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COMPONENTS OF THE LAURACEAE FAMILY—I
NEW LACTONIC COMPOUNDS FROM *LITSEA JAPONICA*

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Abstract- Six new compounds, named litsenolides A_1, A_2, B_1, B_2, C_1 and C_2, have been isolated from the roots of *Litsea japonica* (Japanese name "Hamabiwa"). Spectral and chemical evidence shows that these six compounds are three pairs of β-hydroxy-γ-methyl-αβ'-unsaturated-γ-lactones having a long carbon chain terminated with a methyl (C series), an allyl (A series) or a propargyl (B series) group. The two components of each pair differ only in the structure, *cis* or *trans*, at the double bond conjugated with the lactone group. The absolute stereochemistry of the compounds is also discussed.

Litsea japonica (Thunb.) Juss., growing by the shores of the southern part of Japan, is the sole *Litsea* species found in this country. In the course of our chemical studies on Lauraceae plants, we have examined an ether extract of the plant and isolated six new lactonic compounds, litsenolides A_1 (I), A_2 (II), B_1 (III), B_2 (IV), C_1 (V) and C_2 (VI).

TABLE 1. DATA ON THE NATURAL COMPOUNDS

A_1	I	$C_{17}H_{28}O_3$ oil: $[\alpha]_D^{23}$ −2·4 ± 0·7° (*c* 0·619): λ_{max} 221·7 mμ (ε 10,100): ν_{max} 3600, 3400 (OH), 1755, 1673 (αβ-unsaturated γ-lactone), 1642, 913 (—CH=CH_2) cm^{-1}
A_2	II	$C_{17}H_{28}O_3$ oil: $[\alpha]_D^{23}$ −40·4 ± 1·2° (*c* 0·673): λ_{max} 218·5 mμ (ε 10,900): ν_{max} 3600, 3400 (OH), 1755, 1679 (αβ-unsaturated γ-lactone), 1643, 912 (—CH=CH_2) cm^{-1}
B_1	III	$C_{17}H_{26}O_3$: m.p. 40–41°: $[\alpha]_D^{24}$ −5·9 ± 0·6° (*c* 0·712): λ_{max} 223 mμ (ε 10,450): ν_{max} 3600, 3400 (OH), 1755, 1677 (αβ-unsaturated γ-lactone), 3290, 2150 (—C≡CH) cm^{-1}
B_2	IV	$C_{17}H_{26}O_3$: m.p. 42–43°: $[\alpha]_D^{24}$ −44·9 ± 1·6° (*c* 0·534): λ_{max} 218 mμ (ε 12,250): ν_{max} 3600, 3400 (OH), 1753, 1682 (αβ-unsaturated γ-lactone), 3280, 2140 (—C≡CH) cm^{-1}
C_1	V	$C_{19}H_{34}O_3$: m.p. 60–62°: $[\alpha]_D^{24}$ −9·4 ± 0·8° (*c* 0·617): λ_{max} 221 mμ (ε 10,200): ν_{max} 3600, 3400 (OH), 1755, 1676 (αβ-unsaturated γ-lactone) cm^{-1}
C_2	VI	$C_{19}H_{34}O_3$: m.p. 44–45°: $[\alpha]_D^{26}$ −45·2 ± 0·9° (*c* 0·986): λ_{max} 219 mμ (ε 11,900): ν_{max} 3600, 3400 (OH), 1755, 1678 (αβ-unsaturated γ-lactone) cm^{-1}

All $[\alpha]_D$ were measured in dioxane. IR spectra were measured in $CHCl_3$, and UV spectra were measured in EtOH.

Litsenolide A_1 (I) is an oil, $C_{17}H_{28}O_3$ (M^+ 280), and shows IR bands (Table 1) corresponding to OH, αβ-unsaturated γ-lactone, and —CH=CH_2 groups. The UV absorption also supports the presence of a —C=C—C=O grouping. The presence of one OH and one γ-lactone group accounts for the three oxygen atoms as required by elemental and mass spectral analyses. Thus the compound possesses no ring system other than the lactonic function.

The NMR spectrum (Table 2) of I indicates the presence of a long methylene chain [δ 1·30 (14H)], a CH_3—CH—CH< grouping [δ 1·37 (3H) and 4·33 (1H)], and a

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>CH—O— group [δ 4·37 (1H)]. Absorption peaks in the region of δ 4·8–6·2 (3H)

TABLE 2

		H-1 (CH_3)	H-2	H-3	H-6	H-7 (CH_2)	$(CH_2)_n$	H-15 (CH_2)	H-16, H-17 ($CH{=}CH_2$)	H-17 ($C{\equiv}CH$)	H-19 (CH_3)
A_1	I	1·37 d J = 6·5	4·33 dq J = 4·0; 6·5	4·37 m	6·53 td J = 7·8; 1·5	2·73 br.q	1·30 br.s n = 7	2·05 br.q	4·8–6·2 m	-	-
A_2	II	1·33 d J = 6·8	4·48 dq J = 2·0; 6·8	4·52 m	6·95 td J = 7·8; 1·5	2·40 br.q	1·30 br.s n = 7	2·02 br.q	4·8–6·2 m	—	—
B_1	III	1·38 d J = 6·5	4·33 dq J = 4·0; 6·5	4·38 m	6·53 td J = 7·8; 1·5	2·75 br.q	1·32 br.s n = 7	2·18 m[a]	—	1·93 t J = 2·2	-
B_2	IV	1·33 d J = 6·8	4·48 dq J = 2·5; 6·8	4·55 m	6·95 td J = 7·8; 1·5	2·42 br.q	1·32 br.s n = 7	2·18 m[a]	—	1·92 t J = 2·2	—
C_1	V	1·38 d J = 6·5	4·33 dq J = 4·0; 6·5	4·37 m	6·55 td J = 7·8; 1·5	2·75 br.q	1·27 br.s n = 11		—	—	0·88 br.t
C_2	VI	1·33 d J = 6·5	4·50[b] dq J = 2·2; 6·5	4·53[b] m	6·95 td J = 7·8; 1·5	2·42 br.q	1·27 br.s n = 11	—	—	-	0·88 br.t

