SHORT PAPER

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Photo-oxygenation of phytol and the structure revision of phytene-1,2-diol from *Artemisia annua* to phytene-1-ol-2-hydroperoxide†

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Photo-oxygenation of racemic phytol has yielded two secondary allylic hydroperoxides and an endoperoxide hemi-acetal, which are the expected products from the "ene-type" reaction of singlet oxygen with the tri-substituted double bond in phytol. Spectral properties for one of the diastereoisomers of phytene-1-ol-2-hydroperoxide obtained from synthesis are shown to be identical with those of a natural product previously reported from *Artemisia annua*, which, it is concluded, was wrongly assigned as phytene-1,2-diol.

Keywords: photo-oxygenation of phytol, *Artemisia annua*

In 1994 we reported "phytene-1,2-diol" as a novel natural product from the important anti-malarial plant *Artemisia annua*,[1] together with its presumed biogenetic precursor *trans*-phytol. The NMR data for the natural product from *A. annua* was different from that previously reported for phytene-1,2-diol from *Senecio gallicus*[2] and at the time this discrepancy was ascribed to the possibility of diastereoisomerism at the 2-hydroxyl group, although, unfortunately, no high resolution mass spectrum was given for the novel natural product from *A. annua* to confirm the planar structure. In retrospect, we have come to suspect that the structure of this compound may have been wrongly assigned since the ^{13}C resonance at C-2 of "phytene-1,2-diol" from *A. annua*[1] (δ_C 88.8 ppm) was more than 13 ppm downfield of that reported previously in the literature (δ_C 75.1 ppm).[2] Such a large difference is quite unlikely to be due to a differing configuration at C-2, but would be more consistent with the substitution of a hydroperoxide rather than a hydroxyl group at the C-2 position (typically a carbon substituted by –OOH resonates between 5 and 13 ppm downfield when compared to its –OH analogue).[3,4] If the 2-position were in reality substituted by a hydroperoxide rather than a hydroxyl group, then the true structure would be that of a secondary allylic hydroperoxide, which would in turn be an expectable product from oxygenation of the $\Delta^{2,3}$-double bond in phytol, which has also been isolated as a natural product from *A. annua*. Indeed, several terpenoid allylic hydroperoxides **(1–3)** are now known from this species,[5-8] all of which may be formed by oxygenation reactions of alkene precursors **(4** and **5)** which co-occur as natural products (see Fig. 1). These considerations have led us to re-investigate the structure claimed for "phytene-1,2-diol" from *A. annua* by studying the products obtained from the photo-oxygenation reaction of phytol.

Results and discussion

Racemic phytol **(6)** is commercially available as an approximately 2:1 mixture of *trans* **(6a)** and *cis* **(6b)** geometric isomers. These isomers could be separated by HPLC and their full NMR assignments, rigorously determined by 2D-NMR, are given in Tables 1 and 2. A previous investigation of the photo-oxygenation of phytol has reported various ketones and epoxy-aldehydes as the sole products when the reaction was performed under natural illumination for a period of two days in a variety of solvents.[9] In our hands, photo-oxygenation of **6** in acetone in the presence of methylene blue as photosensitizer yielded predominantly the expected products from the "ene-type" addition of $^1O_2$ to the $\Delta^{2,3}$-double bond in phytol (Scheme 1).[10] These included the secondary allylic hydroperoxides **7** and **8** and the endoperoxide hemi-acetal **9**, which we propose to be formed by tautomerisation of the third possible product of photo-oxgenation, tertiary hydroperoxide enol **10**, to an aldehyde, which is then trapped by the hydroperoxide group. Trace amounts of α,β-unsaturated ketone **11** and diol **12** were also isolated by HPLC. After fully assigning the carbon resonances for each of these products by 2D-NMR (see Table 1) it was clear that all of the products of photo-

