Chiral Route to *cis*-Caronaldehyde from D-Mannitol

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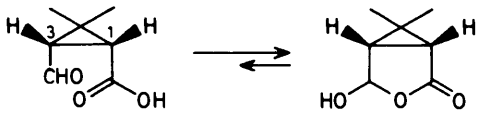
A chiral route to *cis*-caronaldehyde, a key intermediate of *cis*-pyrethroid insecticides as well as an efficient resolving agent for secondary alcohols, has been developed using D-mannitol as the starting material employing a sequential one-pot sodium periodate cleavage and Horner-Emmons condensation in an aqueous medium as the key stage.

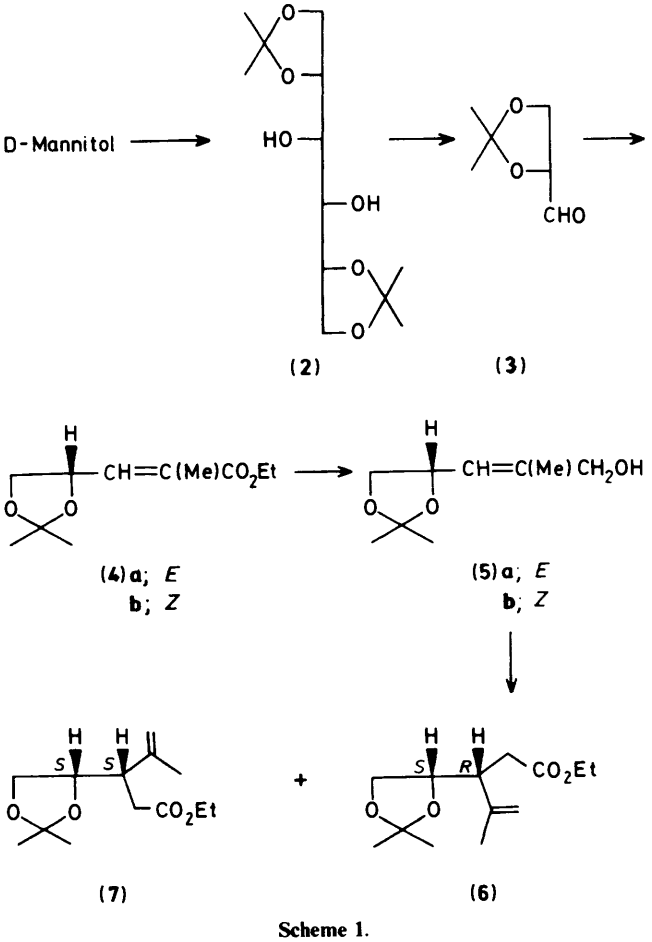
Optically active *cis*-caronaldehyde (**1a**), which exists in the lactone–hemiacetal form (**1b**), has become of interest in recent years since it can be used not only as a key intermediate for the synthesis of potent pyrethroid insecticides possessing a *cis*-configuration [1] but also as an effective resolving agent for various secondary alcohols.[2] Because optically active *cis*-caronaldehyde (**1**), at present, is obtained from optically active *trans*-chrysanthemic acid by tedious sequential oxidative cleavage and base-catalysed epimerization,[3,4] the development of an alternative synthesis producing both enantiomers in a more straightforward manner would have considerable merit both in production of the less toxic pyrethroid insecticides and in the



(1*R*,3*S*)-(**1a**) (1*R*,3*S*)-(**1b**)

construction of optically active materials. Recently, we have developed an efficient one-pot procedure which allows the large scale preparation of (*S*)-ethyl 4,5-*O*-isopropylidene-4,5-dihydroxypent-2-enoate from 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**2**) *via* sequential sodium periodate cleavage and the Horner-Emmons condensation in the same aqueous medium without isolation of the unstable (*R*)-*O*-isopropylideneglyceraldehyde (**3**).[5] We report here an extension of this one-pot procedure to the synthesis of (*S*)-ethyl 4,5-*O*-isopropylidene-4,5-dihydroxy-2-methylpent-2-enoate (**4**) and a utility of this product in the synthesis of optically active caronaldehyde (**1**).

1,2:5,6-di-*O*-Isopropylidene-D-mannitol (**2**)[6] (prepared from D-mannitol) was oxidatively cleaved with sodium periodate in water containing sodium hydrogen carbonate to give (*R*)-*O*-isopropylideneglyceraldehyde (**3**) which without isolation was then treated with triethyl 2-methylphosphonoacetate in the same reaction flask in the presence of potassium carbonate[7] at ambient temperature for 120 h. The product obtained in 58% yield was revealed to be a mixture of the *E*- and *Z*-esters (**4a** and **b**) in 3:2 ratio which were easily separable by column chromatography. Each isomer was then readily converted into the corresponding allyl alcohol (**5a** and **b**) by reduction with di-isobutylaluminium hydride. We first expected that each allylic alcohol would give the corresponding stereoisomer in which the double bond configuration reflects the [3.3]-sigmatropic rearrangement. However, the reaction of the (*E*)-allylic alcohol (**5a**) with two equivalents of triethyl orthoacetate[8] in the presence of a catalytic amount of pivalic acid furnished a 1:1 isomeric mixture, though the overall chemical yield was excellent. Similarly, when the (*Z*)-allylic alcohol (**5b**) was used as the substrate under the same conditions, virtually the same mixture was obtained in an excellent overall yield. We thus concluded that the pre-existing chirality and double bond configuration in both isomers exerted essentially no effect on the stereochemistry of the products under these rearrangement conditions. Fortunately, as the mixture was found to be easily separable by column chromatography to give the (3*R*,4*S*)- and the (3*S*,4*S*)-esters (**6**) and (**7**), we decided to use the (*E*/*Z*) mixture of the α,β-unsaturated esters (**4**) as the starting material without separation. Thus, the mixture was sequentially reduced with di-isobutylaluminium hydride and treated with triethyl orthoacetate to give a 1:1 mixture of the γ,δ-unsaturated esters in excellent overall yield which was separated by silica gel column chromatography to give the (3*R*,4*S*)-ester (**6**) and the (3*S*,4*S*)-ester (**7**).



