Highly Enantioselective Rearrangement of (*S*)-*E*-α-*p*-Tolylsulphinyl-α,β-enoates to (*R*)-*E*-γ-Hydroxy-α,β-enoates

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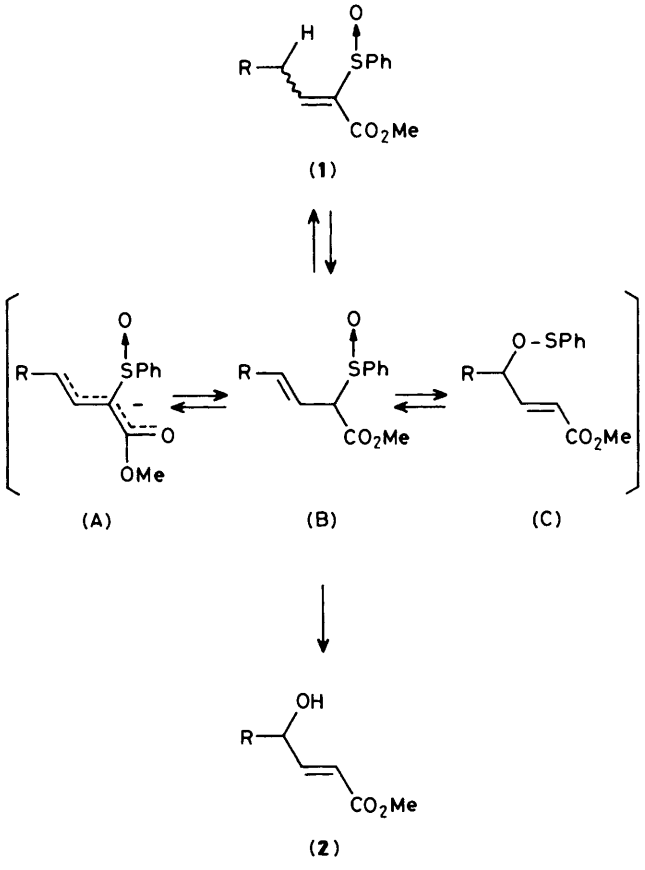
On treatment with pyridine–camphorsulphonic acid, (*S*)-*E*-α-*p*-tolylsulphinyl-α,β-enoates (**4**) undergo enantioselectively a sequential prototropic shift and allylic sulphoxide–sulphenate rearrangement to produce (*R*)-*E*-γ-hydroxy-α,β-enoates (**2**) in 64—72% optical purity.

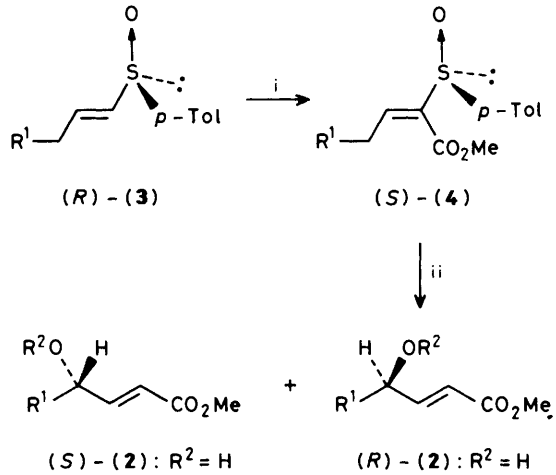
In our earlier work,[1] we showed that α-phenylsulphinyl-α,β-enoates (**1**) undergo, upon treatment with pyridine–water, stereoselectively a sequential prototropic shift and allylic sulphoxide–sulphenate rearrangement[2] [→(A)→(B)→(C)→] to give *E*-γ-hydroxy-α,β-enoates (**2**) in good yields (Scheme 1). In connection with our studies on the synthetic utilisation of chiral sulphoxides,[3] we have studied this rearrangement using chiral α-*p*-tolylsulphinyl-α,β-enoates (**4**). We report herein the results, demonstrating that 1,4-chirality transfer from the sulphoxide sulphur atom to the γ-carbon atom takes place during the rearrangement with considerable enantioselectivity (64—72%) in an acyclic system[4] such as this to produce *E*-γ-hydroxy-α,β-enoates (**2**).

