

## Naturally occurring 1,2,8-trimethoxy-xanthone and biphenyl ether intermediates leading to 1,2-dimethoxy-xanthone

Luis Gales,<sup>a,b</sup> Maria Emilia de Sousa,<sup>c,d</sup> Madalena M. M. Pinto,<sup>c</sup> Anake Kijjoa<sup>a,c</sup> and Ana M. Damas<sup>a,b\*</sup>

<sup>a</sup>Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Largo Prof. Abel Salazar N. 2, 4099-003 Porto, Portugal, <sup>b</sup>Instituto de Biologia Molecular e Celular, Universidade do Porto, R. Campo Alegre N. 823, 4150 Porto, Portugal, <sup>c</sup>Centro de Estudos de Química Orgânica, Fitoquímica e Farmacologia, Faculdade de Farmácia, Universidade do Porto, Rua Anibal Cunha, 4050-017 Porto, Portugal, and <sup>d</sup>Instituto Superior de Ciências de Saúde do Norte, Gandra, Portugal  
Correspondence e-mail: amdamas@ncc.up.pt

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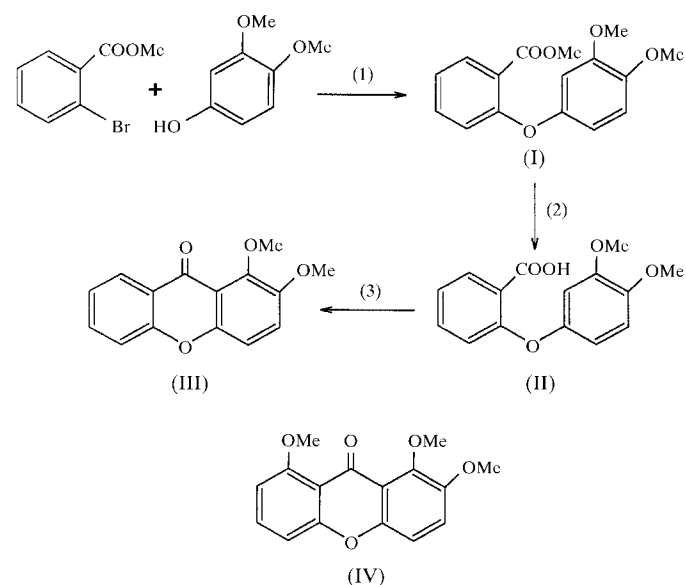
In order to study structure–activity relationships, a series of mono-, di- and trioxxygenated xanthenes has been synthesized and the structures of methyl 2-(3,4-dimethoxyphenoxy)benzoate, C<sub>16</sub>H<sub>16</sub>O<sub>5</sub>, 2-(3,4-dimethoxyphenoxy)benzoic acid, C<sub>15</sub>H<sub>14</sub>O<sub>5</sub>, 1,2-dimethoxy-9*H*-xanthen-9-one, C<sub>15</sub>H<sub>12</sub>O<sub>4</sub>, and 1,2,8-trimethoxy-9*H*-xanthen-9-one, C<sub>16</sub>H<sub>14</sub>O<sub>5</sub>, have been determined. The first two compounds both assume skew conformations, the dihedral angles between the two phenyl rings being 80.04 (8) and 83.0 (1)°, respectively. The latter two compounds are essentially planar and their methoxy substituents assume orientations consistent with minimum steric interactions.

### Comment

Xanthenes are major secondary metabolites of the plants of the family Guttiferae (Bennett & Lee, 1989). Both synthetic and naturally occurring xanthenes have been reported to mediate various biological effects, such as hepatoprotection (Fernandes *et al.*, 1995) and reversible monoamine oxidase A inhibitors (Thull *et al.*, 1993; Fujimoto *et al.*, 1998). As part of our ongoing research concerning the variety of biological properties of this class of compounds, we have investigated the xanthone constituents of *Calophyllum teysmanii* var. inophylloide and studied their immunomodulatory activity (Gonzalez *et al.*, 1999).

