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BARBATUSIN AND CYCLOBUTATUSIN, TWO NOVEL DITERPENOIDS FROM *COLEUS BARBATUS* BENTHAM

RAYMOND ZELNIK,[a] DAVID LAVIE,[b] ELIE C. LEVY,[b] ANDREW H.-J. WANG[c] and IAIN C. PAUL[c]*

[a]Department of Organic Chemistry, Institute Butantan, São Paulo, Brasil
[b]Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel
[c]Department of Chemistry, University of Illinois, Urbana, IL 61801, U.S.A.

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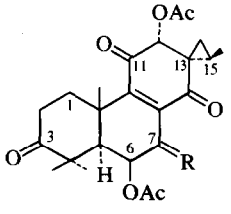
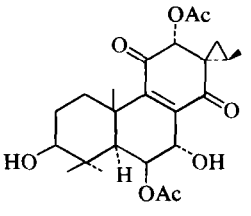
Abstract—The structure of three diterpenoids from *Coleus barbatus*, Bentham (Labiatae) having a spirocyclopropyl side chain have been determined: they are barbatusin (**1a**), 3β-hydroxy-3-deoxybarbatusin (**2**) and cyclobutatusin (**3a**). The structures of **1a** and **3a** were established by X-ray diffraction analysis, and the latter compound has been shown to have an unusual 4-membered ring produced by a bond across C(1) to C(11). Chemical transformations and interconversions are presented, together with spectroscopic studies.

In the course of our search for tumour inhibitors from species of the Brazilian flora[1] the bitter principles of the leaves of *Coleus barbatus* Bentham (Labiatae) were investigated. *Coleus barbatus*, native to India,[2] is well adapted to the São Paulo region and has been used in the practice of folk medicine against intestinal disorders.

Preliminary investigations had shown that an extract of the leaves is active in the *in vivo* test against Ehrlich's ascites tumour in mice.[3] Careful chromatographic separation of the extract led to the isolation and identification of three crystalline diterpenoids.[4] The structure of the major compound, barbatusin (**1a**), was established by spectroscopic and X-ray diffraction studies and was found to be a novel diterpenoid with a spirocyclopropyl unit at C(13). The structure of the second substance, a minor component, 3β-hydroxy-3-deoxybarbatusin (**2**) was determined by spectroscopic analysis and direct conversion to barbatusin, while that of cyclobutatusin (**3a**), also a minor constituent, was established by X-ray diffraction analysis. Cyclobutatusin retains the basic ring skeleton of barbatusin, but has the remarkable new feature of a 4-*membered* ring formed by a bond between C(1) and C(11).



1a: R = α-OH, β-H
b: R = O
c: R = α-OCOCH$_3$, β-H
d: R = α-OCOC$_6$H$_4$Br, β-H



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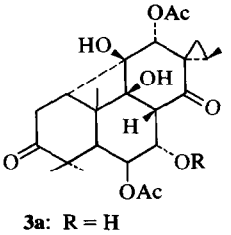


3a: R = H
b: R = COC$_6$H$_4$Br

Barbatusin (**1a**), m.p. 224–228°, has a molecular formula of $C_{24}H_{30}O_8$ assigned on the basis of elemental analysis and mass spectrometry (M^+ 446). The IR spectrum indicated the presence of hydroxy, ester, cyclohexanone and α, β unsaturated cyclohexanone groups as well as an ethylenic bond. In the UV, the absorption maximum at 235 nm (ε 15,000) for the conjugated ketone underwent a bathochromic shift upon addition of ethanolic alkali, to 223 and 272 nm (ε 26,800 and 4600 sh), typical for an enolate system. The NMR spectrum showed signals for three tertiary C–Me (s at δ 1.21, 1.24 and 1.67), one secondary C–Me (d at δ 1.14, J = 6.5 Hz), and two acetate Me functions (s at δ 2.02 and 2.10) as well as two CHOAc protons (dd at δ 5.28, $J_{5,6}$ = 1 and $J_{6,7}$ = 2 Hz; s at δ 5.06) in conjunction with the latter functions. The presence of the OH group was shown by a broad band at δ 3.45 which disappeared upon D_2O exchange, consequently the signal at δ 4.68 ($J_{6,7}$ = 2 Hz) was assigned to the proton on the carbon atom bearing the OH group. Since no vinylic proton could be detected, the IR absorption observed at 1605 cm^{-1} was attributed to a tetrasubstituted double bond.

Oxidation of barbatusin in acidic conditions (Jones reagent) afforded 7-oxo-7-dehydroxybarbatusin (**1b**), m.p. 205–208°; λ_{max} 218, 235 and 253 nm (ε 15,000, 17,700 and 14,000 sh); in ethanolic alkaline solution these maxima were replaced by two intense peaks at 224 and 275 nm (ε 25,900 and 14,000), strongly suggesting the presence of a β-diketone system. This indication is supported by a band in the IR at 1640 cm^{-1} which falls in the range of the absorption frequencies of β-diketones.[5]

Barbatusin readily formed a monoacetate (**1c**), m.p. 184–186°, sharp doublet in the NMR at δ 5.75 ($J_{6,7}$ = 2 Hz) for the CHOAc proton of the additional acetate group (s at δ 2.05). Bromobenzoylation of barbatusin afforded the monoester **1d**, m.p. 173–175°. At this stage, the three dimensional structure of barbatusin was determined by the single crystal X-ray analysis of the 1:1 benzene solvate of the p-bromobenzoyl ester (**1d**) of barbatusin.

The crystals of the 1:1 benzene solvate of **1d** are monoclinic, space group $P2_1$, with a = 10.135(3), b = 24.184(6), c = 7.707(2) Å and β = 109°46′(2′) and there are two molecules of the 1:1 solvate in the unit cell. The crystal structure was refined to an R-factor of 0.065 for 2269 non-zero reflections measured on a Picker FACS-1 computer-controlled diffractometer (CuK$_\alpha$ radiation).[6] A

stereoscopic view of the molecule of **1d** is shown in Fig. 1, thus establishing the structure of barbatusin as that shown in **1a**. The absolute configuration of the molecule was determined by using the anomalous scattering of the Br atom. The absolute configuration about C(10) of barbatusin is the same as that for royleanone.[7] The final values for the bond lengths and angles have been deposited. The torsion angles around the ring system are shown in Fig. 2.

The individual values of the bond lengths (Table 1) require little specific comment. The cyclohexanone ring A adopts a distorted boat conformation with the C(1)–C(2) and C(4)–C(5) bonds having the smallest internal torsion angles. This conformation results in the C(3)–O(15)† group pointing to the β-side of the molecule as to all the

†For numbering in this discussion see Fig. 2.

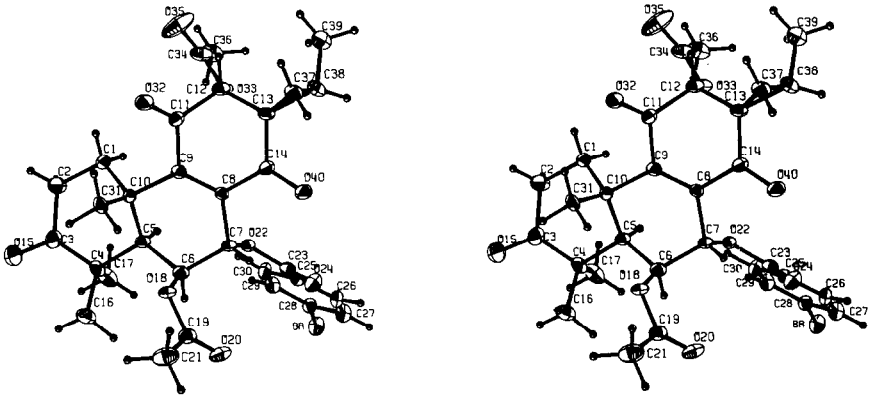


Fig. 1. Stereoscopic view of the molecule of the *p*-bromobenzoyl ester of barbatusin (**1d**).