All spectra were taken in $CDCl_3$ with TMS as internal reference.

[a] Coupling with the acetylenic proton was observed in these signals.

[b] These signals appeared at δ 4·38 (H-2) and δ 4·57 (H-3) in d_6-acetone. Decoupling experiments showed the presence of the following couplings in the signal of H-3: $J_{3,2}$ = 2·2, $J_{3,6}$ = 2 and $J_{3,7} \leqslant 1$ Hz.

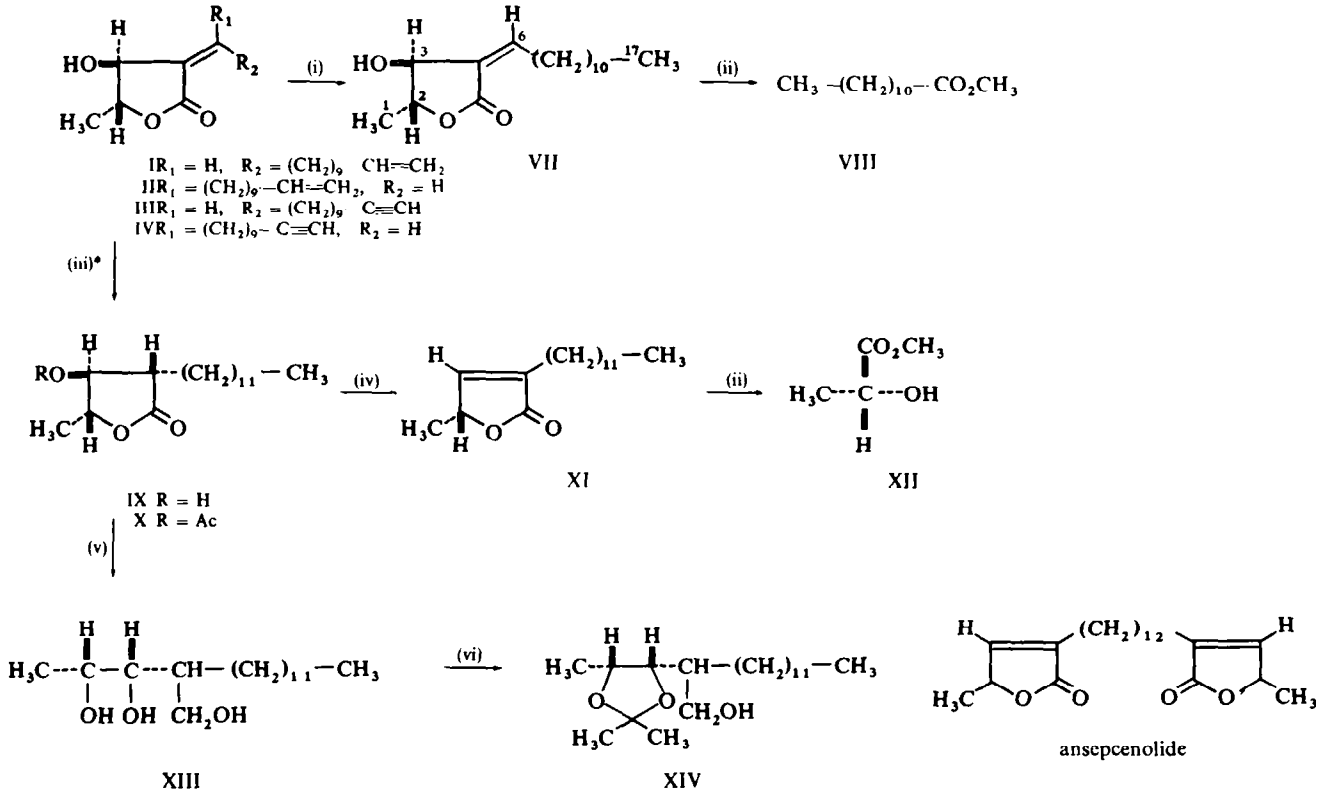
show a similar signal pattern to those of diallyl ether[1] and 4,6,8-trimethyl nonene-1,[2] indicating that these three protons belong to a vinyl group. This group is considered as the terminus of the methylene chain, since no triplet Me signal was observed around δ 0·9 and since a signal at δ 2·05 (2H) is ascribable to a methylene adjacent to the vinyl group. A signal at δ 6·53 (1H) is ascribed to an olefinic β-proton of the αβ-unsaturated lactone system from its chemical shift. The splitting pattern of this signal (t, J = 7·8 Hz) rules out the possibility that the conjugated double bond is endocyclic in the γ-lactone ring, since both carbons carrying an oxygen atom (lactonic or hydroxylic) possess only one proton (see above). Thus the double bond must be exocyclic to the lactone ring. Further, this splitting pattern shows that a free rotating methylene group is present neighbouring the double bond, suggesting that the exocyclic double bond must be the other terminus of the long methylene chain.

