Radical Additions onto Enols and Enol Ethers as a Stratagem in Synthesis. Total Synthesis of the Unique Epoxy-lactone (±)-Alliacolide found in *Marasmius alliaceus*

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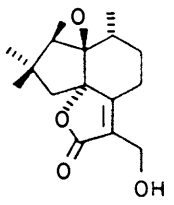
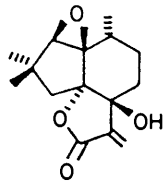
The use of intramolecular radical additions onto enols and enol ethers is illustrated in a total synthesis of (±)-alliacolide (**3**), its methyl ether (**39**), noralliacolide (**25**), and several isomeric compounds. The overall strategy for the synthesis of these unique epoxy-lactones is based on (i) spiro-annulation of the tetronic acid ring in the key intermediate (**11**) *via* the cyclopentenone (**13**); (ii) 6-*exo*-trig radical cyclisation from (**11**) to the tricycle (**10**), and (iii) stereocontrolled epoxidation of the β-orientated hydroxy intermediate (**10**). A novel feature of this synthesis of (±)-alliacolide (**3**) is the regio- and stereoselective radical cyclisation leading to (**10**), which introduces three contiguous chiral centres in the correct relative configuration in the tricycle, in a single step.

The alliacolides, exemplified by alliacol A (**1**), alliacol B (**2**) and alliacolide (**3**) are a unique family of epoxy-lactones which were first isolated in 1977 from the culture fluid of the Basidiomycete *Marasmius alliaceus*.[1] Additional metabolites clearly related biogenetically to compounds (**1**)—(**3**) have been found more recently in the same fungus, and these include the noralliacolide (**4**), the hydroxyalliacolides (**5a**), (**5b**), and (**6**), and the deoxy compound (**7**). Alliacolide (**3**) constitutes 75% of the dry ether extract of the culture fluid of *M. alliaceus*, and the metabolite has been found to exhibit useful antifungal and bacteriostatic activity. By contrast, the unsaturated lactones (**1**) and (**2**) show significant cytotoxic activity against cells of the ascitic form of Erlich carcinoma, and have been shown to inhibit DNA synthesis.[1g]



(**1**)



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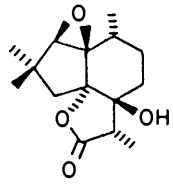

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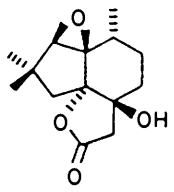
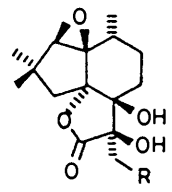
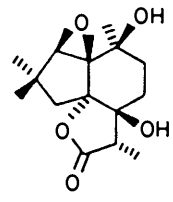


(**4**)

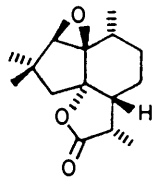


(**5**)

a; R = H
b; R = OH



(**6**)



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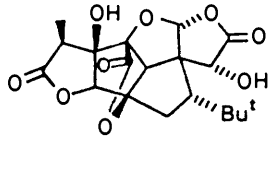
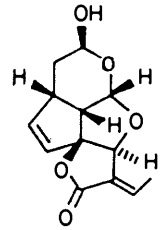
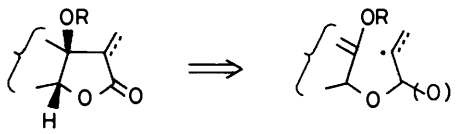


(**8**)



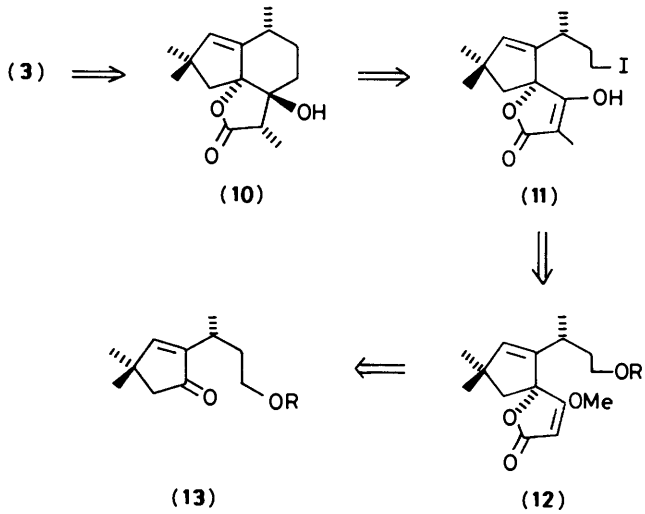
(**9**)

Alliacolide (**3**) and alliacol B(**2**) are related structurally to other natural products such as ginkgolide (**8**)[2] and allamcin (**9**),[3] which show similar novel and unusual β-oxy-γ-butyrolactone units associated with their ring systems. In the previous paper we described a new synthetic approach to the synthesis of β-oxy-γ-butyrolactones, which was based on intramolecular addition of an sp^3 or sp^2 carbon radical centre to the α-centre of an enol ether according to Scheme 1.[4] In this paper we describe a total synthesis of (±)-alliacolide (**3**) which develops the aforementioned principle, and features a novel stereoselective intramolecular radical cyclisation onto an enolic double bond *viz.* (**11**)→(**10**) as a key step to elaborate the tricycle in (**3**).[5]



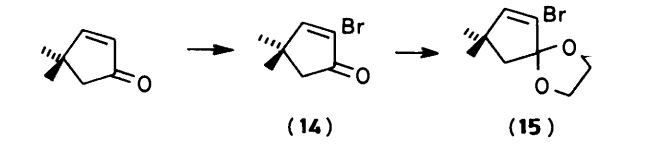
Scheme 1.

The strategy for our synthesis of alliacolide (**3**) is summarised in Scheme 2, and was based on: (i) spiro-annulation of the tetronic ring system onto the substituted cyclopentenone (**13**) *via* the intermediate (**12**); (ii) 6-*exo*-trig radical cyclisation from (**11**) leading to the tricycle (**10**), and (iii) the stereocontrolled epoxidation of the β-hydroxy intermediate (**10**).

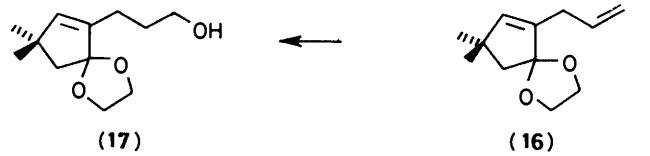


Scheme 2.

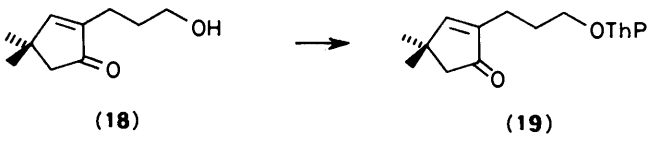
We began our studies of the above strategy to alliacolide (**3**), by first investigating the details using the more easily accessible model compound (**23a**) lacking a side chain methyl group. Thus, conversion of 4,4-dimethylcyclopent-2-enone[6] into the corresponding α-bromo derivative (**14**), followed by protection as the dioxolane (**15**), halogen-metal exchange, and alkylation with 3-bromoprop-1-ene first gave the 1,4-diene (**16**).[7] Hydroboration–oxidation of the 1,4-diene (**16**) then led to the alcohol (**17**), which after de-ketalisation to (**18**) could be converted into the tetrahydropyranyl ether (**19**).



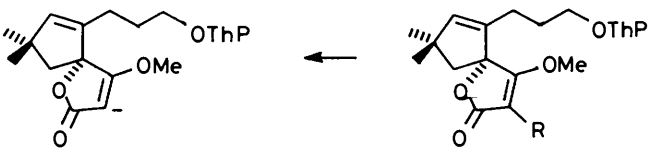
(**14**) (**15**)



(**17**) (**16**)



(**18**) (**19**)



(**21**) (**20**)

a ; R = H
b ; R = Me

(**22**)

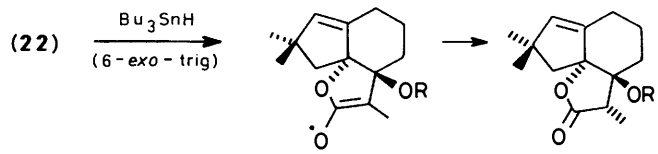
R
a ; OH
b ; OMs
c ; I
d ; H

(**23**)

a ; R = I
b ; R = H

When a solution of the cyclopentenone (**19**) was added to three equivalents of the lithium salt derived from ethyl propiolate, and the resulting hydroxy-ynoate was treated with sodium methoxide in methanol, the required spiro-tetronate (**20a**) was secured in 46% overall yield.[8] Treatment of the spiro-tetronate (**20a**) with lithium di-isopropylamide at −78 °C, followed by quenching the resulting vinyl anion (**21**) with iodomethane, by analogy with our earlier investigations,[9] then provided the α-methyltetronate (**20b**). The conversion of compound (**20b**) into the corresponding iodo-compound (**22c**) was smoothly accomplished following hydrolysis to the alcohol (**22a**), mesylation to (**22b**), and nucleophilic displacement with sodium iodide in hot acetone. Finally, treatment of the iodo methyl ether (**22c**) with trimethylsilyl iodide led to the polar spiro-tetronic acid (**23a**).

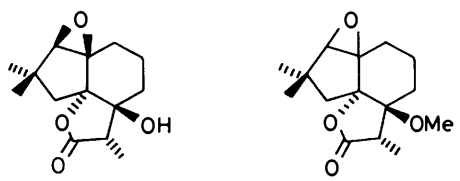
The crucial radical cyclisation step [*cf.* Scheme 2; (**11**)→(**10**)] was first explored using the iodo tetronic acid methyl ether (**22c**). Under optimum conditions, whereby a solution of tributylstannane (Bu_3SnH) and azoisobutyronitrile (AIBN) was added slowly to a solution of the iodide (**22c**) in benzene maintained at 80 °C, a single crystalline diastereoisomer of the tricycle (**24a**) could be secured in over 95% yield. When these reaction conditions were applied to the sparingly soluble tetronic acid (**23a**) however, a more disappointing 30% yield of the corresponding tricycle (**24b**) was obtained. It seemed from the preliminary study, therefore, that the tetronic acid (**23a**) is a much poorer radical acceptor than the corresponding *O*-methyl derivative (**22c**), and that cyclisation to compound (**24**) competes with reduction of the iodo-derivatives, by tributylstannane, to the 'alkanes' (**22d**) and (**23b**) respectively during the periods of reaction. Indeed, depending on reaction conditions, varying amounts of the compounds (**22d**) and (**23b**) could be isolated from the attempted radical cyclisations of (**22c**) and (**23a**) respectively.



(**22**) Bu_3SnH (6-*exo*-trig)

(**24**)

a ; R = Me
b ; R = H



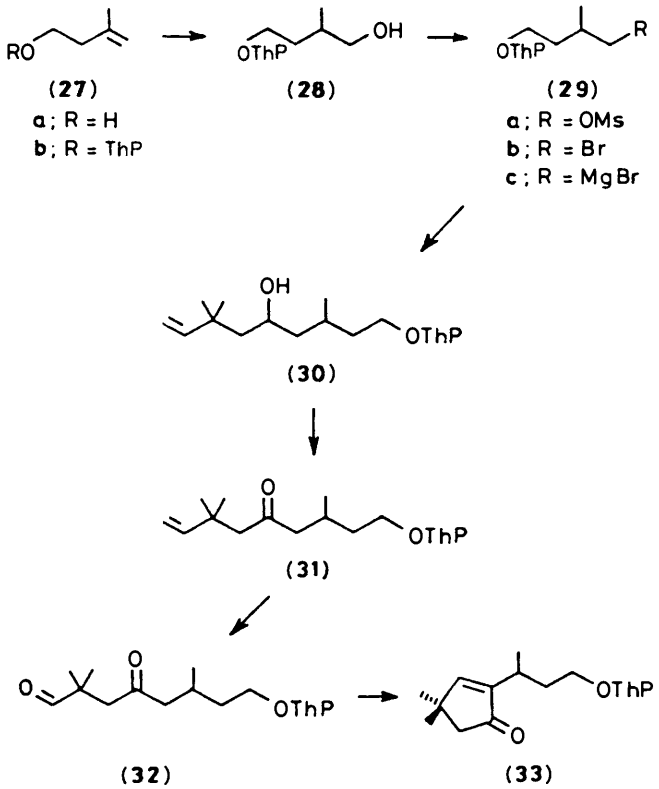
(**25**) (**26**)

a ; β-epoxide
b ; α-epoxide

Each of the radical cyclisations leading to compound (**24a**) and (**24b**) were found to be both regio- and stereo-specific producing single diastereoisomers of the tricycles. Inspection and comparison of ^1H- and ^{13}C-n.m.r. spectral data for (**24a**) and (**24b**), with corresponding data for natural alliacolide (**3**) and its *O*-methyl ether (**39**) clearly demonstrated that the tricycles (**24a**) and (**24b**) had the same relative *trans*-(*anti*)-configurations of the substituents associated with their butyrolactone ring units, as those found in natural alliacolide (**3**). In a single step, therefore, the radical cyclisations leading to

