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NEW OXYGENATED EUDESMANOLIDES FROM *ARTEMISIA HERBA-ALBA*

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Abstract- The aerial parts of *Artemisia herba-alba* Asso subsp. *valentina* Lam. (Asteraceae) yielded the new eudesmanolides **1-11** and the new sesquiterpene-monoterpene adducts **12-13**. The absolute configuration of compound **6** was confirmed with the aid of X-ray diffraction analysis. Some aspects of the thermal and photochemical reactivity of 2,4-cyclohexadienones are discussed.

Sesquiterpene lactones are the most characteristic secondary metabolites of many species of the large genus *Artemisia* (Compositae, tribe Anthemideae).[1,2] Among these, *Artemisia herba-alba* Asso subsp. *valentina* Lam. (= *A. valentina* Lam.) has formerly been shown to contain lactones with eudesmane framework.[3,4] We have now investigated two chemotypes of this species growing in different geographical locations. In addition to previously described compounds,[3,4] we have found eleven new oxygenated eudesmanolides **1-11** and two new sesquiterpene-monoterpene adducts **12-13**. The structures of the new compounds have been established, as described below, with the aid of spectral techniques, X-ray diffraction analysis and chemical reactions.

Compound **1** has the molecular formula $C_{15}H_{18}O_3$. The IR spectrum of the compound shows carbonyl bands characteristic of γ-lactone and conjugated ketone groups (1780, 1670, 1640 cm^{-1}), and the UV spectrum displays a strong band at 319 nm, indicating a dienone moiety. The ^1H NMR spectrum (Table 1) is qualitatively very similar to that of β-santonin,[5,6] with only slight differences in some chemical shift values. In view of the much longer wavelength of the UV band maximum of the compound under study, the isomeric structure **1** (Scheme 1) appears reasonable. The hydrogen connectivities, determined by decoupling experiments, are in complete accord with the proposed structure. The ^{13}C NMR spectrum (Table 4) gives added evidence for the proposed structure as it shows the ketone carbonyl peak at 204.50 ppm, in the range expected for a 2,4-cyclohexadienone.[7,8] Final chemical confirmation of the structure was given by catalytic hydrogenation of **1** to the known eudesmanolide 11-epitaurin[4] and by photooxygenation to **6** (see below).

The ^1H NMR spectra of compounds **2-4** clearly indicate that their structures are similar to that of **1** (see Tables 1 and 4). The most significant differences between the NMR spectra of **1** and **2** are the signals of H-11 and C-13 (eudesmane numbering system, see Scheme 1), which show[5,6,8] that both compounds are epimeric at C-11 (Tables 1 and 4). This was confirmed by the observation of an NOE in **2** between the signals of H-7 and H-13, an effect which is absent in **1**. Furthermore, catalytic hydrogenation of **2** yielded

taurin.[9] Although it is new as a natural product, compound **2** has been obtained earlier in the acid-catalyzed dehydration of vulgarin[10] and as a synthetic intermediate.[11] As regards compounds **3** and **4**, the molecular formula $C_{15}H_{18}O_4$, the IR hydroxyl bands, the position and pattern of the ^1H signal at about 4.1 ppm, and the ^{13}C methine signal at ca. 69 ppm indicate that they are 8α-hydroxy derivatives of **1** and **2**, respectively. Decoupling and NOE experiments supported this conclusion and additionally confirmed the configurations of the other stereogenic centres of these two molecules. In the case of compound **4**, additional chemical evidence for the proposed structure was its catalytic hydrogenation to the known eudesmanolide 8α-hydroxytaurin.[12]

Table 1. ^1H NMR data of compounds **1-5a**[a].

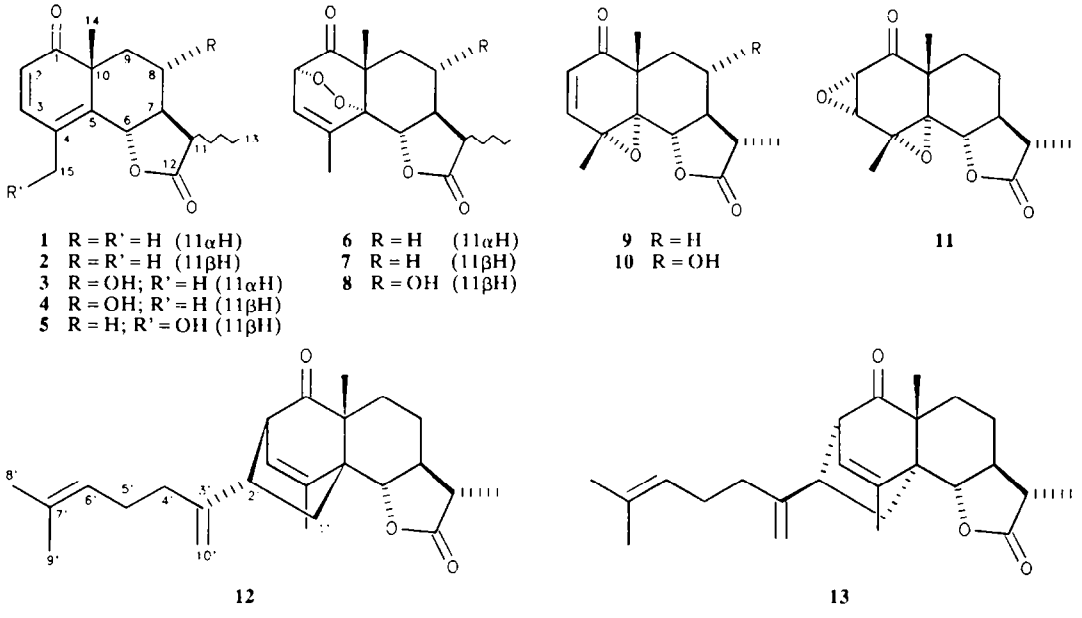
Compound	**1**	**2**	**3**	**4**	**5**[b]	**5a**[c]
Hydrogen						
H-2	6.01 br *d* (10)	6.03 br *d* (10)	6.02 br *d* (10)	6.02 br *d* (10)	6.29 br *d* (10)	6.12 br *d* (10)
H-3	6.82 *d* (10)	6.82 *d* (10)	6.84 *d* (10)	6.84 *d* (10)	7.69 *d* (10)	7.04 *d* (10)
H-6	4.90 br *dq* (12; 1.5)	4.71 br *dq* (11.5; 2)	4.93 br *dq* (12; 1.5)	4.72 br *dq* (12; 1.5)	4.87 br *d* (11)	4.77 br *d* (11.5)
H-7	2.23 *dddd* (13; 12; 7.5; 3.5)	1.78 *dddd* (13; 12; 11.5; 3)	2.28 *ddd* (12; 11; 7.5)	1.88 *ddd* (12; 12; 11)	1.60 *m*	1.86 *dddd* (12; 12; 11.5; 3)
H-8α	1.81 *dddd* (13; 5; 3.5; 3)	2.00 *dddd* (14; 4.5; 3.5; 3)	—	—	1.72 *dddd* (12; 4; 3; 3)	2.04 *dddd* (13; 4.5; 3; 2.5)
H-8β	1.71 *dddd* (13; 13; 13; 4)	1.64 *dddd* (14; 14; 13; 3.5)	4.14 *ddd* (11; 11; 4.5)	4.11 *ddd* (11; 11; 4.5)	1.60 *m*	1.69 *dddd* (13; 13; 12; 3.5)
H-9α	1.48 *ddd* (13; 13; 5)	1.48 *ddd* (14; 14; 4.5)	1.44 *dd* (13.5; 11)	1.46 *dd* (13.5; 11)	1.49 *ddd* (13; 13; 4)	1.57 *ddd* (13.5; 13; 4.5)
H-9β	2.19 *ddd* (13; 4; 3)	2.20 *ddd* (14; 3.5; 3.5)	2.50 *dd* (13.5; 4.5)	2.47 *dd* (13.5; 4.5)	2.26 *ddd* (13; 3; 3)	2.26 *ddd* (13.5; 3.5; 2.5)
H-11	2.68 *dq* (7.5; 7.5)	2.36 *dq* (12; 7)	2.90 *dq* (7.5; 7.5)	2.61 *dq* (12; 7)	2.40 *dq* (12; 7)	2.39 *dq* (12; 7)
H-13	1.22 *d* (7.5)	1.24 *d* (7)	1.36 *d* (7.5)	1.41 *d* (7)	1.10 *d* (7)	1.27 *d* (7)
H-14	1.30 *s*	1.32 *s*	1.33 *s*	1.34 *s*	1.31 *s*	1.38 *s*
H-15	2.14 *d* (1.5)	2.15 *d* (2)	2.17 *d* (1.5)	2.17 *d* (1.5)	4.99 br *d* (14) 4.95 br *d* (14)	5.15 br *d* (12.5) 5.06 br *d* (12.5)

