

The Structure of (11 ξ ,12 ξ)-11,12-Di(7-drimen-11-oxy)-11,12-epoxy-7-drimene

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A new terpenoid — isolated from *Drimys winteri* Forst — was assigned the structure (11 ξ ,12 ξ)-11,12-di(7-drimen-11-oxy)-11,12-epoxy-7-drimene on the basis of spectral and chemical data including hydrolysis to the known sesquiterpenoids drimenol and polygodial. The absolute configurations were established for all but two asymmetric centres, C(11) and C(12), which were tentatively deduced as *R*, *R* from ¹³C and ¹H NMR considerations.

The stem bark of the South American tree *Drimys winteri* Forst (family Winteraceae) has been shown to produce sesquiterpenoids of the drimane type, *i.e.* drimenol (1) and three isomeric lactones, drimenin, isodrimenin and confertifolin, which are oxygenated at C(11)

and C(12).¹⁻³ The present communication deals with the structure of a new constituent isolated from *D. winteri* Forst, (11 ξ ,12 ξ)-11,12-di(7-drimen-11-oxy)-11,12-epoxy-7-drimene (2).

The new compound was obtained as the major component of the methanol-insoluble fraction of the light petroleum extract. It proved to be unstable under acidic conditions and required precautions like pretreatment of adsorbents with pyridine to avoid decomposition during isolation. Elemental analysis and a very weak ion at *m/e* 660.5, observable only in the low voltage mass spectrum (15 eV, low resolution), indicated the composition C₄₈H₇₂O₃ (= *m/e* 660.547); in the 70 eV high resolution

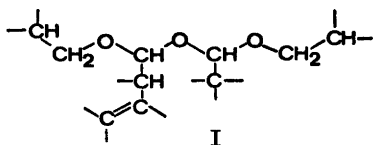
Table 1. Carbon-13 chemical shift data.^a

Compound Carbon	δ_C	2 ^b Carbon	δ_C	Carbon	δ_C	1 ^c Carbon	δ_C	3 ^c δ_C	4 ^c δ_C
1	40.14	1'	40.14	1''	40.14	1	39.37	39.62	39.35
2	18.82	2'	19.33	2''	19.33	2	18.78	18.06	18.82
3	42.38	3'	42.67 ^d	3''	42.54 ^d	3	42.17	41.78	42.03
4	33.50	4'	33.16 ^d	4''	32.89 ^d	4	32.92	32.93	32.98
5	49.52	5'	50.28	5''	50.28	5	49.92	49.05	49.43
6	23.74	6'	24.05	6''	24.05	6	23.62	25.26	23.59
7	138.69	7'	134.56	7''	134.56	7	123.94	154.22	127.54
8	120.22	8'	122.85 ^d	8''	122.65 ^d	8	133.03	138.37	136.97
9	58.52	9'	54.89 ^d	9''	54.74 ^d	9	57.27	60.38	54.51
10	36.32	10'	36.32	10''	36.32	10	36.05	36.91	35.66
11	106.15	11'	65.89	11''	68.07	11	60.85	201.94	61.50
12	104.13	12'	23.05 ^d	12''	22.90 ^d	12	21.95	193.24	67.51
13	33.73	13'	33.73	13''	33.73	13	33.37	33.14	33.19
14	21.60	14'	22.25 ^d	14''	22.13 ^d	14	22.04	21.95	21.91
15	14.41	15'	14.80 ^d	15''	14.65 ^d	15	14.84	15.28	14.55

^a δ -Values relative to TMS. ^b Run in C₆D₆. ^c Run in CDCl₃. ^d These assignments of primed and corresponding doublyprimed carbons may be interchanged.

spectrum, the ion of highest mass occurred at m/e 438 and had the composition $C_{30}H_{46}O_2$.*

