Synthesis of Both Enantiomers of Optically Pure Saturated and α,β-Unsaturated γ-Substituted γ-Lactones from Chiral Sulphoxides. *X*-Ray Molecular structure of (3*R*,4*S*)-4-Methyl-4-t-butyl-3-(*p*-tolylthio)butanolide and of (3*R*,4*R*)-4-(Cyclohex-1-enyl)-4-methyl-3-(*p*-tolylthio)butanolide

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The lithium carbanions of optically pure (+)-(*R*)-*p*-tolyl alkyl sulphoxides (**5**) reacted with lithium bromoacetate and gave (+)-(*R*)-3-(*p*-tolylsulphinyl)carboxylic acids (**3**). Their dimetallation produced a chiral homoenolate dianion equivalent (**6**) which added to carbonyl compounds (**4**) to furnish sulphinyl lactones (**7**) in moderate chemical and optical yields. However, single diastereoisomers of these compounds could be easily separated through chromatography, and were transformed in high yields into both enantiomers of optically pure saturated and α,β-unsaturated γ-lactones (**1**) and (**2**). Relative and absolute stereochemistry of all the products obtained was determined through c.d., nuclear Overhauser effects, and *X*-ray analyses.

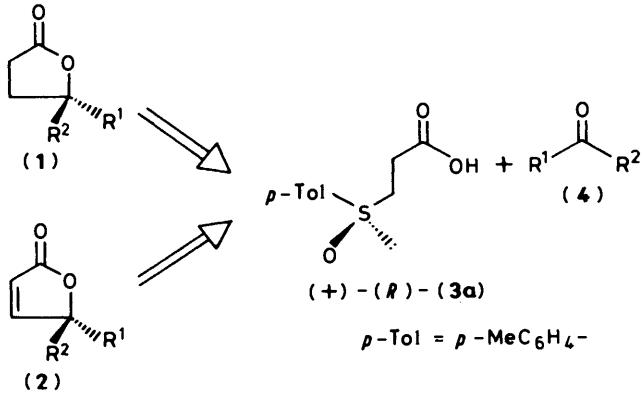
Optically active 4-substituted butanolides are widely present in secondary metabolites and show varied and interesting physiological activities. They are found in flavour components,[1] in cellular signalling substances,[2] and in sex pheromones.[3] Biological activities of the two enantiomers are often different; for instance several insect species are more responsive to the natural occurring isomer,[4] and humans too perceive differences in odour of some pairs of enantiomers.[5]

4-Substituted but-2-enolides also are naturally occurring compounds[1,6] and they have been used as key building blocks in the synthesis of chiral natural products.[7] For these reasons there is great interest in the preparation of optically pure 4-substituted γ-lactones and various methods have recently been proposed. Approaches to such compounds include resolution of precursors,[8] transformation of naturally occurring starting materials,[9] and chemical synthesis of appropriate chiral precursors such as allenecarboxylic acids[10] and α-acetylenic alcohols. These last compounds are obtained through asymmetric addition of an acetylide to aliphatic aldehydes[11] or reduction of alkynyl ketones with chiral hydride species.[12]

Numerous and efficient syntheses of racemic γ-lactones are based on use of organosulphur compounds[13] and in some cases chiral products were obtained. Starting from optically pure sulphoxide derivatives, Posner and co-workers[14] have recently described a highly enantiocontrolled synthesis of 2,3-disubstituted butan-4-olides with anticancer activity, and Solladié[15] reported a nine-step sequence leading to a biologically interesting chiral γ-lactone. In both cases the key step is a C–C bond formation through either a Michael addition[14] to α-sulphinyl γ-butenolides or an aldol condensation of a sulphinyl acetate.[15]

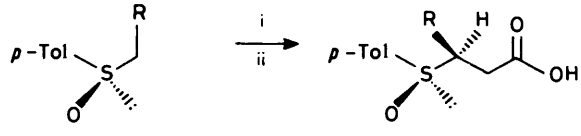
We found that a straightforward way to prepare optically active γ-lactones (**1**) and (**2**) was the addition of the chiral homoenolate dianion obtained from the 3-sulphinylpropionic acid (**3a**) (d^3 synthon)[16] to carbonyl compounds (**4**) and we have already briefly reported[17] our first results.

Synthesis of β-(p-*Tolylsulphinyl*) γ-*Lactones* (**8**) *and their Transformation into Lactones* (**1**) *and* (**2**).—Stabilized[18] and unstabilized[19] carbanions are reported to react with esters of bromoacetic acid through displacement of the halogen atom. In contrast, when we treated α-sulphinyl carbanions derived from (+)-(*R*)-methyl *p*-tolyl sulphoxide (**5a**) and (+)-(*R*)-ethyl *p*-tolyl sulphoxide (**5b**) with methyl, ethyl, or t-butyl esters of chloro-, bromo-, and iodo-acetic acid, the expected 3-sulphinyl carboxylic acid esters were not obtained, as addition of the carbanion onto the carboxy group had occurred to give the corresponding α-halogeno-α'-sulphinyl ketones.[20]



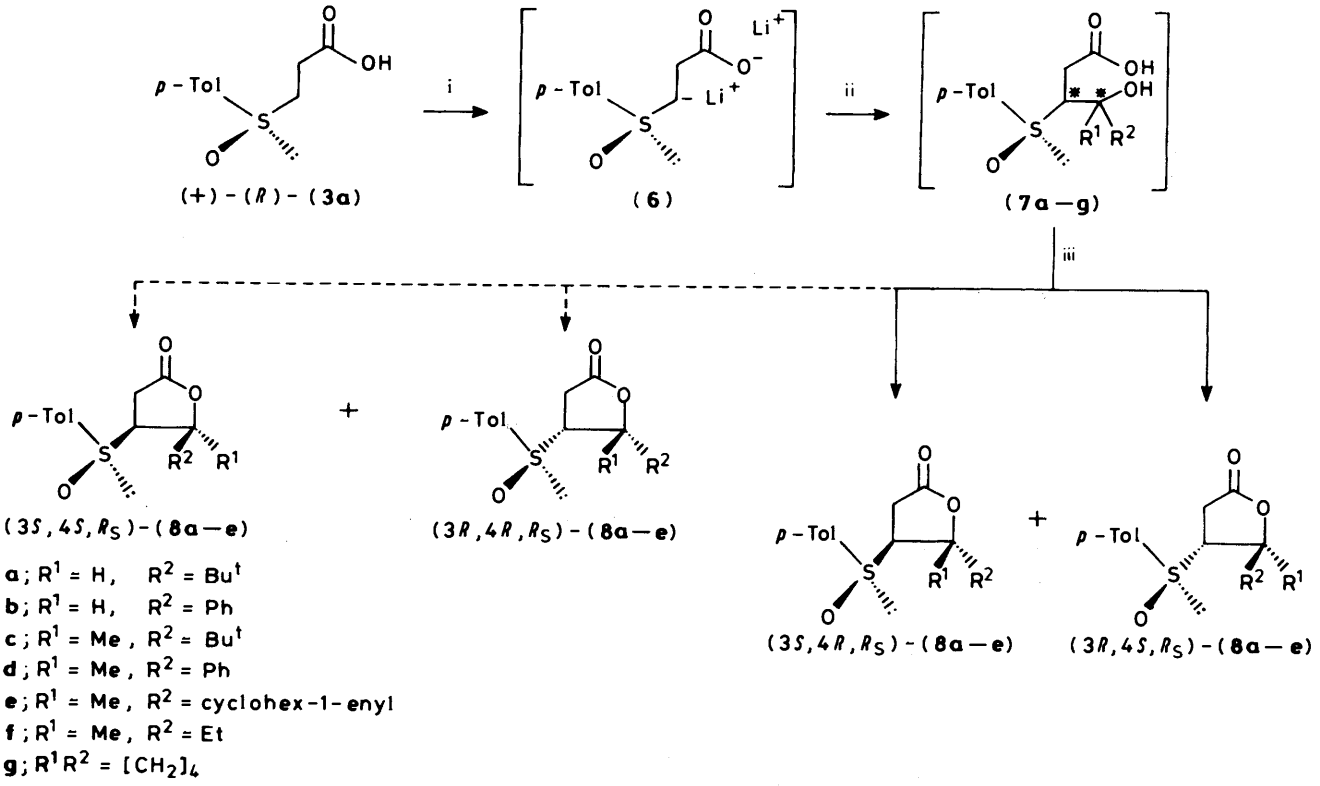
Therefore to diminish the nucleophilicity of the carboxy group we used lithium and sodium salts of the halogenoacetic acids instead of the corresponding esters. Sodium and lithium salts of both bromo- and iodo-acetic acid reacted properly, but the best results were obtained with lithium bromoacetate (Scheme 1).

(+)-(*R*)-3-(*p*-Tolylsulphinyl)propionic acid (**3a**) and (+)-(3*S*,*R*$_S$)-3-(*p*-tolylsulphinyl)butyric acid (**3b**)† were isolated in



Scheme 1. i, LDA; ii, $BrCH_2CO_2Li$

† An 8:2 mixture of diastereoisomers at C-3 of 3-(*p*-tolylsulphinyl)-butyric acid was obtained. The *S* absolute stereochemistry is tentatively attributed to the chiral carbon atom of the major diastereoisomer on similarity with the products of alkylation of the same carbanion with other lithium bromo carboxylates.[21]



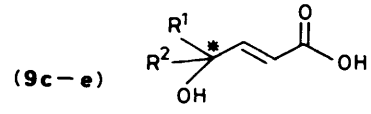
Scheme 2. *Reagents and conditions:* i, LDA, THF, −60 °C; ii, R^1COR^2 (**4a**—**g**), THF, −78 °C; iii, room temperature, neat

76 and 58% yield, respectively, as white crystals which were stable at room temperature for several months.

