

STRUCTURE AND CONFORMATION OF (3*S*^{*}, 4*S*^{*}, 6*R*^{*})- AND (3*R*^{*}, 4*R*^{*}, 6*R*^{*})-3,6-DIMETHYL-4-PHENYLSULPHONYLTETRAHYDROPIRAN-2-ONES

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The nucleophilic ring opening of propylene oxide by the lithio derivative of the trioxabicyclic orthoester **1 leads, after acidic treatment, to the title lactones **3a** and **3b** with no evidence of δ -lactones **3c** and **3d**. The stereochemistry of these two lactones has been established by X-ray diffraction analysis. The ring conformations observed in the solid phase are similar in both lactones and are compared with those observed in related molecules. However, the NMR spectroscopic analysis shows that this similarity does not exist in solution; lactone **3a** adopts a different conformation.**

1. INTRODUCTION

Over the past few years, our laboratory has been interested in synthetic equivalents of homoenolates for the formation of five- and six-membered rings. Preliminary investigations have shown that methyl 3-phenylsulphonylorthopropionate is a particularly useful reagent for this purpose.¹ Recently, we have developed a new homoenolate reagent, **1**, in order to accomplish the stereoselective synthesis of tetrahydropyran-2-ones bearing a C-3 substituent as found in the carpenter bee sex pheromone.² We first investigated the nucleophilic ring opening of propylene oxide (**2**) by the lithio derivative of **1** (Scheme 1). This reaction could have led to four diastereomeric δ -lactones, **3a**, **3b**, **3c** and **3d**, but only **3a** and **3b** were obtained, in a ratio of 54:46 (Scheme 1). This ratio was determined by ¹H NMR analysis of the crude product, more specifically, by integration of the signal corresponding to the proton on C6. This proton resonates at 4.36 and 4.70 ppm for the lactones **3a** and **3b**, respectively. We

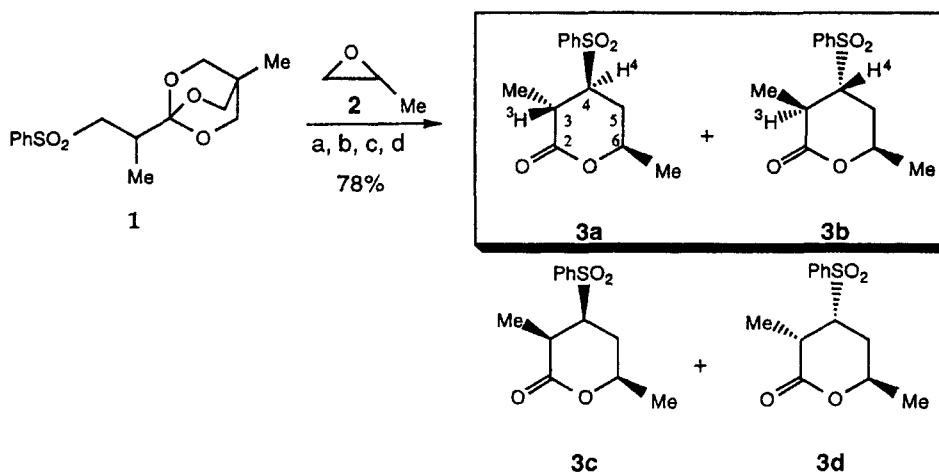
attributed this result to an epimerization at C-3 during the cyclization step, leading to products in which the methyl and the phenylsulphonyl groups possess a *trans* relationship (Scheme 1).³

These two lactones were easily separated by flash chromatography and we decided to undertake an X-ray crystal structure analysis of the two lactones, **3a** and **3b**, in order to assign the relative stereochemistries without ambiguity. In addition, a ¹H and ¹³C NMR study was performed in solution in order to verify the solid-state conformations observed.