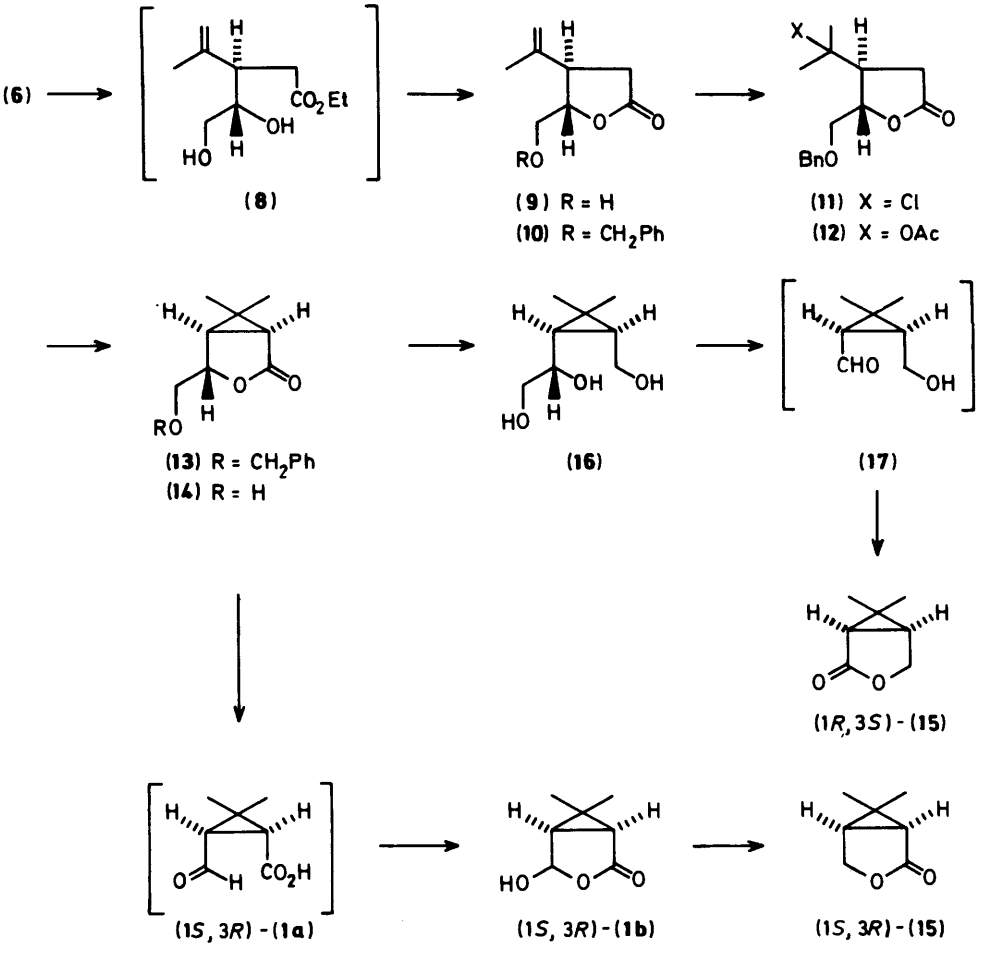
Scheme 1.

Firstly, conversion of the (3*R*,4*S*)-isomer (**6**) into optically active caronaldehyde (**1**) was attempted. When the ester (**6**) was treated with a catalytic amount of concentrated hydrochloric acid in ethanol at room temperature, spontaneous deketaliz-

ation to the diol (**8**) and lactonization occurred without difficulty to give the *trans*-substituted (3*R*,4*S*)-γ-lactone (**9**) in 86% yield. Under these conditions none of the isomeric δ-lactone could be detected. After protecting the primary hydroxy group as a benzyl ether, the lactone ether (**10**) obtained in 73% was then exposed to hydrogen chloride saturated acetic acid to give the tertiary chloride (**11**) accompanied by a minor amount of the tertiary acetate (**12**). Since the chloride (**11**) was found to be unstable under the purification conditions, the mixture was treated directly with potassium t-butoxide in tetrahydrofuran (THF) to afford the (2*S*,3*R*,4*S*)-cyclopropane lactone (**13**) in 92% overall yield from (**10**). Deprotection of (**13**) proceeded efficiently with boron tribromide at low temperature to generate the primary alcohol (**14**) in 90% yield accompanied by about 10% of the starting material which could be recycled. Conversion of compound (**14**) into (1*S*,3*R*)-caronaldehyde (**1b**) was carried out in a straightforward way in 70% overall yield after purification. Thus, the alcohol (**14**) was treated with 20% aqueous potassium hydroxide followed by sodium periodate in the same reaction flask after having been made weakly basic by introducing carbon dioxide into the mixture to furnish crystalline (1*S*,3*R*)-caronaldehyde (**1b**) as a lactone hemiacetal, single epimer after recrystallization. Although the spectral data and melting points were completely identical to those reported for the product obtained from chrysanthemic acid,[3] compound (**1b**) was further converted into the known lactone (1*S*,3*R*)-(**15**) by reduction with sodium borohydride followed by acid work-up, in order to confirm the absolute structure and optical purity. As expected it possessed the (1*S*,3*R*)-configuration and its optical rotation was virtually identical with that reported.[9]

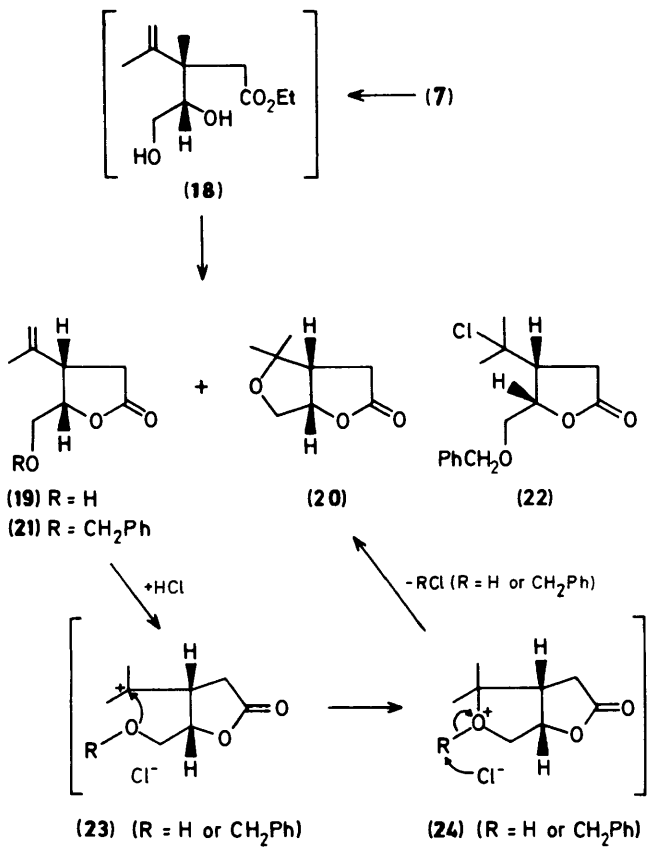
Having established the stereochemistry and optical rotations, we next attempted to convert the hydroxy lactone intermediate (**14**) into the enantiomeric (1*R*,3*S*)-lactone (**15**). Thus, compound (**14**) was reduced with lithium aluminum hydride to give the triol (**16**) which was sequentially treated with sodium periodate and Fetizon reagent (silver carbonate on Celite)[10] to afford the (1*R*,3*S*)-lactone (**15**) in 60% overall yield *via* the hydroxy aldehyde (**17**). However, it showed somewhat lower optical rotations than those reported.[9] This may be due to the prolonged reaction times in the Horner-Emmons reaction stage which could bring partial racemization of the glyceraldehyde (**3**). Improvement of optical purity could not be achieved owing to the difficulty of crystallization of the intermediates. Since conversion of the racemic lactone (**15**) into racemic caronaldehyde has been established recently,[11] (1*R*,3*S*)-caronaldehyde (**1b**) may be prepared from the (1*R*,3*S*)-lactone (**15**) by employing the same procedure.

