Radical Cyclization of Unsaturated α-Sulphonyl Radicals. Preparation and Stereochemistry of Arylsulphonyl-tetrahydrofuran and -pyrrolidine

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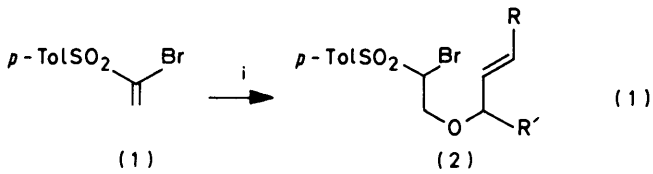
1-Bromo-1-*p*-tolylsulphonyl-2-allyloxyethane derivatives (2) reacted with tri-n-butyltin hydride in the presence of azobisisobutyronitrile (AIBN) in benzene at 70 °C for 7—13 h to afford 3-*p*-tolylsulphonyl-4-alkyltetrahydrofurans (5) in which the *trans*-isomer predominated. The substituents on the olefinic carbon have a marked effect on the stereochemical course of the cyclization. 1-Bromo-1-*p*-tolylsulphonyl-2-allylaminoethane (4) gave the pyrrolidine derivative (6) more stereoselectively. These results are discussed in terms of the steric factors. Similarly, 1-bromo-1-*p*-tolylsulphonyl-2-prop-2-ynyloxyethane derivatives (3) produced 3-*p*-tolylsulphonyl-4-alkylidenetetrahydrofurans (9).

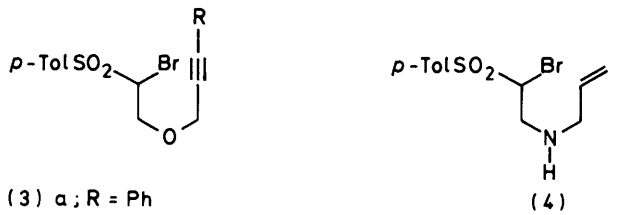
The halogen atoms of α-halogeno sulphones, $ArSO_2CH(Br)R$, in contrast to halogens α to other electron-withdrawing groups, resist substitution by external nucleophiles, presumably owing to polar and steric effects.[1] Accordingly, effective carbon–carbon bond formation at the α position of these sulphones is generally carried out by the alkylation of α-sulphonyl carbanions, $ArSO_2\dot{C}HR$.[2] As an alternative approach, we are interested in the reactivity of α-sulphonyl radicals, $ArSO_2\dot{C}HR$, since an e.s.r. study suggests that these are not stabilized by the sulphur function.[3] In other words, such radicals are expected to be reactive enough for effective carbon–carbon bond formation.

However, little is known about the chemistry of such reactive radicals.[4] We wish to report here the cyclization of these radicals leading to tetrahydrofuran and pyrrolidine derivatives, and the stereochemistry of the reaction.



(1) (2) (1)

Reagents: i, RCH=CHCHR'OH, NaH, room temp.



(3) a; R = Ph
b; R = n-C_5H_{11}

(4)

Results and Discussion

The starting materials, the alkoxy sulphones (2), were easily prepared by the modification of the known procedure using vinyl sulphone (1) [equation (1)].[5]

Similarly, the acetylenic sulphones (3) were prepared in good yield, while allylamine reacted with the vinyl sulphone (1) in the absence of base catalyst to give an addition product, the amino sulphone (4). The results are summarized in Table 1.

The alkoxy sulphones (2) were found to cyclize to give five-membered rings (5), but not six-membered ones, upon treatment with tri-n-butyltin hydride (1.1 equiv.) in the presence of a catalytic amount of AIBN in benzene at 70 °C for 7—13 h under nitrogen. The products (5) were purified by column chromatography followed by Kugelrohr distillation [equation (2)].

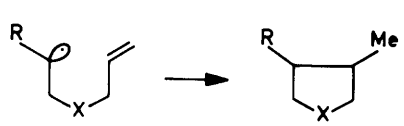
The stereochemistry of the product (5) was examined by both ^1H n.m.r. spectroscopy and g.l.c. The ratio of the two stereoisomers (*trans* : *cis*) was estimated to be 58.4 : 41.6 in the case of (5a). The methyl protons appeared as two doublets at δ 1.01 and 1.41 in $CDCl_3$. The *cis*-protons are believed to appear at lower field owing to the deshielding effect of the adjacent *cis*-*p*-tolylsulphonyl group. This assumption is supported by the fact that normal methyl protons such as those in n-propyl tolyl sulphone ($TolSO_2CH_2CH_2CH_3$) appear at δ 1.0—1.1, and is further confirmed by the following epimerization experiment.

