The Chemistry of Fungi. Part LXIX.[1] A New Synthesis of the Grisane System: X-Ray Crystallographic Examination of (±)-Methyl 5,7-Dibromo-2'α,5'α-epoxy-4-methoxy-3-oxogrisane-6'β-carboxylate

By **Mortaza Ahbab, Alan D. Borthwick, John W. Hooper, Jeffrey S. Millership,** and **W. Basil Whalley,**[*]
The School of Pharmacy, University of London, London WC1N 1AX

George Ferguson and **Frank C. Marsh,** Department of Chemistry, The University, Guelph, Ontario, Canada N1G 2W1

Addition of furan to methyl 4-(2.6-dimethoxyphenyl)-4-oxobut-2-ynoate (4; R = CO_2Me) followed by hydrogenation of the adduct gave methyl 3-(2.6-dimethoxybenzoyl)-7-oxabicyclo[2.2.1]hept-2-ene-2-carboxylate (6; R = Me). This was demethylated to the corresponding 3-(2-hydroxy-6-methoxybenzoyl) derivative (6; R = H), which was cyclised by bases to give (a) (±)-methyl 2'α.5'α-epoxy-4-methoxy-3-oxogrisane-6'β-carboxylate (9: R = H). the structure of which was deduced chemically and spectroscopically. and unequivocally defined by X-ray crystallography, together with (b) the isomeric 6'α-carboxylate. Both grisanes were converted into (±)-methyl 2'α-hydroxy-3-oxogris-5'-ene-6'-carboxylate (11).

IN the course of work directed towards the synthesis of complex xanthones of the ergoflavin type (1),[2] we have uncovered a new route to the grisan-3-one system (2).

Thus, 2,6-dimethoxybenzaldehyde was converted successively, by standard methods, into the hydroxypropyne (3; R = H), the acid (3; R = CO_2H), and the oxo-ester (4; R = CO_2Me). Condensation of this ester with furan gave the unstable Diels–Alder adduct (5), which was immediately hydrogenated to methyl 3-(2,6-dimethoxybenzoyl)-7-oxabicyclo[2.2.1]hept-2-ene-2-carboxylate (6; R = Me). Demethylation of (6; R = Me) with boron trichloride gave the phenol (6; R = H). The same phenol was obtained by debenzylation of the 3-(2-benzyloxy-6-methoxyphenyl) analogue (6; R = Bz), synthesised similarly from 2-benzyloxy-6-methoxybenzaldehyde.

More prolonged action of boron trichloride converted the phenol (6; R = H) into methyl 2-(2-hydroxy-6-methoxybenzoyl)benzoate (7), the identity of which was confirmed by a synthesis in which condensation of

[1] Part LXVIII, W. B. Whalley, G. Ferguson, W. C. Marsh, and R. J. Restivo, preceding paper.

[2] J. W. Hooper, W. Marlow, W. B. Whalley, A. D. Borthwick, and R. Bowden, *J. Chem. Soc. (C)*, 1971, 3580.

phthalic anhydride with 2,6-dimethoxyphenyl-lithium gave 2-(2,6-dimethoxybenzoyl)benzoic acid in high yield. This route to benzoylbenzoic acid appears to be of general applicability.[3]
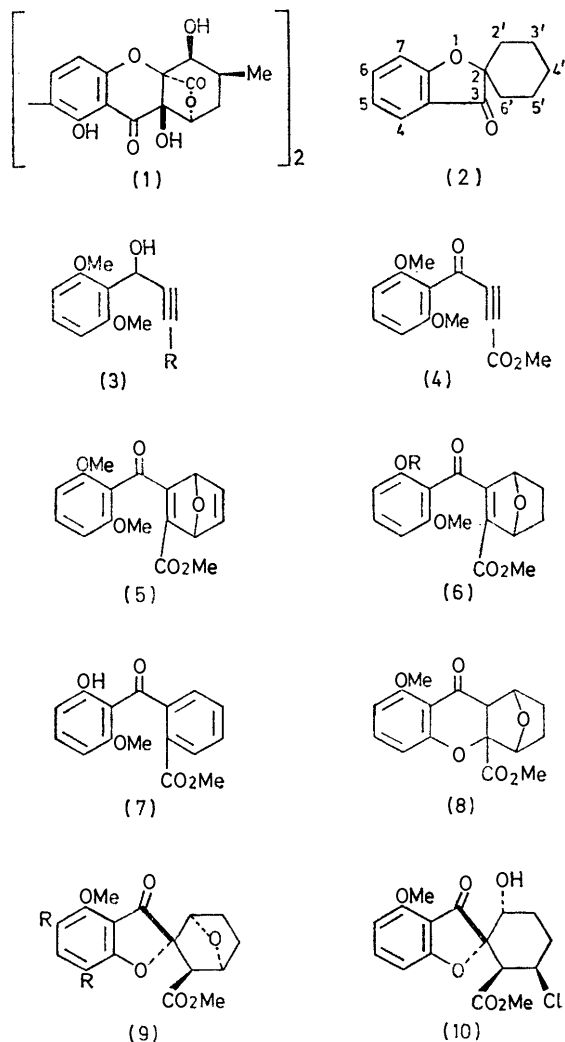
Extensive precedent [4] indicates that base-catalysed nucleophilic addition to the double bond of a β-benzoyl-acrylic ester normally occurs α to the ester residue. Thus we anticipated that the intermolecular cyclisation of the phenol (6; R = H) would yield a xanthone derivative of type (8), in keeping with our initial objective. Although base-catalysed cyclisation of the phenol (6; R = H) occurred readily, giving two products, chemical and spectroscopic evidence, together with the results of a parallel X-ray crystallographic examination, showed that the major product was the spiran (9; R = H), i.e. internal nucleophilic addition of the hydroxy-group had occurred β to the ester residue

[3] R. J. Banham, A. D. Borthwick, and W. B. Whalley, un-published observations.

[4] See, for example, S. Patai, H. Schenhav, and Z. Rappoport, J. Chem. Soc. (B), 1970, 469; K. E. Cook, P. L. Creger, and N. H. Cromwell, J. Amer. Chem. Soc., 1956, 78, 4412; S. Patai and Z. Rappoport, ' The Chemistry of the Alkenes,' ed. S. Patai, Wiley, New York, 1964, ch. 8.

to yield a grisane derivative. The n.m.r. spectrum of the product (9) had signals at τ 5.51 (d, J 5 Hz) and 5.12 (t, J 5 Hz), corresponding to the C-2' and C-5' bridgehead protons, together with signals at τ 6.50 (d, J 5 Hz, C-6' proton), partially obscured by other signals, but readily visible in the spectrum of a solution in [^{2}H$_6$]benzene, at τ 6.56 (d, J 5 Hz). Treatment of the spiran (9; R = H) with boron trichloride gave the chloro-alcohol (10), in the n.m.r. spectrum of which the bridgehead proton signals were absent; the hydroxy-proton furnished a broad singlet signal at τ 6.87 (ex-changeable with deuterium oxide), and the i.r. spectrum had $\nu_{max.}$ 3 390 (OH), 1 743 (CO$_2$R), and 1 705 cm^{-1} (ArCO). The mass spectrum confirmed the presence of one chlorine atom [M^+ 340/342 (3 : 1)]. Dehydro-halogenation occurred rapidly in warm pyridine or alcoholic potassium acetate to form an αβ-unsaturated ester, formulated as (11). The i.r. spectrum showed $\nu_{max.}$ 3 380 (OH), 1 710 (C:C·CO$_2$R), 1 692 (ArCO), and 1 645 cm^{-1} (C:C). The molecular ion (m/e 304) con-firmed that the conversion involved elimination of hydrogen chloride. These observations establish the grisane structure (9; R = H) and exclude the alternative xanthone type (8). On this basis the stereochemistry of (9; R = H) was amenable to further clarification.