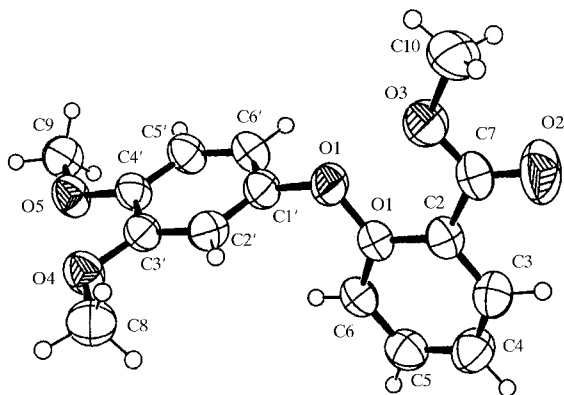
Among the xanthenes tested, 2-hydroxy-1-methoxy-xanthone has been shown to exhibit the highest inhibitory activity on T-cell proliferation. Further examination of the extract of *Calophyllum teysmanii* var. inophylloide has led to an isolation of, among many known xanthenes, the new

xanthenes 1,2,8-trimethoxy-9*H*-xanthen-9-one, (IV), and 1,3,5,7-tetramethoxyxanthone (Kijjoa *et al.*, 2000). However, the biological activities of these xanthenes have not yet been evaluated. Taking into account the variety of biological properties of xanthenes, we have planned the synthesis of a series of 1,2-dioxygenated xanthenes to evaluate their anti-tumour and immunomodulatory activities. The syntheses of some 1,2-dioxygenated xanthenes have been reported previously; 1,2-dimethoxy-9*H*-xanthen-9-one, (III), was obtained in very low yield by a multi-step synthesis of its intermediate 1-formyl-2-hydroxyxanthone (Golberg & Wragg, 1958). More recently, 1-hydroxy-2-methoxyxanthone has been prepared by an LDA-induced (LDA is lithium diisopropylamide) regioselective route from diaryl ether 2-carboxhexamines (Familoni *et al.*, 1997). In contrast, we have succeeded in preparing (III) by a facile one-step conversion of the diaryl ether intermediate 2-(3,4-dimethoxyphenoxy)benzoic acid, (II), into the corresponding xanthone. In this paper, we report the structures of the intermediate compounds, methyl 2-(3,4-dimethoxyphenoxy)benzoate, (I), and 2-(3,4-dimethoxyphenoxy)benzoic acid, (II), obtained during the synthesis of (III), as well as the structure of this xanthone compared with (IV), which is very similar and which was isolated from a plant.



Compounds (I) and (II) (Figs. 1 and 2) differ only in the substituent at C2, which is a methyl ester in (I) and a carboxylic acid group in (II). They both assume a skew conformation, the angle between the phenyl rings being 80.04 (8)° for (I) and 83.0 (1)° for (II). These angles are in close agreement with the value of 84.8 (1)° observed in another open-ring intermediate for the synthesis of xanthenes (Damas *et al.*, 1997).

In (I), the plane defined by C1, O1 and C1' makes an angle of 4.8 (1)° with the C1–C6 phenyl ring plane and 76.5 (2)° with the other ring, C1'–C6'. The methyl ester group is nearly coplanar with the phenyl ring, as shown by the r.m.s. deviations from the ring plane: C7 0.039 (3), O2 0.173 (4), O3 –0.079 (4) and C10 –0.029 (6) Å. Furthermore, the bond

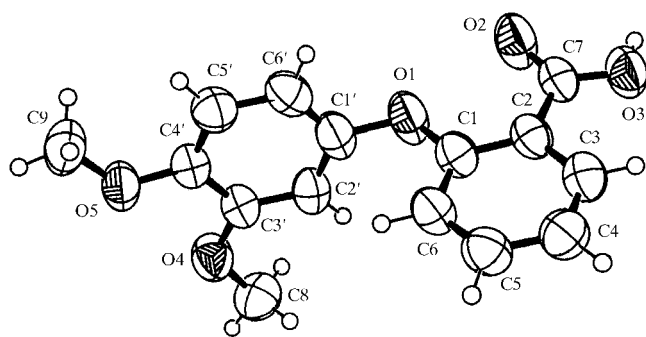


**Figure 1**  
The molecular structure of (I) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

angles between the methyl ester group and the phenyl-ring C atoms adjacent to C2 are  $126.3(2)^\circ$  for C1–C2–C7 and  $115.8(2)^\circ$  for C3–C2–C7. The difference between these angles ( $10.5^\circ$ ) is probably due to a requirement of minimum steric interaction between the methyl ester group and the other phenyl ring.

