (2 H, AB, *J* 7.0, OCH_2O), 4.66 (1 H, t, *J* 4.0, 2-H), 4.11 (1 H, dq, *J* 6.0, 9.5, 4-H), 3.86 and 3.73 (2 H, m, $MeOCH_2CH_2O$), 3.52 (1 H, dd, *J* 4.0, 9.5, 3-H), 3.40 (3 H, s, OMe), 1.62 and 1.34 (both 3 H, s, CMe_2), and 1.32 (3 H, d, *J* 6.0, C_4-Me); δ_C 17.3 (q, C-5), 26.4 and 26.6 (both q, CMe_2), 58.8 (q, OMe), 67.2 and 71.8 (both t, OCH_2CH_2O), 73.7, 78.3, and 82.3 (all d, C-2, C-3, and C-4), 93.4 (t, OCH_2O), 103.8 (d, C-1), 112.2 (s, CMe_2); *m*/*z* (e.i.) 247 (M^+ − Me), (c.i. NH_4^+), 280 ($M^+ + NH_4^+$), and 247 (M^+ − Me).

Methyl 5-*Deoxy*-1,2-O-*isopropylidene*-3-O-(*methoxyethoxymethyl*)-α/β-D-*ribofuranoside* (**15a**).—Methanolic hydrogen chloride (5%, 4 ml) was added to a solution of 5-deoxy-1,2-*O*-isopropylidene-3-*O*-(methoxyethoxymethyl)-α-D-ribofuranose (**14a**) (13.4 g, 0.051 mol) in MeOH (500 ml). After being stirred for 6 h at room temperature the mixture was neutralized with solid sodium hydrogen carbonate, filtered, and concentrated under reduced pressure the residue was taken up in dichloromethane, and the solution filtered and concentrated to give the crude title compound (**15a**) contaminated with a small amount of methyl 5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (**16**), overall yield 10.0 g (83%). A small sample was purified by flash column chromatography [3:1, light petroleum (40—60 °C)–acetone] to give the two 1,2-isopropylidene compounds as an inseparable mixture and the 2,3-isopropylidene derivative in a 7:1 ratio.

Methyl 5-deoxy-1,2-*O*-isopropylidene-α/β-D-ribofuranoside (**15a**): $\nu_{max.}$ 3 450 cm^{-1} (OH); δ_H 4.82 and 4.77 (2 H, AB, *J* 5.5, OCH_2O), 4.81 (1 H, s, 1-H β-anomer), 4.12 (2 H, m, 1-H α-anomer and 2-H β-anomer), 4.09 (1 H, t, *J* 4.0, 2-H α-anomer), 3.91—3.54 (6 H, m, 3-, 4-H, OCH_2CH_2O), 3.41 (3 H, s, OMe β-anomer), 3.37 (3 H, s, OMe, α-anomer), and 1.35 (3 H, d, *J* 6.2, CMe).

Methyl 5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (**16**): δ_H 4.94 (1 H, s, 1-H), 4.64 (1 H, d, *J* 6.0, 2-H), 4.51 (1 H, dd, *J* 6.0, 1.0, 3-H), 4.35 (1 H, dq, *J* 7.0, 1.0, 4-H), 3.33 (3 H, s, OMe), 1.50 and 1.31 (both 3 H, s, CMe_2), 1.29 (3 H, d, *J* 7.0, C_4-Me); δ_C 21.2 (q, C-5), 25.2 and 26.7 (both q, CMe_2), 54.2 (q, OMe), 83.2, 85.5 and 86.1 (all d, C-2, C-3, and C-4), 107.71 (d, C-1), 112.1 (s, CMe_2); *m*/*z* (e.i.) 205 (M^+ − OMe), (c.i. NH_4^+) 254 ($M^+ + NH_4$), (M + H − Me), and 205 (M^+ − OMe).

p-*Methoxybenzyl Chloride*. Thionyl chloride (90 ml) was added dropwise to a *p*-methoxybenzyl alcohol (40.0 g, 290 mmol) cooled in an ice-bath with stirring. After 30 min the mixture was heated under reflux for 2 h. The excess of thionyl chloride was then distilled off at atmospheric pressure, followed by *p*-methoxybenzyl chloride under reduced pressure (70 °C, 1.0 mmHg). The clear oil was stored in the refrigerator and used as required; yield 28.9 g (64%).