EXPERIMENTAL

Crystal measurement and refinement data are summarized in Table 1. Both crystals were obtained by slow evaporation from ethyl acetate. A Huber four-circle diffractometer equipped with a graphite monochromatized Mo K α (for **3a**) or Cu K α (for **3b**) radiation was used for the measurements. A standard reflection was checked every 50 reflections; no significant deviation was observed. Both structures were solved by direct methods using SHELXS86.⁴ All H atom positions were located from Fourier difference synthesis. Anisotropic

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Scheme 1

Table 1. Data collection and refinement parameters

Parameter	3a	3b
Formula	C ₁₃ H ₁₆ O ₄ S	C ₁₃ H ₁₆ O ₄ S
<i>M_r</i>	268.32	268.32
Cell measurement		
No. of reflections	15	20
Range of 2θ (°)	8–30	12–51
System	triclinic	monoclinic
Space group	P-1	P2 ₁ /n
<i>a</i> (Å)	5.685(2)	7.908(2)
<i>b</i> (Å)	9.482(3)	17.121(3)
<i>c</i> (Å)	13.673(5)	10.764(3)
α(°)	70.06(3)	
β(°)	77.67(3)	111.12(2)
γ(°)	80.97(3)	
<i>V</i> (Å ³)	674.0(4)	1359.5(6)
<i>Z</i>	2	4
<i>D_x</i> (g cm ⁻³)	1.32	1.31
λ(Å)	0.71069	1.5418
<i>F</i> (000)	284	568
μ(mm ⁻¹)	0.244	2.167
Approximate crystal size (mm)	0.48 × 0.40 × 0.06	0.48 × 0.15 × 0.12
Collection range		
(sinθ/λ) _{max} (Å ⁻¹)	0.56	0.60
Range of <i>hkl</i>	0 ≤ <i>h</i> ≤ 6 -10 ≤ <i>k</i> ≤ 10 -14 ≤ <i>l</i> ≤ 15	0 ≤ <i>h</i> ≤ 9 0 ≤ <i>k</i> ≤ 20 -12 ≤ <i>l</i> ≤ 12
Indices of standard reflections	0 1 4	1 3 2
No. of independ. measured refl.	2001	2451
No. of observed reflections (<i>I</i> ≥ 2σ(<i>I</i>))	1495	1680
<i>R₁</i>	0.045	0.049
<i>R₁</i> (all data)	0.064	0.068
<i>w</i> = 1/(σ ² <i>F_o</i> ² + (<i>gP</i>) ² <i>g</i>)	0.0678	0.1081
<i>S</i> (on <i>F</i> ²)	0.99	0.92
(Δ/σ)	0.05	0.19
Δσ(max,min) (eÅ ⁻³)	0.22, -0.28	0.24, -0.25

least-squares refinement was performed with SHELXL93⁵ using F^2 ; H atoms were included in the refinement with an isotropic common refined temperature factor. Atomic scattering factors were obtained from *International Tables for X-Ray Crystallography*.⁶

The NMR spectra were recorded under standard conditions on a Bruker AM 500 spectrometer with 3.000 computer using a 5 mm ¹H and ¹³C probe at room temperature (25 °C). The CDCl₃ solvent provided an internal deuterium lock signal and an internal spectral reference (76.9 ppm for ¹³C). The reported chemical shifts and coupling constants are accurate to 0.1 ppm and 0.1 Hz, respectively. The assignments were confirmed by selective H–H and H–C irradiations.

RESULTS AND DISCUSSION

From the stereoscopic views (Figures 1 and 2)⁷ the methyl at C-3 and the sulphone at C-4 are mutually *trans* in both **3a** and **3b**, whereas the methyl at C-6 is

cis with respect to the sulphone in **3a** and *trans* in **3b**.

Atomic coordinates are given in Table 2 and bond distances and angles in Table 3. The endocyclic torsion angles in the six-membered heterocycle and the deviations of the ring atoms from the mean plane through C-6—O-1—C-2—C-3 are compared in Table 4. These results show that the ring conformation is similar in the two δ -lactones. In both **3a** and **3b**, the five atoms of the ester group (O-1, C-2, C-3, C-6 and O-9) are approximately coplanar (maximum deviation 0.02 Å) and the two remaining carbon atoms of the ring both lie on the same side of this plane (deviation 0.7 Å for C-4 and 1.1 Å for C-5) (Table 4). The torsion angles indicate a skew-boat or 1,3-diplanar conformation⁸ which is more regular for **3a** than **3b**.