The length of the chain was determined as follows. On selective hydrogenation over Pd-$CaCO_3$, litsenolide A_1 (I) gave a dihydro-derivative (VII), $C_{17}H_{30}O_3$, m.p. 56–59°. Disappearance of NMR signals related to the three vinyl protons of the allyl group and appearance of a new Me signal at δ 0·87 (3H, broad t) indicated that only the terminal double bond had been hydrogenated. The dihydro compound (VII) was ozonized and esterified with CH_2N_2 to give an oily product, $C_{13}H_{26}O_2$ (M^+ 214), which was identified as methyl laurate (VIII) by its IR, NMR and mass spectra. Thus the long chain proved to contain twelve carbon atoms and to be unbranched. This fact characterized the remaining five carbons in I as a γ-lactone ring bearing a Me group.

Hydrogenation of I over Pd-C gave a tetrahydro-derivative (IX), $C_{17}H_{32}O_3$, m.p. 87–88°, ν_{max} 1773 cm^{-1} (saturated γ-lactone). On passing its acetate (X), m.p. 44–45°, through an alumina column,[3] loss of AcOH resulted giving compound XI, m.p. 46–47°. This compound shows absorptions similar to those of ansepcenolide[4] (Chart 1), an αβ-unsaturated γ-lactone obtained from a kind of gorgonians by Schmitz *et al.*: λ_{max} 209 mμ (ε 11,600); ν_{max} 1763 and 1658 cm^{-1}; δ 6·87 (1H, q,[4] J = 1·5 Hz, H-3) and 4·88 (1H, q–q,[4] J = 6·8 and 1·5 Hz, H-2). The formation of the endocyclic conjugated double bond in XI confirmed the location of the OH group in I at the β-position (C-3) of the γ-lactone. Further, since the presence of one proton at C-3 in XI was shown by the NMR spectrum, the Me group on the ring should be present on the γ-position (C-2). Thus structure I was assigned to litsenolide A_1.

Our next concern was the determination of stereochemistry at C-2 and C-3 in I. Compound XI was ozonized, esterified with CH_2N_2, and distilled, giving rise to a volatile ester (XII), $C_4H_8O_3$. The IR, NMR and mass spectra of XII were superimposable with those of the Me ester prepared from DL-lactic acid, and its optical activity, $[\alpha]_D$ +6·5°, agreed with that of the Me lactate obtained from D-lactic acid.[7] These results established the R-configuration at C-2 in I (2α-Me). Although the coupling constant between H-2 and H-3 in I or IX would seem to provide evidence for the configuration at C-3, the corresponding J values of 4·0 Hz in I and 7·0 Hz in IX are acceptable for both configurations of H-3, so we were forced to look elsewhere.

Anet[8] prepared *cis*- and *trans*-acetonides derived from *meso*- and DL-butane-2,3-diols respectively and found that the coupling constant between *cis*-arranged protons at the 2- and 3-positions was 5·85 Hz whereas the J value observed for the corresponding *trans*-oriented protons was 8·35 Hz. We tried to prepare an acetonide involving the OH group at C-3 and the lactonic oxygen at C-2; tetrahydrolitsenolide



(i) H_2/Pd-$CaCO_3$; (ii) (1) O_3, (2) $KMnO_4$, (3) CH_2N_2; (iii) H_2/Pd-C; (iv) Al_2O_3; (v) LAH; (vi) *p*-TsOH/acetone

* Mitsui[5] and Howard[6] studied the stereochemistry of hydrogenation over Pt and Pd catalysts, and showed that introduction of hydrogen to 2-cyclopentylidene- and 2-isopropylidene-cyclopentanol occurred from the same side of the OH group because of an anchor effect between the OH group and the catalyst.

CHART 1

A_1 (IX) was reduced with LAH to a triol (XIII), which on treatment with *p*-TsOH in acetone gave an acetonide. This compound was found to be a five-membered dioxolane (XIV) from its NMR spectrum: the signal due to protons on C-5 appears as a doublet at δ 3·62 (2H, J = 4·5 Hz), showing that these protons are spatially equivalent to H-4, i.e. the oxygen atom on C-5 in XIV does not participate in the acetonide ring formation. The NMR spectrum of XIV in d_6-acetone gave separate signals for H-2 (δ 4·24) and H-3 (δ 4·00), and decoupling experiments confirmed the coupling constant between these protons to be 5·5 Hz, which is more consistent with that of the isomer having the protons in a *cis*-relationship in the acetonide ring. Since the relative arrangement between H-2 and H-3 was altered during the course of transformation of IX into XIV, the *trans*-relationship should be given to H-2 and H-3 in IX, and thus in I. Thus the OH group at C-3 in I is β-oriented.

The geometry of the exocyclic double bond in I was clarified in connection with structure determination of litsenolide A_2 (II), an oil, $C_{17}H_{28}O_3$ (M^+ 280). The compound was considered to have the same plane structure as I from its spectral properties (Tables 1 and 2). In fact, catalytic hydrogenation of II over Pd-C gave tetrahydrolitsenolide A_1 (IX), m.p. 88°. Thus litsenolide A_2 (II) must be the geometric isomer of I with respect to the exocyclic double bond.

