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α-Haloketal (1′*R*,4*S*,5*S*)-dimethyl 2-(1′-bromoethyl)-2-(3,4-dimethoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate

Pedro H. Ferri,[a] Carlito Lariucci,[b] Leon I. B. Homar,[b] Raquel F. Santos,[a] Elaine R. Maia,[c] Lourivaldo S. Santos[d] and Ivo Vencato[e]*

[a]Instituto de Química, UFG, 74001-970 Goiânia, GO, Brazil, [b]Instituto de Física, UFG, 74001-970 Goiânia, GO, Brazil, [c]Departmento Química, UnB, 70919-970 Brasília, DF, Brazil, [d]Departamento Química, CCEN , UFPa, 66075-970 Belém, PA, Brazil, and [e]Departamento Química, UFSC, 88040-900 Florianópolis, SC, Brazil
Correspondence e-mail: vencato@qmc.ufsc.br

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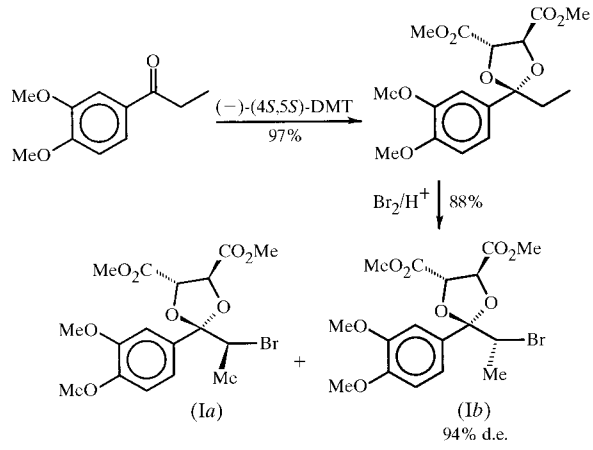
The crystal structure and absolute configuration of the title compound, $C_{17}H_{21}BrO_8$, have been determined by X-ray analysis. They confirmed the 1′*R* absolute configuration at the 1′-bromoethyl moiety which has been assigned previously on the basis of chemical and spectroscopic data. Cohesion of the crystal can be attributed to weak intermolecular C—H···O and van der Waals interactions.

Comment

Single crystals of (I*b*) were obtained by a synthetic route (Castaldi *et al.*, 1987) using 3,4-dimethoxypropylphenone as starting material which requires, in an intermediate step, an acid-promoted bromination of the enol ether by a substrate-controlled diastereoselective synthesis of the bromoketal with an observed stereochemistry, as also confirmed by present X-ray studies of the title diastereomer. The crystal structure determination was undertaken to establish the absolute stereochemistry of the newly formed chiral centre at C10 in the reaction product, (I*b*), according to the scheme below. The absolute configurations of the other asymmetric centres at C12 and C13 were already known. These findings are important in understanding the mechanism of diastereofacial selectivity induced by a chiral auxiliary in the halogenation of aryl enol ethers (Castaldi *et al.*, 1986, 1987; Giordano *et al.*, 1990), which is the key step in the industrial asymmetric synthesis of α-arylpropionic acid derivatives (Giordano *et al.*, 1989; Elks & Gamellin, 1990), the non-steroidal anti-inflammatory drugs widely prescribed as analgesics and in the treatment of rheumatoid arthritis (Reuben & Wittcoff, 1989), and also in the enantiomeric synthesis of the sulfur analogue of an 8,4′-oxyneolignan derivative showing selective antagonistic activity in Platelet Activating Factor-induced platelet aggregation (Lariucci *et al.*, 1995).



A *ZORTEP* (Zsolnai *et al.*, 1996) plot of the molecule and the atomic numbering is shown in Fig. 1. Selected bond distances and angles are given in Table 1. All distances are within their typical values except for C10—C11*B* [1.673 (6) Å] which is longer than expected and Br*B*—C10 [1.936 (5) Å] which is shorter than expected (*cf.* value quoted by Allen *et al.*, 1987). These differences are due to the disorder of the Br and C11 atom sites with Br*A* and Br*B* (C11*A* and C11*B*) in the proportions of 9.9 and 90.1%, respectively (see *Experimental*).