1,2:5,6-*Di*-O-*isopropylidene*-3-O-(p-*methoxybenzyl*)-α-D-*allofuranose* (**11b**).—Dry THF (100 ml) was added to sodium hydride [50% suspension in oil; 4.35 g, 90.6 mmol, pre-washed with distilled light petroleum ether (40—60 °C)] in a dry three-necked flask under a nitrogen atmosphere and the stirred slurry was cooled to 0 °C. 1,2;5,6-Di-*O*-isopropylidene-α-D-allofuranose (**10**) (5.8 g, 22 mmol) in dry THF (80 ml) was added dropwise over 10 min, followed by *p*-methoxybenzyl chloride (3.84 g, 24.2 mmol) in dry THF (30 ml). The reaction mixture was then heated under reflux for 48 h after which t.l.c. [light petroleum (b.p. 40—60 °C)–ethyl acetate, 2:1] showed that the reaction was complete. The stirred reaction was cooled to 0 °C and quenched by the addition of methanol (15 ml), followed by aqueous ammonium chloride (500 ml). The resulting aqueous solution was extracted with dichloromethane and the organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the title compound (**11b**) as a brown oil (quantitative yield). A small sample was purified by flash chromatography [light petroleum (b.p. 40—60 °C)–ethyl acetate, 4:1] to give give a clear oil which solidified on cooling, m.p. 77—78 °C (Found: C, 63.4; H, 7.2. $C_{20}H_{28}O_7$ requires C, 63.1; H, 7.4%); $[\alpha]_D^{20}$ +91.7° (*c* 1.28, $CHCl_3$); δ_H 1.36, 1.38, 1.40, and 1.60 (4 × 3 H, s, acetonides), 3.82 (3 H, s, ArO*Me*), 3.87 (1 H, dd, *J* 9.0 and 4.5 Hz, 3-H), 3.99 (2 H, m, 2 × 6-H), 4.13 (1 H, dd, *J* 9.0 and 3.0 Hz 4-H); 4.38 (1 H, dt, *J* 10.0 and 3.0 Hz 5-H), 4.55 (1 H, t, *J* 4.5, 2-H), 4.49 and 4.74 (2 H, AB, *J* 11.5 Hz, OCH_2Ar), 5.75 (1 H, d, *J* 4.0, 1-H), and 6.85—7.4 (4 H, m, ArH); δ_C 25.0, 26.1, 26.5, and 26.8 (4 × Me, acetonides), 55.2 (ArO*Me*), 64.8 (C-6), 71.7 ($ArCH_2O$), 74.5, 76.8, 77.7, and 77.7 (C-2, C-3, C-4, and C-5), 103.7 (C-1), 109.5, 112.7 (2 × CMe_2), 113.7 (*o*-ArC), 129.4 (*p*-ArC), 129.8 (*m*-ArC), 159.3 (*i*-ArC); *m*/*z* 380 (M^+) and 365 (M^+ − Me).

1,2-O-*Isopropylidene*-3-O-(p-*methoxybenzyl*)-α-D-*allofuranose* (**12b**).—Sulphuric acid (0.8%; 72 ml) was added dropwise to a cooled solution of 1,2-5,6-di-*O*-isopropylidene-3-*O*-(*p*-methoxybenzyl)-α-D-allofuranose (**11b**) (23.0 g, 60.5 mmol) in methanol (420 ml). The solution was allowed to warm to room temperature and stirred for 3 days. The reaction was then quenched with solid barium carbonate and stirred for 24 h. Sodium hydrogen carbonate was added to ensure neutralisation and the slurry filtered through Celite to remove solids. The filtrate was evaporated to dryness under reduced pressure and the resulting brown oil was taken up in dichloromethane, dried (Na_2SO_4), and evaporated to dryness under reduced pressure to give the title compound (**12b**) (quantitative yield). A sample was purified by flash column chromatography [light petroleum ether (40—60 °C)–acetone, 3:2] to give a pale yellow oil (Found: C, 60.1; H, 7.4. $C_{17}H_{24}O_7$ requires C, 60.0; H, 7.1%); $[\alpha]_D^{20}$ +80.0° (*c* 1.06 $CHCl_3$); ν_{max}, 3 460 (OH) cm^{-1}; δ_H 1.36, 1.60 (2 × 3 H, 2 × Me acetonide), 2.4 (2 H, br s, 2 × OH); 3.65 (2 H, dd, *J* 5.0 and 3.0 Hz, 2 × 6-H), 3.84 (3 H, s, ArO*Me*), 3.90 (1 H, dd, *J* 9.0 and 4.5 Hz, 4-H), 4.00 (1 H, m, 5-H), 4.10 (1 H, dd, *J* 9.0 and 3.5 Hz, 3-H), 4.60 (1 H, t, *J* 3.5 Hz, 2-H), 4.45 and 4.75 (2 H, AB, *J* 11.0 Hz, OCH_2Ar), 5.76 (1 H, d, *J* 3.5 Hz, 1-H), 6.90 (2 H, m, *o*-ArC), and 7.30 (2 H, m, *m*-ArC); δ_C 26.5 and 26.7 (2 × Me acetonide), 55.2 (ArO*Me*), 63.0 (C-6), 71.7 ($ArCH_2O$), 70.9, 77.3, 79.0 (C-2, C-3, and C-4), 104.1 (C-1), 113.0 (CMe_2), 113.9 (*o*-ArC), 128.8 (*p*-ArC), 129.8 (*m*-ArC), and 159.6 (*i*-ArC); *m*/*z* 340 (M^+) and 325 (M^+ + Me).