On treatment of the 3-sulphinylpropionic acid (+)-(*R*)-(**3a**) with 2 equiv. of lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) at −60 °C an almost instantaneous metallation at position α to the sulphinyl group occurred. After the reagent solution had been cooled at −78 °C, a THF solution of one of the carbonyl compounds (**4a**—**g**) was added to the yellowish solution of the carbanion (**6**). A rapid condensation occurred as shown by disappearance of colour and, a few minutes after the addition of the carbonyl electrophile, the reaction was quenched with saturated aqueous ammonium chloride. Dil. hydrochloric acid was then added to pH *ca.* 2 and a mixture of β-sulphinyl-γ-hydroxy acids (**7**) was extracted with ethyl acetate from the aqueous layer. In large-scale preparative reactions, formation of the homoenolate dianion (**6**) appears to be nearly quantitative as shown by the fact that the 3-sulphinylpropionic acid (**3a**) was not recovered when either pivalic or benzoic aldehyde (**4a**,**b**) was added to the dianion (6).

However, some of the 3-sulphinylpropionic acid (**3a**) was recovered from the crude reaction mixture when enolizable ketones were used [especially 1-acetylcyclohexene (**4e**)], probably because the lithium dianion (**6**) in those cases behaved as a base.

Initially formed β-sulphinyl-γ-hydroxy acids (**7a**—**g**) spontaneously cyclized to give the corresponding β-sulphinyl γ-lactones (**8a**—**g**) with very different rates depending on the substituents (Scheme 2). γ-Disubstituted lactones formed more slowly than the corresponding γ-monosubstituted products. When alkyl residues were present (**7a**,**c**,**f**) cyclization was almost complete by the end of the work-up. In contrast, 3-sulphinyl carboxylic acids (**7b**,**d**,**e**) bearing aryl or alkenyl substituents were no longer detectable in crude reaction mixtures only after these had been kept at room temperature for 2 days. When the cyclization to lactones (**8**) was particularly slow, a direct elimination of toluene-*p*-sulphenic acid from γ-hydroxy carboxylic acids (**7**) prior to lactonization to compounds (**8**) also occurred [small quantities of optically active (2*E*)-4-hydroxyalkenoic acids (**9c**—**e**) could be isolated from the reaction mixture].

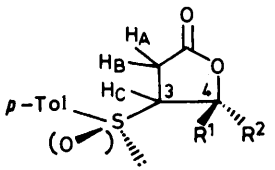


Single diastereoisomers of sulphinyl lactones (**8a**—**f**) were obtained in enantiomerically pure form through flash chromatography of the product mixture which formed in the condensation reaction (Table 1). n-Hexane–ethyl acetate mixtures were always used as the eluting system unless spirolactones (**8g**) were chromatographed. In this case, diastereoisomers were separated only when a di-isopropyl ether–ethyl acetate mixture was employed. The β-sulphinyl lactones (**8**) thus obtained are unstable to heat and therefore we used a rotary evaporator with a cool finger to evaporate the solvent, and we treated pure diastereoisomers immediately after their chromatographic separation.

Two new chiral carbon atoms are formed in the condensation reaction of the (+)-(*R*)-3-sulphinylpropionic acid (**3a**) with carbonyl compounds (**4a**—**f**), and four diastereoisomeric β-sulphinyl γ-lactones (**8a**—**f**) could therefore in principle be obtained (Scheme 2). Under reaction conditions we adopted, only two diastereoisomers were isolated when the carbanion condensed with pivalic aldehyde (**4a**), benzaldehyde (**4b**), and pinacolone (**4c**).

Diastereoselectivity of the condensation reaction diminished when the two residues of the carbonyl group were sterically

Table 1. Yields, and physical and spectral data for compounds (**8**) and (**10**)



Compound	R^1	R^2	Yield (%)	R_F (solvent)[a]	M.p. (°C)[b] (solvent)	$\nu_{max.}$/cm^{-1} (mean)	$[\alpha]_D^{15}$/ (c, $CHCl_3$)	$\delta_H(CDCl_3)$ H_A (^2J)	H_B (^3J)	H_C (^3J)	R^1 [$J(R^1$–$H_C)$]	R^2 [$J(R^2$–$H_C)$]
(3*S*,4*R*,R_S)-(**8a**)[c]	H	Bu^t	35	0.34 (A)	95—97 ($CHCl_3$)	1 775, 1 030 ($CHCl_3$)	+202 (0.7)	2.30 (18.0)	3.17 (5.4)	3.32 (8.5)	4.46 (5.0)	0.98
(3*R*,4*S*,R_S)-(**8a**)[d]	Bu^t	H	31	0.18 (A)	98—100 ($CHCl_3$)	1 765, 1 040 ($CHCl_3$)	+211 (0.7)	2.75	2.75 (6.3)	3.38 (6.3)	0.80	4.43 (2.1)
(3*S*,4*R*,R_S)-(**8b**)[e]	H	Ph	33	0.37 (A)	liq.	1 780, 1 050 ($CHCl_3$)	+78.6 (1.1)	2.35 (18.0)	3.22 (7.8)	3.45 (7.8)	5.70 (6.6)	7.2—7.5
(3*R*,4*S*,R_S)-(**8b**)[f]	Ph	H	28	0.23 (A)	liq.	1 775, 1 050 ($CHCl_3$)	+65.0 (1.0)	2.82	2.93 (7.0)	3.52 (7.8)	6.8—7.6	5.78 (3.6)
(3*S*,4*R*,R_S)-(**8c**)	Me	Bu^t	8.8	0.34 (B)	87—89 (Et_2O)	1 780, 1 040 (Nujol)	+147 (0.7)	2.17	3.2	3.7	1.68	1.04
(3*R*,4*S*,R_S)-(**8c**)	Bu^t	Me	38	0.24 (B)	102—104 (Et_2O)	1 775, 1 040 (Nujol)	+107 (0.7)	2.18	2.22 (8.0)	3.65 (10.5)	1.05	1.82
(3*S*,4*R*,R_S)-(**8d**)	Me	Ph	8.0	0.35 (C)	liq.	1 775, 1 040 (film)	+54.4 (1.2)	~2.2	3.30	3.41	2.08	7.2—7.6
(3*R*,4*S*,R_S)-(**8d**)[g]	Ph	Me	25	0.34 (C)	140—141 (n-hexane-AcOEt)	1 775, 1 040 (Nujol)	+187 (0.7)	2.26	2.30 (7.5)	3.78 (9.0)	7.2—7.7	2.13
(3*R*,4*R*,R_S)-(**8d**)[h]	Me	Ph	18	0.19 (C)	130—131 (n-hexane-AcOEt)	1 770, 1 040 (KBr)	+9.9 (0.7)	1.93 (16.0)	2.50 (11.0)	3.61 (8.0)	2.06	7.1—7.7
(3*S*,4*R*,R_S)-(**8e**)[i]	Me	Cyclohex-1-enyl	10.4	0.50 (C)	80—81 (Et_2O)	1 770, 1 040 (Nujol)	+150 (1.2)	2.27 (18.6)	3.23	3.28	1.82	5.87
(3*R*,4*S*,R_S)-(**8e**)[j]	Cyclohex-1-enyl	Me	16.7	0.40 (C)	110—112 (Et_2O)	1 775, 1 040 (Nujol)	+138 (1.1)	2.26	2.30 (9.0)	3.54 (7.8)	5.91	1.90

Table 1 (*continued*)

Compound	R^1	R^2	Yield (%)	R_F (solvent)[a]	M.p. (°C)[b] (solvent)	$\nu_{max.}$/cm^{-1} (mean)	$[\alpha]_D^{15}$/° (*c*, $CHCl_3$)	$\delta_H(CDCl_3)$ H_A (^2J)	H_B (^3J)	H_C (^3J)	R^1 [$J(R^1$-$H_C)$]	R^2 [$J(R^2$-$H_C)$]
(3*R*,4*R*,R_S)-(**8e**)	Me	Cyclohex-1-enyl	9.0	0.24 (C)	132—134 (Et_2O)	1 770, 1 050 (Nujol)	+81 (1.7)	2.11 (18.0)	2.45 (10.0)	3.43 (9.5)	1.76	6.02
(3*S*,4*R*,R_S)-(**8f**)[k]	Me	Et	14	0.38 (D)	85—87 (Pr^i_2O)	1 780, 1 050 (Nujol)	+251 (0.7)	2.22 (17.0)	3.18	3.27 (7.2)	1.67	1.02, 1.82
(3*R*,4*S*)-(**10a**)	Bu^t	H	92		81—82 (n-hexane)	1 775 ($CHCl_3$)	−16.4 (2.0)	2.62 (18.0)	2.84 (8.5)	3.63 (4.0)	0.89	4.11 (3.5)
								2.37	2.37	3.26	0.61	3.93[l]
(3*R*,4*S*)-(**10b**)	Ph	H	90		liq.	1 780 ($CHCl_3$)	−64.0 (2.0)	2.61 (17.8)	2.92 (8.5)	3.72 (7.0)	7.2—7.5	5.30 (5.0)
								2.28	2.40	3.25	~7.1	4.98[l]
(3*R*,4*S*)-(**10c**)	Bu^t	Me	84		77—78 (pentane)	1 780 (Nujol)	−109 (1.0)	2.77	2.87 (8.9)	3.87 (9.8)	1.02	1.47
(3*R*,4*S*)-(**10d**)	Ph	Me	86		80—81 (n-hexane)	1 775 ($CHCl_3$)	−21.6 (1.0)	2.70 (17.6)	2.85 (7.8)	3.97 (7.1)	7.0—7.6	1.80
(3*R*,4*R*)-(**10d**)	Me	Ph	88		124—125 (n-hexane–AcOEt)	1 775 ($CHCl_3$)	−100 (1.0)	2.66 (17.9)	2.97 (7.3)	3.98 (6.7)	1.87	7.2—7.5
(3*R*,4*S*)-(**10e**)	Cyclohex-1-enyl	Me	88		42—43 (pentane–Et_2O)	1 780 (KBr)	−55 (1.0)	2.60 (17.6)	2.88 (7.35)	3.85 (7.35)	5.79	1.58
(3*R*,4*R*)-(**10e**)	Me	Cyclohex-1-enyl	90		120—121 (Et_2O)	1 780 (KBr)	−132 (1.0)	2.62 (18.2)	2.91 (7.35)	3.75 (3.9)	1.51	5.90