[a] At 400 MHz in $CDCl_3$ (25°). Coupling constants (in Hertz) are given in parentheses after the chemical shifts.
[b] In pyridine-d_5. [c] OAc: 2.07 *s*.

The spectroscopic data of compound **5** are reminiscent of those observed in lactone **4**. The hydroxyl, γ-lactone and conjugated ketone IR bands, and the UV absorption maximum at 319 nm, point to a closely related structure. The absence of both the characteristic signal at about δ 4.1 and the olefinic methyl H-15, together with the appearance of an AB system at δ 4.99 and 4.85 (J = 14 Hz) in the ^1H NMR spectrum (Table 1), and a methylene peak at 59.76 in the ^{13}C NMR spectrum (Table 4) clearly point to the existence of an OH group at C-15. Extensive decoupling experiments in **5** and its acetate **5a** permitted the establishment of the hydrogen connectivities, which are in accord with the proposed structure.

Compound **6** has the molecular formula $C_{15}H_{18}O_5$. The IR spectrum indicates the presence of γ-lactone (1794 cm^{-1}) and nonconjugated ketone (1733 cm^{-1}) carbonyl groups. While the ^1H NMR spectrum of **6** (Table 2) is very similar in the high-field range to that of **1**, some significant differences are visible above δ 4 ppm. A double quadruplet at δ 6.36 (J = 6.5, 1.5 Hz) replaces the two doublets observed in the olefinic range of the spectrum of **1**. Furthermore, a new signal (δ 4.54, d, J = 6.5 Hz) appears in the immediate

vicinity of the lactone proton signal. Decoupling experiments established that this signal is coupled with the olefinic signal at δ 6.36, which is in turn coupled with a methyl doublet (J = 1.5 Hz) at δ 2.15. This suggests the existence of the fragment C-CH(OR)-CH = C(CH_3)-C. The sharp doublet at δ 4.52 (J = 12 Hz) has therefore been assigned to the lactone proton. In view of these data, structure **6**, which contains a peroxide bridge between H-2 and H-5, has been proposed for the compound in question. The ^{13}C NMR spectral data (Table 4) are in good agreement with this proposal. The stereochemistry of the peroxide bridge was first deduced from NOE measurements. For instance, a marked NOE was observed between the signals of H-6 and H-15. Inspection of molecular models revealed that this is to be expected only with an α configuration of the peroxide bridge. Definitive confirmation of the structure was given by an X-ray diffraction analysis (see Figure 1 and data in Table 5). Structure **6** corresponds to a cycloaddition product of dienone **1** with molecular oxygen. Indeed, photooxygenation of the latter compound yielded **6**, thus additionally serving to confirm the stereostructure of **1**.



1 R = R' = H (11αH)
2 R = R' = H (11βH)
3 R = OH; R' = H (11αH)
4 R = OH; R' = H (11βH)
5 R = H; R' = OH (11βH)

6 R = H (11αH)
7 R = H (11βH)
8 R = OH (11βH)

9 R = H
10 R = OH

11

12

13

Scheme 1

The available spectral data clearly suggest that the structures of compounds **7** and **8** are closely related to that of **6**. Careful examination of the NMR spectra of **7** (Tables 2 and 4), and of the results of decoupling and NOE experiments, leads to the conclusion that **6** and **7** are epimeric at C-11. This was further confirmed by the photooxygenation of **2** to yield **7**. As regards compound **8**, the spectral data are strongly indicative that it is an 8α-hydroxy derivative of **7**, a conclusion further supported by the synthesis of **8** via photooxygenation of dienone **4**.

