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OXYGENATED NEROLIDOL DERIVATIVES FROM *ARTEMISIA ALBA*

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Key Word Index—*Artemisia alba*; Compositae; acyclic sesquiterpenoids; nerolidol derivatives; hydroperoxides.

Abstract—From the aerial parts of *Artemisia alba* of Calabrian origin, five oxygenated nerolidol derivatives were isolated, two of them bearing hydroperoxyl groups. Structures were elucidated by spectral data and chemical reactions. Acetylation of the major hydroperoxyl constituent afforded a *tris*-nor aldehydic derivative as a result of loss of acetone from an unstable intermediate perester. An internally consistent set of ^{13}C NMR assignments for the natural products and some derivatives is presented.

INTRODUCTION

Artemisia alba Turra (= *A. camphorata* Vill.) is a plant of uncertain taxonomic position, placed by some authors in the section *Abrotanum* Bess and by others in the section *Absinthium* DC. of the genus *Artemisia* [1]. The plant shows a noteworthy infraspecific morphological variability and several varieties have been recognized [2].

Previous investigation on the non-volatile constituents of *A. alba* revealed the presence of santonin in the aerial parts [3] and one sesquiterpene coumarin ether in the roots [1]. We have now investigated for the first time the sesquiterpene constituents of the aerial parts of *A. alba* of Calabrian origin, which displayed an unexpected sesquiterpenoid pattern. Sesquiterpene lactones, previously found in this species [3], were absent whereas large amounts of oxygenated nerolidol derivatives were isolated. We present here the structural elucidation of five compounds of this type, constituting alone almost 2% of the plant material we examined.

RESULTS AND DISCUSSION

The less polar compound (**1a**, $C_{15}H_{26}O_2$) was an acyclic sesquiterpene diol, as shown by its ^{13}C NMR spectrum (Table 1), which revealed the presence of three double bonds, accounting for all the unsaturation degrees present in the molecular formula. Double resonance experiments allowed assignments of all the protons (Table 2), and led to structure **1a** for this compound. The stereochemistry at the trisubstituted C-6–C-7 double bond was established from the ^{13}C NMR chemical shift of Me-7, which resonated at δ16.90, a position typical of a methyl group on a *trans*-double bond [4].

Acetylation of **1a** with acetic anhydride–pyridine gave

Table 1. ^{13}C NMR data for compounds **1a**–**3c** (25.18 MHz, $CDCl_3$, TMS int standard)

