Tobacco Chemistry. 70.* Six New Cembrane-Derived Compounds from Tobacco

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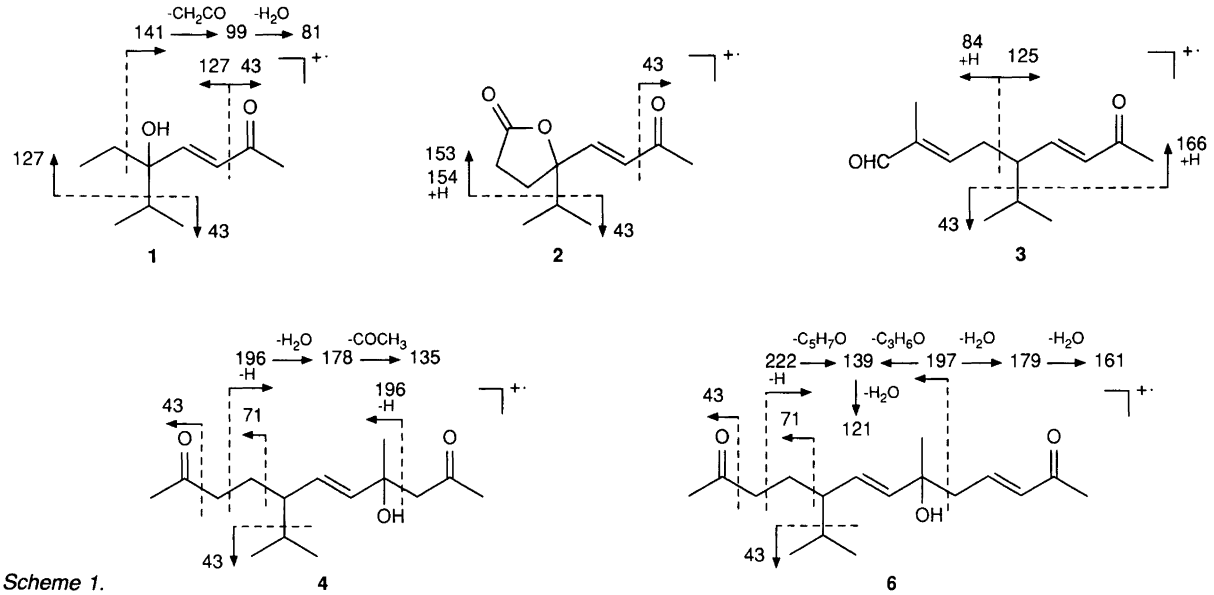
Six new compounds of probable cembrane origin have been isolated from Greek tobacco. They have been identified as (*E*)-5-hydroxy-5-isopropylhept-3-en-2-one (**1**), (*E*)-4-isopropyl-7-oxooct-5-en-4-olide (**2**), (2*E*,6*E*)-5-isopropyl-2-methyl-8-oxononona-2,6-dienal (**3**), (*E*)-4-hydroxy-7-isopropyl-4-methylundec-5-ene-2,10-dione (**4**), (*E*)-3-hydroxy-6-isopropyl-3-methyl-9-oxodec-4-enoic acid (**5**) and (3*E*,7*E*)-6-hydroxy-9-isopropyl-6-methyltrideca-3,7-diene-2,12-dione (**6**) by spectral methods and synthesis (**1**, **2**, **4**–**6**). The biogenesis of **1**–**6** is discussed.

The aroma fractions isolable from tobacco are noted for their large content and wide array of compounds, which are postulated to arise by biodegradation of diterpenoids, carotenoids and higher isoprenoids.[2] As an addition to these, we now report the isolation of six new cembrane-derived compounds (**1**–**6**) from tobacco.[3]

Results

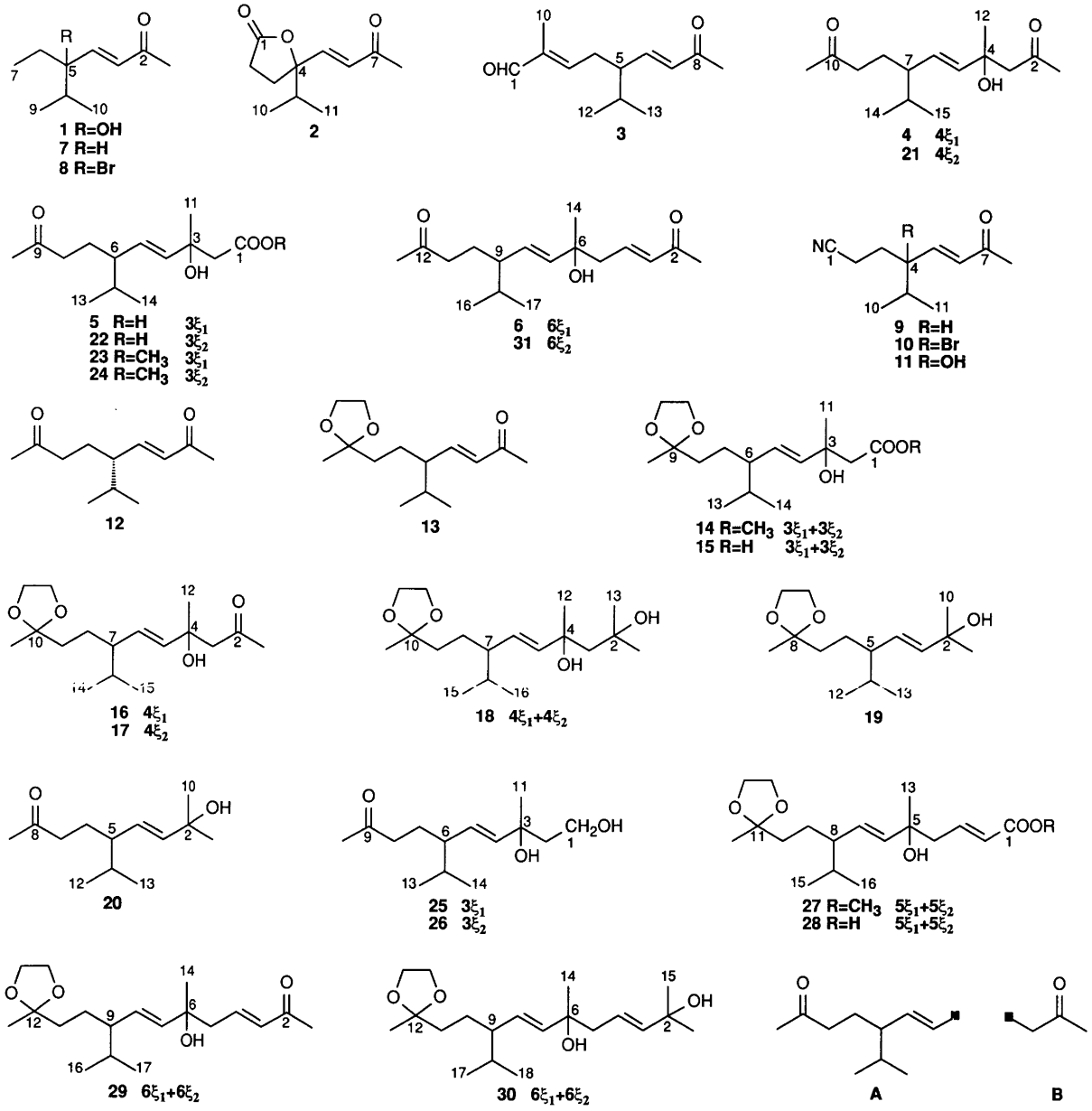
Repetitive liquid chromatography was used to isolate compounds **1**–**4** from a diethyl ether extract of sun-cured leaves of Greek tobacco and compounds **5** and **6** from a chloroform extract of flowers of Greek tobacco.

Structure determination. The first new compound (**1**), $C_{10}H_{18}O_2$, is an α,β-unsaturated ketone [IR: 1679 cm^{-1}; ^1H NMR doublets at δ 6.34 and 6.75 (J = 15.9 Hz)]. The keto group is linked to a methyl group (^1H NMR 3 H singlet δ 2.29) and the β-carbon of the enone moiety to a fully substituted hydroxy-bearing carbon atom [^{13}C NMR: δ 77.8 (s); OH-absorption in the IR spectrum]. Since the latter carbon atom is also attached to an ethyl and an isopropyl group, **1** was identified as (*E*)-5-hydroxy-5-isopropylhept-3-en-2-one. This formulation was consistent with the mass spectrum, which includes peaks at *m/z* 141, 127, 99, 81, and 43 corresponding to ions arising from the fragmentation reactions outlined in Scheme 1.