The spectral data of compounds **9** and **10** display certain similarities to those of **2** and **4**, respectively. As in **2**, carbonyl bands of γ-lactone and conjugated ketone moieties are visible in the IR spectrum of **9**. The UV absorption maximum, however, lies at a shorter wavelength (λ max 232 nm), and the molecular formula, $C_{15}H_{18}O_4$, contains an additional oxygen atom. The most reasonable suggestion is that **9** is one of the two diastereomeric 4,5-epoxides of **2**. Indeed, ^{13}C peaks in the typical epoxide range are visible at 67.75 and

59.91 ppm (Table 4). The suggested structure was confirmed by the synthesis of **9** via deoxygenation of the endoperoxide **7** with triphenylphosphine.[13] Similar considerations indicate that **10** is the 8α-hydroxyderivative of **9**. Synthetic evidence for this is that deoxygenation of **8** with triphenylphosphine yields **10**.

Compound **11** has the same molecular formula as **7**. Its ^{1}H NMR spectrum (Table 2), however, indicates the absence of olefinic hydrogens. Furthermore, two doublets at δ 3.41 and 3.22 (J = 3.5 Hz) suggest a disubstituted epoxide ring. Since other features of the spectrum resemble those of epoxylactone **9**, the diepoxide structure **11** is proposed for the compound. The fact that **11** was formed, albeit in low yield, during the thermal treatment[13] of **7** served not only to confirm the structure of the compound, but also to establish the configuration of both oxirane rings (see below).

Table 2. ^{1}H NMR data of compounds **6-11**[a].

Compound	**6**	**7**	**8**	**9**	**10**	**11**
Hydrogen						
H-2	4.54 *d* (6.5)	4.55 *d* (6.5)	4.57 *d* (6.5)	6.00 *d* (10)	6.02 *d* (10)	3.22 *d* (3.5)
H-3	6.36 *dq* (6.5; 1.5)	6.36 *dq* (6.5; 2)	6.39 *dq* (6.5; 2)	6.89 *d* (10)	6.91 *d* (10)	3.41 *d* (3.5)
H-6	4.52 *d* (12)	4.34 *d* (11.5)	4.36 *d* (11.5)	4.45 *d* (11)	4.46 *d* (11)	4.30 *d* (11.5)
H-7	2.95 *dddd* (13; 12; 7.6; 3)	2.47 *dddd* (12.5; 12; 11.5; 3.5)	2.55 *m*	2.03 *dddd* (13; 12; 11; 4)	2.15 *m*	
H-8α	1.80 *dddd* (13; 4.5; 3; 2.5)	2.00 *m*	– -	2.08 *dddd* (13; 4; 4; 2.5)	– -	1.95 *m*
H-8β	1.60 *dddd* (13; 13; 13; 4)	1.55 *dddd* (12; 12; 12; 3.5)	4.03 *ddd* (11; 11; 4.5)	1.58 *dddd* (13; 13; 13; 3.5)	4.08 *ddd* (11; 11; 4.5)	
H-9α	2.02 *ddd* (13; 13; 4.5)	2.00 *m*	1.96 *dd* (13; 11)	1.74 *ddd* (14; 13; 4)	1.73 *dd* (13.5; 11)	1.49 *ddd* (13; 13; 5)
H-9β	1.85 *ddd* (13; 4; 2.5)	1.85 *ddd* (14; 3.5; 3)	2.14 *dd* (13; 4.5)	2.14 *ddd* (14; 3.5; 2.5)	2.15 *m*	2.06 *ddd* (13; 3.5; 3.5)
H-11	2.72 *dq* (7.6; 7.6)	2.33 *dq* (12.5; 6.5)	2.55 *m*	2.33 *dq* (12; 7)	2.65 *dq* (12; 7)	2.28 *dq* (12; 7)
H-13	1.20 *d* (7.6)	1.26 *d* (6.5)	1.41 *d* (6.5)	1.26 *d* (7)	1.41 *d* (7)	1.24 *d* (7)
H-14	1.18 *s*	1.20 *s*	1.20 *s*	1.25 *s*	1.27 *s*	1.32 *s*
H-15	2.15 *d* (1.5)	2.16 *d* (2)	2.16 *d* (2)	1.81 *s*	1.83 *s*	1.92 *s*

[a] At 400 MHz in $CDCl_3$ (25°). Coupling constants (in Hertz) are given in parentheses after the chemical shifts.

Compounds **12** and **13** both have the molecular formula $C_{25}H_{34}O_3$. The similarity of their spectra suggests that they are closely related isomers. Carbonyl bands of γ-lactone and nonconjugated ketone groups are visible in both IR spectra. A careful examination of the ^{1}H NMR spectra at 400 MHz (Table 3), aided by extensive decoupling experiments, led to the suggestion of structures **12** and **13**, which are formally two Diels-Alder adducts of dienone **2** and the acyclic monoterpene myrcene. The ^{13}C NMR spectra (Table 4) support this conclusion. The synthesis of **12** and **13** by Diels-Alder reaction between dienone **2** and myrcene (see below), provided chemical evidence for the proposed structure.

The configurational assignment of each compound was made by means of NOE measurements. In **12**, for instance, a clear NOE (6%) was observed between the signals of the hydrogens H-14 (angular methyl of the eudesmane part) and of H-2' (myrcene part), indicating the monoterpene moiety connecting C-2 and C-5 (eudesmane numbering) by the upper (β) part of the bicyclic system. This also indicates that the configuration at C-2' is the one represented in Scheme 1. Other NOEs confirming the proposed stereochemistry were observed between the hydrogen pairs H-3/H-10', H-7/H-15, H-14/H-1'β and

H-2'/H-1'β. As regards compound **13**, the NOEs detected between the hydrogen pairs H-3/H-10', H-6/H-15, H-14/H-3, H-14/H-15 and H-1'α/H-2' constitute a definitive confirmation of the stereochemistry depicted in Scheme 1.

