Table IV. Proton Chemical Shifts in 6 and 7[a]

	R = CH_2CH_3	R = $CH_2CH(CH_3)_2$	R = $C(CH_3)_3$
		Compound 6	
CH_3	2.17	2.17	3.88
ArH	6.78, 7.17	6.78, 7.10	6.86, 7.11 6.30, 7.58 (d, 7.4)
R	0.54 (t, 6.7) 2.54 (m)[b]	0.72 (d, 6.5) 1.74 (m) 2.59 (m)[b]	1.12
		Compound 7	
ArH[c]	7.41	7.41	7.46
ArH	6.83, 7.13	6.85, 7.13	6.86, 7.14
$-CH_2-$	2.49 (m)[b]	2.49 (m)[b]	2.69
R	1.66 (m) 0.85 (t, 6.8)	1.43 (m, 3 H) 0.75 (d, 5.9)	0.85

[a] Multiplicities and coupling constants (hertz) are given in parentheses. [b] The resonances of the protons attached to the carbon atoms directly bonded to the aromatic ring appear as complex multiplets, apparently due to hindered rotation about the alkyl carbon-aryl carbon bond. [c] Isolated proton on the central substituted aromatic ring.

of the extent of reaction via **10** and **11**.

1,1-Dimethylallene undergoes cycloaddition only across the C_1–C_2 π system with a partial relative reactivity comparable with those for ethyl- and isobutylallene. Normally, one would have expected 1,1-dimethylallene to react significantly faster than a monoalkylallene due to the higher energy of the π MO.[7] The apparent reduction in rate must be due to the adverse steric interaction present in **8** which cannot be avoided with 1,1-dimethylallene. Replacement of a methyl group by a *tert*-butyl group, as in 1-*tert*-butyl-1-methylallene introduces further steric hindrance and reduction in reactivity.

It is interesting to note that no cycloaddition occurs across the C_2–C_3 π system of 1,1-dimethylallene. The introduction of an alkyl group at C_1 also raises the energy of the C_2–C_3 π system,[7] which should increase its reactivity. However, approach to either face of the C_2–C_3 double bond is sterically hindered by the alkyl groups attached to C_1. This apparently more than offsets the expected increase in reactivity due to the higher energy of the π MO.

Experimental Section

Cycloaddition of Substituted Allenes with Tetraphenylcyclopentadienone (TPCD). In an NMR tube were placed 0.6 mmol of the allene, 0.4 mmol of TPCD, and 1 mL of xylene. The contents of the tube were triply freeze-degassed. The tube was sealed under a vacuum and was placed in a sand bath at 160 °C until the color of the TPCD had disappeared (3–7 days). The contents of the tube were moved and the unreacted allene and the xylene were removed on a vacuum line. A portion of the residue was subjected to preparative HPLC on a 30 × 1 cm column of 5 μm of silica, using 95% hexane–5% dichloromethane as eluent. The 100-MHz NMR spectra of the separated fractions were recorded by FT techniques (see Table IV). Product compositions were determined by integration of the NMR spectra obtained on the crude product mixtures. Elemental compositions were determined by high-resolution *m/e* measurements (see Table V). Insufficient quantities of the pure were obtained to recrystallize and determine melting points.

Table V. High-Resolution *m/e* Values for Adducts 6 and 7

adduct	mol formula	calcd *m/e*	obsd *m/e*
6a	$C_{33}H_{28}$	424.219	424.218
7a	$C_{33}H_{28}$	424.219	424.221
6b	$C_{35}H_{32}$	452.250	452.252
7b	$C_{35}H_{32}$	452.250	452.250
6c + **7c**[a]	$C_{35}H_{32}$	452.250	452.250

[a] Isolated in an inseparable mixture by HPLC.

Measurement of Relative Reactivities. Mixtures were prepared containing 200 μL of ethylallene (the standard allene), 200 μL of the other substituted allene, and 100 μL of heptane or octane (as an internal standard). The mixtures were analyzed by GC to determine standard allene/internal standard and substituted allene/internal standard area ratios. One hundred microliters (~0.7 total mmol of allene) of the mixtures was reacted with 0.17 mmol of TPCD as described above. After the color of the TPCD had disappeared, the tubes were opened and the final standard allene/internal standard and substituted allene/internal standard area ratios were determined by GPC. The changes in area ratios were converted to moles of allene consumed, and the relative rate constants were calculated with an iterative computer program.