A search of the Cambridge Crystallographic Data Base⁹ for non-fused tetrahyran-2-ones, eliminating structures with disorder or high *R* indices (>10%), produced a set of 27 structures. The molecule with the

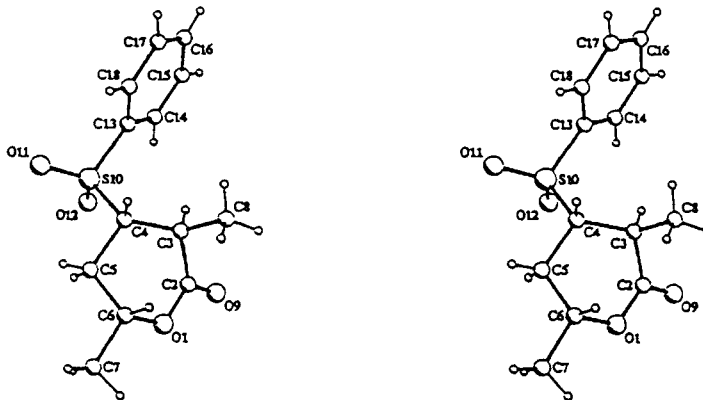


Figure 1. Stereoscopic view of the compound **3a** (Program PLUTO⁷)

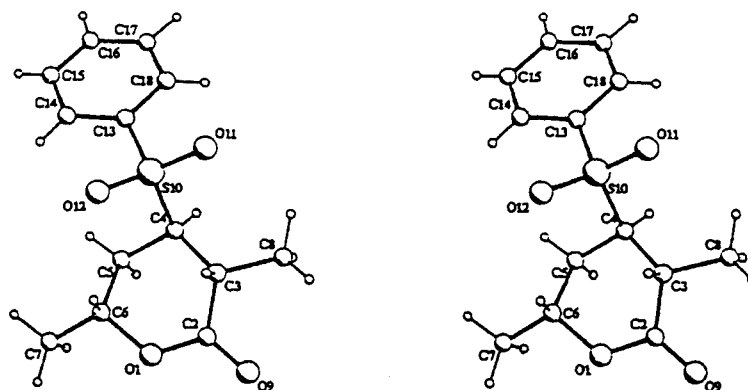


Figure 2. Stereoscopic view of the compound **3b** (Program PLUTO⁷)

Table 2. Atomic coordinates ($\times 10^4$) and equivalent temperature factors (\AA^2) ($\times 10^3$) $U_{eq} = (1/3)\Sigma_i \Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i \mathbf{a}_j$.

Atom	3a				3b			
	x	y	z	U_{eq}^a	x	y	z	U_{eq}^a
O(1)	345(4)	6770(2)	7443(2)	58(1)	4227(3)	3156(1)	7037(2)	97(1)
C(2)	-54(5)	5423(3)	8174(2)	45(1)	5354(4)	3134(2)	6375(2)	83(1)
C(3)	1580(5)	4055(3)	8060(2)	40(1)	4887(3)	3574(2)	5085(2)	72(1)
C(4)	2569(5)	4086(3)	6908(2)	37(1)	2837(3)	3545(1)	4226(2)	71(1)
C(5)	2090(7)	5640(3)	6093(2)	49(1)	1663(4)	3329(2)	5019(3)	86(1)
C(6)	2237(6)	6870(3)	6525(2)	51(1)	2520(4)	3583(2)	6445(3)	93(1)
C(7)	1790(10)	8429(4)	5761(3)	78(1)	1417(7)	3404(4)	7284(5)	129(1)
C(8)	3622(7)	3850(5)	8677(3)	70(1)	6048(6)	3307(3)	4335(4)	107(1)
O(9)	-1662(4)	5363(3)	8915(2)	67(1)	6766(3)	2790(1)	6874(2)	114(1)
S(10)	1291(1)	2731(1)	6583(1)	41(1)	2186(1)	4481(1)	3434(1)	75(1)
O(11)	2515(4)	2721(2)	5553(2)	57(1)	3491(3)	4707(1)	2860(2)	95(1)
O(12)	-1303(3)	3033(2)	6756(2)	58(1)	1869(3)	5005(1)	4367(2)	92(1)
C(13)	2023(5)	979(3)	7515(2)	42(1)	105(4)	4306(2)	2124(2)	74(1)
C(14)	262(6)	281(4)	8324(3)	57(1)	-1497(4)	4438(2)	2321(3)	91(1)
C(15)	827(8)	-1117(4)	9019(3)	72(1)	-3113(5)	4317(2)	1273(4)	107(1)
C(16)	3123(9)	-1815(4)	8902(3)	74(1)	-3113(6)	4068(2)	76(3)	111(1)
C(17)	4883(8)	-1125(4)	8101(3)	69(1)	-1515(6)	3934(2)	-117(3)	108(1)
C(18)	4342(6)	280(4)	7403(3)	56(1)	101(4)	4048(2)	905(2)	88(1)

