Biogenetic-type Synthesis of Santonin, Chrysanolide, Dihydrochrysanolide, Tulirinol, Arbusculin-C, Tanacetin, and Artemin

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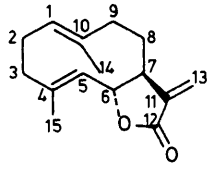
The title compounds were synthesized from their possible biogenetic precursors through hydroperoxide intermediates generated by photo-oxygenation. This route for biological oxygenation may serve as a substitute to epoxidation. The ^{13}C n.m.r. spectral assignments for all intermediates were made. Single-crystal *X*-ray analyses unequivocally established the 1*S* configuration in dihydrochrysanolide (14) and its hydroperoxy-analogue (12). Isomorphous crystals of (12) and (14) belong to the monoclinic system, space group $P2_1$, with a = 14.350(6), b = 5.882(3), c = 10.343(3) Å, β = 107.64(2)°, Z = 2, for (12), and a = 14.461(6), b = 5.887(3), c = 9.698(4) Å, β = 107.44(2)°, Z = 2, for (14). Least-squares refinement of atomic parameters converged to R 0.040 for (12) and 0.033 for (14) over 1 484 and 1 300 reflections, respectively, measured by diffractometer.

Biological oxygenation of carbocyclic skeletons has generally been assumed to occur through processes like hydration of a carbonium ion [1] or epoxidation of an olefin to an epoxide with possible subsequent rearrangement to other oxygenated functional groups.[1] Oxygenation by $^1O_2$ as a biogenetic tool has not been given due consideration until quite recently when the number of reported naturally occurring hydroperoxides has been on the increase. These include sesquiterpenes,[2] diterpenes,[3] steroids,[4] purines,[5] prostaglandins,[6] and chromans.[7]

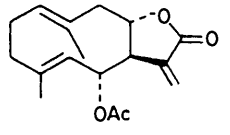
The subject of the present investigation was to design biogenetic-type syntheses for some sesquiterpene lactones involving $^1O_2$-produced hydroperoxides as intermediates. Costunolide (1) was chosen as the starting material for many of these synthetic schemes because it is regarded as the common precursor to other germacranolides, as well as eudesmanolides and guaianolides.[8] Laurenobiolide (2) served as the starting material to other compounds.

It was thought that this study would accomplish the following goals: (a) provide evidence for the possibility that $^1O_2$ oxidation of the proper olefinic intermediate would proceed in the correct direction—regio- and stereo-chemically—leading to a natural product with an allylic oxygenated functional group from an intermediary allylic hydroperoxide; (b) provide a simple and high yielding method for the synthesis of some biologically active sesquiterpenes from readily available natural products like costunolide (1) and laurenobiolide (2); (c) allow comparison of the ^{13}C n.m.r. spectra of all compounds involved in this investigation, especially hydroperoxides which are known to exhibit peculiar chemical shift values.[2]

Biogenetic-type Synthesis of Santonin (8).—The route used (Scheme 1) depended in part on that first postulated [9] by Barton *et al.* which was partially substantiated by feeding radiolabelled substrates. The starting material for this synthesis was santamarine (3) which was available in ample amounts from either bay leaves [10] or by the cyclization of 1,10-epoxycostunolide as previously reported.[11] Sodium borohydride reduction provided dihydrosantamarine (4) which provided the hydroperoxide (5) upon sensitized photo-oxygenation. The formation of (5) was in agreement with the fact that $^1O_2$ prefers to approach the less congested α-face of the olefinic plane. The α-orientation for the hydroperoxy-group was proposed on mechanistic grounds since oxygen



(1)



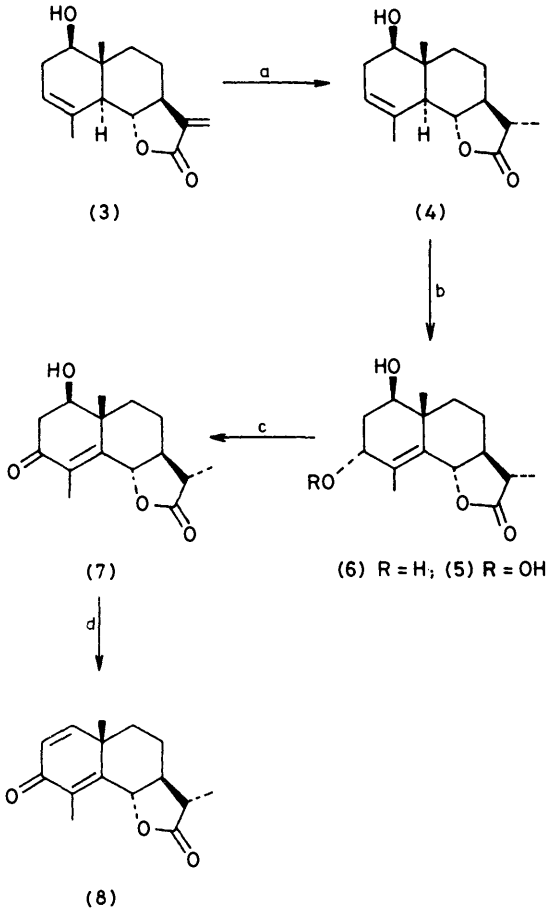
(2)

would be expected to approach the π-orbital perpendicular [12] to the plane with a *cis*-cyclic transition involving the α-proton on C(5) of (4), thus leading to α-hydroperoxidation at C(3). The structure of (5) was further confirmed by reduction to the diol (6) using sodium borohydride. Controlled treatment of the hydroperoxide (5) with acetic anhydride in pyridine [13] gave the α,β-unsaturated ketone (7) as colourless needles, m.p. 152—153 °C. Santonin (8) was readily obtained from (7) by treatment with thionyl chloride, then heating with trimethylamine.

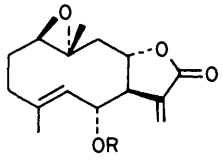
It is worth noting that the intermediate β-hydroxy-ketone (7) was proposed by Barton *et al.* as a possible precursor for santonin (8). However, no attempts were made to confirm this possibility experimentally due to the non-availability of this compound at that time.

Biogenetic-type Synthesis of Chrysanolide (15), *Dihydrochrysanolide* (14), *and Tulirinol* (13).—Laurenobiolide (2) was the key starting material and likely biogenetic precursor for these three germacranolides. Attempts to secure enough laurenobiolide (2) for this purpose by deoxygenation [14] of readily available pyrethrosin (9) were fruitless because pyrethrosin in (9) either underwent cyclization † or (2) was obtained in poor yields. The desired material was finally secured by acetylating deacetyllaurenobiolide (10) which was isolated in

† In another attempt to deoxygenate pyrethrosin (9) to laurenobiolide (2) it was treated with tungsten(VI) chloride and n-butyllithium as described in ref. 17. The exclusive product of this reaction was β-cyclopyrethrosin a constituent of pyrethrum flower (see ref. 18). This regiospecific cyclization represents a biogenetic-type synthesis for β-cyclopyrethrosin which could be obtained only as an inseparable mixture with the α and γ isomers by acid treatment of pyrethrosin (9).



Scheme 1. *Reagents*: a, $NaBH_4$ in EtOH; b, $^1O_2$/Methylene Blue; c, acetic anhydride/pyridine; d, $SOCl_2$ then Me_3N at 75 °C

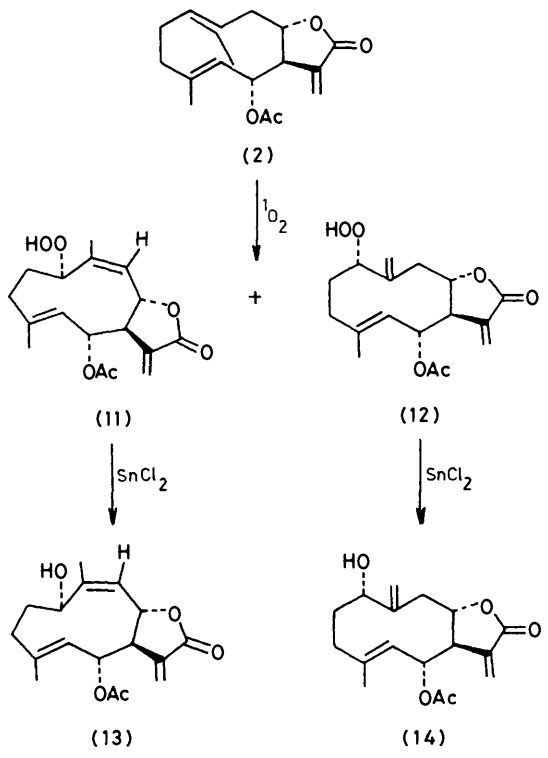


(9) R = Ac
(10) R = H

ca. 1% yield from *Artemisia tridentata* ssp. *vaseyana* as previously described.[15]

Since laurenobiolide (2) was known [16] to exist in solution in four different conformations with the C(10) methyl group β in one pair and α in the other, it was expected that its sensitized photo-oxygenation would yield more than one hydroperoxide. Indeed two products were produced (Scheme 2), the first one, (12), was obtained as colourless needles, m.p. 148—149 °C (with bubbling), while the other one, (11), occurred as a colourless oil which was still partially contaminated with (12).