[a] Solvents: A, n-hexane–ethyl acetate (60:40); B, n-hexane–ethyl acetate (70:30); C, n-hexane–ethyl acetate (65:35); D, di-isopropyl ether–ethyl acetate (80:20). [b] Uncorrected values. [c] $\delta_C(CDCl_3)$ 21.35 (Me), 24.92 (CMe_3), 25.35 (C-2), 34.93 (CMe_3), 59.66 (C-3), 86.38 (C-4), and 173.42 (C-1). [d] $\delta_C(CDCl_3)$ 21.42 (Me), 24.69 (CMe_3), 30.21 (C-2), 34.89 (CMe_3), 58.76 (C-3), 84.69 (C-4), and 173.66 (C-1). [e] $\delta_C(CDCl_3)$ 21.31 (Me), 25.08 (C-2), 66.91 (C-3), 79.58 (C-4), and 172.91 (C-1). [f] $\delta_C(CDCl_3)$ 16.46 (Me), 24.22 (C-2), 59.97 (C-3), 72.77 (C-4), and 168.38 (C-1). [g] $\delta_C(CDCl_3)$ 21.45, 25.77 (Me), 30.73 (C-2), 70.23 (C-3), 88.27 (C-4), and 171.36 (C-1). [h] $\delta_C(CDCl_3)$ 21.44, 29.33 (Me), 29.69 (C-2), 71.47 (C-3), 88.01 (C-4), and 171.86 (C-1). [i] Other ^{1}H n.m.r. signals at δ_H 1.60 (2 H, m, CH_2), 1.68 (2 H, m, CH_2), 2.08 (4 H, m, 2 × CH_2C=), and 7.30—7.41 (ArH). [j] Other ^{1}H n.m.r. signals at δ_H 1.58 (2 H, m, CH_2), 1.73 (2 H, m, CH_2), 2.05—2.20 (4 H, m, 2 × CH_2C=), and 7.35—7.61 (each d, ArH). [k] The other three diastereoisomers could not be obtained in pure form as they were not completely resolved even in h.p.t.l.c.; however, $[\alpha]_D^{15}$ values of optically active γ-lactones (**1f**) prepared on reduction of product mixtures of β-sulphinyl γ-lactones (**8f**), and analyses of ^{1}H n.m.r. spectra of these mixtures, allowed us to establish yields and absolute configurations at C-4 as follows: (+)-(4*S*,R_S)-(**8f**), 5% yield; $\delta_H(CDCl_3)$ 1.09 (t, CH_2Me) and 1.48 (s, Me); (4*S*,R_S)-(**8f**), 16.7% yield; $\delta_H(CDCl_3)$ 1.00 (t, CH_2Me) and 1.73 (s, Me); (3*R*,4*R*,R_S)-(**8f**), 13% yield; $\delta_H(CDCl_3)$ 1.13 (t, CH_2Me) and 1.61 (s, Me). [l] Values obtained in C_6D_6.

Table 2. Yields, and physical and spectral data for compounds (**1**) and (**2**)

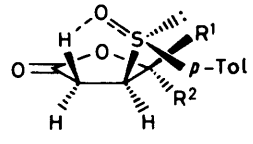
Compounds	R¹	R²	Yields (%)	M.p. (°C)[a] (solvent)	$\nu_{max.}$/cm^{-1} (mean)	$[\alpha]_D^{15}$/ (c, $CHCl_3$)	c.d. (CH_3CN) c	λ/nm	$[\theta]^{20}$	δ_H	δ_C
(*R*)-(**1c**)	Me	Bu^t	80	liq.	1 770 (film)	−14.2 (1.0)				0.99 (9 H, s, Bu^t), 1.36 (3 H, s, Me), 1.80 (1 H, m, 3-H), 2.31 (1 H, m, 3-H), and 2.55 and 2.68 (2 H, m, 2-H_2).	22.29 (Me), 24.80 (CMe_3), 29.35 and 28.85 (CH_2CH_2), 37.23 (CMe_3), 91.26 (C-4), and 176.83 (C-1)
(*R*)-(**1d**)	Me	Ph	78	liq.	1 770 (film)	+72.4[b] (1.3)				1.73 (3 H, s, Me) and 2.3—2.7 (4 H, m, CH_2CH_2)	28.95 and 36.19 (CH_2CH_2), 29.40 (Me), 86.88 (C-4), and 176.33 (C-1)
(*R*)-(**1e**)	Me	Cyclohex-1-enyl	86	liq.	1 770 (film)	+56.0[c] (1.2)				1.48 (3 H, s, Me), 1.4—1.7 (6 H, m, 3 × CH_2), 1.8—2.2 (4 H, m, 2 × CH_2), 2.27 (1 H, m, 2-H), and 2.54 (1 H, m, 2-H)	
(*R*)-(**1f**)	Et	Me	75	liq.	1 770 (film)	+10.4[d] (1.2)				0.97 (3 H, t, CH_2Me), 1.38 (3 H, s, Me), 1.71 (2 H, m, CH_2), 1.9—2.1 (2 H, m, CH_2), and 2.60 (2 H, m, CH_2)	8.16 (Me), 25.13 (Me), 29.18, 32.37, and 33.58 (CH_2CH_2 and CH_2), 87.09 (C-4), and 176.71 (C-1)
(*R*)-(**2a**)	H	Bu^t	84	65—67 (n-hexane–AcOEt)	1 790, 1 750 ($CHCl_3$)	+129[c] (3.7)	7.5×10^{-3}	211	$+3.42 \times 10^4$	0.98 (9 H, s, Bu^t), 4.69 (1 H, dd, 4-H), 6.12 (1 H, dd, ^3J 5.7, ^4J 2.1 Hz, 2-H), and 7.44 (1 H, dd, ^3J 1.6 Hz, 3-H)	25.46 (Me), 34.91 (CMe_3), 90.91 (C-4), 122.55 (C-2), 154.19 (C-3), and 173.08 (C-1)
(*R*)-(**2b**)	H	Ph	80	liq.	1 790, 1 755 (film)	+304[e] (1.0)	5.6×10^{-4} 7.5×10^{-2}	210 253 258 265 271	$+1.4 \times 10^4$ -3.3×10^3 -2.5×10^3 -1.6×10^3 -1.1×10^3	5.97 (1 H, t, $^3J = {}^4J$ = 1.8 Hz, 4-H), 6.18 (1 H, dd, ^3J 5.5 Hz, 2-H), and 7.50 (1 H, dd, 3-H)	84.34 (C-4), 120.78 (C-2), 155.90 (C-3), and 173.03 (C-1)
(*R*)-(**2c**)	Me	Bu^t	84	57—58 (n-hexane)	1 780, 1 750 (KBr)	+24.4 (0.7)	4.5×10^{-3}	214	$+1.8 \times 10^4$	1.09 (9 H, s, Bu^t), 1.53 (3 H, s, Me), 6.12 (1 H, d, ^3J 5.7 Hz, 2-H), and 7.58 (1 H, d, 3-H)	19.89 (Me), 25.45 (CMe_3), 36.81 (CMe_3), 93.68 (C-4), 120.72 (C-2), 159.71 (C-3), and 172.79 (C-1)
(*R*)-(**2d**)	Me	Ph	82	liq.	1 760 (film)	+276[c,f] (3.7)	1.1×10^{-2}	212	$+9.9 \times 10^4$	1.80 (3 H, s, Me), 6.01 (1 H, d, ^3J 5.5 Hz, 2-H), and 7.67 (1 H, d, 3-H)	26.31 (Me), 88.89 (C-4), 119.16 (C-2), 160.47 (C-3), 172.23 (C-1)
(*R*)-(**2e**)	Me	Cyclohex-1-enyl	86	52—53 (n-hexane)	1 750 (KBr)	+173 (1.7)	6.2×10^{-2}	209	$+6.9 \times 10^4$	1.5—1.8 (7 H, m, [2 × CH_2] and Me), 1.8—2.2 (4 H, m, 2 × CH_2C=), 5.81 (1 H, br s, =CH), 6.01 (1 H, d, ^3J 5.6 Hz, 2-H), and 7.41 (1 H, d, 3-H)	21.83, 22.49, 23.09, 23.86, and 25.17 ($[CH_2]_4$ and Me), 90.26 (C-4), 119.82 and 124.75 (C-2 and CH cyclohexenyl), 160.10 (C-3), and 172.59 (C-1)

[a] Uncorrected values; expected mass spectra were obtained. [b] $[\alpha]_D^{25}$ +72.5, CCl_4 (ref. 10). [c] Optical purity of this compound was assessed with Eu(hfc)$_3$. [d] $[\alpha]_D^{22}$ −10.3 (ref. 24 for the enantiomer). [e] Optical purity of this compound was assessed with Eu(tfc)$_3$. [f] $[\alpha]_D^{25}$ +272.8, CCl_4 (ref. 10).