1,2-*Isopropylidene*-3-O-(p-*methoxybenzyl*)-α-D-*ribofuranose* (**13b**).—Sodium periodate (11.7 g, 54.6 mmol) dissolved in distilled water (170 ml) was added dropwise to a solution of 1,2-*O*-isopropylidene-3-*O*-(*p*-methoxybenzyl)-α-D-allofuranose (**12b**) (17.5 g, 51 mmol) in methanol (250 ml) until potassium iodide–starch tests indicated an excess of periodate. A precipitate formed and the slurry was stirred for a further 2 h at room temperature. Sodium borohydride (2.2 g, 57.9 mmol) was added portionwise to the cooled solution and the reaction mixture was allowed to cool to room temperature over 2 h. Aqueous ammonium chloride (200 ml) was added and the aqueous solution was extracted with dichloromethane. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give 1,2-isopropylidene-3-*O*-(*p*-methoxy-

benzyl)-α-D-ribofuranose (**13b**) as a brown oil (13.4 g, 85%). A small sample was purified by flash column chromatography [light petroleum (40—60 °C)–ethyl acetate, 1:1] to give a clear oil which solidified with time, m.p. 60—62 °C (Found: 61.7; H, 7.4. $C_{16}H_{22}O_6$ requires C, 61.9; H, 7.15%), $[\alpha]_D^{20}$ +104.7° (*c* 1.17, $CHCl_3$); $\nu_{max.}$(Nujol) 3 530 (OH) cm^{-1}; δ_H 1.39, 1.60 (2 × 3 H, s, 2 × Me acetonide), 1.77 (1 H, br s, OH), 3.61 and 3.89 (2 H, ABd, *J* 12.5 and 3.5, 5- and 5′-H, 3.80 (3 H, s, ArO*Me*) 3.82 (1 H, dd, *J* 9.0 and 4.5 Hz, 3-H), 4.10 (1 H, dt, *J* 9.0 and 3.0 Hz, 4-H), 4.54 (1 H, t, *J* 4.0 Hz, 2-H), 4.50 and 4.74 (2 H, AB, *J* 12 Hz, OC*H*$_2$Ar), 5.72 (1 H, d, *J* 3.7 Hz, 1-H), 6.86—6.93 (2 H, m, *o*-ArC), and 7.26—7.35 (2 H, m, *m*-ArC); δ_C 26.5 and 26.8 (2 × Me acetonide), 55.2 (ArO*Me*), 60.65 (C-5), 71.9 (Ar*C*H$_2$O), 76.4, 77.6 and 78.8 (C-2, C-3, and C-4), 104.0 (C-1), 113.0 (*C*Me)$_2$, 113.8 (*o*-ArC), 129.5 (*m*-ArC), 129.6 (*p*-ArC), and 159.5 (*i*-ArC); *m/z* (c.i., reagent NH_3) 328 ($M^+ + NH_4$), 311 ($M^+ + H$), and 295 ($M^+ - Me$).