Table 1. Bond lengths[a,b] and angles for barbatusin derivative (1*d*)

C(1)–C(2)	1.536(15)	C(34)–C(36)	1.489(18)	C(11)–C(12)–C(13)	109.6(8)
C(2)–C(3)	1.539(17)	C(13)–C(37)	1.536(14)	C(11)–C(12)–O(33)	109.2(7)
C(3)–C(4)	1.508(17)	C(13)–C(38)	1.516(14)	C(13)–C(12)–O(33)	107.2(7)
C(4)–C(5)	1.590(13)	C(37)–C(38)	1.478(16)	C(12)–C(13)–C(14)	115.7(8)
C(5)–C(10)	1.605(12)	C(38)–C(39)	1.512(17)	C(12)–C(13)–C(37)	118.1(8)
C(1)–C(10)	1.554(13)	C(14)–O(40)	1.196(11)	C(12)–C(13)–C(38)	122.7(8)
C(5)–C(6)	1.500(13)	C(10)–C(1)–C(2)	112.1(8)	C(14)–C(13)–C(37)	114.7(8)
C(6)–C(7)	1.554(14)	C(1)–C(2)–C(3)	115.1(9)	C(14)–C(13)–C(38)	115.1(8)
C(7)–C(8)	1.525(12)	C(2)–C(3)–C(4)	120.0(1.0)	C(37)–C(13)–C(38)	57.9(7)
C(8)–C(9)	1.317(13)	C(2)–C(3)–C(15)	117.3(1.1)	C(13)–C(14)–C(8)	118.5(8)
C(9)–C(10)	1.554(13)	C(4)–C(3)–C(15)	122.7(1.1)	C(8)–C(14)–O(40)	120.2(8)
C(9)–C(11)	1.543(13)	C(3)–C(4)–C(5)	113.1(8)	C(13)–C(14)–O(40)	121.3(8)
C(11)–C(12)	1.530(14)	C(3)–C(4)–C(16)	108.4(9)	C(6)–O(18)–C(19)	117.7(8)
C(12)–C(13)	1.486(13)	C(3)–C(4)–C(17)	105.9(9)	O(18)–C(19)–O(20)	121.3(1.0)
C(13)–C(14)	1.505(12)	C(5)–C(4)–C(16)	116.4(8)	O(18)–C(19)–C(21)	111.4(9)
C(8)–C(14)	1.498(12)	C(5)–C(4)–C(17)	104.0(8)	O(20)–C(19)–C(21)	127.2(1.1)
C(3)–O(15)	1.228(16)	C(16)–C(4)–C(17)	108.4(8)	C(7)–O(22)–C(23)	116.7(7)
C(4)–C(16)	1.504(15)	C(4)–C(5)–C(10)	111.2(7)	O(22)–C(23)–O(24)	122.4(8)
C(4)–C(17)	1.581(14)	C(4)–C(5)–C(6)	115.2(8)	O(22)–C(23)–C(25)	115.1(8)
C(6)–O(18)	1.451(12)	C(6)–C(5)–C(10)	112.3(7)	O(24)–C(23)–C(25)	122.5(8)
O(18)–C(19)	1.367(14)	C(5)–C(10)–C(1)	104.5(7)	C(23)–C(25)–C(26)	120.2(8)
C(19)–O(20)	1.219(15)	C(5)–C(10)–C(9)	104.3(7)	C(23)–C(25)–C(30)	120.5(8)
C(19)–C(21)	1.503(17)	C(1)–C(10)–C(31)	112.1(7)	C(26)–C(25)–C(30)	119.2(9)
C(7)–O(22)	1.454(11)	C(9)–C(10)–C(31)	110.3(7)	C(25)–C(26)–C(27)	122.8(9)
O(22)–C(23)	1.343(11)	C(5)–C(6)–C(7)	112.0(8)	C(26)–C(27)–C(28)	116.8(9)
C(23)–O(24)	1.204(11)	C(5)–C(6)–O(18)	112.7(8)	C(27)–C(28)–C(29)	121.5(1.0)
C(23)–C(25)	1.487(13)	C(7)–C(6)–O(18)	108.7(8)	C(27)–C(28)–Br	118.0(7)
C(25)–C(26)	1.352(14)	C(6)–C(7)–C(8)	110.7(7)	C(29)–C(28)–Br	120.4(8)
C(26)–C(27)	1.389(14)	C(6)–C(7)–O(22)	107.2(7)	C(28)–C(29)–C(30)	120.8(1.0)
C(27)–C(28)	1.413(14)	C(8)–C(7)–O(22)	107.5(7)	C(25)–C(30)–C(29)	118.9(9)
C(28)–C(29)	1.339(15)	C(7)–C(8)–C(9)	124.1(8)	C(12)–O(33)–C(34)	117.5(8)
C(29)–C(30)	1.397(14)	C(7)–C(8)–C(14)	113.5(7)	O(33)–C(34)–O(35)	122.0(1.2)
C(25)–C(30)	1.405(13)	C(9)–C(8)–C(14)	121.4(8)	O(33)–C(34)–C(36)	113.1(1.1)
C(28)–Br	1.884(10)	C(10)–C(9)–C(8)	127.0(8)	O(35)–C(34)–C(36)	124.7(1.2)
C(10)–C(31)	1.506(12)	C(10)–C(9)–C(11)	114.8(7)	C(13)–C(37)–C(38)	60.4(7)
C(11)–O(32)	1.199(11)	C(8)–C(9)–C(11)	118.1(8)	C(13)–C(38)–C(37)	61.7(7)
C(12)–O(33)	1.459(12)	C(9)–C(11)–C(12)	113.5(7)	C(13)–C(38)–C(39)	121.1(9)
O(33)–C(34)	1.331(15)	C(9)–C(11)–O(32)	123.0(8)	C(37)–C(38)–C(39)	121.2(9)
C(34)–O(35)	1.188(18)	C(12)–C(11)–O(32)	123.0(8)	C(1)–C(10)–C(9)	108.6(7)
				C(5)–C(10)–C(31)	116.5(7)

[a]The bond lengths in the benzene molecule range from 1.27(7) to 1.37(9) Å, and the bond angles range from 111(5) to 128(5)°.

[b]The C–H lengths range from 0.6 to 1.5 (1) Å.

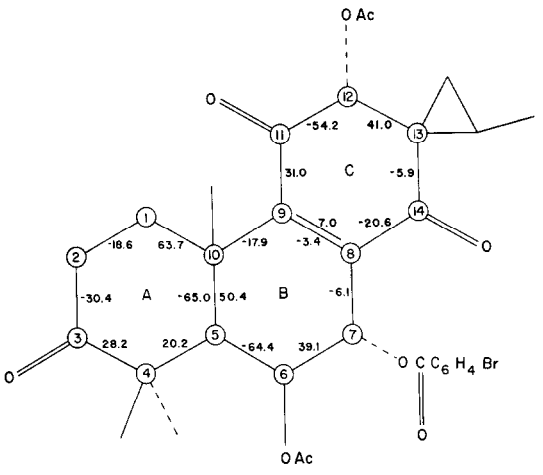
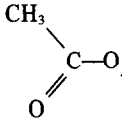


Fig. 2. Torsion angles in the central rings of the molecule of **1d**. The angle A–B–C–D is positive if, when looking along B to C, atom A has to be rotated clockwise to eclipse atom D.

other ketone O atoms and all but one of the ester O atoms. Ring B has a distorted half-chair conformation with the atoms C(5) and C(6) lying 0.539 and 0.214 Å, above and below the best plane through the atoms C(7), C(8), C(9), and C(10) [deviations range from −0.013 to +0.013 Å]. The half-quinone ring C is markedly non-planar and can perhaps best be described as a half-chair with C(11) and C(12) being 0.239 and 0.468 Å on opposite sides of the best plane through the other four atoms [deviations range from −0.092 to 0.084 Å]. The conjugated 1,4-diketone system is very non-planar with torsion angles as large as 31.0° resulting in both CO groups pointing on the β-side of the molecule. In a recent review on quinone structures, Bernstein *et al.*[8] pointed out that most benzoquinones, naphthoquinones, and anthraquinones are planar and that if one of the C–C ring double bonds is saturated, there is little effect on the values of the other bond lengths and angles. In the present much more strained example, it is of interest that the C(9)–C(11) bond is long (1.543(13) Å compared to the average value of 1.480 Å given in Ref. 8), whereas that of C(8)–C(9) is short (1.317(13) Å vs 1.342 Å) and the C(9)–C(11)–C(12) angle is much smaller than those usually found in planar quinones (113.5(7)° vs 118.5°).

There is evidence for considerable steric overcrowding on the β-side of the molecule between C(31) and O(18), C(31) and O(32), and C(16) and O(18); the distances are 2.977(11), 3.018(11), and 2.937(12) Å, respectively. This overcrowding would appear to restrict rather than favour the type of distortion observed in ring C. The two ester groups,  , in the barbatusin derivative adopt a planar conformation with the carbonyl group eclipsing the O–C single bond.

The packing of the molecules in the solvate of **1d** is of some interest (Fig. 3). Often in crystalline solvates, there is a tendency for small, planar molecules to stack on top of each other (see, e.g. Ref. 8–10). In the benzene solvate of **1d**, however, the benzene molecules are separated in the *x*-direction by a *p*-bromobenzoyl group from a barbatusin molecule. The alternating arrangement of a *p*-bromobenzoyl group from **1d** and a benzene molecule does form a somewhat irregular column along the *x*-direction of the crystal. Such columns provide a quite effective separation in the *y*-direction between the more bulky barbatusin moieties, which themselves form columns along the *x*-axis. The reference solvent molecule of benzene is significantly overlapped by the phenyl ring of the *p*-bromobenzoyl group of the molecule at $1-x$, $-\frac{1}{2}+y$, $1-z$; the C atoms of the phenyl ring lie between 3.7 and 4.6 Å from the plane of the benzene molecule.