Scheme 1.

* For part 69 see Ref. 1.



Confirmatory structural evidence was obtained by synthesis involving bromination of (±)-(*E*)-5-isopropylhept-3-en-2-one (**7**)[4] using *N*-bromosuccinimide (NBS) and *tert*-butyl hydroperoxide in CCl_4 to give **8** and subsequent acid-catalyzed hydrolysis.

The second new compound (**2**), $C_{11}H_{16}O_3$, also contains an (*E*)-3-oxobut-1-enyl moiety that is linked to a fully substituted oxygen-bearing carbon atom [^{13}C NMR δ 89.7 (s)]. The latter is part of a five-membered ring lactone system (IR band at 1785 cm^{-1}) and carries an isopropyl substituent. These results allowed the identification of **2** as (*E*)-4-isopropyl-7-oxooct-5-en-4-olide.

A racemic sample of (*E*)-4-isopropyl-7-oxooct-5-en-4-olide, the spectral data of which were identical with those of the natural product (**2**), was obtained in a low yield as follows. (±)-(*E*)-4-Isopropyl-7-oxooct-5-enenitrile (**9**), prepared by analogy with a method used for the synthesis of (±)-(5*E*)-4-isopropyl-7-methylocta-5,7-dienenitrile,[5] was brominated using NBS. The bromo compound formed (**10**) was treated with acid to give, as the major product, a compound, which was identified as (±)-(*E*)-4-hydroxy-4-isopropyl-7-oxooct-5-enenitrile (**11**) from its spectral data, and as the minor product compound **2**.

The third new compound (**3**), $C_{13}H_{20}O_2$, incorporates an aldehyde group and an oxo group, both being α,β-unsaturated [IR: 2711, 1693 and 1625 cm^{-1}; ^{13}C NMR: δ 132.4 (d), 140.4 (s), 148.2 (d), 151.5 (d), 194.9 (d) and 197.9 (s)]. The ^1H NMR spectrum was consistent with the presence of

an isopropyl group and two methyl groups, of which one is vinylic and the other is linked to the keto group [δ: 0.93 (d), 0.98 (d), 1.75 (dt) and 2.26 (s)]. These structural fragments were allocated to a (2*E*,6*E*)-5-isopropyl-2-methyl-8-oxonona-2,6-dienal structure with the aid of the ^1H–^1H shift correlation spectrum. The presence of cross-peaks due to long-range coupling between H-3 and H-10 and between H-7 and H-9 was thereby useful from a diagnostic point of view. The assignment of *E*-geometries to the 2,3 and 6,7 double bonds followed from the shielding of the aldehydic proton, δ 9.38,[6] and the magnitude of the vicinal coupling constant, J = 15.9 Hz, respectively. Structural information was also provided by the mass spectrum, which contains characteristic peaks at *m/z* 166, 125, 84 and 43 (Scheme 1).

Attempts to synthesize **3** from norsolanadione (**12**) or 2-isopropyl-5-oxohexanal were unsuccessful.

The fourth new compound (**4**), $C_{15}H_{26}O_3$, possesses two oxo groups (^{13}C NMR signals at δ 209.4 and 210.4; IR band at 1710 cm^{-1}), which were allocated by the use of ^1H–^1H shift correlation spectroscopy to partial structures **A** and **B**. These were linked via a fully substituted carbon atom, which carries a hydroxy and a methyl group (^{13}C NMR signal at δ 71.6; ^1H NMR methyl singlet at δ 1.28; OH-absorption in the IR spectrum) to an (*E*)-4-hydroxy-7-isopropyl-4-methylundec-5-ene-2,10-dione structure. This assignment was corroborated by the mass spectrum, which includes diagnostically useful ions of masses 196, 178, 135, 71, and 43 (Scheme 1).

The synthesis of racemic **4** was performed as follows. (±)-Norsolanadione monoacetal (**13**)[7] was converted by a Reformatsky reaction using zinc and methyl bromoacetate into a mixture of the C-3 epimers of the methyl ester **14** [^1H NMR: three-proton singlets at δ 1.30, 1.31 and 3.68]. Alkaline hydrolysis gave the acid **15**, which was treated with methyllithium in THF. The desired diastereomeric ketones **16** and **17** were obtained as the major products, while a mixture of the C-4 isomers of the diol **18** (IR: 3613 and 3364 cm^{-1}), the monool **19** and norsolanadione monoacetal (**13**) were minor products. The diol **19** is evidently formed by dialkylation of **15**, while norsolanadione monoacetal (**13**) is likely to arise via a retro-aldol reaction occurring with **16** and **17**. Compound **18** was hydrolyzed to give (*E*)-2-hydroxy-5-isopropyl-2-methylnon-3-en-8-one (**20**), which is a tobacco constituent.[7]

Hydrolysis converted **17** into the desired (±)-(*E*)-4-hydroxy-7-isopropyl-4-methylundec-5-ene-2,10-dione, which was identical with the new tobacco constituent **4**. A C-4 epimer of **4** (**21**), hitherto not encountered in tobacco, was obtained by hydrolysis of **16**.

One of the C-3 isomers of (6*S*)-(*E*)-3-hydroxy-6-isopropyl-3-methyl-9-oxodec-4-enoic acid (**22**) has previously been found in tobacco.[8] We have now isolated this acid and an isomer thereof (**5**) as the corresponding methyl esters (**23**, **24**) from tobacco. Their structures were confirmed by direct comparison with authentic racemic samples prepared by removal of the protective group in **14** and subsequent separation.

With a sample of **14** in hand we also prepared the two (*E*)-1,3-dihydroxy-6-isopropyl-3-methyldec-4-en-9-ones epimeric at C-3 (**25**, **26**) via reduction using LAH and acid-catalyzed hydrolysis. The most polar of these (**25**) gave rise to spectral data identical with those reported for a compound previously found in tobacco.[9]

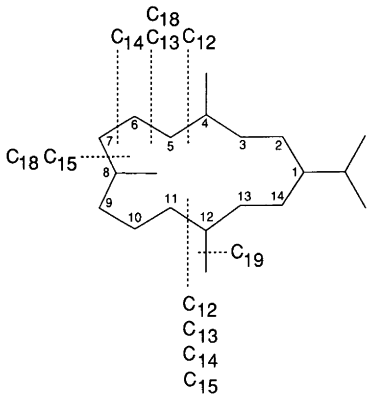
The sixth new compound (**6**), $C_{17}H_{28}O_3$ contains two oxo groups, of which one is α,β-unsaturated [IR: 1718 and 1676 cm^{-1}; ^{13}C NMR: δ 209.1 (s) and 198.2 (s)]. It also possesses one tertiary hydroxy group [IR: 3610 and 3430 cm^{-1}; ^{13}C NMR: δ 72.5 (s)] and two 1,2-disubstituted double bonds [^{13}C NMR: δ 130.2 (d), 134.2 (d), 137.9 (d) and 143.5 (d)]. These were incorporated into a (3*E*,7*E*)-6-hydroxy-9-isopropyl-6-methyltrideca-3,7-diene-2,12-dione structure by using information from the ^1H–^1H shift correlation and mass spectra (Scheme 1).

The structure assigned to **6** was confirmed by synthesis. This involved the reaction of (±)-norsolanadione monoacetal (**13**) with methyl (*E*)-4-bromobut-2-enoate and zinc to give a 1:1 mixture of the C-5 epimers of the methyl ester **27** (^1H NMR: three proton singlets at δ 1.30, 1.32 and 3.72). Hydrolysis under alkaline conditions converted **27** into the corresponding acid **28**. The latter was treated with methyllithium to give, as the major product, a 1:1 mixture of the C-6 epimers of the methyl ketone **29** (^1H NMR: three-proton singlets at δ 1.30, 1.33 and 2.25) and as the minor product diol **30** (IR: 3610 and 3430 cm^{-1}) formed by dialkylation of **28**. The protective group in **29** was removed by hydrolysis under acidic conditions to give an inseparable mixture of the C-6 epimers of (3*E*,7*E*)-6-hydroxy-9-isopropyl-6-methyltrideca-3,7-diene-2,12-dione. A comparison of the ^1H and ^{13}C NMR data revealed that the new compound (**6**) was identical with one of the epimers in this mixture. The other C-6 epimer (**31**) has hitherto not been isolated from tobacco.

