(±)-3α,5α-Bis(methoxycarbonyl)-3β-methyl-6α-phenyltetrahydro-2H-pyran-2-one

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Abstract

The structure determination of the title compound, dimethyl (±)-3β-methyl-2-oxo-6α-phenyl-3,4,5,6-tetrahydro-2H-pyran-3α,5α-dicarboxylate, $C_{16}H_{18}O_6$, unequivocally establishes its relative stereochemistry. The results provide strong support for the proposal that enolates derived from *cis*-5,6-disubstituted tetrahydro-2H-pyran-2-ones react very selectively with electrophiles *trans* to the C(5) and C(6) substituents.

Comment

There are only a few examples of stereoselective alkylations of enolates derived from *cis*-5,6-disubstituted tetrahydro-2H-pyran-2-ones (Grieco, Martinez, Williams, Kanai & Srinivasan, 1982; Grieco, Ohfune, Yokoyama & Owens, 1979). In each case, alkylation occurred from the face opposite to the C(5) and C(6) substituents. The title compound, (I), was obtained from a similar alkylation of a new series of such 5,6-disubstituted tetrahydro-2H-pyran-2-ones (Lawrence & Perlmutter, 1992). The crystal structure shows that the newly introduced methyl group at C(3) bears a *trans* relationship to the C(5) and C(6) substituents. This finding establishes that the stereoselectivity observed in previously reported alkylations holds for this new system as well.

(I)
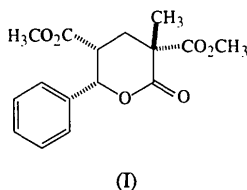
The title compound crystallizes with two independent $C_{16}H_{18}O_6$ molecules in the asymmetric unit which are related by a pseudocentre of symmetry. The two molecules have similar dimensions and conformations. The molecular dimensions are in agreement with anticipated values. The six-membered heterocyclic ring [O(1), C(2)–C(6)] in each molecule has a half-chair conforma-

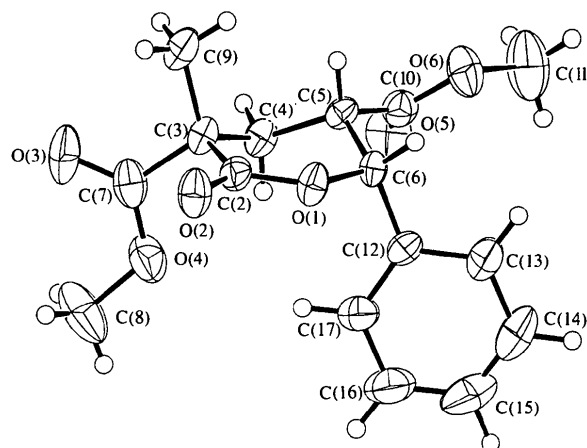tion; relevant torsion angles are listed in Table 2. The aromatic rings are planar.

Fig. 1. A view of one of the independent $C_{16}H_{18}O_6$ molecules showing the labelling of the non-H atoms. Displacement ellipsoids are shown at 40% probability levels and H atoms are drawn as circles of arbitrary radii. A similar view of the second molecule has been deposited with the supplementary material.

Experimental

The title compound was prepared according to the method of Lawrence & Perlmutter (1992). D_m was measured by flotation in CCl_4/hexane solution.

Crystal data

$C_{16}H_{18}O_6$	Cu $K\alpha$ radiation
$M_r = 306.3$	$\lambda = 1.5418$ Å
Monoclinic	Cell parameters from 24
$P2_1/c$	reflections
$a = 11.663\,(2)$ Å	$\theta = 12–18°$
$b = 10.187\,(2)$ Å	$\mu = 0.817$ mm^{-1}
$c = 27.703\,(5)$ Å	$T = 293$ K
$\beta = 102.3\,(1)°$	Tabular
$V = 3216\,(2)$ Å^3	$0.18 \times 0.17 \times 0.07$ mm
$Z = 8$	Colourless
$D_x = 1.27$ Mg m^{-3}	
$D_m = 1.26\,(1)$ Mg m^{-3}	

