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Efficient preparation of enantiomerically pure (*E*)-γ-hydroxy-α,β-unsaturated *p*-tolylsulfoxides using lipase-mediated acylations

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Abstract

(*E*)-γ-Hydroxy-α,β-unsaturated *p*-tolylsulfoxides **1** have been efficiently resolved via irreversible enzymatic acylation with lipase PS (*Pseudonomas cepacia*) and vinyl acetate.

1. Introduction

The sulfoxide group has emerged as an efficient chiral auxiliary in numerous asymmetric syntheses.[1] In particular, enantiomerically pure α,β-unsaturated sulfoxides have been successfully used as chiral dienophiles,[2] dienes,[3] dipolarophiles,[4] and Michael acceptors[5] mainly due to the potential of the sulfoxide moiety as a stereocontrolling element.[6] Related reactions have also been reported for the corresponding sulfones,[7] for which it has been additionally shown that substitution at the γ-position have a strong influence on the facial selectivity for addition reactions to the carbon–carbon double bond.[8] However, γ-hydroxy-α,β-unsaturated sulfoxides have been scarcely investigated in this context, in spite of being intriguing substrates for stereochemical studies due to the presence of two stereocontrolling elements, the sulfoxide group and the alcohol (or its equivalent).[9] Therefore, methods for the preparation of enantiomerically pure γ-hydroxy-α,β-unsaturated sulfoxides are of great importance in asymmetric synthesis. At present the base-catalyzed elimination of diastereomerically pure 2,3-epoxy sulfoxides[10] and the reduction of γ-keto-α,β-unsaturated sulfoxides[11] are the main methods described in the literature for the preparation of this type of sulfoxide.

Recently, we reported a practical one-step procedure for the synthesis of (*E*)-γ-hydroxy-α,β-unsaturated *p*-tolylsulfoxides **1** by SPAC condensation of enantiomerically pure (*S,S*)-bis-*p*-

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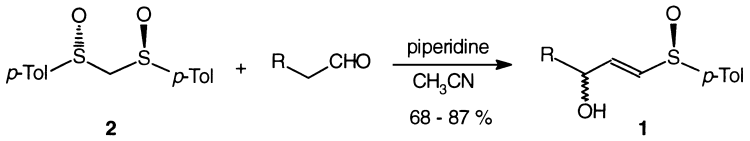
tolylsulfinylmethane **2** with enolizable aldehydes (Scheme 1).[12] The process involves a Knoevenagel type condensation between the aldehyde and the methylene active bis-sulfoxide in tandem with an allylic sulfoxide–sulfenate rearrangement. Unfortunately, the corresponding (*E*)-γ-hydroxy-α,β-unsaturated sulfoxides **1** were obtained as an 1:1 mixture of the two possible epimers at the carbinol center that resulted as being inseparable in our hands. Recently, we have been using several types of bis-sulfoxides differently substituted at sulfur with the aim of improving diastereoselectivity in the allylic sulfoxide–sulfenate rearrangement, without any relevant success.[13]



Scheme 1.

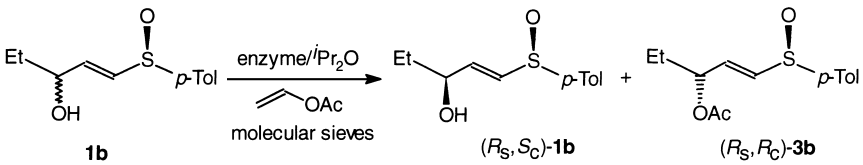
At the present there is a notable interest in the use of lipases as catalysts for the resolution of racemic alcohols.[14,15] Some of the reasons for the popularity of these enzymes are the following: they are readily available and relatively inexpensive; require no expensive cofactors; often exhibit high stereoselectivities with a wide range of substrates; and finally, allow the production of multigram quantities of optically enriched alcohols in a facile laboratory procedure. Herein, we report the results obtained in the lipase-mediated acylation of several (*E*)-γ-hydroxy-α,β-unsaturated sulfoxides **1**.