Reduction of impure (11) with tin(II) chloride gave a mixture of the alcohols (13) and (14) which were readily separated by flash chromatography.[19] The less polar of the two alcohols was found to be identical with tulirinol (13), the gypsy moth antifeedant that was recently isolated [20] from the leaves of *Liriodendron tulipifera* L. Its structure was unambiguously established by X-ray crystallography. The other alcohol, (14), was derived from the hydroperoxide (12) since it was identical



Scheme 2

with the product obtained by reducing (12) with tin(II) chloride.

While the gross structures for (12) and its alcohol analogue (14) were readily deduced from their ^1H n.m.r. (See Experimental section) and ^{13}C n.m.r. data (Table 4), the stereochemical assignment for C(1) was still not clear. It was thought, however, that the formation of (12) would be analogous to the formation of peroxycostunolide,[2] peroxyparthenolide,[2] and peroxyferolide,[13] namely, it would involve $^1O_2$ attack on the β-face of the molecule where the conformation is such that the C(10) methyl group is β. This would lead to a β-configuration (*R*) for the C(1) hydroxy-substituent. To confirm this assumption (which was later found to be incorrect—*vide infra*) the absolute stereochemistry of the analogous alcohol (14) was determined by the Horeau [21] partial resolution method. The results (see Experimental section) showed that the configuration was, unexpectedly, *S* not *R*. This indicated that during formation of (12), $^1O_2$ must also have attacked the α-face of the molecule.

The absence of photo-oxygenation products derived from $^1O_2$ attack on the β-face of laurenobiolide (2) was totally unexpected in view of what was known about its conformational preferences [16] as well as what had been observed with other germacranolides.[2,13] Since Horeau's partial resolution method was known to predict, on occasion, the wrong stereochemistry,[22] single-crystal *X*-ray analyses of (12) and (14) were undertaken to provide unambiguous verification for the 1*S* configurational assignment.

The crystal structures of the hydroperoxide (12) was solved by direct methods and that of dihydrochrysanolide (14) followed by use of the fact that crystals of these compounds are isomorphous. Least-squares adjustment of atomic parameters converged at *R* 0.040 for (12) and 0.033 for (14) over 1 484 and 1 300 reflections, respectively. Non-hydrogen atom fractional co-ordinates are in Table 1 (see p. 359), and views of the solid-state conformations are in Figure 1. The results of

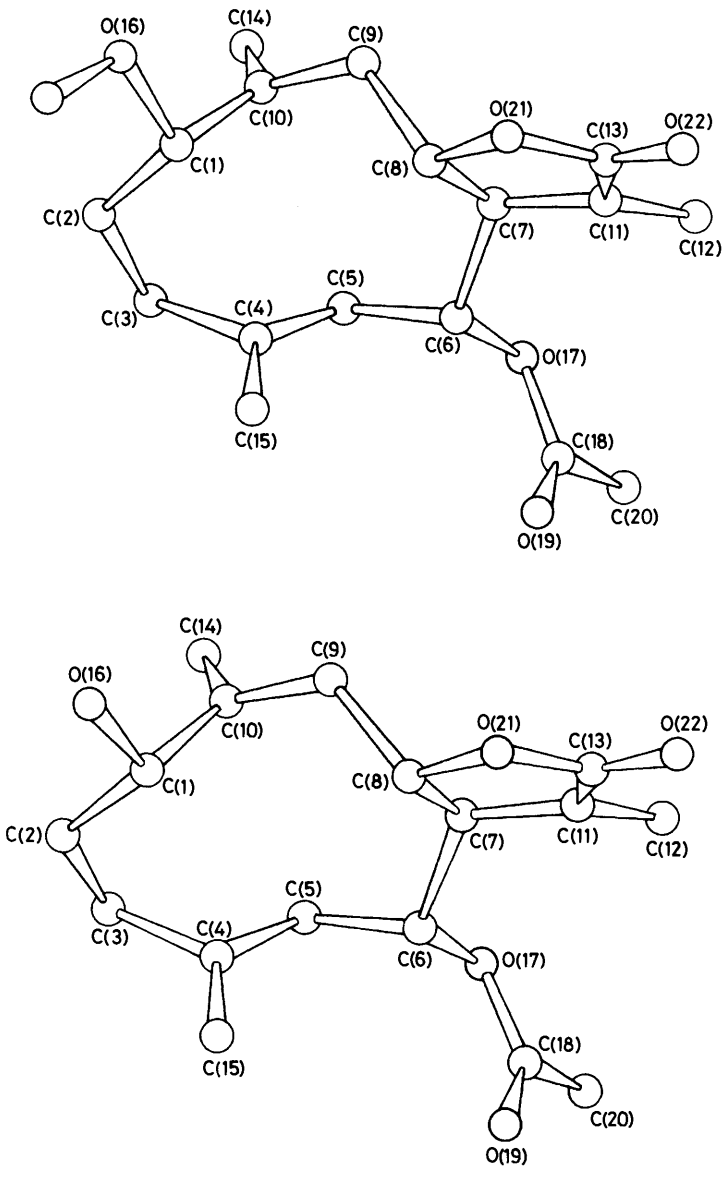


Figure 1. Structure and solid-state conformation of (12), upper, and (14), lower

the *X*-ray analyses confirm that the configuration at C(1) is *S*. The arrangement of molecules of (12) in the crystal is shown in Figure 2.

Comparison of corresponding bond lengths and angles, listed in Table 2 (see p. 360), reveals that the only major difference occurs in the C(10)–C(1)–O(16) bond angle [100.3(2)° in (12) *cf.* 109.7(2)° in (14)]. The small differences in most of the torsion angles listed in Table 3 (see p. 360) attest to the close similarity of the overall molecular conformations. In both compounds, the cyclodecene rings have their C(4) methyl and C(10) methylene substituents oriented *anti*. The rings, like those in *e.g.* shiromodiol acetate *p*-bromobenzoate,[23] dihydromikanolide,[24] and glaucolide A,[25] adopt a conformation related to one of the less favourable cyclodecane forms possessing an approximate C_2 symmetry axis [here passing through the mid-points of the C(1)–C(10) and C(5)–C(6) bonds]. The α-methylene γ-lactone rings, with endocyclic dihedral angles in the range 0.9—4.2° in (12) and 0.5—2.0° in (14), are quite flat. Although the exocyclic torsion angles defining the orientation of the acetate substituent are essentially identical for (12) and (14), appreciable differences occur in those involving C(14) and O(16) owing to variation in the relative dispositions of the hydroperoxy- and hydroxy-groups in order to accommodate their involvement in intermolecular hydrogen bonds with γ-lactone carbonyl groups of molecules related by unit-cell translations along the *c*-direction [O(23) · · · O(22) 2.911 Å in (12); O(16) · · · O(22) 3.016 Å in (14) as indicated for (12) in Figure 2].

Treatment of the hydroperoxide (12) with acetic anhydride in pyridine [13] smoothly converted it into a product identical with the germacranolide chrysanolide (15), a constituent of pyrethrum flowers.[26] This conversion confirmed the structure of this compound as it was originally proposed essentially on the basis of its spectral data.