Data collection

Philips PW1100 diffractometer	2216 observed reflections [$I > 3\sigma(I)$]
θ scans	$R_{int} = 4.14$
Absorption correction:	$\theta_{max} = 60.0°$
De Meulenaer & Tompa (1965)	$h = -13 \rightarrow 12$
$T_{min} = 0.872$, $T_{max} = 0.944$	$k = 0 \rightarrow 11$
	$l = 0 \rightarrow 30$
5207 measured reflections	3 standard reflections
4775 independent reflections	frequency: 240 min
	intensity decay: <4%

Refinement

Refinement on F	$\Delta\rho_{max} = 0.24$ e Å^{-3}
$R = 0.0677$	$\Delta\rho_{min} = -0.26$ e Å^{-3}

$C_{16}H_{18}O_6$

$wR = 0.0628$
$S = 1.584$
2216 reflections
397 parameters
H-atom parameters not refined
Weighting scheme based on measured e.s.d.'s
$(\Delta/\sigma)_{max} = 0.0006$

Extinction correction: none
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Table 2.2A) for C and O atoms, and from Stewart, Davidson & Simpson (1965) for H atoms

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters ($Å^2$)*

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
O(1)	0.0723 (3)	0.1858 (4)	0.6470 (1)	0.047 (1)
O(2)	0.2300 (4)	0.0752 (5)	0.6451 (2)	0.062 (2)
O(3)	0.3705 (4)	0.2237 (6)	0.5599 (2)	0.090 (2)
O(4)	0.3435 (4)	0.3424 (5)	0.6250 (2)	0.076 (2)
O(5)	−0.0591 (4)	0.5625 (5)	0.5592 (2)	0.071 (2)
O(6)	−0.2047 (4)	0.4255 (5)	0.5646 (2)	0.070 (2)
C(2)	0.1633 (6)	0.1605 (7)	0.6262 (2)	0.044 (2)
C(3)	0.1784 (5)	0.2320 (7)	0.5797 (2)	0.044 (2)
C(4)	0.1069 (5)	0.3582 (6)	0.5713 (2)	0.044 (2)
C(5)	−0.0163 (5)	0.3346 (6)	0.5788 (2)	0.039 (2)
C(6)	−0.0151 (5)	0.2890 (6)	0.6318 (2)	0.037 (2)
C(7)	0.3092 (6)	0.2654 (8)	0.5865 (3)	0.058 (3)
C(8)	0.4665 (7)	0.3830 (9)	0.6368 (4)	0.104 (4)
C(9)	0.1402 (6)	0.1341 (8)	0.5369 (2)	0.067 (3)
C(10)	−0.0931 (7)	0.4560 (8)	0.5668 (2)	0.051 (3)
C(11)	−0.2893 (8)	0.5338 (9)	0.5556 (4)	0.110 (4)
C(12)	0.0051 (6)	0.3938 (7)	0.6709 (2)	0.044 (2)
C(13)	−0.0900 (6)	0.4370 (8)	0.6891 (3)	0.070 (3)
C(14)	−0.0744 (9)	0.5294 (10)	0.7273 (4)	0.099 (4)
C(15)	0.0343 (11)	0.5776 (10)	0.7463 (3)	0.100 (4)
C(16)	0.1289 (8)	0.5340 (10)	0.7300 (3)	0.090 (4)
C(17)	0.1138 (6)	0.4428 (8)	0.6924 (3)	0.070 (3)
O(1′)	0.5727 (3)	0.0572 (4)	0.6518 (1)	0.046 (1)
O(2′)	0.7371 (4)	0.1590 (5)	0.6545 (2)	0.059 (2)
O(3′)	0.8828 (4)	0.0108 (5)	0.5724 (2)	0.065 (2)
O(4′)	0.8502 (4)	−0.1107 (5)	0.6347 (2)	0.070 (2)
O(5′)	0.4460 (4)	−0.3246 (5)	0.5643 (2)	0.074 (2)
O(6′)	0.3029 (4)	−0.1890 (5)	0.5737 (2)	0.057 (2)
C(2′)	0.6703 (6)	0.0754 (6)	0.6346 (2)	0.037 (2)
C(3′)	0.6883 (5)	0.0034 (6)	0.5894 (2)	0.037 (2)
C(4′)	0.6150 (5)	−0.1236 (6)	0.5796 (2)	0.044 (2)
C(5′)	0.4903 (5)	−0.0988 (6)	0.5855 (2)	0.037 (2)
C(6′)	0.4898 (5)	−0.0506 (6)	0.6379 (2)	0.039 (2)
C(7′)	0.8186 (6)	−0.0284 (7)	0.5970 (3)	0.048 (2)
C(8′)	0.9727 (6)	−0.1539 (9)	0.6462 (3)	0.088 (3)
C(9′)	0.6557 (6)	0.0989 (7)	0.5458 (2)	0.055 (2)
C(10′)	0.4140 (6)	−0.2185 (8)	0.5733 (2)	0.045 (2)
C(11′)	0.2197 (7)	−0.2946 (9)	0.5653 (3)	0.100 (4)
C(12′)	0.5142 (6)	−0.1527 (6)	0.6780 (2)	0.041 (2)
C(13′)	0.4221 (6)	−0.2093 (9)	0.6932 (3)	0.083 (3)
C(14′)	0.4418 (9)	−0.3031 (12)	0.7308 (4)	0.123 (5)
C(15′)	0.5507 (11)	−0.3378 (10)	0.7527 (3)	0.108 (4)
C(16′)	0.6443 (8)	−0.2793 (10)	0.7395 (3)	0.091 (4)
C(17′)	0.6263 (6)	−0.1880 (8)	0.7019 (3)	0.065 (3)