Optically pure *E*-α-*p*-tolylsulphinyl-α,β-enoates (*S*)-(**4**)† were prepared in 74—82% yield from optically pure *E*-alkenyl sulphoxides (*R*)-(**3**)[3b] according to Posner's procedure:[5] lithiation (2.5 equiv. of LDA–THF,‡ −90 °C, 30 min) followed by carboxylation (CO_2, −110 to −80 °C, 40 min) and esterification (MeI–HMPA,‡ −80 °C to room temp.).



Scheme 1

Base-catalysed sequential rearrangement of compounds (**4**) was attempted under a variety of conditions (base, proton source, thiophile, temperature, time *etc.*), among which the best was the use of pyridine [4 ml for *ca.* 0.8—0.9 mmol of (**4**)] and (±)-camphor-10-sulphonic acid (2 equiv.) as a base and a proton source, respectively, at room temperature, affording *E*-γ-hydroxy-α,β-enoates (**2**) in good chemical and optical yields, as shown in Scheme 2 and Table 1 (entries 1, 2, and 4). The enantiomeric ratios of each product (**2**) were determined by h.p.l.c. analysis of the corresponding benzoate (**5**), prepared in the usual manner, on a chiral column [(CHIRALPAC OT(+)].[6] The major enantiomer from the reaction was shown to be the (*R*)-hydroxy-enoates (*R*)-(**2**) as described later. Furthermore, it was found that, when the reaction of (**4b**) was conducted at a higher temperature (50 °C), the rearrangement proceeded much faster without decrease of the enantioselectivity (entry 3). It should be noted that the observed optical purity [64—72% enantiomeric excess (e.e.)]



a: $R^1 = Pr^n$
b: $R^1 = Bu^n$
c: $R^1 = n\text{-}C_5H_{11}$

p-Tol = *p*-MeC_6H_4

Scheme 2. *Reagents:* i, LDA–THF, CO_2, then MeI–HMPA; ii, pyridine–CSA.‡

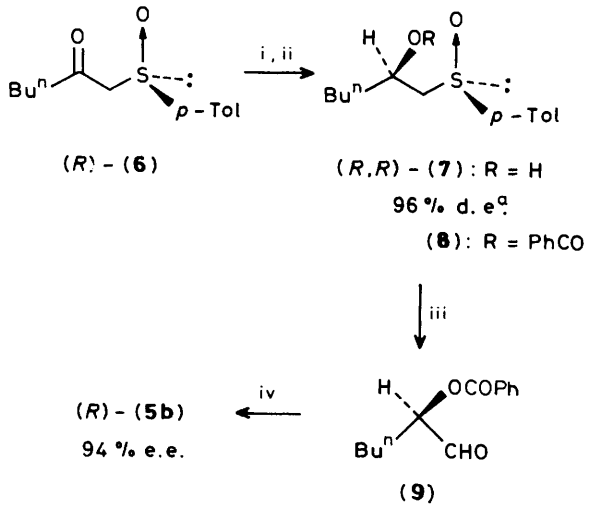
† Satisfactory analytical and spectral data were obtained for all new compounds.

‡ Abbreviations: LDA = lithium di-isopropylamide; THF = tetrahydrofuran; HMPA = hexamethylphosphoric triamide; CSA = (±)-camphorsulphonic acid; DCC = dicyclohexylcarbodiimide; DMAP = 4-*N*,*N*-dimethylaminopyridine.

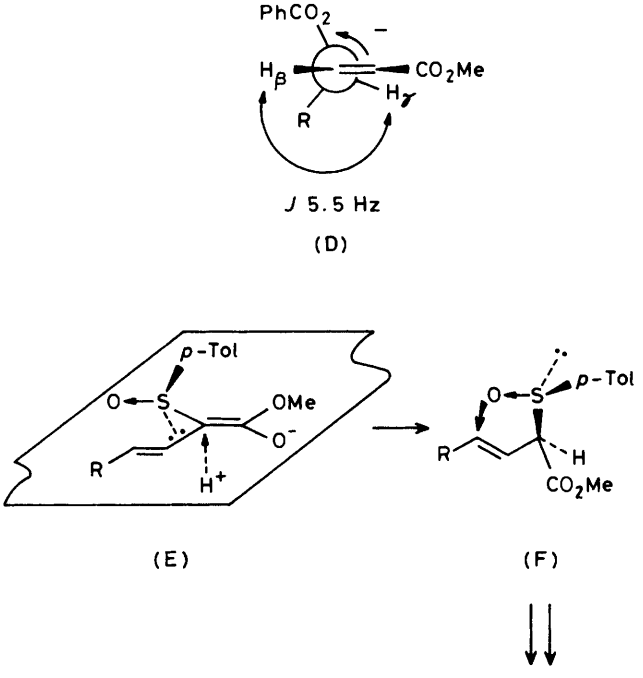
Table 1. Rearrangement of α-*p*-tolylsulphinyl-α,β-enoates (*S*)-(**4**) induced by pyridine–CSA.