The presence of 45 carbon atoms was confirmed by the ^{13}C and 1H NMR spectra (cf. Table 1) which also disclosed that twelve of these were methyl groups on quaternary carbons and three olefinic methyl groups. Two singlets, one of which corresponded to two carbon atoms, and three doublets in the olefinic region (120–140 ppm) of the ^{13}C NMR spectrum and three olefinic proton signals in the 1H NMR spectrum (ca. δ 5.56) revealed the presence of three trisubstituted double bonds. A one-proton doublet at δ 5.10 and a one-proton singlet at δ 5.39 in the latter spectrum and two doublets at δ 104.1 and 106.2 in the ^{13}C NMR spectrum implied the occurrence of two carbon atoms carrying two oxygens and one proton each. The doublet at δ 5.10 was coupled (J 4.5 Hz), as confirmed by spin decoupling experiments, to a one-proton multiplet at δ 2.70 attributable to an allylic proton. Two triplets in the ^{13}C NMR spectrum at δ 65.9 and 68.1 and two AB-parts of two ABX-systems positioned at δ 3.99 and 3.73 (J_{AB} 10 Hz, J_{AX} 6.5 Hz, J_{BX} 3 Hz) and at δ 4.29 and 3.37 ($J_{A'B'}$ 9.5 Hz, $J_{A'X'}$ 7.5 Hz, $J_{B'X'}$ 2 Hz) in the 1H NMR spectrum suggested the presence of two oxygenated methylene groups attached to tertiary carbon atoms. Since the compound comprised totally three oxygens and its IR spectrum showed no hydroxyl absorption, these data could be summarized as shown in the partial structure I.