2. Results

2.1. Kinetic resolution of (E)-γ-hydroxy-α,β-unsaturated sulfoxides *1*

The kinetic resolution of **1** by lipase-catalyzed transesterification in organic media was examined. Initially, we explored the resolution of the ethyl derivative **1b** using different enzymes and vinyl acetate at room temperature in the presence of molecular sieves[16] as illustrated in Table 1.

Table 1
Biocatalytic resolution of (*E*)-1-(*p*-tolylsulfinyl)-1-penten-3-ol **1b**

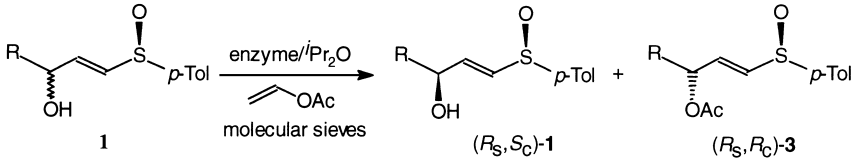


entry	Enzyme	Time (d)	(RS,SC)-1b		(RS,RC)-3b		E
			Yield	d.e. %	Yield	d.e. %	
1	CCL	3	-	-	-	-	-
2	*R. arrhizus*	7	-	-	-	-	-
3	PPL	2	43.0	86	50.0	96	43
4	PS	1	49.9	96	49.6	98	> 50

Among the enzymes used, lipase PS (from *Pseudomonas cepacia*, Amano) was the most effective for the resolution of (*E*)-γ-hydroxy-α,β-unsaturated sulfoxide **1b**, yielding the acetate **3b** and unreacted alcohol with very high diastereoselectivity (entry 4). To isolate the products, the reaction was stopped at ca. 50% conversion, which was determined by NMR analysis (selectivity factors[17] $E > 50$). The resulting acetate **3b** was then separated from unreacted γ-hydroxysulfoxides **1b** by column chromatography. The diastereomeric excesses for **1b** and **3b** were determined by ^{1}H NMR and confirmed by HPLC analysis using a reverse-phase column Lichrocart C-18. The configuration at the carbinol center for both derivatives was assigned by chemical correlation with the known (*E*)-γ-hydroxy and γ-acetoxy-α,β-unsaturated sulphones[18] (see Section 2.2).

In order to explore the scope of the kinetic resolution of (*E*)-γ-hydroxy-α,β-unsaturated sulfoxides mediated by lipase PS, the optimized enzymatic acylation conditions for **1b** were applied to a wide variety of substrates (Table 2).

Table 2
Biocatalytic resolution of (*E*)-γ-hydroxy-α,β-unsaturated Sulfoxides **1a**–**f**



1 (R_S,S_C)-**1** + (R_S,R_C)-**3**

entry		R	Time (d)	(R_S,S_C)-**1**			(R_S,R_C)-**3**			E
				yield(%)	de (%)[a,b]	$[\alpha]_D$	yield(%)[c]	de (%)[a,b]	$[\alpha]_D$	
1	**1a**	Me	0.5	49.0	98	+239.6	50.0	96	+178.0	> 50
2	**1b**	Et	1	49.9	96	+251.0	49.6	98	+226.6	> 50
3	**1c**	^{n}Pr	2	49.5	98	+236.0	49.3	98	+154.8	> 50
4	**1d**	Pent	3	49.0	96	+294.0	49.2	98	+223.0	> 50
5	**1e**	^{i}Pr	10	48.4	96	+225.0	49.2	98	+195.0	> 50
6	**1f**	^{t}Bu	12	-	-		7.4	98	+118.0	25

[a]Determined by ^{1}H-RMN integrals of H_1 and H_2. [b]Determined by HPLC analysis in reverse phase column Lichtocart C-18. [c]Yields determined after flash chromatography

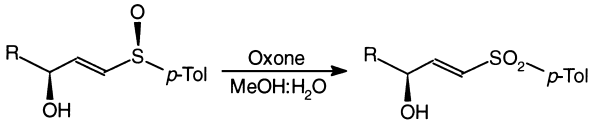
From the results summarized in Table 2, it should be pointed out that the diastereoselectivity of the enzymatic acetylation of (*E*)-γ-hydroxy-α,β-unsaturated sulfoxides **1** is almost independent of the increasing length or size of the R group. Except for the bulkiest derivative **1f** (entry 6), the lipase PS mediated acetylations were very efficient, taking place at very high values of selectivity factors ($E > 50$). In all cases the acetylation reaction was extremely slow with conversions near 50%, the (R_s,R_c)-diastereomer being the most reactive.