There are two other types of intermolecular contacts that involve only the molecules of **1d**. C(29) and C(30) are both close (3.13(1) and 3.14(1) Å) to O(40) in the molecule at x, y, $1+z$. However, the C–H---O angles do not imply H-bonding. There is also a Br---O interaction of some interest. The Br---O(15) $[-x, \frac{1}{2}+y, 2-z]$ distance is 3.201(8) Å and the corresponding C(28)–Br---O(15) and Br---O(15)–(3) angles are 167.6 and 140.7°, respectively. Somewhat similar interactions have been noted previously.[8,11,12]

The second compound, isolated in minor quantities (0.014%), was assigned the structure of 3β-hydroxy-3-deoxybarbatusin (**2**), m.p. 206–210°, on the following grounds: elemental analysis $C_{24}H_{32}O_8$, M^+ 448; UV λ_{max} 235 nm (ϵ 18,270) for the conjugated ketone; IR spectrum

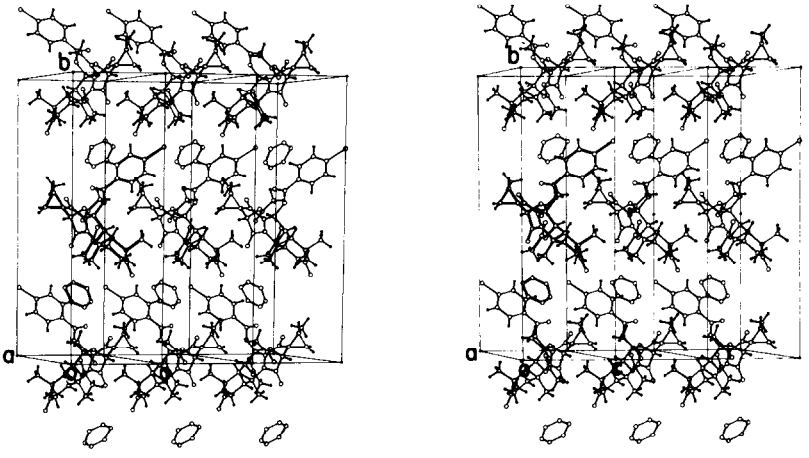


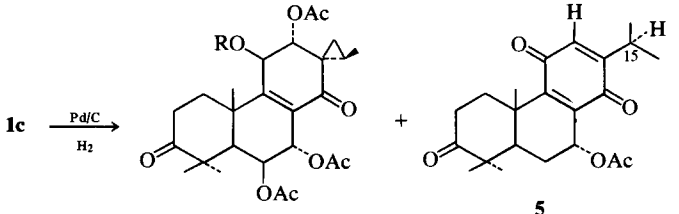
Fig. 3. Stereoscopic view of the molecular packing of the benzene solvate of the *p*-bromobenzoyl ester of barbatusin (**1d**). The bonds of the reference molecule and solvent are shaded darker. The "stacking" of the benzene molecules and the *p*-bromophenyl groups is along the *a*-axis which is almost normal to the plane of the paper.

similar to that of barbatusin. In the NMR spectrum the signals for the three tertiary, one secondary C–Me functions and two acetate Me groups were in agreement with those observed for barbatusin (Table 2). In addition the two OH group protons were observed as a broad signal at δ 2.80 ($W_{1/2}$ = 22 Hz) disappearing upon D_2O exchange, whereas the two CHOH protons are at δ 3.28 (dd, $J_{3,2}$ = 7 and 9 Hz) for the 3α-H and 4.49 (d, $J_{7,6}$ = 2 Hz) for the 7β-H. The signals for the two CHOAc protons are at δ 4.85 (s) for the 12β-H and at 5.44 for the 6α-H(t, $J_{6,7}$ = 2, $J_{6,5}$ = 0.5 Hz); the latter assignment was confirmed by double irradiation experiments at 5-H and 7-H. The spectroscopic data were similar to those observed for barbatusin, the only difference being the presence of a 3β-OH group. The structural assignment was settled by careful oxidation of **2** with Jones reagent whereupon barbatusin was obtained. The β-equatorial configuration of the 3-OH group was deduced by consideration of the coupling constants of the 3α-axial proton.

Catalytic hydrogenation of **1c** over Pd/C afforded two products which were separated by chromatography. One of the compounds (**4a**), obtained in 40% yield, had both UV (λ_{max} 230 nm, ϵ 21,970) and IR spectra similar to those of **1c** except for the presence of a new strong OH absorption band at 3670 cm^{-1}.

5.65 (d, $J_{6,7}$ = 2 Hz) were assigned to the 12β–H, 6α–H and 7β–H. The additional signal, at δ 5.30, was assigned to the 11-H geminal to the OH group. The stereochemistry at C(11) was resolved by a pyridine-induced solvent shift:[13] the 10-Me group exhibited a downfield shift Δ = −0.33 ppm characteristic for a 1,3-diaxial arrangement. It was therefore concluded that the 11–OH group is β-axial.

The other product obtained in 38% yield was assigned structure **5**, $C_{22}H_{28}O_5$, M^+ 372; the UV, λ_{max} 260 nm (ϵ 26,680), was comparable with values recorded for quinonoid diterpenes such as nemorom,[14] royleanone and its 7-acetoxy derivative[7] isolated from species of the Labiatae thereby implying the presence of a 1,4-quinonoid system in ring C. The NMR spectrum showed signals for three tertiary and two seconday C–Me groups, one acetate Me, one vinylic and one CHOAc proton (Table 2). The occurrence of the two secondary C–Me group signals at δ 1.17 (6H, d, J = 9 Hz) combined with the disappearance of the cyclopropyl protons indicated the opening of the latter ring during hydrogenation. This type of reductive opening of cyclopropane rings has been reviewed.[15] In the case of compound **5** the ring fission takes place, as expected, at the least substituted bond and is combined with the elimination of the 12–OAc group leaving a double-bond at 12–13 and an isopropyl side chain at C(13) (Scheme 1).



4a: R = H
b: R = $COCH_3$

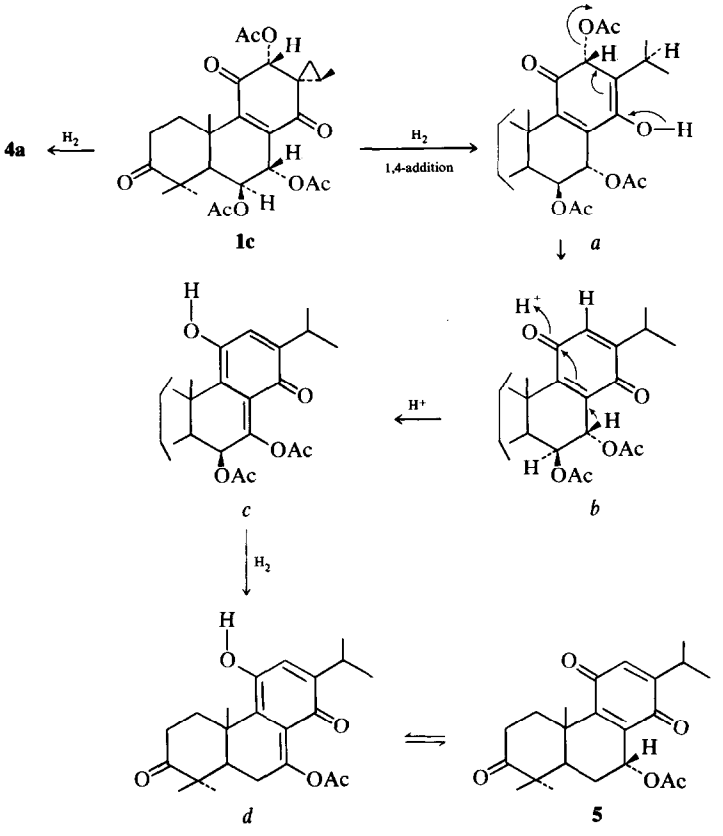
5

In the NMR spectrum of **4a** the signals for most of the Me protons (4α, 4β, the secondary C–Me and the acetoxy groups) were similar to those of **1c** (Table 2), however, the 10β–Me group only was shifted to higher field, δ 1.47. The CHOAc proton signals at δ 5.06 (d, $J_{11,12}$ = 2 Hz), 5.30 and