Thus, addition to the αβ-double bond of the 7-oxa-bicyclo[2.2.1]hept-2-ene system (5) invariably occurs from the less hindered epoxy-bridge side of the molecule.[5] The closure of the phenol (6; R = H) to the grisane (9) may therefore be assumed to follow a similar course. Spin-decoupling of the spectrum of grisane (9; R = H) in [^{2}H]chloroform showed the signal at τ 6.50 (C-6' proton) to be coupled to the signal at τ 5.12 (t), which is due to a bridgehead proton. Thus these two signals may be assigned to the C-6' and C-5' protons, re-spectively. The coupling constant (J 5 Hz) indicates a torsion angle of 45°, with the conclusion that the C-6' proton is on the same side of the spiran ring as the epoxy-bridge. The relative stereochemistry of this grisane may thus be written as in formula (9; R = H), in agreement with the results of X-ray crystallographic analysis (see later).

The cleavage of the epoxy-bridge with boron tri-chloride probably involves initial formation of a 1 : 1 complex,[6] followed by nucleophilic attack at the carbon atom at the other terminus of the epoxy-bridge as in the Scheme. Hence the chloro-alcohol may be repre-sented stereochemically as in (10), with a probable preferred conformation (12) in which the C-5' chlorine and C-6' hydrogen atoms are trans and diequatorial. Conformational inversion of this alicyclic ring would then place these two substituents in trans and diaxial orientations—in keeping with the rapid and ready dehydrochlorination of (10) to (11). The conformation (12) is in accord with the n.m.r. spectrum, in which the

[5] R. B. Woodward and H. Baer, J. Amer. Chem. Soc., 1948, 70, 1161; G. Stork, E. E. van Tamelen, L. J. Friedmann, and A. W. Burgstahler, ibid., 1953, 75, 384.

[6] W. Gerrard, Chem. Rev.. 1958, 58, 1081.

C-5' proton signal at τ 5.06 is a quartet (J 4 and 8 Hz); hence the relevant torsion angle must be 50—60°.
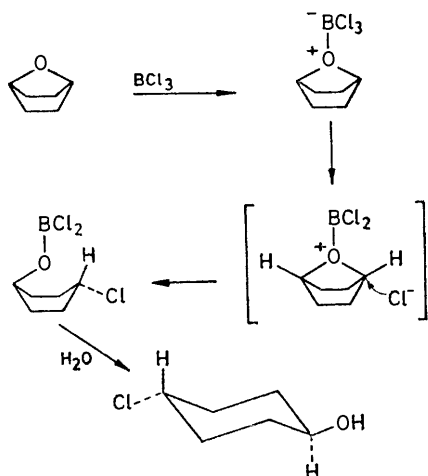
SCHEME

TABLE 1

Atomic positional and thermal parameters ($\times$ 10^5 for Br; $\times$ 10^4 for others)

(a) Co-ordinates of the refined atoms

Atom	x/a	y/b	z/c
Br(1)	19 058(6)	24 026(8)	32 499(8)
Br(2)	8 227(6)	−31 975(8)	31 480(9)
C(1)	−404(5)	2 659(7)	2 534(6)
C(2)	745(5)	1 557(7)	2 992(7)
C(3)	1 123(5)	−177(7)	3 210(7)
C(4)	343(5)	−881(7)	2 973(7)
C(5)	−824(5)	188(7)	2 573(7)
C(6)	−1 217(5)	1 929(7)	2 356(6)
C(7)	−2 518(5)	2 584(7)	2 069(6)
C(8)	−2 789(5)	1 069(7)	1 980(6)
C(9)	−3 860(5)	831(7)	3 044(7)
C(10)	−4 655(5)	814(7)	1 775(7)
C(11)	−5 200(5)	2 545(8)	691(8)
C(12)	−4 105(7)	2 594(9)	−434(7)
C(13)	−3 108(6)	974(8)	278(7)
C(14)	−4 399(5)	1 964(7)	4 285(7)
C(15)	−6 209(6)	3 630(9)	5 570(9)
C(16)	−1 398(6)	5 451(8)	1 094(8)
O(1)	−1 678(3)	−376(5)	2 405(5)
O(2)	−3 719(4)	−152(5)	720(5)
O(3)	−3 270(4)	3 993(5)	1 945(5)
O(4)	−673(4)	4 297(5)	2 386(5)
O(5)	−5 604(4)	2 541(6)	4 377(5)
O(6)	−3 823(4)	2 237(6)	5 137(5)

(b) Co-ordinates of the hydrogen atoms * ($\times 10^3$)

H(3)	203	−97	357
H(9)	−330	−4	4
H(10)	−537	41	231
H(13)	−232	67	−55
H(111)	−552	354	139
H(112)	−592	263	1
H(121)	−391	367	−38
H(122)	−424	260	−167
H(151)	−580	452	551
H(152)	−716	429	534
H(153)	−612	288	677
H(161)	−110	497	−3
H(162)	−234	564	137
H(163)	−132	664	96

* Numbering based on the C atoms to which they are bonded, e.g. H(161) to H(163) are at C(16).

The exclusive attack of chloride ion at C-5' is attributed to the considerable steric crowding at C-2', caused principally by the heterocyclic carbonyl group.