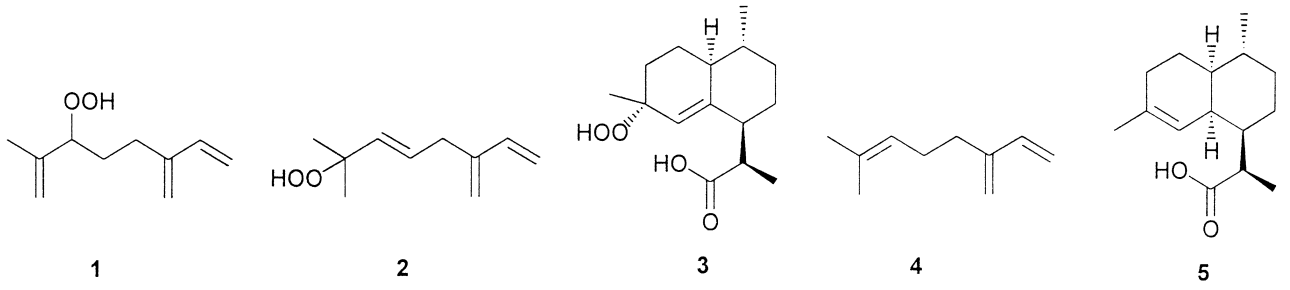

Fig. 1 Allylic hydroperoxides α-myrcene hydroperoxide **(1)**, β-myrcene hydroperoxide **(2)** and dihydroartemisinic acid tertiary hydroperoxide **(3)** and their proposed biogenetic precursors β-myrcene **(4)** and dihydroartemisinic acid **(5)**, all of which have been reported as natural products from *A. annua*.

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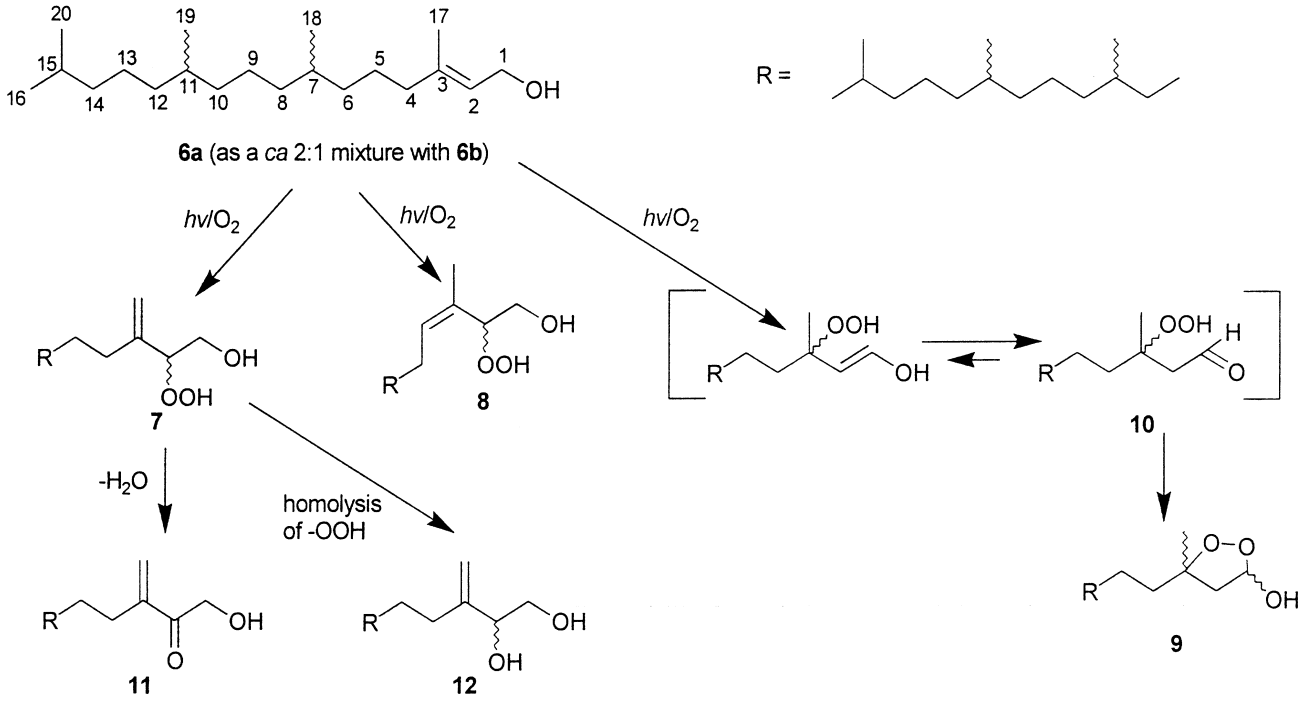