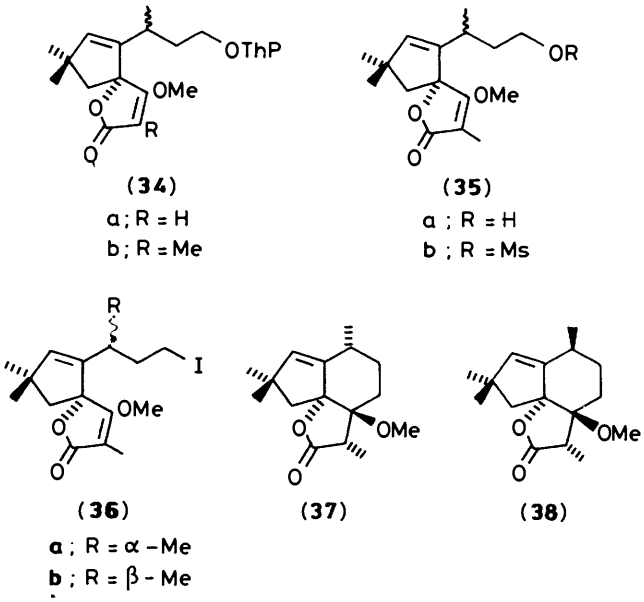
compound (**24**) had created three contiguous chiral centres in the molecule in the correct relative configuration. All that remained to complete our synthesis of noralliacolide (**25**) was to effect a stereoselective epoxidation of the deoxy-compound (**24b**). This was smoothly accomplished by exposure of (**24b**) to two equivalents of *meta*-chloroperbenzoic acid at 25 °C for 14 h, which led to the crystalline β-epoxide (**25**) in 65% yield. Less than 3% of the corresponding α-epoxide [*cf.* (**26**)] was produced concurrently in this reaction, a feature clearly associated with the strong directing effect of the tertiary β-orientated hydroxy group in (**24b**).[10] Interestingly, a similar epoxidation of the *O*-methyl derivative (**24a**) was much less stereoselective and gave rise to a 3:2 mixture of the β- and α-epoxides (**26a**) and (**26b**) respectively. The relative configurations of the isomeric epoxides (**26a**) and (**26b**) followed conclusively from comparison of their ^{1}H n.m.r. shift data with those of natural alliacolide and its *O*-methyl ether (see Table, and also discussion below).

Having established a practical, stereoselective route to noralliacolide (**25**), we next investigated routes to the cyclopentenone (**33**) and the spiro-tetronic acid (**45**) precursors required for the synthesis of alliacolide (**3**) itself. The cyclopentenone (**33**) was elaborated from commercially available 3-methylbut-3-en-1-ol (**27a**) as outlined in Scheme 3. Thus, hydroboration–oxidation of the tetrahydropyranyl ether derivative (**27b**) of (**27a**) first led to the new alcohol (**28**). Conversion of the alcohol (**28**) into the Grignard reagent (**29c**) followed by reaction with 3,3-dimethylpent-4-enal,[11] then provided the sec-alcohol (**30**). Oxidation of compound (**30**) with pyridinium chlorochromate then provided the unsaturated ketone (**31**) which could be converted into the keto-aldehyde (**32**) by treatment with catalytic osmium tetraoxide in the presence of sodium metaperiodate. Exposure of the keto-aldehyde (**32**) to potassium hydroxide in a refluxing mixture of aqueous tetrahydrofuran–diethyl ether, finally, effected smooth aldolisation–dehydration leading to the cyclopentenone intermediate (**33**) in a satisfying 87% yield.



Scheme 3.

The conversion of the cyclopentenone (**33**) to the iodo spiro-tetronic acid intermediate (**45**) was effected along parallel lines to those used to synthesize (**23a**) from (**19**) in the model series, described above. Thus, spiro-annulation of the tetronate ring system onto compound (**33**) first led to compound (**34a**) as a mixture of diastereoisomers which was next converted into the α-methyl derivative (**34b**). Hydrolysis of the tetrahydropyranyl residue in compound (**34b**) next led to the alcohol (**35a**) which was converted into the iodide (**36**) *via* the corresponding methanesulphonate (**35b**). The 1:1 mixture of diastereoisomeric α- and β-methyl iodides, (**36a**) and (**36b**) respectively, was conveniently separated, by careful column chromatography. Although it was not possible, at this stage, to distinguish unambiguously the α- and β-methyl epimers, their relative configurations followed conclusively from examination of their intramolecular radical cyclisations, followed by comparison of spectral data for the resulting tricycles (**37**) and (**38**) with those of natural alliacolide (**3**) and its derivatives (see discussion below).

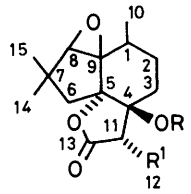


Radical cyclisation of the α-methyl epimer (**36a**) in the presence of Bu_3SnH–AIBN led to the single crystalline diastereoisomeric 8,9-deoxyalliacolide *O*-methyl ether (**37**) in 95% yield. In a similar manner the β-methyl epimer (**36b**) produced the 1-*epi*-8,9-deoxyalliacolide methyl ether (**38**) (81%). When the tricycle (**37**) was treated with *meta*-chloroperbenzoic acid, alliacolide *O*-methyl ether (**39**) was produced in 64% yield, accompanied by approximately 10% of the isomeric α-epoxide (**40**). Similarly, epoxidation of the epimer (**38**) of (**37**) led to a 3:2 mixture of the 1-*epi*-alliacolide methyl ether (**41**) and the corresponding α-epoxide (**42**).

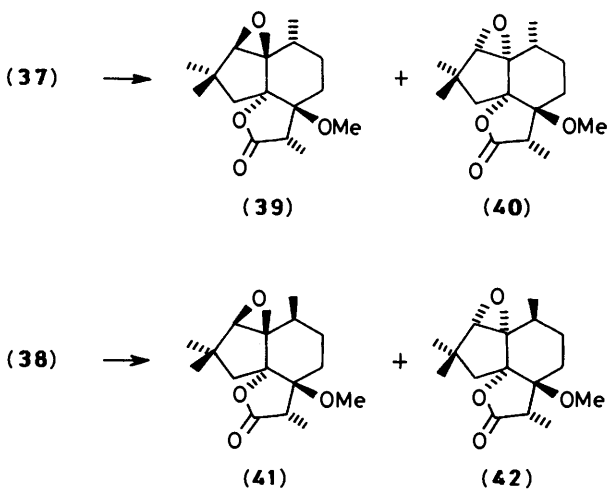
The relative configurations assigned to the isomeric alliacolide methyl ethers (**39**)→(**42**) followed from comparative n.m.r. spectral data with those of natural alliacolide (**3**), its derivatives and its analogues [*e.g.*, (**26**)]. For example, the chemical shift exhibited by the 1-Me group in the ^{1}H n.m.r. spectrum, proved to be a particularly easy way of distinguishing between the 'natural' (β-) and the 'epimeric' (α-) epoxides. In the *epi*-series this resonance is shifted to unusually high field (*ca.* δ 0.8 p.p.m.), whereas in the 'natural' series it is found typically at δ 1.1 p.p.m. (see also Table).

To our surprise, demethylations of the diastereoisomerically pure iodo tetronic acid methyl ethers (**36a**) and (**36b**), using trimethylsilyl iodide, resulted in concomitant epimerisation at the 1-methyl centres in the molecule and the production of

Table. ^{1}H N.m.r. shift data for alliacolides



	6-H_2	8-H	11-H	12-H_3	10-H_3	7-Me_2
'Nat'-(**39**)		3.22	2.78	1.25	1.25	1.18, 1.18
(**39**)	1.27, 1.87	3.23	2.78	1.28	1.14	1.14, 1.14
(**40**)	1.46, 2.29	2.95	2.82	1.31	1.07	1.13, 1.12
(**41**)	1.29, 1.93	3.26	2.76	1.23	0.80	1.11, 1.15
(**42**)	1.48, 2.28	3.08	2.83	1.29	0.81	1.05, 1.14
(**26a**)	1.27, 1.96	3.32	2.79	1.25		1.14, 1.16
(**26b**)	1.47, 2.33	2.96	2.86	1.30		1.10, 1.15
(**25**)	1.33, 1.98	3.32	2.72	1.17		1.12, 1.15
(**47**)	1.34, 2.02	3.31	2.72	1.17	0.80	1.11, 1.15
(+)-(**3**)	1.29, 1.96	3.22	2.69	1.18	1.14	1.12, 1.12
'Nat'-(**3**)	1.29, 1.96	3.22	2.69	1.18	1.14	1.12, 1.12

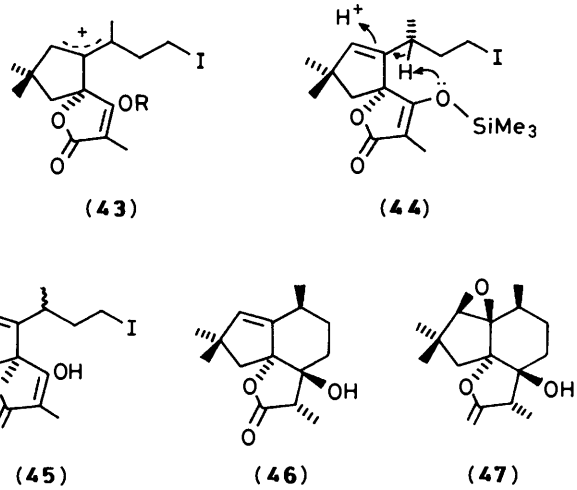


(**39**) (**40**)

(**41**) (**42**)

identical inseparable 2:1 mixtures of β- and α-methyl epimers of the corresponding tetronic acid (**45**). This observation, conceivably due to either the presence of hydroiodic acid in the trimethylsilyl iodide [leading to compound (**43**)], or to an 'intramolecular protiodesilylation' stage, *viz.* (**44**), in the demethylation, was a disappointing blow to our strategy. This was made more so by the fact that all alternative demethylation procedures with (**36a**) and (**36b**) led to intractable tars. We nevertheless pursued the final stages of our synthesis of alliacolide (**3**) with the 2:1 mixture of β- and α-methyl epimers of (**45**).

Treatment of the epimeric mixture (**45**) with Bu_3SnH–AIBN resulted in 6-*exo*-trig cyclisation, and the formation of a crystalline 2:1 isomeric mixture of the deoxyalliacolides (**10**) and (**46**) in a combined yield of 33%. Without separation, the



(**43**) (**44**)

(**45**) (**46**) (**47**)

mixture of deoxyalliacolides was stirred with buffered *meta*-chloroperbenzoic acid for 4 h, and chromatography then separated two crystalline alliacolides. The minor epoxide, m.p. 190—192 °C (~30%) showed i.r., ^{1}H-, and ^{13}C-n.m.r. spectral data identical with those of alliacolide (**3**) produced by *Marasmeus alliaceus*, and the two compounds did not separate from each other in mixed chromatography. The major epoxide, m.p. 183—184 °C displayed spectral data consistent with 1-*epi*-alliacolide (**47**) and this supposition was confirmed unambiguously by a single crystal *X*-ray determination.*

Experimental

For general experimental details see ref. 12.

2-(2-*Bromo*-4,4-*dimethylcyclopent*-2-*enylene*)-1,3-*dioxolane* (**15**).—A solution of 2-bromo-4,4-dimethylcyclopent-2-en-1-one (9.45 g, 50 mmol)[7] in ethylene glycol (33.4 ml, 600 mmol) containing dichloromethane (10 ml) containing toluene-*p*-sulphonic acid (20 mg, 0.1 mmol), was stirred at room temperature for 16 h. The dichloromethane was evaporated at reduced pressure, and the residue extracted with light petroleum (5 × 50 ml). The combined, dried organic extracts were concentrated under reduced pressure to leave a yellow oil which was purified by chromatography on Kieselgel H, eluting with diethyl ether–light petroleum (15%), to give the *dioxolane* (11.2 g, 97%) as a clear colourless oil; $\nu_{max.}$(film) 1 620 (w) cm^{-1}; δ_H 6.10 (=CH), 4.30—4.10 (m, CH_2O), 4.10—3.95 (m, CH_2O), 2.05 (CH_2), and 1.18 (2 × Me) [Found: *m/z* 233.0176 and 235.0177. $C_9H_{14}BrO_2$ requires (*M* + 1) 233.0157 and 235.0177].