	1a	**1b**	**2a**	**2b**	**2c**	**3b**	**3c**
C-1	112.46 (*t*)	111.91 (*t*)	112.69 (*t*)	112.46 (*t*)	111.80 (*t*)	112.46 (*t*)	111.75 (*t*)
C-2	144.04 (*d*)	144.35 (*d*)	143.72 (*d*)	143.86 (*d*)	144.10 (*d*)	143.86 (*d*)	144.30 (*d*)
C-3	73.90 (*s*)	72.39 (*s*)	74 26 (*s*)	74.00 (*s*)	72.31 (*s*)	74.00 (*s*)	72.24 (*s*)
C-4	46.92 (*t*)	47.04 (*t*)	46.89 (*t*)	46.98 (*t*)	46.85 (*t*)	46.98 (*t*)	46.85 (*t*)
C-5	66.90 (*d*)	69.53 (*d*)	67.06 (*d*)	66.97 (*d*)	69 37 (*d*)	66.97 (*d*)	69 30 (*d*)
C-6	127.80 (*d*)	123.98 (*d*)	128 18 (*d*)	127.82 (*d*)	123.75 (*d*)	128.26 (*d*)	124.50 (*d*)
C-7	136.94 (*s*)	139 94 (*s*)	136.17 (*s*)	136.86 (*s*)	138.60 (*s*)	137.01 (*s*)	138.50 (*s*)
C-8	39.22 (*t*)	39.45 (*t*)	42.14 (*t*)	42.01 (*t*)	42.00 (*t*)	35.28 (*t*)	35.07 (*t*)
C-9	26 08 (*t*)	26.24 (*t*)	128 27 (*d*)	124.11 (*d*)	124.40 (*d*)	32.99 (*t*)	30.55 (*t*)
C-10	123.77 (*d*)	123.75 (*d*)	135.78 (*d*)	139.89 (*d*)	140.17 (*d*)	75.10 (*d*)	76.54 (*d*)
C-11	132.04 (*s*)	131.67 (*s*)	81.81 (*s*)	70.80 (*s*)	70.47 (*s*)	147.23 (*s*)	142.80 (*s*)
C-12	25.44 (*q*)	25.63 (*q*)	29.93 (*q*)	29.96 (*q*)	29.80 (*s*)	110.98 (*t*)	112.70 (*t*)
C-13	29.60 (*q*)	28.51 (*q*)	29.93 (*q*)	29.96 (*q*)	28.46 (*q*)	29.25 (*q*)	28.37 (*q*)
C-14	16.90 (*q*)	16.83 (*q*)	16.63 (*q*)	16.52 (*q*)	16.90 (*q*)	16.52 (*q*)	16.77 (*q*)
C-15	17.98 (*q*)	17.66 (*q*)	29.93 (*q*)	29.96 (*q*)	29.80 (*q*)	17.61 (*q*)	18.07 (*q*)
OAc	—	170.05 (*s*)	—	—	169.93 (*s*)	—	169.84 (*s*)
	—	21.38 (*q*)	—	—	21.37 (*q*)	—	21.33 (*q*); 21.08 (*q*)

Table 2. ^{1}H NMR data for compounds **1a–4** (200 MHz, $CDCl_3$, TMS as int. standard)

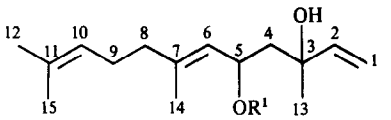
	1a	**1b**	**2a**	**2b**	**2c**	**3a**	**3b**	**3c**	**4**
H-1a	5.35 (*dd*)	5.22 (*dd*)	5.33 (*dd*)	5.34 (*dd*)	5.18 (*dd*)	5.33 (*dd*)	5.34 (*dd*)	5.18 (*dd*)	5.23 (*dd*)
H-1b	5.13 (*dd*)	5.05 (*dd*)	5.13 (*dd*)	5.16 (*dd*)	4.98 (*dd*)	5.13 (*dd*)	5.15 (*dd*)	4.99 (*dd*)	5.07 (*dd*)
H-2	5.89 (*dd*)	5.87 (*dd*)	5.88 (*dd*)	5.90 (*dd*)	5.82 (*dd*)	5.88 (*dd*)	5.90 (*dd*)	5.83 (*dd*)	5.88 (*dd*)
H-4a	1.80 (*dd*)	2.00 (*dd*)	1.80 (*dd*)	1.80 (*dd*)	1.95 (*dd*)	†	†	†	1.96 (*dd*)
H-4b	1.50 *dd*)	1.70 (*dd*)	1.47 (*dd*)	1.49 (*dd*)	1.66 (*dd*)	†	†	†	1.71 (*dd*)
H-5	4.60 (*dq*)	5.59 (*dq*)	4.60 (*dq*)	4.60 (*qd*)	5.58 (*dq*)	4.60 (*dd*)	4.62 (*dd*)	5.53 (*dd*)	5.56 (*dq*)
H-6	5.18 (*dq*)	5.07 (*dq*)	5.19 (*dq*)	5.20 (*dq*)	5.06 (*dq*)	5.19 (*dq*)	5.20 (*dq*)	5.06 (*dq*)	5.09 (*dq*)
H-8a	*ca* 2.05 (*m*)	*ca* 2.05 (*m*)	2.66 (*br d*)	2.65 (*br d*)	2.60 (*br d*)	‡	‡	‡	2.28 (*br t*)
H-8b						‡	‡	‡	
H-9a			—	—	—	†	†	†	
H-9b			5.57 (*m*)	5.58 (*dd*)	5.45 (*dd*)	†	†	†	2.52 (*br td*)
H-10	5.05 (*tq*)	5.05 (*tq*)		5.62 (*d*)	5.59 (*dd*)	4.20 (*br t*)	3.99 (*br t*)	5.50 (*br t*)	9.73 (*t*)
H-12	1.57 (*br s*)	1.57 (*br s*)	1.27 (*s*)*	1.24 (*s*)*	1.22 (*s*)*	4.95 (*br s*)	4.91 (*br s*); 4.82 (*br t*)	4.87 (*br s*); 4.82 (*br t*)	—
H-13	1.24 (*s*)	1.25 (*s*)	1.22 (*s*)*	1.22 (*s*)*	1.23 (*s*)*	1.22 (*s*)	1.22 (*s*)	1.21 (*s*)	1.23 (*s*)
H-14	1.65 (*br d*)	1.70 (*br d*)	1.60 (*br d*)	1.65 (*br d*)	1.62 (*br d*)	1.60 (*br d*)	1.65 (*br d*)	1.64 (*br d*)	1.68 (*br d*)
H-15	1.60 *br d*)	1.65 (*br d*)	1.27 (*s*)*	1.26 (*s*)*	1.22 (*s*)*	1.60 (*br s*)	1.62 (*br s*)	1.64 (*br s*)	—
OH	3.90 (*br s*)	2.45 (*br s*)	2.90 (*br s*)	3.10 (*br*)	—	†	†	†	†
	2.85 (*br s*)	—	—		—	†	†	—	†
OOH	—	—	8.95 (*br s*)	—	—	8.95 (*br s*)	—	—	—
OAc	—	1.98 (*s*)			1.96 (*s*)	—	—	2.00 (*s*); 1.95 (*s*)	1.99 (*s*)