Indeed the newly formed vinylic proton 12–H is observed as a narrow doublet at δ 6.44 (J = 1 Hz) due to allylic coupling with the isopropyl side chain proton, as demonstrated by reciprocal decoupling irradiations. This process can be explained by an initial 1,4-addition of one

Table 2. NMR signals of relevant protons of barbatusin, cyclobutatusin and their derivatives (δ units)

COMPD.	3-H	5-H	6-H	7-H	8-H	12-H	$OCOCH_3$	Methyl groups			
								Side chain	4 α	4β	10β
1a		2.34(dd) J=1	5.28(dd) J=2 & 1	4.68(d) J=2		5.06(s)	2.02(6 β) 2.10(12α)	1.14(d) J=6.5	1.24	1.21	1.67
1b		2.33(d) J=1	5.96(d) J=1			4.94(s)	2.09(6 β & 12α)	1.15(d) J=6.5	1.25	1.25	1.65
1c			5.38(dd) J=2 & 1	5.75(d) J=2		5.00(s)	2.04(6 β) 2.05(7 α) 2.13(12α)	1.17(d) J=6.5	1.21	1.16	1.73
2	3.28(dd) J=7 & 9		5.44(t) J=2 J=0.5	4.49(d) J=2		4.85(s)	2.02(6 β) 2.06(12α)	1.10(d) J=6.5	0.99	1.17	1.66
3a		2.16(d) J=4.5	5.54(dd) J=6 & 4.5	3.97(dd) J=6 & 4.5	2.74(d) J=4.5 ======== 11-H	5.58(s)	2.02(6 β) 2.11(12α)	1.19(d) J=6.5	1.13	1.13	1.34
4a		2.30(d) J=1	5.30	5.65 J=2	5.30	5.06(d) J=2	2.04 2.08 & 2.17	1.24(d) J=6.5	1.18	1.13	1.47
4b		2.30(d) J=1	5.32(dd) J=2 & 1	5.65(d) J=2	6.21(d) J=2	5.47(d) J=2	2.08 2.04 & 2.17	1.27(d) J=6.5	1.21	1.14	1.47
5		2.64(d) J=1	5.51(d) J=1			6.44(d) J=1	2.02	1.17(d) J=9	1.20	1.20	1.57



Scheme 1.

mole of H_2 at C(15) and the formation of the C(14) CO intermediate *a*, from which the 12-OAc group can be readily eliminated. As described above, only one acetate Me signal was observed indicating the loss of two acetate groups from **1c** during the hydrogenation. The 7-H geminal to the acetoxy group appeared as a multiplet at δ 5.51. Its low field position is due to its allylic character. The location and orientation of the geminal 7-H was determined unequivocally by INDOR techniques whereby reciprocal irradiation processes at the signal position of the 5α-H and 7-H were performed. During the former irradiation the 7-H signal collapsed into a rather narrow triplet indicating its β-quasi-equatorial orientation. It can therefore be concluded that the 6-OAc group was the one which had undergone elimination. Such an elimination could be accounted for through a sequence illustrated in Scheme 1. The protonation of the intermediate *b* would give *c*. In this intermediate the C(6) acetoxy group is allylic and therefore can easily undergo hydrogenolysis to form *d*, which is in fact the tautomer of compound **5**, the ultimate product of the reaction. In order to account for the protonation of *b*, it could be inferred from an earlier observation[16] that hydrogen dissolved in palladium is positively charged, however weakly (about one fiftieth of an electronic charge per atom), and this charge could be enough to induce the formation of *c*. Hence the catalytic hydrogenation of **1c** follows two independent pathways, either to the formation of **4a** (1 mole of H_2) or through a combination of a number of steps to the highly conjugated yellow product **5** (2 moles of H_2).

The third component of the original extract, cyclobutatusin (**3a**), was obtained in a pure crystalline form by repeated column chromatography and fractional recrystallisations, $C_{24}H_{32}O_9$, elemental analysis, M^+ 464. No major UV absorption above 210 nm was recorded; in the IR spectrum the presence of hydroxyl, carbonyl and ester functions were observed. The NMR spectrum (Table 2) indicated signals for the three tertiary, one secondary C-Me groups and two acetate functions. The complex signals at δ 4.03 and 4.29 ($W_{1/2}$ = 22 and 14 Hz respectively) integrating for four protons were reduced upon D_2O exchange to a double doublet accounting for one proton at δ 3.97 ($J_{6,7}$ = 6 and $J_{7,8}$ = 4.5 Hz). Since the latter peak could be assigned to the 7-H, the broad original signal was due to three OH groups. The doublet at δ 2.74 ($J_{7,8}$ = 6 Hz) was assigned to the 8β-H from double irradiation experiments. Irradiation at the position of the 7β-H led to the collapse of the doublet at δ 2.74 to a singlet. Conversely irradiation at the signal position of the 8β-led to the collapse of the double doublet of the 7β-H at δ 3.97 to a doublet with a coupling constant of 6 Hz. The location of the 5α-H signal was disclosed by using INDOR techniques. Irradiation at the position of the 6α-H showed that the 5α-H is a doublet at δ 2.16 ($J_{5,6}$ = 4.5 Hz) hidden under the Me signals of the acetate groups.

Cyclobutatusin readily formed a mono-*p*-bromobenzoyl ester (**3b**), indicating that two of the OH groups were tertiary. From the detailed spectroscopic analysis and from biogenetic considerations, a structure related to barbatusin (**1a**) was suggested. However, since several of the physical data, and the large number of O atoms in the molecular formula could not be reconciled with several structural proposals, an X-ray structure determination was carried out on the *p*-bromobenzoyl ester (**3b**), m.p. 286–288°, obtained from benzene solution. The crystals of

3b are orthorhombic, space group $P2_12_12_1$, with a = 14.091(3), b = 15.268(3) and c = 14.018(3) Å and there are four molecules in the unit cell. The structure was solved by the heavy atom method and was refined to an R-factor of 0.069 on 2241 non-zero reflections measured on a Picker FACS-1 diffractometer (CuK_α radiation). A stereoscopic view of the molecule of **3b** is shown in Fig. 4, establishing the structure of this third component as **3a** and leading to the name cyclobutatusin. The final values for the bond lengths and angles are given in Table 3.

The torsion angles around the ring system are shown in Fig. 5. Individual bond lengths and angles do not require extended comment. The central portion of the molecule adopts an overall "bowl"-shape with rings A and C having

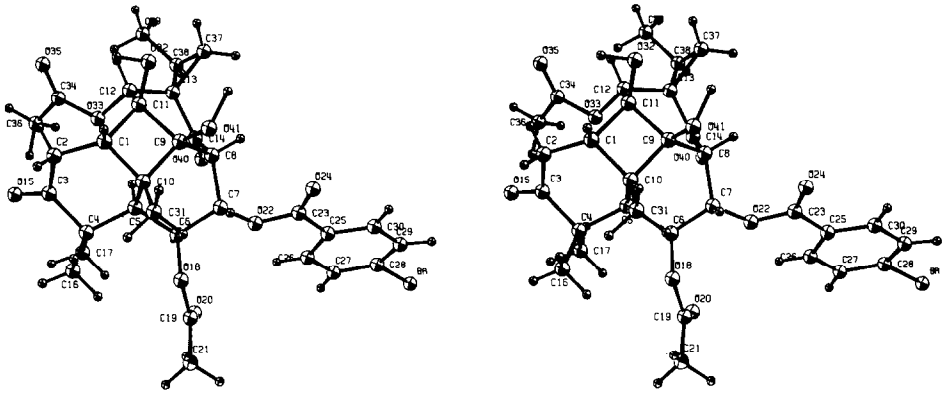


Fig. 4. Stereoscopic view of a single molecule of **3b**. Hydrogen atoms were placed at calculated positions.