2-[4,4-*Dimethyl*-2-(*prop*-2-*enyl*)*cyclopent*-2-*enylene*]-1,3-*dioxolane* (**16**).—A solution of butyl-lithium in hexane (3.60 ml × 2.5M, 9.0 mmol) was added dropwise to a stirred solution of the vinyl bromide (**15**) (2.0 g, 8.6 mmol) in anhydrous diethyl ether (20 ml) cooled in an ice bath and under argon. After being stirred for 15 min, the mixture was cooled to −40 °C and copper(I) iodide (1.72 g, 9.0 mmol) was added at once. The resulting suspension was allowed to warm to −10 °C, and then maintained at this temperature for 45 min, when allyl bromide (2.2 ml, 25 mmol) was added dropwise. The stirred mixture was allowed to warm to room temperature over a further 45 min then filtered through Kieselguhr. The residue was washed with diethyl ether (3 × 30 ml), and the combined filtrate and washings were then washed with saturated aqueous ammonium

* We thank Dr. M. J. Begley, of this Department, for this determination.

chloride (3 × 15 ml), dried, and evaporated at reduced pressure to give a yellow oil which was purified by chromatography on Kiselgel H. Elution with diethyl ether–light petroleum ether (6%) gave the 1,4-*diene* (1.3 g, 77%) as a clear colourless oil; $\nu_{max.}$(film) 3 080 (w) and 1 680 (w) cm^{-1}; δ_H 6.21—5.75 (m, CH_2=C*H*), 5.58 (t, *J ca.* 2 Hz, CH=), 5.28—3.00 (m, =CH_2), 4.00 (OCH_2CH_2O), 2.80 (dt, *J* 7 and *ca.* 2 Hz, CH_2C=), 1.92 (CCH_2), and 1.01 (2 × Me) (Found: *m/z* 194.1308. $C_{12}H_{18}O_2$ requires *M*, 194.1311).

2-[2-(3-*Hydroxypropyl*)-4,4-*dimethylcyclopent*-2-*enylene*]-1,3-*dioxolane* (**17**).—A solution of disiamylborane [from 2-methylbut-2-ene (10.0 ml, 95.0 mmol), borane–dimethyl sulphide (23.6 ml × 2M, 47.2 mmol); 0 °C, 2.5 h] was added dropwise to a stirred and cooled (10 °C) solution of the 1,4-diene (**16**) (8.3 g, 42 mmol) in anhydrous tetrahydrofuran (THF) (80 ml) under argon. After 10 min, the cooling bath was removed and stirring was continued at room temperature for 12 h, when aqueous sodium hydroxide (30 ml × 6M, 180 mmol) followed by aqueous hydrogen peroxide (32 ml × 10.7M, 350 mmol) were added. The mixture was heated under reflux with stirring for 1.5 h and allowed to cool to room temperature, where it was concentrated under reduced pressure. The residue was extracted with diethyl ether (3 × 80 ml), the combined ethereal extracts were dried, and the solvent was evaporated at reduced pressure to give a yellow oil which was purified by chromatography on Kieselgel H, eluting with diethyl ether to give the *alcohol* (8.3 g, 91%) as a clear colourless oil; $\nu_{max.}$(film) 3 400 (br) and 1 670 (w) cm^{-1}; δ_H 5.60 (t, *J* 1 Hz, =CHO), 4.00 (OCH_2CH_2O), 3.65 (m, C*H*$_2$OH), 2.90 (OH), 2.4—1.4 (m, 4 H), 1.90 (CH_2CO), and 1.10 (2 × Me) (Found: *m/z* 212.1415. $C_{12}H_{20}O_3$ requires *M*, 212.1417).

2-(3-*Hydroxypropyl*)-4,4-*dimethylcyclopent*-2-*en*-1-*one* (**18**).—A stirred solution of pyridinium toluene-*p*-sulphonate (1.25 g, 5.0 mmol) and the alcohol (**17**) (4.0 g, 18.9 mmol) in acetone (100 ml) containing water (10 drops) was heated under reflux for 3 h. The solution was allowed to cool to room temperature and the solvent evaporated at reduced pressure to leave an oily residue which was diluted with diethyl ether (100 ml), then washed successively with aqueous sodium carbonate (5%, 3 × 20 ml), aqueous copper(II) sulphate (1M, 1 × 15 ml), and dilute hydrochloric acid (2M, 1 × 15 ml). The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure to leave the *ketone* (2.4 g, 75%) as a clear colourless oil; $\nu_{max.}$(film) 3 400 (br), 1 700 (s), and 1 670 (w) cm^{-1}; δ_H 7.20 (t, *J ca.* 1 Hz, =CH), 3.64 (t, *J* 7 Hz, C*H*$_2$OH), 2.35 (OH), 2.32 ($COCH_2$), 2.30 (t, *J ca.* 7 Hz, CH_2C=O), 1.73 (m, $CH_2CH_2CH_2$), and 1.22 (2 × Me) (Found: *m/z* 168.1150. $C_{10}H_{16}O_2$ requires *M*, 168.1151).

4,4-*Dimethyl*-2-(3-*tetrahydropyranyloxypropyl*)*cyclopent*-2-*en*-1-*one* (**19**).—Activated Amberlyst H15 (730 mg) was added to a stirred mixture of dihydropyran (2.1 ml, 22.7 mmol) and the alcohol (**18**) (2.30 g, 13.7 mmol) in light petroleum (15 ml) and the mixture stirred at room temperature for 12 h. The resin was removed by filtration through a $MgSO_4$ pad and the solvent evaporated at reduced pressure to leave an oil, which was purified by chromatography on Kieselgel H (70 × 120 mm), eluting with diethyl ether–light petroleum (40%) to give the *enone* (3.1 g, 90%) as a clear colourless oil; $\nu_{max.}$(film) 1 710 (s) and 1 640 (w), cm^{-1}; δ_H 7.11 (t, *J ca.* 1 Hz, =CH), 4.60 (m, OCHO), 4.00—3.30 [m, CH_2OThP and $(CH_2)_3CH_2O$], 2.28 ($COCH_2$), 2.26 (t, *J* 7 Hz, CH_2C=), 2.0—1.4 (m, 8 H), and 1.20 (2 × Me); δ_C 209.2, 166.9 (d), 143.6, 98.8 (d), 66.8 (t), 62.1 (t), 50.4 (t), 38.7, 30.7 (t), 28.3 (q), 27.8 (q), 25.5 (t), 21.3 (t), and 19.6 (t) p.p.m. [Found: *m/z* 167.1084. $C_{10}H_{15}O_2$ (*M* − 85) requires 167.1095].

4-*Methoxy*-8,8-*dimethyl*-6-(3-*tetrahydropyranyloxypropyl*)-1-*oxaspiro*[4.4]*nona*-3,6-*dien*-2-*one* (**20a**).—A solution of butyllithium (1.34 ml, 2.5M, 3.3 mmol) in hexane was added dropwise to a stirred solution of ethyl propynoate (0.34 g, 3.5 mmol) in dry THF (1 ml) at −78 °C under argon. The mixture was stirred at −78 °C for 20 min and then a solution of the cyclopentenone (**19**) (0.76 g, 3 mmol) in dry THF (2 ml) was added dropwise over 10 min. After being stirred at −78 °C for 0.75 h the mixture was warmed to −20 °C where it was quenched with saturated aqueous ammonium chloride (10 ml), and extracted with ether. Evaporation of the dried ether extracts left a viscous red oil which was dissolved in methanol and added to a solution of sodium methoxide (from 0.14 g Na) in methanol (4 ml) at 0—5 °C under argon. The mixture was stirred at 25 °C for 18 h, then diluted with saturated aqueous ammonium chloride, concentrated under reduced pressure, and extracted with ether. The combined ether extracts were washed with saturated aqueous sodium chloride, then dried and evaporated. Chromatography of the residue on Kieselgel H using diethyl ether–light petroleum (70%) as eluant gave the *methyl tetronate* (0.16 g, 46%) as an almost colourless oil; $\nu_{max.}$(film) 1 750 and 1 620 cm^{-1}; δ_H 5.6 (m, =CH), 5.06 (m, =CH), 4.6 (m, OCHO), 3.93 (Me), 3.93—3.2 (m, 4 H, CH_2O and C*H*$_2$OThP), 2.22 (d, *J* 14 Hz, CC*H*HC), 2.04 (d, *J* 14 Hz, CH*H*C), 2.0—1.4 (m, 10 H), 1.2 (CMe), and 1.18 (CMe); δ_C 182.1, 171.8, 144.0 (d), 138.8, 98.8 (d), 96.5, 89.0 (d), 66.8 (t), 62.3 and 62.2 (t), 59.5 (q), 48.1 (t), 43.4, 30.8 (t), 29.4 (q), 28.8 (q), 27.8 (t), 22.1 (t), and 19.7 (t) p.p.m. [Found: *m/z* 252.1346. $C_{14}H_{20}O_4$ (*M* − 84) requires 252.1361].

4-*Methoxy*-3,8,8-*trimethyl*-6-(3-*tetrahydropyranyloxypropyl*)-1-*oxaspiro*[4.4]*nona*-3,6-*dien*-2-*one* (**20b**).—A solution of the methyl tetronate (**20a**) (395 mg, 1.17 mmol) in anhydrous THF (1.2 ml) was added dropwise to a stirred solution of lithium di-isopropylamide [from di-isopropylamine (1.04 ml, 7.43 mmol), and BuLi–hexane (2.88 ml × 2.5M, 7.20 mmol); −10 °C, 15 min] in THF (12.0 ml) maintained at −78 °C and under argon. After 1 h, iodomethane (775 µl, 12.4 mmol) was added in one portion, the mixture was stirred at −78 °C for 1 h, then the cooling bath was removed and the mixture allowed to warm to room temperature over a further 0.5 h. The THF was evaporated at reduced pressure and the residue diluted with water (20 ml). The aqueous emulsion was extracted with diethyl ether (3 × 30 ml), the combined organic extracts washed successively with aqueous sodium thiosulphate (2M, 1 × 10 ml) and saturated aqueous sodium chloride (1 × 10 ml), and the dried organic solution concentrated under reduced pressure and filtered through a short Florisil column (diethyl ether) to give the *methylated tetronate* (0.4 g, 93%) as an oil; $\nu_{max.}$(film) 1 760 (s) and 1 680 (s) cm^{-1}; δ_H 5.65 (m, =CH), 4.57 (m, OCHO), 4.12 (OMe), 4.0—3.3 (m, CH_2O and CH_2OThP), 2.18 (d, *J* 14 Hz, CC*H*HC), 2.04 (=C), 1.96 (d, *J* 14 Hz, CH*H*C), 2.0—1.5 (m, 10 H), 1.19 (CMe), and 1.14 (CMe) (Found: *m/z* 350.2092. $C_{20}H_{30}O_4$ requires *M*, 350.2094).

6-(3-*Hydroxypropyl*)-4-*methoxy*-3,8,8-*trimethyl*-1-*oxaspiro*-[4.4]*nona*-3,6-*dien*-2-*one* (**22a**).—Activated Amberlyst H15 (30 mg) was added to a stirred solution of the methyl tetrahydropyranyloxytetronate (**20b**) (102 mg, 290 µmol) in anhydrous methanol (7 ml) under argon. The mixture was stirred at 40 °C for 6 h, then allowed to cool to room temperature, and filtered through a $MgSO_4$ pad. The $MgSO_4$ pad was washed with diethyl ether (2 ml) and the combined organic solutions concentrated under reduced pressure to leave an oil which was subjected to chromatography on Kieselgel H. Elution with (10%) diethyl ether–methanol gave the *alcohol* (72 mg, 93%) as a pale yellow oil; $\nu_{max.}$(film) 3 450 (br s), 1 740 (s), and 1 660 (s), cm^{-1}; δ_H 5.60 (t, *J ca.* 1 Hz, =CH), 4.16 (OMe), 3.65 (t, *J* 6 Hz, C*H*$_2$OH), 2.32 (OH), 2.20 (d, *J* 14 Hz, CC*H*HC), 2.04

(CMe), 1.90 (d, *J* 14 Hz, COCH*H*), 1.9—1.4 (m, 4 H), 1.08 (CMe), and 1.04 (CMe) (Found: *m/z* 266.1514. $C_{14}H_{22}O_4$ requires *M*, 266.1512).