Most coupling constants (J) for the segment C-1–C-6 were virtually the same for compounds **1, 2a, 2b, 3a** and **3b** and for compounds **1b, 2c, 3c** and **4**. Those for **1a** and **1b** are given (in Hz) as representative. For **1a**: $J_{1a,2} = 18.0$; $J_{1a,1b} = 2.0$; $J_{1b,2} = 11.0$; $J_{4a,5} = 11.0$; $J_{4b,5} = 3.1$; $J_{4a,4b} = 15.1$; $J_{5,6} = 11.0$; $J_{6,14} = 1.5$ For **1b**: $J_{1a,2} = 18.0$; $J_{1a,1b} = 2.0$; $J_{1b,2} = 11.0$; $J_{4a,5} = 8.0$; $J_{4a,4b} = 15.1$; $J_{5,6} = 8.0$; $J_{6,14} = 1.5$. The other coupling constants were. For **1a** and **1b**: $J_{9a,10} = J_{9b,10} = 8.0$; $J_{10,15} = 1.2$. For **2a–2c**: $J_{8a,9} = J_{8b,9} = 6.2$; $J_{9,10} = 15.2$. For **3a–3c**. $J_{9a,10} = J_{9b,10} = 6.1$. For **4**: $J_{8,9} = 7.0$; $J_{9,10} = 1.6$

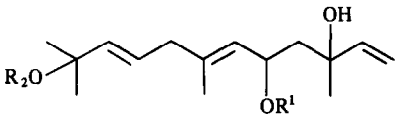
*Signals with the same sign in the same column are interchangeable.

†The signal of these protons could not be identified owing to overlapping or to the presence of complex non-first-order patterns.