Table 3. Bond lengths (Å)[a] and angles (deg.)[b] for the cyclobutatusin derivative of **3b**

C(1)–C(2)	1.501(12)	C(13)–C(37)	1.523(13)	C(9)–C(11)–O(32)	109.9(6)
C(2)–C(3)	1.500(11)	C(13)–C(38)	1.552(15)	C(1)–C(11)–C(12)	120.6(7)
C(3)–C(4)	1.539(12)	C(37)–C(38)	1.522(20)	C(1)–C(11)–O(32)	115.1(6)
C(3)–O(15)	1.212(11)	C(38)–C(39)	1.489(20)	C(12)–C(11)–O(32)	105.5(6)
C(4)–C(5)	1.574(10)	C(2)–C(1)–C(10)	116.8(6)	C(11)–C(12)–C(13)	110.1(7)
C(4)–C(16)	1.541(10)	C(10)–C(1)–C(11)	90.5(6)	C(11)–C(12)–O(33)	116.3(6)
C(4)–C(17)	1.523(11)	C(2)–C(1)–C(11)	129.4(7)	C(13)–C(12)–O(33)	105.0(6)
C(5)–C(6)	1.534(10)	C(1)–C(2)–C(3)	117.8(7)	C(12)–C(13)–C(14)	114.3(7)
C(5)–C(10)	1.519(9)	C(2)–C(3)–C(4)	120.2(7)	C(12)–C(13)–C(37)	120.1(8)
C(1)–C(10)	1.547(11)	C(2)–C(3)–O(15)	120.3(8)	C(12)–C(13)–C(38)	120.3(8)
C(6)–C(7)	1.507(10)	C(4)–C(3)–O(15)	119.3(8)	C(14)–C(13)–C(37)	115.9(8)
C(6)–O(18)	1.457(8)	C(3)–C(4)–C(5)	105.9(6)	C(14)–C(13)–C(38)	116.0(8)
C(7)–C(8)	1.532(10)	C(3)–C(4)–C(16)	105.3(6)	C(37)–C(13)–C(38)	59.4(8)
C(7)–O(22)	1.449(8)	C(3)–C(4)–C(17)	109.6(6)	C(8)–C(14)–C(13)	113.2(6)
C(8)–C(9)	1.566(10)	C(5)–C(4)–C(16)	115.9(6)	C(8)–C(14)–O(40)	122.9(7)
C(9)–C(10)	1.552(10)	C(5)–C(4)–C(17)	110.5(6)	C(13)–C(14)–O(40)	123.9(7)
C(9)–C(11)	1.556(11)	C(16)–C(4)–C(17)	109.4(6)	C(6)–O(18)–C(19)	118.2(6)
C(9)–O(41)	1.420(9)	C(4)–C(5)–C(6)	117.1(5)	O(18)–C(19)–O(20)	122.3(8)
C(1)–C(11)	1.577(12)	C(4)–C(5)–C(10)	115.4(5)	O(18)–C(19)–C(21)	108.9(7)
C(10)–C(31)	1.532(10)	C(6)–C(5)–C(10)	113.7(6)	O(20)–C(19)–C(21)	128.6(9)
C(11)–C(12)	1.548(11)	C(1)–C(10)–C(5)	108.7(6)	C(7)–O(22)–C(23)	119.4(5)
C(11)–O(32)	1.397(10)	C(1)–C(10)–C(9)	88.3(5)	O(22)–C(23)–O(24)	123.2(7)
C(12)–C(13)	1.506(12)	C(1)–C(10)–C(31)	116.6(6)	O(22)–C(23)–C(25)	112.1(6)
C(12)–O(33)	1.449(9)	C(5)–C(10)–C(9)	105.1(5)	O(24)–C(23)–C(25)	124.7(7)
C(13)–C(14)	1.505(12)	C(5)–C(10)–C(31)	117.8(6)	C(23)–C(25)–C(26)	119.6(7)
C(8)–C(14)	1.500(11)	C(9)–C(10)–C(31)	116.2(6)	C(23)–C(25)–C(30)	119.7(7)
C(14)–O(40)	1.204(9)	C(5)–C(6)–C(7)	107.8(6)	C(26)–C(25)–C(30)	120.6(7)
O(18)–C(19)	1.374(11)	C(5)–C(6)–O(18)	110.7(5)	C(25)–C(26)–C(27)	119.0(9)
C(19)–O(20)	1.183(12)	C(7)–C(6)–O(18)	106.9(5)	C(26)–C(27)–C(28)	117.0(7)
C(19)–C(21)	1.495(13)	C(6)–C(7)–C(8)	111.4(6)	C(27)–C(28)–C(29)	123.2(8)
O(22)–C(23)	1.324(9)	C(6)–C(7)–O(22)	106.2(5)	C(27)–C(28)–Br	119.6(6)
C(23)–O(24)	1.211(10)	C(8)–C(7)–O(22)	112.8(5)	C(29)–C(28)–Br	119.0(6)
C(23)–C(25)	1.475(11)	C(7)–C(8)–C(14)	117.1(6)	C(28)–C(29)–C(30)	117.2(8)
C(25)–C(26)	1.410(11)	C(9)–C(8)–C(14)	115.4(6)	C(25)–C(30)–C(29)	119.8(8)
C(26)–C(27)	1.375(12)	C(7)–C(8)–C(9)	104.7(6)	C(12)–O(33)–C(34)	115.5(7)
C(27)–C(28)	1.357(12)	C(8)–C(9)–C(10)	114.5(6)	O(33)–C(34)–O(35)	125.1(9)
C(28)–C(29)	1.378(13)	C(8)–C(9)–C(11)	119.5(6)	O(33)–C(34)–C(36)	112.1(8)
C(28)–Br	1.908(9)	C(8)–C(9)–O(41)	109.2(6)	O(35)–C(34)–C(36)	123.7(1.0)
C(29)–C(30)	1.420(13)	C(10)–C(9)–C(11)	91.1(5)	C(13)–C(37)–C(38)	61.3(8)
C(25)–C(30)	1.375(11)	C(10)–C(9)–O(41)	110.4(6)	C(13)–C(38)–C(37)	59.3(8)
O(33)–C(34)	1.359(12)	C(11)–C(9)–O(41)	111.0(6)	C(13)–C(38)–C(39)	125.3(1.1)
C(34)–O(35)	1.207(13)	C(9)–C(11)–C(12)	117.9(6)	C(37)–C(38)–C(39)	119.3(1.1)
C(34)–C(36)	1.494(15)	C(9)–C(11)–C(1)	87.0(6)		

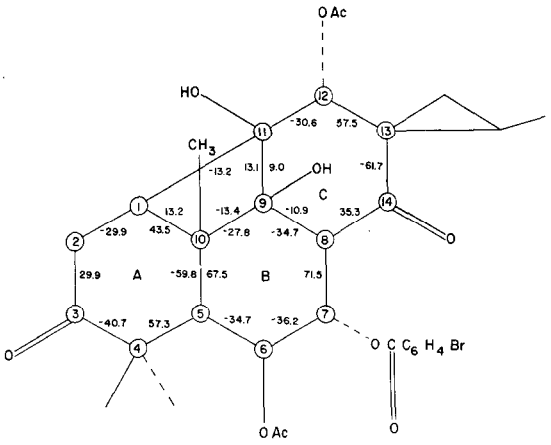


Fig. 5. Torsion angles in the central rings of the molecule of **3b**.

a *cis*-orientation with respect to the cyclobutane ring. Ring A is much less planar than in the molecule of **1d** and adopts a half-chair conformation. Ring B is a very distorted boat, while ring C has five very approximately coplanar atoms (range from −0.053 to 0.053 Å) with C(13) lying out of that plane by 0.624 Å. The cyclobutane ring is nonplanar (Fig. 5) with the group of atoms, C(10), C(1) and C(11), making a dihedral angle of 19.5° with the group of atoms C(10), C(9) and C(11).

The variation of C–C bond lengths with exocyclic substituents in a cyclopropane ring has been examined theoretically by Hoffmann[17] and some experimental results were described recently by Lauher and Ibers.[18] There is definite evidence for shortening of the C–C bond in the cyclopropane ring opposite a carbon that is attached to an unsaturated group (either Ph, or, as in the present case, a CO group). In addition to the examples given by Lauher and Ibers, the effect is clearly shown in the structures of methyl 1-carbamoyl-cyclopropane-1-carboxylate[19] and of *R*-(+)-2,2-diphenyl-1-methylcyclopropanecarboxylic acid.[20] In the present structures, the effect is most noticeable in the solvate of **1d**, where the C(37)–C(38) bond (1.478(16) Å) is shorter than the other two, 1.536(14) and 1.516(14) Å. In **3b**, the C(37)–C(38) bond length is 1.522(20) and the other two are 1.522(15) and 1.552(15) Å. As in the molecule of the solvate of **1d**, all the ester groups in **3b** adopt a *syn*-eclipsed configuration for the O=C and O–C bonds.

The main features of the packing are O–H---O(ester) H-bonding (Fig. 6). The atom, O(41) forms a H-bond to O(35) in the molecule at $-\frac{1}{2}+x$, $1\frac{1}{2}-y$, $1-z$; the O---O distance is 2.89 Å and the C(9)–O(41)---O(35) angle is 114.9°. The atom O(32) forms a H-bond to O(24) in the molecule at $\frac{1}{2}+x$, $1\frac{1}{2}-y$, $1-z$. The O---O distance is 2.82 Å and the C(11)–O(32)---O(24) angle is 126.5°.