The two methoxy substituents do not diverge significantly from the ring plane, as shown by the torsion angles C3'–C4'–O5–C9 [ $177.8(2)^\circ$ ] and C4'–C3'–O4–C8 [ $176.9(2)^\circ$ ]. Again, the orientation of the two methoxy substituents appears to have been determined by the requirement of minimum steric interaction between them.

In (II), the C1–C6 phenyl ring is nearly coplanar with the C1/O1/C1' plane, the relevant angle being  $1.4(2)^\circ$ . The angle between the other ring, C1'–C6', and the C1/O1/C1' plane is  $84.3(2)^\circ$ . The carboxylic acid group is nearly coplanar with the phenyl ring, the r.m.s. deviations from the ring plane being 0.036 (3), 0.132 (4) and  $-0.034(4)$  Å for C7, O2 and O3, respectively. The C1–C2–C7 angle of  $124.1(2)^\circ$  is  $6.2^\circ$  wider than the C3–C2–C7 angle [ $117.9(2)^\circ$ ]; this difference is smaller than observed for (I), probably because the substituent in (I) is larger. The two methoxy substituents are in the plane of the phenyl ring [C3'–C4'–O5–C9  $179.2(2)^\circ$  and

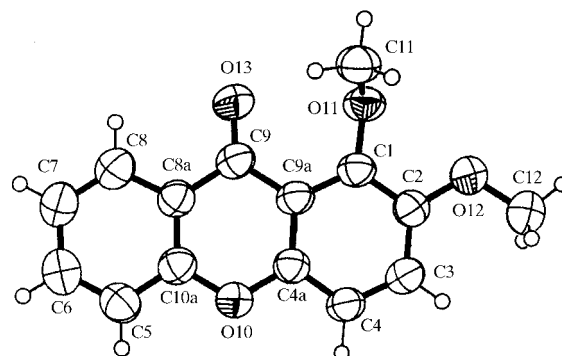


**Figure 2**  
The molecular structure of (II) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

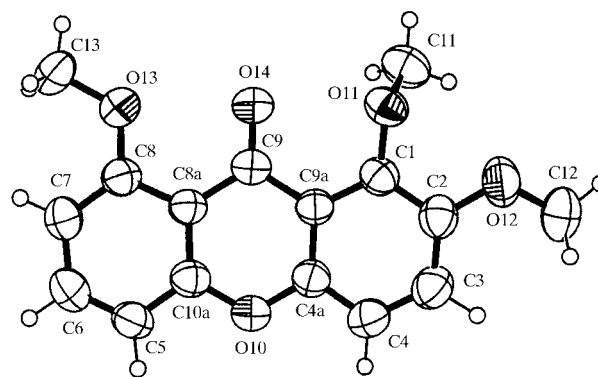
C4'–C3'–O4–C8  $179.8(2)^\circ$ ], as in (I). Compound (II) also shows two intermolecular hydrogen bonds: O3...O2<sup>i</sup> 2.612 (3) Å and O3...O3<sup>i</sup> 3.449 (4) Å [symmetry code: (i)  $1 - x, -y, 3 - z$ ]. Further details of these hydrogen bonds are given in Table 3.

The 1,2-dimethoxy-9*H*-xanthen-9-one molecule in (III) is nearly planar (Fig. 3); the three rings define a plane, with an r.m.s. deviation for the fitted atoms of 0.030 Å. The maximum deviation of the O atoms, which were not included in the calculation of the least-squares plane, is 0.14 Å for O13. Of the two methoxy substituents on the phenyl ring, one methyl group lies much further out of the ring plane than does the other [C2–C1–O11–C11  $-102.5(3)^\circ$ , compared with C1–C2–O12–C12  $179.1(3)^\circ$ ]. Atom C11 is probably forced out of the phenyl plane due to the proximity of atoms O13 and O12. Adoption of these orientations by phenyl rings with multiple methoxy substituents has been observed previously and is consistent with minimum steric interactions (Hibbs *et al.*, 1995; Kijjoo *et al.*, 1998).