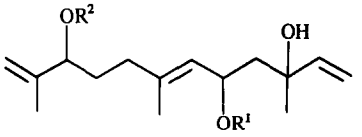
	R^1	R^2
1a	H	
1b	Ac	



2a	H	OH
2b	H	H
2c	Ac	H



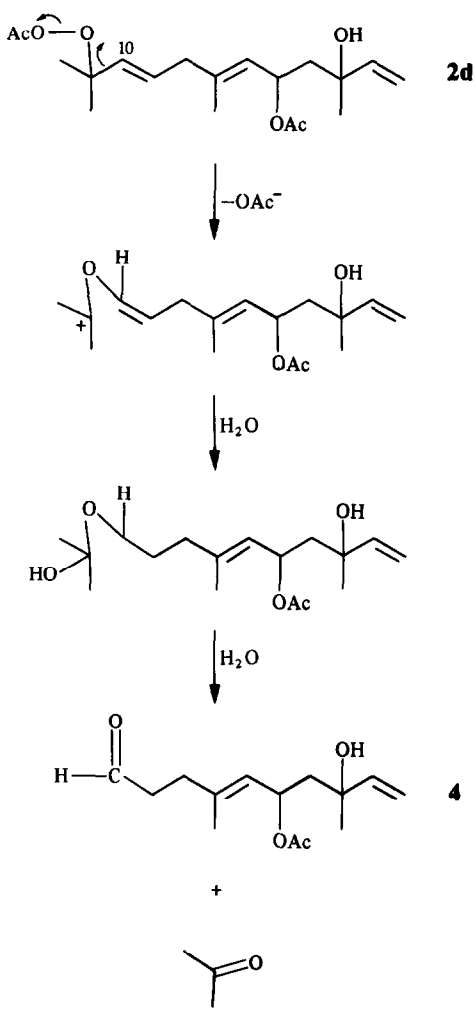
3a	H	OH
3b	H	H
3c	Ac	Ac



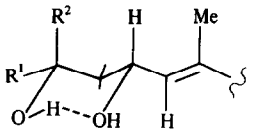
the monoacetate, **1b**. Both **1a** and **1b** had previously been isolated from the Brazilian plant *Calea teucrifolia* (Gardn.) Baker [5]. The other nerolidol derivatives isolated are new compounds. Further elution of the column gave two endo/exo isomeric mixtures of hydroperoxides (**2a** and **3a**) and alcohols (**2b** and **3b**). In these mixtures the ratio between the endo and the exo isomer was different (*ca* 4:1 for the hydroperoxides and 2:1 for the alcohols, as judged by ^{1}H NMR). Only the major constituent of each mixture could be obtained pure by CC. Acetylation of the mixture of alcohols **2b** and **3b**, however, afforded a mixture of the monoacetate, **2c**, and the diacetate, **3c**, which could easily be separated. Reduction of the mixture of hydroperoxides **2a** and **3a** with triphenylphosphine (TPP) gave a mixture of the alcohols **2b** and **3b**. Acetylation and separation by CC yielded the acetyl derivatives **2c** and **3c**, identical ($[\alpha]_D$, ^{1}H NMR) with the products obtained from natural **2b** and **3b**.

Comparison of the ^{1}H NMR and ^{13}C NMR spectra of compounds **2a**, **2b**, **3a** and **3b** with **1a**, showed that they were the products of the photo-oxygenative modification of the C-10–C-11 double bond. To confirm this, **1a** was subjected to photo-oxygenation. A mixture of hydroperoxides, resulting mainly from attack at the C-10–C-11 double bond, was obtained. After reduction of this mixture followed by acetylation, **2c** and **3c** were obtained. Compound **3c** obtained in this way was a mixture (*ca* 3:1) of diastereomers at C-10, in which the natural compound was the major constituent. Treatment of the hydroperoxide, **2a**, with acetic anhydride–pyridine afforded the *tris*-nor aldehydic derivative, **4**, as a result of loss of acetone from the unstable intermediate perester, **2d**. A possible mechanism for the loss of acetone, analogous to the Baeyer–Villiger rearrangement and involving anionotropic migration of the olefinic C-10, is depicted in Scheme 1.