1,2-O-*Isopropylidene*-5-O-*methylsulphonyl*-3-O-(p-*methoxybenzyl*)-α-D-*ribofuranose*.—Methanesulphonyl chloride (5.5 ml) in dry pyridine (10 ml) was added to a cooled solution of 1,2-isopropylidene-3-*O*-(*p*-methoxybenzyl)-α-D-ribofuranose (**13b**) (13.5 g, 43.5 mmol) in dry pyridine (150 ml) over 10 min and the stirred solution allowed to warm to room temperature. The reaction was followed by t.l.c. [light petroleum (40—60 °C)–ethyl acetate, 1:1] which showed that the reaction was complete after 2.5 h. Distilled water (400 ml) was added to quench the reaction and the aqueous solution extracted with dichloromethane. The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness to give the title compound as a brown oil which was used without purification in the next reaction; yield 16.2 g (96%) (Found: C, 52.5; H, 6.2; S, 8.2. $C_{17}H_{24}O_8S$ requires C, 52.6; H, 6.3; S, 8.25%); $[\alpha]_D^{20}$ +90.8° (*c* 5.50, $CHCl_3$); $\nu_{max.}$(film) 1 360 and 1 180 cm^{-1} (OSO_2); δ_H 1.37, 1.60 (2 × 3 H, s, CMe_2), 3.00 (3 H, s, $MeSO_2O$), 3.75 (1 H, dd, *J* 8.5 and 4.0 Hz, 3-H), 3.84 (3 H, s, ArOMe), 4.15—4.35 (2 H, m, 5- and 5′-H), 4.35—4.48 (1 H, m, 4-H), 4.55 (1 H, t, *J* 3.5 Hz, 2-H), 4.5—4.8 (2 H, ABq, *J* 12 Hz, ArCH_2O), 5.71 (1 H, d, *J* 3.5 Hz, 1-H), 6.85—6.94 (2 H, m, *o*-ArC), and 7.20—7.28 (2 H, m, *m*-ArC); δ_C 26.5, 26.8 (*C*Me_2), 37.5 (OSO_2*Me*), 55.3 (ArOMe), 67.7 (C-5), 72.0 (Ar*C*H$_2$O–), 76.3, 76.7, and 77.1 (C-2, C-3, and C-4), 104.1 (C-1), 113.3 (*C*Me_2), 114.0 (*o*-ArC), 129.7 (*p*-ArC), 129.1 (*m*-ArC), and 159.7 (*i*-ArC); *m/z* 388 (M^+) and 373 ($M^+ - Me$).

5-*Deoxy*-1,2-O-*isopropylidene*-3-O-(p-*methoxybenzyl*)-α-D-*ribofuranose* (**14b**).—Lithium aluminium hydride (2.50 g, 66 mmol) in small portions was added to 1,2-isopropylidene-5-*O*-methylsulphonyl-3-*O*-(*p*-methoxybenzyl)-α-D-ribofuranose (16.2 g, 41.8 mmol) dissolved in dry diethyl ether (400 ml). The reaction mixture was heated under reflux for 3 h and then cooled to 0 °C. The reaction was quenched by addition of the minimum amount of distilled water. After filtration through Celite, drying (Na_2SO_4), and concentration under reduced pressure, the title compound (**14b**) was obtained as a pale oil which solidified on cooling (11.6 g, 94%). A small sample was purified by flash column chromatography [light petroleum (b.p. 40—60 °C)–ethyl acetate, 6:1] to give a clear oil which solidified with time, m.p. 73—75 °C (Found: C, 65.4; H, 7.8. $C_{16}H_{22}O_5$ requires C, 65.3; H, 7.5%); $[\alpha]_D^{20}$ +126.0° (*c* 0.98, $CHCl_3$); δ_H 1.25 (2 H, d, *J* 6.5, C_5-*Me*), 1.36 and 1.60 (2 × 3 H, s, 2 × Me acetonide), 3.29 (1 H, dd, *J* 9.0 and 4.0 Hz, 3-H), 3.81 (3 H, s, ArO*Me*), 4.1 (1 H, dq, *J* 9.0 and 6.5 Hz, 4-H), 4.54 (1 H, t, *J* 4.0 Hz, 2-H), 4.46 and 4.75 (2 H, AB, *J* 11.5, OC*H*$_2$Ar), 5.70 (1 H, d, *J* 4.0 Hz, 1-H), 6.85—6.92 (2 H, m, *o*-ArC), and 7.27—7.34 (2 H, m, *m*-ArC); δ_C 17.3 (C-5), 26.4 and 26.6 (2 × Me acetonide), 55.2 (ArO*Me*), 71.7 (O*C*H$_2$Ar), 74.0, 77.2, and 82.9 (C-2, C-3, and C-4), 103.8 (C-1), 112.4 (*C*-Me$_2$), 113.8 (*o*-ArC), 129.5 (*m*-ArC), 129.7 (*p*-ArC), 159.2 (*i*-ArC); *m/z* (e.i.) 294 (M^+), and 279 ($M^+ - Me$).