Secondly, we attempted the same conversion using the isomeric (3*S*,4*S*)-ester (**7**). In contrast to the (3*R*,4*S*)-counterpart (**6**), hydrolytic conversion of compound (**7**) into the *cis*-lactone (**19**) under the same acidic conditions was found to be very difficult as the bicyclic ether (**20**) was formed concurrently. However, treatment of the ester (**7**) with dilute sulphuric acid in ethanol at room temperature gave the desired *cis*-substituted (3*S*,4*S*)-lactone (**19**) solely in 51% yield *via* compound (**18**). When perchloric acid was used as the acid catalyst, only the bicyclic ether (**20**) was formed in 69% yield. Benzylation of the *cis*-lactone (**19**) was difficult under the same conditions as for the *trans*-lactone (**9**) and, moreover, the benzyl ether (**21**), obtained in 34% yield, did not afford our desired tertiary



Scheme 2.

chloride (**22**) but the bicyclic ether (**20**) in 84% yield on exposure to hydrogen chloride saturated in acetic acid. The exclusive formation of compound (**20**) may be explained in terms of a proximal relationship between two *cis*-substituents which, after protonation to generate the carbenium ion (**23**), gives rise to the ether (**20**) *via* initial internal reaction followed by external reaction of chloride ion to the oxonium ion (**24**).



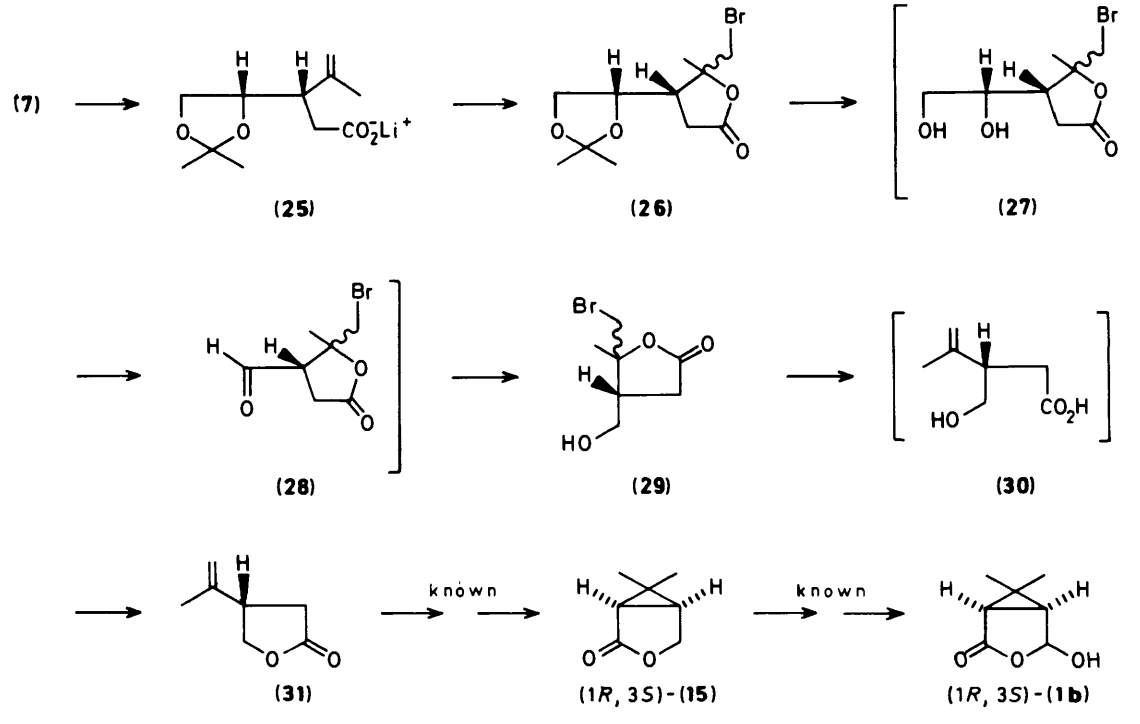
Scheme 3.

Having failed to obtain the desired intermediate (**22**) from the *cis*-(3*S*,4*S*)-isomer (**7**), we explored an alternative route. Thus, compound (**7**) was first hydrolysed with aqueous lithium hydroxide and the mixture containing the lithium carboxylate (**25**), after having been made weakly basic by introducing carbon dioxide, was treated with bromine to give the bromo lactone (**26**) in 76% overall yield as a mixture of two epimers. Upon treatment with aqueous periodic acid followed by sodium borohydride in the same flask, the mixture (**26**) afforded the hydroxy lactone (**29**) as a mixture of epimers in 70% overall yield *via* spontaneous deacetonization and oxidative cleavage followed by reduction *via* the intermediates (**27**) and (**28**).

The epimeric mixture (**29**) thus obtained was treated with zinc in hot acetic acid to give the known isopropenyl lactone (**31**),[12] *via* spontaneous reductive elimination and cyclization of the hydroxy acid intermediate (**30**) in 50% yield. However the optical rotations were found to be lower than those reported[12] which indicated partial racemization of the glyceraldehyde (**3**) at the preceding stage. Since conversion of compound (**31**) into the (1*R*,3*S*)-cyclopropyl lactone (**15**)[12] as well as the conversion of the latter in racemic forms into racemic caronaldehyde has already been achieved by us,[11] the present formation of compound (**31**) also constitutes a formal route to (1*R*,3*S*)-caronaldehyde (**1b**).

Experimental

All the reactions were carried out under argon. M.p.s were determined on a Yanagimoto MP-S2 apparatus and are uncorrected. I.r. spectra were recorded on a JASCO A-102 instrument, and ^{1}H n.m.r. spectra were measured for solutions in deuteriochloroform on JEOL-PMX 60 and JEOL-FX 100 spectrometers. Mass spectra were measured with JEOL-JMS-OISG-2 spectrometer. Optical rotations were measured with a JASCO-DIP-4 automatic polarimeter.



Scheme 4.

A Mixture of Ethyl (E)(S)-4,5-O-*Isopropylidene*-4,5-*dihydroxy*-2-*methylpent*-2-*enoate* (**4a**) *and Ethyl* (Z)(S)-4,5-O-*Isopropylidene*-4,5-*dihydroxy*-2-*methylpent*-2-*enoate* (**4b**) *from* 1,2:5,6-*Di*-O-*isopropylidene*-D-*mannitol* (**2**).—To a stirred solution of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**2**)[6] (11.0 g, 42 mmol) in 5% aqueous sodium hydrogen carbonate (50 ml) was added a saturated aqueous solution of sodium periodate (10.8 g, 50.4 mmol) dropwise at room temperature. After the reaction had been stirred for 1 h, to the mixture was added triethyl 2-methylphosphonoacetate (10 g, 42 mmol) followed by aqueous potassium carbonate (62 g in 70 ml of water) and the mixture was stirred for a further 120 h at room temperature.