Table 3. ^{1}H NMR data of compounds **12** and **13**.[a]

Compound	Sesquiterpene part		Compound	Monoterpene part	
	12	**13**		**12**	**13**
H-2	3.19 *dd* (6.5; 1)	3.12 *dd* (6; 2)	H-1'α	1.64 *dd* (13.5, 7)	2.22 *dd* (14, 10)
H-3	5.74 *dd* (6.5; 2)	5.73 *dd* (6; 2)	H-1'β	2.07 *dd* (13.5, 9)	1.55 *dd* (14, 7)
H-6	4.09 *d* (11.5)	4.36 *d* (11)			
H-7	2.18 *dddd* (13; 12; 11.5; 3.5)	2.06 *m*	H-2'	2.78 *ddd* (9, 7, 1)	2.55 *dd* (10, 7, 2)
H-8α	1.86 *dddd* (13; 4; 3; 3)	1.90 *m*	H-4'	1.97 *m*	1.97 *m*
H-8β	1.50 *dddd* (13; 13; 13; 1)	1.55 *m*	H-5'	2.09 *m*	2.08 *m*
H-9α	1.25 *m*	1.56 *m*			
H-9β	1.90 *ddd* (14; 3; 3)	1.86 *m*	H-6'	5.06 *tqq* (7, 1.5, 1.5)	5.06 *tqq* (7, 1.5, 1.5)
H-11	2.33 *dq* (12; 7)	2.36 *dq* (12.5; 7)	H-8'	1.67 br *s*	1.67 br *s*
H-13	1.26 *d* (7)	1.26 *d* (7)	H-9'	1.59 br *s*	1.59 br *s*
H-14	1.20 *s*	1.07 *s*			
H-15	1.99 *d* (2)	1.97 *d* (2)	H-10'	4.75 br *s* 4.67 br *s*	4.76 br *s* 4.68 br *s*

[a] At 400 MHz in $CDCl_3$ (25°).

The structures of the various isolated compounds are interesting and deserve some comment. The question immediately arises as to whether or not some of them, particularly **6-8** and **11-13**, could be artifacts formed during the isolation procedure. 2,4-Cyclohexadienones, which are rarely found in nature, have been shown to exhibit a varied reactivity under both thermal[14,15] and photochemical[16] conditions. We have tested the photostability of dienone **2**, for instance, in the usual illumination conditions of our laboratory, i. e. in the absence of direct sunlight. After standing at room temperature for 2 weeks, a nondegassed solution of **2** in methylene chloride was shown (by means of NMR) to contain roughly 20 % of peroxide **7**, even without the addition of a sensitizer. The transformation was very clean and did not show any evidence of the formation of hydroperoxides[17] or other compounds. No reaction was observed in the dark or if the solution had been previously deoxygenated with argon. Interestingly, if a *methanolic* solution of **2** is allowed to stand for only two days under the same illumination and temperature conditions, a different compound is obtained, which has been assigned structure **14** (Scheme 2) on the basis of its spectral properties. The NMR data and their temperature dependence indicate that the compound exists as a mixture of two conformers, which interconvert very slowly at room temperature, so that a different set of signals is clearly visible for each one (see Experimental). In all probability, the conformational isomerism is due to a hindered rotation round the C_4-C_5 single bond (eudesmane numbering, see Scheme 1). The fact that **14** lacks any noticeable UV absorption above 220 nm is further evidence of the supposition that the diene moiety cannot attain a planar conformation for steric reasons. The formation of **14** is easily understood in terms of an electrocyclic opening of **2** to a dienylketene,[16] followed by MeOH addition (Scheme 2).

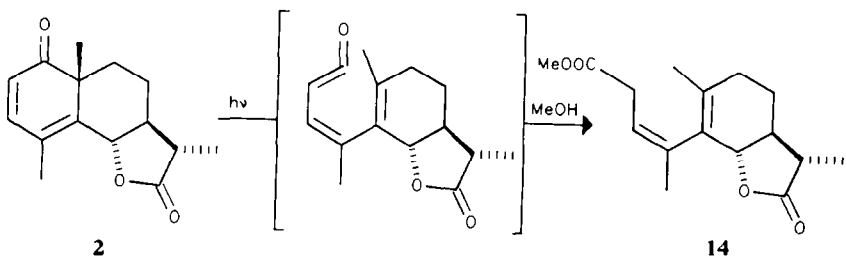
Compound **14**, as well as its corresponding acid, were additionally isolated from some chromatographic fractions of the plant extract. The appreciable rate at which dienone **2** is transformed into these compounds

Table 4. ^{13}C NMR data of compounds **1**-**13**.[a]

Carbon	1	2	3	4	5[b]	5a[c]	6	7	8	9	10	11	12[d]	13[e]
1	204.50	204.56	203.72	204.02	204.12	203.61	203.92	203.96	202.64	199.33	198.81	201.95	211.88	216.44
2	123.33	123.53	123.17	123.00	123.79	124.26	78.30	78.33[f]	78.15	128.96	128.82	46.07	53.06	52.12
3	149.10	149.05	149.17	149.40	145.62	144.48	121.03	121.09	121.60	149.12	149.44	52.85	122.17	119.67
4	121.41	121.47	122.22	122.03	126.91	121.51	149.81	149.70	148.96	59.91[f]	60.41[f]	60.10[f]	149.82	149.55
5	143.63	143.12	141.49	141.76	144.62	148.36	83.85	83.51	82.74	67.75[f]	67.11[f]	69.25[f]	48.73[f]	48.84[f]
6	80.79	81.76	78.04	78.63	81.62	81.25	77.20	78.09[f]	75.67	76.45	73.49	76.45	84.04	80.86
7	49.49	54.07	55.08	58.83	54.00	54.03	39.78	44.50	50.76	48.80	54.65	48.52	48.07	46.00
8	20.19	23.37	64.36	68.59	23.12	23.34	19.39	22.25	68.14	23.00	68.78	22.79	22.69	22.45
9	35.27	35.44	43.97	44.17	35.96	35.65	30.00	30.10	39.85	29.61	39.47	29.11	33.38	30.32
10	50.25	50.53	49.47	49.45	50.72	50.84	47.52	47.74	47.20	48.64	48.04	51.49	47.64[f]	47.92[f]
11	37.84	41.07	36.65	40.77	40.69	40.93	37.86	41.18	41.05	40.47	40.37	40.35	41.68	41.66
12	178.82	178.04	177.98	178.27	177.94	177.17	178.02	177.32	177.20	177.88	178.07	177.55	178.57	178.90
13	9.66	12.43	9.26	14.14	12.39	12.46	9.15	12.36	14.15	12.42	14.11	12.39	12.69	12.49
14	26.04	26.23	27.35	27.36	26.13	26.32	20.75	20.79	21.75	22.30	23.27	19.76	20.26	20.84
15	18.97	19.07	18.92	18.86	59.76	62.48	19.08	19.05	19.00	18.00	17.81	18.86	19.75	18.78