Since the new compounds (**1**–**6**) were isolated in minute quantities only (1.2–6.2 mg), it has not been possible to determine their absolute configurations.

Biogenesis. Compounds **1**–**6** are evidently additions to the large group of isopropyl-containing irregular isoprenoids isolable from the flavour fractions of tobacco. Available results suggest that these compounds arise by biodegradation of the cembranic diterpenoids that are present in substantial amounts in the cuticular wax of the tobacco leaf and flower. The degradation reactions are assumed to be initiated by rupture of the bonds indicated in Scheme 2.[2] The key metabolites formed undergo subsequent chemical alterations which may involve loss of carbon atoms.

Thus as outlined in Scheme 3, the cembra-2,7,11-triene-4,6-diols **32** and **33**[10] are the postulated precursors of norsolanadione (**12**),[11] the C_{12} key metabolite. The prerequisite breakage of their 4,5 and 11,12 bonds may take place via the intermediate formation of the *seco*-aldehyde **34**, the



Scheme 2.

seco-acids **35** and **36**, and/or the ketols **37** and **38** and the *seco*-diketone **39**, which are all tobacco constituents.[12–14]

Norsolanadione (**12**), in turn, undergoes loss of one or two carbon atoms with the formation of the C_{11} acid **40** and the C_{10} enone **7**; **7** may also be formed by decarboxylation of **40**. Allylic oxidation converts **40** and **7** into **2** and **1**, respectively. It is noteworthy that **1** and **2** are the first degraded cembranoids encountered in tobacco, in which the isopropyl-bearing carbon atom also carries oxygen (C-1 in the parent cembranoids).

The C_{13} aldehyde **3** may formally arise via rupture of the 4,5 and 10,11 bonds in the parent cembranoid. This mode of formation was rendered likely by the recent isolation from tobacco of the plausible intermediate **41**,[15] but differs from that of the previously known C_{13} compounds which invariably involves breakage of the 5,6 and 11,12 bonds.

The formation of the C_{14} acids **5** and **22** in tobacco is explained by rupture of the 6,7 and 11,12 bonds in a relevant cembranoid precursor and subsequent oxidation of the intermediate C_{14} aldehyde (Scheme 2).[2] The biogenesis of **4** and **6**, on the other hand, would require the rupture of the 7,8 and 11,12 (Scheme 2) and the 8,9 and 11,12 bonds, respectively, but further insight into the course of these reactions remains to be gained.

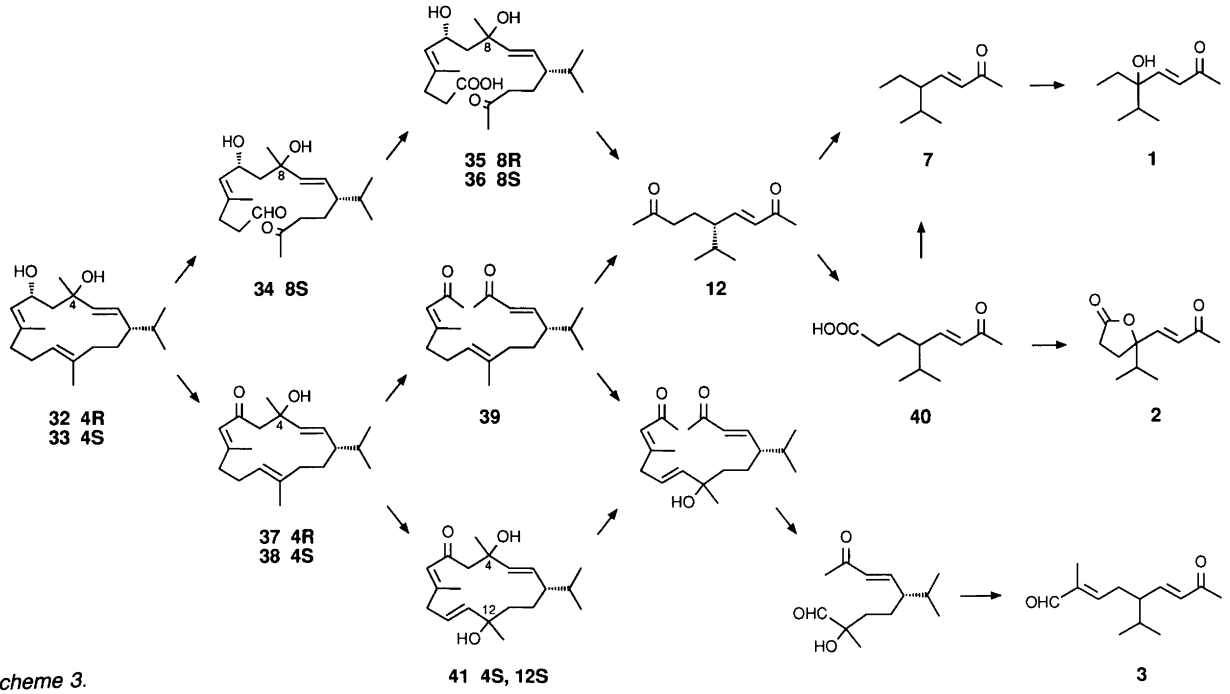
Experimental

Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. For other instrumental details see Ref. 16.

Isolation. (*E*)-5-Hydroxy-5-isopropylhept-3-en-2-one (**1**, 6.2 mg) and (2*E*,6*E*)-5-isopropyl-2-methyl-8-oxonona-2,6-dienal (**3**, 1.2 mg) were isolated from fraction B7 and (*E*)-4-isopropyl-7-oxooct-5-en-4-olide (**2**, 4.8 mg) and (*E*)-4-hydroxy-7-isopropyl-4-methylundec-5-ene-2,10-dione (**4**, 1.6 mg) from fraction B9 of an Et_2O extract of 295 kg of Greek sun-cured tobacco[17] by chromatography over silica gel using hexane/EtOAc as the eluent followed by HPLC using columns packed with Spherisorb 5 and Spherisorb 5 Nitrile and hexane/EtOAc 60:40 as the eluent.

(6*S*)-(*E*)-3-Hydroxy-6-isopropyl-3-methyl-9-oxodec-4-enoic acid (**22**) and an epimer thereof (**5**) were isolated as the corresponding methyl esters (**24**, 11.2 mg and **23**, 2.5 mg) from fraction 2 (64 mg) of the acidic portion of a $CHCl_3$ extract of flowers of Greek tobacco[16] by repetitive HPLC using columns packed with Spherisorb 5 Nitrile (hexane/EtOAc 60:40) and Spherisorb 5 (hexane/EtOAc 75:25).

(3*E*,7*E*)-6-Hydroxy-9-isopropyl-6-methyltrideca-3,7-diene-2,12-dione (**6**, 1.2 mg) was obtained from fraction C3



Scheme 3.

(272 mg) of a $CHCl_3$ extract of flowers of Greek tobacco[18] by HPLC using columns packed with Spherisorb 5 (hexane/EtOAc 40:60) and Spherisorb 5 Nitrile (hexane/EtOAc 1:1).

(*E*)-5-Hydroxy-5-isopropylhept-3-en-2-one (**1**) was an oil and had $[\alpha]_D$ −4.1° (*c* 0.41, $CHCl_3$); (Found: $[M-29]^+$ 141.0884. Calc. for $C_8H_{13}O_2$: 141.0915); IR (CCl_4): 3616, 3450, 1699, 1679, 1627 and 990 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.86 (t, *J* 7.5 Hz, H-7), 0.91 (d, *J* 6.8 Hz)/0.93 (d, *J* 6.8 Hz) (H-9/H-10), 1.63 (dq, *J* 7.5 and −14.0 Hz, H-6a), 1.68 (dq, *J* 7.5 and −14.0 Hz, H-6b), 1.84 (septet, *J* 6.8 Hz, H-8), 2.29 (s, H-1), 6.34 (d, *J* 15.9 Hz, H-3) and 6.75 (d, *J* 15.9 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 7.7 (C-7), 16.4/17.6 (C-9/C-10), 28.0 (C-1), 30.9 (C-6), 36.1 (C-8), 77.8 (C-5), 129.2 (C-3), 150.8 (C-4) and 198.0 (C-2); MS [*m/z* (%, composition)]: 141 (11, *M*−29), 127 (56, $C_7H_{11}O_2$ and $C_8H_{15}O$), 113 (16, $C_7H_{13}O$), 109 (10, C_7H_9O and C_8H_{13}), 99 (31, $C_6H_{11}O$), 85 (16), 81 (11, C_6H_9), 71 (22, C_4H_7O), 57 (24, C_3H_5O) and 43 (100).