The mixture was diluted with methylene dichloride (100 ml), filtered through Celite, and separated. The aqueous layer was further extracted with methylene dichloride (3 × 100 ml) and the combined organic layers were washed with brine, dried (K_2CO_3), and evaporated under reduced pressure. The remaining oil was filtered through a silica gel column (160 g) using a mixture of hexane–ether (4:1) as the eluant to give a *E*/*Z*-mixture of the α,β-unsaturated esters (**4a** and **b**) (5.25 g, 58.4%) with removal of the unchanged phosphonate. The mixture consisted of 3 parts of the *E*-ester (**4a**) to 2 parts of the *Z*-ester (**4b**) the ratio of which was deduced by n.m.r. spectroscopy. The isomers were separable by silica gel chromatography using hexane–ether (20:1) as the eluant.

The E-*ester* (**4a**): a colourless oil, b.p. 50 °C/0.06 mmHg (Kugelrohr), $[\alpha]_D^{27}$ +64.64° (*c* 1.02, $CHCl_3$); $\nu_{max.}$(neat) 1 710 and 1 652 cm^{-1}; δ 1.28 (3 H, t, *J* 7 Hz, CH_2Me), 1.40 (3 H, s, Me), 1.43 (3 H, s, Me), 1.73 (3 H, d, *J* 1.2 Hz, C=CMe), 3.60 (1 H, dd, *J* 8 and 8 Hz, HC*H*), 4.20 (2 H, q, *J* 7 Hz, C*H*$_2$Me), 4.27 (1 H, dd, *J* 8 and 8 Hz, HC*H*), 4.87 (1 H, br q, *J* 8 Hz, CHO), and 6.67 (1 H, dd, *J* 8 and 1.2 Hz, C=CH); *m*/*z* 199 (M^+ − 15) and 72 (100%) (Found: C, 61.35; H, 8.55. $C_{11}H_{18}O_4$ requires C, 61.66; H, 8.47%).

The Z-*ester* (**4b**): a colourless oil; b.p. 60 °C/0.06 mmHg (Kugelrohr), $[\alpha]_D^{21}$ +16.40° (*c* 1.01, $CHCl_3$); $\nu_{max.}$(neat) 1 712 and 1 648 cm^{-1}; δ 1.30 (3 H, t, *J* 7 Hz, CH_2Me), 1.37 (3 H, s, Me), 1.43 (3 H, s, Me), 1.93 (3 H, d, *J* 1.5 Hz, C=CMe), 3.57 (1 H, dd, *J* 8 and 7 Hz, HC*H*), 4.18 (2 H, q, *J* 7 Hz, C*H*$_2$Me), 4.28 (1 H, dd, *J* 8 and 7 Hz, HC*H*), 5.23 (1 H, br q, *J* 7 Hz, CHO), and 6.03 (1 H, dd, *J* 7 and 1.5 Hz, C=CH); *m*/*z* 199 (M^+ − 15) and 111 (100%) (Found: C, 61.85; H, 8.6. $C_{11}H_{18}O_4$ requires C, 61.66; H, 8.47%).

(E)(S)-4,5-O-*Isopropylidene*-2-*methylpent*-2-*ene*-1,4,5-*triol* (**5a**).—To a stirred solution of compound (**4a**) (836 mg, 3.90 mmol) in THF (20 ml) was added 2.23M-di-isobutylaluminium hydride in toluene (3.5 ml, 7.81 mmol) at 0 °C. After 10 min, the mixture was treated with ammonium hydroxide (10 ml) and was stirred with methylene dichloride (50 ml) for 3 h at room temperature. After the reaction mixture had been filtered through Celite, the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure to give (**5a**) (544 mg, 81.1%) as a colourless oil which could be used for the following reaction without further purification, b.p. 75 °C/0.08 mmHg (Kugelrohr); $[\alpha]_D^{18}$ +11.48° (*c* 1.08, $CHCl_3$); $\nu_{max.}$(neat) 3 430 and 1 650 cm^{-1}; δ 1.40 (6 H, s, 2 × Me), 1.73 (3 H, s, C=CMe), 1.73 (1 H, br s, exchangeable, OH), 3.53 (1 H, dd, *J* 8 and 8 Hz, HC*H*), 4.03 (2 H, s, CH_2), 4.07 (1 H, dd, *J* 8 and 6 Hz, HC*H*), 4.83 (1 H, ddd, *J* 8, 8 and 6 Hz, CH), and 5.50 (1 H, br d, *J* 8 Hz, C=CH); *m*/*z* 157 (M^+ − 15) and 72 (100%) (Found: C, 62.7; H, 9.5. $C_9H_{16}O_3$ requires C, 62.76; H, 9.36).

(Z)(S)-4,5-O-*Isopropylidene*-2-*methylpent*-2-*ene*-1,4,5-*triol* (**5b**).—Compound (**4b**) (928 mg, 4.34 mmol) in THF (20 ml) was reduced with 2.23M-di-isobutylaluminium hydride in toluene (3.85 ml, 8.67 mmol) and the mixture was treated as for compound (**4a**) to give the *triol* (**5b**) (692 mg, 92.7%) as a colourless oil; b.p. 90—95 °C/0.3 mmHg (Kugelrohr); $[\alpha]_D^{18}$ +9.68° (*c* 1.01, $CHCl_3$); $\nu_{max.}$(neat) 3 410 and 1 670 cm^{-1}; δ 1.42 (6 H, s, 2 × Me), 1.85 (3 H, d, *J* 1 Hz, Me), 1.98 (1 H, br s, exchangeable, OH), 3.53 (1 H, dd, *J* 8 and 8 Hz, HC*H*), 4.08 (1 H, dd, *J* 8 and 6 Hz, HC*H*), 4.18 (2 H, s, CH_2), 4.87 (1 H, ddd, *J* 8, 8, and 6 Hz, CH), 5.37 (1 H, br d, *J* 8 Hz, C=CH); *m*/*z* 157 (M^+ − 15) and 72 (100%) (Found: C, 62.55; H, 9.8).

Reduction of the Mixture of Compounds (**4a** and **b**).—To a stirred solution of the mixture of (**4a** and **b**) (6.63 g, 31.0 mmol) in THF (70 ml), was added 2.23M-di-isobutylaluminium hydride in toluene (27 ml, 62.0 mmol) at 0 °C. After 10 min, the mixture was treated with ammonium hydroxide (10 ml) and was stirred with methylene dichloride (200 ml) for 3 h at room temperature. After the reaction mixture had been filtered through Celite, the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure to give a mixture of compound (**5a**) and (**5b**) (5.16 g, 96.8%) as a colourless oil which could be used for the following reaction without further purification.