Bromination of the grisane (9; R = H) gave the 5,7-dibromo-derivative (9; R = Br), which was subjected to a single-crystal X-ray crystallographic examination. The crystal structure (Figure 1) consists of discrete, well separated molecules, with most intermolecular contacts corresponding to van der Waals distances, the closest of which are listed in Table 2. The molecular structure and atomic numbering scheme used for the purposes of the crystal structure determination are shown in Figure 2. The molecular skeleton contains a spiro-atom at C(8) at the junction of two main groups of atoms: group 1 is an 8,8-disubstituted coumaran-7-one with bromine atoms at C(2) and C(4), a methoxy-group at C(1) and an oxo-group at C(7); and group 2 is a 7-oxabicyclo[2.2.1]hept-2-ene with an axially substituted methoxycarbonyl group at C(9). Bonded distances in the molecule are in good agreement
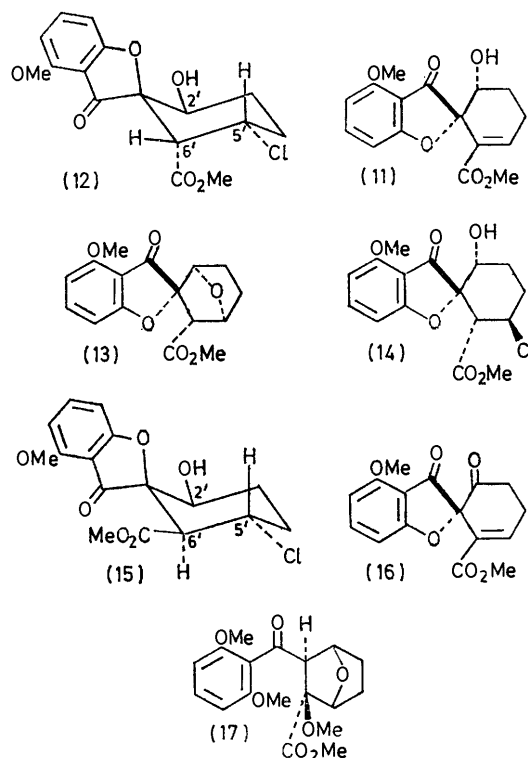
with accepted values (Table 2), with mean distances: $C(sp^2) \cdots C(sp^2)$ (aromatic) = 1.396(6) Å, $C(sp^2)$-Br = 1.901(7) Å; $C(sp^2)$-$C(sp^2)$ (single) = 1.477(8) Å; $C(sp^2)$-$C(sp^3)$ = 1.520(10) Å; $C(sp^3)$-$C(sp^3)$ = 1.542(7) Å; $C(sp^2)$-O = 1.342(7) Å; $C(sp^3)$-O = 1.451(8) Å; and C=O 1.217(9) Å. Similarly the bond angles in the aromatic ring and in the five-membered ring are normal. Many of the bond angles in the oxabicyclo[2.2.1]hept-2-ene reflect the considerable steric strain in this group imposed by the bridging oxygen [O(2)], with the values in the cyclohexane ring C(8)—C(13) in the range 100.8(5)—101.9(5)° at C(8), C(9), C(11), and C(12), and 111.3(6)° and 111.2(5)° at C(1) and C(13), respectively. Similarly there is considerable strain at the bridging oxygen atom [C(10)−O(2)−C(13) = 97.0(5)°].

The torsion angles about the more interesting bonds are listed in Table 3. As expected these show considerable variation from the idealised angles owing to the strain discussed above. Atoms C(10), C(9), C(8), and C(13), and C(10), C(11), C(12), and C(13) are nearly planar (these atoms are listed as planes 3 and 4 in Table 4*), with rotations about the C(8)–C(9) and

and H(121) and O(3) (2.33 Å). The methoxycarbonyl group cannot rotate because of a close contact between O(6) and O(3) (2.96 Å) and another between C(15) and O(6) of another molecule (3.12 Å); however some of the strain is relieved by a rotation about the C(9)–C(10) bond [torsion angle C(14)–C(9)–C(10)–C(11) is 61°; *cf.* −52° for C(12)–C(13)–C(8)–C(7)].
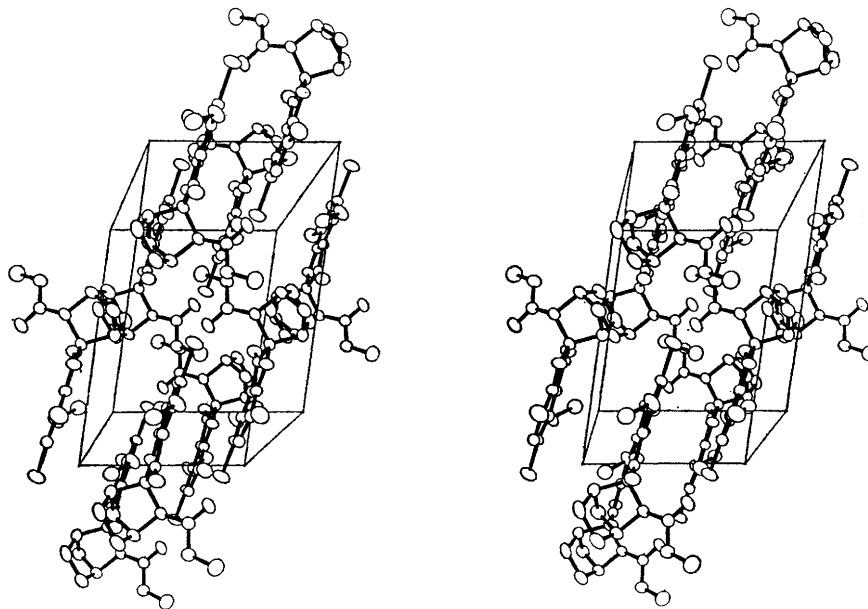

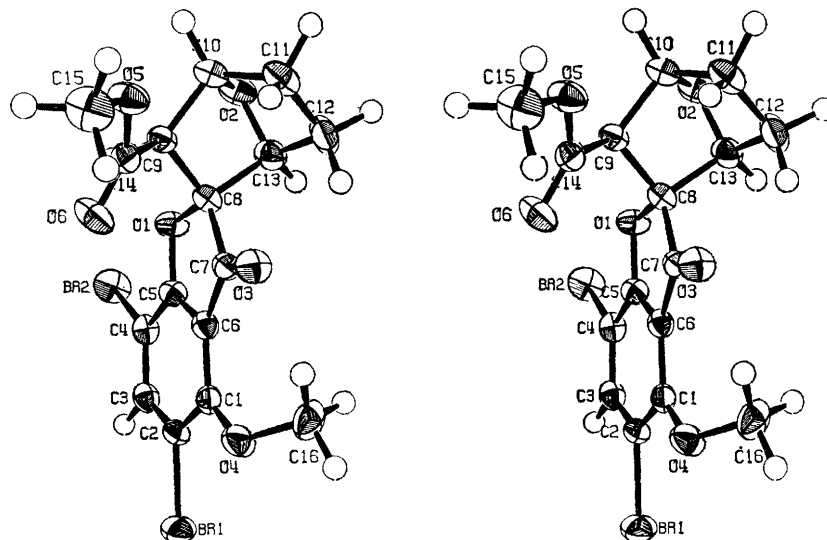FIGURE 1 View of the molecular packing of the spiran (9; R = Br)

FIGURE 2 View of the spiran (9; R = Br) showing the crystallographic numbering scheme

C(11)–C(12) bonds of −5.2 and −4.6°, respectively. The torsion angle between planes 3 and 4 is 114.7°, and reflects the opening of the bond angles at C(10) and C(13) from the tetrahedral due to interaction between axial groups across the boat-shaped cyclohexane ring. Close contacts occur between H(111) and O(5) (2.50 Å)

* Table 4 forms part of the Supplementary Publication; it contains details of mean planes and associated data.