The occurrence [20] of tulirinol (13) with its peculiar stereochemical structure in the leaves of *L. tulipifera* L. along with dihydrochrysanolide [27] (14) makes it highly unlikely that they might have been derived from 1,10-epoxylaurenobiolide [pyrethrosin, (9)]. A biogenetic origin involving $^1O_2$ reacting

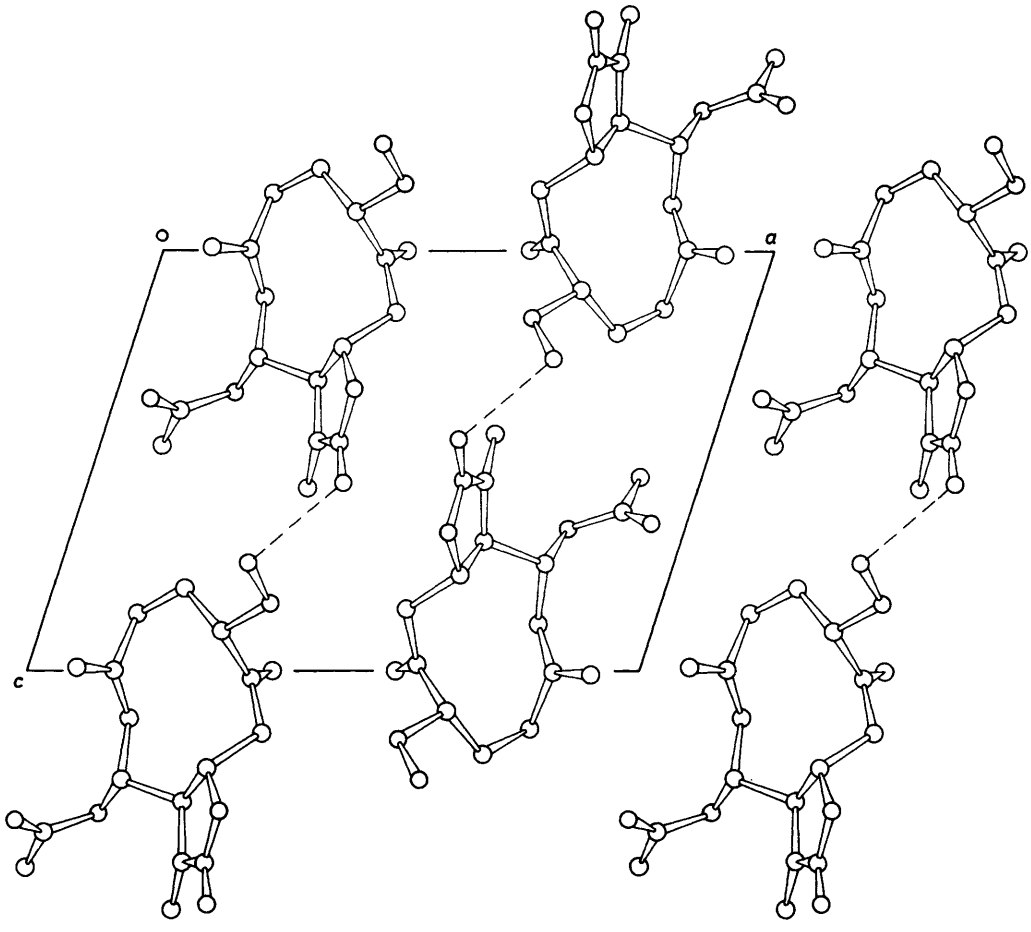
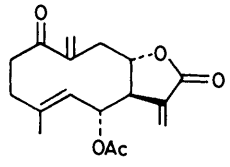


Figure 2. Crystal structure of (12), viewed in projection along the *b*-axis; broken lines denote O–H · · · O hydrogen bonds



(15)

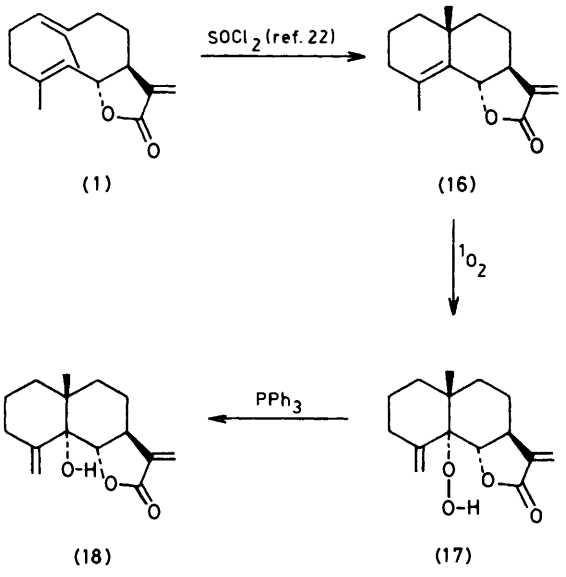
with laurenobiolide (2) in an ene-type reaction appears to be more plausible.

Biogenetic-type Synthesis of Arbusculin-C (18), *Tanacetin* (21), *and Artemin* (22).—Costunolide (1) was used as the starting material for the synthesis of these three compounds. Thus, costunolide (1) was cyclized as previously described [22] to arbusculin-B(γ-cyclocostunolide)(16), the biogenetic precursor of arbusculin-C (18). Sensitized photo-oxygenation of (16) produced the hydroperoxide (17) as the exclusive product (Scheme 3). In this case too, singlet oxygen would be expected to attack the C(4)–C(5) double bond from the less-hindered α-face producing an α-oriented hydroperoxy-group at C(5); an allylic proton will be abstracted from C(15) producing an exocyclic group. The ^{1}H n.m.r. (see Experimental section) and ^{13}C n.m.r. (Table 4) (see p. 361) spectra were in agreement with the assigned structure. The presence of an α-hydroperoxy-group at C(5) exerted a marked deshielding effect on the C(7) hydrogen (it has the same α-configuration) shifting it to δ 3.41, and the shift was even more pronounced when [$^2H_5$]pyridine was used as a solvent, shifting this signal further downfield to δ 3.62. This behaviour is in agreement with the presence of an α-oxygenated function on C(5).[1]

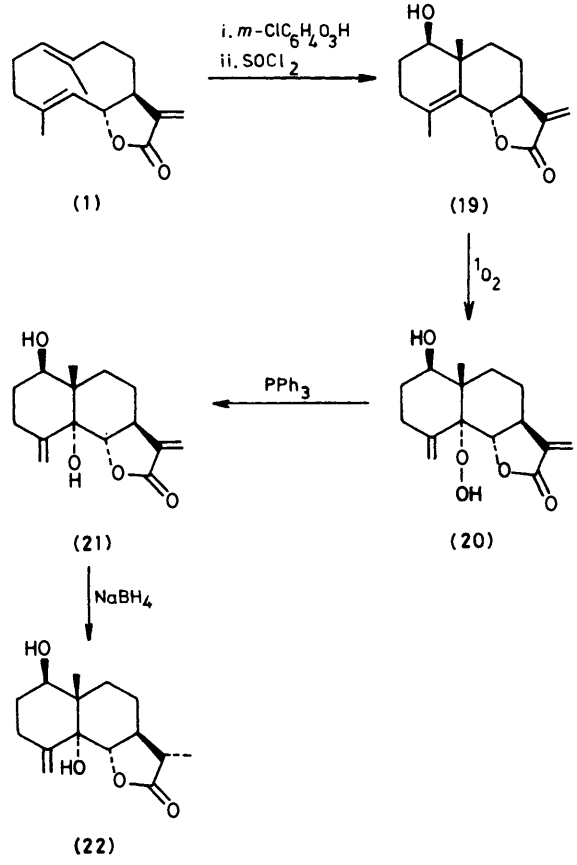
Reduction of the hydroperoxide (17) with triphenylphosphine in acetone produced, almost quantitatively, the corresponding alcohol which was indistinguishable from arbusculin-C (18). It is interesting to note that while the ^{1}H n.m.r. spectrum of (18) exhibited the C(15) exocyclic protons as a broad two-proton singlet at δ 4.98, they were better resolved and more deshielded in (17) appearing as a pair of one-proton singlets at δ 5.39 and 5.34.

Costunolide (1) was again used as the starting material for the synthesis of tanacetin (21) and artemin (22) (Scheme 4) by conversion into magnolialide (19) as previously described.[28] Sensitized photo-oxygenation furnished a crystalline hydroperoxide which was characterized as (20) based on its spectral data and by comparison with those of (17). The α-disposition of the hydroperoxy group on C(5) was assigned based on mechanistic grounds and the downfield position of the C(7) proton in the ^{1}H n.m.r. spectrum, especially in the presence of [$^2H_5$]pyridine as solvent (δ 3.41 for $CDCl_3$ and δ 3.77 for [$^2H_5$]pyridine).

Reduction of the hydroperoxide (20) with triphenylphosphine produced the alcohol (21) which was identical with tanacetin.



Scheme 3



Scheme 4

Sodium borohydride reduction of tanacetin (21) as previously reported [25] produced its 11,13,α-dihydro-derivative which is also a naturally occurring sesquiterpene lactone named artemin (22). The synthetic material was indistinguishable from an authentic sample of the natural product.[29]

The availability of numerous hydroperoxides with their analogous alcohols and other derivatives provided an opportunity to interrelate the ^{13}C n.m.r. signals of those different compounds (Table 4). Assignments were made with the aid of off-resonance decoupling and literature values of related compounds. In all cases, hydroperoxy-bearing carbons are always more deshielded than the corresponding alcohols by *ca.* 6 p.p.m. or more. This effect was observed regardless of whether the substituent is on a secondary or a tertiary carbon. As reported for other allylic hydroperoxy sesquiterpenes, there was a consistent downfield shift of the β-carbon of the allylic system accompanied by an upfield shift of the γ-carbon of the same system in going from the hydroperoxide series to the corresponding alcohol series.