Biological results

In the tumour-inhibitory tests against Lewis lung carcinoma and lymphocytic leukemia P 388 in mice, the screening data[21] indicated significant inhibitory activity for barbatusin at dose levels of 200 and 400 mg/kg respectively. These preliminary results confirm recent reports of anti-tumour activity of other quinonoid diterpenes.[22]

DISCUSSION

Barbatusin seems to be biosynthetically related to the ferruginol class of diterpenoids[23] and to a number of naturally occurring quinonoid diterpenes such as royleanone,[7] taxodione,[22] fuerstion,[24] tanshinon[25] and is the first example of a diterpene of the abietane group containing a spirocyclopropane ring in lieu of an open side-chain at C(13). Recently, a scheme for the transformation of an isopropyl to a n-propyl side-chain in the ferruginol class of compounds has been postulated,[26] involving a nucleophilic acid-catalyzed attack on a hypothetical spirocyclopropyl-cyclohexadienone intermediate; the resulting product could also be further used in the biosynthesis of the tanshinons. The structure of barbatusin leads support for the mechanism of such biogenetic sequences which have received further confirmation through the recent description of two closely related diterpenoids with a spiro(2,5)-octane system, coleons G and J, both isolated from *Coleus somaliensis*.[27] The structure of cyclobutatusin reveals the outstanding feature of a *4-membered ring* formed by a bond between C(1) and C(11). Although naturally occurring monoterpenes and sesquiterpenes with 4-membered rings are known,[28] cyclobutatusin appears to be the first instance of a diterpene with such a characteristic.

EXPERIMENTAL

M.ps were taken on a Kofler hot stage microscope. IR spectra were recorded on a Unicam SP-200 model using KBr pellets and UV spectra on a Beckman DU and Cary 14 models in 95% EtOH solutions. NMR spectra were measured on a Varian HA 100 MHz and Brucker HFX-10 90 MHz spectrometers, for 5–10% solutions in $CDCl_3$, using TMS as internal standard. Elemental analyses

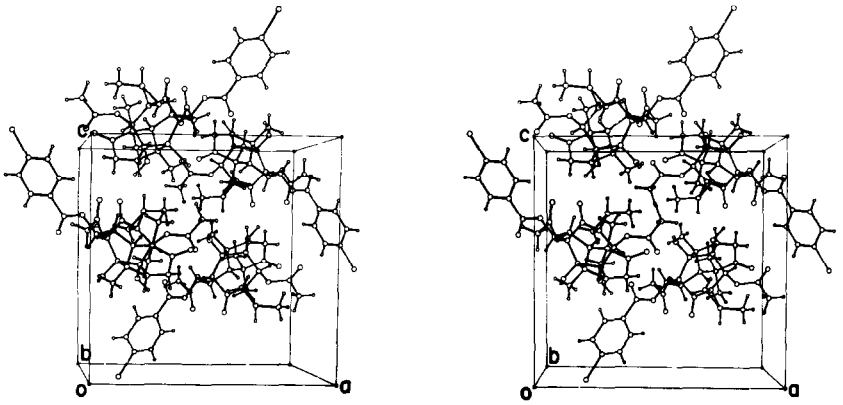


Fig. 6. Stereoscopic view of the molecular packing of **3b**. The reference molecule is shown with heavier bonds.

were performed in the Departments of Chemistry of the University of Illinois and the Weizmann Institute of Science. Merck silica gel 0.05–0.20 mm and Kieselgel H respectively were used for column and thin layer chromatographies.

Isolation procedure. 3.5 kgs of dried, finely ground leaves, were extracted with hot acetone (30 l). Concentration under reduced pressure gave a viscous dark green mass which was washed with petroleum ether (b.p. 40–60°). The ensuing ppt was dried, yield 39.8 g and chromatographed. Elutions with C_6H_6–$CHCl_3$ 1:4 and $CHCl_3$ afforded 10.3 g of **1a** (0.3%), yellow plates m.p. 224–228° (acetone–ether); ν_{max} 3500, 1740, 1705, 1670, 1605, 1390, 1230 and 1140 cm^{-1}. (Found: C, 64.71; H, 6.79; O, 28.48. $C_{24}H_{30}O_8$ requires: C, 64.58; H, 6.73; O. 28.68%). Elutions with $CHCl_3$–acetone (19:1) afforded mixtures of compounds more polar than barbatusin and from which **2** and **3a** were separated after repeated chromatography (same proportions of $CHCl_3$–acetone) and fractional recrystallisations from ether–petroleum ether.

3β-Hydroxy-3-deoxybarbatusin (**2**), yield 0.52 g (0.014%), m.p. 206–210° (Et_2O); ν_{max} 3600, 1735, 1680, 1605, 1370, 1240 and 1100 cm^{-1}. (Found: C, 64.33; H, 7.22; O, 28.34. $C_{24}H_{32}O_8$ requires: C, 64.26; H, 7.19; O. 28.54%).

Cyclobutatusin (**3a**), yield 0.31 g (0.008%), m.p. 196–200° (Et_2O); ν_{max} 3600, 1740 (sh), 1710, 1380, 1260, 1200 and 1080 cm^{-1}. (Found: C, 61.99; H, 6.83. $C_{24}H_{32}O_9$ requires: C, 62.05; H, 6.94%).

7-Oxo-7-dehydroxybarbatusin (**1b**). To a cold solution (0–5°) of **1a** (400 mg) in acetone (10 ml), Jones reagent (0.7 ml) was added and the mixture stirred for 7 hr. After the usual work up the ppt was washed, dried and recrystallised from acetone–ether, yield 257 mg, m.p. 205–208°; ν_{max} 1735, 1715, 1700, 1670, 1640, 1590, 1380, 1240 and 1040 cm^{-1}. (Found: C, 64.71; H, 6.66; O, 28.80. $C_{24}H_{28}O_8$ requires: C, 64.85; H, 6.35; O, 28.79%).

7α-Acetoxybarbatusin (**1a**). To a soln of barbatusin (413 mg) in Ac_2O (3 ml) two drops of pyridine were added and left for 90 min at room temp. The mixture was then poured into ice-water and the ppt washed and dried, yield 383 mg, m.p. 184–186° (MeOH). (Found: C, 64.47; H, 6.73. $C_{26}H_{32}O_9$ requires: C, 63.92; H, 6.60%).

p-Bromobenzoyl ester of barbatusin (**1d**). To a hot soln of barbatusin (0.2 g) in freshly distilled *p*-bromobenzoyl chloride (1 g) three drops of pyridine were added and the mixture was left overnight at room temp. After treatment with petroleum ether, the ppt was dried and chromatographed. Elution with C_6H_6 gave 96 mg of the product (**1d**), m.p. 173–175° (C_6H_6). The C_6H_6 of crystallisation was removed by vacuum drying. (Found: C, 59.39; H, 5.29; M^+ 628, 630). $C_{31}H_{33}O_9Br$ requires: C, 59.15; H, 5.28%; M.wt. 629.49).

Catalytic hydrogenation of 7α-acetoxybarbatusin (**1c**). 7α-Acetoxybarbatusin (1 g) in EtOAc solution (20 ml) was hydrogenated over Pd/C 10% (2 g) at atm press and 87 ml of H_2 were absorbed within 30 min. After filtration from the catalyst, the solvent was removed *in vacuo* and the residue (940 mg), two spots on a chromatoplate was chromatographed. (a) Elutions with C_6H_6–$CHCl_3$ (1:1) gave 291 mg (38%) of **5**, m.p. 137–140° (ether–petroleum ether); ν_{max} 1735, 1710, 1645, 1605, 1380, 1240 and 1020 cm^{-1}. (Found: C, 71.62; H, 7.41; M^+ 372. $C_{22}H_{28}O_5$ requires: C, 71.33; H, 7.07%; M.wt. 372.44). (b) Further elutions with $CHCl_3$ yielded 402 mg (40%) of **4a**, m.p. 144–146° (acetone–ether); ν_{max} 3670, 1760, 1710, 1665, 1610, 1380, 1230 and 1020 cm^{-1}. (Found: C, 63.59; H, 7.26; O, 29.31. $C_{26}H_{34}O_9$ requires: C, 63.66; H, 6.99; O, 29.35%).

Jones oxidation of compound **4a**. To an ice-cooled solution of **4a** (200 mg) in acetone (5 ml), 0.15 ml of Jones reagent was added and the mixture stirred for 20 min. After the usual work up the ppt was dried. Recrystallisation from acetone–ether yielded exclusively **1c** undepressed mixture m.p. The IR spectrum was identical with that of an authentic sample of **1c**.

11β-Acetoxy-11-deoxy-7α-acetoxybarbatusin (**4b**). To a soln of **4a** (250 mg) in Ac_2O (1 ml), pyridine (0.2 ml) was added and the mixture left for 15 hr at room temp. After the usual work up, the product (230 mg) was dried and recrystallised from Et_2O, m.p. 180–185°; ν_{max} 1750, 1710, 1670, 1375, 1230 and 1015 cm^{-1}. (Found: C, 63.02; H, 6.91. $C_{28}H_{36}O_{10}$ requires: C, 63.14; H, 6.81%).