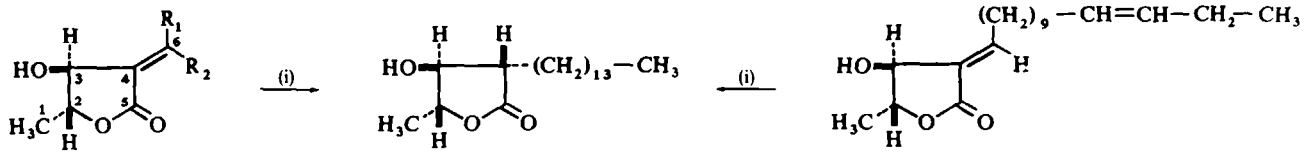
It is well known that in the NMR spectrum of a cisoid enone system a signal for the β-*cis* vinyl proton resonates 0·3–0·9 ppm downfield from that of the corresponding β-*trans* proton.[9] Comparison of the chemical shifts of the corresponding olefinic proton in I and II (Table 2) indicated that litsenolide A_1 has a β-*trans* proton (structure I) and A_2 has a β-*cis* proton (structure II).

Litsenolides B_1 (III), m.p. 40–41°, $C_{17}H_{26}O_3$, and B_2 (IV), m.p. 42–43°, $C_{17}H_{26}O_3$, show physical properties similar to those of I and II (Tables 1 and 2). However, the B series compounds show IR absorptions due to a —C≡CH group instead of the bands due to the —CH=CH_2 group present in the A series lactones. The NMR spectra of both the compounds also indicate the presence of a —CH_2—C≡CH grouping in the molecules.

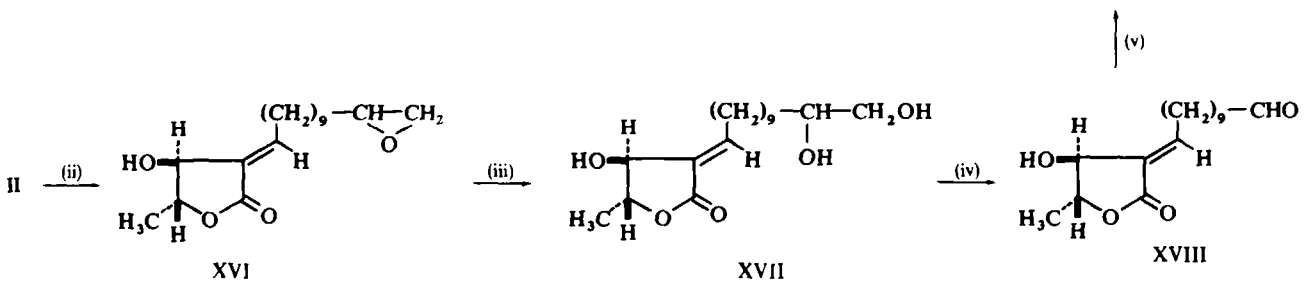
On hydrogenation over Pd-C, litsenolides B_1 (III) and B_2 (IV) yielded the same hexahydro-derivative, m.p. 87–88°, identical with tetrahydrolitsenolide A_1 (IX) in all respects. Thus, both compounds (III and IV) proved to have the same stereochemistry on the lactone ring as the A series compounds, and to be a pair of geometric isomers of the double bond. Assignment of the signals of the conjugated olefinic protons was done as described before, confirming that litsenolide B_1 has a β-*trans* proton (structure III) and B_2 has a β-*cis* proton (structure IV).

Litsenolides C_1 (V), m.p. 60–62°, $C_{19}H_{34}O_3$, and C_2 (VI), m.p. 44–45°, $C_{19}H_{34}O_3$, show the molecular ion peak of M^+ 310, indicating that they each have a side chain two methylene units longer than the A and B series. The NMR spectrum of litsenolide C_1 (V) shows almost the same pattern as dihydrolitsenolide A_1 (VII), indicating the presence of a Me group at the terminal of the methylene chain. Hydrogenation of V and VI over Pd-C gave the same dihydro compound (XV), m.p. 90–92°, $[\alpha]_D$ +10·4°, showing that they are also geometric isomers about the exocyclic double bond. Conversion of litsenolide A_2 (II) into dihydrolitsenolide C_2 (XV) confirmed the structure of the C series compounds.

Compound II was oxidized with one molar equivalent of *m*-chloroperbenzoic acid to give an oily product (XVI), whose NMR spectrum shows signals corresponding to



V R_1 = H, R_2 = $(CH_2)_{12}$—CH_3
VI R_1 = $(CH_2)_{12}$ CH_3, R_2 = H



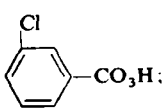
(i) H_2/Pd-C; (ii)  —CO_3H; (iii) $HClO_4$; (iv) H_5IO_6; (v) ϕ_3—P=CH—CH_2—CH_3

CHART 2

two protons on the epoxide ring at δ 2·43 (H-17 *trans*) and 2·72 (H-17 *cis*). The product (XVI) was treated with $HClO_4$ to yield a mixture of triols (XVII), which was oxidized with H_5IO_6 to afford an oily aldehyde (XVIII), $C_{16}H_{26}O_4$. The aldehyde was treated with propylidene triphenylphosphorane[10] to yield a mixture of stereoisomers (XIX) with respect to the newly introduced double bond. The mixture was hydrogenated over Pd-C yielding a C_{19}-lactone, m.p. 90–92°, $[\alpha]_D$ +10·9°, which was identified as XV by m.m.p. determination and by IR, NMR and mass spectral comparison. Comparison of the chemical shifts of the olefinic proton in litsenolides C_1 and C_2 (Table 2) established structure V for the former compound, and structure VI for the latter.