6-(3-*Methanesulphonyloxypropyl*)-4-*methoxy*-3,8,8-*trimethyl*-1-*oxaspiro*[4.4]*nona*-3,6-*dien*-2-*one* (**22b**).—Methanesulphonyl chloride (91 µl, 1.17 mmol) was added dropwise to a stirred solution of the methyl hydroxy-tetronate (**22a**) (273 mg, 970 µmol) and triethylamine (203 µl, 1.46 mmol) in anhydrous dichloromethane (4.85 ml, ~0.2M) maintained at −10 °C under argon. After 0.5 h, the suspension was allowed to warm to room temperature, where it was stirred for a further 0.5 h, and then diluted with dichloromethane (20 ml). The solution was washed with water (10 ml) and saturated aqueous sodium chloride (10 ml), and then dried. The solvent was evaporated at reduced pressure to leave an amber oil which was filtered through a short Florisil column (eluting with diethyl ether) to give the *methansulphonate* (0.34 g, 98%) as a white semi-crystalline solid; $\nu_{max.}$(KBr) 1 740 (s) and 1 670 (s) cm^{-1}; δ_H 5.65 (=CH), 4.15 (t, *J* 7 Hz, CH_2OMs), 4.10 (OMe), 2.95 ($MeSO_3$), 2.15 (d, *J* 14 Hz, CC*H*HC), 2.00 (=Me), 1.90 (d, *J* 14 Hz, CCH*H*C), 1.5—2.0 (m, 4 H), 1.15 (CMe), and 1.12 (CMe).

6-(3-*Iodopropyl*)-4-*methoxy*-3,8,8-*trimethyl*-1-*oxaspiro*-[4.4]*nona*-3,6-*dien*-2-*one* (**22c**).—Finely powdered, oven-dried sodium iodide (1.42 g, 9.5 mmol) was added to a rapidly stirred solution of the methanesulphonate (**22b**) (340 mg, 990 µmol) in acetone (10 ml). The mixture was heated under reflux with stirring for 0.5 h, then allowed to cool to room temperature, whereupon the acetone was evaporated at reduced pressure. The residue was diluted with water (15 ml) and the resulting aqueous emulsion was then extracted with diethyl ether (2 × 10 ml). The combined ether extracts were washed with aqueous sodium thiosulphate (2M, 5 ml) and saturated aqueous sodium chloride (5 ml), and then dried. Evaporation of the solvent at reduced pressure left an off-white solid which was purified by filtration through a short Florisil column (eluting with diethyl ether) to give the *iodide* (0.32 g, 87%) which crystallised from diethyl ether, as needles, m.p. 86.0—86.5 °C; $\nu_{max.}$(KBr) 1 730 (s) and 1 660 (s) cm^{-1}; $\lambda_{max.}$ 231 nm (ε 9, 140); δ_H 5.73 (=CH), 4.68 (OMe), 3.20 (m, CH_2I), 2.16 (d, *J* 14, CC*H*HC), 2.06 (=CMe), 1.94 (d, *J* 14 Hz, CCH*H*C), 2.05—1.85 (m, 4 H), 1.20 (CMe), and 1.16 (CMe); δ_C 175.1, 173.9, 145.8 (d), 136.8, 98.6, 96.2, 60.1 (q), 49.1 (t), 44.2, 32.6 (t), 30.5 (q), 29.8 (q), 27.4 (t), 9.7 (q), and 7.2 (t) p.p.m. (Found: C, 48.2; H, 5.6%; *m/z* 376.0529. $C_{15}H_{21}IO_3$ requires C, 47.9; H, 5.9%; *M*, 376.0535).

8,9-*Deoxynoralliacolide Methyl Ether* (**24a**).—(*a*) A solution of tributylstannane (123 µmol) and AIBN (14.5 mg, 90 µmol) in anhydrous benzene (3.0 ml) was added dropwise over 4.5 h to a stirred solution of the iodotetronate (**22c**) (97 mg, 258 µmol) in anhydrous, degassed benzene (11.7 ml, 0.021—0.019M) maintained at 80 °C under argon. After 16 h, the solution was allowed to cool to room temperature and the benzene evaporated off at reduced pressure to leave an oil. ^1H N.m.r. analysis indicated the presence of *ca.* 30% starting material. The crude product mixture was subjected to the above experimental procedure again. After evaporation of the benzene at reduced pressure, the residue was purified by chromatography on Kieselgel H (30 × 120 mm), eluting with diethyl ether–light petroleum (20—40%), to give the desired *tricyclic lactone* as a colourless oil (63 mg, 97%) which crystallised from diethyl ether–light petroleum as colourless rhombs, m.p. 76—78 °C; $\nu_{max.}$(KBr) 1 770 (s), 1 350 (m), 1 120 (s), and 960 (m) cm^{-1}; δ_H 5.58 (d, *J* 2.1 Hz, =CH), 3.37 (OMe), 2.79 (q, *J* 7.1 Hz, C*H*Me), 2.47 (d, *J* 14.2 Hz, CC*H*HC), 2.35 (dtd, *J* 14.3, 2.6, and 2.5 Hz, =CC*H*H), 2.15 (dtd, *J* 14.3, 2.6, and 2.5 Hz, =CCH*H*), 2.03 (t, *J* 12.8 Hz, CH), 1.72—1.58 (m, 4 H), 1.29 (d, *J* 7.1, CH*Me*), 1.14 (CMe), and 1.11 (CMe); δ_C 176.9, 142.9 (d), 134.8, 96.1, 80.2, 52.3 (q), 45.4 (d), 44.6 (t), 42.3, 29.4 (q), 28.8 (q), 25.1 (t), 24.1 (t), 20.4 (t), 10.0 (t), and 10.0 (q) p.p.m. (Found: C, 72.2; H, 9.1%; *m/z* 150.1569. $C_{15}H_{22}O_3$ requires C, 72.0; H, 8.9%; *M*, 250.1567).

(*b*) A solution of tributylstannane (214 µl, 800 µmol) and AIBN (25 mg, 160 µmol) in anhydrous benzene (3.0 ml) was added dropwise over 3 h to a stirred solution of the iodotetronate (**22c**) (166 mg, 440 µmol) in anhydrous, degassed benzene (20.0 ml, 0.022—0.019M) maintained at 80 °C under argon. After 18 h, the solution was allowed to cool to room temperature and the benzene was then removed by evaporation at reduced pressure. The residual oil was carefully preadsorbed onto silica (Woelm, diethyl ether–benzene), and then subjected to chromatography of Kieselgel H. Elution with diethyl ether–light petroleum (20—40%) gave: (i) the *tricyclic lactone* (**24a**) as a colourless oil, which crystallised from diethyl ether–light petroleum (88 mg, 80%), m.p. 76—78 °C; having spectral data identical with those described above, and (ii) 4-*methoxy*-3,8,8-*trimethyl*-6-*propyl*-1-*oxaspiro*[4.4]*nona*-3,6-*dien*-2-*one* (**22d**) as a colourless oil (22 mg, 20%), which crystallised from diethyl ether as needles, m.p. 73—75°C; $\nu_{max.}$(film) 1 740 (s), 1 660 (s), and 1 340 (s) cm^{-1}; δ_H 5.68 (t, *J ca.* 2 Hz, =CH), 4.18 (OMe), 2.26 (d, *J* 14 Hz, CC*H*HC), 2.07 (=CMe), 1.94 (d, *J* 14 Hz, CCH*H*C), 1.8—1.2 (m, 7 H), 1.20 (CMe), and 1.15 (CMe) (Found: *m/z* 250.1580. $C_{15}H_{22}O_3$ requires *M*, 250.1568).

(*c*) A solution of AIBN (10 mg, 60 µmol) in anhydrous benzene (0.5 ml) was added dropwise over *ca.* 15 min to a stirred solution of the iodotetronate (**22c**) (102 mg, 270 µmol) and tributylstannane (100 µl, 370 µmol) in anhydrous, degassed benzene (19.0 ml, 0.02M) maintained at 80 °C under argon. After 1 h, a further solution of tributylstannane (100 µl, 370 µmol) and AIBN (10 mg, 60 µmol) in anhydrous benzene (0.5 ml) was added dropwise over 3 h, and the heating was then continued for another 18 h, after which the solution was allowed to cool to room temperature. The benzene was evaporated at reduced pressure, and the residue purified by chromatography on Kieselgel H (20 × 100 mm), eluting with diethyl ether–light petroleum (35%), to give: (i) the desired *tricyclic lactone* (**24a**) as a clear colourless oil (40 mg, 60%), having spectral data identical with those already described, and (ii) the product (**22d**) (21 mg, 30%) of reduction which crystallised from diethyl ether and had spectral data identical with those described above.

1-*Noralliacolide Methyl Ether* (**26a**) *and* 8-epi-9-epi-1-*Noralliacolide Methyl Ether* (**26b**).—A solution of *m*-chloroperbenzoic acid (55 mg × 95%, 299 µmol) in anhydrous dichloromethane (1.5 ml) was added dropwise to a stirred solution of 8,9-deoxy-1-noralliacolide methyl ether (68 mg, 272 µmol) in dichloromethane (2.0 ml) maintained at 4 °C under argon. The solution became red immediately, and was stirred at room temperature for 48 h, when a further solution of *m*-chloroperbenzoic acid (15 mg × 95%, 82 µmol) in dichloromethane (0.5 ml) was added. After 64 h, the white suspension was diluted with dichloromethane (30 ml), and the organic solution washed successively with aqueous sodium sulphite (2M, 8 ml), saturated aqueous sodium hydrogen carbonate (2 × 8 ml) and dilute hydrochloric acid (10%, 8 ml). Evaporation of the dried solvent left a colourless oil, which was preadsorbed onto silica (Woelm, dichloromethane) and then subjected to chromatography on Kieselgel H. Gradient elution with diethyl ether–light petroleum (1 × 40%, 1 × 60%, 1 × 80%) gave: (i) 1-*noralliacolide methyl ether* (**26a**) (31.3 mg, 43%), which crystallised from diethyl ether–light petroleum as white needles, m.p. 94—95 °C; $\nu_{max.}$(KBr) 1 780 (s), 1 340 (s), 1 200 (s), and 1 140 (s) cm^{-1}; δ_H 3.50 (MeO), 3.32 (Me_2CCH), 2.79 (q, *J* 7 Hz, C*H*Me), 1.96 (d, *J* 14 Hz, CC*H*HC), 1.27 (d, *J* 14 Hz, CH*H*C), 1.25 (d, *J* 7 Hz, CH*Me*), 1.16 (MeC), and 1.14 (MeC); δ_C 175.9, 91.4, 80.8, 70.1 (d), 65.3, 52.9 (q), 46.6 (d), 40.3 (t), 38.0, 25.0 (t),

24.6 (q), 24.0 (q), 23.8 (t), 19.6 (t), and 8.9 (q) p.p.m. (Found: C, 67.5; H, 8.5%; *m/z* 266.1526. $C_{15}H_{22}O_4$ requires C, 67.6; H, 8.3%; *M*, 266.1518), and (ii) the *α-epoxide* (**26b**) (22 mg, 31%) as a clear colourless oil; $\nu_{max.}$(film) 1 770 (s), 1 450 (s), and 1 100 (s) cm^{-1}; δ_H 3.42 (MeO), 2.96 (Me_2CCH), 2.86 (q, *J* 7 Hz, C*H*Me), 2.33 (d, *J* 14 Hz, CC*H*HC), 2.3—1.3 (m, 6 H), 1.47 (d, *J* 14 Hz, CCH*H*C), 1.30 (d, *J* 7 Hz, C*Me*CH), 1.15 (MeC), and 1.10 (MeC); δ_C 176.0, 91.1, 81.9, 72.7 (d), 66.5, 51.6 (q), 43.8 (d), 43.1 (t), 37.4, 25.9 (t), 25.2 (q), 24.2 (q), 23.9 (t), 18.7 (t), and 10.6 (q) p.p.m.; *m/z* 266.1515.

4-*Hydroxy*-6-(3-*iodopropyl*)-3,8,8-*trimethyl*-1-*oxaspiro*[4.4]-*nona*-3,6-*dien*-2-*one* (**23a**).—Iodotrimethylsilane (150 μl, 1.07 mmol) was added to a stirred solution of the iodotetronate (**22c**) (334 mg, 890 μmol) in anhydrous acetonitrile (2.0 ml) under argon. The mixture was stirred at room temperature in the dark for 4 days, then the solvent was evaporated at reduced pressure. The residual oil was taken up in ethyl acetate (50 ml), and the organic extract washed with aqueous sodium thiosulphate (2M, 2 × 10 ml) and saturated aqueous sodium chloride (10 ml), then dried. Evaporation of the solvent at reduced pressure left a viscous, pale yellow oil which crystallised from diethyl ether to give the *enol* (320 mg, 99%) as needles, m.p. 132—134 °C; $\nu_{max.}$(KBr) 3 100 (br s), 1 720 (s), 1 650 (s) cm^{-1}; δ_H 9.70 (br, OH), 5.80 (=CH), 3.19 (t, *J ca.* 7 Hz, CH_2I), 2.32 (d, *J* 14 Hz, CC*H*HC), 2.1—1.8 (m, 4 H), 1.90 (d, *J* 14 Hz, CCH*H*C), 1.80 (=Me), and 1.20 (2 × CMe) (Found: *m/z* 362.0314. $C_{14}H_{19}IO_3$ requires *M*, 362.0378).