The stereochemistry at the disubstituted C-9–C-10 double bond in compounds **2a**–**2c** was established as *trans* from ^{1}H NMR and ^{13}C NMR data. In these compounds the olefinic vicinal coupling was in fact 15.2 Hz and the methylene carbon allylic to the C-9–C-10 double bond (C-

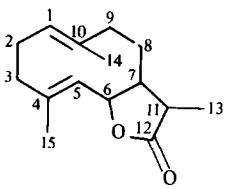


Scheme 1. Possible mechanism of the fragmentation of **2d**.



A

R^1 = Me, R^2 = CH=CH$_2$



B

8) resonated around at *ca* δ40 (Table 1). This downfield value is characteristic of allylic methylenes lacking γ-*gauche*-type shielding interactions with the other substituents of the double bond, whereas upfield values should be expected for methylene groups experiencing interactions of this type [6] [cf. the C-4 resonance of geraniol (δ39.7) and nerol (δ32.2) [7] as well as the values reported for several polyprenoids [8]].

The stereochemistry at C-3 in the nerolidol derivatives isolated is not known; thus, the configuration at C-5 could not be established on the basis of spectral data alone. However, from the conformational point of view, in all these compounds an intramolecular hydrogen bonding between OH-3 and OH-5 is present (^{1}H NMR and IR evidence). This locks the segment C-3–C-5 in the A conformation, which can explain the presence of high values of $J_{5,6}$ and $J_{4a,5}$, characteristic of an approximatively antiperiplanar relationship between these protons (Table 2). Natural (−)-nerolidol has an S-configuration at C-3 [9]. If the same configuration at this centre is assumed for compounds **1**–**3**, then the observed values of $J_{5,6}$ and $J_{4a,5}$ require an *R*-configuration at C-5. The segment C-7–C-12 of compounds **3a**–**3c** is mobile and, therefore, no stereochemical information could be derived from the values of $J_{9a,b/10}$.

The ^{13}C NMR spectra of the nerolidol derivatives from *A. alba* and their derivatives are presented in Table 1. It is worth noting that acetylation of the OH-5 group resulted in the expected [10] β-upfield and γ-downfield shifts on the olefinic C-6 and C-7, whereas these effects were not observed on C-4 and C-3, the latter being moved upfield. These anomalies might result from conformational differences in the segment C-3–C-5 between the compounds with a free OH-5 group and their acetates. In these compounds, owing to the poor acceptor ability of the electronegative alkoxyl oxygen of the ester group, the hydrogen bonding presumably involves the carbonyl oxygen of the ester and, therefore, hydrogen bonding of different geometry (eight- vs six-membered) and nature is obtained. It is known [11] that ^{13}C NMR signal positions can be strongly affected by hydrogen bonding and the influence of this on the carbons of fragment C-3–C-5 might not be the same for the alcohols and their acetates. Conformational changes upon acetylation of the OH-5 group are also evident from the different values of $J_{4a,5}$ and $J_{4a,5}$ in the alcohols and their acetates, as well as from the different chemical shift of the protons of the vinyl group in compounds of these two classes.

The resonances of the olefinic C-9 and C-10 in compounds **2a**–**2c** were assigned on the basis of the characteristic β-downfield and γ-upfield shifts observed upon reduction of allylic hydroperoxides [12]. The very large difference (*ca* δ13) between the methylene carbons of the diallylic system C-7–C-10 in compounds **1a** and **1b** is worth noting and is reminiscent of an analogous difference observed in germacrolides between the methylenes of the diallylic system C-1–C-4 [13]. In compounds **1a** and **1b**, the higher field resonance was assigned to C-9 on account of the presence, in the latter, of a γ-*gauche*-type interaction with C-15 [6]. On these bases, the higher field resonance of the diallylic methylenes in germacrolides should be assigned to C-2 (γ-*gauche*-type interaction with C-14, B).