Litsenolides are considered to be synthesized in the plant from a C_{14}-fatty acid (A and B series) or a C_{16}-one (C series) and a C_3-unit e.g. pyruvyl CoA as shown by Lybing and Reio[11] for the biosynthesis of carolic acid.

EXPERIMENTAL

Optical rotations were taken in dioxane. UV spectra were measured in EtOH. Unless otherwise stated, IR spectra were measured in $CHCl_3$ and NMR spectra were recorded on a Varian A-60 spectrometer in $CDCl_3$ with TMS as internal reference. Mass spectra were recorded on a Hitachi RMU-6 spectrometer. Aluminium oxide Woelm neutral was used for coloumn chromatography. M.ps were measured with a Kofler hot stage apparatus.

Extraction and isolation of litsenolides. Dried and ground roots of *Litsea japonica* (8·77 kg), collected at Osumi Peninsula in Kagoshima Prefecture, were extracted with ether (25 l × 3) at room temp for 3 days. The extract was evaporated to give a brown viscous oil (190·0 g). This oil (25·15 g) was chromatographed on silica gel [0·2–0·5 mm (Merck), 750 g] and eluted successively with light petroleum, light petroleum–ether (9:1, 3:1 and 1:1), and ether. A part (1·38 g) of the fraction eluted with light petroleum–ether (1:1) (20·73 g) was separated by prep. TLC [$AgNO_3$–Kieselgel GF_{254},[12] EtOAc–C_6H_6 (1:3)] into three fractions: fraction C (R_f 0·7, 0·134 g), fraction A (R_f 0·6, 0·782 g) and fraction B (R_f 0·1, 0·415 g). Each fraction was further divided by prep. TLC [Kieselgel GF_{254}, EtOAc–C_6H_6 (1:9), 3–5 developments] into two components: fraction A (101 mg) gave litsenolides A_1 (I, R_f 0·6, 25 mg) (Found: C, 72·31; H, 10·17. $C_{17}H_{28}O_3$ requires C, 72·82; H, 10·06%) and A_2 (II, R_f 0·5, 40 mg) (Found: C, 72·70; H, 10·18. $C_{17}H_{28}O_3$ requires C, 72·82; H, 10·06%), fraction B (80 mg) gave litsenolides B_1 (III, R_f 0·6, 23 mg) (Found: C, 73·29; H, 9·41. $C_{17}H_{26}O_3$ requires C, 73·34; H, 9·41%) and B_2 (IV, R_f 0·5, 41 mg) (Found: C, 73·54; H, 9·44. $C_{17}H_{26}O_3$ requires C, 73·34; H, 9·41%), and fraction C (98 mg) gave litsenolides C_1 (V, R_f 0·6, 19 mg) (Found: C, 73·37; H, 11·04. $C_{19}H_{34}O_3$ requires C, 73·50; H, 11·04%) and C_2 (VI, R_f 0·5, 55 mg) (Found: C, 73·24; H, 10·99. $C_{19}H_{34}O_3$ requires C, 73·50; H, 11·04%). The physical properties of these compounds (I–VI) are listed in Tables 1 and 2.

Selective hydrogenation of litsenolide A_1 (I). Litsenolide A_1 (I, 170 mg) was hydrogenated over Pd-$CaCO_3$ (1·2%, 41 mg) in EtOH (3 ml) at room temp until 1·0 mole of H_2 (13·6 ml) had been absorbed. Removal of catalyst and solvent gave a white solid (181 mg), which was purified by prep. TLC [$AgNO_3$–Kieselgel GF_{254}, EtOAc–C_6H_6 (1:4)] to afford dihydrolitsenolide A_1 (VII, R_f 0·65, 143 mg) as prisms, m.p. 56–59° from ether–*n*-hexane), $[\alpha]_D^{22}$ −5·2 ± 0·5° (*c* 0·924); ν_{max} 3600 and 3400 (OH), 1753 and 1674 ($\alpha\beta$-unsaturated γ-lactone) cm^{-1}; δ 0·87 [3H, broad t, H-17 (Me)], 1·27 [18H, broad s, —$(CH_2)_9$—], 1·38 [3H, d, J = 6·5 Hz, H-1 (Me)], 2·75 (2H, m, H-7), 4·33 (1H, d–q, J = 2·0 and 6·5 Hz, H-2), 4·38 (1H, m, H-3) and 6·58 (1H, t–d, J = 8·0 and 1·8 Hz, H-6) (Found: C, 72·56; H, 10·64. $C_{17}H_{30}O_3$ requires C, 72·30; H, 10·71%).