Methyl 5-*Deoxy*-3-O-(p-*methoxybenzyl*)-α/β-D-*ribofuranoside* (**15b**).—Concentrated hydrochloric acid (4.75 ml) dissolved in methanol (50 ml) was added to a cooled solution of 5-deoxy-1,2-isopropylidene-3-*O*-(*p*-methoxybenzyl)-α-D-ribofuranose (**14b**) (9.5 g, 32.3 mmol) dissolved in methanol (200 ml). The solution was stirred overnight at room temperature and then quenched with solid sodium hydrogen carbonate. The mixture was concentrated to dryness under reduced pressure and taken up in dichloromethane. After drying (Na_2SO_4), filtration through Celite, and concentration under reduced pressure, a brown oil was obtained. The brown oil was purified by column chromatography [light petroleum ether (b.p. 40—60 °C)–ethyl acetate, 3:1, then 3:2]. The product was a mixture of α and β anomers in a 1:10 ratio which were not separated. Yield of pure compound (**15b**) 4.70 g [45.7% from 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**10**)] (Found: C, 62.4; H, 7.7, $C_{14}H_{20}O_5$ requires C, 62.7; H, 7.5%); $\nu_{max.}$(neat) 3 460 cm^{-1} (OH); δ_H (for β-anomer) 1.30 (3 H, d, *J* 6.5, C_5-*Me*), 2.55 (1 H, br s, OH), 3.36 (3 H, s, C_1-O*Me*), 3.83 (3 H, s, ArO*Me*), 3.83 (1 H, dd, *J* 6.5 and 5.0 Hz, 3-H), 4.00 (1 H, d, *J* 5.0 Hz, 2-H), 4.10 (1 H, quint., *J* 6.5, 4-H), 4.40 and 4.60 (2 H, AB, *J* 11.5 OC*H*$_2$Ar), 4.81 (1 H, s, 1-H), 6.85—6.95 (2 H, m, *o*-ArC), and 7.2—7.4 (2 H, m, *m*-ArC); δ_C 20.8 (C-5), 54.8 (1-O*Me*), 55.2 (ArO*Me*), 72.5 (Ar*C*H$_2$O), 73.5, 77.3, and 83.6 (C-2, C-3, and C-4), 108.3 (C-1), 114.09 (*o*-ArC), 129.2 (*p*-ArC), 129.5 (*m*-ArC), and 159.6 (*i*-ArC); *m/z* (c.i., NH_4^+) 286 ($M^+ + NH_4$), 269 ($M^+ + H$), and 237 ($M^+ + MeO$).

Oxidation of Methyl 5-*Deoxy*-3-O-(p-*methoxybenzyl*)-α,β-*ribofuranoside* (**15b**).—(*a*) *Oxidation with pyridinium chlorochromate*. Pyridinium chlorochromate (0.23 g, 1.08 mmol) was suspended in dichloromethane (3 ml, previously dried over calcium chloride) and stirred rapidly. Methyl 5-deoxy-3-*O*-(*p*-methoxybenzyl)-α,β-D-ribofuranoside (0.1 g, 0.37 mmol) in dry dichloromethane (2 ml) was added dropwise. The solution was stirred for 2 h and then refluxed for 40 h, after which no starting material remained (as determined by t.l.c.). The black solution was filtered through Celite and concentrated to dryness under reduced pressure to give a black oil. This oil was thoroughly washed with diethyl ether and the combined ether extracts evaporated to dryness to give a brown oil. Examination of the oil by ^1H n.m.r. (220 MHz) showed the presence of *p*-methoxybenzaldehyde (from deprotection at C-3) amongst other products.

(*b*) *Oxidation with ruthenium dioxide–potassium periodate*. The same method as used for the oxidation of 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (**8**) was applied to methyl 5-dexoy-3-*O*-(*p*-methoxybenzyl-α/β-D-ribofuranoside (**15b**) with the exception that the biphasic solution was stirred for 5 days. T.l.c. of the reaction mixture demonstrated that the product consisted of almost entirely starting material.