Table 3. Bond distances (\AA) and angles ($^\circ$)

Bond	3a	3b	Angle	3a	3b
O(1)—C(2)	1.343(3)	1.326(3)	C(2)—O(1)—C(6)	119.7(2)	118.2(2)
O(1)—C(6)	1.454(4)	1.464(4)	O(9)—C(2)—O(1)	118.6(3)	118.0(3)
C(2)—O(9)	1.204(3)	1.204(3)	O(9)—C(2)—C(3)	122.4(3)	122.4(3)
C(2)—C(3)	1.506(4)	1.504(3)	O(1)—C(2)—C(3)	119.0(2)	119.5(2)
C(3)—C(8)	1.528(5)	1.496(4)	C(2)—C(3)—C(8)	107.7(3)	110.5(3)
C(3)—C(4)	1.546(4)	1.551(3)	C(2)—C(3)—C(4)	115.0(2)	112.4(2)
C(4)—C(5)	1.540(4)	1.515(4)	C(8)—C(3)—C(4)	111.6(3)	113.0(2)
C(4)—S(10)	1.788(3)	1.802(2)	C(5)—C(4)—C(3)	113.0(2)	113.1(2)
C(5)—C(6)	1.496(4)	1.502(4)	C(5)—C(4)—S(10)	107.9(2)	110.8(2)
C(6)—C(7)	1.512(5)	1.496(5)	C(3)—C(4)—S(10)	111.5(2)	108.2(2)
S(10)—O(11)	1.434(2)	1.434(2)	C(6)—C(5)—C(4)	110.5(2)	111.3(2)
S(10)—O(12)	1.442(2)	1.434(2)	O(1)—C(6)—C(5)	109.0(3)	106.4(3)
S(10)—C(13)	1.767(3)	1.764(3)	O(1)—C(6)—C(7)	105.4(3)	107.8(3)
C(13)—C(14)	1.378(4)	1.376(4)	C(5)—C(6)—C(7)	113.2(3)	114.3(3)
C(13)—C(18)	1.382(4)	1.383(4)	O(11)—S(10)—O(12)	118.6(1)	117.9(1)
C(14)—C(15)	1.379(5)	1.382(4)	O(11)—S(10)—C(13)	108.7(1)	108.1(1)
C(15)—C(16)	1.371(6)	1.358(5)	O(12)—S(10)—C(13)	107.7(1)	108.5(1)
C(16)—C(17)	1.370(6)	1.372(5)	O(11)—S(10)—C(4)	107.4(1)	108.4(1)
C(17)—C(18)	1.382(5)	1.366(4)	O(12)—S(10)—C(4)	108.5(1)	108.5(1)
			C(13)—S(10)—C(4)	105.2(1)	104.6(1)
			C(14)—C(13)—C(18)	120.1(3)	120.7(3)
			C(14)—C(13)—S(10)	120.1(2)	119.6(2)
			C(18)—C(13)—S(10)	119.7(2)	119.7(2)
			C(15)—C(14)—C(13)	119.6(3)	118.8(3)
			C(16)—C(15)—C(14)	120.2(4)	120.3(4)
			C(17)—C(16)—C(15)	120.4(3)	120.7(3)
			C(16)—C(17)—C(18)	119.9(4)	120.0(3)
			C(17)—C(18)—C(13)	119.7(3)	119.4(3)