Degradation of VII *to methyl laurate* (VIII). Ozone (3·2%, 40 ml/min) was introduced into a soln of dihydrolitsenolide A_1 (VII, 106 mg) in EtOAc (10 ml) under cooling with dry ice–acetone for 2 hr and the solvent evaporated *in vacuo*. To a soln of the residual oil in acetone (10 ml), a soln of $KMnO_4$ (240 mg) in acetone (10 ml) was added dropwise, and the mixture stirred at room temp for 3 hr. Excess reagent was decomposed by addition of 10% $NaHSO_3$ aq. The ppt (MnO_2) was filtered and the filtrate evaporated *in vacuo* to dryness. The residual solid was dissolved in 2N H_2SO_4 (2 ml) and the soln extracted with ether. The ether extract was washed, dried (Na_2SO_4), and evaporated to leave a white wax (105 mg). The wax

was dissolved in ether (2 ml) and esterified with CH_2N_2 to give an oil (117 mg), which was chromatographed on alumina (activity IV, 3·3 g). Elution with *n*-pentane gave methyl laurate (VIII, 80 mg) as an oil, ν_{max}^{film} 1744 and 1255 (ester) cm^{-1}; δ 0·87 (3H, broad t, terminal Me), 1·27 [18H, broad s, —(CH_2)$_9$—], 2·30 (2H, m, —O_2C—CH_2), and 3·63 (3H, s, —CO_2Me); MS (*m/e*) 214 (M^+ $C_{13}H_{26}O_2$), 199, 183, 171, 157, 143, 129, 115, 101, 87, 74 (base peak), 55, 43, 41 and 29, identical with an authentic sample (IR, NMR and mass spectra).

Tetrahydrolitsenolide A_1 (IX). (a) From litsenolide A_1 (I). Compound I (55 mg) was hydrogenated over Pd-C (1·5%, 51 mg) in EtOH (1·5 ml). The reaction ceased when 2 moles of H_2 (8·5 ml) had been absorbed. Removal of catalyst and solvent gave tetrahydrolitsenolide A_1 (IX) as prisms (53 mg), m.p. 87–88° (from ether–*n*-hexane), $[\alpha]_D^{25}$ +10·3 ± 0·5° (*c* 0·964); ν_{max} 3600 and 3400 (OH), 1773 (γ-lactone) cm^{-1}; δ 0·87 [3H, broad t, H-17 (Me)], 1·27 [22H, broad s, —(CH_2)$_{11}$—], 1·42 [3H, d, J = 6·0 Hz, H-1 (Me)], 2·50 (1H, m, H-4), 3·78 (1H, d–d, J = 7·0 and 8·5 Hz, H-3) and 4·20 (1H, d–q, J = 7·0 and 6·0 Hz, H-2) (Found: C, 71·68; H, 11·21. $C_{17}H_{32}O_3$ requires C, 71·78; H, 11·34%).

(b) From litsenolide A_2 (II). Hydrogenation of II (52 mg) over Pd-C (1·5%, 54 mg) gave a tetrahydro compound (47 mg) as prisms, m.p. 87–88°, $[\alpha]_D^{23}$ +10·4 ± 0·5° (*c* 0·977), identical with IX (m.m.p. and IR spectrum).

(c) From litsenolide B_1 (III). Hydrogenation of III (44 mg) over Pd-C (1·5%, 47 mg) gave a hexahydro compound (40 mg) as prisms, m.p. 87–88°, $[\alpha]_D^{25}$ +10·6 ± 0·5° (*c* 0·968), identical with IX (m.m.p. and IR spectrum).

(d) From litsenolide B_2 (IV). Hydrogenation of IV (35 mg) over Pd-C (1·5%, 34 mg) gave a hexahydro compound (30 mg) as prisms, m.p. 87–88°, $[\alpha]_D^{25}$ +10·6 ± 0·5° (*c* 0·980), identical with IX (m.m.p. and IR spectrum).

Acetylation of tetrahydrolitsenolide A_1 (IX). Tetrahydrolitsenolide A_1 (IX, 336 mg) was treated with Ac_2O (2 ml) and pyridine (2 ml) overnight at room temp. Ice was added to the mixture and the ppt formed was collected (376 mg), washed with water, and crystallized from *n*-hexane to yield an acetate (X) as prisms (220 mg), m.p. 44–45°, $[\alpha]_D^{21}$ −4·5 ± 0·5° (*c* 0·939); ν_{max} 1776 (γ-lactone), 1740 (acetate) cm^{-1}; δ 0·88 [3H, broad t, H-17 (Me)], 1·27 [22H, broad s, —(CH_2)$_{11}$—], 1·45 [3H, d, J = 6·8 Hz, H-1 (Me)], 2·08 (3H, s, —OAc), 2·68 (1H, m, H-4), 4·37 (1H, d–q, J = 4·5 and 6·8 Hz, H-2) and 4·92 (1H, d–d, J = 4·5 and 5·5 Hz, H-3) (Found: C, 69·94; H, 10·44. $C_{19}H_{34}O_4$ requires C, 69·90; H, 10·50%).

Treatment of the acetate (X) *with alumina.* The acetate (X, 247 mg) was placed on the top of a column of alumina (activity III, 9·0 g) and eluted with *n*-pentane to give the αβ-unsaturated lactone (XI, 177 mg) as prisms, m.p. 46–47° (from *n*-pentane), $[\alpha]_D^{22}$ −29·8 ± 1·3° (*c* 0·541); λ_{max} 209 mμ (ε 11,600); $\nu_{max}^{CCl_4}$ 1763 and 1658 (αβ-unsaturated γ-lactone) cm^{-1}; δ (CCl_4): 0·88 [3H, broad t, H-17 (Me)], 1·27 [20H, broad s, —(CH_2)$_{10}$—], 1·38 [3H, d, J = 6·8 Hz, H-1 (Me)], 2·22 (2H, m, H-6), 4·88 (1H, q–q, J = 1·5 and 6·8 Hz, H-2) and 6·87 (1H, q, J = 1·5 Hz, H-3) (Found: C, 76·94; H, 11·12. $C_{17}H_{30}O_2$ requires C, 76·64; H, 11·35%).