Treatment of the above mixture of *trans* and *cis* isomers with potassium t-butoxide in t-butyl alcohol caused an increase in the peak area at δ 1.01 and a decrease in the peak area at δ 1.41.† Accordingly, *trans* and *cis* isomers were assigned as shown in equation (3). The *trans* : *cis* ratios of sulphones (5b) and (5c) were estimated by the similarity of their g.l.c. behaviour to that of (5a).

In a similar manner, the amino sulphone (4) cyclized to give the pyrrolidine derivative (6). The corresponding six-membered heterocycle, the piperidine derivative, was not isolated from the reaction mixture.

The results of these cyclizations and the stereochemistry of the products are summarized in Table 2.

The radical cyclization of the hex-5-enyl radical and related species has been well studied mainly from the mechanistic point of view.[7] Much effort has been devoted to exploring the cyclization mode leading to the five-membered and/or six-membered cyclic products. However, there are differing reports on the stereochemistry of the radical cyclization. For example, the following results have been reported in the literature.[8]



(7) (8)

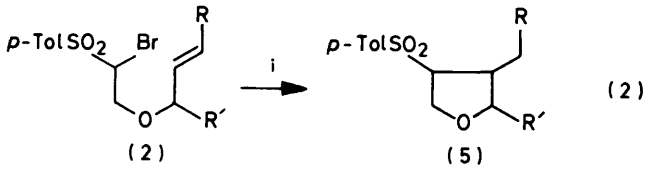
R = Me, X = CH_2 or O; *cis* : *trans* = 2.3 : 1.0
R = Ph, 2 = CH_2 *trans* only

† A similar epimerization has been reported in the case of 2-methyl-1-phenylsulphonylcyclopentane.[6]

Table 1. Alkoxy and amino sulphone derivatives (2), (3), and (4)

Sulphone	Yield (%)	Formula	Found (Required) (%) C	H
(2a)	87	$C_{12}H_{15}BrO_3S$	45.0 (45.15)	4.7 (4.73)
(2b)	93	$C_{13}H_{17}BrO_3S$	46.1 (46.30)	5.0 (5.08)
(2c)	97	$C_{15}H_{21}BrO_3S$	49.9 (50.09)	6.0 (5.86)
(2d)	78	$C_{13}H_{17}BrOS$	46.5 (46.85)	5.1 (5.14)
(3a)	85	$C_{18}H_{17}BrO_3S$	55.4 (54.97)	4.3 (4.35)
(3b)	93	$C_{17}H_{22}BrO_3S$	53.1 (52.71)	6.0 (5.98)
(4)	89	$C_{12}H_{16}BrNO_3S$ [a]	44.8 (45.29)	5.0 (5.07)

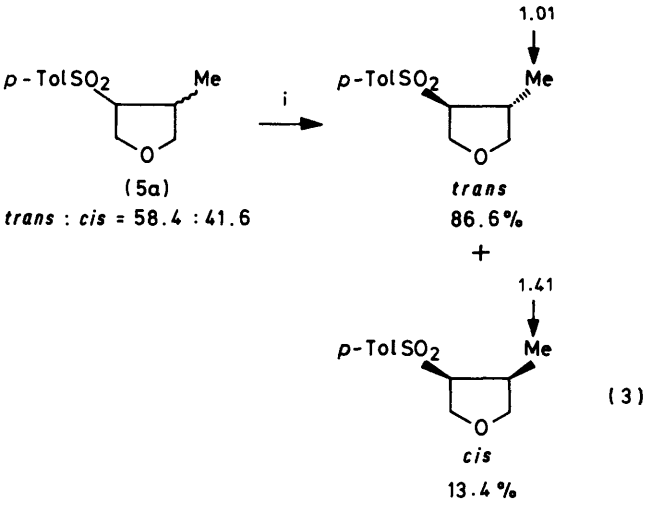
[a] Found: N, 4.3. Required N, 4.40%.