Acknowledgment. We thank the National Science Foundation for partial support of the research (Grant No. CHE77-08627).

Registry No. 1a, 591-95-7; **1b**, 13865-36-6; **1c**, 26981-77-1; **1d**, 598-25-4; TPCD, 479-33-4; hexachlorocyclopentadiene, 77-47-4.

---

[7] For a discussion of the effect of alkyl substitution on the energy of the π systems of an allene, and on the chemical reactivity of the π systems, see: Pasto, D. J.; Warren, S. E. *J. Org. Chem.* **1981**, *46*, 2842.

Crystal Structure and Stereochemistry of Frutescin[†1]

Werner Herz* and J. Siva Prasad

Department of Chemistry, Florida State University, Tallahassee, Florida 32306

John F. Blount

Research Division, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received December 7, 1981

The sesquiterpene lactone frutescin was the first[2] and long remained the only C-8 lactonized melampolide isolated from natural sources;[3] its occurrence in an *Iva* species is somewhat of an anomaly. Our assumption[2] that its lactone ring was cis fused as in **1** (Chart I) was based primarily on an empirical rule[4] which relates the sign of the Cotton effect associated with the lactone n,π^* transition to the stereochemistry of the lactone ring if the absolute configuration is known. However, it has since been shown[5] that the rule is frequently violated and is only applicable to a limited number of sesquiterpene lactone types, with melampolides presenting a particularly confusing picture.[3]

In such cases a better guide to the mode of lactone ring fusion may be Samek's rule which, as modified recently,[6] relates the magnitude of $J_{7,13}$ to the conformation of the lactone ring. For a C-8 lactonized melampolide like frutescin where $J_{7,13}$ = 3 Hz[2], model considerations, deceptive though these can be, then suggest the presence of a trans lactone ring as in **2**. Indeed, in a recent publication dealing with the melampolide schkuhriolide (**4**), Samek and coworkers,[7] commenting on differences in the ^{1}H NMR spectra of frutescin and **4**, suggested that frutescin either differed from **4** conformationally or possessed a trans lactone ring fusion. To resolve this question, we have

---

[†] Dedicated to the memory of Zdeněk Samek, deceased Nov 25, 1980.

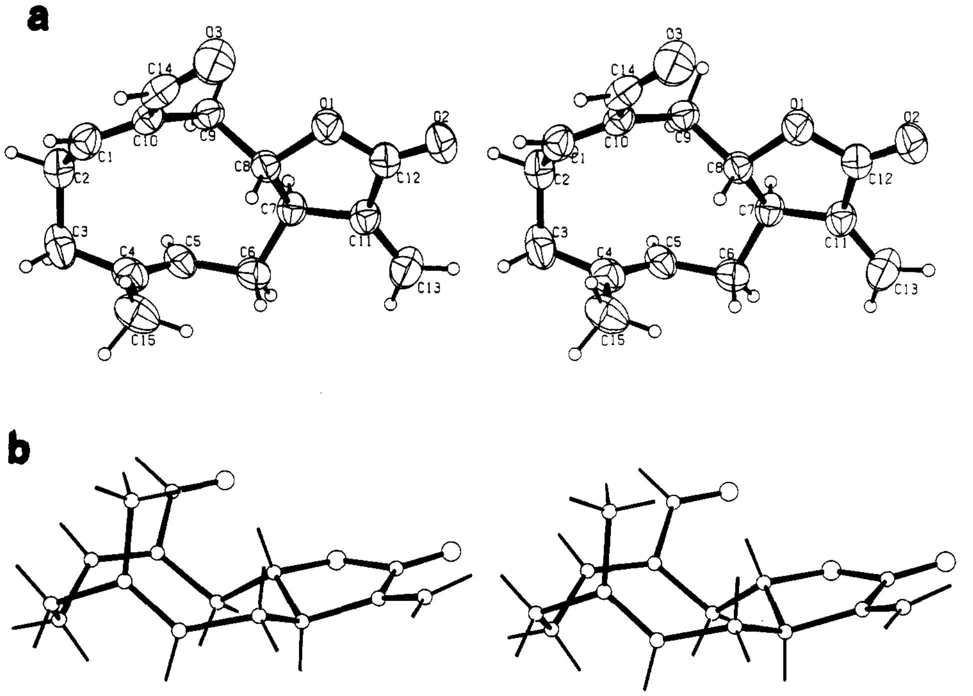
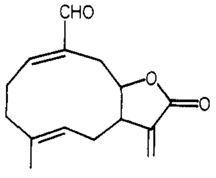
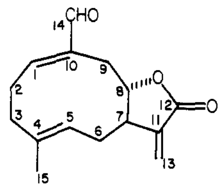


Figure 1. (a) Stereoscopic view of frutescin molecule with ellipsoids of thermal motion. (b) Side view of the molecular framework.