8,9-*Deoxy*-1-*alliacolide* (**24b**).—A solution of tributylstannane (440 μl, 1.64 mmol) and AIBN (40 mg, 0.25 mmol) in anhydrous benzene (3.0 ml) was added dropwise over 4 h to a stirred solution of the iodotetronic acid (**23a**) (300 mg, 0.829 mmol) in anhydrous, degassed benzene (46.0 ml, 0.018M) maintained at 80 °C under argon. After a further 17 h, the solution was allowed to cool to room temperature and the solvent was evaporated at reduced pressure. ^1H N.m.r. analysis indicated the presence of *ca.* 60% of the starting iodide. The crude product was diluted with degassed benzene (44.0 ml, 0.019M) and heated at 80 °C under argon whilst a solution of tributylstannane (220 μl, 0.82 mmol) and AIBN (20 mg, 0.12 mmol) in benzene (5.0 ml) was added dropwise over 4 h. After a further 16 h, the solution was allowed to cool to room temperature, and the benzene was evaporated at reduced pressure to leave an oil, which contained no starting material (by ^1H n.m.r. analysis). Chromatography on Kieselgel H, eluting with diethyl ether–light petroleum (60%), gave the *tricyclic lactone* (59 mg, 30%) as a white solid, which crystallised from diethyl ether–light petroleum as colourless plates, m.p. 152.5—153.5 °C; $\nu_{max.}$(KBr) 3 450 (br s), 1 740 (s), 1 350 (m), 1 270 (s), and 1 230 (m) cm^{-1}; δ_H 5.70 (=CH), 2.78 (q, *J* 7 Hz, C*H*Me), 2.47 (d, *J* 14 Hz, C*H*HC), 2.4—1.2 (m, 7 H), 1.72 (d, *J* 14 Hz, CCH*H*C), 1.17 (d, 7 Hz, MeCH), 1.16 (CMe), and 1.14 (CMe); δ_C 176.7, 143.6 (d), 134.3, 96.5, 46.3 (d), 44.7 (t), 42.4, 30.6, 29.4 (q), 29.2 (t), 29.0 (q), 25.0 (t), 20.6 (t), and 6.8 (q) p.p.m. (Found: *m/z* 236.1416. $C_{14}H_{20}O_3$ requires *M*, 236.1412).

Elution with methanol containing conc. hydrochloric acid (36%, 10 drops), followed by drying ($MgSO_4$), and evaporation gave the crude tetronic acid (**23b**) (*ca.* 20 mg); δ_H 5.70 (=CH), 2.80 (d, *J* 14 Hz, CC*H*HC), 1.75 (3 H, =CMe), 2.0—1.1 (m, 7 H), and 1.20 (2 × CMe).

1-*Noralliacolide* (**25**).—A solution of *m*-chloroperbenzoic acid (47 mg × 95%, 259 μmol) in anhydrous dichloromethane (1.0 ml) was added dropwise to a stirred solution of 8,9-deoxy-1-noralliacolide (38 mg, 159 μmol) in dichloromethane (1.5 ml) maintained at 4 °C under argon. The solution immediately became red and stirring was continued at room temperature for 4 h, whereupon a further solution of *m*-chloroperbenzoic acid (11.0 mg × 95%, 60 μmol) in dichloromethane (0.5 ml) was added. After being stirred at room temperature for a further 10 h, the red colouration had disappeared and had been replaced by a white precipitate. The dichloromethane was evaporated off at reduced pressure, and the residue was then diluted with diethyl ether (15 ml). The ether solution was washed successively with saturated aqueous sodium sulphate (4 ml), aqueous sodium hydrogen carbonate (5%, 4 ml), and dilute hydrochloric acid (10%, 4 ml), and then dried. Evaporation of the solvent at reduced pressure left a white crystalline solid which was preadsorbed onto silica, and subjected to chromatography on Kieselgel H. Elution with diethyl ether–light petroleum (65%) gave: (i) 1-*noralliacolide* (26 mg, 65%) (eluted first) as a white crystalline solid, which crystallised from diethyl ether–light petroleum as platelets, m.p. 161—163 °C; $\nu_{max.}$(KBr) 3 450 (br s), 1 740 (s), 1 280 (s), and 1 140 (m) cm^{-1}; δ_H 3.32 (Me_2CCH), 2.72 (q, *J* 7.1 Hz, C*H*Me), 2.40 (br, OH), 2.11 (m, 1 H), 1.98 (d, *J* 14.0 Hz, CC*H*HC), 1.9—1.7 and 1.7—1.5 (m, 5 H), 1.33 (d, *J* 14.0 Hz, CH*H*C), 1.17 (d, *J* 7.1, *Me*CH), 1.15 (CMe), and 1.12 (CMe); δ_C 175.9, 90.2, 77.2, 70.5 (d), 66.1, 46.8 (d), 40.4 (t), 38.1, 30.5 (t), 24.3 (q), 24.0 (q), 23.9 (t), 18.6 (t), and 6.8 (q) p.p.m. (Found: C, 66.8; H, 8.1%; *m/z* 252.1336. $C_{14}H_{20}O_4$ requires: C, 66.6; H, 8.0%; *M*, 252.1361), and (ii) the corresponding α-epoxide (~1 mg) (eluted second) as a colourless solid, δ_H 3.02 (Me_2CCH), 2.72 (q, *J* 7.1 Hz, C*H*Me); *m/z* 252.1345.

2-*Methyl*-4-*tetrahydropyranyloxybut*-1-*ene* (**27b**).—Activated Amberlyst H15 (3.5 g) was added slowly to a stirred, cooled (ice-water) solution of 3-methylbut-3-en-1-ol (95.8 g, 1.10 mol) and dihydropyran (112 g, 1.33 mol) in light petroleum (250 ml) under argon. After 1 h, the cooling bath was removed, and the mixture was stirred at room temperature for 23 h. Further dihydropyran (11.7 g, 0.14 mol) and Amberlyst H15 (2.0 g) were added, and the mixture was then stirred at room temperature for a further 24 h, by which time no starting material remained. The mixture was filtered through a Florisil pad, and then the solvents were evaporated at reduced pressure to leave a pale yellow oil. Distillation gave the *tetrahydropyranyl ether* (173 g, 92%) as a fruity smelling, colourless oil, b.p. 48 °C at 1.0 mmHg; $\nu_{max.}$(film) 1 650 (w) and 1 140 (s) cm^{-1}; δ_H 4.70 (m, $=CH_2$), 4.63 (m, OCHO), 4.2—3.8 (m, 2 H), 3.8—3.4 (m, 2 H), 2.35 (t, *J* 7 Hz, $CH_2C=$), 1.80 (br, Me), 1.95—1.35 (m, 3 × CH_2); *m/z* M^+ (2.0%), 153 (4), 115 (12), 101 (30), 85 (100), 69 (59) (Found: *m/z* 170.1298. $C_{10}H_{18}O_2$ requires *M*, 170.1289).

2-*Methyl*-4-*tetrahydropyranyloxybutan*-1-*ol* (**28**).—2-Methyl-4-(tetrahydropyranyloxy)but-1-ene (17.0 g, 100 mmol) was added dropwise to a rapidly stirred, cooled (ice–water) mixture of borane-1,4-oxathiane (50.7 ml × 7.8M, 395 mmol) and anhydrous light petroleum (40 ml) under argon. The mixture was stirred at room temperature for 2 h, then re-immersed in the ice-bath whilst first ethanol (20 ml), then aqueous sodium hydroxide (13 ml × 3M, 39 mmol), and finally (very cautiously so as to just maintain gentle reflux) aqueous hydrogen peroxide (15.4 ml × 9.8M, 151 mmol) were added. The stirred solution was heated under reflux for 1.5 h and then ice–water (50 ml) was added. The organic solvents were removed by evaporation at reduced pressure, and then the aqueous residue was extracted with diethyl ether (80, 60, and 40 ml). The combined ethereal extracts were stirred with dilute aqueous sodium hypochlorite solution (50 ml) for 0.5 h, and the organic layer was then separated and washed with saturated aqueous sodium chloride (30 ml). Evaporation of the solvent at reduced pressure left the *alcohol* (18.4 g, 98%) as a clear, colourless oil, b.p. (oven temp.) 125 °C at 0.5 mmHg; $\nu_{max.}$(film) 3 450 (br s) and 1 120 (s) cm^{-1}; δ_H 4.14 (m, OCHO), 4.0—3.8 (m, 2 H), 3.6 (m, 2 H), 3.50 (d, *J* 7

Hz, C*H*$_2$OH), 2.47 (OH), 1.9—3.4 (m, 9 H), and 0.95 (d, *J* 7 Hz, Me); *m/z* M^+ (0.7%), 101 (2), 87 (73), 85 (100), 69 (38) (Found: *m/z* 188.1424. $C_{10}H_{20}O_3$ requires *M*, 188.1428).

1-*Methanesulphonyloxy*-2-*methyl*-4-*tetrahydropyranyloxybutane* (**29a**).—Freshly distilled methanesulphonyl chloride (26 ml, 340 mmol) was added dropwise to a stirred, cooled (ice–water) solution of 2-methyl-4-(tetrahydropyranyloxy)butan-1-ol (58 g, 300 ml) and triethylamine (60 ml, 430 mmol) in dichloromethane (450 ml) under argon. After 0.5 h, the cooling bath was removed, and the white suspension was stirred at room temperature for 0.5 h. The organic solution was washed successively with water (60 ml), dilute hydrochloric acid (1M, 100 mol) and saturated aqueous sodium hydrogen carbonate (100 ml), and then dried. The solvent was evaporated off at reduced pressure to leave an oil, which was purified by filtration through a Florisil column (eluting with diethyl ether) to give the *methanesulphonate* (76 g, 95%) as a pale yellow oil which was used without further purification; $\nu_{max.}$(film) 1 350 (s) cm^{-1}; δ_H 4.62 (m, OCHO), 4.15 (m, CH_2OMs), 3.80 (m, 2 H), 3.50 (m, 2 H), 3.04 (MeSO_3), 2.08 (m, C*H*Me), 1.8—1.2 (m, 8 H), and 1.04 (d, *J* 7 Hz, MeCH).

1-*Bromo*-2-*methyl*-4-*tetrahydropyranyloxybutane* (**29b**).—A solution of the methanesulphonate (**29a**) (153 g, 575 mmol) in acetone (100 ml) was added to a rapidly stirred suspension of finely powdered anhydrous lithium bromide (78 g, 900 mmol) and sodium hydrogen carbonate (76 g, 900 mmol) in acetone (100 ml) under argon. Anhydrous dimethylformamide (400 ml) was added, and the stirred mixture was then heated at 70 °C for 24 h. The cooled mixture was filtered and then concentrated under reduced pressure. The residue was dissolved in diethyl ether (300 ml), and the ether extract washed with water (3 × 150 ml) and saturated aqueous sodium chloride (2 × 100 mol), then dried and evaporated. The residual yellow oil was distilled to give the *bromide* (123 g, 85%) as a clear, colourless oil, b.p. 82—84 °C at 0.5 mmHg; $\nu_{max.}$(film) 1 120 (s) cm^{-1}; δ_H 4.12 (m, OCHO), 4.1—3.8 (m, 2 H), 3.8—3.4 (m, 2 H), 3.46 (d, *J* 7 Hz, CH_2Br), 2.00 (m, C*H*Me), 2.0—1.4 (m, 8 H), and 1.17 (d, *J* 7, Me); δ_C 98.5 and 98.3 (both d), 64.6 (t), 61.8 (t), 61.7 (t), 41.0 (t), 34.4 (t), 32.0 (d), 25.2 (t), 19.2 (t), and 18.5 and 18.3 (both q) p.p.m. (Found: *m/z* 253.0697. $C_{10}H_{20}BrO_2$ requires *M*, 253.0627).