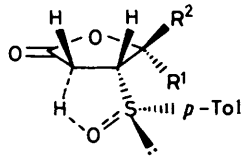
similar. Starting from acetophenone (**4d**) and 1-acetylcyclohexene (**4e**) we separated three sulphinyl lactones (**8d,e**), and when butan-2-one (**4f**) was used as electrophile all four possible diastereoisomers of (**8f**) were obtained. The two sulphinyl lactones (+)-(3*R*,4*S*,R_S)-(**8a—e**), and (+)-(3*S*,4*R*,R_S)-(**8a—e**), having opposite absolute configuration at both chiral carbon atoms and having the sulphinyl group in a *trans* relationship with the bulkier substituent at C-4, were formed in all cases.

Starting from acetophenone (**4d**) and 1-acetylcyclohexene (**4e**), the third diastereoisomer, with 3*R*,4*R*,R_S stereochemistry, was also isolated.

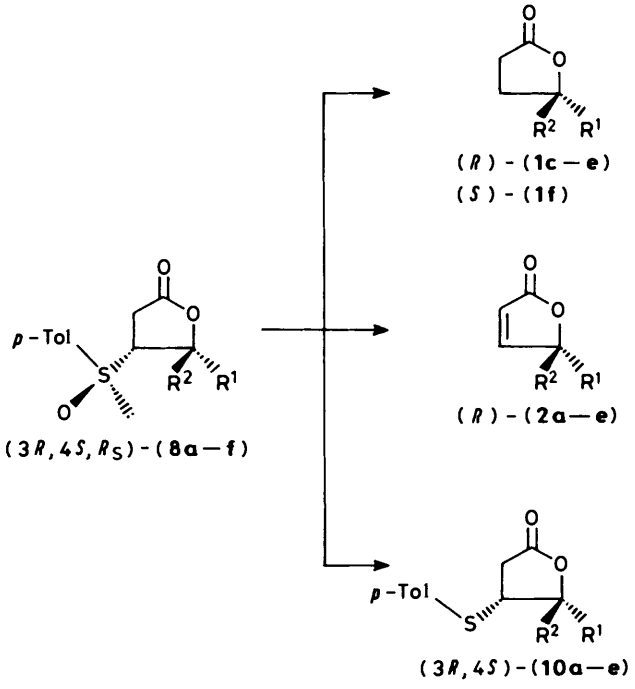
In a single step diastereoisomerically pure β-sulphinyl γ-lactones (**8a—f**) gave saturated and α,β-unsaturated γ-lactones (**1**) and (**2**) in high yields and in optically pure form. Both enantiomers of these products could be obtained starting from sulphinyl derivatives with opposite chirality at the γ-carbon. Specifically, reductive elimination of the sulphinyl residue of lactones (**8c—f**) was obtained by adding powdered sodium amalgam to a methanolic solution of lactones (**8**) cooled at −40 °C and buffered with sodium dihydrogen phosphate (Scheme 3). Under these conditions butanolides (**1c—f**) were isolated in high yields (Table 2), while when disodium hydrogen phosphate was used[22] traces of α,β-unsaturated compounds (**2**) were also formed, probably as a consequence of a base-catalysed elimination[23] of toluene-*p*-sulphenic acid. Optically pure butenolides (**2a—e**) were formed cleanly *via* a thermal process by heating sulphinyl lactones (**8a—e**) in toluene in the presence of an excess of ethylene glycol. The relative rates of elimination of toluene-*p*-sulphenic acid are in accord with steric hindrance of different diastereoisomers. In fact, 3*S*,4*R*,R_S compounds pyrolyse faster than 3*R*,4*S*,R_S compounds, since in the cyclic transition state of the concerted elimination the tolyl group of the sulphinyl substituent is directed away from the lactone ring for the former diastereoisomers, while it must face the *cis* group at C-4 for the latter ones. In this case, prolonged heating is required because of the highly hindered conformation necessary for cyclic elimination.



(3*S*,4*R*,R_S)-(**8a—e**)



(3*R*,4*S*,R_S)-(**8a—e**)



(3*R*,4*S*,R_S)-(**8a—f**)

(*R*)-(**1c—e**)
(*S*)-(**1f**)

(*R*)-(**2a—e**)

(3*R*,4*S*)-(**10a—e**)

Scheme 3.

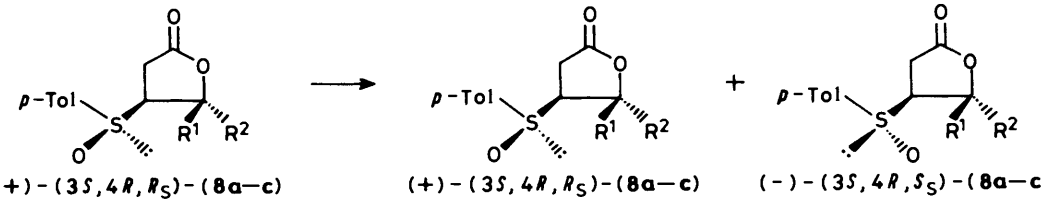
Both enantiomers of mono- and di-substituted saturated and α,β-unsaturated γ-lactones (**1**) and (**2**) are accessible through the synthetic sequence we devised and alkyl, alkenyl, and aryl residues can be present on the chiral carbon atom.

β-Tolylthio γ-lactones (**10a—e**) were obtained through deoxygenation of the sulphoxide group of compounds (**8a—e**) with trifluoroacetic anhydride (TFAA)–sodium iodide[24] at low temperature (Table 1). No racemization at carbon occurred in this reaction and we preferred to use these β-tolylthio compounds (**10**), rather than the corresponding β-tolylsulphinyl derivatives (**8**), for the determination of the relative stereochemistry of the ring substituents, as they were stable for a much longer period and they lacked the further chiral centre at the sulphur atom.

Stereochemical Results.—Upon reduction of the sulphoxide group, the pairs of diastereoisomeric sulphinyl lactones (**8a—c**), formed when homoenolate dianion (**6**) condensed with pivalic aldehyde (**4a**), benzaldehyde (**4b**), and pinacolone (**4c**), gave pairs of β-sulphide γ-lactones (**10a—c**) which were shown to be enantiomers. This means the diastereoisomeric starting compounds (**8a—c**) have the same relative stereochemistry at the two carbon atoms, but opposite absolute configurations at both these centres.*

* These stereochemical relationships could also be deduced from the reaction of sulphinyl γ-lactones (**8**) under Pummerer conditions, which was expected to cause epimerization at sulphur. Specifically, when we treated (+)-4-t-butyl-3-tolylsulphinyl γ-lactone (**8a**), m.p. 95—97 °C, we obtained a mixture of starting compound and a product (**8a**), m.p. 98—100 °C; $[\alpha]_D^{15}$ −211°, which was shown to be the enantiomer of the second 4-t-butyl-3-tolylsulphinyl γ-lactone (**8a**), m.p. 98—100 °C; $[\alpha]_D^{15}$ +211° we isolated from the condensation of the sulphinylpropionic acid (**3a**) with pivalic aldehyde.

The same behaviour was observed when sulphinyl lactones (**8b**) [higher R_F compound] and (**8c**) [m.p. 87—89 °C] were similarly treated. All compounds could be isolated in pure form by flash chromatography, and their structures were determined by their ^{1}H n.m.r. spectra and $[\alpha]_D^{15}$ values (see Experimental section).

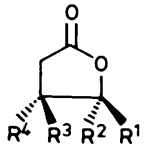


(+)-(3*S*,4*R*,R_S)-(**8a—c**)

(+)-(3*S*,4*R*,R_S)-(**8a—c**)

(−)-(3*S*,4*R*,S_S)-(**8a—c**)

Table 3. Positive nuclear Overhauser effect experiments in degassed solvents, measured on a 300 MHz spectrometer



Compound	Solvent	Irradiated peak and percentage enhancement upon irradiation (error *ca.* 0.2%) R¹	R²	R³	R⁴
(−)-(3*R*,4*S*)-(**10c**)	$CDCl_3$	*a*	irr.	0.90	0.25[b]
		irr.	4.0	20.0	1.32[b]
	C_6D_6	*a*	irr.	0.80	0.19[b]
		irr.	1.90	9.54	0.33[b]
(−)-(3*R*,4*S*)-(**10d**)	$CDCl_3$	*a*	irr.	2.10	*a*
(−)-(3*R*,4*R*)-(**10d**)	$CDCl_3$	irr.	*a*	11.8	*a*
(+)-(3*S*,4*R*)-(**10e**)	$CDCl_3$	irr.	10.18[c]	*a*	1.46
(−)-(3*R*,4*R*)-(**10e**)	$CDCl_3$	irr.	5.60[c]	10.50	*a*

[a] Unmeasured value. [b] Methyl group of *p*-tolylthio substituent. [c] Vinyl proton.