[a] At 50.32 MHz in $CDCl_3$ (25°). [b] In pyridine-d_5. [c] Acctate signals: δ 170.73 and 20.93. [d] Signals from the monoterpene part: 144.97 (C-3'), 131.96 (C-7'), 123.72 (C-6'), 109.34 (C-10'), 39.42 (C-2'), 35.56 (C-4'), 33.60 (C-1'), 26.55 (C-5'), 25.66 (C-8'), 17.74 (C-9'). [e] Signals from the monoterpene part: 145.26 (C-3'), 131.95 (C-7'), 123.76 (C-6'), 109.77 (C-10'), 40.55 (C-2'), 35.49 (C-4'), 26.73, 26.59 (C-1', C-5'), 25.68 (C-8'), 17.78 (C-9'). [f] The signals with this superscript may be interchanged within the same column.

in the presence of methanol or water clearly indicates that they are artifacts of the isolation procedure. Even when the plant was extracted under mild conditions in the dark and the chromatographic separations were performed as quickly as possible, the formation of minor amounts of the aforementioned artifacts was practically unavoidable. The oxygenation reaction which gives rise to the cyclic peroxides is, however, much slower, leading us to believe that compounds **6**-**8** can be formed, at least in part, in the course of biological oxygenations inside the plant tissues, i. e. they are true natural products. The isolation of cyclic peroxides from plant extracts is well precedented, ascaridol being a classic example.[18]



2 **14**

Scheme 2

Vicinal bisepoxides are known to arise in the thermal rearrangement of certain endoperoxides.[13] Since the reaction occurs stereospecifically, the configuration of the resulting oxirane rings can be deduced from that of the initial peroxide. This helped to establish the stereochemistry of compound **11**, since it is formed in low yield by refluxing a toluene solution of peroxide **7**. The reaction is very slow and more than one day is required for the complete transformation of the starting material. During this time extensive decomposition of the peroxide to ill-defined products also takes place. At room temperature, there is no trace of any transformation product, even after two months. Attempts to accelerate the reaction by addition of acid catalysts met with decomposition of **7**. This indicates that diepoxide **11** is not an artifact of the isolation procedure. Indeed, similar cyclic diepoxides have already been isolated, together with the parent endoperoxides, from diverse plant sources.[19]

Table 5. Final atomic coordinates of compound **6**[a]

Atom	x	y	z
C(1)	0.3330(7)	0.7033(5)	0.9072(4)
C(2)	0.1862(8)	0.7610(6)	0.8684(5)
C(3)	0.0985(7)	0.6676(6)	0.8162(5)
C(4)	0.1680(6)	0.6195(5)	0.7398(4)
C(5)	0.3249(6)	0.6586(4)	0.7234(4)
C(6)	0.4114(6)	0.6151(4)	0.6362(4)
C(7)	0.5570(6)	0.6772(4)	0.6233(4)
C(8)	0.6533(6)	0.6569(6)	0.7148(5)
C(9)	0.5705(7)	0.6991(5)	0.8091(4)
C(10)	0.4207(6)	0.6429(5)	0.8223(4)
C(11)	0.5961(6)	0.6440(5)	0.5141(4)
C(12)	0.4469(7)	0.6400(5)	0.4644(4)
C(13)	0.6781(8)	0.5314(7)	0.5016(5)
C(14)	0.4352(6)	0.5164(5)	0.8517(4)
C(15)	0.1011(7)	0.5252(7)	0.6767(5)
O(1)	0.3707(6)	0.7122(4)	0.9910(3)
O(2)	0.2390(5)	0.8429(4)	0.7923(3)
O(3)	0.3039(4)	0.7805(3)	0.7046(3)
O(4)	0.3389(4)	0.6257(3)	0.5374(2)
O(5)	0.4139(5)	0.6456(4)	0.3775(3)

[a]Estimated standard deviations in the least significant digit are shown in parentheses. Only the non-hydrogen atoms are included. For atom numbering, see Figure 1.

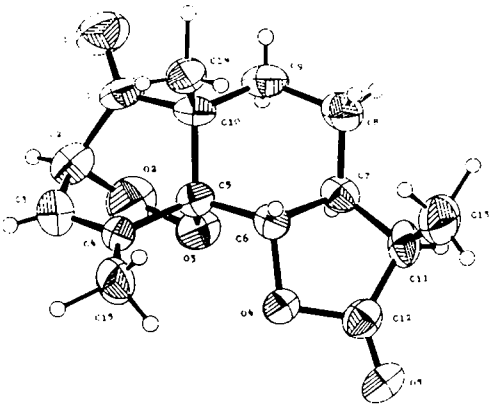


Figure 1. Molecular structure of compound **6**

Compounds **12** and **13** are formally derived from a Diels-Alder reaction with inverse electron demand, between the dienone **2** as the diene, and the monoterpene hydrocarbon myrcene. Here myrcene acts as the dienophile, in spite of its actually being a diene. It is already known[14,15] that 2,4-cyclohexadienones can react as both dienes and dienophiles, although the former mode has been observed less frequently. In fact, in our experiments, dienone **2** reacted with myrcene to give a mixture of both diastereoisomeric adducts. The reaction conditions, however, were rather harsh, since the hydrocarbon had to be used in great excess as the solvent, and the mixture had to be heated at 100° for 2 days (see Experimental). No reaction was observed at room temperature. As in the case of **11**, this result supports the idea that these compounds are not fortuitous artifacts of the isolation procedure. No Diels-Alder adducts of this type had been isolated from natural sources so far.

EXPERIMENTAL

NMR spectra were measured on Bruker NMR spectrometers WM-400 and AC-200 at the frequencies indicated in the Tables. Two-dimensional correlation spectra were measured with standard Bruker software. Mass spectra were run on a Varian MAT 711 spectrometer. IR spectra were recorded as oily films on a Perkin Elmer IR spectrophotometer mod. 281. Optical rotations were measured at 24° in the solvent indicated in each case. HPLC was performed in the reverse phase mode (LiChrosorb RP-8, 250 x 8 mm, flow = 3 mL/min; elution with MeOH-H_2O mixtures). Medium pressure column chromatography (MPCC) was made on silica gel Merck (40-63 μ).

Extraction and chromatography: Specimens of *Artemisia herba-alba* subsp. *valentina* were collected in October 1986 in Villena, Alicante, Spain (chemotype 1), and in November 1987 at the border between the provinces of Valencia and Teruel, Spain (chemotype 2). Both plant materials were subjected to the same treatment: aerial parts (600 g in each case) were air-dried at room temperature, ground and macerated with hexane-Et_2O-MeOH 1:1:1. The extract (ca. 60 g) was dissolved in hot MeOH (600 mL) and then cooled to -15°. The waxy precipitate was then eliminated by filtration, and the material obtained by evaporation of the solution was prefractionated by column chromatography on silica gel: A, hexane-Et_2O 1:1; B, hexane-Et_2O 1:3, C, Et_2O and D, Et_2O-MeOH 9:1 (length, 70 cm, i.d. 5 cm, 4 L of each solvent mixture). The four fractions were subjected to further chromatographic separations as described below.