The results obtained with (*E*)-γ-hydroxy-α,β-unsaturated sulfoxides **1a** (R = Me), **1e** (R = ^{i}Pr) and **1f** (R = ^{t}Bu) show the effect of the increasing size of the *R* alkyl group in the reactivity and diastereoselectivity of this enzymatic reaction. Thus, despite the large steric requirement of the ^{i}Pr group, γ-hydroxy sulfoxide **1e** (entry 5) was diastereoselectively acetylated ($E > 50$), although the rate was about 20 times slower than that of γ-hydroxy sulfoxide **1a** (entry 1). By contrast, after 12 days the reaction of γ-hydroxy sulfoxide **1f** (entry 6) took place with poor selectivity factor ($E = 25$) and only 7% of conversion was observed in the acetylation.[19]

2.2. Assignment of the relative configuration for (E)-γ-hydroxy-α,β-unsaturated sulfoxides *1*

The configuration at the hydroxylic carbon atom for unreacted γ-hydroxysulfoxides **1** was determined by chemical correlation with the known γ-hydroxy-α,β-unsaturated sulfones **4**. Thus, γ-hydroxysulfoxides **1c** and **1d** were oxidated using the conditions developed by Trost[20] to afford γ-hydroxy-α,β-unsaturated sulfones **4c** and **4d** with high chemical yields (Table 3).

Table 3
Preparation of (*E*)-γ-hydroxy-α,β-unsaturated sulfones **4**



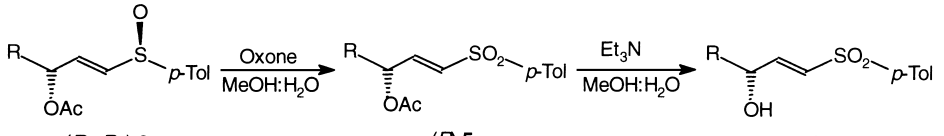
(R_S,S_C)-**1** (*S*)-**4**

entry	R	Yield (**4**)	$[\alpha]_D$	[b]$[\alpha]_D$	e.e. %
1	nPr	94.8 %	+ 42.6	+44.5	96
2	Pent	98.2 %	+ 39.0	+40.5	96

[b]$[\alpha]_D$ reported values, ref. 18.

At this point, specific rotations, melting points, and the ^{1}H and ^{13}C NMR spectra of **4c** and **4d** were essentially identical to those described in the literature.[18] This chemical correlation allows the assignment of the relative configuration (*S*) for the hydroxylic carbon in the unreacted (*E*)-γ-hydroxy-α,β-unsaturated sulfoxides **1c** and **1d**, while the opposite (*R*) configuration at C_3 can be assumed for (*E*)-γ-acetyl-α,β-unsaturated sulfoxides **3** and **3d**. The configuration for the γ-acetylsulfoxides **3c** and **3d** was further confirmed by chemical correlation. Thus, compounds **3c** and **3d** were first transformed into the γ-acetylsulfones **5c** and **5d** by oxidation. The latter were hydrolyzed using Et_3N in MeOH–H_2O to give the (*E*)-γ-hydroxy-α,β-unsaturated sulfones **6c** and **6d** in 98% and 95% yields, respectively (Table 4). The specific rotations for compounds **6c** and **6d** were opposite to that described for sulfones **4c** and **4d**, confirming the (*R*) configuration for C_3 in (*E*)-γ-acetyl-α,β-unsaturated sulfoxides **3**.