With regard to the bond lengths in the 1,3-dioxolane ring, the distance C9—O3 [1.432 (5) Å] is significantly longer than O3—C13 [1.407 (5) Å], while the difference between C9—O4 [1.420 (5) Å] and O4—C12 [1.427 (5) Å] is not significant, showing a smaller distortion than observed in strongly distorted 1,4-dioxaspiro structures (Ianelli *et al.*, 1992). Within the limits of experimental error, the C atoms of the ring are situated in the aromatic ring plane, with mean deviations being close to 0.003 Å. The methoxyl-O atoms are almost coplanar with the respective ring [O1 0.012 (6) and O2 −0.011 (6) Å], while the methoxyl-C atoms C7 and C8 are not [−0.233 (8) and −0.109 (9) Å, respectively]. The ring O3→ C13→···C9 shows a twisted conformation, with Cremer & Pople (1975)

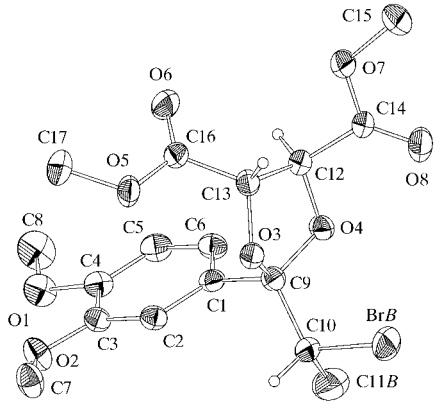


Figure 1
View of the title molecule showing the labelling of the non-H atoms. Displacement ellipsoids are shown at the 30% probability level. Methyl- and phenyl-H atoms have been omitted for clarity. Disordered Br*A* and C11*A* atoms are not shown.

puckering parameters Q_2 = 0.334 (4) Å and φ_2 = 347.7 (7)°. The orientation of the two methoxycarbonyl substituents is nearly anticlinal with respect to one another, as indicated by the C16—C13—C12—C14 torsion angle of 125.2 (4)°. However, the torsion angles O3—C13—C16—O6 [−144.9 (4)°] and O4—C12—C14—O8 [−0.5 (7)°] show that the situation of these groups are not the same, presumably as a result of a short intramolecular contact between the C12 and O6 atoms with a geometry that would qualify as a C—H···O bond (Desiraju, 1996): C12—H12···O6 [C—H···O 107.5°, O···H 2.40 and C···O 2.856 (6) Å]. The application of semi-empirical (AM1, PM3 MNDO), molecular mechanics and *ab initio* methods carried out with the *MOPAC*6.0 (Stewart, 1990), *DISCOVER* CFF91 force field (Molecular Simulations, 1997) and *GAUSSIAN*94 (Frisch *et al.*, 1994; Hehre *et al.*, 1986) packages, respectively, show that these torsion angles are similar [81.5 and 3.2°, respectively]. Additionally, the CFF91 force-field computations show that the 1,3-dioxolane ring adopts a C13β-envelope conformation which is 16.8 kJ mol^{-1} more stable than the C13α-conformer obtained in the solid state. These different situations have shown that packing interactions are the most important factors determining the conformation of these groups in the crystal. There is another intramolecular and two intermolecular C—H···O interactions: C6—H6···O4 [C—H···O 102.1°, O···H 2.42 and C···O 2.767 (5) Å]; C10—H10···O2^{i} [C—H···O 150.4°, O···H 2.50 and C···O 3.384 (5) Å]; C13—H13···O6^{ii} [C—H···O 130.2°, O···H 2.59 and C···O 3.308 (6) Å]; symmetry codes: (i) $2-x, -\frac{1}{2}+y, 2-z$; (ii) $2-x, -\frac{1}{2}+y, 1-z$.

Experimental

To prepare the title compound, a stirred solution of a mixture of (4*S*,5*S*)-dimethyl 2-(3′,4′-dimethoxyphenyl)-2-ethyl-1,3-dioxolane-4,5-dicarboxylate (1.20 g, 33.9 mmol), easily obtained from the available 3,4-dimethoxypropylphenone in the presence of (−)-(4*S*,5*S*)-dimethyl tartrate, methyl orthoformate and methanesulfonic acid (Castaldi *et al.*, 1987), was treated in carbon tetrachloride with 2-methoxynaphthalene (8 mg, 0.05 mmol) followed by bromine (0.55 g, 34.4 mmol) at 263 K for 2 h. After pH neutralization, the solution was extracted with dichloromethane and the extract washed with water, dried over magnesium sulfate and evaporated to dryness to give a diastereomeric mixture of (I*a*)/(I*b*) with 1.38 g, 88% chemical yield and a diastereomeric ratio of 7:93. The title compound was isolated by slow crystallization (m.p. 369–372 K; from diethyl ether); $[\alpha]_D^{20}$ −39.2° ($CHCl_3$): ν_{max} (KBr)/cm^{-1} 1772 and 1745; δ_H (250 MHz, $CDCl_3$; Me_4Si; p.p.m.) 1.65 (3H, *d*, *J* = 7.0 Hz, 2′-H), 3.60 (3H, *s*, 5-CO_2CH_3), 3.85 (3H, *s*, 4-CO_2CH_3), 3.88 (3H, *s*, 3′′-OCH_3), 3.90 (3H, *s*, 4′′-OCH_3), 4.40 (1H, *d*, *J* = 9.0 Hz, 5′′-H), 7.05–7.15 (2H, *m*, 2′′,6′′-H); δ_C (63 MHz, $CDCl_3$; Me_4Si; p.p.m.) 20.7 (C-2′), 59.7 (C-1′); *m*/*z* (EI) 434 [M^+ + 2] (<1%), 432 [M^+] (<1), 325 [$M^+-C_2H_4Br$] (100).