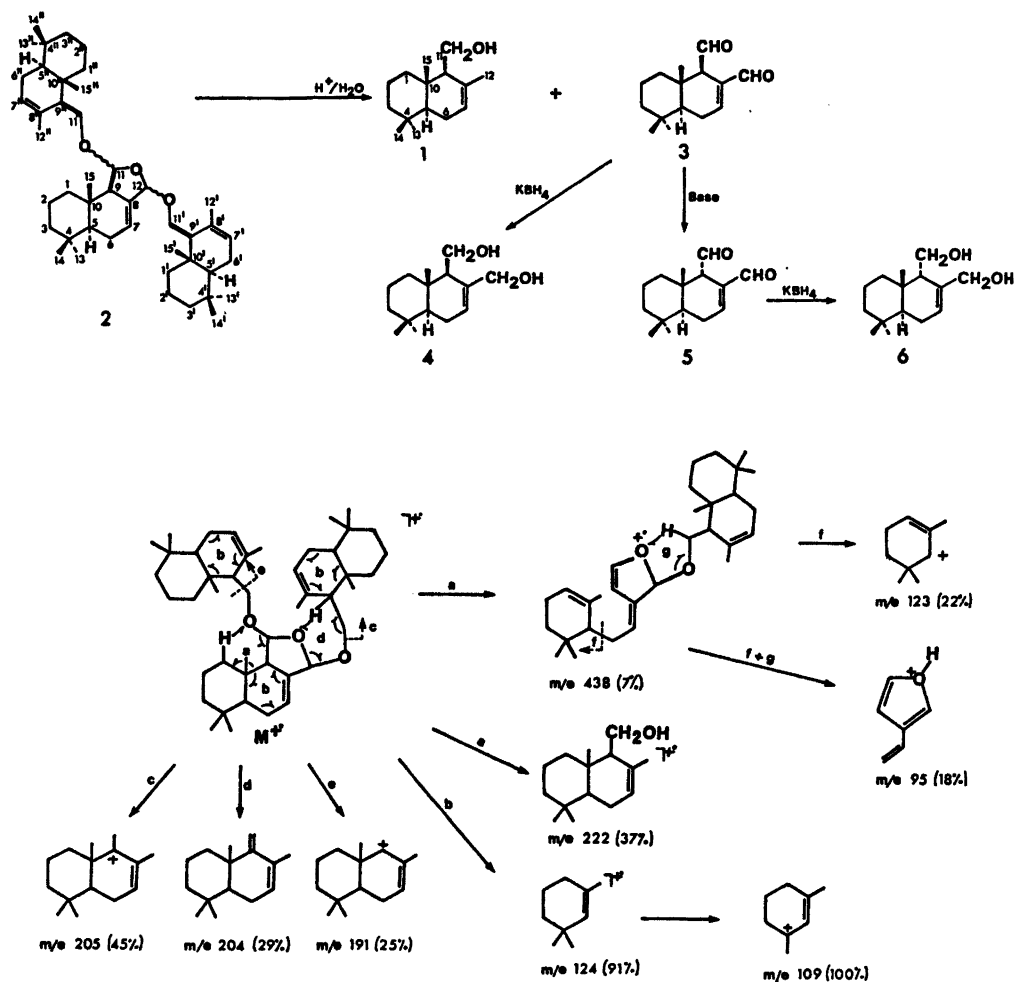


Acid hydrolysis of the new compound yielded two products in a 1:2 ratio. The major product was readily recognized as drimenol (1) by direct comparison with an authentic sample, while the minor product was identified as polygodial (3) on the basis of comparison of its

* A preliminary report on the present compound, then designated Acetal-B and erroneously assumed to have a molecular weight of 438, was presented at the XI Congreso Latino-americano de Quimica, Santiago, 1972; cf. Ref. 4.

spectral data with those for natural^{5,6} (*e. Polygonum hydropiper* L.) and synthetic⁷ polygodial, kindly provided by Drs. Loder and Kato. The identity of polygodial was further manifested by hydride reduction to the known drim-7-en-11,12-diol (4), and by base-catalysed epimerization to the more stable 9 α -drim-7-en-11,12-dial (5), which on reduction furnished 9 α -drim-7-en-11,12-diol (6). The ^{13}C NMR assignments of drimenol (1), polygodial (3), and drim-7-en-11,12-diol (4) are given in Table 1 and were made on the basis of chemical shift considerations and comparison of data for structurally related diterpenoids.^{8,9} The data thus obtained for drimenol (1) were used to assist the assignments given for the new compound (Table 1), which on the basis of the above chemical and spectral data could be formulated as (11 ξ , 12 ξ)-11,12-di(7-drimen-11-oxy)-11,12-epoxy-7-drimene (2).

Its fragmentation on electron impact provided confirmatory evidence since the formation of the eight most abundant ions could on the basis of results for structurally related diterpenoids¹⁰ readily be accounted for in terms of this structure, as indicated in Scheme 1. Although several routes of similar probability exists in many cases, only one – preferentially that involving the molecular ion as the parent species – is detailed here. Thus decomposition of the molecular ion by a cyclic reaction encompassing rupture of the C(11)–O and C(9)–C(10) bonds with transfer of a hydrogen at C(1) to the oxygen (path a) yields the m/e 438 ion and the drimenol ion (m/e 222). Retro-Diels-Alder fragmentation of the molecular ion, furnishes the m/e 124 species (path b), which by loss of a methyl generates the m/e 109 fragment. Simple cleavage of the C(11')–O [or the C(11'')–O] bond in the molecular ion, accompanied by a 1,2-hydride shift in the smaller charged fragment, produces the m/e 205 species (path c), while rupture of the same bond with hydrogen transfer to the larger neutral fragment accounts for the formation of the m/e 204 ion (path d). Simple cleavage of the 9'–11' (or 9''–11'') bond in the molecular ion gives the m/e 191 ion (path e), while simple cleavage of the 5,6-bond in the m/e 438 species accounts for the formation of the m/e 123 ion (path f). When the last reaction is accompanied by elimination of drimenal



Scheme 1.

through rupture of the C(12)–O bond and transfer of 11'–H to the smaller fragment the *m/e* 95 species (path *f* + *g*) is generated.