The coumaranone unit is significantly non-planar in the strict statistical sense; however, it seems doubtful that the deviations from planarity are important chemically. There is a close contact between O(3) and C(16) (2.98 Å) which does not seem to be due to any attractive C–H · · · O force, since C(6)–C(1)–C(16) is 125°, however it may result from a close contact between C(16) atoms of neighbouring molecules (3.51 Å), which

TABLE 2

Interatomic distances (Å) and angles (°)

(a) Bonded distances and angles

	Distance	Av.
Br(1)–C(2)	1.909(7) †	}1.901(7)
Br(2)–C(4)	1.892(6) †	
C(1)–C(2)	1.389(7)	
C(1)–C(6)	1.418(10)	
C(2)–C(3)	1.397(8)	
C(3)–C(4)	1.381(10)	}1.396(6)
C(4)–C(5)	1.386(7)	
C(5)–C(6)	1.402(8)	
C(6)–C(7)	1.477(8)	
C(7)–C(8)	1.529(10)	}1.520(10)
C(9)–C(14)	1.511(8)	
C(8)–C(9)	1.539(8)	
C(8)–C(13)	1.568(9)	
C(9)–C(10)	1.542(10)	
C(10)–C(11)	1.545(8)	}1.542(7)
C(11)–C(12)	1.537(10)	
C(12)–C(13)	1.522(8)	
C(1)–O(4)	1.338(7)	
C(5)–O(1)	1.353(9)	}1.342(7)
C(14)–O(5)	1.335(7)	
C(7)–O(3)	1.224(6) †	}1.217(9)
C(14)–O(6)	1.210(9) †	
C(8)–O(1)	1.459(6)	
C(10)–O(2)	1.446(7)	
C(13)–O(2)	1.434(10)	}1.451(8)
C(15)–O(5)	1.477(9) †	
C(16)–O(4)	1.441(7) †	

	Angle		Angle
C(2)–C(1)–C(6)	116.2(5)	C(9)–C(8)–O(1)	109.7(4)
C(2)–C(1)–O(4)	118.1(6)	C(9)–C(8)–C(13)	100.8(5)
C(6)–C(1)–O(4)	125.6(5)	C(13)–C(8)–O(1)	106.9(4)
C(1)–C(2)–C(3)	123.3(7)	C(8)–C(9)–C(10)	101.9(5)
C(1)–C(2)–Br(1)	119.6(5)	C(8)–C(9)–C(14)	115.4(6)
C(3)–C(2)–Br(1)	117.0(4)	C(10)–C(9)–C(14)	120.4(4)
C(2)–C(3)–C(4)	120.3(5)	C(9)–C(10)–C(11)	111.3(6)
C(3)–C(4)–C(5)	117.7(5)	C(9)–C(10)–O(2)	99.2(4)
C(3)–C(4)–Br(2)	122.2(4)	C(11)–C(10)–O(2)	103.0(4)
C(5)–C(4)–Br(2)	120.1(5)	C(10)–C(11)–C(12)	101.7(5)
C(4)–C(5)–C(6)	122.6(6)	C(11)–C(12)–C(13)	101.5(5)
C(4)–C(5)–O(1)	122.4(5)	C(12)–C(13)–C(8)	111.2(5)
C(6)–C(5)–O(1)	114.9(4)	C(12)–C(13)–O(2)	102.5(6)
C(5)–C(6)–C(1)	119.8(5)	C(8)–C(13)–O(2)	101.1(5)
C(5)–C(6)–C(7)	105.5(6)	C(9)–C(14)–O(5)	111.7(6)
C(1)–C(6)–C(7)	134.6(5)	C(9)–C(14)–O(6)	124.3(5)
C(6)–C(7)–C(8)	105.9(4)	O(5)–C(14)–O(6)	124.0(6)
C(6)–C(7)–O(3)	130.3(7)	C(5)–O(1)–C(8)	108.1(4)
C(8)–C(7)–O(3)	123.8(6)	C(10)–O(2)–C(13)	97.0(5)
C(7)–C(8)–O(1)	105.2(5)	C(1)–O(4)–C(16)	120.0(6)
C(7)–C(8)–C(9)	117.8(5)	C(14)–O(5)–C(15)	115.7(6)
C(7)–C(8)–C(13)	116.0(5)		

(b) Shortest intermolecular contacts (Å) ‡

Br(1) · · · O(5^{I})	3.34	C(3) · · · C(4^{V})	3.59
Br(1) · · · Br(2^{II})	3.57	C(9) · · · O(5^{VII})	3.55
Br(1) · · · C(16^{III})	3.77	C(10) · · · O(2^{VIII})	3.36
Br(2) · · · O(4^{IV})	3.58	C(11) · · · O(2^{VIII})	3.38
Br(2) · · · O(4^{V})	3.70	C(11) · · · O(3^{VII})	3.39
C(2) · · · C(4^{V})	3.51	C(15) · · · O(6^{IX})	3.12
C(3) · · · O(6^{V})	3.36	C(16) · · · C(16^{III})	3.51
C(3) · · · C(5^{V})	3.54	O(2) · · · O(2^{VIII})	3.37
C(3) · · · C(13^{VI})	3.56		

† Corrected for thermal motions based on the riding model approximation.

‡ Roman numerals refer to the following symmetry elements:

I	$1 + x, y, z$	VI	$-x, -y, -z$
II	$x, 1 + y, z$	VII	$-1 -x, -y, 1 - z$
III	$-x, 1 - y, -z$	VIII	$-1 - x, -y, -z$
IV	$x, y - 1, z$	IX	$-1 - x, 1 - y, 1 - z$
V	$-x, -y, 1 - z$		

prevents further rotation of the methyl group about C(1)–O(4).

A minor product from the base-catalysed cyclisation

of the phenol (6; R = H) is formulated as the 6'α-carboxylate (13), in accord with spectral (see Experimental section) and chemical evidence. Thus treatment of (13) with boron trichloride gave the chloro-alcohol (14), isomeric with (10) and having m/e 340/342 (3 : 1). Dehydrochlorination proceeded slowly to produce the αβ-unsaturated ester (11). The preferred conformation of this chloro-alcohol appears to be (15) in accord with the n.m.r. spectrum in which the C-6' proton signal appears at τ 6.91 (d, J 12 Hz): hence the C-6' and C-5' protons must be *trans* and diaxial with a torsion angle of 180°. The C-6' proton and C-5' chlorine atom must therefore be *cis*-oriented, in accord with the slow dehydrochlorination.

Oxidation of the unsaturated alcohol (11) gave the corresponding ketone (16).

This route provides a method for the preparation of novel grisanes, particularly those devoid of oxygen at C-4'.