(*E*)-4-Isopropyl-7-oxooct-5-en-4-olide (**2**) was an oil and had $[\alpha]_D$ +0.7° (*c* 0.43, $CHCl_3$); (Found: $M^{+\cdot}$ 196.1108. Calc. for $C_{11}H_{16}O_3$: 196.1100); IR (CCl_4): 1785, 1705, 1685 and 1635 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.98 (d, *J* 6.4 Hz)/1.00 (d, *J* 7.0 Hz) (H-10/H-11), 2.29 (s, H-8), 6.36 (d, *J* 16.0 Hz, H-6) and 6.76 (d, *J* 16.0 Hz, H-5); ^{13}C NMR ($CDCl_3$): δ 17.0/17.1 (C-10/ C-11), 28.2 (C-3), 29.0 (C-8), 30.4 (C-2), 37.2 (C-9), 89.7 (C-4), 129.1 (C-6), 143.9 (C-5), 176.1 (C-1) and 197.1 (C-7); MS [*m/z* (%, composition)]: 196 (4, *M*), 181 (1), 154 (40, $C_8H_{10}O_3$), 153 (100, $C_8H_9O_3$ and $C_9H_{13}O_2$), 125 (32, $C_7H_9O_2$ and $C_8H_{13}O$), 111 (13, $C_6H_7O_2$ and $C_7H_{11}O$), 97 (27, $C_5H_5O_2$ and C_6H_9O), 84 (7, C_5H_8O), 69 (9, C_4H_5O and C_5H_9), 55 (19, C_3H_3O and C_4H_7) and 43 (66, C_2H_3O and C_3H_7).

(2*E*,6*E*)-5-Isopropyl-2-methyl-8-oxonona-2,6-dienal (**3**) was an oil and had $[\alpha]_D$ +3.5° (*c* 0.26, $CHCl_3$); (Found: $[M-43]^+$ 165.1256. Calc. for $C_{11}H_{17}O$: 165.1279); IR (CCl_4): 2820, 2711, 1693, 1625, 1371, 1359 and 985 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.93 (d, *J* 6.8 Hz)/0.98 (d, *J* 6.8 Hz) (H-12/H-13), 1.75 (dt, *J* 0.9 and 1.4 Hz, H-10), 1.80 (d septet, *J* 5.9 and 6.8 Hz, H-11), 2.20 (ddd, *J* 5.2, 5.9 and 8.2 Hz, H-5), 2.26 (s, H-9), 2.42 (dddq, *J* 0.9, 7.3, 8.2 and −15.2 Hz, H-4a), 2.59 (dddq, *J* 0.9, 5.2, 7.3 and −15.2 Hz, H-4b), 6.07 (dd, *J* 0.8 and 15.9 Hz, H-7), 6.39 (tq, *J* 1.4 and 7.3 Hz, H-3), 6.63 (dd, *J* 9.2 and 15.9 Hz, H-6) and 9.38 (s, H-1); ^{13}C NMR ($CDCl_3$): δ 9.5 (C-10), 19.1/20.6 (C-12/C-13), 27.4 (C-9), 31.0 (C-4), 31.5 (C-11), 48.7 (C-5), 132.4 (C-7), 140.4 (C-2), 148.2 (C-6), 151.5 (C-3), 194.9 (C-1) and 197.9 (C-8); MS [*m/z* (%, composition)]: 193 (1, *M*−15), 166 (1), 165 (2), 147 (1), 126 (16, $C_8H_{14}O$), 125 (35, $C_8H_{13}O$), 107 (7, C_8H_{11}), 95 (10, C_6H_7O and C_7H_{11}), 84 (22, C_5H_8O), 69 (7, C_4H_5O and C_5H_9), 55 (23, C_4H_7 and C_3H_3O) and 43 (100).

(*E*)-4-Hydroxy-7-isopropyl-4-methylundec-5-ene-2,10-dione (**4**) was an oil and had $[\alpha]_D$ +6.2° (*c* 0.13, $CHCl_3$); (Found: $[M-18]^{+\cdot}$ 236.1793. Calc. for $C_{15}H_{24}O_2$: 236.1776); IR (CCl_4): 3500, 1710, 1385, 1365 and 980 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.81 (d, *J* 6.8 Hz)/0.86 (d, *J* 6.6 Hz) (H-14/H-15), 1.28 (s, H-12), 1.44 (m, H-8a), 1.56 (m, H-13), 1.70 (m, H-7), 1.74 (m, H-8b), 2.11 (s, H-11), 2.17 (s, H-1), 2.28 (m, H-9a), 2.39 (m, H-9b), 2.63 (d, *J* −17.0 Hz, H-3a), 2.78 (d, *J* −17.0 Hz, H-3b), 4.03 (br s, –OH), 5.33 (dd, *J* 9.0 and 15.6 Hz, H-6) and 5.45 (d, *J* 15.6 Hz, H-5); ^{13}C NMR ($CDCl_3$): δ 19.1/20.7 (C-14/C-15), 26.1 (C-8), 28.8 (C-12), 30.0 (C-11), 31.8 (C-1), 32.1 (C-13), 41.9 (C-9), 48.6 (C-7), 53.1 (C-3), 71.6 (C-4), 129.7 (C-6), 137.7 (C-5), 209.4 (C-10) and 210.4 (C-2); MS [*m/z* (%, composition)]: 236 (1, *M*−18), 218 (3, $C_{15}H_{22}O$), 196 (3), 178 (4, $C_{12}H_{18}O$), 163 (2, $C_{11}H_{15}O$), 151 (3), 135 (15, $C_{10}H_{15}$), 121 (12, C_9H_{13}), 109 (16, C_8H_{13} and C_7H_9O), 95 (21, C_6H_7O and C_7H_{11}), 81 (9, C_6H_9), 71 (13, C_4H_7O), 55 (11, C_4H_7 and C_3H_3O) and 43 (100, C_2H_3O and C_3H_7).

(*E*)-Methyl 3-hydroxy-6-isopropyl-3-methyl-9-oxodec-4-enoate (**23**) was an oil and had $[\alpha]_D$ −4.2° (*c* 0.24, CH_3OH); (Found: $[M-36]^{+\cdot}$ 234.1623. Calc. for $C_{15}H_{22}O_2$: 234.1620); IR (CCl_4): 3519, 1721, 1386, 1367 and 982 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.80 (d, *J* 6.8 Hz)/0.85 (d, *J* 6.6 Hz) (H-13/H-14), 1.32 (s, H-11), 2.12 (s, H-10), 2.56 (d, *J* −15.7 Hz, H-2a), 2.59 (d, *J* −15.7 Hz, H-2b), 3.68 (s, –OCH_3), 5.37 (dd, *J* 8.6 and 15.3 Hz, H-5) and 5.45 (d, *J* 15.3 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 19.0/20.7 (C-13/C-14), 26.2 (C-7), 28.9 (C-11), 30.0 (C-10), 32.0 (C-12), 41.9 (C-8), 45.3 (C-2), 48.5 (C-6), 51.7 (–OCH_3), 71.0 (C-3), 130.0 (C-5), 137.1 (C-4), 173.1 (C-1) and 209.2 (C-9); MS [*m/z* (%)]: 234 (5, *M*−36), 153 (5), 135 (9), 125 (9), 121 (19), 107 (8), 97 (13), 95 (16), 93 (13), 85 (7), 81 (8), 71 (11), 69 (11), 55 (11) and 43 (100).