Fraction A was fractionated by MPCC on silica gel (gradient elution with hexane-Et_2O from 3:1 to 1:3). The intermediate fractions were further separated by preparative TLC and HPLC. In this way, a ca. 1:1 mixture of compounds **12** and **13** (30 mg) was

isolated from chemotype 2, together with waxes, sterols and several compounds already described in our former communications.[3,4] Separation of **12** and **13** was performed by HPLC. Fraction B was subjected to MPCC on silica gel (gradient elution with hexane-Et_2O from 1:1 to 1:5). The intermediate fractions were further processed by preparative TLC and HPLC. This gave compound **1** (400 mg) and trace amounts of compound **2** from chemotype 1. The corresponding fractions from chemotype 2 yielded compound **2** (ca. 1.5 g), together with trace amounts of **1**.

MPCC of fraction C on silica gel was carried out with gradient elution from Et_2O to Et_2O-MeOH 3:1. The intermediate fractions were further processed as before by preparative TLC and HPLC. This gave compounds **3** (8 mg) and **6** (60 mg) from chemotype 1, whereas compounds **4** (650 mg), **7** (80 mg), **9** (13 mg) and **11** (12 mg) were found in chemotype 2. MPCC of fraction D (gradient elution with $CHCl_3$-MeOH 100:1 to 100:5) and subsequent fractionation by prep. TLC and HPLC yielded compounds **8** (22 mg), **10** (7 mg) and **5** (7 mg) from chemotype 2 only.

1-*Oxoeudesma*-2,4-*dien*-11αH-12,6α-*olide* (**1**). Colourless needles, mp 108-110° (pentane-Et_2O); $[\alpha]_D$ -35°, (c, 4.58; $CHCl_3$). IR ν max (film): 1780, 1740 (lactone), 1670, 1640 (ketone), 1575, 1220, 1190, 1035, 1000 cm^{-1}. UV λ max (MeOH): 319 nm. EIMS *m/z* (% rel. int.): 246 (M^+, 81), 231 (M^+-Me, 18), 218 (M^+-CO, 18), 203 (M^+-CO-Me, 20), 190 (M^+-2CO, 21), 172 (100), 145 (37), 122 (61), 91 (45). Exact mass measurement for the molecular ion: found, M = 246.1259; calcd. for $C_{15}H_{18}O_3$: M = 246.1255. For NMR data, see Tables 1 and 4.

1-*Oxoeudesma*-2,4-*dien*-11βH-12,6α-*olide* (**2**). Colourless needles, mp 138.5-139.5° (pentane-Et_2O), lit. mp[10] 134-135°, lit. mp[11] 145°; $[\alpha]_D$ -98°, (c, 1.26; $CHCl_3$). IR ν max (film): 1778 (lactone), 1655 (ketone), 1635, 1570, 1448, 1020, 825 cm^{-1}. UV λ max (MeOH): 319 nm. EIMS *m/z* (% rel. int.): 246 (M^+, 42), 231 (M^+-Me, 11), 218 (M^+-CO, 25), 203 (M^+-CO-Me, 26), 190 (M^+-2CO, 20), 173 (87), 172 (100), 145 (64), 122 (55), 119 (30), 107 (41), 105 (33), 91 (62), 55 (62). Exact mass measurement for the molecular ion: found, M = 246.1262; calcd. for $C_{15}H_{18}O_3$: M = 246.1255. For NMR data, see Tables 1 and 4.

1-*Oxo*-8α-*hydroxyeudesma*-2,4-*dien*-11αH-12,6α-*olide* (**3**). Yellowish gum which could not be crystallized; $[\alpha]_D$ +37°, (c, 0.2; $CHCl_3$). IR ν max (film): 3400 (OH), 1780 (lactone), 1660 (ketone), 1635, 1450, 1375, 1255 cm^{-1}. UV λ max (MeOH): 318 nm. EIMS *m/z* (% rel. int.): 262 (M^+, 5), 244 (M^+-H_2O, 35), 234 (M^+-CO, 8), 226 (10), 198 (12), 161 (31), 135 (43), 122 (44), 121 (49), 119 (61), 107 (36), 105 (81), 91 (90), 86 (66), 84 (80), 79 (39), 71 (89), 69 (100), 57 (50), 55 (98). Exact mass measurement for the molecular ion: found, M = 262.1205; calcd. for $C_{15}H_{18}O_4$: M = 262.1205. For NMR data, see Tables 1 and 4.

1-*Oxo*-8α-*hydroxyeudesma*-2,4-*dien*-11βH-12,6α-*olide* (**4**). Colourless needles, mp 181-183° (EtOAc); $[\alpha]_D$ +14°, (c, 9.45; $CHCl_3$). IR ν max (film): 3400 (OH), 1770 (lactone), 1662 (ketone), 1625, 1565, 1450, 1220, 1130, 1060, 1025, 970 cm^{-1}. UV λ max (MeOH): 318 nm. EIMS *m/z* (% rel. int.): 262 (M^+, 2), 244 (M^+-H_2O, 10), 226 (7), 183 (40), 136 (36), 135 (100), 134 (30), 85 (45), 83 (74), 71 (31), 69 (32), 59 (55), 55 (32). Exact mass measurement for the molecular ion: found, M = 262.1205; calcd. for $C_{15}H_{18}O_4$: M = 262.1205. For NMR data, see Tables 1 and 4.

1-*Oxo*-15-*hydroxyeudesma*-2,4-*dien*-11βH-12,6α-*olide* (**5**). Colourless needles, mp 251-253° (MeOH); $[\alpha]_D$ -83°, (c, 0.57; MeOH). IR ν max (KBr): 3370 (OH), 1783 (lactone), 1659 (ketone), 1626, 1033, 848 cm^{-1}. UV λ max (MeOH): 316 nm. EIMS *m/z* (% rel. int.): 262 (M^+, 6), 244 (M^+-H_2O, 100), 229 (M^+-H_2O-Me, 10), 219 (M^+-Me-CO, 8), 201 (20), 189 (28), 173 (31), 171 (48), 161 (24), 151 (13), 133 (14), 121 (23), 109 (32), 91 (21). Exact mass measurement for the molecular ion: found, M = 262.1205; calcd. for $C_{15}H_{18}O_4$: M = 262.1205. For NMR data, see Tables 1 and 4.