Among the eudesmanolides examined, it was observed that the presence of a hydroxy- or a hydroperoxy-group on C(5) shifted the neighbouring C(6) (β-effect) downfield by *ca.* 1—2 p.p.m. The effect on C(7), however, was more dramatic, shifting it upfield (γ-effect) by an average of *ca.* 5 p.p.m. This

Table 1. Non-hydrogen atom fractional co-ordinates (× 10^4), with standard deviations in parentheses

Atom	*x*	*y*	*z*
(a) (12)			
C(1)	7 042(2)	5 441(6)	941(2)
C(2)	7 862(2)	4 082(8)	1 954(3)
C(3)	8 483(2)	2 543(8)	1 348(3)
C(4)	8 583(2)	3 428(7)	23(3)
C(5)	8 094(2)	2 388(6)	−1 114(3)
C(6)	7 888(2)	3 208(6)	−2 539(3)
C(7)	6 796(2)	3 827(5)	−3 085(2)
C(8)	6 560(2)	5 902(5)	−2 296(2)
C(9)	5 867(2)	5 464(6)	−1 477(2)
C(10)	6 311(2)	4 154(6)	−182(2)
C(11)	6 457(2)	4 619(6)	−4 549(3)
C(12)	6 387(3)	3 473(7)	−5 651(3)
C(13)	6 111(2)	6 986(6)	−4 553(3)
C(14)	6 015(2)	2 068(7)	−3(3)
C(15)	9 208(2)	5 546(9)	98(4)
O(16)	6 390(1)	6 504(5)	1 606(2)
O(17)	8 084(1)	1 408(—)	−3 373(2)
C(18)	8 866(2)	1 565(8)	−3 796(3)
O(19)	9 423(2)	3 142(8)	−3 484(3)
C(20)	8 984(3)	−418(10)	−4 602(4)
O(21)	6 138(2)	7 668(4)	−3 306(2)
O(22)	5 822(2)	8 263(5)	−5 520(2)
O(23)	6 965(2)	8 203(5)	2 587(2)
(b) (14)			
C(1)	7 237(2)	6 312(6)	1 093(3)
C(2)	8 003(2)	4 961(7)	2 198(3)
C(3)	8 537(2)	3 105(7)	1 598(3)
C(4)	8 629(2)	3 743(6)	140(3)
C(5)	8 077(2)	2 664(7)	−1 010(3)
C(6)	7 852(2)	3 337(5)	−2 551(3)
C(7)	6 769(2)	4 013(6)	−3 086(3)
C(8)	6 611(2)	6 276(5)	−2 397(3)
C(9)	5 970(2)	6 209(6)	−1 398(3)
C(10)	6 424(2)	5 017(5)	13(3)
C(11)	6 380(2)	4 462(6)	−4 674(3)
C(12)	6 258(2)	3 122(8)	−5 797(3)
C(13)	6 032(2)	6 837(7)	−4 880(3)
C(14)	6 099(2)	3 053(6)	302(3)
C(15)	9 288(2)	5 682(8)	85(4)
O(16)	6 832(1)	7 999(4)	1 812(2)
O(17)	7 997(1)	1 408(—)	−3 394(2)
C(18)	8 738(2)	1 486(7)	−3 944(3)
O(19)	9 290(2)	3 041(7)	−3 722(3)
C(20)	8 792(2)	−588(8)	−4 769(3)
O(21)	6 149(1)	7 813(4)	−3 592(2)
O(22)	5 690(2)	7 832(6)	−5 995(2)

Table 2. Interatomic distances (Å) and angles (°), with standard deviations in parentheses

	(12)	(14)
(a) Bond Lengths		
C(1)-C(2)	1.536(5)	1.516(4)
C(1)-C(10)	1.508(4)	1.524(4)
C(1)-O(16)	1.457(4)	1.434(4)
C(2)-C(3)	1.527(5)	1.548(5)
C(3)-C(4)	1.511(5)	1.508(4)
C(4)-C(5)	1.320(4)	1.323(4)
C(4)-C(15)	1.513(6)	1.498(5)
C(5)-C(6)	1.491(4)	1.485(4)
C(6)-C(7)	1.539(4)	1.547(4)
C(6)-O(17)	1.438(3)	1.451(3)
C(7)-C(8)	1.551(4)	1.538(4)
C(7)-C(11)	1.496(4)	1.496(4)
C(8)-C(9)	1.511(4)	1.529(4)
C(8)-O(21)	1.460(3)	1.464(3)
C(9)-C(10)	1.504(4)	1.503(4)
C(10)-C(14)	1.318(5)	1.310(4)
C(11)-C(12)	1.316(4)	1.313(5)
C(11)-C(13)	1.463(5)	1.479(5)
C(13)-O(21)	1.339(3)	1.338(4)
C(13)-O(22)	1.214(4)	1.199(4)
O(16)-O(23)	1.477(3)	
O(17)-C(18)	1.325(4)	1.333(3)
C(18)-O(19)	1.196(6)	1.192(5)
C(18)-C(20)	1.464(6)	1.475(6)
	(12)	(14)
(b) Bond Angles		
C(2)-C(1)-C(10)	118.7(3)	118.2(3)
C(2)-C(1)-O(16)	111.4(2)	109.7(2)
C(10)-C(1)-O(16)	100.3(2)	109.7(2)
C(1)-C(2)-C(3)	116.4(2)	116.5(2)
C(2)-C(3)-C(4)	113.6(3)	111.8(3)
C(3)-C(4)-C(5)	118.7(3)	118.1(3)
C(3)-C(4)-C(15)	116.7(3)	117.3(3)
C(5)-C(4)-C(15)	124.5(3)	124.4(3)
C(4)-C(5)-C(6)	128.8(3)	128.0(3)
C(5)-C(6)-C(7)	108.3(2)	107.5(2)
C(5)-C(6)-O(17)	110.1(3)	109.5(2)
C(7)-C(6)-O(17)	108.2(2)	108.4(2)
C(6)-C(7)-C(8)	110.4(2)	110.2(2)
C(6)-C(7)-C(11)	115.2(2)	114.9(2)
C(8)-C(7)-C(11)	103.2(2)	103.6(2)
C(7)-C(8)-C(9)	116.7(2)	116.8(2)
C(7)-C(8)-O(21)	106.3(2)	106.4(2)
C(9)-C(8)-O(21)	108.6(2)	107.4(2)
C(8)-C(9)-C(10)	114.3(2)	114.0(2)
C(1)-C(10)-C(9)	116.2(3)	115.4(2)
C(1)-C(10)-C(14)	121.9(3)	123.2(2)
C(9)-C(10)-C(14)	121.6(3)	121.3(2)
C(7)-C(11)-C(12)	129.7(3)	131.5(3)
C(7)-C(11)-C(13)	108.2(2)	108.3(2)
C(12)-C(11)-C(13)	121.9(3)	120.0(3)
C(11)-C(13)-O(21)	110.7(2)	109.7(2)
C(11)-C(13)-O(22)	128.3(3)	128.0(3)
O(21)-C(13)-O(22)	121.0(3)	122.3(3)
C(1)-O(16)-O(23)	107.7(2)	
C(6)-O(17)-C(18)	119.1(2)	117.9(2)
O(17)-C(18)-O(19)	121.9(3)	122.0(3)
O(17)-C(18)-C(20)	112.9(3)	111.6(3)
O(19)-C(18)-C(20)	125.1(3)	126.3(3)
C(8)-O(21)-C(13)	111.4(2)	111.9(2)