Claisen Rearrangement of the (E)-*Allyl Alcohol* (**5a**).—A stirred mixture of compound (**5a**) (528 mg, 3.07 mmol) and triethyl orthoacetate (3.9 ml, 21.5 mmol) was heated at 140 °C in the presence of pivalic acid (19 mg); low boiling material so generated was removed using a Dean-Stark separator. After 3 h, low boiling material was removed under reduced pressure and the residue was chromatographed on a silica gel column (75 g) using hexane–ether (9:1) as the eluant to give a mixture of (3*R*,4*S*)-ethyl 4,5-*O*-isopropylidene-4,5-dihydroxy-3-isopropenylpentanoate (**6**) and (3*S*,4*S*)-ethyl 4,5-*O*-isopropylidene-4,5-dihydroxy-3-isopropenylpentanoate (**7**) (543 mg, 73.0%) as a colourless oil. The mixture consisted of *ca.* equal amounts of the two isomers as deduced by n.m.r. spectroscopy. The isomers were separable by silica gel column chromatography using hexane–ether (20:1) as the eluant.

The (3R,4S)-*ester* (**6**): b.p. 95—100 °C/0.3 mmHg (Kugelrohr); $[\alpha]_D^{25}$ +0.87° (*c* 2.07, $CHCl_3$); $\nu_{max.}$(neat) 1 735 and 1 645 cm^{-1}; δ 1.23 (3 H, t, *J* 7 Hz, CH_2Me), 1.33 (3 H, s, Me), 1.40 (3 H, s, Me), 1.72 (3 H, d, *J* 1 Hz, C=CMe), 2.30—2.93 (3 H, m), 3.60—4.27 (5 H, m), and 4.83 (2 H, br s, =CH_2); *m*/*z* 242 (M^+), 227 (M^+ − 15), and 101 (100%) (Found: C, 64.9; H, 9.2. $C_{13}H_{22}O_4$ requires C, 64.44; H, 9.15).

The (3S,4S)-*ester* (**7**): b.p. 95—100 °C/0.3 mmHg (Kugelrohr); $[\alpha]_D^{25}$ +6.12° (*c* 2.03, $CHCl_3$); $\nu_{max.}$(neat) 1 733 and 1 645 cm^{-1}; δ 1.23 (3 H, t, *J* 7 Hz, CH_2Me), 1.33 (3 H, s, Me), 1.40 (3 H, s, Me), 1.80 (3 H, s, C=CMe), 2.07—3.02 (3 H, m), 3.50—4.43 (5 H, m), 4.73 (1 H, br s, =CH_2), and 4.83 (1 H, br s, =CH_2); *m*/*z* 227 (M^+ − 15) and 101 (100%) (Found: C, 64.15; H, 9.0).

Claisen Rearrangement of the (Z)-*Allyl Alcohol* (**5b**).—A mixture of compound (**5b**) (682 mg, 3.97 mmol) and triethyl orthoacetate (3.6 ml, 19.85 mmol) was treated as for compound (**5a**) in the presence of pivalic acid (24 mg) to give a 1:1 mixture of compounds (**6**) and (**7**) (867 mg, 90.0%).

Claisen Rearrangement of the Mixture of the (E)-*Allyl Alcohol* (**5a**) *and* (Z)-*Allyl Alcohol* (**5b**).—A mixture of the *E*/*Z* mixture (3:2) (6.77 g, 39.4 mmol) and triethyl orthoacetate (12.77 g, 78.7 mmol) was treated as for (**5a**) and (**5b**) in the presence of pivalic acid (241 mg, 2.36 mmol) to give a 1:1 mixture of compounds (**6**) and (**7**) (8.74 g, 91.7%), which was separated by silica gel column chromatography using hexane–ether (20:1) as the eluant.

(3R,4S)-4,5-*Dihydroxy*-3-*isopropenylpentanoic Acid* γ-*Lactone* (**9**).—A solution of the ester (**6**) (2.74 g, 11.3 mmol) in ethanol (30 ml) containing concentrated hydrochloric acid (0.3

ml) was stirred at room temperature for 24 h. The mixture was evaporated under reduced pressure and the residue was distilled to give the γ-lactone (**9**) (1.51 g, 85.9%) as a colourless oil; b.p. 160—170 °C/0.03 mmHg (Kugelrohr); $[\alpha]_D^{28}$ +50.98° (*c* 1.02, $CHCl_3$); $\nu_{max.}$(neat) 3 410, 1 765, and 1 642 cm^{-1}; δ 1.76 (3 H, t, *J* 1 Hz, Me), 2.48 (1 H, dd, *J* 17 and 8.5 Hz, HC*H*), 2.78 (1 H, dd, *J* 17 and 18 Hz, HC*H*), 3.10 (1 H, br s, exchangeable, OH), 3.01—3.26 (1 H, m, CH), 3.52—4.04 (2 H, m, CH_2OH), 4.33—4.47 (1 H, m, CHO), 4.87 (2 H, br s, $=CH_2$); *m/z* 125 ($M^+ - 31$), 68 (100%) (Found: C, 61.15; H, 7.65. $C_8H_{12}O_3$ requires C, 61.52; H, 7.75).

(3R,4S)-5-*Benzyloxy*-4-*hydroxy*-3-*isopropenylpentanoic Acid Lactone* (**10**).—To a stirred suspension of sodium hydride (559 mg, 13.98 mmol; obtained from 60% mineral oil dispersion by washing with hexane) in DMF (40 ml) was added compound (**9**) (1.98 g, 12.7 mmol) at −20 °C and the mixture was stirred for 1 h at room temperature. Then to the cooled (−20 °C) mixture, was added benzyl bromide (2.1 ml, 15.2 mmol) with stirring and the stirring was continued overnight. The mixture was evaporated under reduced pressure and the residue was diluted with ether (100 ml). The organic layer was washed with water (2 × 20 ml) and the aqueous layer was made acidic with 10% hydrochloric acid. The aqueous layer was extracted with methylene dichloride (3 × 50 ml) and the extract was washed with brine (2 × 20 ml). The combined organic layers were dried ($MgSO_4$), evaporated under reduced pressure, and purified on a silica gel column (100 g) using hexane–ether (2:1) as the eluant to give the benzyl ether (**10**) [1.66 g, 53.1%; 72.8% based on the consumed starting material (**9**)] and the starting material (**9**) (536 mg, 27.1%).

The benzyl ether (**10**): b.p. 160—170 °C/0.3 mmHg (Kugelrohr); $[\alpha]_D^{23}$ +25.24° (*c* 1.02, $CHCl_3$); $\nu_{max.}$(neat) 1 775 and 1 642 cm^{-1}; δ 1.73 (3 H, s, Me), 2.17—2.70 (2 H, m, CH_2), 2.90—3.27 (1 H, m, CH), 3.52 (1 H, dd, *J* 11 and 4 Hz, HC*H*), 3.73 (1 H, dd, *J* 11 and 3 Hz, HC*H*), 4.30—4.50 (1 H, m, CHO), 4.53 (2 H, s, $PhCH_2O$), 4.80 (2 H, d, *J* 1 Hz, $=CH_2$), and 7.23 (5 H, s, ArH); *m/z* 246 (M^+), 91 (100%) (Found: C, 73.25; H, 7.45. $C_{15}H_{18}O_3$ requires C, 73.14; H, 7.37).