Oxygenated nerolidol derivatives were first isolated from caparrapì oil (from *Ocotea caparrapí*, family *Lauraceae*) [14]. In the last few years, however, several new derivatives have been discovered in the Compositae co-occurring, generally, in small amounts with other structural types of sesquiterpenoids (see, e.g. ref. [5]). *Artemisia alba* of Calabrian origin contains instead oxygenated nerolidol derivatives as the only non-volatile sesquiterpenes and appears to be the richest source of compounds of this type described so far.

EXPERIMENTAL

Silica gel 60 (70–230 mesh) was used for CC; silica gel precoated plates were used for prep. TLC (thickness: 2 mm).

Plant material. Artemisia alba was collected near the Monte Pollino (Cs) and identified by Domenico Pontillo (Botanical Garden, University of Calabria). A voucher specimen is held in the herbarium of the University of Calabria, Arcavacata di Rende (Cs, Italy)

Isolation of compounds. Non-woody aerial parts (leaves and flowers, 980 g) were ground and extracted with Me_2CO at room temp. The black residue obtained was purified by standard procedures [15] to give 32 g of a black syrup, part of which (16 g) was chromatographed on a silica gel column (500 g) eluted with $CHCl_3$ containing increasing amounts of MeOH and fractions (300 ml) were collected. Fractions 14–20 ($CHCl_3$) gave 1 g **1a** (yield: 0.2%); fractions 50–56 ($CHCl_3$–MeOH, 95:5) gave 4 g of a mixture of **2a** and **3a** (yield: 0.8%), fractions 59–75 ($CHCl_3$–MeOH, 95:5) gave 5 g (yield 1%) of a mixture of **2b** and **3b**. Further separation of fractions 50–56 and 59–75 [silica gel, petrol (bp. 50–70°)–EtOAc, 3:2] gave pure **2a** and **3a**.

(E)-3,7,11-*Trimethyl*-1,6,10-*dodecatriene*-3,5-*diol* (**1a**). Colourless oil; $[\alpha]_D^{25}$ +46° ($CHCl_3$; *c* 0.8); IR $\nu_{max}^{liquid\ film}$ cm^{-1}: 3320, 3090, 1450, 1000, 940, 930, EIMS 70 eV, *m/z* (rel. int.): no molecular ion, 223 $[M-15]^+$ (0.8), 220 $[M-18]^+$ (2), 123 (75), 69 (100).

Acetylation of **1a**. A 100 mg sample of **1a** was dissolved in 1 ml C_5H_5N and 2 ml Ac_2O were added. After standing overnight, ice was added and the reaction mixture was extracted with $CHCl_3$ The organic phase was washed with 5% aq. $NaHCO_3$, H_2O, diluted HCl, H_2O and then dried ($MgSO_4$). Evaporation of the solvent gave 104 mg of a yellow oil. Purification by prep. TLC ($CHCl_3$–Me_2CO, 6:1) gave 90 mg **1b** as a colourless oil; $[\alpha]_D^{25}$ +23° ($CHCl_3$; *c* 1.5); IR $\nu_{max}^{liquid\ film}$ cm^{-1}: 3400, 3090, 1740, 1250, 950, 820; EIMS 70 eV, *m/z* (rel. int.): 280 $[M]^+$ (0.8), 220 $[M-60]^+$ (4), 69 (100).

(E,E)-11-*Hydroperoxy*-3,7,11-*trimethyl*-1,6,9-*dodecatrien*-3,5-*diol* (**2a**). Colourless oil; $[\alpha]_D^{25}$ +31° ($CHCl_3$; *c* 1.1); IR $\nu_{max}^{liquid\ film}$ cm^{-1}: 3400, 3090, 1450, 1300, 1000, 925; EIMS 70 eV, *m/z* (rel. int.): no molecular ion, 253 $[M-OH]^+$ (1), 252 $[M-H_2O]^+$ (3), 235 $[M-OOH]^+$ (3), 43 (100).