Table 3. Torsion angles [a] (°), with standard deviations in parentheses

	(12)	(14)
C(10)-C(1)-C(2)-C(3)	53.7(3)	54.9(3)
O(16)-C(1)-C(2)-C(3)	169.4(3)	−178.3(3)
C(2)-C(1)-C(10)-C(9)	−150.7(3)	−153.7(3)
C(2)-C(1)-C(10)-C(14)	35.0(3)	29.7(3)
O(16)-C(1)-C(10)-C(9)	87.8(3)	79.5(2)
O(16)-C(1)-C(10)-C(14)	−86.6(3)	−97.2(3)
C(2)-C(1)-O(16)-O(23)	64.1(2)	
C(10)-C(1)-O(16)-O(23)	−169.4(2)	
C(1)-C(2)-C(3)-C(4)	30.4(3)	31.6(3)
C(2)-C(3)-C(4)-C(5)	−106.2(3)	−106.9(3)
C(2)-C(3)-C(4)-C(15)	70.9(3)	68.6(3)
C(3)-C(4)-C(5)-C(6)	164.8(4)	163.5(3)
C(15)-C(4)-C(5)-C(6)	−12.1(4)	−11.7(4)
C(4)-C(5)-C(6)-C(7)	−108.1(3)	−110.9(3)
C(4)-C(5)-C(6)-O(17)	133.7(3)	131.6(3)
C(5)-C(6)-C(7)-C(8)	65.4(2)	70.8(2)
C(5)-C(6)-C(7)-C(11)	−178.2(2)	−172.6(2)
O(17)-C(6)-C(7)-C(8)	−175.3(2)	−170.9(2)
O(17)-C(6)-C(7)-C(11)	−58.9(2)	−54.4(2)
C(5)-C(6)-O(17)-C(18)	−107.5(3)	−110.8(2)
C(7)-C(6)-O(17)-C(18)	134.3(2)	132.2(2)
C(6)-C(7)-C(8)-C(9)	−116.1(3)	−116.2(2)
C(6)-C(7)-C(8)-O(21)	122.7(2)	123.9(2)
C(11)-C(7)-C(8)-C(9)	120.3(3)	120.4(2)
C(11)-C(7)-C(8)-O(21)	−0.9(2)	0.5(2)
C(6)-C(7)-C(11)-C(12)	67.3(4)	65.2(4)
C(6)-C(7)-C(11)-C(13)	−117.5(3)	−119.7(3)
C(8)-C(7)-C(11)-C(12)	−172.3(4)	−174.6(4)
C(8)-C(7)-C(11)-C(13)	2.9(3)	0.6(3)
C(7)-C(8)-C(9)-C(10)	74.9(3)	70.4(2)
O(21)-C(8)-C(9)-C(10)	−165.0(2)	−170.2(2)
C(7)-C(8)-O(21)-C(13)	−1.6(2)	−1.6(3)
C(9)-C(8)-O(21)-C(13)	−127.9(2)	−127.4(2)
C(8)-C(9)-C(10)-C(1)	71.8(3)	73.0(3)
C(8)-C(9)-C(10)-C(14)	−113.9(3)	−110.3(3)
C(7)-C(11)-C(13)-O(21)	−4.2(3)	−1.6(3)
C(7)-C(11)-C(13)-O(22)	176.3(3)	178.4(4)
C(12)-C(11)-C(13)-O(21)	171.5(3)	174.2(3)
C(12)-C(11)-C(13)-O(22)	−8.1(4)	−5.8(4)
C(11)-C(13)-O(21)-C(8)	3.6(2)	2.0(2)
O(22)-C(13)-O(21)-C(8)	−176.8(2)	−178.0(3)
C(6)-O(17)-C(18)-O(19)	1.4(4)	2.5(3)
C(6)-O(17)-C(18)-C(20)	178.4(4)	180.0(3)

[a] The torsion angle A-B-C-D is defined as positive if, when viewed along the B-C bond, atom A must be rotated clockwise to eclipse atom D.

shift undoubtedly could have a valuable diagnostic value. Even a more interesting effect was observed in the same group of compounds, namely the *downfield* γ-effect on the angular methyl group [C(10)] when there was a hydroxy- or a hydroperoxy-group on C(5). This yet to be explained effect has been previously reported and is only observed in bridgehead substituted compounds or whenever the intervening atoms are heavily substituted.[30] It appears that electronegativity of the substituent is of no value in explaining this effect, rather it takes place because of the high degree of substitution around the atoms involved.

Experimental

M.p.s are uncorrected and were determined on a Thomas-Hoover Unimelt capillary apparatus. Optical rotations were taken on a Perkin-Elmer model 141 automatic polarimeter. The u.v. absorption spectra were obtained on a Beckman-Acta model III recording spectrophotometer, i.r. absorption spectra were recorded using a Beckman IR-33 spectrophotometer or Perkin-Elmer 281B infrared spectrophotometer. Continuous wave ^{1}H n.m.r. spectra were recorded on a JEOL model C-60 HL or a Varian EM 390 nuclear magnetic

Table 4. ^{13}C N.m.r. signals (δ/p.p.m.) for hydroperoxysesquiterpenes and related compounds (signal preceded by multiplicity)

Carbon	(3)	(4)	(5)	(6)	(7)	(12) [a]	(14)	(15)	(16)
1	d, 75.4	d, 75.4	d, 72.9	d, 72.7 [1]	d, 74.0	d, 84.0	d, 70.4	s, 202.8	t, 23.2 [1]
2	t, 34.6 [1]	t, 34.8 [1]	t, 38.1 [1]	t, 39.2 [2]	t, 42.5 [1]	t, 43.7 [1]	t, 34.6 [1]	t, 36.5 [1]	t, 26.2 [1]
3	d, 121.6	d, 121.2	d, 85.6	d, 71.7 [1]	s, 197.6	t, 35.4 [1]	t, 31.1 [1]	t, 35.7 [1]	t, 34.4 [1]
4	s, 133.6	s, 133.8	s, 122.3	s, 127.6	s, 129.0	s, 139.2	s, 138.7	s, 146.7	s, 127.0
5	d, 51.5 [2]	d, 50.7 [2]	s, 137.9	s, 134.3	s, 153.2	s, 127.5	s, 126.7	s, 127.7	s, 130.1
6	d, 81.7	d, 81.3	d, 82.6	d, 83.0	d, 82.1	d, 73.2	d, 72.7	d, 72.3	d, 83.4
7	d, 51.3 [2]	d, 53.9 [2]	d, 52.7	d, 53.8	d, 52.2	d, 48.8	d, 48.9	d, 47.7	d, 50.5
8	t, 33.1 [1]	t, 22.9 [1]	t, 24.2 [1]	t, 24.8 [2]	t, 24.3 [1]	d, 78.6	d, 78.2	d, 76.7	t, 37.3 [1]
9	t, 21.4 [1]	t, 32.9 [1]	t, 38.1 [1]	t, 37.2 [2]	t, 38.0 [1]	masked by [1] $[^2H_6]$acetone	t, 41.8 [1]	t, 40.4 [1]	t, 40.9 [1]
10	s, 41.1	s, 40.7	s, 42.5	s, 43.3	s, 43.9	s, 143.4	s, 146.8	s, 139.4	s, 41.4
11	s, 139.4	d, 40.9	d, 41.1	d, 41.3	d, 41.1	s, 137.9	s, 136.2	s, 135.9	s, 139.8
12	s, 170.6	s, 179.5	s, 178.8	s, 178.7	s, 178.0	s, 170.0 [2]	s, 169.5 [2]	s, 169.9 [2]	s, 170.3
13	t, 116.5	q, 12.5	q, 12.3	q, 12.6	q, 12.3	t, 124.2	t, 124.9	t, 124.1 [3]	t, 117.7
14	q, 11.2	q, 11.2	q, 18.4 [2]	q, 17.7 [3]	q, 11.2	t, 118.3	t, 114.7	t, 125.5 [3]	q, 18.9 [2]
15	q, 23.2	q, 23.3	q, 17.5 [2]	q, 18.1 [3]	q, 17.5	q, 17.6	q, 17.4	q, 17.4	q, 19.9 [2]
Other	—		—	—	—	(20.8 and 169.5 [2] for CH_3CO)	(20.9 and 169.6 [2] for CH_3CO)	(20.8 and 169.3 [2] for CHCO)		