In the 1,2,8-trimethoxy-9*H*-xanthen-9-one compound, (IV), isolated from the wood of *Callophyllum teysmanii* var. *inophylloide*, two of the methyl groups of the three methoxy



**Figure 3**  
The molecular structure of (III) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.



**Figure 4**  
The molecular structure of (IV) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. Atom C12 wholly obscures one of the attached H atoms.

substituents are much closer to the plane of the molecule than the third (Fig. 4), as shown by the torsion angles C1–C2–O12–C12 [ $-162.0(2)^\circ$ ], C2–C1–O11–C11 [ $79.6(3)^\circ$ ] and C7–C8–O13–C13 [ $3.9(4)^\circ$ ]. As in (III), atom C11 lies out of the ring plane, probably to minimize the steric interactions due to the presence of atoms O12 and O14 on either side of the methoxy group.

Papers describing the biological activities of these four compounds are in preparation. Comparison of the three-dimensional structure of molecules (III) and (IV) with those of the xanthone constituents of *Calophyllum teysmanii* var. *inophylloide*, whose activities have been studied, will reveal details of the relationship between structure and activity for this class of compounds.

## Experimental

The synthesis of (I) [step (1) in the Scheme] was carried out according to the method of Fernandes *et al.* (1995). A mixture of methyl 2-bromobenzoate (16.2 g, 75 mmol), 3,4-dimethoxyphenol (11.9 g, 77 mmol), copper bronze (9.8 g, 155 mmol) and  $\text{Na}_2\text{CO}_3$  (21.3 g, 154 mmol) in dry pyridine (240 ml) was thoroughly degassed with nitrogen and refluxed for 26 h. The mixture was then cooled to room temperature, filtered and concentrated, furnishing a dark-brown oily liquid which was dissolved in methylene chloride and then washed with 0.5 M NaOH. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to provide an oily brown liquid (18.2 g). This was purified by column chromatography [petroleum ether (313–333 K boiling fraction)/diethyl ether (5:5)]. Evaporation of the solvent under reduced pressure furnished a solid product, (I) (9.0 g, 41%), which was crystallized from a diethyl ether/*n*-hexane mixture.

The synthesis of (II) [step (2) in the Scheme] was carried out according to the method of Fernandes *et al.* (1995). Compound (I) (8.2 g, 28 mmol) was dissolved in methanol/tetrahydrofuran (1:1) and treated with aqueous 5 M NaOH solution (12 ml) at room temperature for 96 h. The crude product was washed with ether, and the aqueous layer was separated, washed with methylene chloride, acidified with 5 M HCl and extracted with methylene chloride. The organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure, furnishing a white solid, (II) (7.6 g, 98%), which was crystallized from methylene chloride.

The synthesis of (III) [step (3) in the Scheme] was carried out according to the method of Fernandes *et al.* (1995). To a 2 M solution of LDA in tetrahydrofuran/heptane/ethylbenzene (2.5 ml, 5 mmol), a solution of (II) (2.688 mg, 2.5 mmol) in dry tetrahydrofuran (25 ml) was added dropwise over 1 h at 273 K under a nitrogen atmosphere. The reaction mixture was allowed to reach room temperature over 1 h. The reaction was quenched by addition of 5% HCl and then extracted with methylene chloride. The organic phase was washed with 5%  $\text{Na}_2\text{CO}_3$ , dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to furnish an oily brown liquid. This crude product was purified by column chromatography [chloroform/*n*-hexane (7:3)]. After evaporation of the solvent, the solid, (III) (476.3 mg, 74%), was crystallized from a methylene chloride/*n*-hexane mixture.

Compound (IV) was isolated from the wood of *Calophyllum teysmanii* var. *inophylloide* according to the method of Kijjoa *et al.* (2000).