(6*S*)-(*E*)-Methyl 3-hydroxy-6-isopropyl-3-methyl-9-oxodec-4-enoate (**24**) was an oil and had $[\alpha]_D$ −3.8° (*c* 1.12, CH_3OH); IR (CCl_4): 3523, 1720, 1385, 1367 and 982 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.81 (d, *J* 6.8 Hz)/ 0.87 (d, *J* 6.6 Hz) (H-13/H-14), 1.32 (s, H-11), 2.12 (s, H-10), 2.57 (d, *J* −15.7 Hz, H-2a), 2.60 (d, *J* −15.7 Hz, H-2b), 3.69 (s, –OC*H*$_3$), 5.37 (dd, *J* 8.8 and 15.6 Hz, H-5) and 5.47 (d, *J* 15.6 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 18.9/20.7 (C-13/C-14), 26.1 (C-7), 28.7 (C-11), 30.0 (C-10), 32.0 (C-12), 41.9 (C-8), 45.4 (C-2), 48.6 (C-6), 51.7 (–OCH_3), 71.0 (C-3), 130.0 (C-5), 137.3 (C-4), 173.1 (C-1) and 209.2 (C-9); MS [*m/z* (%)]: 234 (5, *M*−36), 153 (4), 135 (8), 125 (8), 121 (17), 107 (8), 97 (11), 95 (14), 93 (11), 85 (6), 81 (7), 71 (10), 69 (9), 55 (10) and 43 (100). The optical rotation, IR, ^1H NMR and MS data agreed well enough with corresponding data previously reported for an authentic sample to establish the identity of **24**.[8]

(3*E*,7*E*)-6-Hydroxy-9-isopropyl-6-methyltrideca-3,7-diene-2,12-dione (**6**) was an oil and had $[\alpha]_D$ 0° (*c* 0.16, $CHCl_3$); (Found: $[M-18]^{+\cdot}$ 262.1976. Calc. for $C_{17}H_{26}O_2$: 262.1933); IR (CCl_4): 3610, 3421, 1718, 1676, 1628 and 982 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.83 (d, *J* 6.8 Hz)/ 0.88 (d, *J* 6.7 Hz) (H-16/H-17), 1.34 (s, H-14), 2.13 (s, H-13), 2.25 (s, H-1), 2.35 (m, H-11), 2.46 (dd, *J* 1.4 and 7.5 Hz, H-5a and H-5b), 5.38 (dd, *J* 8.9 and 15.6 Hz, H-8), 5.48 (d, *J* 15.6 Hz, H-7), 6.11 (dt, *J* 1.4 and 16.0 Hz, H-3) and 6.81 (dt, *J* 7.5 and 16.0 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 19.1/20.7 (C-16/C-17), 26.1 (C-10), 26.8 (C-1), 28.9 (C-14), 30.0

(C-13), 32.0 (C-15), 42.0 (C-11), 45.7 (C-5), 48.7 (C-9), 72.5 (C-6), 130.2 (C-8), 134.2 (C-3), 137.9 (C-7), 143.5 (C-4), 198.2 (C-2) and 209.1 (C-12); MS [*m/z* (% composition]: 262 (2, *M*−18) 204 (1, $C_{14}H_{20}O$), 197 (21, $C_{12}H_{21}O_2$), 179 (10, $C_{12}H_{19}O$), 161 (19, $C_{12}H_{17}$), 139 (16, $C_9H_{15}O$), 121 (63, C_9H_{13}), 109 (33, C_8H_{13} and C_7H_9O), 97 (27, C_7H_{13} and C_6H_9O), 84 (23, C_5H_8O), 71 (54, C_4H_7O), 55 (18, C_4H_7 and C_3H_3O) and 43 (100, C_3H_7 and C_2H_3O).

*Preparation of (±)-(*E*)-5-hydroxy-5-isopropylhept-3-en-2-one* (**1**). To a solution of 19.6 mg of (±)-(*E*)-5-isopropylhept-3-en-2-one (**7**)[4] in 5 ml of CCl_4 was added a solution of 15.8 mg of NBS and 30 µl of *tert*-butyl hydroperoxide in 0.5 ml of CCl_4. The reaction mixture was refluxed for 2 h, diluted with water and extracted with CCl_4. The organic phase was washed with water and concentrated. The residue was separated by chromatography over silica gel (hexane/EtOAc 98:2) to give 6.3 mg of starting material and 10.9 mg of (±)-(*E*)-5-bromo-5-isopropylhept-3-en-2-one (**8**), which had ^{1}H NMR ($CDCl_3$): δ 0.97 (d, *J* 6.9 Hz)/1.10 (d, *J* 6.6 Hz) (H-9/H-10), 1.01 (t, *J* 7.2 Hz, H-7), 1.85–2.05 (m, H-6), 2.13 (septet, *J* 6.8 Hz, H-8), 2.30 (s, H-1), 6.35 (d, *J* 15.7 Hz, H-3) and 6.68 (d, *J* 15.7 Hz, H-4).

To a solution of 4 ml of THF, 0.4 ml of water, and 0.2 ml of aqueous H_2SO_4 (5 %) was added a solution of 10 mg of **8** in 1 ml of THF. The reaction mixture was refluxed for 15 h. Work-up and separation by chromatography over silica gel (hexane/EtOAc 10:90) gave 2.1 mg of (±)-(*E*)-5-hydroxy-5-isopropylhept-3-en-2-one, the IR, ^{1}H and ^{13}C NMR and mass spectra of which were identical with those of the naturally occurring **1**.

*Preparation of (±)-(*E*)-4-isopropyl-7-oxooct-5-en-4-olide* (**2**). To a solution of 188 mg of (±)-(*E*)-4-isopropyl-7-oxooct-5-enenitrile (**9**) in 6 ml of CCl_4 was added a solution of 259 mg of NBS and 35 µl of *tert*-butyl hydroperoxide in 1 ml of CCl_4. The reaction mixture was refluxed for 1.5 h, diluted with water and extracted with CCl_4. The organic phase was washed with water and concentrated. The residue was separated by chromatography over silica gel (hexane/EtOAc gradient) to afford 33.7 mg of starting material (**9**) and 60.5 mg of (±)-(*E*)-4-bromo-4-isopropyl-7-oxooct-5-enenitrile (**10**), which had ^{1}H NMR ($CDCl_3$): δ 0.99 (d, *J* 6.6 Hz)/1.12 (d, *J* 6.6 Hz) (H-10/ H-11), 1.95 (septet, *J* 6.6 Hz, H-9), 2.33 (s, H-8), 6.42 (d, *J* 15.5 Hz, H-6) and 6.52 (d, *J* 15.5 Hz, H-5).

A solution of 60.5 mg of 10 and 0.8 ml of aqueous H_2SO_4 (20 %) in 6 ml of THF and 0.4 ml of water was refluxed for 30 h. Work-up and separation by HPLC (Spherisorb 5; hexane/EtOAc 60:40) yielded 11.6 mg of (±)-(*E*)-4-hydroxy-4-isopropyl-7-oxooct-5-enenitrile (**11**), which had IR (CCl_4): 3618, 3496, 1702, 1682 and 1629 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.95 (d, *J* 6.9 Hz)/0.95 (d, *J* 6.6 Hz) (H-10/ H-11), 1.84 (septet, *J* 6.8 Hz, H-9), 2.31 (s, H-8), 6.37 (d, *J* 15.7 Hz, H-6) and 6.66 (d, *J* 15.7 Hz, H-5); MS [*m/z* (%)]: 162 (0.5, *M*−33), 152 (20), 124 (6), 113 (29), 110 (19), 95 (20), 82 (13), 71 (13), 67 (7), 55 (12) and 43 (100) and 2.5 mg of (±)-(*E*)-4-isopropyl-7-oxooct-5-en-4-olide, the spectral data of which were identical with those of the naturally occurring **2**.

*Preparation of (±)-(*E*)-methyl 9,9-ethylenedioxy-3-hydroxy-6-isopropyl-3-methyldec-4-enoate* (**14**). A mixture of 288 mg of racemic norsolanadione monoacetal (**13**)[7] and 133 mg of activated zinc powder in 12 ml of dry benzene was refluxed with 195 µl of methyl bromoacetate under nitrogen for 30 min. The reaction mixture was cooled (0 °C), stirred with aqueous acetic acid (10 %) for 30 min. and extracted with Et_2O. The organic phase was washed with aqueous acetic acid (10 %), aqueous $NaHCO_3$ and water, dried and concentrated. Flash chromatography over silica gel using hexane/EtOAc (80:20) as the eluent gave 343 mg of a 1:1 mixture of the C-3 epimers of racemic (*E*)-methyl 9,9-ethylenedioxy-3-hydroxy-6-isopropyl-3-methyldec-4-enoate (**14**), which had ^{1}H NMR ($CDCl_3$): δ 0.80 (d, *J* 6.7 Hz)/0.84 (0.86) (d, *J* 6.7 Hz) (H-13/H-14), 1.30 (s)/ 1.31 (s) (H-10/H-11), 2.55 (d, *J* −15.5 Hz, H-2a), 2.59 (2.60) (d, *J* −15.5 Hz, H-2b), 3.68 (3.69) (s, $-OCH_3$) 3.92 (m, $-OCH_2CH_2O-$), 5.40 (5.41) (dd, *J* 8.3 and 15.6 Hz, H-5) and 5.46 (d, *J* 15.6 Hz, H-4); MS [*m/z* (%)]: 314 (0.2, *M*), 299 (1), 296 (0.1), 253 (0.4), 234 (2), 225 (3), 139 (2), 121 (3), 99 (10), 87 (100), 81 (4), 71 (3), 59 (5), 55 (5) and 43 (35).