Carbon	(17)	(18)	(19)	(20) [b]	(21)	(22)	(23)	(24)	(25)
1	t, 22.4 [1]	t, 21.4 [1]	d, 77.6	d, 71.0	d, 71.7	d, 71.8	d, 78.2	t, 39.5 [1]	t, 23.4 [1]
2	t, 22.6 [1]	t, 21.9 [1]	t, 23.1 [1]	t, 31.8 [1]	t, 30.5 [1]	t, 30.5 [1]	t, 35.9 [1]	t, 37.9 [1]	t, 36.1 [1]
3	t, 35.7 [1]	t, 34.6 [1]	t, 27.1 [1]	t, 31.1 [1]	t, 29.8 [1]	t, 30.0 [1]	t, 33.7 [1]	d, 122.5	t, 41.1 [1]
4	s, 145.7	s, 146.5	s, 126.2	s, 144.8	s, 144.8	s, 145.3	s, 142.8	s, 133.3	s, 144.9
5	s, 86.7	s, 79.3	s, 129.3	s, 87.8	s, 77.1	s, 76.8	d, 53.2	d, 51.5 [2]	d, 54.7
6	d, 82.6	d, 82.1	d, 83.2	d, 82.9	d, 81.9	d, 82.9	d, 79.7	d, 82.2	d, 79.8
7	d, 42.8	d, 43.3	d, 49.8	d, 42.8	d, 43.3	d, 45.5	d, 49.8	d, 51.7 [2]	d, 53.0
8	t, 34.6 [1]	t, 34.0 [1]	t, 33.3 [1]	t, 31.1 [1]	t, 29.8 [1]	t, 29.8 [1]	t, 31.4 [1]	t, 23.5 [1]	t, 42.0 [1]
9	t, 32.5 [1]	t, 31.6 [1]	t, 38.3 [1]	t, 22.4 [1]	t, 21.2 [1]	t, 22.9 [1]	t, 21.6 [1]	t, 21.6 [1]	t, 23.0 [1]
10	s, 42.6	q, 40.6	s, 42.1	s, 47.5	s, 44.8	s, 44.7	s, 43.1	s, 36.1	s, 38.6
11	s, 141.3	s, 140.3	s, 139.2	s, 141.3	s, 140.0	d, 41.3	s, 139.6	s, 139.9	d, 40.7
12	s, 170.6	s, 170.7	s, 170.3	s, 170.6	s, 170.6	s, 179.3	s, 170.6	s, 170.6	s, 179.3
13	t, 116.0	t, 116.9	t, 118.4	t, 116.4	t, 116.4	q, 12.3 [2]	t, 116.8	t, 116.0	q, 12.3
14	q, 21.9	q, 20.6	q, 18.5 [2]	q, 14.4	q, 13.3	q, 13.3 [2]	q, 11.7	q, 17.5	q, 18.1
15	t, 113.3	t, 111.2	q, 19.6 [2]	t, 114.4	t, 112.6	t, 112.3	t 110.7	q, 20.3	t,, 108.8

All spectra were taken in $CDCl_3$ unless superscripted with a letter; a = $[^2H_6]$acetone, b = $[^2H_8]$dioxan. [1,2, and 3]Represent signals that may be interchanged within their own set.

resonance spectrometers. Fourier transform ^1H and ^{13}C n.m.r. spectra were obtained on a JEOL NJM-FX60 Fourier transform NMR spectrometer. Chemical shifts were reported in δ units with tetramethylsilane (TMS) as the internal standard. The solvents used in n.m.r. measurements were deuteriated and are specified for each compound. The low-resolution mass spectral analyses were performed on a DuPont 21-492 mass spectrometer at 70 eV or Finnigan 3200 F GC/MS/DS.

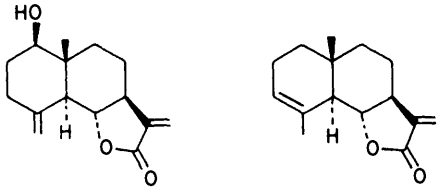
Microanalyses were performed by Scandinavian Microanalytical Laboratories, Herlev, Denmark or Galbraith Laboratories, Knoxville, Tennessee.

T.l.c. was performed on Brinkmann pre-coated silica gel G plates (0.25 mm Silica G-F_{254}). Developed plates were visualized under u.v. light (short or long wavelengths) and/or with one of the following spray reagents: (1) 0.5% aqueous solution of potassium permanganate; (2) anisaldehyde spray: prepared by adding 0.5 ml of anisaldehyde to a solution of 10 ml of acetic acid and 1 ml of concentrated sulphuric acid in 90 ml of methanol.

Silica gel G (for t.l.c.) used for column chromatography was prepared by making a slurry with silica gel G and twice its weight of water. The slurry was poured into a dish and placed in a 110 °C oven for 24 h. The dried material was passed through a 60 mesh sieve and activated at 110 °C for 1 h before use.

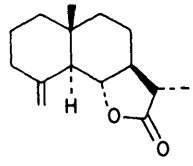
Sensitized photo-oxygenations of the solutions containing the sesquiterpene lactones and Methylene Blue in absolute ethanol were performed by placing the solution in a Dudley bubbling apparatus connected to an oxygen source. Oxygen was gently bubbled through the solution. The reaction tube was inserted in a 4-l silver-lined Dewar flask 10 cm from a Sylvania DWY 650 W quartz-halogen lamp. Cooling water was passed into the Dewar which maintained the temperature at 17 ± 1 °C.

Authentic samples of costunolide (1), santamarine (3), reynosin (23), α-cyclocostunolide (24), and dihydro-β-cyclocostunolide (25), were available from previous work. The laurenobiolide (2) used during the initial phase of this study was a gift from Dr. H. Tada, Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-Ka, Osaka 535, Japan. A generous supply of *Artemisia tridentata* ssp. *vaseyana* and copies of the i.r. and ^1H n.m.r. spectra of arbusculin-C (18) were obtained, courtesy of Dr. Rick G. Kelsey, Wood Chemistry Laboratory, University of Montana, Missoula, Montana 59812. Copies of the i.r. and ^1H n.m.r. spectra of tanacetin (21), on the other hand, were obtained from Dr. V. Herout of the Institute of Organic Chemistry and Biochemistry, Czechoslovakia. An authentic sample of artemin (22) together with copies of its i.r. and ^1H n.m.r. spectra were obtained from Dr. A. G. Gonzalez, Institute of Natural Products, University of Laguna, Tenerife, Spain.



(23)

(24)



(25)

Copies of the i.r. and ^{1}H n.m.r. spectra of tulirinol (13) and dihydrochrysanolide (14) were obtained from Dr. Raymond W. Doskotch of the Ohio State University, College of Pharmacy, Columbus, Ohio 43210.

Sensitized Photo-oxygenation of 11,13-*Dihydrosantamarine* (4) *to the Hydroperoxide* (5).—11,13, Dihydrosantamarine [31] (4) (60 mg) was dissolved in absolute ethanol (20 ml) to which Methylene Blue (2 mg) was added. The solution was then photo-oxygenated for 3 h as described above. T.l.c. of the mixture using 7% ethanol in chloroform as solvent revealed one spot, R_F 0.20 [(4) had an R_F value of 0.50 in the same system]. The product was isolated by evaporating the solution to dryness and dissolving the residue in chloroform (1 ml); this was then passed through a short column of silica gel using chloroform as solvent. The filtrate was evaporated and chromatographed over 15% $AgNO_3$-impregnated silica gel (8 g) using 15% $CHCl_3$ in ether to yield crude (5) (48 mg) as a brownish oil. Treatment with activated charcoal in chloroform gave pure (5) as a colourless oil (Found: C, 63.75; H, 7.75. Calc. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.86%), $\nu_{max.}$ ($CHCl_3$) 3 680, 3 520, 3 350, and 1 775 cm^{-1}; $\lambda_{max.}$ (MeOH) (log ε) 212 nm (3.68); *m/z* 264 ($M^+ - 18$, 18%); δ($CDCl_3$) 3.88 (1 H, m, 1-H), 4.29br (1 H, s, 3-H), 4.63br (1 H, d, *J* 9.0 Hz, 6-H), and 9.31 (exchangeable, OOH). For the ^{13}C n.m.r. spectrum see Table 4.

Dehydration of the Hydroperoxide (5) *to the Ketone* (7).—The hydroperoxide (5) (86 mg) was stirred in pyridine (1 ml) and acetic anhydride (24 μl) for 15 min. The reaction mixture was then taken up in $CHCl_3$ (125 ml), washed with 5% aqueous H_2SO_4 (3 × 10 ml), 5% aqueous $NaHCO_3$ (3 × 10 ml), and water (3 × 10 ml), and dried (Na_2SO_4). Evaporation of the extract left a colourless oil (84 mg) which yielded upon crystallization from $CHCl_3$–Pr^i_2O colourless cubes of (7) (70 mg), m.p. 152—153 °C (Found: C, 68.25; H, 7.75. Calc. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63%), $[\alpha]_D^{20}$ +58° (*c* 0.03, abs. ethanol); $\nu_{max.}$ (KBr) 3 420, 1 780, 1 650, and 1 612 cm^{-1}; $\lambda_{max.}$ (MeOH) (log ε) 243 nm (4.02) and 209sh (3.50); *m/z* 264 (M^+) 32%; δ_H 3.88 (1 H, m, 1-H), 4.81br (1 H, d, *J* 7.5 Hz, 6-H), and 2.02 (3 H, d, *J* 1.5 Hz, 15-H). For the ^{13}C n.m.r. spectrum see Table 4.