(*c*) *Oxidation with DMSO–acetic anhydride*. Methyl 5-deoxy-3-*O*-(*p*-methoxybenzyl)-α,β-D-ribofuranoside (**15b**) (4.9 g, 18.3 mmol) was dissolved in DMSO (65 ml) and acetic anhydride was added dropwise. The reaction vessel was stoppered and stirred at room temperature for 48 h whereupon the reaction was complete as determined by t.l.c. [light petroleum (b.p. 40—60 °C)–ethyl acetate, 2:1]. The reaction was quenched by pouring into aqueous sodium hydrogen carbonate (250 ml) and stirring for 30 min. The product was extracted into dichloromethane, and the extract dried (Na_2SO_4), and concentrated under reduced pressure to give a mixture of methoxy 5-deoxy-3-*O*-(*p*-methoxybenzyl)-α,β-*erythro*-pentofuranoside (**17b**) and its hydrate in a 3:1 ratio. This oil was taken up in dichloromethane and stirred over activated molecular sieves for 12 h.

After filtration and concentration under reduced pressure the ketone:ketone hydrate ratio was reduced to 15:1. This crude product was used in the next step without further purification; yield 4.6 g (94%); $\nu_{max.}$ (before dehydration) 3 440 (OH) and 1 780 cm^{-1} (C=O); δ_H (220 MHz) 1.38 (3 H, d, *J* 6.5 Hz, 5-Me), 3.48 (3 H, s, 1-Me), 3.80 (3 H, s, ArO*Me*), 3.8 (1 H, m, 3-H), 4.10 (1 H, quint., *J* 6.5 Hz, 4-H), 4.55 and 5.00 (2 H, AB, *J* 11.5 Hz, ArCH_2O), 4.70 (1 H, s, 1-H), 6.8—7.0 (2 H, m, *o*-ArC), and 7.2—7.4 (2 H, m, *m*-ArC).

Wittig Reaction of Methyl 5-Deoxy-3-O-(p-*methoxybenzyl*)-α,β-D-erythro-*pentofuranoside* (**17b**).—Tetradecyltriphenylphosphonium bromide (1.52 g, 2.8 mmol) was dissolved in dry THF (25 ml) under a nitrogen atmosphere and butyl-lithium (1.6M solution in hexane; 1.9 ml, 3.1 mmol) and added dropwise *via* a syringe. The stirred solution turned orange as the ylide was formed and was stirred for a further 20 min; it was then cooled to −70 °C. The ketone (0.5 g, 1.88 mmol) in dry THF (10 ml) was added dropwise and the solution maintained at −70 °C for 1 h. The solution was then allowed to warm to room temperature and stirred for a further 2 h until t.l.c. [light petroleum (b.p. 40—60 °C)–ethyl acetate, 8:1] indicated that the reaction was complete. The reaction was quenched by pouring into aqueous sodium hydrogen carbonate and stirring for 10 min; it was then extracted with dichloromethane, and the extract dried (Na_2SO_4), and concentrated under reduced pressure to give the crude alkene (**18b**) as an oil. The oil was purified by flash chromatography [light petroleum (b.p. 40—60 °C)–ethyl acetate, 12:1 then 8:1]; yield 0.58 g, (69%) as a mixture of four compounds. This mixture was used directly in the next step.

Hydrolysis of Methyl Furanosides.—The mixture of alkenes (**18b**) described above (0.38 g, 0.85 mmol) was dissolved in THF (16 ml) and distilled water (6 ml) and concentrated hydrochloric acid (4 drops) were added. The solution was stirred at room temperature for 1 h after which time the reaction was complete as determined by t.l.c. [light petroleum (b.p. 40—60 °C)–ethyl acetate, 10:1]. Solid sodium hydrogen carbonate was added to quench the reaction, followed by distilled water (50 ml). The aqueous solution was extracted with dichloromethane, and the extract dried (Na_2SO_4) and concentrated under reduced pressure to give a mixture of two lactols in quantitative yield. These compounds were not purified before being used in the next reaction.