(3R,4S)-5-*Benzyloxy*-3-(1-*chloro*-1-*methylethyl*)-4-*hydroxypentanoic Acid Lactone* (**11**) *and* (3R,4S)-3-(1-*Acetoxy*-1-*methylethyl*)-5-*benzyloxy*-4-*hydroxypentanoic Acid Lactone* (**12**).—The benzyl lactone (**10**) (839 mg, 3.41 mmol) was dissolved in stirred acetic acid saturated with hydrogen chloride (40 ml) at room temperature. After the reaction had been stirred for 48 h, the mixture was poured into ice–water (100 ml) and the solution was extracted with methylene dichloride (3 × 150 ml). The extract was washed with saturated aqueous sodium hydrogen carbonate (50 ml) and brine (50 ml), and was then dried ($MgSO_4$) and evaporated under reduced pressure to give the crude compound (**11**) containing about 10% of compound (**12**) (1.11 g, *ca.* 100%) which could be used for the next reaction without further purification. Separation was achieved by silica gel column chromatography though a considerable amount of (**11**) decomposed during the purification.

The chloro lactone (**11**): $[\alpha]_D^{26}$ +2.66° (*c* 1.05, $CHCl_3$); $\nu_{max.}$(neat) 1 770 cm^{-1}; δ 1.57 (6 H, s, 2 × Me), 2.37—2.97 (3 H, m, CH_2CH), 3.57 (1 H, dd, *J* 11 and 3 Hz, HC*H*), 3.80 (1 H, dd, *J* 11 and 3 Hz, HC*H*), 4.57 (2 H, s, $PhCH_2$), 4.63—4.77 (1 H, m, CHO), and 7.30 (5 H, s, ArH); *m/z* 282 (M^+), 284 ($M^+ + 2$), 91 (100%) (Found: C, 63.75; H, 6.9; Cl, 12.85. $C_{15}H_{19}ClO_3$ requires C, 63.72; H, 6.77; Cl, 12.54).

The acetoxy lactone (**12**): $\nu_{max.}$(neat) 1 768 and 1 725 cm^{-1}; δ 1.47 (6 H, s, 2 × Me), 1.95 (3 H, s, Me), 2.43—2.72 (3 H, m, CH_2CH), 3.50 (1 H, dd, *J* 11 and 4 Hz, HC*H*), 3.73 (1 H, dd, *J* 11 and 3 Hz, HC*H*), 4.53 (2 H, s, $PhCH_2O$), 4.50—4.67 (1 H, m, CHO), and 7.25 (5 H, s, ArH); *m/z* 247 ($M^+ - 59$) and 91 (100%).

(1S,3R)-3-(2-*Benzyloxy*-1-*hydroxyethyl*)-2,2-*dimethylcyclopropanecarboxylic Acid Lactone* (**13**).—A THF (5 ml) solution of the crude compound (**11**), containing *ca.* 10% of compound (**12**), (1.11 g, *ca.* 3.4 mmol) was added to a THF (10 ml) solution containing potassium t-butoxide (553 mg, 4.43 mmol) at 0 °C with stirring. After 10 min, the reaction mixture was diluted with ether (50 ml) and the solution was washed with water (2 × 20 ml), brine (20 ml), dried ($MgSO_4$), and then evaporated under reduced pressure. The combined aqueous layers were made acidic with 5% hydrochloric acid and extracted with ether (3 × 30 ml). The extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to leave a residue containing the seco-acid which was refluxed in toluene (5 ml) for 12 h and evaporated under reduced pressure.

The combined concentrates were distilled to give (**13**) (770 mg, 91.8%) as a colourless oil which crystallized gradually with time as colourless needles, b.p. 180 °C/0.8 mmHg (Kugelrohr); m.p. 66—67 °C (hexane–ether); $[\alpha]_D^{28}$ +46.80° (*c* 1.00, $CHCl_3$); $\nu_{max.}$(neat) 1 758 cm^{-1}; δ 1.10 (3 H, s, Me), 1.13 (3 H, s, Me), 1.97 (2 H, s, 2 × CH), 3.60 (2 H, d, *J* 4 Hz, $PhCH_2OCH_2$), 4.32 (1 H, br t, *J* 4 Hz, CHO), 4.53 (2 H, s, $PhCH_2O$), and 7.30 (5 H, s, ArH); *m/z* 246 (M^+) and 91 (100%) (Found: C, 72.95; H, 7.2. $C_{15}H_{18}O_3$ requires C, 73.14; H, 7.37).

(1S,3R)-3-(1,2-*Dihydroxyethyl*)-2,2-*dimethylcyclopropanecarboxylic Acid* γ-*Lactone* (**14**).—To a stirred solution of the distilled compound (**13**) (207 mg, 0.84 mmol) in methylene dichloride (2 ml) was added dropwise 1M-boron tribromide in methylene dichloride (0.93 ml) at −73 °C. After 1.5 h, the reaction was quenched by addition of saturated aqueous hydrogen carbonate (1 ml) and the organic layer was separated and the aqueous layer was extracted with methylene dichloride (3 × 20 ml). The combined organic layers were washed with brine, dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed on a silica gel column (13 g) using hexane–ethyl acetate (2:1) as the eluant to give (**14**) [118 mg, 89.7%, 97.7% based on the consumed starting material (**13**)] as a colourless oil, b.p. 100—110 °C/0.9 mmHg (Kugelrohr); $[\alpha]_D^{26}$ +42.10° (*c* 0.57, $CHCl_3$); $\nu_{max.}$(neat) 3 330 and 1 745 cm^{-1}; δ 1.20 (6 H, s, 2 × Me), 1.98 (2 H, s, 2 × CH), 2.57 (1 H, br s, exchangeable, OH), 3.53—4.07 (2 H, m, CH_2O), 4.32 (1 H, br t, *J* 5 Hz, CHO); *m/z* 157 ($M^+ + 1$) and 96 (100%) (Found: C, 61.15; H, 7.9. $C_8H_{12}O_3$ required C, 61.52; H, 7.75).

cis-(1S,3R)-*Caronaldehyde* (**1b**).—The lactone (**14**) (100 mg, 0.64 mmol) was stirred with 20% aqueous potassium hydroxide (2.0 ml) for 30 min at room temperature. Carbon dioxide was then introduced to make reaction mixture nearly neutral and saturated aqueous sodium periodate (206 mg, 0.96 mmol) solution was added dropwise at 0 °C. After 30 min, the mixture was made acidic (pH 2) with 5% hydrochloric acid and extracted with methylene dichloride (3 × 30 ml). The extract was dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed on a silica gel column (3 g) using hexane–ether (1:1) as the eluant. Recrystallization from pentane–ether then gave (1*S*,3*R*)-(**1b**) (63 mg, 69.7%) as colourless prisms, m.p. 114.5—115.5° C; $[\alpha]_D^{28}$ +99.41° (*c* 0.68, EtOH) {lit.,[3] m.p. 116 °C; $[\alpha]_D^{20}$ +103° (*c* 0.9, EtOH)}; $\nu_{max.}$(neat) 3 300 and 1 720 cm^{-1}; δ 1.20 (6 H, s, 2 × Me), 2.10 (2 H, s, 2 × CH), 5.50 (1 H, br s, exchangeable, OH), and 5.13—5.87 (1 H, m, CHO); *m/z* 127 ($M^+ - 15$) and 67 (100%).