## Compound (I)

### Crystal data

$\text{C}_{16}\text{H}_{16}\text{O}_5$   
 $M_r = 288.29$   
 Monoclinic,  $P2_1/c$   
 $a = 15.306(7) \text{ \AA}$   
 $b = 7.788(4) \text{ \AA}$   
 $c = 16.426(7) \text{ \AA}$   
 $\beta = 132.31(3)^\circ$   
 $V = 1448.0(12) \text{ \AA}^3$   
 $Z = 4$

$D_x = 1.322 \text{ Mg m}^{-3}$   
 Mo  $K\alpha$  radiation  
 Cell parameters from 1232 reflections  
 $\theta = 5.0\text{--}28.1^\circ$   
 $\mu = 0.10 \text{ mm}^{-1}$   
 $T = 293(2) \text{ K}$   
 Square prism, colourless  
 $0.30 \times 0.25 \times 0.20 \text{ mm}$

### Data collection

Stoe IPDS diffractometer  
 Image-plate  $\varphi$  scans  
 13 194 measured reflections  
 3439 independent reflections  
 2221 reflections with  $I > 2\sigma(I)$   
 $R_{\text{int}} = 0.068$

$\theta_{\text{max}} = 28.1^\circ$   
 $h = -20 \rightarrow 19$   
 $k = -10 \rightarrow 10$   
 $l = -21 \rightarrow 21$   
 Intensity decay: none

### Refinement

Refinement on  $F^2$   
 $R[F^2 > 2\sigma(F^2)] = 0.055$   
 $wR(F^2) = 0.165$   
 $S = 1.05$   
 3439 reflections  
 254 parameters  
 All H-atom parameters refined

$w = 1/[\sigma^2(F_o^2) + (0.068P)^2 + 0.376P]$   
 where  $P = (F_o^2 + 2F_c^2)/3$   
 $(\Delta/\sigma)_{\text{max}} < 0.001$   
 $\Delta\rho_{\text{max}} = 0.23 \text{ e \AA}^{-3}$   
 $\Delta\rho_{\text{min}} = -0.22 \text{ e \AA}^{-3}$

**Table 1**

Selected bond lengths ( $\text{\AA}$ ) for (I).

O1–C1	1.370 (3)	C2'–C3'	1.389 (3)
O1–C1'	1.405 (2)	C3'–C4'	1.410 (3)
O4–C3'	1.371 (2)	C4'–C5'	1.383 (3)
O4–C8	1.429 (3)	C5'–C6'	1.397 (3)
O5–C4'	1.369 (2)	C1–C6	1.391 (3)
O5–C9	1.422 (3)	C1–C2	1.411 (3)
O2–C7	1.200 (2)	C2–C3	1.394 (3)
O3–C7	1.310 (3)	C2–C7	1.493 (3)
O3–C10	1.444 (3)	C3–C4	1.380 (3)
C1'–C6'	1.368 (3)	C4–C5	1.387 (3)
C1'–C2'	1.393 (3)	C5–C6	1.377 (3)

## Compound (II)

### Crystal data

$\text{C}_{15}\text{H}_{14}\text{O}_5$   
 $M_r = 274.26$   
 Triclinic,  $P\bar{1}$   
 $a = 7.920(4) \text{ \AA}$   
 $b = 8.550(5) \text{ \AA}$   
 $c = 11.360(7) \text{ \AA}$   
 $\alpha = 76.02(7)^\circ$   
 $\beta = 82.46(7)^\circ$   
 $\gamma = 64.20(6)^\circ$   
 $V = 671.8(7) \text{ \AA}^3$

$Z = 2$   
 $D_x = 1.356 \text{ Mg m}^{-3}$   
 Mo  $K\alpha$  radiation  
 Cell parameters from 854 reflections  
 $\theta = 4.7\text{--}24.2^\circ$   
 $\mu = 0.10 \text{ mm}^{-1}$   
 $T = 293(2) \text{ K}$   
 Rectangular prism, colourless  
 $0.7 \times 0.4 \times 0.3 \text{ mm}$

### Data collection

Stoe IPDS diffractometer  
 Image-plate  $\varphi$  scans  
 4584 measured reflections  
 1923 independent reflections  
 1618 reflections with  $I > 2\sigma(I)$   
 $R_{\text{int}} = 0.047$