The absolute configuration of all but two asymmetric centres, C(11) and C(12), follows from the known absolute stereochemistry of drimenol and polygodial. It might be expected, if (11 ξ ,12 ξ)-11,12-di(7-drimen-11-oxy)-11,12-epoxy-7-drimene (2) is formed *in vivo* from polygodial (3) and drimenol (1), that the sterically less congested 11 α -isomer would result. While no conclusive evidence could be obtained from the coupling constant (4.5 Hz) for the vicinal 9 α - and 11 ξ -hydrogens, it can be inferred that the interaction from an 11 β ether

oxygen on the C(15) methyl group, if present, would probably have caused one of the three angular methyl signals to appear further down-field (about 2 ppm) of the other two, C(15') and C(15''), in the ^{13}C NMR spectrum than actually encountered (observed difference 0.4 ppm).⁹ A corresponding difference in chemical shift, about 0.2 ppm, between the methyl signals in the ^1H NMR spectrum would also be expected if the exocyclic 11-oxygen were β -oriented, but is not observed since all occur in the δ 0.91–1.02 region (CDCl_3).¹¹

The difference between the 12 α and 12 β isomers with respect to steric congestion is small as judged by Dreiding models. However,

examination of these models suggests that the upfield-shift of one (δ 3.37) and the downfield shift of the other (δ 4.28) of the two protons on one of the oxygenated methylene groups relative to those on the other oxygenated methylene group (δ 3.99 and 3.73) in the ^1H NMR spectrum (in C_6D_6) is best explained if the oxygen linked to this methylene group, C(11'), is β -oriented. Thus these chemical shifts are most readily accounted for as a result of a long-range anisotropic shielding by the 7,8-double bond.* Moreover, such an orientation of the C(11') methylene group, which makes it essentially anti-periplanar to the tetrahydrofuran oxygen, is also consistent with the occurrence of the C(11') signal in the ^{13}C NMR spectrum 2.2 ppm upfield of that due to C(11'').¹² It seems likely therefore that the compound is (11*R*, 12*R*)-11,12-di(7-drimen-11-oxy)-11,12-epoxy-7-drimene.

Polygodial has not previously been detected in *D. winteri*, but it has been isolated by Loder⁶ from a related shrub, *Drimys lanceolata*, which is confined to the mountains of southeast Australia and Tasmania. The recent isolation of scalaradiol,¹³ and several related hemiacetals such as scalarin,¹⁴ deoxoscalarin,¹⁵ and heteronemin¹⁶ from sponges of the order Dictyoceratida is also of interest in the present context because of the close structural relationship with the compounds considered here and the less frequent occurrence of dialdehydes in Nature.

EXPERIMENTAL

IR spectra, rotations and mass spectra were recorded on Digilab FTS-14, Perkin-Elmer 141 and LKB 2091 instruments, respectively. ^{13}C and ^1H NMR spectra were obtained in CDCl_3 or C_6D_6 solutions in FT-mode on a Varian XL-100-12 spectrometer equipped with S-124 FT accessory and controlled by a Varian 620 L computer. Accurate mass determinations were carried out at the Laboratory for Mass Spectrometry, Karolinska Institutet, Stockholm. GLC-MS was performed on a Varian 1700 chromatograph attached to the LKB 2091

instrument using glass capillary columns (50 \times 0.25 mm) coated with Emulphor.

Extraction. The bark of *Drimys winteri* was cut into small pieces and exhaustively extracted with light petroleum (b.p. 70–80 °C) in a Soxhlet apparatus. Removal of the solvent yielded a brown, oily residue. The yield varies with the sample of the bark, but is usually between 20 and 30 %.