Jones oxidation of 3β-hydroxy-3-deoxybarbatusin (**2**). To an ice-cooled solution of **2** (100 mg) in acetone (10 ml), 0.1 ml of Jones reagent was added and the mixture stirred for 60 min. After the

Table 4. Final atomic coordinates in fractions of the unit cell for **1d**

	x	y	z
Br	-0.07502(13)	0.75	0.93694(15)
C(1)	0.4595(9)	0.4066(4)	0.6907(12)
C(2)	0.4265(11)	0.3647(5)	0.8200(14)
C(3)	0.2694(12)	0.3527(6)	0.7776(13)
C(4)	0.1621(11)	0.3970(4)	0.6929(12)
C(5)	0.2114(8)	0.4397(4)	0.5701(11)
C(6)	0.0957(10)	0.4642(4)	0.4113(13)
C(7)	0.1467(8)	0.5146(4)	0.3262(12)
C(8)	0.2937(8)	0.5044(4)	0.3203(11)
C(9)	0.3711(9)	0.4610(4)	0.3940(12)
C(10)	0.3344(8)	0.4141(4)	0.5076(12)
C(11)	0.5125(9)	0.4538(4)	0.3621(11)
C(12)	0.5818(9)	0.5085(4)	0.3426(12)
C(13)	0.4817(9)	0.5425(4)	0.1954(11)
C(14)	0.3322(9)	0.5423(4)	0.1914(11)
O(15)	0.2377(9)	0.3068(4)	0.8191(12)
C(16)	0.0223(10)	0.3696(5)	0.6018(13)
C(17)	0.1530(11)	0.4331(5)	0.8595(13)
O(18)	0.0319(6)	0.4243(3)	0.2662(8)
C(19)	-0.1048(12)	0.4326(5)	0.1583(14)
O(20)	-0.1661(7)	0.4753(4)	0.1673(9)
C(21)	-0.1595(11)	0.3854(5)	0.0266(15)
O(22)	0.1551(6)	0.5615(2)	0.4476(7)
C(23)	0.0671(9)	0.6037(4)	0.3776(12)
O(24)	0.0051(7)	0.6087(3)	0.2148(8)
C(25)	0.0476(9)	0.6425(4)	0.5165(11)
C(26)	-0.0307(10)	0.6887(4)	0.4612(12)
C(27)	-0.0686(11)	0.7225(4)	0.5821(13)
C(28)	-0.0158(10)	0.7080(4)	0.7710(13)
C(29)	0.0667(11)	0.6638(4)	0.8300(13)
C(30)	0.1010(10)	0.6297(4)	0.7053(13)
C(31)	0.3006(9)	0.3616(3)	0.3962(12)
O(32)	0.5558(7)	0.4097(3)	0.3346(11)
O(33)	0.6152(7)	0.5396(3)	0.5145(8)
C(34)	0.7410(13)	0.5317(6)	0.6414(16)
O(35)	0.8200(10)	0.4977(5)	0.6236(12)
C(36)	0.7745(10)	0.5725(5)	0.7950(14)
C(37)	0.4984(10)	0.5435(5)	0.0046(13)
C(38)	0.5257(11)	0.5942(5)	0.1181(13)
C(39)	0.6724(13)	0.6173(5)	0.2015(15)
O(40)	0.2452(6)	0.5712(3)	0.0872(9)
CB(1)[a]	0.674(4)	0.275(1)	0.447(10
CB(2)	0.580(7)	0.256(2)	0.283(7)
CB(3)	0.507(3)	0.211(2)	0.310(6)
CB(4)	0.544(5)	0.188(2)	0.481(9)
CB(5)	0.650(3)	0.206(2)	0.624(6)
CB(6)	0.703(3)	0.253(2)	0.612(6)
H(1a)[b]	0.508(8)	0.370(3)	0.635(11)
H(1b)	0.511(6)	0.443(2)	0.746(8)
H(2a)	0.492(8)	0.378(3)	0.977(11)
H(2b)	0.465(9)	0.323(4)	0.797(12)
H(5)	0.249(5)	0.472(2)	0.653(6)

Table 4 (*Cont.*)

	x	y	z
H(6)	0.026(6)	0.480(2)	0.445(7)
H(7)	0.065(6)	0.536(3)	0.206(8)
H(12)	0.650(7)	0.502(3)	0.323(9)
H(16a)	0.014(10)	0.338(4)	0.498(13)
H(16b)	0.000(9)	0.323(4)	0.693(12)
H(16c)	-0.023(6)	0.383(3)	0.551(8)
H(17a)	0.120(7)	0.393(3)	0.938(9)
H(17b)	0.094(10)	0.474(4)	0.844(12)
H(17c)	0.230(9)	0.456(4)	0.933(12)
H(21a)	-0.096(8)	0.338(3)	0.051(10)
H(21b)	-0.239(9)	0.360(4)	0.072(12)
H(21c)	-0.180(7)	0.410(3)	-0.009(9)
H(26)	-0.097(9)	0.700(4)	0.276(11)
H(27)	-0.168(6)	0.762(3)	0.532(8)
H(29)	0.088(11)	0.653(4)	0.958(15)
H(30)	0.139(6)	0.597(2)	0.737(7)
H(31a)	0.420(8)	0.335(3)	0.398(10)
H(31b)	0.269(7)	0.332(3)	0.428(9)
H(31c)	0.224(9)	0.350(4)	0.282(12)
H(36a)	0.854(9)	0.571(4)	0.872(11)
H(36b)	0.706(9)	0.613(4)	0.763(11)
H(36c)	0.747(11)	0.543(4)	0.839(13)
H(37a)	0.566(7)	0.513(3)	-0.008(10)
H(37b)	0.403(8)	0.535(4)	-0.120(10)
H(38)	0.445(8)	0.633(3)	0.057(11)
H(39a)	0.682(9)	0.633(4)	0.326(12)
H(39b)	0.701(9)	0.669(3)	0.100(12)
H(39c)	0.709(7)	0.579(3)	0.237(9)

[a] C8 refers to carbon atom in the benzene solvate molecule.

[b] Hydrogen atoms are given the numbers of the atoms to which they are attached.

usual work up the ppt was dried and chromatographed. Elution with $CHCl_3$ gave 79 mg of *barbatusin*, undepressed m.m.p. and IR spectra identical with that of an authentic sample.

p-*Bromobenzoyl ester of cyclobutatusin* (**3b**). A mixture of **3a** (75 mg), freshly distilled *p*-bromobenzoyl chloride (100 mg) and pyridine (1 ml), was left overnight at room temp. After usual work up the ppt was dried and washed with Et_2O. The product (105 mg) was chromatographed and elution with $CHCl_3$ yielded 85 mg of **3b**, m.p. 286–288° (Et_2O). (Found: C, 56.95; H, 5.49; M^+ 646. $C_{31}H_{35}O_{10}Br$ requires: C, 57.49; H, 5.44%; M.wt. 646.648).

X-Ray analysis of the p-*bromobenzoyl ester* (**1d**) *of barbatusin as a benzene solvate.* Yellow, parallelepiped crystals of **1d** were obtained by evaporation from benzene as the 1:1 benzene solvate. *Crystal data*: $C_{31}H_{33}O_9Br \cdot C_6H_6$, mol. wt. = 707.7, monoclinic, $a = 10.135(3)$, $b = 24.184(6)$, $c = 7.707(2)$ Å, $\beta = 109°46'(2')$, $V = 1777$ Å^3, $Z = 2$, $\rho_c = 1.32$ g cm^{-3}, $F(000) = 736$, $\mu(CuK_\alpha) = 21.8$ cm^{-1}. Systematic absences, $0k0$ when $k = 2n + 1$; Space Group, $P2_1$. Cell-data were obtained by a least squares fit to the settings for eleven hand-centred reflections (CuK_α, $\lambda = 1.54178$ Å). Intensity data were collected by procedures described previously.[29] Over the 13-day period in which data were collected, an approximately uniform decrease of 5–10% was noted in the intensities of three standard reflections. Out of a total of 3128 independent reflections within the $2\theta = 130°$ sphere, 2269 were considered above zero at the 2σ significance level. The structure was solved by the heavy atom method and the positions of the non-H atoms comprising both the molecule of **1d** and the benzene solvent molecule were readily determined.