$\theta_{\text{max}} = 24.1^\circ$   
 $h = -9 \rightarrow 8$   
 $k = -9 \rightarrow 9$   
 $l = -12 \rightarrow 12$   
 Intensity decay: none

Refinement

Refinement on  $F^2$   
 $R[F^2 > 2\sigma(F^2)] = 0.050$   
 $wR(F^2) = 0.159$   
 $S = 1.06$   
 1923 reflections  
 189 parameters  
 H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.098P)^2 + 0.065P]$   
 where  $P = (F_o^2 + 2F_c^2)/3$   
 $(\Delta/\sigma)_{\max} = 0.001$   
 $\Delta\rho_{\max} = 0.14 \text{ e } \text{\AA}^{-3}$   
 $\Delta\rho_{\min} = -0.15 \text{ e } \text{\AA}^{-3}$

Table 2

Selected bond lengths (Å) for (II).

O1—C1	1.376 (2)	C1—C2	1.403 (3)
O1—C1'	1.403 (2)	C2—C3	1.397 (3)
O2—C7	1.257 (3)	C2—C7	1.480 (3)
O3—C7	1.268 (2)	C3'—C2'	1.384 (3)
O4—C3'	1.370 (2)	C6—C5	1.375 (3)
O4—C8	1.425 (3)	C2'—C1'	1.393 (3)
O5—C4'	1.366 (2)	C1'—C6'	1.369 (3)
O5—C9	1.410 (3)	C5—C4	1.382 (3)
C4'—C5'	1.376 (3)	C5'—C6'	1.394 (3)
C4'—C3'	1.407 (3)	C3—C4	1.369 (3)
C1—C6	1.391 (3)		

Table 3

Hydrogen-bonding geometry (Å, °) for (II).

$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
O3—H3 $\cdots$ O2 <sup>i</sup>	0.82	1.81	2.612 (3)	168
O3—H3 $\cdots$ O3 <sup>i</sup>	0.82	2.78	3.449 (4)	140

Symmetry code: (i)  $1 - x, -y, 1 - z$ .

Compound (III)

Crystal data

$C_{15}H_{12}O_4$   
 $M_r = 256.25$   
 Monoclinic,  $P2_1/n$   
 $a = 4.953 (2) \text{ \AA}$   
 $b = 13.930 (6) \text{ \AA}$   
 $c = 17.670 (8) \text{ \AA}$   
 $\beta = 97.23 (6)^\circ$   
 $V = 1209.5 (9) \text{ \AA}^3$   
 $Z = 4$

$D_x = 1.407 \text{ Mg m}^{-3}$   
 Mo  $K\alpha$  radiation  
 Cell parameters from 1542 reflections  
 $\theta = 3.7\text{--}24.1^\circ$   
 $\mu = 0.10 \text{ mm}^{-1}$   
 $T = 293 (2) \text{ K}$   
 Rectangular prism, yellow  
 $0.60 \times 0.25 \times 0.20 \text{ mm}$

Data collection

Stoe IPDS diffractometer  
 Image-plate  $\varphi$  scans  
 7542 measured reflections  
 1807 independent reflections  
 1225 reflections with  $I > 2\sigma(I)$   
 $R_{\text{int}} = 0.056$

Refinement

Refinement on  $F^2$   
 $R[F^2 > 2\sigma(F^2)] = 0.052$   
 $wR(F^2) = 0.168$   
 $S = 1.07$   
 1807 reflections  
 180 parameters  
 H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.08P)^2 + 0.422P]$   
 where  $P = (F_o^2 + 2F_c^2)/3$   
 $(\Delta/\sigma)_{\max} = 0.001$   
 $\Delta\rho_{\max} = 0.17 \text{ e } \text{\AA}^{-3}$   
 $\Delta\rho_{\min} = -0.16 \text{ e } \text{\AA}^{-3}$

Table 4

Selected bond lengths (Å) for (III).