Scheme 1
Photo-oxygenation of racemic phytol and further transformations of secondary allylic hydroperoxide **7** in organic solution.

Table 1 ^{13}C NMR assignments for racemic *trans* and *cis* phytol **(6a/6b)** and their photo-oxygenation products **7–9** and **11** and **12**[a]

Position	6a	6b	7	8	9a	9b	11	12
1	59.42	59.14	63.08	63.07	98.62	98.88	64.75	65.68
2	123.10	123.96	88.73	85.15	53.68/ 53.71	53.97	199.88	75.05
3	140.29	140.63	144.96	129.10	85.37	84.92	145.97	148.74
4	39.89	32.21	33.54	132.92/ 132.89	38.01	40.06	31.00	33.02
5	25.16 25.16	25.73/ 25.72	25.22	25.20	24.84/ 24.82		25.69	25.53
6	36.77/ 36.67	36.95/ 36.87	g	37.20/ 37.19	k		37.61/ 36.62	n
7	32.70/ 32.68[c]	32.70/ 32.68[c]	32.73[c]	32.52	32.76/ 32.69[c]		32.61/ 32.59	32.73
8	e	f	h	i	k		m	o
9	24.48	24.47	24.50	24.43	24.49		24.43	24.49
10	e	f	h	i	k		m	o
11	32.80/ 32.78[c]	32.80/ 32.78[c]	32.80[c]	32.80	32.81[c]		32.79/ 32.78	32.80
12	e	f	h	i	k		m	o
13	24.81	24.82/ 24.81	24.83	24.81	24.84/ 24.82		24.79/ 24.78	24.82
14	39.38	39.39	39.39	39.37	39.39		39.37	39.39
15	28.00	28.00	27.99	27.99	28.00		27.99	28.00
16[b]	22.64	22.65	22.65	22.63	22.66		22.63	22.65
17	16.18	23.47	112.76	18.69	24.91/ 24.89	21.96/ 21.92	124.70	110.55
18	19.73/ 19.66[d]	19.70/ 19.63[d]	19.70/ 19.64[d]	j	l		19.64/ 19.58[d]	p
19	19.76/ 19.69[d]	19.76/ 19.70[d]	19.76/ 19.70[d]	19.75/ 19.68	19.77/ 19.70		19.75/ 19.68[d]	19.77/ 19.70
20[b]	22.73	22.74	22.74	22.73	22.75		22.73	22.74

[a]Assignments were made by the 2D-NMR experiments HSQC, HMBC, ^{1}H-^{1}H COSY and NOESY; [b]interchangeable within column; [c]interchangeable within column; [d]interchangeable within column; [e]37.44/37.40/37.37/37.33/37.30 (1:2:1:1:1); [f]37.44/37.40/37.33/37.30 (1:3:1:1); [g]36.88/36.85/36.79/36.76 (1:1:1:1); [h]37.44/37.40/37.36/37.31 (3:6:1:2); [i]37.43/37.40/37.30/37.27/37.24 (2:3:3:3:1); [j]19.57/19.54/19.51/19.48 (1:1:1:1); [k]37.50/37.44/37.40/37.35/37.30 (1:6:10:4:3); [l]19.70/19.68/19.64/19.61 (2:2:3:1); [m]37.42/37.38/37.34/37.29 (1:2:1:2); [n]36.96/36.93/36.87/36.84 (1:1:1:1); [o]37.45/37.41/37.39/37.34/37.31 (2:5:2:1:2); [p]19.77/19.71/19.70/19.66/19.64 (2:1:3:1:1)