Crystal data

$C_{17}H_{21}BrO_8$
M_r = 433.25
Monoclinic, $P2_1$
a = 9.728 (2) Å
b = 8.414 (2) Å
c = 11.674 (2) Å
β = 92.23 (3)°
V = 954.8 (3) Å^3
Z = 2
D_x = 1.507 Mg m^{-3}
Mo *K*α radiation
Cell parameters from 25 reflections
θ = 19.64–22.96°
μ = 2.19 mm^{-1}
T = 293 (2) K
Irregular, colourless
0.50 × 0.43 × 0.40 mm

Data collection

Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: ψ scan (*PLATON*; Spek, 1998)
T_{min} = 0.39, T_{max} = 0.42
3275 measured reflections
3024 independent reflections
1916 reflections with $I > 2\sigma(I)$
R_{int} = 0.018
θ_{max} = 27.95°
$h = -12 \rightarrow 12$
$k = -5 \rightarrow 11$
$l = 0 \rightarrow 15$
3 standard reflections
frequency: 60 min
intensity decay: 0.4%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.035
$wR(F^2)$ = 0.086
S = 0.997
3024 reflections
237 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0352P)^2 + 0.4675P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.35 e Å^{-3}
$\Delta\rho_{min}$ = −0.31 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.022 (2)

A previous refinement with Br and C11 atoms at their full occupancy factors gave distances C10—C11 of 1.664 (10) Å and Br—C10 of 1.928 (8) Å. Consulting the Cambridge Structural Database (1999) we found that the Br—C10 distance was shorter than the mean value (1.962 Å). Furthermore, the displacement ellipsoid for C11 was too small and somewhat oddly shaped. These facts indicated that a small fraction of the molecules have the other configuration at C10. The best of the several disorder models tried gave a lower *R*(*F*) index and lower s.u.'s for most parameters. Each of the disordered Br/C11 sites was treated as being composed of Br and C11 atoms at the same positions using *SHELXL*97 *EXYZ* and *EADP* instructions (Sheldrick, 1997). The site occupancies for the major component (Br*B* and C11*B*) refined to 0.901 (2). The values of *R*1 and *wR*2 for the refinement without disorder (NV = 236) were 0.050 and 0.158. A Flack (1983) parameter of −0.018 (11) was obtained and the number of Friedel-related reflections was 587.

Data collection: *CAD-4 EXPRESS* (Enraf–Nonius, 1994); cell refinement: *SET*4 in *CAD-4 EXPRESS*; data reduction: *HELENA* (Spek, 1996); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ZORTEP* (Zsolnai *et al.*, 1996); software used to prepare material for publication: *SHELXL*97.

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Table 1
Selected geometric parameters (Å, °).

Br*B*—C10	1.936 (5)	O4—C12	1.427 (5)
O3—C13	1.407 (5)	C9—C10	1.518 (5)
O3—C9	1.432 (5)	C10—C11*B*	1.673 (6)
O4—C9	1.420 (5)	C12—C13	1.547 (6)
C13—O3—C9	105.8 (3)	C10—C9—C1	112.4 (3)
C9—O4—C12	107.2 (3)	C9—C10—C11*B*	112.8 (3)
O4—C9—O3	104.6 (3)	C9—C10—Br*B*	110.5 (3)
O4—C9—C10	110.7 (3)	C11*B*—C10—Br*B*	110.0 (3)
O3—C9—C1	110.0 (3)		
C12—O4—C9—O3	−33.0 (4)	O4—C12—C13—O3	7.6 (4)
C13—O3—C9—O4	38.1 (4)	C14—C12—C13—C16	125.2 (4)
C9—O4—C12—C13	15.5 (4)	O4—C12—C14—O8	−0.5 (7)
C9—O3—C13—C12	−27.6 (4)	O3—C13—C16—O6	−144.9 (4)

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: BK1479). Services for accessing these data are described at the back of the journal.

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