Table 4. Endocyclic torsion angles ($^{\circ}$) ($\sigma=0.5^{\circ}$) and deviations (\AA) from the mean plane through C(6)—O(1)—C(2)—C(3)

Angle	3a	3b	Atom	3a	3b
C(6)—O(1)—C(2)—C(3)	3.8	2.8	C(6)*	-0.008	-0.006
O(1)—C(2)—C(3)—C(4)	-32.6	-38.1	O(1)*	0.017	0.012
C(2)—C(3)—C(4)—C(5)	11.0	19.4	C(2)*	-0.017	-0.012
C(3)—C(4)—C(5)—C(6)	34.8	28.8	C(3)*	0.008	0.006
C(4)—C(5)—C(6)—O(1)	-63.1	-63.2	C(4)	-0.692	-0.835
C(5)—C(6)—O(1)—C(2)	44.8	48.2	C(5)	-1.051	-1.105
			O(9)	-0.022	0.021

most similar conformation is ($4R^*$, $5S^*$, $6R^*$)-4-tert-butyl-4-hydroxy-5-methyl-6-phenyl-1-tetrahydropyran-2-one¹⁰ with endocyclic torsion angles of 5, -49, 32, 20, -63 and 51 $^{\circ}$. In the series, the most frequent conformation (eight cases) is a boat with one mirror plane bisecting the O-1—C-2 bond and the second mirror through the C-3 and C-6 atoms.

For the same set of 27 structures the average values for the bond lengths O-1—C-2 and C-2=O-9 are 1.343(3) and 1.204(2) \AA , respectively; the observed values of 1.343(3), and 1.204(3) \AA for **3a** and 1.326(3) and 1.204(3) \AA for **3b** compare favourably with these means.

Crystallographic data indicate that the δ -lactones **3a** and **3b** in the solid phase adopt a skew-boat conformation characterized notably by the five dihedral angles between protons listed in Table 5. In order to verify the stability of these conformations in solution, we attempted to reproduce, with the help of a modified Karplus relationship¹¹ (for discussion of the scope and limitations of conformational analysis based on such a relationship, see Ref. 12), the experimental coupling constants $^3J(\text{H,H})_E$ also listed in Table 5. The limited number of molecules studied does not allow us to refine the parameters $J(0)$ and $J(180)$ and then to propose a Karplus relationship specific to each type of coupling. However, as indicated by the calculated values of $^3J(\text{H,H})_C$, the experimental coupling constants are, in the case of the lactone **3b**, well reproduced qualitatively

with the help of a relationship of the form

$$^3J(\text{H,H})_C = 10 \cos^2 \phi + 1.8 \text{ Hz}$$

The constant $J(4,5B)$ representing a dihedral angle of approximately 90 $^{\circ}$ corresponds to the value of C; the coupling constant $J(5A,6)$ corresponds to two protons in a *trans* diaxial configuration. For the lactone **3b**, the conformation observed in the solid phase persists in solution with three substituents in pseudo-equatorial orientations. Conversely, for the lactone **3a**, the application of the relationship leads to calculated coupling constants $^3J(\text{H,H})_C$ markedly incompatible with the experimental values $^3J(\text{H,H})_E$.

Whereas the constants $J(5A,6)$ and $J(5B,6)$ and the related dihedral angles maintain values close to those observed for the lactone **3b**, the constant $J(3,4)$ is more compatible with a dihedral angle of the order of -145 $^{\circ}$. Moreover, the constant $J(4,5A)$ is more characteristic of a dihedral angle of 180 $^{\circ}$ between diaxial protons. In rigid six-membered rings such as in substituted cyclohexanes, the observed coupling constants between vicinal protons in a *trans* diaxial relationship are definitely larger (8–14 Hz; usually 8–10 Hz) than those observed between protons in an axial–equatorial or equatorial–equatorial relationship (1–7 Hz; usually 2–3 Hz).¹² The angle $\phi(4,5B)$, under these conditions, has to be equal to 60 $^{\circ}$, a value consistent with a coupling constant of 4.7 Hz and the Karplus relationship described as above. The new values of dihedral