Purification. The crude extract (50 g) was extracted at room temperature with methanol (3 \times 100 ml) which removed about 50 % of the material (including drimenol). The methanol-insoluble residue was dissolved in a mixture of pyridine/butanol (4:96) and methanol added to turbidity. The mixture was kept at –15 °C for 24 h and the amorphous slightly yellow precipitate (ca. 18 g) collected. TLC revealed the presence of three components (ratio about 1:2:3) of which (11 ξ ,12 ξ)-11,12-di(7-drimen-11-oxy)-11,12-epoxy-7-drimene was the major constituent. An aliquot (4 g) of the precipitate was chromatographed on neutral alumina (May and Baker) which had been pretreated for 24 h with pyridine-light petroleum (4:96) to avoid decomposition which readily takes place on acidic adsorbents. Pure (11 ξ ,12 ξ)-11,12-di(7-drimen-11-oxy)-11,12-epoxy-7-drimene (0.9 g) was recrystallised from a mixture of dioxane and methanol by evaporation of part of the solvent mixture at room temperature. M.p. 128–131 °C. $[\alpha]_{\text{D}}^{20}$ –24.0° (c 1; benzene). Found C 81.87; H 11.13. Calc. for $\text{C}_{46}\text{H}_{72}\text{O}_8$: C 81.75, H 11.00. MS at 15 eV: M^+ at m/e 660.5 (ca. 0.2 %, calc. for $\text{C}_{46}\text{H}_{72}\text{O}_8$ 660.547) ($\text{M} + 1$)⁺ at m/e 661.5 (48.8 % of M^+ ; calc. 49.5 %); MS at 70 eV: M^+ not visible, 109 (100), 124 (91), 205 (45), 222 (37), 204 (29), 191 (25), 123 (22), 95 (16), 98 (16), 135 (12), 234 (11), ions at m/e > 300: 438 (7), 439 (5); accurate mass determination: found 438.3506, calc. for $\text{C}_{30}\text{H}_{46}\text{O}_2$ 438.3498; UV: no absorption above 210 nm; IR: ν_{max} (KBr): 2949 (s), 2918 (s), 2845 (s), 1459 (m), 1440 (m), 1389 (m), 1365 (m), 1257 (w), 1218 (w), 1145 (w), 1105 (m), 1069 (m), 1021 (m), 992 (m), 957 (s), 920 (m), 880 (w), 825 (m) cm^{-1} . δ_{C} (C_6D_6): Table 1. δ_{H} (CDCl_3): 0.91 (3 H, s), 0.93 (3 H, s), 0.96 (3 H, s), 1.01 (12 H, s), 1.02 (6 H, s), 1.87 (9 H, broad s), 3.38 (1 H, dd, J 7 and 10 Hz), 3.71 (2 H, m), 4.16 (1 H, dd, J 1 and 10 Hz), 5.07 (1 H, d, J 4 Hz), 5.31 (1 H, s), ca. 5.56 (2 H, br), 5.86 (1 H, m). δ_{H} (C_6D_6): 0.69 (3 H, s), 0.79 (6 H, s), 0.83 (3 H, s), 0.87 (6 H, s), 0.89 (6 H, s), 1.02 (3 H, s) 1.98 (3 H, broad s), 2.07 (6 H, broad s), ca. 2.70 (1 H, m), 3.37 (1 H, dd, J 7.5 and 9.5 Hz), 3.73 (1 H, dd, J 3 and 10 Hz), 3.99 (1 H, dd, J 6.5 and 10 Hz), 4.29 (1 H, dd, J 2 and 9.5 Hz), 5.10 (1 H, d, J 4.5 Hz), 5.39 (1 H, s), ca. 5.55 (3 H, m). Irradiation at δ 2.70 simplified the signal at δ 5.10 to a singlet. On irradiation at δ 4.29 the doublet of doublets centered at δ 3.38 collapsed to a doublet. Irradiations at δ 1.98 and 2.07, respectively, sharpened the multiplet at δ 5.55. Irradiation

* The same magnitude of the shift differences for these protons [4.16 (dd, J 10.1); 3.38 (dd, J 10.7); 3.71 (2 H, m)] were observed when CDCl_3 was used as solvent, which implies that the shift difference mentioned above was not due to an aromatic solvent induced shift but of intramolecular origin.

at δ 2.18 simplified the two doublets of doublets at δ 3.73 and 3.99 to an AB-system with J 10 Hz.