^{1}H N.m.r. spectroscopy was used to determine the relative stereochemistry of ring substituents in compounds (**10a**—**e**); and specifically, aromatic solvent-induced shifts (ASIS) were employed for γ-monosubstituted products (**10a**,**b**), and nuclear Overhauser effects (n.O.e.) for γ-disubstituted compounds (**10d**,**e**). On changing the n.m.r. solvent from $CDCl_3$ to C_6D_6 (Table 1) the Δδ values for ring protons of compounds (**10a**,**b**) are almost constant, revealing that there is a nearly equal solvation on each side of the ring. Bulkier substituents on the lactone are therefore in a *trans* relationship, since significantly greater differences in Δδ values of the same protons were observed for similarly *cis*-substituted β-sulphide γ-lactones.[13] The ASIS technique could not give unambiguous information for γ-disubstituted lactones (**10c**—**e**) and therefore n.O.e. experiments were undertaken. Our results are reported in Table 3 and their inspection shows that diastereoisomeric β-tolylthio γ-lactones have a marked difference in percentage enhancement of 3-H on irradiation of the methyl group at C-4. Compounds with a higher n.O.e. must have irradiated and enhanced nuclei in a *cis* relationship.

Absolute stereochemistry of (+)-(*R*)-5-methyl-5-phenylfuran-2(5H)-one (**2d**) and of (+)-(*R*)-4-methyl-γ-hexanolide (**1f**) have already been reported in the literature.[10,25] For butenolides (**2a**), (**2b**), and (**2e**) the absolute configuration was determined by use of the empirical correlation existing between the chirality at the γ-carbon atom and the sign of the $\pi \rightarrow \pi^*$ transition in the 210 nm region of their c.d. spectra.[26] This rule correctly predicted also the absolute configurations of butenolides (**2c**,**d**) which were known through *X*-ray analyses and correlation[10] respectively. In this way, having already determined the relative stereochemistry, we then established absolute configurations at all chiral centres of sulphinyl lactones (**8a**—**e**) and these are reported in Table 1.

Through a careful inspection of ^{1}H n.m.r. spectra of all isolated sulphinyl lactones (**8**) (Table 1) it was found that a good correlation exists between the pattern of 2-H_2-3-H protons and the relative stereochemistry of the C-3 and sulphur centres. Lactones (3*R*,4*S*,R_S)-(**8a**—**e**) all show an ABX system in which the AB and X parts are represented by protons on C-2 and C-3 respectively [O–C(O)–CH_AH_B–CH_X–S(O)Ar]. In contrast, in (3*S*,4*R*,R_S)-(**8a**—**e**) diastereoisomers, one of the two hydrogens on C-2 shifts to lower field and becomes isochronous with 3-H [O–C(O)–CH_AH_X–CH_B–S(O)Ar]. This probably means that in the 3*R*,4*S*,R_S sulphinyl lactones (**8a**—**e**) the sulphoxide group exerts a similar deshielding effect on the two C-2 protons, while in 3*S*,4*R*,R_S diastereoisomers, which are also more prone to undergo thermal elimination of toluene-*p*-sulphenic acid, one of these two protons is more strongly deshielded than the other one. Through these observations, as chemical correlation had already given absolute configurations at the C-4 and sulphur centres, we could assign chirality also at C-3 of the sulphinyl lactones (**8f**), and similarly we determined the relative stereochemistry of the spirolactones (**8g**).

To confirm our stereochemical assignments, we made an *X*-ray crystal structure determination on (−)-(3*R*,4*S*)-4-methyl-4-t-butyl-3-(*p*-tolylthio)butanolide (**10c**) and of (−)-(3*R*,4*R*)-4-(cyclohex-1-enyl)-4-methyl-3-(*p*-tolylthio)butanolide (**10e**). Also, absolute stereochemistry could be obtained with this technique for the tolylthio compound (3*R*,4*S*)-(**10c**).

Moderate chemical and optical yields of the process and loss of some sulphinyl hydroxy acids (**7c**—**e**) through side-product formation [*i.e.*, 4-hydroxy acids (**9**)] prevent us from giving a detailed discussion on the mechanism of deprotonation of the (+)-(*R*)-sulphinylpropionic acid (**3a**) and of the condensation of the product homoenolate dianion (**6**) on carbonyl compounds (**4**). Some general considerations can nevertheless be made. Prevailing diastereoisomers of γ-lactones (**8**) have in all cases opposite stereochemistry at the sulphinylated carbon and, since in the adopted reaction conditions the generated carbanion is probably stereochemically stable,[27] we can deduce that deprotonation occurs with low stereospecificity.* Since *p*-tolyl alkyl sulphoxides are generally metalled with high diastereoselection,[21] the particular behaviour of (+)-(*R*)-(**3a**) is probably due to the presence of the polar lithium carboxylate group in the sulphoxide molecule. Similarly to other cases,[27] formation of *threo* adducts[28] is preferred and this implies that when replacement of the *pro-R* proton of compound (**3a**) occurs, the carbanion adds preferentially to the *si* face of the carbonyl to give γ-hydroxy carboxylic acids (3*S*,4*R*,R_S)-(**7**), and when the *pro-S* proton is replaced an opposite stereochemical course is followed. Therefore, single diastereoisomeric anions (**6**) attack enantiotopic faces of the carbonyl group with medium (**2d**—**f**) to high (**2a**—**c**) diastereoselection.

Crystal Structure Determination of (−)-(3R,4S)-4-*Methyl*-4-*t-butyl*-3-(p-*tolylthio*)*butanolide* (**10c**) *and* (−)-(3R,4R)-4-(*Cyclohex*-1-*enyl*)-4-*methyl*-3-(p-*tolylthio*)*butanolide* (**10e**).—Prismatic crystals of compound (**10c**), recrystallized from carbon tetrachloride, and of compound (**10e**), from diethyl ether, were mounted on a glass fibre on a Philips PW1100 diffractometer, and were used for all the subsequent analysis. Crystal data and data-collection conditions are reported in Table 4. For compound (**10c**) data were empirically corrected for absorption using ψ-scan values of two reflections ($3\bar{1}3$ and $4\bar{1}4$), while no correction was deemed necessary for compound (**10e**). The calculated structure factors for compound (**10c**) were also corrected for secondary extinction according to the formula $F_c' = F_c(1 - x|F_c|^2/\sin\theta)$, with x 6.235 × 10^{-6} (refined value). Both structures were solved using the program MULTAN[29] and refined by blocked full-matrix least-squares using the SHELX set of programs.[30] In compound (**10c**) anisotropic thermal factors were used for all the non-hydrogen atoms; in compound (**10e**) the sulphur atom and the lactone

* To confirm this, we treated the anion of racemic acid (**3a**) with non-prochiral cyclopentanone (**4g**) and the two diastereoisomeric β-sulphinyl γ-lactones (4R*,R_S^*)-(**8g**) and (4R*,S_S^*)-(**8g**) were isolated. With similar substrates Iwai *et al.* claimed to have obtained a single compound (K. Iwai, H. Kosugi, A. Miyazaki, and H. Uda, *Synth. Commun.*, 1976, **6**, 357).

Table 4. Crystal data and data-collection conditions for compounds (**10c**) and (**10e**)

	(**10c**)	(**10e**)
Chemical formula	$C_{16}H_{22}O_2S$	$C_{18}H_{22}O_2S$
Molecular weight	278.41	302.43
Crystal system	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$ (No. 19)	$P2_1$ (No. 4)
a (Å)	22.507(4)	13.516(3)
b (Å)	10.724(2)	6.416(2)
c (Å)	6.406(2)	9.717(2)
β (°)		96.70(8)
V (Å^3)	1 546	837
Z	4	2
D_c (g cm^{-3})	1.196	1.200
Radiation	Cu-K_α graphite-monochromated (λ 1.5418 Å)	Mo-K_α graphite-monochromated (λ 0.710 69 Å)
μ (cm^{-1})	17.8	1.86
Crystal dimensions (mm)	0.3 × 0.2 × 0.2	0.4 × 0.2 × 0.2
Scan mode	θ/2θ	θ/2θ
Scan speed (° s^{-1})	0.08	0.025
Scan width (°)	1.1	1.1
θ range (°)	6.5—56.0	2.0—25.0
Total background (s)	10	24
Standard reflections	3 every 180′: 10 4 2, $\bar{1}0$ 4 $\bar{2}$, $\bar{1}0$ $\bar{4}$ $\bar{2}$	3 every 120′: $\bar{2}$ 1 1, $\bar{2}$ $\bar{1}$ 1, 2 $\bar{1}$ $\bar{1}$
No. of independent reflections	1 385	1 623
Observed reflections	1 205 [$F_o/\sigma(F_o) > 2.0$]	1 050 [$F_o/\sigma(F_o) > 1.5$]
R[a]	0.0497	0.0653
R_w[b]	0.0520	0.0703

[a] $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $R_w = \Sigma w^{\frac{1}{2}}||F_o| - |F_c||/\Sigma w^{\frac{1}{2}}|F_o|$.

moiety were refined anisotropically, while the tolyl and the cyclohexenyl groups were treated isotropically. Hydrogen-atom contributions in their calculated positions (assuming a C–H distance of 1.08 Å) were taken into account using thermal factors differentiated for each group. The function minimized was $\Sigma w(|F_o| - |F_c|)^2$. The weighting scheme was $w = k/\{\sigma^2(F_o) + g|F_o|^2\}$ with k 0.1212 and g 0.064 358 for (**10c**), and k 2.4742 and g 0.000 933 for (**10e**) (refined values). The final disagreement factors are reported in Table 4. Scattering factors, with the inclusion of $\Delta f'$ and $\Delta f''$ in both cases, were taken from ref. 31. The absolute configuration of compound (**10c**) was determined through the Hamilton test.[32] The experimental $\mathcal{R} = R^1_{2w}/R^2_{2w}$ (where $R_{2w} = \{\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2\}^{\frac{1}{2}}$ and 1 and 2 refer to the two enantiomers) is 1.164, while the theoretical value at the 99.5% probability level is 1.004 in our case. Fractional co-ordinates are in Table 5. [Of course, for compound (**10c**) the co-ordinates correspond to the correct absolute configuration.] Selected bond lengths and angles are in Table 6 and some torsion angles in Table 7. Isotropic and anisotropic thermal parameters, calculated hydrogen co-ordinates, and relevant least-squares planes and lines are deposited as Supplementary Publication No. SUP 56560 (7 pp.).*

ORTEP[33] views of compounds (**10c**) and (**10e**) are shown in Figure 1 and 2 respectively. In both cases the five-membered lactone ring adopts an 'envelope' conformation with C(1), C(2), C(4), and O(1) lying approximately in the same plane [the maximum deviations from the least-squares planes being for C(1) 0.020(4) Å in (**10c**) and 0.033(10) Å in (**10e**)], while C(3) is above it at a distance of 0.492(4) Å in (**10c**) and 0.484(7) Å in (**10e**). The puckering angles, defined as the dihedral angle

Table 5. Fractional co-ordinates.