4-O-(p-*Methoxybenzyl*)*litsenolide* C_1 (**21b**) *and* 4-O-(p-*methoxybenzyl*)*litsenolide* C_2 (**22b**).—The mixture of lactols described above (0.37 g, 0.86 mmol) was dissolved in dry benzene (67 ml) and Fetizon's reagent (4.23 g) was added. The resulting green slurry was heated to reflux and rapidly became black. After 30 min, t.l.c. [light petroleum (b.p. 40—60 °C)–ethyl acetate, 4:1] indicated that the reaction was complete and the reaction mixture was cooled, filtered through Celite, and concentrated under reduced pressure to give a yellow oil. T.l.c. [light petroleum (b.p. 40—60 °C)–ethyl acetate, 12:1] showed the product to contain two compounds: A (R_F 0.19) and B (R_F 0.31). These compounds were separated by flash column chromatography [light petroleum (b.p. 40—60 °C)–ethyl acetate, 12:1 then 10:1] to give the title compounds (**21b**) (0.09 g, 25%) and (**22b**) (0.25 g, 68%), respectively. Overall yield 0.34 g (93%). 4-O-(p-*Methoxybenzyl*)*litsenolide* C_1 (**21b**). M.p. 39—41 °C (Found: C, 74.9; H, 9.6. $C_{27}H_{42}O_4$ requires C, 75.3; H, 9.8%), $[\alpha]_D^{20}$ +6.8° (*c* 1.16, $CHCl_3$); $\nu_{max.}$(neat) 2 920, 2 850 (alkyl chain), and 1 755 cm^{-1} (γ-lactone); δ_H 0.87 [3 H, t, $(CH_2)_{12}Me$], 1.25 [20 H, $(CH_2)_{10}CH_2$)], 1.29 (3 H, d, *J* 6.5 Hz, 5-Me), 1.4 (2 H, m, RCH_2CH_2CH=), 2.76 (2 H, m, RCH_2CH_2CH=), 3.80 (3 H, s, ArO*Me*), 4.08 (1 H, dd, *J* 2.0 and 1.0 Hz, 3-H), 4.37 and 4.55 (2 H, AB, *J* 11.5 Hz, ArCH_2O), 4.4 (1 H, dq, *J* 6.5 and 2.0 Hz, 4-H), 6.47 (1 H, dt, *J* 8.0 and 1.0 Hz, C=C*H*CH_2R), 6.83—6.92 (2 H, m, *o*-ArC), and 7.2—7.28 (2 H, m, *m*-ArC); δ_C 14.1 (*Me*-alkyl), 19.6 (C-5), 22.7, 26.9, 27.9, 28.9, 29.3, 29.6, and 31.9 [Me(CH_2)$_{12}$], 55.3 (ArO*Me*), 69.6 (ArCH_2O), 79.5, 81.1 (C-3 and C-4), 114.0 (*o*-ArC), 125.7 (C-2), 129.3 (*m*-ArC), 129.5 (*p*-ArC), 150.6 (C=*C*HR), 159.4 (*i*-ArC), and 168.2 (C-1); *m/z* 430 (M^+) and 386 ($M^+ - CO_2$).

4-O-(p-*Methoxybenzyl*)*litsenolide* C_2 (**22b**). M.p. 52—54 °C (Found: C, 75.4; H, 9.6. $C_{27}H_{42}O_4$ requires C, 75.3; H, 9.8%), $[\alpha]_D^{20}$ −44.9° (*c* 0.94, $CHCl_3$), $\nu_{max.}$(neat) 2 920, 2 850 (alkyl chain) and 1 755 cm^{-1} (γ-lactone); δ_H 0.87 [3 H, t, $(CH_2)_{12}Me$], 1.25 [20 H, s, $(CH_2)_{10}Me$], 1.29 (3 H, d, *J* 6.5 Hz, 5-*Me*), 1.46 (2 H, m, RCH_2CH_2CH=), 2.28 (2 H, m, RCH_2CH_2CH=), 3.81 (3 H, s, ArO*Me*), 4.32 (1 H, t, *J* 1.8 Hz, 3-H), 4.38 and 4.53 (2 H, AB, *J* 11.5 Hz, ArCH_2O), 4.65 (1 H, dq, *J* 7.0 and 1.5 Hz, 4-H), 6.84—6.92 (2 H, m, *o*-ArC), 7.03 (1 H, td, *J* 8.5 and 1.5 Hz, C=C*H*CH_2R), 7.2—7.28 (2 H, m, *m*-ArC); δ_C 14.0 (*Me*-alkyl), 20.2 (C-5), 22.6, 28.3, 29.3, 29.5, 29.6, 30.1, and 31.9 [$(CH_2)_{12}$Me], 55.2 (ArO*Me*), 70.0 (ArCH_2O), 77.5 and 79.4 (C-3 and C-4); 113.9 (*o*-ArC), 126.9 (C-2), 129.1 (*p*-ArC), 129.5 (*m*-ArC), 148.9 (C=*C*HR), 159.5 (*i*-ArC), and 169.5 (C-1); *m/z* 430 (M^+) and 386 ($M^+ - CO_2$).