5-*Hydroxy*-3,3,7-*trimethyl*-9-*tetrahydropyranyloxynon*-1-*ene* (**30**).—Anhydrous 1,2-dibromoethane (100 μl, 2.3 mmol) was injected into a stirring suspension of magnesium gravel (3.04 g, 127 mol) under THF (12 ml) and argon. When the reaction had initiated neat 1-bromo-2-methyl-4-tetrahydropyranyloxybutane (12.7 g, 50.6 mmol) was added steadily over 10 min, followed by THF (90 ml). After being stirred for 0.25 h, the suspension was heated under reflux for 15 min. The Grignard reagent was cooled to −10 °C (ice–methanol) and a solution of 3,3-dimethylpent-4-enal (2.55 g, 22.8 mmol)[11] in THF (15 ml) was added. After 15 min, the cooling bath was removed and the mixture was allowed to warm to room temperature over a further 45 min. Saturated aqueous ammonium chloride (100 ml) was added, and stirring was continued for 1 h before the organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 50 ml). The combined organic extracts were washed with saturated aqueous sodium chloride (1 × 50 ml), dried, and the solvent evaporated at reduced pressure to leave an oil, which was purified by column chromatography on Kieselgel G (70 × 150 mm). Elution with diethyl ether–light petroleum (35%) gave the alcohol (5.6 g, 87%) as a clear, colourless oil, b.p. (oven temperature) 170 °C at 0.4 mmHg; $\nu_{max.}$(film) 3 470 (br) and 1 640 (w) cm^{-1}; δ_H 6.02 (dd, *J* 14 and 10 Hz, C*H*=CH_2), 5.04 (dd, *J* 14 and *ca.* 1, *trans*-CH=C*H*H), 5.02 (dd, *J* 10 and *ca.* 1 Hz, *cis*-CH=CH*H*), 4.60 (m, OCHO), 4.05—3.70 (m, 3 H), 3.70—3.40 (m, 2 H), 2.05—1.30 (m, 14 H), 1.10 (2 × CMe), and 0.96 (d, *J* 7 Hz, CHMe); δ_C 148.8 (d), 110.5 (t), 98.8 and 98.5 (both d), 66.7 (d), 65.7, 65.5 (t), 61.9 (t), 50.8, 50.3 (t), 46.2 (t), 37.1 and 25.9 (t), 36.0, 30.5 (t), 28.1 (q), 26.4 (d), 25.1 (q), 25.3 (t), 20.4 (q), and 19.4 (t) p.p.m. (Found: C, 71.5; H, 11.3%; *m/z* 285.2445. $C_{17}H_{32}O_3$ requires C, 71.8; H, 11.3%; *M*, 285.2429).

3,3,7-*Trimethyl*-9-*tetrahydropyranyloxynon*-1-*en*-5-*one* (**31**).—Pyridinium chlorochromate on alumina (73 g, *ca.* 60 mmol) was added gradually to a rapidly stirred cooled (ice–water) solution of the alcohol (**30**) (5.6 g, 19.7 mmol) in anhydrous benzene (250 ml) under argon. After 11 h, further pyridinium chlorochromate on alumina (24 g, *ca.* 20 mmol) was added and the mixture was stirred for a further 7 h. The oxidising agent was removed by filtration, and the residue was then washed thoroughly with diethyl ether (3 × 70 ml). The combined filtrate and washings were concentrated under reduced pressure, and the residue was filtered through a Florisil column (eluting with diethyl ether). Evaporation of the solvent at reduced pressure left the *ketone* (5.2 g, 93%) as a clear, colourless oil; $\nu_{max.}$(film) 3 090 (w), 1 720 (s), and 1 640 (w) cm^{-1}; δ_H 6.00 (dd, *J* 14 and 10 Hz, C*H*=CH_2), 5.00 (dd, *J* 14 and *ca.* 1 Hz, *trans*-CH=C*H*H), 5.00 (dd, *J* 10 and *ca.* 1, *cis*-CH=CH*H*), 4.60 (m, OCHO), 4.00—3.70 (m, 2 H), 3.70—3.30 (m, 2 H), 2.40 (CH_2CO), 2.32 (d, *J* 7 Hz, COCH_2CH), 1.80—1.40 (m, 9 H), 1.12 (2 × Me), and 0.92 (d, *J* 7 Hz, CH*Me*); δ_C 209.0, 147.0 (d), 110.4 (t), 98.7 and 98.4 (both d), 65.2 and 65.1 (both t), 62.0 (t), 54.2 (t), 51.8 and 51.9 (both t), 36.0, 36.2 (t), 36.1 (t), 35.8, 30.5 (t), 26.9 and 26.7 (both q), 26.3 (d), 19.7 (q), 19.4 (q), and 19.4 (t) p.p.m. [Found: *m/z* 283.2271. $C_{17}H_{31}O_3$ requires (*M* + 1) 283.2272].

2,2,6-*Trimethyl*-4-*oxo*-8-*tetrahydropyranyloxyoctan*-1-*al* (**32**).—A solution of osmium tetraoxide in diethyl ether (200 mg in 20 ml, 0.79 mmol) was added to a mixture of the alkene (**31**) (6.23 g, 22.1 mmol), diethyl ether (60 ml) and water (89 ml) under argon. The mixture was immersed in a water-bath and stirred vigorously whilst finely ground sodium metaperiodiate was added (9.5 g after 0.25 h; 9.5 g after 4 h). After 18 h, the organic layer had become pale yellow and was separated. The aqueous layer was extracted with diethyl ether (3 × 30 ml), the combined organic solutions washed with aqueous potassium hydroxide (1M, 2 × 40 ml), and saturated aqueous sodium chloride (1 × 30 ml) and the organic solution dried and evaporated at reduced pressure to give the *keto-aldehyde* (5.7 g, 90%) as a clear, colourless oil which was used without further purification, $\nu_{max.}$(film) 2 700 (w) and 1 720 (s) cm^{-1}; δ_H 9.75 (CHO), 4.57 (m, OCHO), 4.95—3.65 (m, 2 H), 3.65—3.30 (m, 2 H), 2.70 (CH_2CO), 2.31 (q, *J* 7 Hz, C*H*Me), 1.8—1.3 (m, 10 H), 1.13 (2 × Me), and 0.94 (d, *J* 7 Hz, CH*Me*).

4,4-*Dimethyl*-2-(4-*tetrahydropyranyloxybutan*-2-*yl*)*cyclopent*-2-*en*-1-*one* (**33**).—A mixture of the keto-aldehyde (**31**) (4.0 g, 14.1 mmol), aqueous potassium hydroxide (5%, 21 ml), diethyl ether (12 ml) and THF (21 ml) was stirred vigorously at 70 °C under argon for 42 h. After being cooled to room temperature, the aqueous phase was saturated with sodium chloride and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3 × 20 ml), and the combined organic solutions were washed with saturated aqueous sodium chloride (10 ml), dried, and evaporated at reduced pressure to leave a pale yellow oil (3.6 g). Purification by column chromatography on Kieselgel G (65 × 120 mm), eluting with diethyl ether–light petroleum (35%), gave the *enone* (3.3 g, 87%) as a colourless oily mixture of diastereoisomers; $\nu_{max.}$(film) 1 700 (s) and 1 630 (w) cm^{-1}; δ_H 6.95 (d, *J* 1 Hz, =CH), 4.48 (t, *J* 3.4 Hz, OCHO), 3.72—3.64 (m, 2 H), 3.33—3.24 (m, 2 H), 2.50 (m,

C*H*Me), 2.20 ($COCH_2$), 1.97—1.37 (m, 8 H), 1.13 (2 × CMe), and 1.03 and 1.02 (d, *J* 6.7 Hz, CH*Me*); δ_C 208.5, 165.6 (d), 147.7, 98.7 (d), 65.5 and 65.4 (both t), 62.1 (t), 50.85 (t), 38.3, 35.1 (t), 30.7 (t), 28.4 (q), 26.9 and 26.7 (both d), 25.5 (t), 19.5 (t), and 19.4 (q) p.p.m. [Found: *m/z* 267.1982. $C_{16}H_{27}O_3$ requires (*M* + 1) 267.1970].

4-*Methoxy*-8,8-*dimethyl*-6-(4-*tetrahydropyranyloxybutan*-2-*yl*)-1-*oxaspiro*[4.4]*nona*-3,6-*dien*-2-*one* (**34a**).—Ethyl propynoate (4.46 ml, 44.2 mmol) was added dropwise to a rapidly stirred solution of lithium di-isopropylamide [from di-isopropylamine (6.18 ml, 44.2 mmol), BuLi–hexane (27.5 ml × 1.6M, 44.2 mmol); −20 °C, 20 min] in THF (100 ml) at −100 °C (methcol/nitrogen) under argon. The mixture was stirred at −80 °C for 0.5 h, and then re-cooled to −100 °C. A solution of the cyclopentenone (**33**) (4.70 g, 17.76 mmol) in THF (4.0 ml) was added over 10 min, and the mixture was stirred at −80 °C for a further 2 h. Finally, the mixture was allowed to warm to room temperature over 3 h with the cooling bath in place, whereupon saturated aqueous ammonium chloride (40 ml) was added. The organic layer was separated, and the aqueous layer extracted with diethyl ether (3 × 40 ml). The combined organic solutions were washed with saturated aqueous sodium chloride (1 × 30 ml) dried, and evaporated at reduced pressure to leave the crude product as a viscous red oil. The crude product in anhydrous methanol (20 ml) was added to a solution of sodium methoxide [from sodium (610 mg, 26.4 mmol), methanol (36 ml)] cooled in an ice-bath and under argon. This mixture was stirred at room temperature for 16 h, and then saturated aqueous ammonium chloride (4 ml) was added cautiously. The methanol was evaporated off at reduced pressure and the residue was diluted with water (30 ml). The aqueous mixture was extracted with diethyl ether (3 × 40 ml), and the combined organic extracts washed with saturated aqueous sodium chloride (20 ml), dried, and concentrated under reduced pressure to leave a red oil, which was purified by column chromatography on Kieselgel H (60 × 140 mm). Elution with diethyl ether–light petroleum (70%) gave the *methyl tetronate* (2 g, 33%) as a yellow oil; $\nu_{max.}$(film) 1 760 (s) and 1 630 (s) cm^{-1}; $\lambda_{max.}$ 220 nm (ε 9 755); δ_H 5.70 (C=CH), 5.09 (COCH=), 4.54 (m, OCHO), 3.87 and 3.86 (OMe), 3.87—3.25 [m, 4 × 1 H, CH_2OTHP and $(CH_2)_3CH_2O$], 2.16 (d, *J* 14 Hz, CC*H*HC), 2.02 (d, *J* 14 Hz, CH*H*C), 2.00 (m, MeC*H*), 1.87—1.45 (m, 8 H), 1.18 (CMe), 1.14 (CMe), and 1.06 and 0.96 (d, *J* 7 Hz, CH*Me*, epimers); δ_C 181.9, 171.4, and 171.3 (epimers), 143.2 (d), 141.9, 98.9 and 98.5 (d, epimers), 96.6 and 96.2 (epimers), 88.8 (d), 65.2 and 65.0 (t, epimers), 62.1 and 62.7 (t, epimers), 59.0 (q), 48.1 (t), 42.7, 36.4 and 36.1 (t, epimers), 30.5 (t), 29.1 and 2.84 (q, epimers), 27.5 and 27.3 (d, epimers), 25.2 (t), 21.1 and 20.7 (q, epimers), and 19.5 and 19.2 (t, epimers) p.p.m. [Found: C, 68.6; H, 9.0%; *m/z* 351.2142. $C_{20}H_{30}O_5$ requires: C, 68.5; H, 8.6%. $C_{20}H_{31}O_5$ requires (*M* + 1) 351.2171].

4-*Methoxy*-3,8,8-*trimethyl*-6-(4-*tetrahydropyranyloxybutan*-2-*yl*)-1-*oxaspiro*[4.4]*nona*-3,6-*dien*-2-*one* (**34b**).—A solution of the methyl tetronate (**34a**) (683 mg, 1.96 mmol) in THF (2.0 ml) was added over 10 min to a stirred solution of lithium di-isopropylamide [from di-isopropylamine (1.74 ml, 12.4 mmol), BuLi–hexane (4.79 ml × 2.5M, 12.0 mmol); −15 °C, 15 min] in THF (21 ml) at −78 °C under nitrogen. After 1 h, iodomethane (1.29 ml, 20.6 mmol) was added steadily and stirring was continued at −78 °C for a further 45 min, whereupon the cooling bath was removed and the mixture allowed to warm to room temperature with stirring over 0.5 h. The solvents were evaporated off at reduced pressure and the residue diluted with water (20 ml). The aqueous mixture was extracted with diethyl ether (3 × 15 ml), and the combined organic extracts were then washed with saturated aqueous sodium chloride (10 ml), dried, and concentrated under reduced pressure to leave an oil. Purification by filtration in diethyl ether, through a Florisil column gave the *C-methylated methyl tetronate* (0.69 g, 97%) as a yellow oily mixture of diastereoisomers; $\nu_{max.}$(film) 1 760 (s) and 1 670 (s) cm^{-1}; δ_H 5.54 (=CH), 4.33 (m, OCHO), 3.98 (OMe), 3.9—3.1 (m, 2 × CH_2), 2.00 (d, *J* 14 Hz, CC*H*HC), 1.91 (=CMe), 1.80 (d, *J* 14 Hz, CH*H*C), 1.9—1.2 (m, 9 H), 1.05 (CMe), 1.02 (CMe), and 0.93 and 0.97 (d, *J* 7 Hz, 3 H, CH*Me*, epimers); δ_C 173.8, 172.8, 142.8 (d), 98.9 and 98.4 (d, epimers), 97.2, 95.4, and 95.1 (epimers), 65.4 and 65.1 (t, epimers), 62.2 and 61.8 (t, epimers), 58.4 (q), 48.0 (t), 42.6, 36.6 and 36.2 (t, epimers), 30.6 (t), 29.3 and 28.5 (q, epimers), 27.5 and 27.2 (d, epimers), 25.3 (t), 21.2 and 20.7 (q, epimers), 19.6 and 19.3 (t, epimers), and 8.3 (q) p.p.m. (Found: *m/z* 364.2155. $C_{21}H_{32}O_5$ requires *M*, 364.2249).