O10—C10a	1.379 (3)	C9a—C9	1.480 (4)
O10—C4a	1.381 (3)	C8a—C10a	1.397 (4)
O11—C1	1.388 (3)	C8a—C8	1.412 (4)
O11—C11	1.439 (4)	C8a—C9	1.465 (4)
O12—C2	1.373 (3)	C4a—C4	1.389 (4)
O12—C12	1.426 (4)	C10a—C5	1.387 (4)
O13—C9	1.242 (3)	C5—C6	1.372 (5)
C2—C1	1.396 (4)	C8—C7	1.365 (5)
C2—C3	1.400 (4)	C7—C6	1.400 (5)
C9a—C1	1.406 (4)	C3—C4	1.376 (4)
C9a—C4a	1.408 (4)		

Compound (IV)

Crystal data

$C_{16}H_{14}O_5$   
 $M_r = 286.27$   
 Orthorhombic,  $P2_12_12_1$   
 $a = 5.2730 (10) \text{ \AA}$   
 $b = 15.443 (4) \text{ \AA}$   
 $c = 16.550 (6) \text{ \AA}$   
 $V = 1347.7 (7) \text{ \AA}^3$   
 $Z = 4$   
 $D_x = 1.411 \text{ Mg m}^{-3}$

Mo  $K\alpha$  radiation

Cell parameters from 1345 reflections

$\theta = 4.1\text{--}24.2^\circ$

$\mu = 0.11 \text{ mm}^{-1}$

$T = 293 (2) \text{ K}$

Rectangular prism, colourless  
 $0.8 \times 0.5 \times 0.3 \text{ mm}$

Data collection

Stoe IPDS diffractometer  
 Image-plate  $\varphi$  scans  
 8453 measured reflections  
 2068 independent reflections  
 1887 reflections with  $I > 2\sigma(I)$   
 $R_{\text{int}} = 0.039$

$\theta_{\max} = 24.2^\circ$

$h = -5 \rightarrow 5$

$k = -17 \rightarrow 17$

$l = -18 \rightarrow 18$

Intensity decay: none

Refinement

Refinement on  $F^2$   
 $R[F^2 > 2\sigma(F^2)] = 0.042$   
 $wR(F^2) = 0.108$   
 $S = 1.03$   
 2068 reflections  
 210 parameters  
 H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.046P)^2 + 0.426P]$

where  $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\max} = 0.001$

$\Delta\rho_{\max} = 0.14 \text{ e } \text{\AA}^{-3}$

$\Delta\rho_{\min} = -0.11 \text{ e } \text{\AA}^{-3}$

Table 5

Selected bond lengths (Å) for (IV).

O10—C4a	1.375 (3)	C5—C6	1.371 (4)
O10—C10a	1.379 (3)	C5—C10a	1.382 (4)
O11—C1	1.372 (3)	C8—C7	1.385 (4)
O11—C11	1.438 (3)	C4a—C4	1.388 (4)
O12—C2	1.378 (3)	C4a—C9a	1.396 (3)
O12—C12	1.413 (4)	C7—C6	1.395 (4)
O13—C8	1.360 (3)	C9a—C1	1.404 (3)
O13—C13	1.436 (3)	C9a—C9	1.488 (3)
O14—C9	1.229 (3)	C4—C3	1.379 (4)
C8a—C10a	1.403 (3)	C1—C2	1.398 (4)
C8a—C8	1.424 (4)	C2—C3	1.387 (4)
C8a—C9	1.470 (3)		

All the H atoms in (I), H5 and H6 in (II), H4 and H8 in (III) and the aromatic H atoms in (IV) were located from difference Fourier maps and refined freely with isotropic displacement parameters. The remaining H atoms could not be clearly located from the difference maps, and were placed geometrically and refined riding on their

parent C atoms at distances of 0.93 (aromatic) and 0.96 Å (methyl), with  $U_{\text{iso}}(\text{H}) = xU_{\text{eq}}(\text{C})$ , where  $x = 1.2$  and  $1.5$  for aromatic and methyl H atoms, respectively. A degree of racemic twinning was indicated for compound (IV) and a twin correction with two equal components was applied. This improved the refinement marginally.

For all four compounds, data collection: *IPDS* (Stoe & Cie, 1994); cell refinement: *IPDS*; data reduction: *IPDS*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97* and *ORTEP-3*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM1457). Services for accessing these data are described at the back of the journal.

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