		Reaction conditions		Product (**2**)				
Entry	Substrate	Temp./ °C	Time/ h	Yield,[a] %	Ratio[b] (*R*) : (*S*)	$[\alpha]_D^{c}$/° (*c*)		Abs. confn.[d]
1	(**4a**)	20	40	72	82 : 18	−11.8	(0.625)	*R*
2	(**4b**)	20	50	68	85 : 15	−15.4	(0.481)	*R*[e]
3	(**4b**)	50	8	85	85 : 15			
4	(**4c**)	20	40	84	86 : 14	−18.7	(0.283)	*R*

[a] Yields are for the isolated total products. [b] Determined by h.p.l.c. of the benzoates (**5**) on chiral column [CHIRALPAC OT(+)] using 95—100% methanol. [c] Measured for solutions in chloroform at 19 °C. [d] Determined by the c.d. spectra of the benzoates (**5**). [e] Also determined by alternative synthesis of the (*R*)-benzoate (**5b**). See text.



Scheme 3. *Reagents:* i, $ZnCl_2$–Bu^i_2AlH–THF; ii, $PhCO_2H$–DCC–DMAP–CH_2Cl_2; iii, $(CF_3CO)_2O$–pyridine–CH_2Cl_2 then MeOH–$NaHCO_3$; iv, $Ph_3P{=}CHCO_2Me$–CH_2Cl_2.‡ [a] d.e. = diastereoisomeric excess.



Scheme 4

in the products (**2**) was much higher than the values observed in the same type of rearrangement reaction of both acyclic and alicyclic chiral vinyl sulphoxides.[4]

The absolute configurations of the major enantiomers (*R*)-(**2**) were determined by an alternative synthesis of the benzoate (*R*)-(**5b**) and by application of the c.d. allylic benzoate method[7] to the benzoates (**5**). Diastereoselective reduction[3a,8] of the chiral β-ketosulphoxide (*R*)-(**6**) gave in 83% yield the (*R*,*R*)-hydroxysulphoxide (**7**) with 98 : 2 selectivity, which was converted into the benzoate (**8**). Pummerer rearrangement of the benzoate (**8**) followed by alkaline hydrolysis and Wittig reaction of the resulting α-benzoyloxy-aldehyde (**9**) furnished the benzoyloxy-enoate (*R*)-(**5b**) of 94% e.e. in 75% overall yield (Scheme 3). The h.p.l.c. behaviour of this compound on a chiral column matched perfectly that of the major enantiomer of (**5b**) derived from the hydroxy-enoate (**2b**). From the observed coupling constant values, *J* 5.5 Hz, between two protons H_β and H_γ in the ^1H n.m.r. spectra of compounds (**5**), it was suggested that these two protons exist in an almost *trans*-relationship, as depicted in the conformation (D). The c.d. spectra of (**5**) exhibit a negative Cotton effect in the region of the benzoate π → π* transition at 228 nm,§ indicating an anticlockwise relationship between the double bond and benzoate chromophores, the (*R*) absolute configuration, as shown.

The asymmetry-determining step in this rearrangement reaction is presumably the stereoselective protonation of the diene-type enolate anion species (A or E) to produce the allylic sulphoxide (B or F), and the major (*R*)-enantiomer of (**2**) would arise from the stereoisomer (F) (Scheme 4) which would also rearrange stereoselectively to the allylic sulphenate species such as (C). The preferential formation of the stereoisomer (F) may tentatively be rationalised in terms of an approximately planar conformation such as (E), because of dipolar interactions between two negatively charged oxygen atoms, which suffers protonation from that side of the plane

§ For the 94% e.e. sample of (*R*)-(**5b**), $\lambda_{ext.}$ 228 nm, Δε −11.1 in ethanol.

containing sulphur's nonbonding electron pair and opposite to that side containing the tolyl group.

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