Table 2. *Selected geometric parameters (Å, °)*

O(1)—C(2)	1.336 (7)	O(1′)—C(2′)	1.338 (6)	
O(1)—C(6)	1.462 (6)	O(1′)—C(6′)	1.460 (7)	
O(2)—C(2)	1.209 (7)	O(2′)—C(2′)	1.206 (7)	
O(3)—C(7)	1.208 (8)	O(3′)—C(7′)	1.184 (7)	
O(4)—C(7)	1.316 (8)	O(4′)—C(7′)	1.329 (8)	
O(4)—C(8)	1.462 (8)	O(4′)—C(8′)	1.463 (8)	
O(5)—C(10)	1.189 (7)	O(5′)—C(10′)	1.187 (8)	
O(6)—C(10)	1.327 (7)	O(6′)—C(10′)	1.333 (7)	
O(6)—C(11)	1.465 (9)	O(6′)—C(11′)	1.434 (8)	
C(2)—C(3)	1.521 (9)	C(2′)—C(3′)	1.505 (8)	
C(3)—C(4)	1.523 (8)	C(3′)—C(4′)	1.542 (8)	
C(3)—C(7)	1.535 (9)	C(3′)—C(7′)	1.523 (8)	
C(3)—C(9)	1.543 (9)	C(3′)—C(9′)	1.534 (8)	
C(4)—C(5)	1.515 (7)	C(4′)—C(5′)	1.519 (8)	
C(5)—C(6)	1.535 (7)	C(5′)—C(6′)	1.534 (8)	
C(5)—C(10)	1.522 (9)	C(5′)—C(10′)	1.504 (9)	
C(6)—C(12)	1.504 (8)	C(6′)—C(12′)	1.504 (8)	
C(12)—C(13)	1.383 (8)	C(12′)—C(13′)	1.363 (8)	
C(12)—C(17)	1.375 (8)	C(12′)—C(17′)	1.381 (8)	
C(13)—C(14)	1.400 (11)	C(13′)—C(14′)	1.397 (11)	
C(14)—C(15)	1.356 (12)	C(14′)—C(15′)	1.333 (12)	
C(15)—C(16)	1.354 (12)	C(15′)—C(16′)	1.361 (12)	
C(16)—C(17)	1.378 (11)	C(16′)—C(17′)	1.379 (10)	
C(2)—O(1)—C(6)	125.7 (5)	O(1)—C(6)—C(12)	108.0 (5)	
C(2′)—O(1′)—C(6′)	125.1 (5)	C(5)—C(6)—C(12)	116.3 (5)	
C(7)—O(4)—C(8)	117.7 (6)	O(1′)—C(6′)—C(5′)	110.8 (5)	
C(7′)—O(4′)—C(8′)	117.1 (6)	O(1′)—C(6′)—C(12′)	108.3 (5)	
C(10)—O(6)—C(11)	116.7 (6)	C(5′)—C(6′)—C(12′)	116.1 (5)	
C(10′)—O(6′)—C(11′)	117.1 (6)	O(3)—C(7)—O(4)	125.9 (7)	
O(1)—C(2)—O(2)	116.6 (6)	O(3)—C(7)—C(3)	123.4 (8)	