Table 2 ^{1}H NMR assignments for racemic *trans* and *cis*-phytol **(6a/6b)** and their photo-oxygenation products **7–9** and **11** and **12**[a]

Position	6a	6b	7	8	9a	9b	11	12
1	4.15,4.15	4.12,4.12	3.76,3.72	3.83,3.59	5.66	5.64	4.57,4.57	3.70,3.54
2	5.41	5.41	4.52	5.01	2.57,2.37	2.68,2.31	-	4.20
4	1.99, 1.99	2.05,2.05	2.07,1.97	5.49	1.64,1.64	1.60,1.47	2.30,2.20	2.04,1.97
5	1.41, 1.41	1.37,1.37	1.47,1.47	2.14,2.04	1.23,1.23		1.43,1.43	1.46,1.46
6	1.40, 1.32	1.40,1.32	1.33,1.14	1.37,1.15	1.25,1.08		1.30,1.12	1.32,1.13
7	1.39	1.38	1.39c	1.40	1.37		1.37	1.39
8	1.25, 1.08	1.26,1.08	1.26,1.08	1.25,1.08	1.25,1.08		1.25,1.07	1.25,1.07
9	1.28, 1.28	1.28,1.28	1.26,1.26	1.26,1.26	1.23,1.23		1.25,1.25	1.27,1.27
10	1.25, 1.08	1.26,1.08	1.26,1.08	1.25,1.08	1.25,1.08		1.25,1.07	1.25,1.07
11	1.39	1.38	1.37[c]	1.38	1.37		1.37	1.39
12	1.25, 1.08	1.26,1.08	1.26,1.08	1.25,1.08	1.25,1.08		1.25,1.07	1.25,1.07
13	1.28, 1.28	1.28,1.28	1.26,1.26	1.26,1.26	1.23,1.23		1.25,1.25	1.27,1.27
14	1.14, 1.14	1.14,1.14	1.14,1.14	1.13,1.13	1.13,1.13		1.13,1.13	1.14,1.14
15	1.52	1.52	1.52	1.52	1.52		1.52	1.52
16	0.87	0.87	0.87	0.87	0.87		0.86	0.87
17	1.67	1.73	5.12,5.06	1.69	1.31	1.38	5.94,5.83	5.13,4.97
18	0.86[b]	0.85[b]	0.86[b]	0.87	0.85[b]		0.85[b]	0.86
19	0.85[b]	0.84[b]	0.85[b]	0.84	0.84[b]		0.84[b]	0.84
20	0.87	0.87	0.87	0.87	0.87		0.86	0.87

[a]Assignments were made by the 2D-NMR experiments HSQC, HMBC, ^{1}H-^{1}H COSY and NOESY; [b]interchangeable within column; [c]interchangeable within column.

oxygenation are racemic at the newly created chiral centres (as well as at the already racemic 7- and 11-positions).