Degradation of XI *into methyl* D-*lactate* (XII). Ozone (3·4%, 40 ml/min) was introduced into a soln of the lactone (XI, 334 mg) in CH_2Cl_2 (10 ml) under ice-cooling for 3 hr. Water (10 ml) was added to the mixture and CH_2Cl_2 removed under reduced pressure. Powdered $KMnO_4$ (66 mg) and $NaHCO_3$[13] (17 mg) was added to the aqueous soln, which was stirred under ice-cooling for 4 hr and left at 3° for 16 hr. The ppt (MnO_2) was collected by filtration and washed with water. The filtrate and washing were combined, made alkaline with NaOH (0·5 g) and set aside at 0° for 1 hr. Then the mixture was acidified with conc. H_2SO_4 and extracted continuously with ether for 6 hr. The ether layer was esterified with CH_2N_2. Removal of solvent gave an oil (291 mg), which on distillation using a Kugelrohr (b.p.$_{20}$ 40°) gave methyl lactate (XII) as an oil (40 mg), $[\alpha]_D^{21}$ +6·5 ± 0·5° (*c* 1·087); ν_{max} 3600 (OH), 1742 (ester) cm^{-1}; δ 1·47 (3H, d, J = 7·0 Hz, CH_3—CH—OH), 3·00 (1H, d, J = 5·5 Hz, —CH—OH), 3·77 (3H, s, —CO_2Me) and 4·28 (1H, d–q, J = 5·5 and 7·0 Hz, CH_3—CH—OH); MS (*m/e*) 88 (M-16), 59 ($^+O{\equiv}C$—O—CH_3), 45 (base peak, M-59), 28 and 15 (Found: C, 45·97; H, 7·79. $C_4H_8O_3$ requires C, 46·15; H, 7·75%). Its IR, NMR and mass spectra are superimposable with those of an authentic sample prepared by methylation of DL-lactic acid.

Reduction of tetrahydrolitsenolide A_1 (IX) *with* LAH. A soln of tetrahydrolitsenolide A_1 (IX, 100 mg) in THF (4 ml) was added dropwise to a stirred suspension of LAH (40 mg) in THF (3 ml) under N_2 atm and ice-cooling. Stirring was continued for a further 30 min, the excess reagent was decomposed with water, and the ppt formed was filtered off. The filtrate was dried (Na_2SO_4) and evaporated to leave a white solid (112 mg), which was chromatographed on alumina (activity IV, 3·3 g). Elution with light petroleum–ether (2:1 and 1:1) gave the triol (XIII, 54 mg) as prisms, m.p. 55–57° (from ether–*n*-pentane), $[\alpha]_D^{22}$ −23·5 ± 1·3° (*c* 0·528); ν_{max} 3600 and 3400 (OH) cm^{-1} (Found: C, 70·54; H, 12·42. $C_{17}H_{36}O_3$ requires C, 70·78; H, 12·58%).

Preparation of the acetonide (XIV) *from the triol* (XIII). A mixture of the triol (XIII, 206 mg) and *p*-TsOH (22 mg) in acetone (8 ml) was heated under reflux for 2 hr. The mixture was worked up as usual to give an

oil (251 mg). The oil (192 mg) was separated by prep. TLC [Kieselgel G-I_2, EtOAc–C_6H_6 (1:4)] into four fractions: fraction 1 (R_f 0·6, 15 mg), fraction 2 (R_f 0·5, 29 mg), fraction 3 (R_f 0·3, 115 mg) and fraction 4 (R_f 0·03, 18 mg). Fraction 3 gave the acetonide (XIV) as an oil, $[\alpha]_D^{22}$ −3·0 ± 1·0° (*c* 0·440); ν_{max} 3600 and 3500 (OH) cm^{-1}; δ (d_6-acetone–$CHCl_3$, 100 MHz) 0·87 [3H, broad t, H-17 (Me)], 1·10 [3H, d, *J* = 6·0 Hz, H-1 (Me)], 1·23 and 1·34 [each 3H, s, H-19 (Me) and H-20 (Me)], 1·28 [22H, broad s, —$(CH_2)_{11}$—], 3·51 (2H, d, *J* = 4·5 Hz, H-5), 4·00 (1H, d–d, *J* = 5·5 and 8·5 Hz, H-3) and 4·24 (1H, d–q, *J* = 5·5 and 6·0 Hz, H-2) (Found: C, 72·89; H, 12·02. $C_{20}H_{40}O_3$ requires C, 73·12; H, 12·27%).

Dihydrolitsenolide C_2 (XV). (a) From litsenolide C_2 (VI). Compound VI (30 mg) was hydrogenated over Pd-C (5%, 30 mg) in EtOH (2 ml). The reaction ceased when 1·0 mole of H_2 had been absorbed. Removal of catalyst and solvent gave dihydrolitsenolide C_2 (XV) as needles (31 mg), m.p. 90–92° (from ether–*n*-pentane), $[\alpha]_D^{24}$ +10·4 ± 1·0° (*c* 0·527); ν_{max} 3400 (OH), 1775 (γ-lactone) cm^{-1}; δ 0·88 [3H, broad t, H-19 (Me)], 1·23 [26H, broad s, —$(CH_2)_{13}$—], 1·43 [3H, d, *J* = 6·0 Hz, H-1 (Me)], *ca.* 2·50 (1H, m, H-4), 3·82 (1H, d–d, *J* = 7·0 and 8·2 Hz, H-3) and 4·20 (1H, d–q, *J* = 7·0 and 6·0 Hz, H-2) (Found: C, 73·12; H, 11·51. $C_{19}H_{36}O_3$ requires C, 73·03; H, 11·61%).