(2)

a; R = H, R′ = H
b; R = Me, R′ = H
c; R = Pr^n, R′ = H
d; R = H, R′ = Me

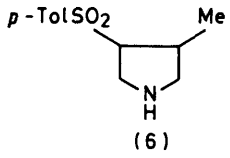
Reagents: i, Bu_3SnH, AIBN, 70 °C



(3)

Reagents: i, Bu^{t}OK, Bu^{t}OH, 80 °C, 8 h

The stereochemistry of the products was observed to change markedly on varying the substituent, methyl for phenyl group. These results have been explained in terms of the stability of the initial radicals (7). That is, a relatively stabilized benzylic radical affords the *trans* product only, while a less stabilized radical gives a *cis*-rich product. However, this explanation conflicts with our data, since the α-sulphonyl radical is not stabilized by the sulphonyl function (*vide supra*).

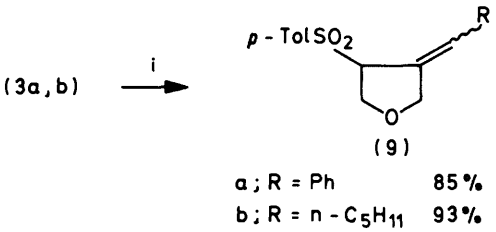


(6)

Table 2. Cyclization products and their stereochemistry

Product	Yield (%)	*trans* : *cis* Ratio
(5a)	67	58.4 : 41.6 [a,b]
(5b)	56	75.8 : 24.2 [b]
(5c)	63	99.7 : 0.3 [b]
(5d)	71	*c*
(6)	79	90.3 : 9.7 [a]

[a] N.m.r. analysis. [b] G.l.c. analysis. [c] A complex mixture of stereoisomers.



(4)

Reagents: i, Bu_3SnH, AIBN

We have recently reported a highly stereoselective radical cyclization, although the system used was different from the present one.[9] There is very little understanding of the stereochemistry of the radical cyclization at the present time. Although such information is highly desirable for consideration of the synthetic application of such a radical process.

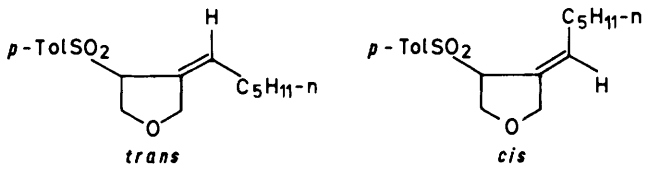
Two significant points arise from the data in Table 2. The first point is the remarkable effect of the substituents (R) on the olefinic carbon. The substrates having a more bulky substituent produce the more *trans*-rich product, the order of substituents (R) being H < Me < Pr^n. The n-propyl group causes an almost completely stereoselective reaction, and the *trans* isomer is formed in 99.7% yield. As far as we know, the stereochemistry has previously been discussed in only the simplest substrates without any substituent on the olefinic carbon, such as the species (7).

The second point is a difference between oxygen and nitrogen heterocycles. Thus, the selectivity was noticeably higher in the pyrrolidine derivative (6) (90.3% *trans*-product obtained) in comparison with the tetrahydrofuran (5a) (58.4% of *trans*-product). All these data indicate that steric factors are crucial in governing the stereochemistry in this case. For example, a PCK model shows that the arrangement of the *cis* isomer of the pyrrolidine derivative (6) is more unfavourable than that of the tetrahydrofuran (5a), presumably owing to the fact that the nitrogen atom is smaller than the oxygen. In other words, the smaller size of the pyrrolidine molecule may cause the compound to be more stereochemically sensitive than (5a), leading to a more *trans*-rich product. Our results also suggest that the steric factors due to the aromatic nucleus in the species (7; R = Ph) are important.

In addition to the cyclization involving an olefinic function described above, the acetylenic sulphone (3) also cyclized to give the five-membered rings (9) in good yield [equation (4)].

One olefinic proton of compound (9a) appeared as two

singlets at δ 6.55 and 6.73 in the ratio 54.5 : 45.5, respectively, while the same olefinic proton in (9b) appeared as only one triplet at δ 5.62, indicating the presence of only one stereoisomer. From the PCK model we tentatively assigned the preferred *trans* configuration for the carbon–carbon double bond.



In summary, α-sulphonyl radicals, in spite of the bulkiness of the sulphonyl function, cyclized cleanly to give five-membered heterocycles but not six-membered ones. Such a radical cyclization proceeds in a highly stereoselective manner leading to the formation of *trans*-rich products or exclusively the *trans* isomer. The present reactions demonstrate that the radical cyclization is equally effective for the preparation of functionalized heterocycles. Furthermore, both the bulkiness of the substituents and the heteroatoms in the ring govern the stereochemistry of the cyclization.