6-(4-*Hydroxybutan*-2-*yl*)-4-*methoxy*-3,8,8-*trimethyl*-1-*oxaspiro*[4.4]*nona*-3,6-*dien*-2-*one* (**35a**).—Activated Amberlyst H15 (460 mg) was added to a stirred solution of the methyl tetrahydropyranyloxytetronate (**34b**) (1.40 g, 3.8 mmol) in anhydrous methanol (100 ml) under argon. The mixture was maintained at 40 °C for 6 h, then allowed to cool to room temperature, whereupon the resin was removed by filtration, and the methanol was evaporated at reduced pressure. The residual oil was dissolved in diethyl ether and the solution was passed through a short column of magnesium sulphate. The filtrate was concentrated under reduced pressure and the residue then subjected to chromatography on Kieselgel H (40 × 120 mm). Elution with methanol–diethyl ether (5%) gave the *alcohol* (1.03 g, 96%) as a pale yellow oil; $\nu_{max.}$(film) 3 420 (br), 1 740 (s), and 1 660 (s) cm^{-1}; δ_H 5.56 (=CH), 4.10 (OMe), 3.56 (m, CH_2OH), 2.50 (br, OH), 2.15 (d, *J* 14 Hz, CC*H*HC), 2.02 (=CMe), 1.92 (d, *J* 14 Hz, CCH*H*C), 1.8—1.4 (m, MeC*H* and CH_2CH), 1.16 (CMe), 1.12 (CMe), and 1.03 and 0.98 (d, *J* 7 Hz, *Me*CH epimers) [Found: *m/z* 281.1776. $C_{16}H_{25}O_4$ requires (*M* + 1) 281.1789].

6-(4-*Methylsulphonyloxybutan*-2-*yl*)-4-*methoxy*-3,8,8-*trimethyl*-1-*oxaspiro*[4.4]*nona*-3,6-*dien*-2-*one* (**35b**).—Methanesulphonyl chloride (414 μl, 5.4 mmol) was slowly added to a stirred cooled (ice-water) solution of the hydroxytetronate (**35a**) (1.00 g, 3.6 mmol) and triethylamine (994 μl, 7.1 mmol) in anhydrous dichloromethane (18.0 ml) under argon. After 0.5 h, the cooling bath was removed, and the white suspension was stirred at room temperature for a further 0.5 h. The separated organic solution was washed successively with dilute hydrochloric acid (10%, 5 ml), saturated aqueous sodium hydrogen carbonate (5 ml), and saturated aqueous sodium chloride (5 ml), and then dried. Evaporation of the solvent at reduced pressure left an amber oil, which was purified by filtration through a short column of Florisil (eluting with diethyl ether) to give the *methanesulphonate* (1.28 g, 98%) as a pale yellow oily mixture of diastereoisomers which were used without further purification; $\nu_{max.}$(film) 1 750 (s), 1 660 (s), and 1 350 (s) cm^{-1}; δ_H 5.70 (=CH), 4.15 (t, *J* 7 Hz, CH_2O), 4.12 (OMe), 3.02 and 2.95 ($MeSO_3$, epimers), 2.15 (d, *J* 14 Hz, CC*H*HC), 2.02 (=Me), 1.90 (d, *J* 14 Hz, CCH*H*C), 2.05—1.65 (m, MeC*H* and $CHCH_2$), 1.17 (CMe), 1.13 (CMe), and 0.97 and 0.92 (d, *J* 7 Hz, CH*Me*, epimers).

6-(4-*Iodobutan*-2-*yl*)-4-*methoxy*-3,8,8-*trimethyl*-1-*oxaspiro*-[4.4]*nona*-3,6-*dien*-2-*one* (**36**).—Finely powdered, oven dried sodium iodide (2.84 g, 18.9 mmol) was added to a stirred solution of the methanesulphonyl tetronate (**35b**) (1.28 g, 3.6 mmol) in anhydrous acetone (28 ml) maintained under argon. The mixture was heated at 56 °C with stirring for 0.5 h, and was then allowed to cool to room temperature, whereupon the acetone was evaporated at reduced pressure. The residue was diluted with water (30 ml), extracted with diethyl ether (3 × 20

ml), and the combined ethereal extracts were dried and evaporated at reduced pressure to leave an oil consisting of a mixture of the two crude diastereoisomeric *iodides*. These were separated by column chromatography on Kieselgel H (60 × 140 mm), eluting with diethyl ether–light petroleum (35%) to give: (i) the *rel*-(2′*S*,5*R*) diastereoisomer [(±)-2′-*epi*-(**36b**)] (0.53 g, 38%) (eluted first) as a viscous, pale yellow oil; $\nu_{max.}$(film) 2 960 (s), 1 750 (s), and 1 665 (s) cm^{-1}; $\lambda_{max.}$ 231 nm (ε 10 700); δ_H 5.65 (=CH), 4.16 (MeO), 3.15 (m, CH_2I), 2.13 (d, *J* 14 Hz, CC*H*HC), 2.06 (MeC=), 1.94 (d, *J* 14 Hz, CCH*H*C), 2.1—1.7 (m, 3 H), 1.17 (MeC), 1.13 (MeC), and 1.05 (d, *J* 6.8 Hz, *Me*CH); δ_C 174.1, 172.7, 143.7 (d), 141.4, 97.5, 95.5, 59.1 (q), 48.2 (t), 43.1, 40.2 (t), 31.1 (d), 29.5 (q), 28.8 (q), 21.1 (q), 8.7 (q), and 5.0 (t) p.p.m. (Found: *m/z* 390.0677. $C_{16}H_{23}IO_3$ requires *M*, 390.0692), and (ii) the *rel*-(2′*R*,5*R*) diastereoisomer [(±)-*nat*-(**36a**)] (0.57 g, 41%) (eluted second) as a viscous, pale yellow oil; $\nu_{max.}$(film) 2 960 (s), 1 760 (s), and 1 670 (s) cm^{-1}; $\lambda_{max.}$ 232 (ε 9 980); δ_H 5.69 (=CH), 4.13 (MeO), 3.12 (t, *J* 7 Hz, CH_2I), 2.13 (d, *J* 14 Hz, CC*H*HC), 2.05 (MeC=), 1.90 (d, *J* 14 Hz, CCH*H*C), 2.0—1.7 (m, 3 H), 1.18 (MeC), 1.13 (MeC), and 0.98 (d, *J* 6.6 Hz, *Me*CH); δ_C 173.9, 172.7, 144.0 (d), 141.2, 97.7, 95.1, 58.7 (q), 48.3 (t), 42.9, 41.0 (t), 32.0 (d), 29.4 (q), 28.5 (q), 20.3 (q), 8.6 (q), and 4.1 (t) p.p.m. (Found: *m/z* 390.0704. $C_{16}H_{23}IO_3$ requires *M*, 390.0692).

(±)-8,9-*Deoxyalliacolide Methyl Ether* (**37**).—A solution of tributylstannane (80 μl, 297 μmol) and AIBN (6.5 mg, 40 μmol) in anhydrous benzene (0.7 ml) was added dropwise over 4 h to a stirred, degassed solution of the [*rel*-(2′*R*,5*R*)] methyl iodotetronate (**36a**) (55.5 mg, 142 μmol) in benzene (6.8 ml, 0.021—0.019M) maintained at 80 °C under argon. An additional solution of AIBN (1 mg) in benzene (0.1 ml) was injected steadily dropwise after 2 h, and again after a further 14 h. After a total of 22 h, the mixture was allowed to cool to room temperature, and the benzene was then evaporated at reduced pressure to leave an oil containing none of the starting iodide and 5% of the product of simple reduction (according to ^1H n.m.r. analysis). Purification by column chromatography on Kieselgel H (20 × 120 mm), eluting with diethyl ether–light petroleum (30%), gave the *tricyclic methyl ether* (36 mg, 95%), which crystallised from light petroleum as platelets, m.p. 125.5—126.5 °C; $\nu_{max.}$(KBr) 1 760 (s), 1 350 (m), 1 270 (s), 1 320 (s), and 970 (s) cm^{-1}; δ_H 5.63 (=CH), 3.35 (MeO), 2.79 (q, *J* 7.2 Hz, CHCO), 2.68 (m, CHC=), 2.45 (d, *J* 13.8 Hz, C*H*CMe_2), 1.94 (dm, *J ca.* 13 Hz, 1 H), 1.38—1.7 (m, 4 H), 1.31 (d, *J* 7.2 Hz, *Me*CHCO), 1.14 (*Me*CMe), 1.10 (MeC*Me*), and 1.10 (d, *J* 7.4 Hz, *Me*CHC) (Found: C, 72.7; H, 9.4%; *m/z* 264.1721. $C_{16}H_{24}O_3$ requires C, 72.7; H, 9.2%; *M*, 264.1726).

(±)-1-epi-8,9-*Deoxyalliacolide Methyl Ether* (**38**).—A solution of tributylstannane (157 μl, 582 μmol) and AIBN (14 mg, 85 μmol) in anhydrous benzene (2.0 ml) was added dropwise over 7 h, to a stirred degassed solution of the *rel*-(2′*S*,5*R*) methyl iodotetronate (**36b**) (115 mg, 294 μmol) in anhydrous benzene (13.7 ml, 0.020—0.023M) maintained at 80 °C under argon. After a total of 48 h, the solution was allowed to cool to room temperature, and the benzene was then evaporated off at reduced pressure. The residual oil obtained was subjected to column chromatography on Kieselgel H (20 × 120 mm), eluting with diethyl ether–light petroleum (25%), to give the *tricyclic methyl ether* (63 mg, 81%) as a solid, which crystallised from hexane as needles, m.p. 135—136 °C; $\nu_{max.}$(KBr) 3 015 (w), 1 760 (s), 1 460 (m), 1 330 (s), 1 095 (s), and 960 (s) cm^{-1}; δ_H 5.55 (d, *J* 2.2 Hz, CH=), 3.35 (MeO), 2.79 (q, *J* 7.1 Hz, CHCO), 2.48 (d, *J* 13.9 Hz, C*H*HCMe_2), 2.18 (m, 1 H), 2.12 (m, 1 H), 1.64 (d, *J* 13.9 Hz, CH*H*CMe_2), 1.60 (m, 1 H), 1.37 (td, *J* 13.7 and 3.0 Hz, 1 H), 1.29 (d, *J* 7.1 Hz, *Me*CHCO), 1.17 (td, *J* 12.1 and 3.0 Hz, 1 H), 1.15 (*Me*CMe), 1.11 (MeC*Me*), 1.11 (d, *J* 6.6 Hz, *Me*CHCH) (Found: C, 72.7; H, 9.4%; *m/z* 264.1722. $C_{16}H_{24}O_3$ requires C, 72.7; H, 9.2%; *M*, 264.1726).