(b) From litsenolide C_1 (V). Hydrogenation of V (23 mg) over Pd-C (5%, 22 mg) gave a dihydro compound (20 mg) as needles, m.p. 90–92° (from ether–*n*-pentane), $[\alpha]_D^{25}$ +9·6 ± 0·7° (*c* 0·825), identical with XV (m.m.p. and IR spectrum).

Conversion of litsenolide A_2 (II) *into dihydrolitsenolide* C_2 (XV). To a soln of litsenolide A_2 (II, 86 mg) in CH_2Cl_2 (5 ml) was added dropwise a soln of *m*-chloroperbenzoic acid (85%, 63 mg) in CH_2Cl_2 (5 ml) under ice-cooling. The mixture was left at 3° for 24 hr, concentrated and diluted with ether (50 ml). The ether soln was washed, dried and evaporated to give an oil (94 mg), which was separated by prep. TLC [Kieselgel GF_{254}, EtOAc–C_6H_6 (1:4)] into the starting material (II, R_f 0·4, 21 mg) and a mixture of two epoxides (XVI, R_f 0·2, 61 mg), ν_{max} 3400 (OH), 1749 and 1677 (αβ-unsaturated γ-lactone) cm^{-1}.

To a soln of the epoxides (XVI, 57 mg) in acetone (4 ml), 1·5N $HClO_4$ (3 ml) was added and the mixture stirred at room temp for 18 hr. Water (5 ml) was added, which was then extracted with ether. The ether soln was washed, dried and evaporated to leave an oil (64 mg), which on trituration with ether gave a crystalline product (XVII, 17 mg). The residue (46 mg) from the mother liquor was separated by prep. TLC [Kieselgel GF_{254}, EtOAc–C_6H_6 (1:1)] to the starting material (XVI, R_f 0·7, 34 mg) and another crop of the product (XVII, R_f 0·1, 10 mg), ν_{max} 3600 and 3400 (OH), 1747 and 1675 (αβ-unsaturated γ-lactone) cm^{-1}.

A mixture of the product (XVII, 27 mg) and H_5IO_6 (20 mg) in 50% aqueous EtOH (2 ml) was stirred at room temp for 2 hr. Ether (50 ml) was added to the mixture, which was washed, dried and evaporated to give an oil (30 mg). The oil was purified by prep. TLC [Kieselgel GF_{254}, EtOAc–C_6H_6 (1:4)]. The compound showing R_f 0·23 was an aldehyde (XVIII, 14 mg), an oil, $[\alpha]_D^{25}$ −35·3 ± 2·5° (*c* 0·312); ν_{max} 3600 and 3400 (OH), 2820, 2740 and 1727 (CHO), 1750 and 1680 (αβ-unsaturated γ-lactone) cm^{-1}; δ 1·30 [14H, broad s, —$(CH_2)_7$—], 1·35 [3H, d, *J* = 6·5 Hz, H-1 (Me)], 2·17–2·67 (4H, m, H-7 and H-15), 4·50 (1H, d–q, *J* = 2·5 and 6·5 Hz, H-2), 4·57 (1H, m, H-3), 6·97 (1H, t–d, *J* = 7·5 and 1·5 Hz, H-6) and 9·73 (1H, t, *J* = 2·0 Hz, H-16) (Found: C, 67·91; H, 9·39. $C_{16}H_{26}O_4$ requires C, 68·05; H, 9·28%).

A soln of t-BuOK (163 mg) in THF (5 ml) was added to a stirred soln of triphenyl-*n*-propylphosphonium bromide[11] (689 mg) in THF (20 ml) under N_2 atm. The orange-red mixture was stirred at room temp for 10 min. A soln of the aldehyde (XVIII, 307 mg) in THF (5 ml) was added dropwise to the coloured mixture under ice-cooling and the colour faded gradually. Stirring was continued for a further 1 hr and the ppt formed was filtered. The filtrate was evaporated to give a viscous light brown oil (680 mg), which was chromatographed on silica gel (Merck, 70–325 mesh, 21 g) and eluted with *n*-pentane–ether (9:1, 4:1, 2:1 and 1:1). The head eluate from *n*-pentane–ether (1:1) gave a mixture of products (XIX, 52 mg), ν_{max} 3500 (OH), 1765 (αβ-unsaturated γ-lactone) cm^{-1}. The tail eluate from the same solvent system afforded the starting aldehyde (XVIII, 196 mg).

The product (XIX, 48 mg) was hydrogenated over Pd-C (5%, 45 mg) in EtOH (2 ml), 2 moles of H_2 (6·8 ml) being absorbed. Removal of the catalyst and solvent gave a crystalline substance (44 mg), which on recrystallization from ether–*n*-pentane gave an analytical sample, m.p. 90–92°, $[\alpha]_D^{24}$ +10·9 ± 1·4° (*c* 0·366), identical with XV (m.m.p. and IR, NMR and mass spectra).

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