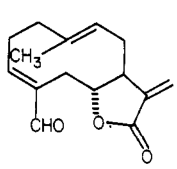
Chart I



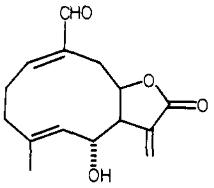
1



2



3



4

carried out an X-ray analysis of frutescin using the very small sample of frutescin still extant from the earlier work. The results show that formula 2 is correct.

Crystal data for frutescin are listed in the Experimental Section. Figure 1a is a stereoscopic drawing of the molecule; Figure 1b shows a side view of the atom framework. Tables I–IV, listing final atomic and final anisotropic thermal parameters, bond lengths, and bond angles are available as supplementary material; Table V presents selected torsion angles.

Table V. Torsion Angles (Degrees) in 2 with Standard Deviations in Parentheses

C(1)-C(2)-C(3)-C(4)	−53.6 (4)
C(2)-C(3)-C(4)-C(5)	−67.8 (4)
C(3)-C(4)-C(5)-C(6)	168.6 (3)
C(4)-C(5)-C(6)-C(7)	−106.0 (4)
C(5)-C(6)-C(7)-C(8)	56.1 (3)
C(6)-C(7)-C(8)-C(9)	−88.7 (3)
C(7)-C(8)-C(9)-C(10)	131.3 (3)
C(8)-C(9)-C(10)-C(1)	−111.5 (4)
C(9)-C(10)-C(1)-C(2)	0.9 (6)
C(10)-C(1)-C(2)-C(3)	97.2 (4)
C(8)-C(7)-C(11)-C(12)	−24.7 (3)
C(7)-C(11)-C(12)-O(1)	11.3 (4)
C(11)-C(12)-O(1)-C(8)	8.4 (3)
C(12)-O(1)-C(8)-C(7)	−24.0 (3)
O(1)-C(8)-C(7)-C(11)	28.8 (3)
O(2)-C(12)-C(11)-C(13)	14.6 (6)

The γ-lactone ring of 2 is quite puckered, the sum of the internal torsion angles being 98°, and can be described as a twist envelope with C-7 as the flap and C-8 slightly depressed from the C-8, O-1, C-12, C-11 plane. The conformation of the ten-membered ring to which the lactone ring is attached pseudodiequatorially is somewhat less strained than and quite different from that exhibited by comparable C-6 lactonized melampolides which have been studied by X-ray or neutron diffraction.[8-11] The C-4 methyl and the C-10 aldehyde group are syn (and β to the

---

(1) Work at the Florida State University was supported in part by a grant (CA-13121) from the U.S. Public Health Service through the National Cancer Institute.

(2) Herz, W.; Bhat, S. V.; Sudarsanam, V. *Phytochemistry* **1972**, *11*, 1829. In this reference, through an unfortunate oversight, the incorrect phrase "positive Cotton effect" appears on p 1830, line 8 from the bottom, although the argument was based on the *negative* Cotton effect reported in the Experimental section.

(3) Fischer, N. H.; Olivier, E. J.; Fischer, H. D. *Fortschr. Chem. Org. Naturst.* **1979**, *38* 47.

(4) Stöcklin, W.; Waddell, T. G.; Geissman, T. A. *Tetrahedron* **1970**, *26*, 2397.

(5) E.g.: Sundararaman, P.; McEwen, R. S.; Herz, W. *Tetrahedron Lett.* **1973**, 3809.

(6) Samek, Z. *Collect. Czech. Chem. Commun.* **1978**, *43*, 3210. Samek, Z.; Harmatha, J. *Ibid.* **1978**, *43*, 2779.

(7) Samek, Z.; Holub, M.; Bloszyk, F.; Drozdz, B. *Z. Chem.* **1979**, *19*, 449.

(8) Neidle, S.; Rogers, D. *J. Chem. Soc., Chem. Commun.* **1972**, 140.

(9) Watkins, S. F.; Fischer, N. H.; Bernal, I. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *79*, 2434.