Dehydration of the Ketone (7) *to Santonin* (8).—The ketone (7) (80 mg) was stirred at room temperature with pyridine (1 ml) to which four 0.4 ml-portions of $SOCl_2$ were added during a period of 2 h. Monitoring of the reaction by t.l.c. on silica gel G plates using 5% ethanol in $CHCl_3$ showed two major spots with R_F values of 0.24 (starting material) and 0.61 with a minor spot, R_F 0.49 corresponding to santonin (8). Evaporation of the reaction mixture left an oily residue that was taken up in $CHCl_3$ (100 ml), washed with water, dried (Na_2SO_4) and then evaporated to leave a yellow oil (75 mg). This residue was heated at 75 °C for 2.5 h in chloroform solution (1 ml) to which was added triethylamine (3 ml). Evaporation and chromatography of the residue over silica gel G (8 g) packed in a column using 5% ethanol in $CHCl_3$ as eluant yielded santonin (8) (68 mg) which was crystallized from ethyl acetate–hexane, m.p. 171—172 °C (Found: C, 72.9; H, 7.35. Calc. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37%), $[\alpha]_D^{25}$ −174° (*c* 0.35, $CHCl_3$) (lit.[32] m.p. 172—173 °C; $[\alpha]_D$ −176° (*c* 4.05); $\nu_{max.}$ ($CHCl_3$) 1 780, 1 660, 1 635, and 1 615 cm^{-1}; *m/z* 246 (M^+, 24%); δ($CDCl_3$) 6.25 (1 H, d, *J* 8.5 Hz, 1-H) and 6.71 (1 H, *J* 8.5 Hz, 2-H). The i.r., ^{1}H n.m.r., and ^{13}C n.m.r. spectra were identical with those of a sample of santonin obtained from National Biochemicals Corporation, Cleveland, Ohio, U.S.A.

Reduction of the Hydroperoxide (5) *to the Alcohol* (6).—The hydroperoxide (5) (150 mg) was stirred for 30 min in ethanolic solution (5 ml) with $NaBH_4$ (20 mg). The unchanged borohydride was quenched with 5% acetic acid and the mixture was evaporated. Extraction with chloroform in the usual manner yielded a colourless oil (150 mg) which crystallized from ether to give colourless needles (119 mg), m.p. 92—94 °C (Found: C, 67.65; H, 8.55. Calc. for: $C_{15}H_{22}O_4$: C, 67.64; H, 8.33%), $[\alpha]_D^{25}$ +61° (*c* 0.46 in abs. ethanol); $\nu_{max.}$ (KBr) 3 170, 3 360, 3 430, and 1 777 cm^{-1}; *m/z* 266 (M^+, 13%); the ^{1}H n.m.r. spectrum ($CDCl_3$) was similar to that of (5) except for the absence of the exchangeable signal at δ 9.31. For the ^{13}C n.m.r. spectrum see Table 4.

Sensitized Photo-oxygenation of Laurenobiolide (2) *to the Hydroperoxides* (10) *and* (11).—Laurenobiolide (2) (1.09 g) was dissolved in abs. ethanol (25 ml) containing Methylene Blue (3 mg). The solution was subjected to photo-oxygenation for 2.5 h as before, evaporated, and the residue dissolved in $CHCl_3$ and filtered over silica gel to remove the dye. Evaporation of the filtrate left a reddish oily residue (1.2 g) which crystallized readily from ether to give (12) (0.721 g). The oily mother liquor was mostly (11) but was still contaminated by (12) as shown by an examination of its ^{1}H n.m.r. spectrum. It could not be purified by chromatography.

The hydroperoxide (12) was obtained as colourless needles, m.p. 148—149 °C (with frothing), $[\alpha]_D^{25}$ −10.5° (*c* 0.4 in acetone) (Found: C, 63.3; H, 6.9. Calc. for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88), $\nu_{max.}$ (KBr) 3 340, 1 720, 1 755, and 1 653 cm^{-1}; *m/z* 262 ($M^+ - 60$, 5%); δ($CDCl_3$) 8.24 (1 H, s, exchangeable, OOH), 2.08 (3 H, s, OAc) and 1.82 (3 H, s, Me). For the ^{13}C n.m.r. spectrum see Table 4.

Reduction of the Hydroperoxides (11) *and* (12) *to Dihydrochrysanolide* (14) *and Tulirinol* (13), *respectively*.—The mother liquor left from the crystallization of (12) (0.47 g) was stirred for 5 min in ethyl acetate solution (25 ml) with $SnCl_2$ (0.56 g). The mixture was evaporated and the residue extracted with $CHCl_3$. Filtration over silica gel then evaporation left a crystalline residue (400 mg) which showed two spots on t.l.c. (silica gel G plates, using 20% acetone in benzene as eluant), R_F 0.25 and 0.35. Separation of the two components was accomplished by flash chromatograph [19] to give tulirinol (13) and then dihydrochrysanolide (14). Tulirinol (13) (0.145 g) was obtained as a white powder, m.p. 204—205 °C, $[\alpha]_D^{25}$ −47° (*c* 0.60, MeOH) [lit.,[20] m.p. 204—205 °C, $[\alpha]_D^{23}$ −51 (*c*, 0.3, MeOH)] (Found: C, 66.6; H, 7.3. Calc. for $C_{17}H_{22}O_5$:

C, 66.65; H, 7.24%), $\nu_{max.}$ ($CHCl_3$) 3 580, 1 758, 1 738, and 1 650 cm^{-1}; *m/z* 306 (M^+, less than 1%). The i.r. and ^1H n.m.r. spectra were identical with those of authentic tulirinol [20] (13). Dihydrochrysanolide (14) (235 mg) was obtained as colourless needles, m.p. 160—161 °C, $[\alpha]_D^{25}$ +7° (*c* 0.62, MeOH); *m/z* 288 (M^+ − 18, less than 1%); $\nu_{max.}$ ($CHCl_3$) 3 585, 3 480, 1 755, 1 730, and 1 650 cm^{-1}; δ($CDCl_3$) 6.34 (1 H, d, *J* 3.3 Hz, 13-H), 5.88 (1 H, d, *J* 3.0 Hz, 13-H), 2.08 (3 H, s, OAc), and 1.80, (3 H, d, *J* 1.5 Hz, C=CMe). For the ^{13}C n.m.r. spectrum see Table 4. The i.r. and ^1H n.m.r. spectra were identical to those of dihydrochrysanolide (14).[27]

Reduction of the Hydroperoxide (11) *to Dihydrochrysanolide* (14).—The hydroperoxide (11) (50 mg) was reduced with $SnCl_2$ as described before to give dihydrochrysanolide (14) (42 mg) as the sole product.

Chrysanolide (15).—The hydroperoxide (12) (25 mg) was dissolved in a mixture of pyridine (0.5 ml) and acetic anhydride (0.5 ml). The reaction mixture was set aside at room temperature for 2 h and then worked up in the usual manner to give a crude crystalline residue (20 mg) which yielded upon recrystallization from $CHCl_3$–Pr^i_2O (15) as colourless needles (17 mg), m.p. 202 °C, $[\alpha]_D^{25}$ −50° (*c*, 0.3, MeOH) (Found: C, 67.1; H, 6.5. Calc. for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62%) [lit.,[23] m.p. 204—205 °C; $[\alpha]_D^{25}$ −52° (*c*, 0.315, MeOH]; $\nu_{max.}$ ($CHCl_3$) 1 770, 1 745, 1 685, 1 635, and 1 610 cm^{-1}; δ($CDCl_3$) 1.77br (3 H, s, Me) and 2.07 (3 H, s, OAc); *m/z* 304 (M^+, 31%). The i.r. and ^1H n.m.r. spectra were identical with those of chrysanolide (15). For the ^{13}C n.m.r. spectrum see Table 4.

Sentisized Photo-oxygenation of γ*-Cyclocostunolide* (*Arbusculin-C*) (16) *to the Hydroperoxide* (17).—γ-Cyclocostunolide (16) [22] (105 mg) was dissolved in absolute ethanol (15 ml) containing 2 mg of Methylene Blue. The solution was photo-oxygenated as described before for 4 h. After the usual work-up, crude (17) was obtained (120 mg) and was recrystallized from acetone–ether to give colourless needles (98 mg), turning brown at 98 °C and melting at 164—165 °C; $[\alpha]_D^{20}$ +135° (*c*, 0.27, absolute ethanol) (Found: C, 67.75; H, 7.6. Calc. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63%), $\nu_{max.}$ (KBr) 3 425, 1 760, 1 675, and 1 650 cm^{-1}; $\lambda_{max.}$ (MeOH) (log ε) 214 nm (4.17); *m/z* 248 (M^+ − 16, 22%); δ([$^2H_5$]pyridine) 4.54 (1 H, d, *J* 11, 6-H) and 13.19br (1 H, s, exchangeable, OOH). For the ^{13}C n.m.r. spectrum see Table 4.