Table 5. Dihedral angles ($^{\circ}$) and experimental [$^3J(\text{H,H})_E$] and calculated $^3J(\text{H,H})_C$ coupling constants (Hz) for lactones **3a** and **3b**

Dihedral angle	3a			3b		
	Angle	$^3J(\text{H,H})_E$	$^3J(\text{H,H})_C$	Angle	$^3J(\text{H,H})_E$	$^3J(\text{H,H})_C$
H(3)—C(3)—C(4)—H(4)	-110	8.3	2.9	141	7.9	7.8
H(4)—C(4)—C(5)—H(5A)	153	12.7	9.7	36	8.6	8.3
H(4)—C(4)—C(5)—H(5B)	36	4.7	8.3	-87	1.8	1.8
H(5A)—C(5)—C(6)—H(6)	171	11.4	11.5	168	11.0	11.4
H(5B)—C(5)—C(6)—H(6)	-70	1.9	2.9	-72	1.9	2.7

angles proposed for the lactone **3a** are more representative of a half-chair conformation in which atoms C-4 and C-5 are above and below, respectively, the plane C-6—O-1—C-2—C-3 and where, again, all substituents are in pseudo-equatorial orientations. This would explain the absence of a nuclear Overhauser effect between the two methyl groups.

Experimental NMR data

Lactone **3a**.

^{13}C NMR (125 MHz, CDCl_3 ; δ (ppm) 18.8 (C-8), 21.3 (C-7), 30.9 (C-5), 34.6 (C-3), 63.6 (C-4), 73.3 (C-6), 128.8 (C-15, C-17), 129.5 (C-14, C-18), 134.4 (C-16), 136.3 (C-13), 171.4 (C-2).

^1H NMR (500 MHz, CDCl_3 ; δ (ppm) 1.32 (d, 3H, H-7), 1.40 (d, 3H, H-8), 1.71 (ddd, 1H, H-SA), 2.10 (ddd, 1H, H-5B), 2.93 (dq, 1H, H-3), 3.26 (ddd, 1H, H-4), 4.32 (dq, 1H, H-6), 7.60–7.90 (m, 5H, H-14, H-15, H-16, H-17, H-18).

Coupling constants $J(\text{H,H})$ (Hz): $J(3,4) = 8.3$; $J(3,8) = 7.4$; $J(4,5\text{A}) = 12.7$; $J(4,5\text{B}) = 4.7$; $J(5\text{A},5\text{B}) = 13.9$; $J(5\text{A},6) = 11.4$; $J(5\text{B},6) = 1.9$; $J(6,7) = 6.2$.

The protons 5A and 5B are *cis* and *trans*, respectively, with respect to the sulphone moiety.

Lactone **3b**.

^{13}C NMR (125 MHz, CDCl_3 ; δ (ppm) 16.7 (C-8), 20.7 (C-7), 30.8 (C-5), 33.3 (C-3), 62.0 (C-4), 72.0 (C-6), 128.7 (C-15, C-17), 129.7 (C-14, C-18), 134.5 (C-16), 137.3 (C-13), 172.1 (C-2).

^1H NMR (500 MHz, CDCl_3 ; δ (ppm) 1.24 (d, 3H, H-8), 1.30 (d, 3H, H-7), 1.79 (ddd, 1H, H-5A), 2.29 (ddd, 1H, H-5B), 3.04 (dq, 1H, H-3), 3.19 (ddd, 1H, H-4), 4.65 (dq, 1H, H-6), 7.60–7.90 (m, 5H, H-14, H-15, H-16, H-17, H-18).

Coupling constants $J(\text{H,H})$ (Hz): $J(3,4) = 7.9$; $J(3,8) = 6.8$; $J(4,5\text{A}) = 8.6$; $J(4,5\text{B}) = 1.8$; $J(5\text{A},5\text{B}) = 15.8$; $J(5\text{A},6) = 11.0$; $J(5\text{B},6) = 1.9$; $J(6,7) = 6.3$.

The protons 5A and 5B are *trans* and *cis*, respectively, with respect to the sulphone moiety.

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