Compound (**10c**)

Atom	x	y	z
S	0.604 77(5)	0.241 20(9)	−0.513 27(18)
O(1)	0.648 7(1)	−0.116 1(2)	−0.486 7(5)
O(2)	0.740 9(1)	−0.130 3(3)	−0.367 7(6)
C(1)	0.698 7(2)	−0.067 2(4)	−0.407 3(7)
C(2)	0.692 6(1)	0.069 8(3)	−0.386 3(7)
C(3)	0.625 6(1)	0.091 8(3)	−0.401 9(6)
C(4)	0.604 6(2)	−0.019 5(3)	−0.539 1(6)
C(5)	0.614 1(2)	0.007 1(5)	−0.774 5(6)
C(6)	0.542 9(2)	−0.074 0(4)	−0.485 9(7)
C(7)	0.538 6(2)	−0.109 4(6)	−0.254 6(8)
C(8)	0.494 2(2)	0.018 5(5)	−0.537 8(13)
C(9)	0.532 2(2)	−0.193 8(4)	−0.613 4(10)
C(10)	0.633 3(2)	0.350 6(3)	−0.333 7(6)
C(11)	0.651 7(2)	0.325 3(4)	−0.130 0(7)
C(12)	0.673 6(2)	0.419 1(3)	−0.004 0(7)
C(13)	0.677 1(2)	0.541 3(4)	−0.073 9(7)
C(14)	0.657 7(2)	0.567 3(4)	−0.278 3(8)
C(15)	0.636 6(2)	0.472 4(4)	−0.405 8(8)
C(16)	0.700 3(2)	0.644 1(4)	0.065 9(10)

Compound (**10e**)

Atom	x	y	z
S	0.193 98(14)	1/4	0.155 32(20)
O(1)	0.407 4(4)	0.003 5(10)	0.240 1(6)
O(2)	0.402 6(5)	−0.225 8(13)	0.065 8(7)
C(1)	0.390 2(7)	−0.051 8(18)	0.105 4(9)
C(2)	0.354 1(6)	0.130 7(15)	0.019 6(8)
C(3)	0.324 6(5)	0.289 9(13)	0.125 7(7)
C(4)	0.393 2(5)	0.225 1(15)	0.257 7(7)
C(5)	0.495 1(6)	0.330 6(17)	0.258 2(9)
C(6)	0.350 5(5)	0.262 4(14)	0.392 1(7)
C(7)	0.325 2(6)	0.109 5(15)	0.470 5(8)
C(8)	0.285 8(7)	0.142 8(15)	0.609 3(8)
C(9)	0.301 7(7)	0.360 5(15)	0.661 6(10)
C(10)	0.272 1(7)	0.511 8(18)	0.547 4(10)
C(11)	0.339 2(7)	0.489 0(15)	0.431 4(9)
C(12)	0.133 9(6)	0.326 5(13)	−0.009 1(8)
C(13)	0.072 1(7)	0.182 6(16)	−0.081 1(9)
C(14)	0.015 4(7)	0.234 9(18)	−0.206 9(9)
C(15)	0.022 1(7)	0.428 8(16)	−0.256 7(9)
C(16)	0.082 8(7)	0.574 7(17)	−0.188 7(10)
C(17)	0.138 9(7)	0.522 2(17)	−0.062 1(9)
C(18)	−0.039 6(9)	0.492 4(22)	−0.395 2(11)

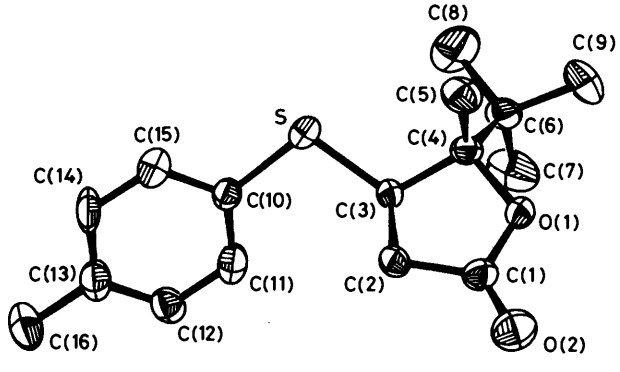


Figure 1. An ORTEP view of compound (**10c**). H atoms have been omitted for clarity

* For details of the Supplementary Publications Scheme see Instructions for Authors (1986), in *J. Chem. Soc., Perkin Trans. 1*, 1986, issue 1. Structure factors are available from the editorial office on request.

Table 6. Selected bond lengths (Å) and angles (°)

	Compound (**10c**)	Compound (**10e**)
S–C(3)	1.816(4)	1.839(7)
S–C(10)/(12)	1.764(4)	1.774(8)
C(1)–O(1)	1.342(5)	1.350(11)
C(1)–O(2)	1.193(5)	1.199(14)
C(1)–C(2)	1.481(5)	1.486(14)
C(2)–C(3)	1.529(5)	1.536(12)
C(3)–C(4)	1.555(5)	1.549(9)
O(1)–C(4)	1.473(4)	1.447(12)
C(4)–C(5)	1.549(6)	1.535(12)
C(4)–C(6)	1.546(5)	1.506(10)
C–C(Ph)[a]	1.391(6)	1.377(13)
C(1)–O(1)–C(4)	112.0(3)	111.3(7)
O(1)–C(1)–O(2)	121.7(4)	122.8(8)
O(1)–C(1)–C(2)	110.1(3)	110.2(8)
O(2)–C(1)–C(2)	128.1(4)	127.1(8)
C(1)–C(2)–C(3)	103.8(3)	104.0(7)
S–C(3)–C(2)	114.6(3)	110.0(5)
S–C(3)–C(4)	112.2(3)	109.0(5)
C(2)–C(3)–C(4)	102.5(3)	101.6(6)
C(3)–C(4)–O(1)	102.0(3)	103.9(6)
C(3)–C(4)–C(5)	111.6(3)	109.5(6)
C(3)–C(4)–C(6)	116.0(3)	115.0(6)
C(5)–C(4)–C(6)	114.0(3)	111.2(7)
C(5)–C(4)–O(1)	105.0(3)	107.6(7)
C(6)–C(4)–O(1)	106.8(3)	109.2(6)
C(3)–S–C(10)/(12)	103.7(2)	99.6(3)

[a] Average value for the six C–C bonds of the phenyl ring.

Table 7. Some relevant torsion angles (°)

	Compound (**10c**)	Compound (**10e**)
S–C(3)–C(4)–O(1)	152.8(2)	86.7(6)
S–C(3)–C(4)–C(5)	41.2(4)	−158.6(6)
S–C(3)–C(4)–C(6)	−91.6(3)	−32.6(8)
O(1)–C(1)–C(2)–C(3)	16.7(4)	−15.0(10)
O(2)–C(1)–C(2)–C(3)	−165.1(4)	164.3(10)
C(2)–C(1)–O(1)–C(4)	3.1(4)	−4.6(10)
O(2)–C(1)–O(1)–C(4)	−175.3(4)	176.0(9)
C(1)–C(2)–C(3)–C(4)	−28.1(4)	26.6(8)
C(1)–C(2)–C(3)–S	−149.9(3)	−88.7(7)
C(1)–O(1)–C(4)–C(3)	−21.1(4)	22.1(9)
C(1)–O(1)–C(4)–C(5)	95.4(4)	−94.0(8)
C(1)–O(1)–C(4)–C(6)	−143.2(3)	145.2(7)
C(2)–C(3)–C(4)–O(1)	29.4(3)	−29.3(8)
C(2)–C(3)–C(4)–C(5)	−82.2(4)	85.3(8)
C(2)–C(3)–C(4)–C(6)	145.0(3)	−148.6(7)
C(2)–C(3)–S–C(10)/(12)	−63.3(3)	−67.8(6)
C(4)–C(3)–S–C(10)/(12)	−179.6(3)	−178.3(5)

between this and the plane defined by C(2), C(3), and C(4), are 30.5(3)° and 29.6(6)° respectively. The conformation so defined is close to that found for other γ-lactones,[13,34] where the atoms C–C(O)–O–C are always found to lie on the same plane while the fifth atom is above it at a distance within the range 0.47–0.59 Å, quite independently of the number or position of the substituents.