Compounds **11** and **12** were believed to be formed from the secondary allylic hydroperoxide **7** by known dehydration and homolysis reactions of hydroperoxides.[10] In the case of compound **11** this could be confirmed by studying the transformations of **7** in $CDCl_3$ solution by ^{1}H NMR spectroscopy, which showed ca 10% conversion into compound **11** (and two other unidentified compounds) after several days. The structure of racemic phytene-1,2-diol **(12)** was confirmed by reduction of **7** with triphenylphosphine. NMR spectra for **12** agreed well with those reported for phytene-1,2-diol as a natural product from Senecio gallicus,[2] but were clearly different from those of "phytene-1,2-diol" from *A. annua*,[1] confirming that the structure claimed for the natural product from this species must be in error. On the other hand, NMR data for the racemic secondary allylic hydroperoxide **7** from photo-oxygenation of synthetic phytol gave an extremely good match with NMR data previously reported for "phytene-1,2-diol" as a natural product from *A. annua*, leaving little doubt that the structure of this natural product should be re-assigned as phytene-1-ol-2-hydroperoxide. Owing to the presence of three chiral centres in racemic **7** obtained from synthesis, there are expected to be eight possible diastereoisomers for this compound which would result in four sets of NMR spectra, one for each enantiomeric pair. Although resonances from these four distinct spectra were partially or completely overlapped for many positions in the molecule, four distinct peaks were seen for the for the C-6 position in ^{13}C NMR (δ_C 36.88, 36.85, 36.79, 36.76 ppm) in a 1:1:1:1 ratio, which confirmed the presence of all eight possible diastereoisomers in the synthetic product. It should be noted that the ^{13}C NMR spectrum reported for phytene-1-ol-2-hydroperoxide obtained as a natural product from *A. annua* was reported to consist of only a single resonance for each position in the molecule,[1] and the natural form must therefore be either a single diastereoisomer or a mixture of enantiomers at C-2. The latter is more likely if a spontaneous autoxidation process resembling that described in Scheme 1 is also operating *in vivo* in *A. annua*, because trans-phytol from *A. annua*,[1] which would be the presumed precursor of the natural product phytene-1-ol-2-hydroperoxide from this species, was also reported to have only a single resonance at each position and was presumably the *7R*, *11R*-diastereoisomer which is normally found in nature[11] (cf. ^{13}C NMR data for synthetic *trans*-phytol in Table 1, which shows two resonances for some positions, consistent with the presence of all four possible diastereoisomers in the synthetic starting material used for photo-oxygenation).

Experimental

Chemical shifts are expressed in ppm (δ) relative to TMS as internal standard. Proton chemical shifts, multiplicities, coupling constants and integrals reported in this section are those which are clearly resolved in one-dimensional ^{1}H NMR without recourse to 2D-NMR analysis (see Tables in the main text for full assignments by 2D-NMR). All NMR experiments were run on a Bruker DRX 500 instrument. HSQC, HMBC, ^{1}H-^{1}H COSY and NOESY spectra were recorded with 1024 data points in F_2 and 256 data points in F_1. High-resolution MS were recorded in EI mode at 70 eV on a Finnigan-MAT 95 MS spectrometer. Positive ion electrospray mass spectrometry was performed on a Finnigan LCQ spectrometer - the sample was infused at 5 µl/min (capillary temperature 180 K; capillary voltage 5 V; sheath gas flow rate 60 l/min), the ions were produced in an API ion source (spray voltage 5.5 kV at the probe tip) and the quadrupole mass analyser was scanned at 100 amu/s (mass range of 150 to 500 Da; mass accuracy within 0.5 *m*/*z* units). IR spectra were recorded in $CHCl_3$ on a Shimadzu FTIR-8201 PC instrument. Column chromatography (CC) was performed using silica gel 60–200 µm (Merck). HPLC separations were performed using a Varian chromatograph equipped with RI star 9040 and UV 9050 detectors and a YMC diol 20 mm × 25 cm column, flow rate 8 ml/min.

Racemic phytol supplied by Aldrich (cat. no. 13,991-2) was shown to be a *ca* 2:1 mixture of *trans* and *cis* geometric isomers by NMR. These isomers could be separated by HPLC (12% EtOAc/*n*-hexane) for characterisation by 2D-NMR. *trans*-Phytol (R_t 18.2 min): Oil. ^{1}H NMR (δ, $CDCl_3$): 5.41 (1H, t, *J*=7.0 Hz), 4.15 (2H, d, *J*=7.0 Hz), 1.99 (2H, m), 1.67 (3H, s), 1.52 (1H, m), 0.87 (6H, d, *J*=6.9 Hz), 0.86 (3H, d, *J*=7.1 Hz), 0.85 (3H, d, *J*=6.4 Hz), – see also Table 2; ^{13}C NMR: see Table 1. *cis*-Phytol (R_t 17.2 min): Oil. ^{1}H NMR (δ, $CDCl_3$): 5.41 (1H, t, *J*=6.9 Hz), 4.12 (2H, d, *J*=6.9 Hz), 2.05 (2H, m), 1.73 (3H, s), 1.52 (1H, m), 0.87 (6H, d, *J*=6.6 Hz), 0.85 (3H, d, *J*=6.6 Hz), 0.84 (3H, d, *J*=6.6 Hz), see also Table 2; ^{13}C NMR: see Table 1.