TABLE 3

Selected torsion angles (°)

C(2)–C(1)–O(4)–C(16)	141.4(7)
C(6)–C(1)-O(4)–C(16)	−42.7(1.0)
C(6)–C(7)–C(8)–C(9)	129.0(6)
C(6)–C(7)–C(8)–C(13)	−111.5(7)
O(3)–C(7)–C(8)–C(9)	−49.8(1.0)
O(3)–C(7)–C(8)–C(13)	69.7(9)
C(7)–C(8)–C(9)–C(10)	122.0(6)
C(7)–C(8)–C(9)–C(14)	−10.2(9)
O(1)–C(8)–C(9)–C(10)	−117.7(6)
O(1)–C(8)–C(9)–C(14)	110.1(7)
C(13)–C(8)–C(9)–C(10)	−5.2(7)
C(13)–C(8)–C(9)–C(14)	−137.4(6)
C(8)–C(9)–C(10)–C(11)	−68.1(7)
C(8)–C(9)–C(10)–O(2)	39.8(6)
C(14)–C(9)–C(10)–C(11)	61.1(9)
C(14)–C(9)–C(10)–O(2)	169.0(6)
C(9)–C(10)–C(11)–C(12)	75.8(8)
O(2)–C(10)–C(11)–C(12)	−29.6(7)
C(10)–C(11)–C(12)–C(13)	−4.6(8)
C(11)–C(12)–C(13)–C(8)	−69.3(8)
C(11)–C(12)–C(13)–O(2)	38.0(8)
C(12)–C(13)–C(8)–C(7)	−51.6(9)
C(12)–C(13)–C(8)–C(9)	76.8(7)
C(12)–C(13)–C(8)–O(1)	−168.6(6)
O(2)–C(13)–C(8)–C(7)	−159.8(6)
O(2)–C(13)–C(8)–C(9)	−31.4(7)
O(2)–C(13)–C(8)–O(1)	83.2(6)
C(9)–C(10)–O(2)–C(13)	−61.0(6)
C(11)–C(10)–O(2)–C(13)	53.5(7)
C(8)–C(13)–O(2)–C(10)	57.8(6)
C(12)–C(13)–O(2)–C(10)	−57.1(7)
C(5)–O(1)–C(8)–C(7)	−5.1(7)
C(5)–O(1)–C(8)–C(9)	−132.7(6)
C(5)–O(1)–C(8)–C(13)	118.8(6)

Although the intramolecular cyclisation of (6; R = H) gives β-addition, the intermolecular addition of methanol to (6; R = H) furnishes a substance to which we assign structure (17), in accord with spectral evidence, particularly n.m.r. signals at τ 6.70 (alkyl OMe), 6.32 (ester OMe), 6.19 (2 aryl OMe), 5.83 (C-2 proton), and 5.27 and 4.93 (bridgehead protons). In 7-oxabicyclo-[2.2.1]heptane derivatives, the chemical shifts of protons α to an aryl oxo-group occur in the region τ 5.83—6.25, whereas for protons α to a methoxycarbonyl function the corresponding signals occur in the region τ 6.84—7.19. Hence the signal at τ 5.83 can be attributed to a

C-2 proton. In the i.r. spectrum of (17) the ester carbonyl band occurs at 1 743 cm^{-1}; this unusually high value agrees with the presence of an α oxygen substituent (OMe), as in (17) (cf. the ester carbonyl frequency of 1 755 cm^{-1} in derivatives of secalonic acids).[2]

The cyclisation of the phenol (6; R = H) to the grisane (9; R = H) rather than the xanthone (8) may be attributed to the more favourable geometry for the relevant transition states.

EXPERIMENTAL

I.r. spectra were determined for Nujol mulls with Perkin-Elmer 237 and Unicam SP 200 spectrophotometers. Unless stated otherwise n.m.r. spectra were determined for solutions in [^{2}H]chloroform at 60 MHz. Mass spectra were determined with an A.E.I. MS902 spectrometer.

Methyl 4-(2,6-Dimethoxyphenyl)-4-oxobut-2-ynoate (4; R = CO$_2$Me).—A rapid stream of acetylene was passed into liquid ammonia (750 ml) while sodium (19 g) was introduced in small pieces at a rate such that the blue colour was transient. Passage of acetylene was continued for 0.5 h, and then slowly for the remainder of the reaction. A solution of 2,6-dimethoxybenzaldehyde (130 g) in tetrahydrofuran (50 ml) was added during 15 min. The resultant solution was refluxed for 2.5 h, when the ammonia was allowed to evaporate. Isolated in the normal manner, 1-(2,6-*dimethoxyphenyl*)*prop-2-yn-1-ol* (130 g) formed small, stout, prisms, m.p. 88° (from ether) [Found: C, 68.5; H, 6.4; OMe, 32.9. C$_9$H$_6$O(OMe)$_2$ requires C, 68.7; H, 6.3; OMe, 32.3%].

A solution of this propyne (7.5 g) in tetrahydrofuran (100 ml) was added to ethylmagnesium bromide [from magnesium (2.5 g), ethyl bromide (11.5 g), and ether (20 ml)] during 20 min. The mixture was refluxed for 0.5 h, cooled to 0 °C and treated with an excess of powdered solid CO$_2$, more being added hourly during 6 h. Next day the product was isolated to yield 4-(2,6-*dimethoxyphenyl*)-*4-hydroxybut-2-ynoic acid* (2.6 g) in pale yellow prisms, m.p. 125—130° (decomp.) (from benzene–acetone) [Found: C, 61.2; H, 5.3; OMe, 26.2. C$_{10}$H$_6$O$_3$(OMe)$_2$ requires C, 61.0; H, 5.1; OMe, 26.3%]. Unchanged propyne (4 g) was recovered.

Esterification of this acid with diazomethane gave the corresponding ester (50 g) as an oil which was not characterised but was dissolved in acetone (1 l), and maintained at 5 °C during addition of Jones reagent (100 ml). After 4 h, the product was isolated to yield methyl 4-(2,6-*dimethoxyphenyl*)-*4-oxobut-2-ynoate* (32.5 g) in pale yellow prisms, m.p. 92° (from methanol) [Found: C, 62.7; H, 5.0; OMe, 37.3. C$_{10}$H$_3$O$_2$(OMe)$_3$ requires C, 62.9; H, 4.9; OMe, 37.5%], ν$_{max.}$ 1 720, 1 665, 1 595, 1 260, and 1 110 cm^{-1}, τ 6.17 (3 H, s, CO$_2$·CH$_3$), 6.13 (6 H, s, 2 × OCH$_3$), 3.37 (2 H, d, ArH), and 2.57 (1 H, q, ArH).

In one experiment where the excess of Jones reagent was destroyed with methanol a second product was obtained (as the ester) in pale yellow prisms, m.p. 137° (from acetone–methanol) (Found: C, 59.9; H, 5.7; OMe, 35.3%).