Table 5. Final atomic coordinates in fractions of the unit cell for **3b**

	x	y	z
Br	-0.31289(9)	0.57576(8)	1.05170(8)
C(1)	0.2818(5)	0.5674(6)	0.4218(5)
C(2)	0.3700(6)	0.5127(5)	0.4295(5)
C(3)	0.3774(7)	0.4504(6)	0.5119(6)
C(4)	0.2874(5)	0.4095(4)	0.5550(5)
C(5)	0.2114(5)	0.4849(4)	0.5579(5)
C(6)	0.1234(5)	0.4700(5)	0.6203(5)
C(7)	0.0559(5)	0.5448(4)	0.6031(5)
C(8)	0.1091(5)	0.6311(5)	0.5877(5)
C(9)	0.1561(5)	0.6215(5)	0.4870(5)
C(10)	0.1894(5)	0.5274(5)	0.4623(5)
C(11)	0.2578(6)	0.6580(5)	0.4701(5)
C(12)	0.3146(6)	0.6901(4)	0.5580(6)
C(13)	0.2479(7)	0.7253(5)	0.6328(7)
C(14)	0.1742(6)	0.6607(5)	0.6659(6)
O(15)	0.4545(4)	0.4276(4)	0.5410(4)
C(16)	0.2636(7)	0.3309(5)	0.4903(6)
C(17)	0.3085(6)	0.3768(5)	0.6554(6)
O(18)	0.0743(3)	0.3901(3)	0.5922(3)
C(19)	0.0435(6)	0.3345(6)	0.6628(7)
O(20)	0.0570(5)	0.3486(4)	0.7446(5)
C(21)	0.0003(7)	0.2553(5)	0.6175(7)
O(22)	-0.0069(3)	0.5474(3)	0.6849(3)
C(23)	-0.0856(5)	0.5947(5)	0.6807(6)
O(24)	-0.1076(4)	0.6381(4)	0.6119(4)
C(25)	-0.1434(5)	0.5861(5)	0.7680(5)
C(26)	-0.1091(6)	0.5355(5)	0.8448(6)
C(27)	-0.1611(6)	0.5319(5)	0.9277(6)
C(28)	-0.2430(6)	0.5782(6)	0.9351(6)
C(29)	-0.2820(6)	0.6248(6)	0.8605(7)
C(30)	-0.2281(6)	0.6302(5)	0.7752(6)
C(31)	0.1270(5)	0.4763(5)	0.3922(5)
O(32)	0.2542(4)	0.7294(4)	0.4080(4)
O(33)	0.3712(4)	0.6249(3)	0.6068(4)
C(34)	0.4667(7)	0.6359(7)	0.6005(7)
O(35)	0.5054(5)	0.6801(5)	0.5408(5)
C(36)	0.5188(7)	0.5822(8)	0.6728(7)
C(37)	0.2169(11)	0.8207(6)	0.6300(11)
C(38)	0.2839(10)	0.7912(7)	0.7088(9)
C(39)	0.3815(10)	0.8286(8)	0.7131(10)
O(40)	0.1652(4)	0.6377(3)	0.7476(4)
O(41)	0.0922(4)	0.6529(3)	0.4164(4)
H(1)[a]	0.263	0.579	0.368
H(2a)	0.395	0.474	0.368
H(2b)	0.421	0.566	0.400
H(5)	0.255	0.526	0.605
H(6)	0.171	0.474	0.684
H(7)	0.013	0.526	0.540
H(8)	0.066	0.690	0.558
H(12)	0.361	0.755	0.526
H(16a)	0.316	0.271	0.513
H(16b)	0.211	0.284	0.526

Table 5 (Cont.)

	x	y	z
H(16c)	0.263	0.329	0.429
H(17a)	0.263	0.350	0.684
H(17b)	0.311	0.434	0.684
H(17c)	0.368	0.342	0.658
H(21a)	-0.026	0.197	0.671
H(21b)	-0.053	0.276	0.558
H(21c)	0.068	0.232	0.661
H(26)	-0.053	0.479	0.837
H(27)	-0.142	0.490	0.987
H(29)	-0.332	0.690	0.842
H(30)	-0.276	0.671	0.726
H(31a)	0.069	0.434	0.434
H(31b)	0.092	0.513	0.329
H(31c)	0.184	0.434	0.355
H(32)	0.303	0.710	0.353
H(36a)	0.487	0.540	0.671
H(36b)	0.505	0.618	0.745
H(36c)	0.571	0.526	0.171
H(37a)	0.184	0.842	0.684
H(37b)	0.253	0.829	0.553
H(38)	0.263	0.763	0.784
H(39a)	0.408	0.855	0.790
H(39b)	0.421	0.755	0.724
H(39c)	0.408	0.829	0.640
H(41)	0.079	0.724	0.395

[a] Hydrogen atoms were given the numbers of the atom to which they are covalently bonded.

H atoms for the molecule of **1d** but not for the benzene solvent molecule were located from a difference map. Full-matrix least squares refinement on positional and anisotropic thermal parameters for the non-H atoms and positional and isotropic thermal parameters of the hydrogens gave final values for R and R_w of 0.065 and 0.055, respectively.[30] During the last few cycles of refinement, the structure was divided into three parts because of computer storage limitations. In this refinement, the reflections were weighted according to the scheme proposed by Corfield *et al.*[31] The scattering curves for Br, C and O were those compiled by Cromer and Mann,[32] that for hydrogen is due to Stewart *et al.*[33] The final atomic coordinates for the solvate of **1d** are listed in Table 4 the final values for the thermal parameters and the observed and calculated structure factors have been deposited.

The absolute configuration was assigned by carrying out a refinement also on the $-x, -y, -z$ coordinates for the structure. The final values of R and R_w in this refinement were 0.068 and 0.057. The configuration depicted in Fig. 1 was indicated by Hamilton's test[34] for a one-dimensional hypothesis with rejection of the alternative configuration at the 99.5% confidence level ($R_w^+/R_w^- = 0.055/0.057$). This assignment was confirmed by measuring the Bijvoet pairs for eight reflections which showed large differences in F_{calc} in a structure factor calculation.

X-Ray analysis of the p-*bromobenzoyl ester* (**3b**) *of cyclobutatusin.* Colorless, rectangular-shaped crystals of the *p*-bromobenzoyl ester **3b** of cyclobutatusin, suitable for X-ray work, were obtained by evaporation from benzene solution. *Crystal data*: $C_{31}H_{35}O_{10}Br$, mol. wt. = 647.5, orthorhombic, $a = 14.091(3)$, $b = 15.268(3)$, $c = 14.018(3)$ Å; $V = 3016$ Å^3, $\rho_{obsd} = 1.44$ g cm^{-3}, $Z = 4$, $\rho_{calcd} = 1.43$ g cm^{-3}, $F(000) = 1344$, $\mu(CuK_\alpha) = 25.6$ cm^{-1}. Systematic absences, $h00$ when $h = 2n + 1$, $0k0$, when $k = 2n + 1$, and $00l$ when $l = 2n + 1$ established the space group as $P2_12_12_1$. Cell data were obtained by a least squares fit to the settings for eleven hand-centred reflections (CuK_α, $\lambda = 1.54178$ Å). Intensity data were collected as described previously.[29]

During the course of data collection (~8 days), the intensities of the three standards fell off gradually and the orientation matrix had to be recalculated several times. At the end of data collection the standards had fallen to an average of 83% of their initial values and the cell dimensions were remeasured and found to be $a = 14.141(5)$, $b = 15.250(6)$, and $c = 14.075(5)$ Å. These differences suggested that in some of the unit cells the compound may have undergone some change under X-ray irradiation. However, no clear evidence to indicate the nature of this change could be obtained from our X-ray study. A linear scale factor was applied to correct the decrease in the intensities. Out of a total of 2907 reflections in the $2\theta \leq 130°$ sphere, 2241 were considered to be non-zero at the 2σ significance level. The structure was solved by the heavy atom method and the positional and anisotropic thermal parameters for the non-hydrogen atoms were refined by full-matrix least squares methods to values of R and R_w of 0.092 and 0.096. Hydrogen atoms were positioned from difference maps and were included in the structure factor calculations, but their positions were not refined. Three low-order reflections whose F_{obs} appeared to suffer significantly from extinction or absorption errors were removed from the data set during the final cycles of refinement. Least squares refinement was terminated with values for R and R_w of 0.068 and 0.062 for the 2238 reflections. The final R-factor on all 2241 non-zero reflections was 0.069. The weighting scheme and atomic scattering factors used were as described above. The final atomic coordinates are listed in Table 5. The absolute configuration was assumed to be consistent with that determined for barbatusin. The final values for the thermal parameters and the observed and calculated structure factors have been deposited.

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Supplementary Information: The lists of thermal parameters and structure factors for both structures are available from Professor I. C. Paul, Department of Chemistry, University of Illinois, Urbana, Illinois, 61801, U.S.A.

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