(1S,3R)-3-*Hydroxymethyl*-2,2-*dimethylcyclopropanecarboxylic Acid Lactone* (**15**) *from the* cis-(1S,3R)-*Caronaldehyde* (**1b**).—To a stirred solution of (1*S*,3*R*)-(**1b**) (67 mg, 0.47 mmol)

in ethanol (5 ml) was added sodium borohydride (36 mg, 0.94 mmol) at 0 °C. After 30 min most of ethanol was evaporated under reduced pressure and the residue was dissolved in water (5 ml) which was then made acidic (pH 2) with 5% hydrochloric acid. After the reaction had been stirred for 3 h, the mixture was extracted with methylene dichloride (3 × 20 ml) and the extract was dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed on a silica gel column (3 g) using hexane–ether (3:1) as the eluant to give the (1*S*,3*R*)-lactone (**15**) (40 mg, 67.5%) as a colourless oil; b.p. 70—75 °C/18 mmHg (Kugelrohr); $[\alpha]_D^{24}$ +72.83° (*c* 2.12, $CHCl_3$) {lit., b.p. 70 °C/10.5 mmHg;[11] $[\alpha]_D^{25}$ −72.8° (*c* 1.4, $CHCl_3$) for the (1*R*,3*S*)-enantiomer (**15**)[9]}. Spectral data (i.r., n.m.r., and mass) were identical with those reported.[11]

(1R,3S)-3-*Hydroxymethyl*-2,2-*dimethylcyclopropanecarboxylic Acid Lactone* (**15**) *from* (1S,3R)-3-(1,2-*Dihydroxyethyl*)-2,2,-*dimethylcyclopropanecarboxylic Acid* γ-*Lactone* (**14**).—To a stirred solution of lithium aluminium hydride (69 mg, 1.87 mmol) in THF (5 ml), was added (1*S*,3*R*)-(**14**) (191 mg, 1.23 mmol) in THF (1 ml) at 0 °C. After 30 min, the reaction was quenched by the addition of ammonium hydroxide. The mixture was filtered through Celite and the filtrate was evaporated under reduced pressure to give the crude triol (**16**) (185 mg). The crude triol (**16**) (185 mg) was dissolved in water (1 ml) and was treated with sodium periodate (296 mg, 1.38 mmol) in water (1 ml) at 0 °C. After 30 min, the mixture was made acidic with 10% hydrochloric acid and extracted with methylene dichloride (3 × 30 ml). The extract was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give the crude aldehyde (**17**) (129 mg). The crude compound (**17**) (129 mg) thus obtained in methylene chloride (4 ml) was then refluxed with Fetizon reagent (645 mg, *ca.* 11 mmol) in benzene (10 ml) for 1 h with stirring. The filtered reaction mixture was evaporated under reduced pressure and chromatographed on a silica gel column (1 g) using hexane–ether (4:1) as the eluant to give (1*R*,3*S*)-(**15**) (92 mg, 60% overall) as a colourless oil: b.p. 70—75 °C/15 mmHg (Kugelrohr); $[\alpha]_D^{27}$ −53.37° (*c* 1.08, $CHCl_3$) {lit., 70 °C/10.5 mmHg;[11] $[\alpha]_D^{25}$ −72.8° (*c* 1.4, $CHCl_3$)[9]}. Spectral data (i.r., n.m.r., and mass) were identical with those reported.[11]

(3S,4S)-4,5-*Dihydroxy*-3-*isopropenylpentanoic Acid* γ-*Lactone* (**19**).—A solution of the ester (**7**) (318 mg, 1.31 mmol) in a mixture of ethanol (5 ml) and 10% sulphuric acid (5 ml) was stirred at room temperature for 7 h. Most of the ethanol was removed under reduced pressure, and the remaining aqueous mixture was extracted with methylene dichloride (3 × 20 ml). The extract was washed with brine, dried (Na_2SO_4), evaporated under reduced pressure, and chromatographed on a silica gel column (20 g) using hexane–ether (1:2) as the eluant to give the γ-lactone (**19**) (104 mg, 50.9%) as a colourless oil: $[\alpha]_D^{30}$ + 59.94° (*c* 0.82, $CHCl_3$); $\nu_{max.}$(neat) 3 420, 1 770, and 1 642 cm^{-1}; δ 1.80 (3 H, s, Me), 2.51 (1 H, dd, *J* 17 and 8.5 Hz, HC*H*), 2.78 (1 H, br s, exchangeable, OH), 2.80 (1 H, dd, *J* 17 and 8 Hz, HC*H*), 3.28 (1 H, br q, *J* 8.5 Hz, CH), 3.69 (2 H, br t, *J* 5 Hz, CH_2OH), 4.58—4.75 (1 H, m, CHO), 4.87 (1 H, br s, =CH_2), and 4.99 (1 H, br s, =CH_2); *m/z* 156 (M^+), 68 (100%) (Found: C, 61.5; H, 7.8. $C_8H_{12}O_3$ requires C, 61.52; H, 7.75).

(3R)-[(4S)-*Hydroxy*-2,2-*dimethyltetrahydrofuranyl*]*acetic Acid Lactone* (**20**) *from the* (3S,4S)-*Ester* (**7**).—A solution of (3*S*,4*S*)-(**7**) (2.10 g, 8.69 mmol) in THF (19 ml) containing 70% perchloric acid (1 ml) was stirred at room temperature for 1 h. The mixture was diluted with methylene dichloride (100 ml) and the solution was washed with brine (20 ml). The washing was re-extracted with methylene dichloride (2 × 50 ml). The combined organic layers were dried ($MgSO_4$), evaporated under reduced pressure and the residue was distilled to give the bicyclic lactone (**20**) (940 mg, 69.3%), b.p. 90—95 °C/0.4 mmHg (Kugelrohr); $[\alpha]_D^{23}$ +10.32° (*c* 1.01, $CHCl_3$); $\nu_{max.}$(neat) 1 770 cm^{-1}; δ 1.23 (6 H, s, 2 × Me), 2.50—3.00 (3 H, m, CH_2CH), 3.98 (2 H, d, *J* 3 Hz, CH_2), and 4.97—5.23 (1 H, m, CHO); *m/z* 141 (M^+ − 15, 100%) (Found: C, 61.2; H, 8.2. $C_{18}H_{12}O_3$ requires C, 61.52; H, 7.75).