1-*Oxo*-15-*acetoxyeudesma*-2,4-*dien*-11βH-12,6α-*olide* (**5a**). Obtained by acetylation of **5** with Ac_2O-pyridine. Colourless oil; $[\alpha]_D$ -129°, (c, 0.41; $CHCl_3$). IR ν max (film): 1785 (lactone), 1732 (acetate), 1667 (ketone), 1634, 1452, 1380, 1240, 1140, 1038 cm^{-1}. UV λ max (MeOH): 316 nm. EIMS *m/z* (% rel. int.): 262 (M^+-C_2H_2O, 6), 244 (M^+-HOAc, 100), 234 (12), 229 (M^+-HOAc-Me, 10), 219 (8), 201 (20), 189 (70), 188 (42), 171 (22), 159 (22), 131 (78), 119 (26), 105 (24), 91 (35). Exact mass measurement for *m/z* 244: found, M = 244.1104; calcd. for $C_{15}H_{16}O_3$: M = 244.1100. For NMR data, see Tables 1 and 4.

1-*Oxo*-2α,5α-*peroxyeudesm*-3-en-11αH-12,6α-*olide* (**6**). Colourless needles, mp 173-175° (EtOAc); $[\alpha]_D$ -263°, (c, 1.14; $CHCl_3$). IR ν max (film): 1794 (lactone), 1733 (ketone), 1196, 1182, 1029, 1002, 981 cm^{-1}. EIMS *m/z* (% rel. int.): 278 (M^+, 20), 250 (M^+-CO, 6), 234 (M^+-CO_2, 5), 232 (5), 219 (12), 206 (13), 177 (10), 165 (100), 137 (45), 125 (20), 109 (40), 105 (41), 97 (50), 69 (46), 55 (62). Exact mass measurement for the molecular ion: found, M = 278.1157; calcd. for $C_{15}H_{18}O_5$: M = 278.1154. For NMR data, see Tables 2 and 4.

1-*Oxo*-2α,5α-*peroxyeudesm*-3-*en*-11βH-12,6α-*olide* (**7**). Colourless needles, mp 165-167° (MeOH); $[\alpha]_D$ -298°, (c, 0.75; $CHCl_3$) IR ν max (film): 1780 (lactone), 1733 (ketone) cm^{-1}. EIMS *m/z* (% rel. int.): 278 (M^+, 2), 263 (M^+-Me, 1), 250 (M^+-CO, 3), 246

(M^+-O_2, 1), 234 (M^+-CO_2, 3), 219 (18), 177 (9), 165 (16), 125 (26), 109 (27), 69 (40), 55 (100). Exact mass measurement for the molecular ion: found, M = 278.1160; calcd. for $C_{15}H_{18}O_5$: M = 278.1154. For NMR data, see Tables 2 and 4.

1-*Oxo*-8α-*hydroxy*-2α,5α-*peroxyeudesm*-3-*en*-11βH-12,6α-*olide* (**8**). Colourless cubes, mp 176-177° ($CHCl_3$); $[\alpha]_D$ -210°, (c, 1.2; $CHCl_3$). IR ν max (film): 3500 (OH), 1777 (lactone), 1744 (ketone), 1629, 1230, 1163, 1142, 1116, 1069, 1028, 1010, 975, 942, 907, 718 cm^{-1}. EIMS *m/z* (% rel. int.): 276 (M^+-H_2O, 8), 250 (5), 235 (20), 233 (7), 205 (10), 189 (13), 181 (100), 176 (23), 163 64), 151 (42), 135 (55), 125 (51), 105 (53), 95 (80). For NMR data, see Tables 2 and 4.

1-*Oxo*-4α,5α-*epoxyeudesm*-2-*en*-11βH-12,6α-*olide* (**9**). Colourless needles, mp 179-180° (hexane-Et_2O). IR ν max (film): 1767 (lactone), 1673 (ketone), 1446, 1375, 1260, 1236, 1164, 1139, 1025, 988, 899, 858, 808, 738 cm^{-1}. UV λ max (MeOH): 232 nm. For NMR data, see Tables 2 and 4. EIMS *m/z* (% rel. int.): 262 (M^+, 2), 247 (M^+-Me, 1), 234 (M^+-CO, 4), 219 (M^+-CO-Me, 11), 165 (100), 97 (32). Exact mass measurement for the molecular ion: found, M = 262.1212; calcd. for $C_{15}H_{18}O_4$: M = 262.1205

1-*Oxo*-8α-*hydroxy*-4α,5α-*epoxyeudesm*-2-*en*-11βH-12,6α-*olide* (**10**). Colourless needles (MeOH), dec. above 175°. IR ν max (film): 3500 (OH), 1759 (lactone), 1683 (ketone), 1439, 1376, 1344, 1278, 1258, 1135, 1078, 1023, 976, 880, 800 cm^{-1}. UV λ max (MeOH): 232 nm. EIMS *m/z* (% rel. int.): 278 (M^+, 5), 263 (M^+-Me, 2), 250 (M^+-CO, 7), 235 (M^+-CO-Me, 10), 181 (100), 163 (25), 161 (21), 151 (25), 135 (27), 109 (20), 97 (35). Exact mass measurement for the molecular ion: found, M = 278.1154; calcd. for $C_{15}H_{18}O_5$: M = 278.1154. For NMR data, see Tables 2 and 4.

1-*Oxo*-2α,3α;4α,5α-*diepoxyeudesman*-11βH-12,6α-*olide* (**11**). Colourless needles, mp 248-250° (EtOAc). IR ν max (film): 1775 (lactone), 1720 (ketone), 1445, 1376, 1225, 1165, 1135, 1018, 980, 910, 850 cm^{-1}. EIMS *m/z* (% rel. int.): 278 (M^+, 1), 263 (M^+-Me, 6), 250 (M^+-CO, 3), 235 (M^+-CO-Me, 1), 165 (100), 151 (19), 137 (25), 125 (16), 109 (24), 97 (30). Exact mass measurement for the molecular ion: found, M = 278.1154; calcd. for $C_{15}H_{18}O_5$: M = 278.1154. For NMR data, see Tables 2 and 4.