Photo-oxygenation of phytol: A solution of phytol (200 mg, ex. Aldrich, as above) in acetone (20 ml) containing methylene blue (2 mg) as photosensitiser was irradiated with strong light (500 W lamp) for 6 h at 0°C, until most of the starting material had disappeared, as judged by TLC (some unreacted *cis*-phytol **(6b)** was isolated at the end of the reaction; presumably, *cis*-phytol is less reactive towards photo-oxygenation than *trans*-phytol). The solvent was removed on a rotary evaporator, and the residue was taken up into Et_2O (60 ml), filtered to remove the photosensitiser, dried ($MgSO_4$) and solvent removed to yield a crude product (199 mg; 99% w/w) which was separated by HPLC (20% EtOAC/*n*-hexane): compound **6b** (5 mg; R_t

13.3 min); compound **7** (45 mg, 20%; R_t 38.9 min); compound **8** (2 mg, 1%; R_t 40.8 min); compounds **9a/9b** (57 mg, 26%; R_t 16.7/15.0 min); compound **11** (4 mg, 2%; R_t 11.0 min); and compound **12** (1 mg, 0.5%; R_t 39.0 min).

It appears that the *cis* and *trans* isomers of **9** are separated by HPLC, since two peaks were observed in the chromatogram for **9**. However, these two isomers must then rapidly interconvert with one another when prepared for NMR in $CDCl_3$ solution, resulting in identical spectra (corresponding to a 6:5 mixture of **9a/9b**) being recorded for both chromatographic fractions.

Compound **7:** Oil. IR ν_{max} ($CHCl_3$): 3599, 3348 (br), 2955, 2928, 2856, 1460, 1375 cm^{-1}; ^1H NMR (δ, $CDCl_3$): 8.91 (1H, br s, -OOH), 5.12 (1H, s), 5.06 (1H, s), 4.52 (1H, dd, *J*=7.1, 3.2 Hz), 3.76 (1H, dd, *J*=12.2, 3.2 Hz), 3.72 (1H, dd, *J*=12.2, 7.1 Hz), 2.54 (1H, br s, -OH), 2.10–1.93 (2H, m), 1.52 (1H, m), 0.87 (6H, d, *J*=6.4 Hz), 0.86 (3H, d, *J*=6.7 Hz), 0.85 (3H, d, *J*=6.7 Hz), see Table 2 for full assignments; ^{13}C NMR: see Table 1; Electrospray-MS: *m*/*z* (rel. int.) 351.5 [M^+ ($C_{20}H_{40}O_3$) + Na^+].

Compound **8:** Oil. IR ν_{max} ($CHCl_3$): 3385 (br), 2957, 2928, 2849, 1460, 1375 cm^{-1}; ^1H NMR (δ, $CDCl_3$): 8.09 (1H, br s, -OOH), 5.49 (1H, t, *J*=6.9 Hz), 5.01 (1H, dd, *J*=8.5, 3.4 Hz), 3.83 (1H, dd, *J*=11.2, 8.5 Hz), 3.59 (1H, dd, *J*=11.2, 3.4 Hz), 2.20–1.90 (2H, m), 1.69 (3H, s), 1.52 (1H, m), 0.87 (9H, d, *J*=6.6 Hz), 0.84 (3H, d, *J*=6.6 Hz) – see Table 2 for full assignments; ^{13}C NMR: see Table 1; Electrospray-MS: *m*/*z* (rel. int.) 351.6 [M^+ ($C_{20}H_{40}O_3$) + Na^+].