(3S,4S)-5-*Benzyloxy*-4-*hydroxy*-3-*isopropenylpentanoic Acid Lactone* (**21**).—To a stirred suspension of sodium hydride (129 mg, 3.22 mmol; obtained from 60% mineral oil dispersion by washing with hexane) in THF (10 ml) was added (**19**) (419 mg, 2.69 mmol) at 0 °C and the mixture was stirred for 1 h at room temperature. Benzyl bromide (0.48 ml, 4.03 mmol) was then added at 0 °C and the stirring was continued for a further 12 h at room temperature. The mixture was diluted with ether (30 ml) and the solution was washed with water (3 × 20 ml), and brine (20 ml), then dried ($MgSO_4$), evaporated under reduced pressure. Chromatography on a silica gel column (30 g) using hexane–ether (2:1) as the eluant gave the lactone (**21**) (224 mg, 33.9%) as a colourless oil, b.p. 150 °C/0.2 mmHg (Kugelrohr); $[\alpha]_D^{26}$ +43.5° (*c* 1.02, $CHCl_3$); $\nu_{max.}$(neat) 1 775, 1 640 cm^{-1}; δ 1.77 (3 H, s, CH_3), 2.20—2.73 (2 H, m, CH_2), 3.00—3.40 (1 H, m, CH), 3.58 (2 H, d, *J* 3 Hz, PhCH_2OCH_2), 4.48 (2 H, s, PhCH_2), 4.57—4.77 (1 H, m, CHO), 4.83 (1 H, br s, =CH_2), 4.98 (1 H, br s, =CH_2), and 7.28 (5 H, s, ArH); *m/z* 246 (M^+) and 91 (100%) (Found: C, 72.75; H, 7.7. $C_{15}H_{18}O_3$ requires C, 73.14; H, 7.37).

(3R)-[(4S)-*Hydroxy*-2,2-*dimethyltetrahydrofuranyl*]*acetic Acid Lactone* (**20**) *from Compound* (**21**).—The benzyloxy lactone (**21**) (138 mg, 0.56 mmol) was dissolved in stirred acetic acid saturated with hydrogen chloride (7 ml) at room temperature. After the reaction had been stirred for 16 h, the mixture was poured into ice–water (50 ml) and the solution was extracted with methylene dichloride (3 × 30 ml). The extract was washed with saturated aqueous sodium hydrogen carbonate (2 × 50 ml) and brine (50 ml), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed on a silica gel column (7 g) using hexane-ether (3:1) as the eluant to give the bicyclic lactone (**20**) (73 mg, 83.6%) as a colourless oil. Spectral data were identical with those of the product (**20**) obtained from compound (**7**).

Preparation of the Bromo Lactone Acetonide (**26**) *from the* (3S,4S)-*Ester* (**7**).—The (3*S*,4*S*)-ester (**7**) (287 mg, 1.18 mmol) was stirred with lithium hydroxide (monohydrate, 149 mg, 5.9 mmol) in water (5 ml) for 15 h at room temperature. The pH of the reaction mixture was adjusted to 7 with carbon dioxide, prior to the addition of bromine (0.07 ml, 1.3 mmol) at 0 °C. After the mixture had been stirred for 30 min at the same temperature, the mixture was extracted with methylene dichloride (3 × 20 ml). The extract was washed successively with saturated aqueous sodium hydrogen carbonate (10 ml), 10% aqueous sodium thiosulphate (10 ml), brine (10 ml), and was then dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed on a silica gel column (10 g) using hexane–ether (1:1) as eluant to give the bromo lactone (**26**) (263 mg, 76%) as two epimers.

Epimer A: $\nu_{max.}$(neat) 1 778 cm^{-1}; δ 1.33 (3 H, s, Me), 1.43 (3 H, s, Me), 1.63 (3 H, s, Me), 2.50—2.77 (3 H, m), and 3.47—4.63 (5 H, m); *m/z* 279 (M^+ − 13), 277 (M^+ − 15), 141 (100%).

Epimer B: $\nu_{max.}$(neat) 1 776 cm^{-1}; δ 1.33 (3 H, s, Me), 1.43 (3 H, s, Me), 1.53 (3 H, s, Me), 2.20—3.10 (3 H, m), 3.47—3.83 (3 H, m), and 3.90—4.30 (2 H, m); *m/z* 279 (M^+ − 13) and 277 (M^+ − 15, 100%).

Preparation of the Hydroxy Lactone (**29**) *from the Bromo Lactone Acetonide* (**26**).—A solution of the acetonide (**26**) (263

mg, 0.89 mmol) and periodic acid (98%, 621 mg, 2.68 mmol) in 50% aqueous THF (4 ml) was stirred at room temperature for 24 h. After the mixture had been made alkaline (pH 9) with saturated aqueous sodium hydrogen carbonate, sodium borohydride (101 mg, 2.86 mmol) was added with stirring at 0 °C. Stirring was continued for 30 min at the same temperature, before the mixture was made acidic (pH 2) with 5% hydrochloric acid and then for a further 1 h at room temperature. The mixture was extracted with methylene dichloride (3 × 20 ml) and the extract was successively washed with saturated aqueous sodium hydrogen carbonate, 10% aqueous sodium thiosulphate, brine (10 ml each), and then dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed on a silica gel column (8 g) using hexane-ether (1:2) as the eluant to give the oily hydroxy lactone (**29**) (140 mg, 70.3%) as an inseparable diastereoisomeric mixture, $\nu_{max.}$(neat) 3 440 and 1 760 cm^{-1}; δ 1.53 and 1.63 (3 H, each s, Me), 2.33—3.17 (4 H, m), and 3.66—3.97 (4 H, m); *m/z* 130 ($M^+ - 94$, 100%).

(S)-4-*Hydroxy*-3-*isopropenylbutanoic Acid Lactone* (**31**).—A suspension of the hydroxy lactone (**29**) (133 mg, 0.59 mmol) and zinc powder (388 mg, 5.94 mmol) in acetic acid (1 ml) was refluxed with stirring for 5 h. The mixture was diluted with ether (20 ml) and the solution was filtered through Celite. The filtrate was evaporated under reduced pressure and the residue was chromatographed on a silica gel column (10 g) using hexane–ether (4:1) as eluant to give the isopropenyl lactone (**31**) (37 mg, 49.8%) as a colourless oil: b.p. 80—85 °C/15 mmHg (Kugelrohr); $[\alpha]_D^{28}$ +11.77° (*c* 1.07, $CHCl_3$) [lit.,[12] b.p. 70 °C/0.4 mmHg; $[\alpha]_D$ +15.09° (*c* 4.958, $CHCl_3$)]. Spectral data (i.r., n.m.r., and mass) were identical with those reported.[12]

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