Methyl 3-(2,6-Dimethoxybenzoyl)-7-oxabicyclo[2.2.1]hept-2-ene-2-carboxylate (6; R = Me).—A solution of the oxo-ester (4; R = CO$_2$Me) (15.3 g) in acetone (20 ml) and furan (5 ml) was refluxed in a closed system for 38 h. After isolation, the excess of furan was removed *in vacuo*, the oily product dissolved in acetone (350 ml) and hydrogenated

using 5% palladium–charcoal (0.15 g), when hydrogen (1 370 ml = 1.05 equiv.) was absorbed during 25 min. Isolation of the product followed by purification on silica from benzene, using ether–benzene (5 : 95) as eluant gave the *oxabicycloheptene* (6; R = Me) (16 g) in yellow prisms, m.p. 94° (from ether) [Found: C, 63.7; H, 5.8; OMe, 29.3. C$_{14}$H$_9$O$_3$(OMe)$_3$ requires C, 64.1; H, 5.7; OMe, 29.3%], ν$_{max.}$ 1 730 and 1 655 cm^{-1}, τ 8.6—7.8 (4 H, m, CH$_2$·CH$_2$), 6.66 (3 H, s, CO$_2$·CH$_3$), 6.24 (6 H, s, 2 × OCH$_3$), 4.77 (1 H, m, CH), 4.55 (1 H, m, CH), 3.43 (2 H, d, ArH), and 2.70 (1 H, q, ArH).

A solution of boron trichloride (12.5 g) in dichloromethane (50 ml) was added (at −70 °C) during 1 min to a solution of this ester (10 g) in dichloromethane (250 ml) at −70 °C. Five min later the product was isolated, after addition of aqueous 10% sodium acetate (200 ml), and purified from ethanol to yield *methyl 3-(2-hydroxy-6-methoxybenzoyl)-7-oxabicyclo[2.2.1]hept-2-ene-2-carboxylate* (6; R = H) (8.6 g) in pale yellow prisms, m.p. 109° [Found: C, 63.3; H, 5.3; OMe, 19.9. C$_{14}$H$_{10}$O$_4$(OMe)$_2$ requires C, 63.2; H, 5.3; OMe, 20.4%]. This phenol gives a green colouration with iron(III) in alcohol.

A solution of this oxabicycloheptene (8 g) in acetone (50 ml) containing potassium carbonate (1 g) was refluxed gently until the initial yellow colour had been discharged (*ca.* 5 min). Purification of the product from ethanol gave (±)-*methyl 2′α,5′α-epoxy-4-methoxygrisane-6′β-carboxylate* (9; R = H) (7.3 g) in prisms, m.p. 156° [Found: C, 63.2; H, 5.4; OMe, 25.4%; *M*$^+$, 304. C$_{14}$H$_{10}$O$_4$(OMe)$_2$ requires C, 63.2; H, 5.3; OMe, 20.4%; *M*, 304], ν$_{max.}$ 1 738 and 1 705 cm^{-1}, τ 8.7—7.35 (4 H, m, CH$_2$·CH$_2$), 6.50 (1 H, d), 6.42 (3 H, s, CO$_2$·CH$_3$), 6.03 (3 H, s, O·CH$_3$), 5.51 (1 H, d, *J* 5 Hz), 5.12 (1 H, t, *J* 5 Hz), 3.47 (1 H, d, *J* 8 Hz), 3.30 (1 H), and 2.42 (1 H).

Purification of the mother liquor remaining after separation of this grisan-3-one by t.l.c. on silica [ethyl acetate–chloroform (1 : 9)] gave the isomeric 6′α-*carboxylate* (13) (0.5 g) in stout prisms, m.p. 200° (from acetone) (Found: C, 63.4; H, 5.5%; *M*$^+$, 304). ν$_{max.}$ 1 728 and 1 703 cm^{-1}, τ 8.5—7.4 (4 H, m, CH$_2$·CH$_2$), 6.97 (1 H), 6.37 (3 H, s, CO$_2$·CH$_3$), 6.04 (3 H, s, O·CH$_3$), 5.51 (1 H, d, *J* 5 Hz), 4.81 (1 H, d, *J* 5 Hz), 3.48 (1 H, d, *J* 8 Hz), 3.33 (1 H), and 2.46 (1 H).

The same cyclisation was effected by dissolution of the precursor in pyridine or triethylamine.

2-(2-Benzyloxy-6-methoxybenzoyl)-3-methoxycarbonyl-7-oxabicyclo[2.2.1]hept-2-ene (6; R = Bz).—Prepared by the interaction of 2-hydroxy-6-methoxybenzaldehyde (30 g) with benzyl bromide (40 ml) in boiling acetone (250 ml) containing potassium carbonate (100 g) during 8 h, 2-*benzyloxy-6-methoxybenzaldehyde* formed prisms (28 g), m.p. 73° (from ether) (Found: C, 74.1; H, 5.9. C$_{15}$H$_{14}$O$_3$ requires C, 73.4; H, 5.8%).

A solution of this aldehyde (25 g) in tetrahydrofuran (100 ml) and ether (100 ml) was added with stirring during 15 min to a suspension of sodamide [from sodium (2.5 g) in liquid ammonia (200 ml)], through which a stream of acetylene had previously been passed for 1 h. After 4 h, with continued passage of acetylene, ammonium chloride (20 g) and ether (300 ml) were added. Next day, the product was isolated with more ether, and 1-(2-*benzyloxy-6-methoxyphenyl*)*prop-2-yn-1-ol* (25 g) was obtained in pale yellow needles, m.p. 119° [from ether–acetone (1 : 1)] (Found: C, 70.5; H, 6.0. C$_{17}$H$_{16}$O$_3$,H$_2$O requires C, 71.3; H, 6.3%).

This propyne (12 g) was carboxylated by way of the Grignard complex as for the methoxy-analogue to yield 4-(2-*benzyloxy*-6-*methoxyphenyl*)-4-*hydroxybut*-2-*ynoic acid* (4.8 g) in stout, yellow prisms, m.p. 119° (from ethyl acetate) (Found: C, 69.6; H, 5.3. $C_{18}H_{16}O_5$ requires C, 69.2; H, 5.2%).

Prepared quantitatively from this acid, by using diazomethane, the methyl ester formed an oil which did not crystallize. A solution of this ester (2.6 g) in dichloromethane (125 ml) was stirred with activated manganese dioxide (5 g) during 0.5 h. Isolated in the normal manner, *methyl* 4-(2-*benzyloxy*-6-*methoxyphenyl*)-4-*oxobut*-2-*ynoate* (2.2 g) formed an oil (Found: C, 69.8; H, 5.3. $C_{19}H_{16}O_5$ requires C, 70.4; H, 5.0%), $v_{max.}$ 3 505, 2 940, 2 225, and 1 710 cm^{-1}.

A solution of this ester (5.4 g) in acetone (10 ml) containing furan (5 ml) was refluxed in a closed system for 47 h; the reaction was then complete (t.l.c.). Solvents were removed at 18 °C, *in vacuo*, and the residue, dissolved in acetone (100 ml), was hydrogenated over 5% palladium–charcoal (0.25 g). When 310 ml (1.01 mol. equiv.) had been absorbed, methyl 3-(2-benzyloxy-6-methoxybenzoyl)-7-oxabicyclo[2.2.1]hept-2-ene-2-carboxylate (5.1 g) was obtained as an oil, which was dissolved in dichloromethane (150 ml) and cooled to −70 °C. A solution of boron trichloride (7 g) in dichloromethane (35 ml) was introduced during 1 min, at −70 °C: 1 min later an excess of 10% sodium acetate solution was added, to give methyl 3-(2-hydroxy-6-methoxybenzoyl)-7-oxabicyclo[2.2.1]hept-2-ene-2-carboxylate (3.2 g) in pale yellow prisms, m.p. 108° (from ethanol), identical (m.p., mixed m.p., n.m.r., and i.r.) with the previously prepared specimen.