*Preparation of (±)-(*E*)-9,9-ethylenedioxy-3-hydroxy-6-isopropyl-3-methyldec-4-enoic acid* (**15**). A solution of 49 mg of **14** in 3 ml of ethanol and 0.1 ml of aqueous KOH (45 %) was kept at 50 °C and under nitrogen for 3 h. The reaction mixture was poured into water (0 °C), acidified with acetic acid and extracted with EtOAc. The organic phase was washed with water, dried and concentrated to give 44 mg of a 1:1 mixture of the C-3 diastereoisomers of (±)-(*E*)-9,9-ethylenedioxy-3-hydroxy-6-isopropyl-3-methyldec-4-enoic acid (**15**), which had ^{1}H NMR ($CDCl_3$): δ 0.80 (0.82) (d, *J* 6.8 Hz)/0.85 (0.86) (d, *J* 6.7 Hz) (H-13/ H-14), 1.30 (1.31) (s, H-10), 1.35 (1.36) (s, H-11), 2.58 (2.61) [d, *J* −15.2 (−15.6) Hz, H-2a], 2.60 (2.65) [d, *J* −15.2 (−15.6) Hz, H-2b], 3.94 (m, $-OCH_2CH_2O-$), 5.42 (5.44) (dd, *J* 8.6 and 15.7 Hz, H-5) and 5.50 (5.47) (d, *J* 15.7 Hz, H-4).

*Treatment of (±)-(*E*)-9,9-ethylenedioxy-3-hydroxy-6-isopropyl-3-methyldec-4-enoic acid* (**15**) *with methyllithium.* To a solution of 33 mg of **15** in 3 ml of dry THF was added 1 ml of a dry solution of methyllithium in Et_2O (5 %). After being stirred under nitrogen at 0 °C for 45 min, the reaction mixture was slowly poured into 50 ml of aqueous acetic acid (10 %) kept at 0 °C for 30 min. Work-up and separation by HPLC (Spherisorb 5; hexane/EtOAc 60:40) gave 1.6 mg of racemic norsolanadione monoacetal (**13**), 2.4 mg of (±)-(*E*)-8,8-ethylenedioxy-5-isopropyl-2-methylnon-3-en-2-ol (**19**), 5.7 mg of (±)-(*E*)-10,10-ethylenedioxy-4-hydroxy-7-isopropyl-4-methylundec-5-en-2-one (**16**), 7.1 mg of a C-4 diastereoisomer (**17**) of **16**, 1.0 mg of a 1:1 mixture of C-4

diastereoisomers of (±)-(*E*)-10,10-ethylenedioxy-7-isopropyl-2,4-dimethylundec-5-ene-2,4-diol (**18**) and 4.0 mg of starting material (**15**).

(±)-(*E*)-8,8-Ethylenedioxy-5-isopropyl-2-methylnon-3-en-2-ol (**19**) had ^{1}H NMR ($CDCl_3$): δ 0.82 (d, *J* 6.7 Hz)/0.87 (d, *J* 6.6 Hz) (H-12/H-13), 1.31 (s)/1.32 (s)/1.32 (s) (H-1/H-9/H-10), 3.93 (m $-OCH_2CH_2O-$), 5.36 (dd, *J* 9.0 and 15.7 Hz, H-4) and 5.56 (d *J* 15.7 Hz, H-3). MS [*m/z* (%)]: 256 (0.2, *M*), 241 (2), 223 (0.5), 195 (1), 176 (3), 136 (5), 121 (4), 111 (9), 99 (9), 87 (100), 81 (4), 71 (9), 69 (9), 59 (21), 55 (11) and 43 (89).

(±)-(*E*)-10,10-Ethylenedioxy-4-hydroxy-7-isopropyl-4-methylundec-5-en-2-one (**16**) had ^{1}H NMR ($CDCl_3$): δ 0.80 (d, *J* 6.8 Hz)/0.84 (d, *J* 6.8 Hz) (H-14/H-15), 1.28 (s, H-12), 1.30 (s, H-11), 2.16 (s, H-1), 2.60 (d, *J* −16.9 Hz, H-3a), 2.78 (d, *J* −16.9 Hz, H-3b), 3.92 (m, $-OCH_2CH_2O-$), 5.37 (dd, *J* 8.5 and 15.8 Hz, H-6) and 5.44 (d, *J* 15.8 Hz, H-5); ^{13}C NMR ($CDCl_3$): δ 18.9/20.8 (C-14/C-15), 23.8 (C-11), 26.7 (C-8), 28.9 (C-12), 31.9 (C-1), 32.0 (C-13), 37.3 (C-9), 49.1 (C-7), 53.0 (C-3), 64.6/64.6 ($-OCH_2CH_2O-$), 71.7 (C-4), 110.2 (C-10), 130.1 (C-6), 137.0 (C-5) and 210.5 (C-2).

(±)-(*E*)-10,10-Ethylenedioxy-4-hydroxy-7-isopropyl-4-methylundec-5-en-2-one (**17**) had ^{1}H NMR ($CDCl_3$): δ 0.80 (d, *J* 6.7 Hz)/0.86 (d, *J* 6.7 Hz) (H-14/H-15), 1.28 (s, H-12), 1.30 (s, H-11), 2.16 (s, H-1), 2.60 (d, *J* −16.8 Hz, H-3a), 2.79 (d, *J* −16.8 Hz, H-3b), 3.93 (m $-OCH_2CH_2O-$), 5.35 (dd, *J* 8.9 and 15.6 Hz, H-6) and 5.45 (d, *J* 15.6 Hz, H-5); ^{13}C NMR ($CDCl_3$): δ 18.9/20.8 (C-14/C-15), 23.8 (C-11), 26.6 (C-8), 28.8 (C-12), 31.9 (C-1), 31.9 (C-13), 37.2 (C-9), 49.1 (C-7), 53.0 (C-3), 64.6/64.6 ($-OCH_2CH_2O-$), 71.7 (C-4), 110.2 (C-10), 130.1 (C-6), 137.1 (C-5) and 210.4 (C-2).

(±)-(*E*)-10,10-Ethylenedioxy-7-isopropyl-2,4-dimethylundec-5-ene-2,4-diol (**18**) had IR (CCl_4): 3613 and 3364 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.83 (0.85) (d, *J* 7.0 Hz)/ 0.87 (0.88) (d, *J* 6.8 Hz) (H-15/H-16), 1.28 (s)/1.30 (s)/1.30 (1.31) (s)/1.32 (1.33) (s) (H-1/H-11/H-12/H-13), 1.77 (d, *J* −14.6 Hz, H-3a), 1.87 (d, *J* −14.6 Hz, H-3b), 3.92 (m, $-OCH_2CH_2O-$), 5.46 (5.49) (dd, *J* 8.6 and 15.6 Hz, H-6) and 5.58 (d, *J* 15.6 Hz, H-5); MS [*m/z* (%)]: 299 (0.3, *M*−15), 296 (0.5), 281 (0.3), 271 (0.8), 253 (0.8), 223 (2), 183 (3), 179 (3), 176 (4), 161 (3), 136 (17), 121 (14), 115 (10), 99 (13), 93 (19), 87 (99), 71 (12), 59 (23), 55 (13) and 43 (100).