Hydrolysis of (11 ξ ,12 ξ)-11,12-di(7-drimen-11-oxy)-11,12-epoxy-7-drimene (2). A mixture of (11 ξ , 12 ξ)-11,12-di(7-drimen-11-oxy)-11,12-epoxy-7-drimene (92 mg), ether (15 ml) and water (1 ml) containing 2 drops of acetic acid was stirred for 3 h at room temperature. Water was added and the products extracted with ether. The extract was dried over Na_2SO_4 and the solvent removed *in vacuo* leaving an oil which was chromatographed on a silica gel column yielding drimenol (1, 25 mg) and polygodial (3, 13 mg). The identity of drimenol was confirmed by direct comparison, optical activity included, with an authentic sample of the naturally occurring compound. The more polar polygodial (3) had the following properties: $[\alpha]_{\text{D}}^{20} - 121^\circ$ (589 nm), -126° (578), -146° (546), -271° (436) (c 0.44 in CHCl_3); lit.⁵ $[\alpha]_{\text{D}}^{19} - 131^\circ$ (c 0.96 in EtOH); lit.⁶ $[\alpha]_{\text{D}}^{19} - 126^\circ$ (c 2.07 in CHCl_3); MS: m/e 234 (M^+ , 6%), 206 (100), 43 (68), 121 (59), 41 (59), 109 (58), 110 (50), 191 (49); MS kindly provided by Dr. Loder: m/e 234 (M^+ 5%), 206 (100), 109 (100), 121 (80), 191 (49); δ_{H} (CDCl_3): 0.82 (3 H, s), 0.93 (3 H, s), 0.95 (3 H, s), *ca.* 7.12 (1 H, m), 9.47 (1 H, s), 9.56 (1 H, d, J 5 Hz); chemical shifts of olefinic and aldehydic protons in the spectrum kindly provided by Dr. Loder: *ca.* δ 7.15 (m), 9.45 (s), and 9.52 (d, J 5 Hz), respectively (these values differ from those originally published by Barnes and Loder⁵ for polygodial); δ_{C} (CDCl_3): Table 1. IR: ν_{max} (film): 2929 (s), 2721 (w), 1724 (s), 1680 (s), 1645 (w), 1391 (w), 1369 (w), 1269 (w), 1180 (w), 1136 (w), 1117 (w), 1072 (w), 837 (w), 824 (w), 697 (w) cm^{-1} ; the spectrum was nearly identical with those of natural (CS_2) and synthetic (CCl_4) polygodial. An aliquot of the dialdehyde isolated from the hydrolysis of (11 ξ ,12 ξ)-11,12-di(7-drimen-11-oxy)-11,12-epoxy-7-drimene was reduced with KBH_4 to a diol which was identified as drim-7-en-11,12-diol by comparison with an authentic sample: m.p. 73–75 °C; $[\alpha]_{\text{D}} - 2^\circ$ (c 2.47, CHCl_3); IR: ν_{max} (KBr): 3330, 1655, 1385, 1360, 680 cm^{-1} ; MS: m/e 238 (M^+ , 7%), 109 (100), 190 (47), 124 (35), 44 (32?), 41 (23), 69 (20), 55 (18), 81 (17), 105 (17), 119 (13), 175 (10); δ_{C} (CDCl_3): Table 1; δ_{H} (CDCl_3): 0.77 (3 H, s), 0.88 (6 H, s), 3.68 (1 H, dd, J 7.5 and 11 Hz), 3.91 (1 H, dd, J 2.5 and 11 Hz), 3.98 (1 H, d, J 12.5 Hz), 4.34 (1 H, d, J 12.5 Hz), 5.81 (1 H, m); on treatment with basic Al_2O_3 the dialdehyde epimerized to 9 α -drim-7-en-11,12-dial which on reduction with KBH_4 furnished 9 α -drim-7-en-11,12-diol: m.p. 128–129.5 °C. $[\alpha]_{\text{D}} - 136^\circ$ (c 2.05, CHCl_3); IR: ν_{max} (KBr): 3330, 1660, 1380, 1360 cm^{-1} .

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