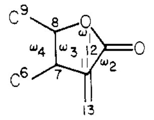
(10) Kartha, G.; Go, K. T.; Joshi, B. S. *J. Chem. Soc., Chem. Commun.* **1972**, 1327.

(11) Lotter, H.; Wagner, H.; Saleh, A. A.; Cordell, G. A.; Farnsworth, N. R. *Z. Naturforsch. C: Biosci.* **1979**, *34c*, 677.

(12) McPhail, A. T.; Sim, G. A. *Tetrahedron* **1973**, *29*, 1751.

(13) For exceptions in certain cis-fused γ-lactones of known absolute configuration, see: (a) Sundararaman, P.; McEwen, R. S. *J. Chem. Soc., Perkin Trans. 2*, **1975**, 400. (b) Herz, W.; Govindan, S. V.; Bierner, M. W.; Blount, J. F. *J. Org. Chem.* **1980**, *45*, 493. (c) Herz, W.; Kumar, N.; Blount, J. F. *Ibid.* **1981**, *46*, 1356.

plane of the ring in the configuration depicted in Figure 1) but project away from each other as the result of a small movement of C-3 and C-6 out of the nodal plane of the C-4, C-5 double bond which produces a torsion angle of 168°. The conformation in solution does not appear to depart significantly from that observed in the crystal as judged by the observed[2] coupling constants for H-1, H-5, H-8, and H-9; in particular, the dihedral angles involving H-1 and H-9β and involving H-9α and H-14 (see Figure 1) satisfy the requirements for allylic and W coupling, respectively. With ω_4 (the C(6)–C(7)–C(8)–C(9) torsion angle) = −89°, the lactone ring of frutescin belongs to Samek's pseudorotational S type[7] for which $J_{7,13} \geq 3$ Hz as is actually observed.[2]



The remaining problem is the absolute configuration of frutescin, which on the basis of the generalization that H-7 in sesquiterpene lactones from higher plants is axial and α would be expected to that shown in Figure 1. In that case the C=C—C=O and the C(11)–C(7)–C(8)–O(1) torsion angles (ω_2 and ω_3, respectively) are both positive and thus of like sign (see Table V), as is the case in most α-methylene γ-lactones previously examined by X-ray diffraction.[12,13] Hence either by Beecham's rule,[14] which relates the chirality of the lactone chromophore (the sign of ω_2) in trans-fused lactones to the sign of the lactone Cotton effect, or by the more recent suggestion[15,17] that the sign of ω_3 and the magnitude of ω_4 provide a better correlation with the sign of the Cotton effect, frutescin if represented by absolute configuration **2** should exhibit a positive Cotton effect in the 250-nm region.

We previously[2] reported a negative lactone Cotton effect for frutescin. However, reexamination of the original trace showed that the observed molecular ellipticity at 247 nm (−7900) did not represent a true negative maximum but was a reading near the cut off point of the instrument. Redetermination of the CD curve on an instrument of more recent vintage afforded the values $[\Theta]_{319}$ −2160 (negative maximum), $[\Theta]_{290}$ −1080 (negative minimum), $[\Theta]_{250}$ −10800 (sh), $[\Theta]_{223}$ −28000 (negative maximum), and $[\Theta]_{210}$ −8600 (last reading). The negative maxima at 319 and 223 nm represent the n,π^* and π,π^* transitions of the α,β-unsaturated aldehyde which effectively swamp the n,π^* transition of the α,β-unsaturated lactone chromophore. If the latter were responsible for the observed slight negative hump near 250 nm, frutescin would be the mirror image of **2** and should be rewritten as **3** to maintain H-7α.[18a] Additional work which requires reisolation of frutescin is necessary to decide whether this is really so.[18b]

Experimental Section

Single crystals of frutescin were obtained by slow crystallization from ethyl acetate. They were orthorhombic, space group $P2_12_12_1$, with a = 7.684 (1) Å, b = 10.506 (2) Å, c = 16.092 (2) Å, and d_{calcd} = 1.2598 cm^3 for Z = 4 ($C_{15}H_{18}O_3$, M_r = 246.31). The intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu Kα radiation, θ–2θ scans, pulse-height discrimination). The size of the crystal used for data collection was approximately 0.08 × 0.35 × 0.4 mm. A total of 1046 accessible reflections were measured for $\theta < 57°$ of which 955 were considered to be observed [$I < 2.5\sigma(I)$]. The structure was solved by a multiple-solution procedure and was refined by full-matrix least-squares methods. In the final refinement, anisotropic thermal parameters were used for the nonhydrogen atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices are R = 0.033 and R_w = 0.041 for the 955 observed reflections. The final difference map has no peaks greater than 0.1 e Å^{-3}.