*Hydrolysis of (±)-(*E*)-8,8-ethylenedioxy-5-isopropyl-2-methylnon-3-en-2-ol* (**19**). A solution of 4.1 mg of **19** in 2 ml of dioxane/aqueous (3 %) H_2SO_4 (2:1) was stirred at room temperature and under nitrogen for 2 h. Work-up of the reaction mixture and separation of the crude product by HPLC (Spherisorb 5; hexane/EtOAc 60:40) gave 0.9 mg of a product which was indistinguishable from (*E*)-2-hydroxy-5-isopropyl-2-methylnon-3-en-8-one (**20**).[7]

*Hydrolysis of the (±)-(*E*)-10,10-ethylenedioxy-4-hydroxy-7-isopropyl-4-methylundec-5-en-2-ones* **16** *and* **17**. A solution of 5.7 mg of **16** in 1.5 ml of dioxane/aqueous (3 %) H_2SO_4 (2:1) was stirred at room temperature and under nitrogen for 2 h. Work up and separation by HPLC (Spherisorb 5; hexane/EtOAc 40:60) yielded 3.8 mg of (±)-(*E*)-4-hydroxy-7-isopropyl-4-methylundec-5-ene-2,10-dione (**21**), which was an oil and had IR (CCl_4): 3509, 1716, 1385, 1367 and 978 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.81 (d, *J* 6.8 Hz)/0.85 (d, *J* 6.6 Hz) (H-14/H-15), 1.28 (s, H-12), 1.42 (m, H-8a), 1.65 (m, H-13), 1.68 (m, H-7), 1.75 (m, H-8b), 2.12 (s, H-11), 2.16 (s, H-1), 2.30 (m, H-9a), 2.38 (m, H-9b), 2.62 (d, *J* −17.1 Hz, H-3a), 2.78 (d, *J* −17.1 Hz, H-3b), 4.10 (br s, –OH), 5.32 (dd, *J* 9.0 and 15.5 Hz, H-6) and 5.44 (d, *J* 15.5 Hz, H-5); ^{13}C NMR ($CDCl_3$): δ 19.1/20.7 (C-14/C-15), 26.2 (C-8), 29.0 (C-12), 30.0 (C-11), 31.9 (C-1), 32.0 (C-13), 41.9 (C-9), 48.6 (C-7), 52.7 (C-3), 71.6 (C-4), 129.7 (C-6), 137.6 (C-5), 209.3 (C-10) and 210.4 (C-2); MS [*m/z* (%)]: 236 (2, *M*−18), 218 (2), 196 (1), 178 (4), 163 (3), 151 (1), 135 (25), 121 (15), 109 (51), 95 (25), 81 (11), 71 (12), 55 (14) and 43 (100).

Using the method described above, **17** (7.1 mg) was converted into (±)-(*E*)-4-hydroxy-7-isopropyl-4-methylundec-5-ene-2,10-dione (4.9 mg), the IR, ^{1}H and ^{13}C NMR and mass spectra of which were identical with those of the naturally occurring **4**.

*Hydrolysis of (±)-(*E*)-methyl 9,9-ethylenedioxy-3-hydroxy-6-isopropyl-3-methyldec-4-enoate* (**14**). A solution of 820 mg of **14** in 5 ml of dioxane/aqueous (3 %) H_2SO_4 (2:1) was stirred at room temperature and under nitrogen for 4 h. Work-up and flash chromatography over silica gel using hexane/EtOAc (70:30) as the eluent gave 602 mg of a mixture of (±)-(*E*)-methyl 3-hydroxy-6-isopropyl-3-methyl-9-oxodec-4-enoates epimeric at C-3. Part of this mixture (10 mg) was separated by HPLC (Spherisorb 5; hexane/EtOAc 75:25); the least polar epimer (2.8 mg) had ^{1}H and ^{13}C NMR spectra identical with those of the methyl ester (**23**) derived from the new (*E*)-3-hydroxy-6-isopropyl-3-methyl-9-oxodec-4-enoic acid (**5**). The most polar epimer (3.7 mg) had ^{1}H and ^{13}C NMR spectra identical with those of the methyl ester (**24**) obtained from acid **22**, previously reported as a tobacco constituent.[8]

*Preparation of the (±)-(*E*)-1,3-dihydroxy-6-isopropyl-3-methyldec-4-en-9-ones epimeric at C-3* (**25**, **26**). A solution of 110.6 mg of racemic methyl 9,9-ethylenedioxy-3-hydroxy-6-isopropyl-3-methyldec-4-enoate (**14**) in 5 ml of dry Et_2O was treated with an excess of LAH at room temperature for 4 h. The reaction mixture was worked up in the usual manner. Without further purification the crude product was dissolved in 1.5 ml of dioxane/aqueous H_2SO_4 (3 %) (2:1) and kept at room temperature and under nitrogen for 3 h. Work-up and flash chromatography over silica gel using a hexane/EtOAc gradient as the eluent gave 48 mg of a mixture of C-3 diastereomers. Part of this mixture (16 mg) was separated by HPLC (Spherisorb 5; hexane/EtOAc 30:70) into **25** and **26**.

The most polar of these (±)-(*E*)-1,3-dihydroxy-6-iso-

propyl-3-methyldec-4-en-9-ones epimeric at C-3 (5.8 mg) had IR, ^{1}H and ^{13}C NMR and mass spectra identical with those of naturally occurring **25**.[9]

The least polar epimer (**26**, 5.5 mg) had IR ($CHCl_3$): 3603, 3491, 1710 and 981 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.85 (d, *J* 6.8 Hz)/0.89 (d, *J* 6.7 Hz) (H-13/H-14), 1.32 (s, H-11), 1.70 (ddd, *J* 3.9, 5.5 and −14.7 Hz, H-2a), 1.87 (ddd, *J* 4.9, 8.2 and −14.7 Hz, H-2b), 2.12 (s, H-10), 2.33 (m, H-8a), 2.40 (m, H-8b), 3.82 (ddd, *J* 4.9, 5.5 and −10.9 Hz, H-1a), 3.86 (ddd, *J* 3.9, 8.2 and −10.9 Hz, H-1b), 5.43 (dd, *J* 8.3 and 15.5 Hz, H-5) and 5.45 (d, *J* 15.5 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 19.1/20.8 (C-13/C-14), 26.3 (C-7), 29.7 (C-11), 30.1 (C-10), 32.1 (C-12), 42.0 (C-8), 42.6 (C-2), 48.8 (C-6), 60.4 (C-1), 74.1 (C-3), 129.7 (C-5), 138.1 (C-4) and 209.4 (C-9); MS [*m/z* (%)]: 224 (2, *M*−18), 197 (2), 194 (3), 181 (1), 179 (2), 161 (5), 151 (3), 139 (6), 136 (9), 121 (26), 109 (13), 97 (21), 95 (13), 93 (18), 81 (16), 71 (26), 55 (20) and 43 (100).

*Preparation of (±)-(2*E*,6*E*)-methyl 11,11-ethylenedioxy-5-hydroxy-8-isopropyl-5-methyldodeca-2,6-dienoate* (**27**). A mixture of 303 mg of (±)-norsolanadione monoacetal (**13**) and 139 mg of activated zinc powder in 12 ml of dry benzene was refluxed with 325 µl of (*E*)-methyl 4-bromobut-2-enoate under nitrogen for 2 h. Work-up and flash chromatography (silica gel; hexane/EtOAc gradient) gave 130 mg of starting material (**13**) and 97 mg of a 1:1 mixture of the C-5 epimers of racemic (2*E*,6*E*)-methyl 11,11-ethylenedioxy-5-hydroxy-8-isopropyl-5-methyldodeca-2,6-dienoate (**27**), which had IR (CCl_4): 3610, 3483, 1726, 1658 and 982 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.82 (d, *J* 6.8 Hz)/0.87 (d, *J* 6.8 Hz) (H-15/H-16), 1.30 (s)/1.32 (s) (H-12/H-13), 2.44 (dd, *J* 1.3 and 7.7 Hz, H-4a and H-4b), 3.72 (s, –OC*H*$_3$), 3.93 (m, –OC*H*$_2$C*H*$_2$O–), 5.40 (dd, *J* 8.8 and 15.6 Hz, H-7), 5.48 (5.49) (d, *J* 15.6 Hz, H-6), 5.87 (5.88) (dt, *J* 1.3 and 15.7 Hz, H-2) and 6.96 (6.97) (dt, *J* 7.7 and 15.7 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 18.9/20.8 (C-15/C-16), 23.8 (C-12), 26.5 (26.6) (C-9), 28.3 (28.6) (C-13), 31.9 (C-14), 37.3 (C-10), 45.5 (45.6) (C-4), 49.1 (C-8), 51.4 (–O*C*H$_3$), 64.6/64.6 (–O*C*H$_2$*C*H$_2$O–), 72.5 (C-5), 110.2 (C-11), 124.1 (C-2), 130.6 (130.7) (C-7), 137.5 (C-6), 144.7 (144.8) (C-3) and 166.5 (C-1); MS [*m/z* (%)]: 325 (2, *M*−15), 241 (1), 223 (3), 183 (7) 179 (9) 161 (4), 139 (9), 121 (14), 115 (12), 109 (9), 99 (10), 87 (100), 81 (6), 71 (21), 59 (10), 55 (12) and 43 (93).