(±)-*Methyl* 2′α-*Hydroxy*-4-*methoxy*-3-*oxogris*-5′-*ene*-6′-*carboxylate*.—(a) A solution of the grisan-3-one (9; R = H) (0.1 g) in dichloromethane (25 ml), cooled to −70 °C was treated with boron trichloride (0.28 g) in dichloromethane (1.5 ml). The mixture was then allowed to attain room temperature, and 20 min later diluted with aqueous 10% sodium acetate. Purification of the product from dichloromethane–ether gave (±)-*methyl* 5′β-*chloro*-2′α-*hydroxy*-4-*methoxy*-3-*oxogrisane*-6′β-*carboxylate* (94 mg) in prisms, m.p. 194° (Found: C, 55.9; H, 4.7; Cl, 10.9%; M^+, 340. $C_{18}H_{17}ClO_6$ requires C, 56.4; H, 5.0; Cl, 10.4%; M, 340), $v_{max.}$ 3 480, 3 390, 1 743, and 1 705 cm^{-1}, τ 8.4—7.5 (4 H + 1 H, m, CH$_2$·CH$_2$), 6.87br (1 H, s, OH, replaceable + D$_2$O), 6.33 (3 H, s, CO$_2$·CH$_3$), 6.02 (3 H, s, O·CH$_3$), 6.33—6.02br (1 H, m), 5.06 (1 H, q, J 4 and 8 Hz), 3.48 (1 H, d, J 8.5 Hz), 3.25 (1 H, d, J 8.5 Hz), and 2.41 (1 H, t, J 8.5 Hz).

A solution of this grisan-3-one (90 mg) in pyridine (2 ml) was warmed at 100 °C during 2 min, then diluted with ethyl acetate, and pyridine was removed by washing with 2N-hydrochloric acid. The product was purified from acetone to yield the *gris*-5′-*ene* (11) (80 mg) in prisms, m.p. 194° (Found: C, 63.2; H, 5.2%; M^+, 304. $C_{18}H_{16}O_6$ requires C, 63.2; H, 5.3%; M, 304), $v_{max.}$ 3 380 and 1 710 cm^{-1}, τ 8.2—7.2 (4 H, m, CH$_2$·CH$_2$), 6.37 (1 H, m, OH exchanged + D$_2$O), 6.37 (3 H, s, CO$_2$·CH$_3$), 6.12 (1 H), 6.01 (3 H, s, O·CH$_3$), 3.48 (1 H, d, J 8 Hz), 3.35 (1 H, d, J 8 Hz), 2.45 (1 H, m), and 2.44 (1 H, m).

A solution of this gris-5′-ene (90 mg) in acetone (50 ml) was oxidised at room temperature by gradual addition of Jones reagent with stirring. The reaction was monitored by t.l.c. After 30 min the excess of reagent was destroyed with methanol and the product isolated with chloroform. Purification from dichloromethane gave (±)-*methyl* 4-

methoxy-2′,3-*dioxogris*-5′-*ene*-6′-*carboxylate* (76 mg) in cubes, m.p. 191° (Found: C, 62.0; H, 4.6%; M^+, 302. $C_{18}H_{14}O_6$ requires C, 63.6; H, 4.7%; M, 302), $v_{max.}$ 1 733, 1 715, and 1 700 cm^{-1}, τ 7.7—6.6 (4 H, m, CH$_2$·CH$_2$), 6.38 (3 H, s, CO$_2$·CH$_3$), 6.05 (3 H, s, O·CH$_3$), 3.49 (1 H, d, J 8 Hz), 3.22 (1 H, d, J 8 Hz), 2.50 (1 H, m), and 2.42 (1 H, m).

(b) A solution of the 6′α-carboxylate (13) (60 mg) was treated with boron trichloride as for the 6′β-isomer to yield (±)-*methyl* 5′β-*chloro*-2′α-*hydroxy*-4-*methoxy*-3-*oxogrisane*-6′α-*carboxylate* (50 mg) in prisms, m.p. 220° (from ether–dichloromethane) (Found: C, 56.0; H, 5.0%; M^+, 340. $C_{18}H_{17}ClO_6$ requires C, 56.4; H, 5.0%; M, 340), $v_{max.}$ 3 530, 1 723, and 1 708 cm^{-1}, τ 8.5—7.25 (4 H, m, CH$_2$·CH$_2$), 7.08br (1 H, s, OH, exchangeable + D$_2$O), 6.91 (1 H, d, J 12 Hz), 6.52 (3 H, s, CO$_2$·CH$_3$), 6.11 (3 H, s, O·CH$_3$), 6.01 (1 H, m), 5.08 (1 H, d, J 4 Hz), 3.54 (1 H, d, J 8 Hz), 3.36 (1 H, d, J 8 Hz), and 2.49 (1 H, m).

A solution of this grisan-3-one (48 mg) in pyridine (8 ml) was heated on a steam-bath for 8 h to yield the gris-5′-ene (11) (40 mg), identical (m.p., mixed m.p., n.m.r. and mass spectra) with that prepared by method (a).

(±)-*Methyl* 5,7-*Dibromo*-2′α,5′α-*epoxy*-4-*methoxy*-3-*oxogrisane*-6′β-*carboxylate* (9; R = Br).—A solution of the grisane-6′β-carboxylate (9; R = H) (0.2 g) in acetic acid (12 ml) was treated with bromine (1.3 ml) in acetic acid (8 ml) during 15 min. After 1 h, the solution was poured into an excess of aqueous sodium hydrogen sulphite containing 2% of acetone. Isolated with ethyl acetate, the *dibromo-derivative* (9; R = Br) (0.15 g) formed prisms, m.p. 185° (from dichloromethane–ether) (Found: C, 41.7; H, 3.1; Br, 34.9. $C_{18}H_{14}Br_2O_4$ requires C, 41.6; H, 3.1; Br, 34.7%).

Methyl 3β-(2,6-*Dimethoxybenzoyl*)-2β-*methoxy*-7-*oxabicyclo*[2.2.1]*heptane*-2α-*carboxylate* (17).—A solution of the oxabicycloheptene (6; R = Me) (0.1 g) in methanol (5 ml) was treated with 30% sodium methoxide in methanol (5 ml); further portions (5 ml) were added after 20 and 40 min (with stirring); 1 h later, the product was isolated. Purification from ether gave the *oxabicycloheptane* (62 mg) in prisms, m.p. 127° (Found: C, 61.6; H, 5.9%; M^+, 350. $C_{18}H_{22}O_7$ requires C, 61.7; H, 6.3%; M, 350), $v_{max.}$ 1 743. 1 693, and 1 595 cm^{-1}, τ 8.9—7.9 (4 H, m, CH$_2$·CH$_2$), 6.70 (3 H, s, CH$_3$), 6.32 (3 H, s, CH$_3$), 6.19 (6 H, s, 2 × ArO·CH$_3$), 5.83 (1 H), 5.27 (1 H), 4.93 (1 H), 3.47 (1 H, d, J 8 Hz), and 2.70 (1 H, m).