Compound **9:** Oil. IR ν_{max} ($CHCl_3$): 3587, 3393 (br), 2928, 2868, 1464, 1377 cm^{-1}; Electrospray-MS: *m*/*z* (rel. int.) 351.5 [M^+ ($C_{20}H_{40}O_3$) + Na^+]. *Compound* **9a** (*trans*): NMR assignments made as a mixture with **9b:** ^1H NMR (δ, $CDCl_3$): 5.66 (1H, d, *J*=5.4 Hz), 3.00 (1H, br s, -OH), 2.57 (1H, dd, *J*=13.0, 5.4 Hz), 2.37 (1H, d, *J*=13.0 Hz), 1.52 (1H, m), 0.87 (6H, d, *J*=6.3 Hz), 0.85 (3H, d, *J*=5.8 Hz), 0.84 (3H, d, *J*=6.4 Hz) – see Table 2 for full assignments; ^{13}C NMR: see Table 1; *Compound* **9b** (*cis*): NMR assignments made as a mixture with **9a:** ^1H NMR (δ, $CDCl_3$): 5.64 (1H, d, *J*=7.6 Hz), 3.00 (1H, br s, -OH), 2.68 (1H, ddd, *J*=13.0, 7.6, 1.0 Hz), 2.31 (1H, dd, *J*=13.0, 1.3 Hz), 1.52 (1H, m), 0.87 (6H, d, *J*=6.3 Hz), 0.85 (3H, d, *J*=5.8 Hz), 0.84 (3H, d, *J*=6.4 Hz), see Table 2 for full assignments; ^{13}C NMR: see Table 1.

Compound **11:** Oil. IR ν_{max} ($CHCl_3$): 3491 (br), 2955, 2928, 2868, 1718, 1678, 1460, 1375 cm^{-1}; ^1H NMR (δ, $CDCl_3$): 5.94 (1H, s), 5.83 (1H, dd, *J*=1.3, 1.3 Hz), 4.57 (2H, d, *J*=4.7 Hz), 3.30 (1H, t, *J*=4.7 Hz, -OH), 2.35–2.15 (2H, m), 1.52 (1H, m), 0.86 (6H, d, *J*=6.6 Hz), 0.85 (3H, d, *J*=6.6 Hz), 0.84 (3H, d, *J*=6.7 Hz), see Table 2 for full assignments; ^{13}C NMR: see Table 1; HREIMS: *m*/*z* (rel. int.) 310.2873 [M^+, $C_{20}H_{38}O_2$, requires 310.2872] (10), 292 (10), 279 (35), 261 (28), 125 (70), 111 (100).

Compound **12:** Oil. IR ν_{max} ($CHCl_3$): 3580, 3420 (br), 2955, 2930, 2870, 1464, 1375 cm^{-1}; ^1H NMR (δ, $CDCl_3$): 5.13 (1H, s), 4.97 (1H, s), 4.20 (1H, br), 3.70 (1H, d, *J*=10.0 Hz), 3.54 (1H, dd, *J*=10.0, 6.4 Hz), 2.28 (1H, br s, -OH), 2.15–1.90 (2H, m), 1.70 (1H, br s, -OH), 1.52 (1H, m), 0.87 (6H, d, *J*=6.6 Hz), 0.86 (3H, d, *J*=6.7 Hz), 0.84 (3H, d, *J*=6.0 Hz), see Table 2 for full assignments; ^{13}C NMR: see Table 1; HREIMS: *m*/*z* (rel. int.) 312.3019 [M^+, $C_{20}H_{40}O_2$, requires 312.3028] (8), 294 (4), 281 (20), 276 (6), 263 (19), 125 (65), 111 (100).

*Reduction of phytene-1-ol-2-hydroperoxide(**7**) to phytene-1,2-diol* **(11):** To a solution of **7** (22 mg) in MeOH (0.85 ml) was added PPh_3 (19 mg) and the reaction mixture was stirred at room temperature for 2 h. After completion, solvent was removed on a rotatry evaporator to yield a crude product (43 mg) which consisted mainly of **11** and triphenylphosphine oxide. This was purified by column chromatography (35% EtOAc/*n*-hexane) yielding **11** (16 mg, 77%; R_f 0.38) with spectral properties identical to those described for phytene-1,2-diol obtained directly from photo-oxygenation.

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