*Hydrolysis of (±)-(2*E*,6*E*)-methyl 11,11-ethylenedioxy-5-hydroxy-8-isopropyl-5-methyldodeca-2,6-dienoate* (**27**). A solution of 49 mg of **27** in 3 ml of ethanol and 0.1 ml of aqueous KOH (45 %) was kept at 50 °C and under nitrogen for 2 h. Work-up gave 30 mg of a crude 1:1 mixture of the C-5 diastereoisomers of (±)-(2*E*,6*E*)-11,11-ethylenedioxy-5-hydroxy-8-isopropyl-5-methyldodeca-2,6-dienoic acid (**28**), which had ^{1}H NMR ($CDCl_3$): δ 0.82 (d, *J* 6.8 Hz)/0.87 (d, *J* 6.8 Hz) (H-15/H-16), 1.30 (s, H-12), 1.33 (s, H-13), 2.47 (dd, *J* 1.4 and 7.6 Hz, H-4a and H-4b), 3.93 (m, –OC*H*$_2$C*H*$_2$O–), 5.40 (dd, *J* 8.8 and 15.7 Hz, H-7), 5.49 (d, *J* 15.7 Hz, H-6), 5.87 (dt, *J* 1.4 and 15.6 Hz, H-2) and 7.06 (7.07) (dt, *J* 7.6 and 15.6 Hz, H-3); MS [*m/z* (%)]: 311 (1, *M*−15), 225 (1), 223 (1), 183 (3), 179 (3), 161 (2), 139 (3), 121 (5), 115 (5), 99 (7), 87 (100), 81 (4), 71 (8), 59 (6), 55 (7) and 43 (69).

*Treatment of (±)-(2*E*,6*E*)-11,11-ethylenedioxy-5-hydroxy-8-isopropyl-5-methyldodeca-2,6-dienoic acid (**28**) with methyllithium.* To a solution of 30 mg of the crude **28** in 3 ml of dry THF was added 0.8 ml of a dry solution of methyllithium in Et_2O (5 %). After being stirred under nitrogen at 0 °C for 1 h, the reaction mixture was slowly poured into 50 ml of aqueous acetic acid (10 %) kept at 0 °C. Work-up of the reaction mixture and separation of the crude product by HPLC (Spherisorb 5; hexane/EtOAc 1:1) gave as the main products 6.0 mg of a 1:1 mixture of C-6 diastereoisomers of (±)-(3*E*,7*E*)-12,12-ethylenedioxy-6-hydroxy-9-isopropyl-6-methyltrideca-3,7-dien-2-one (**29**) and 2.4 mg of a 1:1 mixture of C-6 diastereoisomers of (±)-(3*E*,7*E*)-2,6-dimethyl-12,12-ethylenedioxy-9-isopropyltrideca-3,7-diene-2,6-diol (**30**).

(±)-(3*E*,7*E*)-12,12-Ethylenedioxy-6-hydroxy-9-isopropyl-6-methyltrideca-3,7-dien-2-one (**29**) had ^{1}H NMR ($CDCl_3$): δ 0.83 (d, *J* 6.8 Hz)/0.87 (d, *J* 6.8 Hz) (H-16/H-17), 1.30 (s, H-13), 1.33 (s, H-14), 2.25 (s, H-1), 2.46 (dd, *J* 1.3 and 7.5 Hz, H-5a and H-5b), 3.93 (m, –OC*H*$_2$C*H*$_2$O–), 5.41 (dd, *J* 8.7 and 15.6 Hz, H-8), 5.50 (5.51) (d, *J* 15.6 Hz, H-7), 6.10 (dt, *J* 1.3 and 16.0 Hz, H-3) and 6.81 (dt, *J* 7.5 and 16.0 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 18.9/20.8 (C-16/C-17), 23.8 (C-13), 26.5 (26.6) (C-10), 26.7 (26.8) (C-1), 28.6 (28.9) (C-14), 31.9 (C-15), 37.4 (37.5) (C-11), 45.7 (45.8) (C-5), 49.1 (C-9), 64.6/64.6 (–O*C*H$_2$*C*H$_2$O–), 72.5 (72.6) (C-6), 110.1 (110.2) (C-12), 130.6 (130.7) (C-8), 134.2 (C-3), 137.5 (C-7), 143.6 (143.7) (C-4) and 198.4 (C-2); MS [*m/z* (%)]: 309 (0.1, *M*−15), 306 (0.1), 225 (1), 183 (1), 179 (1), 161 (1), 139 (2), 121 (3), 115 (3), 109 (2), 99 (7), 95 (4), 87 (100), 71 (5), 69 (7), 59 (8), 55 (6) and 43 (67).

(±)-(3*E*,7*E*)-12,12-ethylenedioxy-9-isopropyl-2,6-dimethyltrideca-3,7-diene-2,6-diol (**30**) had IR (CCl_4): 3610, 3430 and 978 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.83 (d, *J* 6.8 Hz)/0.88 (d, *J* 6.7 Hz) (H-17/H-18), 1.28 (s)/1.30 (s)/1.30 (1.31) (s)/1.31 (s) (H-1/H-13/H-14/H-15), 2.23 (2.25) [dd, *J* 7.3 (6.1) and −13.8 (−13.6) Hz, H-5a], 2.30 [dd, *J* 5.2 (6.1) and −13.8 (−13.6) Hz, H-5b], 3.93 (m, –OC*H*$_2$C*H*$_2$O–), 5.34 (dd, *J* 9.0 and 15.6 Hz, H-8), 5.46 (5.47) (d, *J* 15.6 Hz, H-7), 5.62 [ddd, *J* 5.2, 7.3 and 15.6 Hz (dt, *J* 6.1 and 15.6 Hz), H-4] and 5.71 (d, *J* 15.6 Hz, H-3); MS [*m/z* (%)]: 325 (0.1, *M*−15), 304 (1), 241 (2), 223 (3), 202 (4), 183 (6), 179 (7), 159 (12), 121 (10), 115 (11), 99 (7), 93 (8), 87 (84), 82 (28), 71 (18), 55 (14) and 43 (100).

*Hydrolysis of (±)-(3*E*,7*E*)-12,12-ethylenedioxy-6-hydroxy-9-isopropyl-6-methyltrideca-3,7-dien-2-one* (**29**). A solution of 6.0 mg of **29** in 1.5 ml of dioxane/aqueous (3 %) H_2SO_4 (2:1) was stirred at room temperature and under nitrogen for 2 h. Work-up of the reaction mixture and purification of

the crude product by HPLC (Spherisorb 5; hexane/EtOAc 1:1) yielded 3.6 mg of a 1:1 mixture of the C-6 diastereoisomers of (±)-(3*E*,7*E*)-6-hydroxy-9-isopropyl-6-methyltrideca-3,7-diene-2,12-diones, the IR and mass spectra of which were identical with those of the naturally occurring **6**. The ^{1}H and ^{13}C NMR spectra of **6** were superimposable on those of the mixture. The NMR spectra also contained signals derived from the other C-6 diastereomer **31**: ^{1}H NMR ($CDCl_3$): δ 0.83 (d, *J* 6.8 Hz)/0.88 (d, *J* 6.7 Hz) (H-16/H-17), 1.34 (s, H-14), 2.13 (s, H-13), 2.25 (s, H-1), 2.35 (m, H-11a and H-11b), 2.46 (dd, *J* 1.4 and 7.5 Hz, H-5a and H-5b), 5.37 (dd, *J* 8.9 and 15.6 Hz, H-8), 5.49 (d, *J* 15.6 Hz, H-7), 6.12 (dt, *J* 1.4 and 16.0 Hz, H-3) and 6.82 (dt, *J* 7.5 and 16.0 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 19.1/20.7 (C-16/C-17), 26.1 (C-10), 27.0 (C-1), 28.6 (C-14), 30.0 (C-13), 32.0 (C-15), 42.0 (C-11), 45.7 (C-5), 48.7 (C-9), 72.5 (C-6), 130.3 (C-8), 134.0 (C-3), 137.8 (C-7), 143.6 (C-4), 198.4 (C-2) and 209.3 (C-12).

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