The relative configuration of the ring and of the substituents is best described by the torsion angles listed in Table 7. The sulphur atom is in an equatorial position *cis* to methyl C(5) in (**10c**), while they are *trans* diaxial in (**10e**). In the latter compound the bond S–C(3) is almost perpendicular to the plane of the envelope [87.5(4)°], as found for example in (4*R**,5*R**)-4,5-dihydro-4-phenylthio-5-t-butylfuran-2(3H)-one.[13]

Bond lengths and angles are as expected. Some distortions in the bond angles at C(3), C(4), and S may be ascribed to steric interactions between the substituents, most notably

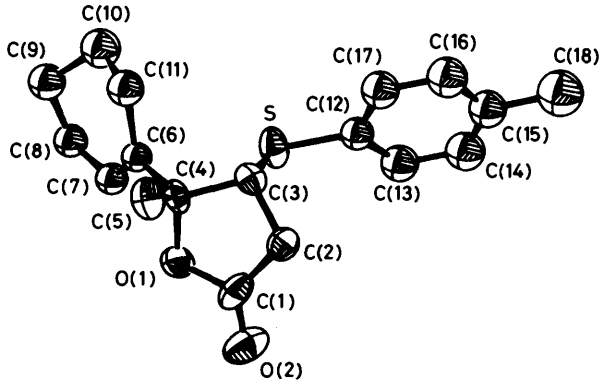


Figure 2. An ORTEP view of compound (**10e**). H atoms have been omitted for clarity

H[C(3)]···H[C(11)] (2.10 Å), S···C(5) [3.025(5) Å], and H[C(3)]···C(7) {2.66 Å, with H[C(3)]···H$_1$[C(7)] 1.96 Å} in (**10c**) and S···C(6) [2.939(7) Å] and H[C(3)]···C(5) (2.67 Å) in (**10e**).

No short intermolecular contacts are present and the molecules are held together in the crystal by Van der Waals forces.

Conclusions.—Although the methodology we describe here proceeds on the whole in moderate yields, it appears to be quite general and gives both enantiomers of saturated and α,β-unsaturated γ-lactones. Also the γ-disubstituted γ-lactones, for which only some specific syntheses have been reported,[3d,8b,9b,10,25] can be obtained. The synthetic sequence was applied to the preparation of natural products or their structural analogues such as (+)-(*R*)-4-ethyl-4-methylbutan-4-olide (**1f**) which is a component of tobacco flavour[25] and (+)-(*R*)-4-(cyclohex-1-enyl)-4-methylbutan-4-olide (**1e**) which is an isomer of naturally occurring norbisabolide.[1] The synthesis of compounds bearing a hydroxy function in the γ-side-chain has also been realized[17b] and will be reported in due course. Moreover, spectroscopic studies and *X*-ray analyses allowed the assignment of the absolute stereochemistry of all the reported compounds and a useful empirical correlation was observed, for β-sulphinyl lactones (**8**), between the relative configuration of chiral centres and their ^{1}H n.m.r. spectra.

Experimental

I.r. spectra were taken on a Perkin-Elmer 137 Infracord Spectrophotometer, ^{1}H n.m.r. spectra on a Varian EM-390 or on a Bruker CPX-300 spectrometer using tetramethylsilane as internal standard and $CDCl_3$ as solvent unless otherwise stated. ^{13}C N.m.r. spectra were registered on a XL-100 instrument; $[\alpha]_D^{15}$ values were obtained on a Jasco DIP-181 polarimeter and c.d. measurements were taken on a Jasco J 500A spectrophotometer. Mass spectra were registered on an Hitachi-Perkin-Elmer RMU 6D or on a VG MM ZAB 2F instrument. M.p.s are uncorrected and were obtained on a capillary apparatus; t.l.c. were run on silica gel 60 F_{254} Merck. For condensation reactions of (+)-(*R*)-(**3a**) an argon atmosphere was used; THF was freshly distilled from lithium aluminium hydride and di-isopropylamine was distilled from calcium hydride and stored over molecular sieves (4 Å). A 1.6M-solution of n-butyl-lithium in hexanes (Aldrich) was employed. In other cases commercially available reagent grade solvents were employed without purification.

Reaction of (+)-(R)-*Methyl* p-*Tolyl Sulphoxide* (**5a**).—A solution of LDA [prepared from di-isopropylamine (5.04 ml,

35.6 mmol) and a solution of n-butyl-lithium in hexanes (22.3 ml, 35.6 mmol)] in THF (34 ml) was cooled to −78 °C and treated dropwise with a solution of (+)-(*R*)-(**5a**) (5.0 g, 32.42 mmol) in THF (37 ml). A suspension of lithium bromoacetate [prepared from bromoacetic acid (6.75 g, 48.6 mmol) and lithium hydride (5.15 g, 64.84 mmol)] in THF (50 ml) was added at the same temperature to the yellow solution of the α-sulphinyl anion. After the mixture had been stirred for 5 min at −78 °C, saturated aqueous ammonium chloride was added, then 10M-hydrochloric acid was added dropwise (to pH 2). Extraction with ethyl acetate and crystallization gave (+)-(*R*)-(**3a**), (5.22 g, 76%) m.p. 131—133 °C (from ethyl acetate) (Found: C, 56.6; H, 5.7; S, 15.0. $C_{10}H_{12}O_3S$ requires C, 56.58; H, 5.70; S, 15.11%); $[\alpha]_D^{15}$ +188° (*c* 0.7 in MeOH); $\nu_{max.}$(KBr) 3 500—2 200 (CO_2H), 1 710, and 1 010 cm^{-1}; δ_H($CDCl_3$) 2.40 (3 H, s, Me), 2.5—3.5 (4 H, m, $[CH_2]_2$), and 7.25—7.65 (4 H, q, ArH); δ_C ($CDCl_3$) 21.40 (CH_3), 26.44 (CH_2CO_2), 50.85 (CH_2SO), 124.21, 130.06, 138.50, and 142.00 (C aryl), and 174.35 (CO).

Reaction of (+)-(**R**)-*Ethyl p-Tolyl Sulphoxide* (**5b**).—Formation of the anion of (+)-(*R*)-(**5b**), addition of lithium bromoacetate, and work-up were as described above for (**5a**). Compound (+)-(3*S*,R_S)-(**3b**) was isolated by chromatography in 58% yield, m.p. 53—55 °C (from n-hexane–diethyl ether) (Found: C, 58.5; H, 6.2; S, 14.2. $C_{11}H_{14}O_3S$ requires C, 58.38; H, 6.24; S, 14.17%); $[\alpha]_D^{15}$ +130° (*c* 0.7 in $CHCl_3$); $\nu_{max.}$(Nujol) 3 500—2 200, 1 715, and 1 030 cm^{-1}; δ_H($CDCl_3$) 1.04 (3 H, d, *J* 7.0 Hz, 3-Me), 2.30 (1 H, q, ^2J 16 and ^3J 8 Hz, 2-H), 2.40 (3 H, s, ArMe), 2.90 (1 H, q, ^3J 6 Hz, 2-H), 3.20 (1 H, m, 3-H), and 7.2—7.6 (4 H, q, ArH); δ_C($CDCl_3$) 11.00 (CH_3), 21.35 (CH_3), 34.65 (CH_2), 54.96 (CHSO), 124.93, 129.74, 136.09, and 141.83 (aryl C), and 173.70 (CO).

Condensation of (+)-(**R**)-3-(p-*Tolylsulphinyl*)*propionic Acid* (**3a**) *with Carbonyl Compounds* (**4a**—**f**).—A solution of the (+)-(*R*)-sulphinylpropionic acid (**3a**) (5.0 g, 23.5 mmol) in THF (300 ml) was added dropwise to a stirred solution of LDA (47.5 mmol) in THF (210 ml) at −60 °C. A solution of the carbonyl compound (28.2 mmol) in THF (50 ml) was added immediately to the resulting yellow anion at −78 °C, and after being stirred at the same temperature for 3 min the reaction mixture was quenched with saturated aqueous ammonium chloride. The aqueous layer was acidified with dil. hydrochloric acid (to pH 2), and extracted with ethyl acetate (3 × 150 ml); the extract was dried with sodium sulphate and evaporated under reduced pressure. The crude mixture of 4-hydroxy-3-(*p*-tolylsulphinyl) acids (**7**) and the respective β-sulphinyl γ-lactones (**8**) was left at room temperature until no more acids (**7**) were present [t.l.c. analysis, ethyl acetate–chloroform–acetic acid (25 : 25 : 1) as eluant]. When ketones (**4c**—**e**) were used as electrophiles, at this point the crude reaction mixture was diluted with ether, washed with saturated aqueous sodium hydrogen carbonate, and then the organic layer was dried, evaporated under reduced pressure, and flash chromatographed on silica gel. Pure sulphinyl lactones (**8a**—**f**) were isolated and yields, and physical and some spectral properties, are reported in Table 1. Correct microanalyses (C ±0.14, H ±0.20, S ±0.12%) were also obtained.

The aqueous sodium hydrogen carbonate washings were acidified to pH *ca.* 2 with dil. hydrochloric acid, and were then extracted with ethyl acetate. The combined organic layers were dried and evaporated to dryness. Starting from pinacolone (**4c**), flash chromatography ($CHCl_3$/AcOEt/AcOH) gave 0.38 g (4.5%) of (−)-(*E*)-4-hydroxy-4,5,5-trimethylhex-2-enoic acid (**9c**), m.p. 100—101 °C (from AcOEt) (Found: C, 62.9; 9.4. $C_9H_{16}O_3$ requires C, 62.76; H, 9.36%); $[\alpha]_D^{20}$ −17.2° (*c* 2.0 in $CHCl_3$); $\nu_{max.}$(KBr) 3 410 and 1 710 cm^{-1}; δ_H(90 MHz) 1.00 (9 H, s, Bu^t), 1.79 (3 H, s, Me), 6.06 (1 H, d, *J* 14 Hz, 2-H), 7.27 (1 H, d, 3-H); *m/z* 192 (M^+).