(±)-*Alliacolide Methyl Ether* (**39**).—A solution of purified *m*-chloroperbenzoic acid (19.2 mg, 112 μmol) in anhydrous dichloromethane (350 μl) was added to a stirred cooled (ice-water) solution of 8,9-deoxyalliacolide methyl ether (18.4 mg, 70 μmol) in anhydrous dichloromethane (350 μl), under argon. The resulting solution was stirred for 24 h with the water-bath in place, by which time no starting material remained, according to t.l.c. analysis (SiO_2, 30% diethyl ether–light petroleum). Solid calcium hydroxide (50 mg) was added, and the resulting suspension was stirred vigorously for 15 min, whereupon it was then filtered through a short column of Florisil (eluting with dichloromethane). The organic solution was concentrated under reduced pressure, then diluted with diethyl ether (0.5 ml) and passed through a second short column of Florisil. Evaporation of the solvent at reduced pressure left the crude *epoxide* (17 mg, 88%) as a clear, colourless oil, which formed white needles upon standing. Analysis of the crude product by ^1H n.m.r. (250 MHz) indicated it to be a 87:13 mixture of the β/α-epoxides. These were separated by careful column chromatography on Kieselgel H (10 × 120 mm), eluting with diethyl ether–light petroleum (25—40%), to give the major β-epoxide, (±)-*alliacolide methyl ether* (12.4 mg, 64%) (eluted first) as a solid which crystallised from hexane in polymorphic forms, m.p. 81—82 °C; $\nu_{max.}$(film) 1 760 (s), 1 140 (m), and 980 (s) cm^{-1}; δ_H 3.40 (MeO), 3.23 (CHO), 2.78 (q, *J* 7.3 Hz, MeC*H*CO), 2.1—1.8 (m, 4 H), 1.87 (d, *J* 14.5 Hz, CC*H*HC), 1.28 (d, *J* 7.3 Hz, *Me*CHCO), 1.27 (d, *J* 14.5 Hz, CCH*H*C), 1.20 (m, 1 H), 1.14 (d, *J* 7.3 Hz, *Me*CH), and 1.14 (2 × MeC); δ_C 176.2, 93.7, 81.4, 68.2 (d), 67.8, 52.3 (q), 44.8 (d), 41.1 (t), 38.6, 31.6 (d), 25.8 (t), 24.6 (q), 24.0 (q), 23.1 (t), 18.3 (q), and 8.8 (q) p.p.m. [Found: C, 68.6; H, 8.7%; *m/z* 280.1664. $C_{16}H_{24}O_4$ requires C, 68.5; H, 8.6%; *M*, 280.1674], and (ii) the minor α-epoxide (**40**) (2 mg, 10%) (eluted second) as a solid, which crystallised from hexane as colourless needles, m.p. 155—156 °C; $\nu_{max.}$(KBr) 1 760 (s), 1 200 (s), and 990 (s) cm^{-1}; δ_H 3.28 (MeO), 2.96 (CHO), 2.82 (d, *J* 2 Hz, MeC*H*CO), 2.29 (d, *J* 13.6 Hz, CC*H*C), 2.02—1.79 (m, 1 H), 1.6—1.4 (m, 4 H), 1.46 (d, *J* 13.6 Hz, CCH*H*C), 1.31 (d, *J* 7.2 Hz, *Me*CHCO), 1.12 (d, *J* 7.3 Hz, *Me*CHC), 1.13 (MeC), and 1.07 (MeC) (Found: *m/z* 280.1691. $C_{16}H_{24}O_4$ requires *M*, 280.1675).

(±)-1-epi-*Alliacolide Methyl Ether* (**41**).—A solution of purified *m*-chloroperbenzoic acid (21.3 mg, 123 μmol) in anhydrous dichloromethane (420 μl) was added to a stirred cooled (ice-water) solution of 1-*epi*-8,9-deoxyalliacolide methyl ether (20.4 mg, 77 μmol) in anhydrous dichloromethane (250 μl), under argon. The resulting solution was stirred for 24 h with the water-bath in place, by which time no starting material remained, according to t.l.c. analysis (SiO_2, 3 × 20% diethyl ether–light petroleum). Solid calcium hydroxide (50 mg) was added, and the mixture was then stirred vigorously for 15 min, before being filtered through a short column of Florisil (eluting with dichloromethane). The solvent was evaporated at reduced pressure, and the residue was then diluted with ether and filtered through another short column of Florisil. Evaporaton of the solvent at reduced pressure left the crude *epoxide* (20 mg, 93%) as a clear colourless oil. Analysis of the crude mixture by PFT (250 MHz) indicated it to be a 59:41 mixture of the β/α-epoxides. These were separated by chromatography on Kieselgel H (10 × 120 mm), eluting with diethyl ether–light petroleum ether (25—40%), to give: (i) the major β-epoxide, (±)-1-epi-*alliacolide methyl ether* (11.8 mg, 55%) (eluted first) as a clear, colourless oil, $\nu_{max.}$(film) 1 780 (s), 1 100 (m), and 980 (s) cm^{-1}; δ_H 3.45 (MeO), 3.26 (CHO), 2.76 (q, *J* 7.1 Hz, MeC*H*CO), 2.24 (m, CC*H*Me), 2.10 (2 × m, 1 H), 1.93 (d, *J* 13.8 Hz, CC*H*HC), 1.6—1.4 (m, 3 H), 1.29 (d, *J* 13.8 Hz, CH*H*C), 1.23 (d,

J 7.1 Hz, *Me*CO), 1.15 (MeC), 1.11 (MeC), and 0.80 (d, *J* 6.8 Hz, *Me*CHC); δ_C 175.8, 92.2, 80.4, 68.1 (d), 67.9, 53.0 (q), 46.9 (d), 40.6 (t), 37.7, 28.5 (t), 26.7 (t), 24.6 (q), 24.0 (q), 14.0 (q), and 8.8 (q) p.p.m. (Found: C, 68.7; H, 8.9%; *m/z* 280.1654. $C_{16}H_{24}O_4$ requires C, 68.5; H, 8.6%; *M*, 280.1674), and (ii) the minor α-*epoxide* (**42**) (8.5 mg, 39%) (eluted second) as a solid, which crystallised from hexane as colourless platelets, m.p. 121—122 °C; $\nu_{max.}$(KBr) 1 770 (s), 1 210 (s), 1 080 (m), and 930 (s) cm^{-1}; δ_H 3.36 (MeO), 3.08 (CHO), 2.83 (q, *J* 7.2 Hz, MeC*H*CO), 2.28 (d, *J* 13.5 Hz, CC*H*HC), 2.21 and 2.16 (2 × m, 1 H), 2.08 (m, CC*H*Me), 1.74 and 1.70 (m, 1 H), 1.48 (d, *J* 13.5 Hz, CCH*H*C), 1.4—1.2 (m, 2 H), 1.29 (d, *J* 7.2 Hz, *Me*CHCO), 1.14 (MeC), 1.05 (MeC), and 0.81 (d, *J* 6.7 Hz, *Me*CHC); δ_C 176.0, 91.7, 82.1, 70.2, 67.9 (d), 51.5 (q), 44.0 (d), 43.2 (t), 37.0 (d), 30.4 (d), 27.4 (t), 25.5 (q), 24.2 (q), 24.0 (q), 15.2 (q), and 10.5 (q) p.p.m. (Found: C, 68.8; H, 8.9%; *m/z* 280.1681).

(±)-8,9-*Deoxyalliacolide* (**10**).—Iodotrimethylsilane (118 μl, 830 μmol; 1.3 equiv.) was injected into a solution of the *rel*-(2′*R*,5R) methyl iodotetronate (**36a**) (250 mg, 641 μmol) in deuteriochloroform (320 μl, 2.0M) maintained under argon in an n.m.r. tube. The tube was sealed, and stored in the dark until the reaction was judged to be complete by ^{1}H n.m.r. analysis (*ca.* 24 h). The mixture was poured into methanol (0.5 ml), and the resulting solution was then concentrated under reduced pressure. The residue was diluted with ethyl acetate (20 ml), and the solution was then washed successively with aqueous sodium thiosulphate (2M, 2 × 10 ml) and saturated aqueous sodium chloride (5 ml), and finally dried. The solvent was evaporated off at reduced pressure to leave the corresponding tetronic acid (240 mg) as a pale yellow glass, $\nu_{max.}$(film) 3 100 (br s), 1 720 (s), and 1 650 (s) cm^{-1}; δ_H 10.00 (br, OH), 5.90 (=CH), 3.10 (m, *Me*CH), 2.3–1.6 (m, 3 H), 1.83 (MeC=), 1.20 (2 × MeC), and 1.10 (m, *Me*CH) (Found: *m/z* 376.0516. $C_{15}H_{21}IO_3$ requires *M*, 376.0537). The purity of the sample was estimated to be *ca.* 80% from examination of the ^{1}H n.m.r. spectrum; further purification was not attempted.

A solution of tributylstannane (300 μl, 1.12 mmol) and AIBN (25 mg, 160 μmol) in anhydrous benzene (2.0 ml) was added dropwise over 5 h to a rapidly stirred solution of the tetronic acid (200 mg, *ca.* 80%) in degassed, anhydrous benzene (26.1 ml, *ca.* 0.02M) maintained at 80 °C under argon. After 12 h, a second solution of AIBN (10 mg, 62 μmol) in anhydrous benzene (2.5 ml) was added dropwise over a further 5 h, and then, after a total of 24 h, the mixture was allowed to cool to room temperature. The benzene was evaporated off at reduced pressure, and the residual oil was then subjected to chromatography on Kieselgel H, eluting with diethyl ether–light petroleum (5—45%), to give an oily, white solid (32.1 mg, 33% overall). ^{1}H N.m.r. analysis showed this product to be an inseparable *ca.* 2:1 mixture of (±)-1-epi-8,9-*deoxyallicacolide* (**46**) [δ_H 5.68 (CH=)] and (±)-8,9-*deoxyallicacolide* (**10**) [δ_H 5.60 (d, *J* 2.1 Hz, CH=)]; $\nu_{max.}$(KBr) 3 430 (s), 3 020 (w), 1 740 (s), 1 680 (w), and 960 (m) cm^{-1}; δ_H 5.68 (minor: CH=) and 5.60 (major: d, *J* 2.1 Hz, CH=), 2.76 (both: q, *J* 7.1 Hz, MeC*H*CO), 2.40 (major: d, *J* 4.1 Hz, CC*H*HC) and 2.36 (minor: d, *J* 13.9 Hz, CCH*H*C), 2.17 (m), 1.95—1.50 (both: m), and 1.20—1.0 (both: m, MeC and *Me*CH) (Found: *m/z* 250.1544. $C_{15}H_{22}O_3$ requires *M*, 250.1569).

(±)-*Alliacolide* (**3**) *and* (±)-1-epi-*Alliacolide* (**47**).—A solution of *m*-chloroperbenzoic acid (37 mg × 85%, 182 μmol) in anhydrous dichloromethane (500 μl) was added dropwise over 5 min to a rapidly stirred mixture of the tricyclic lactones (**10**) and (**46**) (24.0 mg, 96 μmol) and disodium hydrogen phosphate (34 mg, 239 μmol) in anhydrous dichloromethane (500 μl) cooled in a water-bath. The cooling bath was removed, and the red solution was stirred at room temperature for 10 h, when additional disodium hydrogen phosphate (23 mg, 162 μmol), and then *m*-chloroperbenzoic acid (25 mg × 85%, 123 μmol) were added. After being stirred at room temperature for a further 4 h, the mixture was diluted with anhydrous dichloromethane (10 ml), and the organic extract was then washed separately with aqueous sodium sulphite (2M, 12 ml), saturated aqueous sodium hydrogen carbonate (2 ml), and saturated aqueous sodium chloride (2 ml). The organic solution was dried, and the solvent was evaporated off at reduced pressure to leave a white crystalline solid (25 mg). The solid was subjected to careful chromatography on Kieselgel H (20 × 120 mm), eluting with diethyl ether–petroleum (40%) to give: (i) (±)-1-epi-*alliacolide* (11 mg, 44%) (eluted first) which crystallised from hexane as colourless rhombs, m.p. 183—184 °C; $\nu_{max.}$(KBr) 3 420 (s), 1 780 (s), and 1 200 (m) cm^{-1}; δ_H 3.31 (OCHO), 2.72 (q, *J* 7.1 Hz, MeC*H*CO), 2.37 (OH), 2.24 (m, 1 H), 2.10 (d, *J* 14.0 Hz, CC*H*HC), 1.82 (m, 1 H), 1.7—1.5 (m, 3 H), 1.34 (d, *J* 14.0 Hz, C*H*O), 1.17 (d, *J* 7.1 Hz, *Me*CHCO), 1.15 (*Me*CMe), 1.11 (MeC*Me*), and 0.80 (d, *J* 6.7 Hz, *Me*CHC) (Found: *m/z* 266.1515. $C_{15}H_{20}O_4$ requires *M*, 266.1518) and (ii) (±)-*alliacolide* (7 mg, 28%) (eluted second) which crystallised from light petroleum as colourless needes, m.p. 191—192 °C (natural material showed m.p. 192—194 °C); $\nu_{max.}$(KBr) 3 450 (br s), 2 940 (s), 1 740 (s), 1 450 (m), 1 100 (s), and 990 (s) cm^{-1}; δ_H 3.22 (OC*H*), 2.69 (q, *J* 7.2 Hz, MeC*H*CO), 2.10 (OH), 1.80—2.15 (m, 2 H), 1.96 (d, *J* 13.8 Hz, CC*H*HC), 1.64 (m, 1 H), 1.29 (d, *J* 13.8 Hz, CCH*H*C), 1.25 (m, 2 H), 1.18 (d, *J* 7.2 Hz, *Me*CHCO), 1.14 (d, *J* 7.4 Hz, *Me*CHCH), and 1.12 (2 × Me) (Found: *m/z* 266.1513. $C_{15}H_{22}O_4$ requires *M*, 266.1518). Synthetic (±)-*alliacolide* did not separate from naturally derived material in mixed chromatography, and their ^{1}H n.m.r. and m.s. data were superimposable.

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