Reduction of the Hydroperoxide (17) *to Arbusculin-C* (18).—The hydroperoxide (17) (83 mg) was stirred for 30 min in acetone solution (2 ml) with triphenylphosphine (84 mg). Evaporation of the solvent and chromatography of the residue on silica gel G using $CHCl_3$ as solvent gave crude (18) which upon crystallization from diethyl ether–ethyl acetate gave colourless needles (59 mg), m.p. 150—151 °C; $[\alpha]_D^{25}$ +113° (*c* 0.3, $CHCl_3$) (same as literature values) (Found: C, 72. 5; H, 8.0. Calc. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%), $\nu_{max.}$ ($CHCl_3$) 3 590, 1 765, and 1 640 cm^{-1}; δ($CDCl_3$) 4.27 (1 H, d, *J* 11.0 Hz, 6-H) and 1.72br (1 H, s, exchangeable, OH); *m/z* 248 (M^+, 42%). For the ^{13}C n.m.r. spectrum see Table 4.

Sensitized Photo-oxygenation of Magnolialide (19) *to the Hydroperoxide* (20).—Magnolialide [17] (19) (139 mg) was dissolved in absolute ethanol (16 ml) containing Methylene Blue (2 mg) and the solution was photo-oxygenated as described before for 7 h. After the usual work-up, crude (20) (106 mg) was obtained and was crystallized from acetone–ether to yield colourless plates (106 mg), decomposing without melting at 192 °C, $[\alpha]_D^{21}$ +79° (*c* 0.21, abs. ethanol) (Found: C, 64.0; H, 7.15. Calc. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19%), $\nu_{max.}$ (KBr) 3 430, 3 240, 1 750, 1 675, and 1 650 cm^{-1}; *m/z* 280 (M^+, 16%); δ($CDCl_3$) 4.39 (1 H, d, *J* 9.5 Hz, 6-H) and 8.02br (1 H, s, exchangeable OOH). For the ^{13}C n.m.r. spectrum see Table 1.

Reduction of the Hydroperoxide (20) *to Tanacetin* (21).—The hydroperoxide (20) (53 mg) was stirred for 30 min in acetone (3 ml) with triphenylphosphine (48 mg). The solvent was evaporated and the residue chromatographed on silica gel G using 20% acetone in $CHCl_3$ as eluant to yield crude (21) (47 mg) which crystallized from $CHCl_3$–Me_2CO to give colourless cubes (40 mg), m.p. 205—206 °C (lit.,[33] m.p. 205 °C), $[\alpha]_D^{25}$ +154° (*c* 0.15, absolute ethanol) (Found: C, 67.8; H, 7.6. Calc. for $C_{15}H_{20}O_4$: C, 68.15; H, 7.63%), $\nu_{max.}$ (KBr) 3 500, 1 750, 1 675, and 1 650 cm^{-1}; δ 4.29 (1 H, d, *J* 11.0 Hz, 6-H) and 4.16 (1 H, dd, *J* 11.0 and 5.0); *m/z* 264 (M^+, 60%). For the ^{13}C n.m.r. spectrum see Table 4.

Horeau Esterification of Dihydrochrysanolide (14).—A sample of (14) (100 mg, 0.326 mmol) and α-phenylbutyric anhydride (266 mg, 0.858 mmol) were stirred in pyridine (3 ml) for 48 h at room temperature. The mixture was then stirred with water (10 ml) for 6 h, diluted with further water (30 ml) and extracted with diethyl ether (75 ml). The diethyl ether layer was extracted successively with water (3 × 25 ml), 5% $NaHCO_3$ (3 × 50 ml), and water (4 × 25 ml). All the aqueous phases were combined, acidified with 1M-H_2SO_4 to pH 2, and extracted with $CHCl_3$. The $CHCl_3$ phase was washed (H_2O), dried (Na_2SO_4), and evaporated to leave α-phenylbutyric acid (205 mg), $[\alpha]_D^{25}$ −5.34° (*c* 4.1, benzene), corresponding to an optical yield [21] of 23.6%. These data are in agreement with an *S* configuration for C(1).

Crystal Data.—(a) (12), $C_{17}H_{22}O_6$, *M* = 322.4, Monclinic, *a* = 14.350(6), *b* = 5.822(3), *c* = 10.343(4) Å, β = 107.64(2)°, *U* = 8.21.1 Å, *Z* = 2, D_c = 1.304 g cm^{-1}. Cu-K_α radiation, λ = 1.5418 Å; μ(Cu-K_α) = 8.3 cm^{-1}. Space group $P2_1(c_2^2)$ from the systematic absences: 0*k*0 when *k* 2*n* and (12) is chiral.

(b) (14), $C_{17}H_{22}O_5$, *M* = 306.4, Monoclinic, *a* = 14.461(6), *b* = 5.887(3), *c* = 9.698(4) Å, β = 107.44(2)°, *U* = 787.7 Å, *Z* = 2, D_c = 1.292 g cm^{-3}. Cu-$K_\sim$ radiation, μ(Cu-K_α) = 7.9 cm^{-1}. Space group *P*2 (α_2^2) as for (11).

Crystallographic Measurements.—Oscillation and Weissenberg photographs, taken with Cu-K_α radiation, yielded preliminary unit-cell parameters and space group information. That (12) and (14) were isomorphous was apparent from the strong similarities in the intensity distributions of their *h*0*l* and *h*1*l* reciprocal lattice nets. For intensity measurements, crystals of dimensions *ca.* 0.20 × 0.20 × 0.70 mm (12) and 0.10 × 0.20 × 0.40 mm (14) were oriented, in turn, on an Enraf-Nonius CAD-3 automated diffractometer (Ni-filtered Cu-K_α radiation) where one quadrant of reciprocal space was surveyed by means of the θ—2θ scanning procedure as described previously.[34] In neither case was any significant variation noted when the intensity of a reference reflection was remeasured periodically throughout. Totals of 1 484 (12) and 1 300 (14) reflections with $I > 2.0\sigma(I)$[$\sigma^2(I)$ = scan count + total background count] were judged to be observed and were retained for use in the structure analyses. The usual Lorentz and polarization corrections were applied; no absorption corrections were necessary. For each crystal, refined unit-cell parameters were evaluated by least-squares treatment of the diffractometer setting angles for 40 high order reflections widely separated in reciprocal space.

Structure Analyses.—The crystal structure of (12) was solved by direct methods by use of the MULTAN76 [35] suite

of programmes and the highest 250 $|E|$-values. Approximate positions for all non-hydrogen atoms were obtained from an E-map generated by use of the phase set which yielded the highest combined figure-of-merit; enantiomer co-ordinates were chosen such that the hydrogen atom at C(7) was in the known α-configuration. Least-squares adjustment of non-hydrogen atom positional and isotropic thermal parameters reduced R smoothly to 0.129 from that of 0.254 for the initial model. When co-ordinates for all non-hydrogen atoms in (12), save for those of hydroperoxy oxygen O(23), were then employed in a structure-factor calculation with data for (14), R was 0.466, and this decreased to 0.115 after several rounds of least-squares refinement of the positional and isotropic thermal parameters. Hydrogen atoms in (12) and (14) were then located in difference Fourier syntheses. Variation of hydrogen atom positional and isotropic thermal parameters in addition to non-hydrogen atom positional and anisotropic thermal parameters in the subsequent least-squares iterations led to convergence at R 0.040 for (12) and 0.033 for (14). Final non-hydrogen atom positional parameters are in Table 1. Hydrogen atom positional and thermal parameters, and lists of observed and calculated structure amplitudes have been deposited as a Supplementary Publication [SUP. No. 23430 (24 pages)].*

Atomic scattering factors used in all structure-factor calculations were those for carbon and oxygen from ref. 36, and for hydrogen from ref. 37. In the least-squares iterations, $\Sigma w\Delta^2(\Delta = |F_o| - |F_c|)$ was minimized with weights, w, assigned according to the scheme: $\sqrt{w} = 1$ for $|F_o| < 8.0$, and $\sqrt{w} = 8.0/|F_o|$ for $|F_o| > 8.0$. The y co-ordinate of O(17) was held constant throughout to define the origin in this direction.

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* For details of the Supplementary publications scheme, see Notice to Authors No. 7, *J. Chem. Soc., Perkin Trans. 1*, 1981, Index issue.

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