Registry No. 2, 36790-43-9.

Supplementary Material Available: Tables I–IV containing final atomic parameters, final anisotropic parameters, bond lengths, and bond angles for compound **2** (3 pages). Ordering information is given on any current masthead page.

---

(14) Beecham, A. F. *Tetrahedron* **1972**, *28*, 5543.

(15) As has been pointed out by McPhail and Onan[16] the sign of ω_3 is also related to the magnitude of ω_4 such that if $\omega_4 < 120°$, ω_3 is negative, and if $\omega_4 > 120°$, ω_3 is positive. For negative values of ω_4, if $|\omega_4| < 120°$, ω_3 is positive (as Table V also shows), and for $|\omega_4| > 120°$, ω_3 is negative.

(16) McPhail, A. T.; Onan, K. D. *J. Chem. Soc., Perkin Trans. 2*, **1976**, 578.

(17) Cox, P. J.; Sim, G. A. *J. Chem. Soc., Perkin Trans. 2*, 1977, 255.

(18) (a) In that case, frutescin would not be classified as a melampolide, (a *cis*-1(10),*trans*-4-germacradienolide) by the current classification scheme (Neidle, S.; Rogers, D. *J. Chem. Soc., Chem. Commun.* **1972**, 140) but as a *cis*-4,*trans*-9-germacradienolide. (b) Note Added in Proof: The CD curve of schkuhriolide (**4**), kindly supplied by Dr. A. Romo de Vivar, is strikingly different from that of frutescin in the n,π^* and π,π^* region of the α,β-unsaturated aldehyde chromophore: $[\theta]_{316}$ +1890, $[\theta]_{241}$ −12600; $[\theta]_{210}$ +24600 (last reading).

(19) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* 1971, *A27*, 368.

Extensions of the Hydrazone and Beckmann Rearrangements[1]

Kenneth Nolon Carter* and James E. Hulse, III

Department of Chemistry, Presbyterian College, Clinton, South Carolina 29325

Received November 3, 1981

The rearrangement of hydrazones to amides, $R_2C{=}NNH_2 \rightarrow RCONHR$, in a sodium nitrite-concentrated sulfuric acid medium was discovered by Pearson and Greer in 1949.[2] When the rearrangement was applied to the stereoisomeric hydrazones[3] of 4-methoxybenzophenone and 4-bromobenzophenone, the results obtained allowed assignments of structures if anti migration was assumed to occur as in the Beckmann rearrangement of oximes. Later, subjection of the *Z* and *E* isomers of camphorquinone-3-hydrazone, the configurations of which were known from other work, to hydrazone rearrangement conditions gave α-camphoramic acid.[4] It was concluded that this product was produced by a cleavage-type rearrangement similar to the Beckmann rearrangement of camphorquinone 3(*E*)-oxime.[5]

The purpose of the work here reported was to modify the rearrangement medium by using commercial nitrosylsulfuric acid and to extend the scope of the rearrangement to include a series of aromatic diketone monohydrazones (Scheme IB). In addition to this, the simultaneous oximation and Beckmann rearrangement method using hydroxylamine-*O*-sulfonic acid was applied to the corresponding diketones (Scheme IA). An examination of the literature showed that this method had been used with aryl alkyl ketones,[6] diaryl ketones,[7] and alicyclic

---

(1) Presented at the 181st National Meeting of the American Chemical Society, Atlanta, GA, Mar 1981; Abstract ORGN 38.

(2) D. E. Pearson and C. M. Greer, *J. Am. Chem. Soc.*, **71**, 1895 (1949).

(3) D. E. Pearson, K. N. Carter, and C. M. Greer, *J. Am. Chem. Soc.*, **75**, 5905 (1953).

(4) K. N. Carter, *J. Org. Chem.*, **23**, 1409 (1958).

(5) W. Nagata and K. Takeda, *Yakugaku Zasshi*, **72**, 1566 (1952).

(6) J. K. Sanford, F. T. Blair, J. Arroya, and K. W. Sherk, *J. Am. Chem. Soc.*, **67**, 1941 (1945).

0022-3263/82/1947-2208$01.25/0