Similarly, starting from 1-acetylcyclohexene (**4e**) (+)-(*E*)-4-(cyclohex-1-enyl)-4-hydroxy-2-pent-2-enoic acid (**9e**) (0.36 g, 4.2%) was obtained, m.p. 106—108 °C (from diethyl ether) (Found: C, 67.5; H, 8.3. $C_{11}H_{16}O_3$ requires C, 67.32; H, 8.22%); $[\alpha]_D^{15}$ +2.41° (*c* 2.1 in $CHCl_3$); $\nu_{max.}$(KBr) 3 360 and 1 700 cm^{-1}; δ_H(90 MHz) 1.48 (3 H, s, Me), 1.4—1.7 (4 H, m, $CH_2[CH_2]_2CH_2$), 1.8—2.2 (4 H, m, $[C{=}CH_2]_2$), 5.78 (1 H, m, ring =CH), 6.03 (1 H, d, *J* 15 Hz, 2-H), and 7.08 (1 H, d, 3-H); *m/z* 196 (M^+).

Condensation of Racemic Sulphoxide (**3a**) *with Cyclopentanone* (**4g**).—The general condensation procedure was followed and flash chromatography [benzene–ethyl acetate (60:40)] gave two diastereoisomers. The higher-R_F compound was (4*R**,S_S^*)-4-(*p*-tolylsulphinyl)-1-oxaspiro[4.4]nonan-2-one (**8g**) (1.28 g, 28%), R_F 0.55, m.p. 83—85 °C (from ethyl acetate–n-hexane); $\nu_{max.}$ 1 775 and 1 055 cm^{-1}; δ_H(90 MHz) 1.7—2.1 (8 H, m, $[CH_2]_4$), 2.15—2.50 (1 H, m, 3-H), 2.39 (3 H, s, ArMe) 2.97—3.33 (2 H, m, 3- and 4-H), and 7.28—7.52 (4 H, q, ArH); δ_C($CDCl_3$) 66.14 (C-4). The lower-R_F compound was (4*R**,S_S^*)-(**8g**) (1.77 g, 48%), R_F 0.50; m.p. 111—113 °C (from ether–n-hexane); $\nu_{max.}$ 1 775 and 1 050 cm^{-1}; δ_H(90 MHz) 1.70—2.20 (8 H, m, $[CH_2]_4$) 2.41 (3 H, s, ArMe), 2.20—2.65 (2 H, m, 3-H_2), 3.61 (1 H, t, *J* 3.1 Hz, 4-H), and 7.23—7.67 (4 H, q, ArH); δ_C ($CDCl_3$) 21.46 (Me), 22.57, 23.81, 31.31, 33.72, and 39.75 (CH_2), 66.13 (C–SO), 96.24 (CO), 125.08, 130.28 (C aryl), and 138.72, 143.21, and 171.45 (C aryl and C=O).

Reductive Desulphenylation of Butanolides (+)-(**8c**—**f**).—A solution of a β-sulphinyl-γ-lactone (**8**) (1 mmol) and sodium dihydrogen phosphate (4 mmol) in methanol (30 ml) was cooled to −40 °C and powdered 8% sodium amalgam was added. After 20 min at the same temperature, the mixture was filtered to remove the residue of amalgam (sintered glass filter), brine was added to the filtrate, and the reaction mixture was extracted with ether. Dehydration of the combined extracts with sodium sulphate, evaporation and chromatography of the residue gave saturated γ-lactones (**1c**—**f**) in optically pure form. Yields of the reaction and some spectral data of the products obtained are reported in Table 2. Correct microanalyses were also obtained (C ±0.13, H ±0.21%). (+)-(3*R*,4*S*,R_S)-4-Methyl-4-t-butyl-3-(*p*-tolylsulphinyl)-γ-butyrolactone (**8c**) gave (−)-(*R*)-4,5,5-trimethylhexan-4-olide (**1c**), and similarly (+)-(3*R*,4*S*,R_S)-4-methyl-4-phenyl-3-(*p*-tolylsul phinyl) -γ-butyrolactone (**8d**), (+)-(3*R*,4*S*,R_S)-4-(cyclohex-1-enyl)-4-methyl-3-(*p*-tolylsulphinyl)-γ-butyrolactone (**8e**), and (+)-(3*S*,4*R*,R_S)-4-ethyl-4-methyl-3-(*p*-tolylsulphinyl)-γ-butyrolactone (**8f**) gave respectively (+)-(*R*)-4-phenylpentan-4-olide (**1d**), (+)-(*R*)-4-(cyclohex-1-enyl)pentan-4-olide (**1e**), and (+)-(*R*)-4-methylhexan-4-olide (**1f**). Similarly, (+)-(3*S*,4*R*,R_S)-(**8c**), (+)-(3*S*,4*R*,R_S)-(**8d**) and (+)-(3*R*,4*R*,R_S)-(**8d**), and (+)-(3*S*,4*R*,R_S)-(**8e**) and (+)-(3*R*,4*R*,R_S)-(**8e**) gave (+)-(*S*)-(**1c**), (−)-(*S*)-(**1d**), and (−)-(*S*)-(**1e**) respectively.

Pyrolyses of β-*Sulphinyl* γ-*Lactones* (+)-(**8a**—**e**).—A solution of a compound (+)-(**8a**—**e**) (1 mmol) and ethylene glycol (5 mmol) in toluene (15 ml) was refluxed until no more starting material was present (10—90 min). Water was added, the two phases were separated, and the aqueous phase was extracted with ether. The combined organic phases were dried over sodium sulphate, then evaporated. The residue was flash chromatographed [particular care was used in the purification of (**2b**) as it tended to isomerize to the β,γ-unsaturated isomer] and α,β-unsaturated lactones (**2a**—**e**) were separated in yields reported in Table 2, where some spectral data are also reported. Correct microanalyses were obtained (C ±0.14, H ±0.24%).

(+)-(3*R*,4*S*,R_S)-4-(t-butyl)-3-(*p*-tolylsulphinyl)-γ-butyrolactone (**8a**) gave (+)-(*R*)-5-(t-butyl)furan-2(5*H*)-one (**2a**) and similarly, (+)-(3*R*,4*S*,R_S)-4-phenyl-3-(*p*-tolylsulphinyl)-γ-butyrolactone (**8b**), (+)-(3*R*,4*S*,R_S)-(**8c**), (+)-(3*R*,4*S*,R_S)-(**8d**), and (+)-(3*R*,4*S*,R_S)-(**8e**) gave, respectively, (+)-(*R*)-5-phenylfuran-2-(5*H*)-one (**2b**), (+)-(*R*)-5-methyl-5-(t-butyl)furan-2(5*H*)-one (**2c**), (+)-(*R*)-5-methyl-5-phenylfuran-2(5*H*)-one (**2d**), and (+)-(*R*)-5-(cyclohex-1-enyl)-5-methylfuran-2(5*H*)-one (**2e**). Similarly, (+)-(3*S*,4*R*,R_S)-(**8a**), (+)-(3*S*,4*R*,R_S)-(**8b**), (+)-(3*S*,4*R*,R_S)-(**8c**), (+)-(3*S*,4*R*,R_S)-(**8d**) and (+)-(3*R*,4*R*,R_S)-(**8d**), and (+)-(3*S*,4*R*,R_S)-(**8e**) and (+)-(3*R*,4*R*,R_S)-(**8e**) gave, respectively, (−)-(*S*)-(**2a**), (−)-(*S*)-(**2b**), (−)-(*S*)-(**2c**), (−)-(*S*)-(**2d**), and (−)-(*S*)-(**2e**).

Deoxygenation of the Sulphoxide Group of Lactones (+)-(**8a**—**e**).—A solution of a lactone (**8a**—**e**) (1 mmol) and sodium iodide (3.5 mmol) in acetone (15 ml) was cooled to −50 °C and a solution of TFAA (5 mmol) in acetone (5 ml) was added. The reaction mixture was left for 20 min, during which time its temperature rose to −20 °C. Excess of saturated aqueous sodium sulphite and of sodium hydrogen carbonate were added dropwise in that order until no more iodine was present and until CO_2 evolution had ceased, respectively. Acetone was evaporated off under reduced pressure and the mixture was extracted with ether. The extract was dried (sodium sulphate) and evaporated, and the residue was chromatographed to give β-tolylthio γ-lactones (**10a**—**e**) as reported in Table 1. Expected mass spectra and correct microanalyses were also obtained (C ±0.19, H ±0.26, S ±0.18%).

Epimerization of the Sulphoxide Group in β-*Sulphinyl* γ-*Lactones* (+)-(**8a**—**c**).—A solution of TFAA (2.0 mmol) in acetonitrile (3 ml) was added to a solution of a lactone (+)-(**8a**—**c**) (1 mmol) and 2,4,6-lutidine (2 mmol) in the same solvent (5 ml), while the temperature was maintained at 0 °C. After the mixture had been stirred at 0 °C for 30 min, a solution of copper(II) chloride in water (4 ml) was added and the mixture was left until it attained a temperature of 25 °C. After 2.5 h at 25 °C, the reaction mixture was extracted with ethyl acetate, the combined extracts were dried and evaporated, and the residue was chromatographed to give a 1:1 mixture of starting material and its epimer (at sulphur) in *ca.* quantitative yield.

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