Litsenolide C_2 (**2c**).—4-*O*-(*p*-Methoxybenzyl)litsenolide C_2 (0.21 g, 0.49 mmol) was dissolved in dichloromethane (8 ml) and distilled water (0.25 ml) and 2,3-dichloro-5,6-dicyanobenzoquinone (0.18 g, 0.67 mmol) were added; the slurry was stirred rapidly for 8 h after which t.l.c. [light petroleum (b.p. 40—60 °C)–ethyl acetate, 4:1] showed that the reaction was complete. The reaction mixture was filtered through Celite, washed with dichloromethane, and poured into aqueous sodium hydrogen carbonate. The product was extracted into dichloromethane, dried (Na_2SO_4), and concentrated under reduced pressure to give a brown oil which was purified by flash column chromatography [light petroleum (b.p. 40—60 °C)–ethyl acetate, 6:1 then 4:1] to give (**2c**) (0.11 g, 72%), m.p. 45—47 °C, $[\alpha]_D^{20}$ −44.0° (*c* 1.12, $CHCl_3$) (lit.,[6] m.p. 44—45 °C; $[\alpha]_D^{20}$ −45.2°) (*c* 0.99 in dioxane) (Found: C, 73.6; H, 11.2. $C_{19}H_{34}O_3$ requires C, 73.5; H, 11.0%); $\nu_{max.}$(Nujol) 3 380 (OH) and 1 730 cm^{-1} (γ-lactone); δ_H 0.87 [3 H, t, *J* 7.0 Hz, $(CH_2)_{12}Me$], 1.26 [20 H, s, $(CH_2)_{10}$Me]; 1.35 (3 H, d, *J* 6.5 Hz, 5-Me), 1.52 (2 H, m, RCH_2CH_2CH=), 2.14 (1 H, br d, OH), 2.40 (2 H, m, RCH_2CH_2CH=), 4.46 and 4.58 (2 H, m, 3- and 4-H), 6.95 (1 H, td, *J* 7.5 and 1.7 Hz, C=C*H*CH_2R); δ_C 14.0 (*Me*-alkyl), 19.6 (C-5), 22.6, 28.4, 29.3, 29.5, 29.6, and 31.9 [$(CH_2)_{12}$Me], 72.0 (C-3), 82.8 (C-4), 129.2 (C-2), 148.7 (C=*C*HR), and 170.1 (C-1); *m/z* 310 (M^+) and 292 ($M^+ - H_2O$).

Litsenolide C_1 (**1c**).—4-*O*-(*p*-Methoxybenzyl)litsenolide C_1 (0.054 g, 0.13 mmol) was treated as above to give litsenolide C-1 (0.034 g, 87%), m.p. 66—68 °C; $[\alpha]_D^{20}$ −10.0° (*c* 0.97, $CHCl_3$), {lit.,[6] m.p. 60—62 °C; $[\alpha]_D^{20}$ −9.2° (*c* 0.62 in dioxane)}; $\nu_{max.}$(Nujol) 3 460 (OH) and 1 735 cm^{-1} (γ-lactone); δ_H 0.88 [3 H, t, *J* 7 Hz, $(CH_2)_{10}Me$]; 1.25 [20 H, s, $(CH_2)_{10}$Me], 1.38 (3 H, d, *J* 6.5 Hz, 5-*Me*), 1.45 (2 H, m, RCH_2CH_2CH=), 2.2 (1 H, s, OH), 2.75 (2 H, m, RCH_2CH_2CH=), 4.3 and 4.41 (2 H, m, 3- and 4-H), 6.48 (1 H, dt, *J* 7.5 and 1.5 Hz, C=C*H*CH_2R); δ_C 14.1 (*Me*-alkyl), 19.1 (C-5), 22.7, 27.8, 28.8, 29.3, 29.4, 29.5, and 29.6 [-(CH_2)$_{12}$Me], 75.4, 81.3 (C-3 and C-4), 128.6 (C-2), 149.4 (C=*C*HR), 168.4 (C-1); *m/z* 310 (M^+) and 292 ($M^+ - H_2O$) (Found: M^+, 310.2484. $C_{13}H_{34}O_3$ requires *M*, 310.2508).

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