O(1)—C(2)—C(3)	121.2 (6)	O(4)—C(7)—C(3)	110.7 (6)	
O(2)—C(2)—C(3)	122.1 (6)	O(3′)—C(7′)—O(4′)	124.1 (7)	
O(1′)—C(2′)—O(2′)	116.8 (6)	O(3′)—C(7′)—C(3′)	125.7 (7)	
O(1′)—C(2′)—C(3′)	120.7 (6)	O(4′)—C(7′)—C(3′)	110.2 (6)	
O(2′)—C(2′)—C(3′)	122.3 (6)	O(5)—C(10)—O(6)	124.5 (7)	
C(2′)—C(3′)—C(4′)	112.7 (5)	O(5)—C(10)—C(5)	125.2 (7)	
C(2′)—C(3′)—C(7′)	107.5 (5)	O(6)—C(10)—C(5)	110.2 (6)	
C(2′)—C(3′)—C(9′)	106.8 (5)	O(5′)—C(10′)—O(6′)	123.8 (7)	
C(4′)—C(3′)—C(7′)	110.2 (5)	O(5′)—C(10′)—C(5′)	126.0 (7)	
C(4′)—C(3′)—C(9′)	111.0 (5)	O(6′)—C(10′)—C(5′)	110.3 (6)	
C(7′)—C(3′)—C(9′)	108.5 (5)	C(6)—C(12)—C(13)	118.3 (6)	
C(2)—C(3)—C(4)	112.1 (5)	C(6)—C(12)—C(17)	123.9 (6)	
C(2)—C(3)—C(7)	107.1 (5)	C(13)—C(12)—C(17)	117.6 (7)	
C(2)—C(3)—C(9)	106.0 (6)	C(6′)—C(12′)—C(13′)	118.9 (6)	
C(4)—C(3)—C(7)	109.2 (6)	C(6′)—C(12′)—C(17′)	123.0 (6)	
C(4)—C(3)—C(9)	111.6 (5)	C(13′)—C(12′)—C(17′)	118.0 (7)	
C(7)—C(3)—C(9)	110.7 (6)	C(12)—C(13)—C(14)	120.3 (7)	
C(3)—C(4)—C(5)	110.5 (5)	C(12′)—C(13′)—C(14′)	120.3 (8)	
C(3′)—C(4′)—C(5′)	110.5 (5)	C(13)—C(14)—C(15)	119.8 (9)	
C(4′)—C(5′)—C(6′)	110.6 (5)	C(13′)—C(14′)—C(15′)	120.7 (9)	
C(4′)—C(5′)—C(10′)	112.1 (6)	C(14)—C(15)—C(16)	120.8 (9)	
C(6′)—C(5′)—C(10′)	110.5 (5)	C(14′)—C(15′)—C(16′)	120.1 (9)	
C(4)—C(5)—C(6)	111.3 (5)	C(15)—C(16)—C(17)	119.5 (8)	
C(4)—C(5)—C(10)	111.9 (6)	C(15′)—C(16′)—C(17′)	119.8 (8)	
C(6)—C(5)—C(10)	109.9 (5)	C(12)—C(17)—C(16)	122.0 (7)	
O(1)—C(6)—C(5)	110.9 (5)	C(12′)—C(17′)—C(16′)	120.9 (7)	