Compound (**12**). Colourless solid, mp 172-176° (pentane-EtOAc). IR ν max (film): 1775 (lactone), 1715 (ketone), 1635, 1450, 1180, 1140, 1000 cm^{-1}. EIMS *m/z* (% rel. int.): 382 (M^+, 4), 367 (M^+-Me, 1), 354 (M^+-CO, 1), 339 (M^+-CO-Me, 3), 247 (M^+-$C_{10}H_{15}$, 16), 173 (47), 136 (41), 93 (100), 79 (19), 69 (83), 55 (56). For NMR data, see Tables 3 and 4.

Compound (**13**). Colourless cubes, mp 106-108° (pentane-EtOAc). IR ν max (film): 1780 (lactone), 1720 (ketone), 1640, 1450, 1185, 1145, 1010 cm^{-1}. EIMS *m/z* (% rel. int.): 382 (M^+,3), 367 (M^+-Me, 1), 354 (M^+-CO, 1), 339 (M^+-CO-Me, 2), 247 (M^+-$C_{10}H_{15}$, 12), 173 (66), 136 (50), 93 (100), 79 (10), 69 (55), 55 (79). For NMR data, see Tables 3 and 4.

Compound (**14**). Obtained by photooxygenation of a methanolic solution of **2**, under the conditions described below. Colourless oil. IR ν max (film): 1775 (lactone), 1731 (ester) cm^{-1}. UV λ max (MeOH): no absorption above 220 nm. ^1H NMR: 5.56, 5.52 (2 x *tq*, J = 7.5, 2 Hz, H-3), 4.47, 4.35 (2 x *ddq*, J = 10; 2.5, 2 Hz, H-6), 3.63, 3.62 (2 x s, 3H, OMe), 2.90, 2.86 (2 x br *dq*, J = 7.5, 2 Hz, H-2), 2.30 (*dq*, J = 12, 7 Hz, H-11), 2.25-2.15 (*m*, H-9/9'), 2.05-1.95 (*m*, H-8), 1.90-1.80 (*m*, H-7), 1.81, 1.80 (2 x br *dt*, J = 2, 2 Hz, H-15), 1.65-1.55 (*m*, H-8'), 1.50, 1.49 (2 x br *d*, J = 2 Hz, H-14), 1.22, 1.21 (2 x d, J = 7 Hz, H-13). ^{13}C NMR: 172.40, 172.28 (C-1), 34.83, 34.58 (C-2), 120.44, 118.92 (C-3), 136.60, 134.76 (C-4 or C-5), 131.31, 131.02 (C-5 or C-4), 82.28, 80.05 (C-6), 49.27, 48.66 (C-7), 22.90, 22.85 (C-8), 31.26 (C-9), 130.86, 130.23 (C-10), 41.81, 41.52 (C-11), 179.54 (C-12), 12.34 (C-13), 19.15, 18.70 (C-14), 24.32, 22.45 (C-15).

Photooxygenation reactions.- Dienone **1** (100 mg) and Methylene Blue (5 mg) were dissolved in dry MeCN (100 mL) and photooxygenated under the reported conditions[20] at 10° for 40 min. After this time, the reaction mixture was concentrated *in vacuo* and chromatographed on silica gel (hexane-EtOAc 3:2). This gave **6** (57 mg, 51%). With the same experimental procedure, dienones **2** and **4** were photooxygenated to **7** and **8**, respectively, with similar yields. Substitution of MeOH for MeCN gave rise to the formation of methyl ester **14** from **2** or the corresponding methyl esters from **1** and **4**.

Deoxygenation of peroxides with triphenylphosphine.- Peroxide **7** (55 mg) was dissolved in CH_2Cl_2 (3 mL) and treated with triphenylphosphine (149 mg, 3 equiv.). After stirring at room temp. for 16 hr (monitoring by TLC), the mixture was concentrated *in vacuo* and chromatographed on silica gel (hexane-EtOAc 3.2). This gave **9** (12 mg, 23% yield). In the same way, peroxide **8** was deoxygenated to epoxylactone **10** with a similar yield.

Thermal rearrangement of peroxide **7**.- A solution of compound **7** (175 mg) in toluene (4 mL) was refluxed for 26 hr under Ar atmosphere. The reaction mixture was then evaporated *in vacuo* and chromatographed on silica gel (Et_2O). This gave diepoxide **11** (20 mg, 12% yield).

Diels-Alder reaction of dienone **2** *with myrcene*.- A mixture of dienone **2** (50 mg) and myrcene (1 mL) was heated at 100° under Ar in the dark for 48 hr. The reaction mixture was then put on the top of a short silica gel column and eluted with hexane until elimination of the excess of myrcene. Further elution with Et_2O gave a residue which was then rechromatographed on silica gel

(flash chromatography, $CHCl_3$-Et_2O 100:1). This gave a ca. 1:1 mixture of **12** and **13** (30 mg, 51% yield, based on recovered **2**), as well as 13 mg of unreacted **2**.

X-ray diffraction data of compound **6**.-Crystals of **6** are orthorhombic, space group $P2_12_12_1$ (No. 19), a = 9.039 (2), b = 11.603 (3), c = 13.157 (3) Å, V = 1380.00 Å^3; Z = 4, D_{calc} = 1.339 g/cm^3, μ = 0.94 cm^{-1}. Crystals were sealed in Lindemann capillaries (crystal dimensions: 0.10 x 0.15 x 0.20 mm^3). All data were collected using an Enraf-Nonius CAD-4 diffractometer. A total of 1414 reflections were measured at room temperature with graphite-monochromated MoK radiation up to θ = 25, using an ω-2 scan mode with ω scan width = 0.70 + 0.35 tan θ, and ω scan speed 1.1 deg/min. After data reduction, 961 reflections with $I \geq 2(I)$ were taken as observed. The structure was solved by direct methods (MULTAN11/82),[21] hydrogen atoms were obtained from a Fourier difference map. The following full-matrix least-squares refinement with anisotropic thermal parameters for all non-hydrogen atoms, and isotropic thermal parameters for hydrogen atoms, led to R = 0.059 and 0.063 for 253 variables (weighting scheme: $w^{-1} = \sigma^2(F) + (p[F])^2$, with p = 0.04). The final Fourier difference map showed no significant features. Scattering factors are from Cromer and Waber.[22] All crystallographic calculations were performed by using the Enraf-Nonius SDP package.[23,24]

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24.-Positional and thermal parameters, tables of bond distances and angles, torsion angles and other crystallographic data are available from the Cambridge Crystallographic Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, United Kingdom.