(E,E)-3,7,11-*Trimethyl*-1,6,9-*dodecatriene*-3,5,11-*triol* (**2b**). Colourless oil; $[\alpha]_D^{25}$ +43° ($CHCl_3$; *c* 0.9); IR $\nu_{max}^{liquid\ film}$ cm^{-1}: 3400, 3090, 1450, 1380, 1250, 950; EIMS 70 eV, *m/z* (rel. int.): 254 $[M]^+$ (0.5), 239 $[M-15]^+$ (1), 71 (100).

Reduction of **2a** A soln of **2a** (200 mg, 0.75 mM) in MeOH (10 ml) was treated with TPP (210 mg, 0.80 mM). After stirring for 2 hr at room temp, the soln was evaporated to dryness and the residue was purified by prep. TLC ($CHCl_3$–Me_2CO, 6:1) to give 140 mg **2b**, identical (^1H NMR, IR) with the natural product.

Acetylation of the mixture of **2b** *and* **3b**. A mixture of natural **2b** and **3b** (400 mg) was acetylated as described for **1a**, to give 390 mg of a mixture of the diacetates **2c** and **3c**. The latter was separated on a short silica gel column (10 g) eluted with petrol–EtOAc, 5:1 to yield pure **2c** (190 mg) and **3c** (100 mg). Compound **2c** was a colourless oil; $[\alpha]_D^{25}$ +8.2° ($CHCl_3$; *c* 1); IR $\nu_{max}^{liquid\ film}$ cm^{-1}: 3400, 3090, 1740, 1240; EIMS 70 eV, *m/z* (rel int.): no molecular ion, 236 $[M-60]^+$ (5), 218 $[M-60-18]^+$ (9), 43 (100). Compound **3c** was a colourless oil; $[\alpha]_D^{25}$ +4.4° ($CHCl_3$; *c* 0.8); IR $\nu_{max}^{liquid\ film}$ cm^{-1}: 3400, 3090, 1740, 1240; EIMS 70 eV, *m/z* (rel. int.): no molecular ion, 278 $[M-60]^+$ (2), 218 $[M-60-60]^+$ (4), 43 (100). Acetylation of a mixture of **2b** and **3b**, obtained from reduction of the mixture of **2a** and **3a**, gave **2c** and **3c** identical ($[\alpha]_D$, ^1H NMR) with the products obtained from natural **2b** and **3b**.

Photo-oxygenation of **1a**. A soln of **1a** (200 mg) dissolved in MeOH (15 ml) containing methylene blue (15 mg) was irradiated with a 700 W halogen lamp together with the introduction of O_2 and cooling. After 1 hr all the **1a** had reacted and the reaction was worked-up by evaporating the solvent. The residue, dissolved in CH_2Cl_2, was passed through a short column of silica gel to remove the dye. Evaporation of the solvent gave a brownish oil which was purified by prep. TLC ($CHCl_3$–Me_2CO, 6:1) to yield a pale yellow oil (175 mg) which, when analysed by ^1H NMR, was found to contain mainly compound **2a**. Reduction with TPP as described previously, and acetylation gave a mixture of acetates, which was separated by CC to give 60 mg **2c** and 18 mg **3c**.

Fragmentation of the hydroperoxide, **2a**. A sample of **2a** (150 mg) was treated with Ac_2O–C_5H_5N as described for **1a**. Separation of the reaction mixture (80 mg) by CC (silica gel, petrol–EtOAc, 5:1) afforded 22 mg **4** as a pale yellow oil; $[\alpha]_D^{25}$ +13° ($CHCl_3$; *c* 0.9); IR $\nu_{max}^{liquid\ film}$ cm^{-1}: 3400, 3090, 2860, 2730, 1740, 1240.

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