Experimental

I.r. spectra were taken in a film for liquids and KBr pellets for solids using a Hitachi EPI-S2 IR spectrometer. All n.m.r. spectra were measured in $CDCl_3$ with tetramethylsilane as internal standard using a Varian EM-360 or JEOL-C100 instrument. Gas chromatography of the cyclized products was carried out with a flame ionization detector using a column (SE-30). The oven temperature was programmed from 100—310 °C at 10 °C min^{-1}. The carrier gas was nitrogen, and the injector and detector were set at 300 and 280 °C, respectively.

1-*Bromovinyl* p-*Tolyl Sulphone* (1).—To a solution of *p*-tolyl vinyl sulphone (13.0 g, 71.34 mmol) in carbon tetrachloride (90 ml), was added bromine (4.3 ml, 81.38 mmol) dropwise at room temperature and the mixture was stirred for 24 h. The solvent was evaporated under reduced pressure at room temperature. The resulting yellow solid was chromatographed on silica gel (Wakogel C-200) eluting with dichloromethane to give 1,2-*dibromo*-1-p-*tolylsulphonylethane* as a colourless crystals (20.01 g, 82%), m.p. 72—74 °C (hexane–methanol), $\nu_{max.}$ 1 330 and 1 150 cm^{-1}; δ 2.5 (s, 3 H), 3.38—3.81 (m, 1 H), 4.14—4.48 (m, 1 H), 4.82—5.11 (m, 1 H), and 7.46, 7.95 (dd, *J* 8 Hz, 4 H) (Found: C, 31.7; H, 2.8. $C_9H_{10}Br_2O_2S$ requires C, 31.60; H, 2.94%).

To a solution of the above bromine addition product (19.77 g, 57.8 mmol) in dry dichloromethane (120 ml), was added triethylamine (9.4 ml, 67.43 mmol) dropwise during 10 min, and the mixture was stirred for 3.5 h. It was then washed with water (50 ml × 3), dried ($MgSO_4$), the solvent evaporated, and the resulting dark brown solid recrystallized from hexane to give colourless crystals (1) (10.49 g, 70%), m.p. 71—72 °C, $\nu_{max.}$ 1 300 and 1 155 cm^{-1}; δ 2.45 (s, 3 H), 6.23 (d, *J* 2.5 Hz, 1 H), 7.07 (d, *J* 2.5 Hz, 1 H), and 7.36, 7.86 (dd, *J* 8 Hz, 4 H) (Found: C, 41.3; H, 3.5. $C_9H_9BrO_2S$ requires C, 41.39; H, 3.47%).

General Procedure for the Michael Addition of Allylic or Prop-2-ynyl Alcohols to Vinyl Sulphone (1).—To a suspended mixture of the sulphone (1) (1.0 g, 3.83 mmol) and allyl alcohol (2.0 ml, 29.40 mmol) was added sodium hydride (0.01 g, 0.41 mmol) under nitrogen. The mixture immediately became a clear orange solution, which was stirred for 5 h at room temperature, and then acidified with a small amount of acetic acid. Water (10 ml) was added to the resulting mixture, and it was extracted with dichloromethane (30 ml), washed with water (15 ml × 3), dried, and evaporated. The resulting yellow oil was chromatographed on silica gel eluting with dichloromethane to give 2-*allyloxy*-1-*bromo*-1-p-*tolylsulphonylethane* (2a) as a pale yellow oil (1.06 g, 87%), $\nu_{max.}$ 1 325 and 1 145 cm^{-1}; δ 2.48 (s, 3 H), 3.63—4.37 (m, 4 H), 4.83—5.40 (m, 3 H), 5.50—6.21 (m, 1 H), and 7.34, 7.84 (dd, *J* 8 Hz, 4 H). This procedure was used in the following cases.

3-Methylallyl derivative (2b), $\nu_{max.}$ 1 325 and 1 150 cm^{-1}; b.p. 154—156 °C/0.25 mmHg (Kugelrohr distillation), δ 1.68 (d, *J* 4.5 Hz, 3 H), 2.43 (s, 3 H), 3.66—4.36 (m, 4 H), 4.95 (dd, *J* 5 and 7 Hz, 1 H), 5.13—6.00 (m, 2 H), and 7.38, 7.85 (dd, *J* 8 Hz, 4 H).