O(1)—C(2)—C(3)—C(4)	18.7 (8)
C(2)—C(3)—C(4)—C(5)	−45.6 (7)
C(3)—C(4)—C(5)—C(6)	61.1 (6)
C(4)—C(5)—C(6)—O(1)	−46.5 (7)
C(5)—C(6)—O(1)—C(2)	19.5 (8)
C(6)—O(1)—C(2)—C(3)	−5.9 (9)
O(1′)—C(2′)—C(3′)—C(4′)	−22.8 (8)
C(2′)—C(3′)—C(4′)—C(5′)	44.9 (7)
C(3′)—C(4′)—C(5′)—C(6′)	−59.5 (6)
C(4′)—C(5′)—C(6′)—O(1′)	49.6 (6)
C(5′)—C(6′)—O(1′)—C(2′)	−28.2 (7)
C(6′)—O(1′)—C(2′)—C(3′)	15.1 (8)

The θ-scan width was $\pm(0.75 + 0.1\tan\theta)°$ in θ from the calculated Bragg angle. Measurements were made using a scan speed of $0.04° \text{ s}^{-1}$ and background counts for 50% of the scan time on each side of every scan.

The two distinct moecules within the asymmetric unit are related by a pseudocentre of symmetry. A cell-reduction program identifies an orthorhombic cell as an alternative setting, which could reduce the number of molecules in the asymmetric unit to one. The matrix that relates these two cells is $-1,0,0/-1,0,-2/0,-1,0$, which is also the conversion matrix for indices (monoclinic to orthorhombic). Thus, for example, the −118 and 117 reflections, which convert in the orthorhombic setting to $1,-15,-1$ and $-1,-15,-1$, should have the same intensity if the data have *mmm* symmetry. They do not. The same is true for any other 'equivalent' pair of

reflections. Thus, the assignment of crystal class and space group to monoclinic, $P2_1/c$, is correct.

Data collection: Philips PW1100 software. Cell refinement: Philips PW1100 software. Data reduction: Philips PW1100 software. Program(s) used to solve structure: *SAPI*91 (Fan, 1991). Program(s) used to refine structure: *TEXSAN* (Molecular Structure Corporation, 1985, 1992). Software used to prepare material for publication: *TEXSAN*.

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Formylation *versus* Alkylation of Secondary Amines in DMF

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Abstract

2,2'-(Formamidedi-1,2-ethanediyl)bis[1*H*-isoindole-1,3-(2*H*)-dione] (1), $C_{21}H_{17}N_3O_5$, is a product of a slow formylation reaction between refluxing DMF and 2,2'-(iminodi-1,2-ethanediyl)bis[1*H*-isoindole-1,3(2*H*)-dione] (DPDA) which appears to be more efficient than the competing base-promoted alkylation with tris(chloro-

ethyl)amine. The molecules adopt a folded conformation and pack efficiently to form sheets (in the *a* and *c* directions) having a 'W in W' and 'M in M' motif running along the *c* direction.

Comment

Compound (1) was produced as part of a programme of development of synthetic routes to novel, kinetically inert and thermodynamically stable lanthanide polynuclear macrocyclic and dendritic complexes with potential biomedical applications (Matthews, Kahwa & Williams, 1994). Since alkylation of secondary amines in refluxing dimethylformamide (DMF) is readily accomplished using bromoalkyl derivatives and mild base (sodium carbonate or sodium bicarbonate) (Hancock, Cukrowski, Cukrowska, Hosken & Gansow, 1994; Ng, Motekiatis & Martell, 1979), we sought to determine whether significant alkylation yields could be achieved with chloroalkyl starting materials such as tris(chloroethyl)amine (TCEA). However, we find that unlike the bromoalkyls, chloroalkyls appear to be such poor alkylating agents in refluxing DMF that the competing slow formylation reaction (Iwata & Kuzuhara, 1989; Kraus, 1973) dominates. For example, DPDA is readily alkylated in a refluxing sodium carbonate/DMF mixture by α,α'-dibromo-*p*-xylene (Ng, Motekiatis & Martell, 1979) but with TCEA the new compound (1) is a major product. The formation of (1) was determined from elemental, mass and ^{1}H NMR spectroscopic and X-ray crystallographic analyses.

(1)
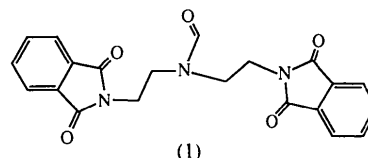
The molecular structure and the extended molecular array of (1) are shown in Figs. 1 and 2. The molecule adopts a folded geometry with the phthalimide rings inclined by *ca* 74.7 (1)° with respect to each other. Interatomic distances and angles within the phthalimide residues are normal (Barrett, Kahwa, Mague & McPherson, 1995; Colquhoun, O'Mahoney, Williams, Askari & Mayo, 1994; Barlow, Davidson, Lewis & Russell, 1979). The geometry of the linking N—CH_2—CH_2—N—CH_2—CH_2—N chain is essentially *gauche* with torsion angles about the N—C—C—N bonds in the range 58.6 (3)–79.2 (3)°. Inspection of the geometry of the formamide component of the molecule reveals the expected partial delocalization with a shortening of the N(12)—C(24) bond [1.339 (2) Å] and lengthening of the carbonyl C(24)—O(24) distance [1.218 (2) Å]. There are small out-of-plane deformations within the group, the C(11)—N(12)—C(24)—O(24) and C(13)—N(12)—C(24)—O(24) torsion angles being