Methyl 2-(2-*Hydroxy*-6-*methoxybenzoyl*)*benzoate*.—(a) A solution of the oxabicycloheptene (6; R = H) (0.1 g) in dichloromethane (25 ml) at −70 °C was treated with boron trichloride (0.3 g) in dichloromethane (1.6 ml). The mixture was allowed to warm to room temperature and the product isolated 2 h later to yield *methyl* 2-(2-*hydroxy*-6-*methoxybenzoyl*)*benzoate* in plates (0.07 g), m.p. 115° (from ether–dichloromethane) (Found: C, 67.1; H, 4.9. $C_{16}H_{14}O_5$ requires C, 67.1; H, 4.9%).

(b) A solution of 2,6-dimethoxyphenyl-lithium (2 g) in ether (100 ml) was added to a solution of phthalic anhydride (2 g) in tetrahydrofuran (50 ml). After 2 h (under nitrogen) at 50 °C the product was isolated and purified from ether–dichloromethane to yield 2-(2,6-*dimethoxybenzoyl*)*benzoic acid* (1.2 g) in needles, m.p. 202° (Found: C, 67.1; H, 5.1. $C_{16}H_{14}O_5$ requires C, 67.1; H, 4.9%). The *methyl ester* formed needles, m.p. 75° [from ether–light petroleum (b.p. 40—60°)] (Found: C, 68.1; H, 5.3. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%). Demethylation of methyl 2-(2,6-dimethoxybenzoyl)benzoate with boron trichloride at −70 °C

gave (quantitatively), methyl (2-hydroxy-6-methoxy-benzoyl)benzoate, identical with the specimen from method (a).

X-*Ray Crystal Structure Analysis of* ($\pm$)-*Methyl*-5,7-*Dibromo*-2'α,5'α-*epoxy*-4-*methoxy*-3-*oxogrisane*-6'β-*carboxylate.*—*Crystal data.* $C_{16}H_{14}Br_2O_6$, $M = 462.1$. Triclinic, $a = 12.117(2)$, $b = 8.889(1)$, $c = 8.470(1)$ Å, $\alpha = 77.71(1)$, $\beta = 82.36(2)$, $\gamma = 66.20(1)°$, $U = 814.4$ Å^3, $Z = 2$, $D_c = 1.884$ g cm^{-3} (20 °C; Mo-K_α, $\lambda = 0.710\ 69$ Å). Space group $P1$ (C_i^1, No. 2); linear absorption coefficient for X-rays $\mu = 31.94$ cm^{-1}.

Preliminary precession and Weissenberg photographs indicated a triclinic space group. The cell dimensions were obtained by least-squares refinement from the setting angles of 12 reflections. The Delaunay-reduced unit cell [7] confirmed the triclinic lattice and yielded the reduced cell parameters $a = 8.47$, $b = 11.786$, $c = 10.902$ Å, $\alpha = 105.00$, $\beta = 127.17$, $\gamma = 91.32°$, corresponding to the transformation 001/110/011. Because of the inconveniently large β angle of the reduced cell the structure was solved and refined by using the non-reduced lattice. The crystal chosen for the data collection was a centrosymmetric polyhedron bound by the following faces, with the perpendicular distances between them given in parentheses: 011 (0.076 mm), 010 (0.054 mm), 110 (0.163 mm), 10 − 1 (0.120 mm), and 101 (0.217 mm). Intensity data were collected to a maximum Bragg angle (θ) of 35° on a Hilger–Watts Y290 computer-controlled diffractometer. The $\theta/2\theta$ scan method was used, with an integrated symmetric scan of 0.6°, consisting of 60 1 s steps. Stationary counter–stationary crystal background counts of 15 s duration were measured at each end of the scan. Three standard reflections were measured at regular intervals throughout the data collection to monitor crystal and X-ray beam stability. The maximum variation in intensity of θ of the standard reflections was less than 5.0%. A total of 5 790 independent intensities was accessible, of which 2 178 were greater than three times their e.s.d.s and were treated as 'observed.' Few such intensities had θ values greater than 27°. The data were corrected for Lorentz, polarisation, and absorption factors.

Structure solution and refinement. The co-ordinates of the bromine atoms were located from a three-dimensional Patterson function. An initial structure factor calculation yielded agreement factors R_1 ($= \Sigma||F_o| - |F_c||/\Sigma|F_o|$) and R_2 ($= [\Sigma\omega(F_o - F_c)^2/\Sigma\omega F_o^2]^{1/2}$) of 0.34 and 0.44, respectively. In all calculations of F_c the usual atomic

scattering factors for C, O, Br,[8] and H[9] were used. A difference map of the electron density distribution, calculated by using the phases derived from the heavy atom positions, yielded chemically sensible positions for all the non-hydrogen atoms. Three cycles of full matrix refinement of the structure, with all atoms isotropic, converged with $R_1 = 0.12$. Only the 2 178 reflections greater than 3σ were included in the least-squares calculations and the function minimised was R_2 (above). Absolute weights [based on $\sigma(F_o)$] were used throughout the refinement. Further refinement cycles followed in which first the bromine atoms, then the remaining non-hydrogen atoms, were allowed anisotropic motion. Corrections for anomolous dispersion for Br were included at later stages of the refinement. A final difference synthesis contained a number of peaks, of which the highest corresponded to chemically sensible positions for the 14 hydrogen atoms. The theoretical positions of these were calculated (by assuming a tetrahedral angle where appropriate and a C–H distance of 1.08 Å) and these hydrogens were included, but not refined, in the final two cycles of refinement. The refinement converged with $R_1 = 0.047$ and $R_2 = 0.058$. On the last cycle the maximum shift in any of the positional parameters was 0.25 of an e.s.d. and that for a thermal parameter was 0.5 e.s.d. The final atomic positional parameters are listed in Table 1 and observed and calculated structure factors are available as Supplementary Publication No. SUP 21740 (10 pp.),* which also includes Table 4 and thermal parameters.

The final error in an observation of unit weight calculated over all 'observed' data was 0.979, and ranged from 0.885 to 1.209 over 10 ranges of intensity in a random manner indicating that the weighting scheme is quite good. The final values of the agreement factors for all data including those less than 3σ are: $R_1 = 0.139$, $R_2 = 0.094$. These rather high values, in comparison with the satisfactory values obtained for the observed data only, reflect the extremely large number of unobserved intensities within the 35° sphere over which the data were collected.

* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1975, Index issue.

[7] 'International Tables for X-Ray Crystallography,' vol. I, Kynoch Press, Birmingham, 1965.

[8] 'International Tables for X-Ray Crystallography, vol. III, Kynoch Press, Birmingham, 1968.
[9] R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 1965, **42**, 3178.