3-Propylallyl derivative (2c), $\nu_{max.}$ 1 335 and 1 155 cm^{-1}; δ 0.86 (m 3 H), 1.11—1.75 (m, 2 H), 1.78—2.25 (m, 2 H), 2.46 (s, 3 H), 3.61—4.35 (m, 4 H), 4.95 (dd, *J* 4.5 and 7 Hz, 1 H), 5.15—5.98 (m, 2 H), and 7.37, 7.86 (dd, *J* 8 Hz, 4 H).

1-Methylallyl derivative (2d), $\nu_{max.}$ 1 320 and 1 125 cm^{-1}; δ 1.16 (d, *J* 6.5 Hz, 3 H), 2.43 (s, 3 H), 3.55—4.34 (m, 3 H), 4.85—5.32 (m, 3 H), 5.39—5.99 (m, 1 H), and 7.37, 7.86 (dd, *J* 8 Hz, 4 H).

1-Bromo-1-*p*-tolylsulphonyl-2-(3-phenylprop-2-ynyl)oxyethane (3a) was prepared from the sulphone (1) (3.83 mmol) and 3-phenylprop-2-yn-1-ol (10.17 mmol). The crude mixture was distilled at 95 °C/0.26 mmHg to remove the excess of alcohol. The residual oil was chromatographed as usual; $\nu_{max.}$ 2 125, 1 325, and 1 150 cm^{-1}; δ 2.39 (s, 3 H), 3.85—4.53 (m, 4 H), 5.02 (dd, *J* 5 and 7 Hz, 1 H), 7.34 (m, 7 H), and 7.85 (d, *J* 8 Hz, 2 H).

Oct-2-ylyloxy derivative (3b), $\nu_{max.}$ 2 280, 2 110, 1 325, and 1 150 cm^{-1}; δ 0.65—1.82 (m, 9 H), 1.17 (s, 2 H), 2.49 (s, 3 H), 3.75—4.49 (m, 4 H), 5.04 (dd, *J* 5 and 7 Hz, 1 H), and 7.40, 7.91 (dd, *J* 8 Hz, 4 H).

2-*Allylamino*-1-*bromo*-1-p-*tolylsulphonylethane* (4).—A suspension of (1) (0.5 g, 1.9 mmol) and allylamine (0.12 g, 2.1 mmol) in dry tetrahydrofuran (15 ml) was stirred at room temperature for 3.5 h. The solvent was evaporated to give an orange oil, which was chromatographed on silica gel eluting with chloroform to give compound (4) as a pale yellow oil (0.54 g, 86%), $\nu_{max.}$ 3 325, 1 300, and 1 150 cm^{-1}; δ 1.77 (s, 1 H), 2.47 (s, 3 H), 3.02—3.66 (m, 4 H), 4.92—5.32 (m, 3 H), 5.63—6.05 (m, 1 H), and 7.57, 7.80 (dd, *J* 8 Hz, 4 H).

General Procedure for the Radical Cyclization.—To a hot solution (60 °C) of the ether (2a) (0.6 g, 1.88 mmol) and AIBN (0.01 g, 0.06 mmol) in dry benzene (6 ml) under nitrogen, was added tri-n-butyltin hydride (0.6 g, 2.06 mmol) in dry benzene (6 ml) dropwise during 30 min. The mixture was stirred for 8 h at 70 °C and the solvent was evaporated. The resulting oil was chromatographed on silica gel eluting with hexane followed by dichloromethane. The latter fraction gave a colourless oil, 4-*methyl*-3-p-*tolylsulphonyltetrahydrofuran* (5a) (0.3 g, 67%), b.p. 152—153 °C/0.2 mmHg (Kugelrohr), $\nu_{max.}$ 1 345 and 1 145 cm^{-1}; δ 1.01 (57%), 1.41 (43%) (each d, *J* 7 Hz, 3 H), 2.43 (s, 3 H), 2.55—2.96 (m, 1 H), 3.18—3.56 (m, 1 H), 3.60—4.36 (m, 4 H), and 7.35, 7.80 (dd, *J* 8 Hz, 4 H) (Found: C, 59.5; H, 6.9. $C_{12}H_{16}O_3S$ requires C, 59.98; H, 6.71%). The *trans*-isomer came first on g.l.c. analysis, the isomers appearing in the ratio *trans* : *cis* 58.4 : 41.6. This procedure was used in the following cases. The reaction course was routinely monitored by i.r. spectroscopy (Bu_3Sn–*H*, 1 800 cm^{-1}).

4-Ethyl derivative (5b), b.p. 139—149 °C/0.25 mmHg (Kugelrohr); $\nu_{max.}$ 1 300 and 1 145 cm^{-1}; δ 0.65—1.78 (m,

6 H), 2.45 (s, 3 H), 2.61—4.38 (m, 5 H), and 7.30, 7.73 (dd, *J* 8 Hz, 4 H) (Found: C, 61.2; H, 7.1. $C_{13}H_{18}O_3S$ requires C, 61.40; H, 7.14%).

4-Butyl derivative (5c), b.p. 167—170 °C/0.23 mmHg (Kugelrohr), $\nu_{max.}$ 1 305 and 1 150 cm^{-1}; δ 0.55—1.74 (m, 10 H), 2.42 (s, 3 H), 3.07—3.51 (m, 1 H), 3.52—4.21 (m, 4 H), and 7.27, 7.71 (dd, *J* 8 Hz, 4 H) (Found: C, 63.7; H, 8.0. $C_{15}H_{22}O_3S$ requires C, 63.8; H, 7.85%).

4,5-Dimethyl derivative (5d), b.p. 163—164 °C/0.25 mmHg, $\nu_{max.}$ 1 300 and 1 145 cm^{-1}; δ 0.86—1.52 (m 6 H), 2.43 (s, 3 H), 3.16—4.52 (m, 5 H), and 7.32, 7.75 (dd, *J* 8 Hz, 4 H) (Found: C, 60.9; H, 7.2. $C_{13}H_{18}O_3S$ requires C, 61.39; H, 7.13%).

4-Methyl-3-*p*-tolylsulphonylpyrrolidine (6) was prepared at 70 °C for 3 h, and eluted with chloroform–ethanol (1 : 1), b.p. 140—142 °C/0.3 mmHg (Kugelrohr); $\nu_{max.}$ 3 350, 1 300, and 1 145 cm^{-1}; δ 0.96, 1.42 (each d, *J* 7 Hz, 3 H in a ratio 90.3 : 9.7), 2.30—2.80 (m, 5 H), 2.84—3.68 (m, 5 H), and 7.33, 7.71 (dd, *J* 8 Hz, 4 H) (Found: C, 60.2; H, 7.4; N, 5.5. $C_{12}H_{17}NO_2S$ requires C, 60.24; H, 7.16; N, 5.85%).

4-Benzylidene-3-*p*-tolylsulphonyltetrahydrofuran (9a), b.p. 206—208 °C/0.25 mmHg (Kugelrohr), $\nu_{max.}$ 1 305 and 1 140 cm^{-1}; δ 2.41, 2.34 (each s, 3 H), 3.73—5.0 (m, 5 H), 6.55, 6.73 (each s, 1 H in the ratio 54.5 : 45.5), 6.93—7.46 (m, 7 H), and 7.50—8.03 (m, 2 H) (Found: C, 68.7; H, 5.7. $C_{18}H_{18}O_3S$ requires C, 68.77; H, 5.77%).

4-Hexylidene derivative (9b), b.p. 140—142 °C/0.15 mmHg (Kugelrohr), $\nu_{max.}$ 1 315 and 1 145 cm^{-1}; δ 0.72—1.0 (m, 3 H), 1.04—1.64 (m, 6 H), 1.73—2.28 (m, 2 H), 2.46 (s, 3 H), 3.64—4.64 (m, 5 H), 5.62 (t, *J* 8 Hz, 1 H), and 7.26, 7.68 (dd, *J* 8 Hz, 4 H) (Found: C, 66.0; H, 8.0. $C_{17}H_{24}O_3S$ requires C, 66.21; H, 7.85%).

Epimerization of the Tetrahydrofuran (5a).—The mixture of *trans*- and *cis*-(5a) (0.27 g, 1.12 mmol) was treated with potassium t-butoxide (0.13 g, 1.12 mmol) in t-butyl alcohol (15 ml) at 80 °C for 8 h under nitrogen. Compound (5a) was recovered in 60% yield after purification by column chromatography on silica gel eluting with chloroform. The n.m.r. of the recovered (5a) showed the *trans* : *cis* ratio to be 86.6 : 13.4.

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