Table 4
Preparation of (*E*)-γ-hydroxy-α,β-unsaturated sulfones **6c** and **6d**



(R_S,R_C)-**3** (*R*)-**5** (*R*)-**6**

entry	R	yield (**5**)	$[\alpha]_D$ (**5**)	yield (**6**)	$[\alpha]_D$ (**6**)	e.e. %
1	nPr	98.0 %	+ 12.8	86.4 %	-43.6	98
2	Pent	95.0 %	+ 7.8	87.5 %	-39.5	98

Since all the studied compounds are closely related, and lipase PS gave normally highly stereoselective resolutions of several types of alcohols always being acylated the same isomer.[14–16] It seems reasonable to assume that the absolute configuration for C_3 in unreacted (*E*)-γ-hydroxy-α,β-unsaturated sulfoxides **1** is (*S*) and that for the corresponding (*E*)-γ-acetyl-α,β-unsaturated sulfoxides **3** it is (*R*) in all cases.

In summary, the ready access to (*E*)-γ-hydroxy-α,β-unsaturated sulfoxides **1**, via one-pot SPAC condensation between aldehydes and bis-sulfoxides, coupled with the efficient enzymatic resolution described in this paper make this experimental operation a good and simple method to obtain enantiomerically pure (*E*)-γ-hydroxy and (*E*)-γ-acetyl-α,β-unsaturated sulfoxides which are difficult to prepare by other means. The use of the allylic acetate moiety in these substrates is being currently investigated in palladium-catalyzed allylic substitution reactions and the results will be reported in due course.

3. Experimental

Melting points were determined in open capillary tubes on a Gallenkamp apparatus and are uncorrected. ^{1}H NMR spectra were registered on a Bruker AC-200 (200 MHz) or AMX-500 (500 MHz) instrument and ^{13}C NMR on an AC-200 (50.3 MHz) or AMX-500 (125.72 MHz) spectrometer. All spectra were obtained using $CDCl_3$ as solvent and TMS as internal standard. Chemical shifts are reported in ppm, and coupling constants in hertz. Optical rotations were taken on a Perkin–Elmer 241-MC polarimeter in a 1 dm tube; concentrations are given in g/100 mL. High resolution mass measurements were performed on a Kratos MS-80-RFA spectrometer. HPLC analysis was carried out on a Waters, Millipore 600A model using a Chiral OD (Diacel) column or reverse phase column Lichrocart C-18. Routine monitoring of reactions was performed using Merck 60 F 254 silica gel, aluminium supported TLC plates. For the flash chromatography,[21] silica gel 60 (230–400 mesh ASTM, Merck) was used.

Flasks, stirrings bars, and hypodermic needles used for the generation of organometallic compounds were dried for ca. 12 h at 120°C and allowed to cool in a dessicator over anhydrous calcium sulfate. Anhydrous solvents (ethers) were obtained by distillation from benzophenone ketyl.[22] The *n*-BuLi employed was titrated according to the method described by Juaristi et al.[23]

3.1. (S,S)-*Bis*-p-*tolylsufinylmethane* **2**

A solution of *i*-Pr_2NH 1.99 mL (14.3 mmol) in 15 mL of anhydrous THF was cooled to –78°C before the slow addition of 8.9 mL (14.3 mmol) of *n*-BuLi in hexane (1.6 M). The resulting solution was stirred at –78°C for 30 min and then treated with 1.0 g (6.5 mmol) of (+)-(*R*)-methyl *p*-tolyl sulfoxide[24] in 10 mL of THF. The yellow solution formed was stirred at –78°C for 1 h before the addition of the 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl (–)-(*S*)-*p*-toluenesulfinate[24] in 10 mL of THF. The reaction mixture was stirred at this temperature for 1 h and at room temperature for 10 min. The mixture was then treated with 5 mL of saturated ammonium chloride solution. The aqueous phase was extracted with CH_2Cl_2 (50 mL). The combined extracts were dried (Na_2SO_4), filtered, evaporated under reduced pressure and the crude product was purified by recrystallization from hot hexane to yield enantiomerically pure (*S*,*S*)-bis-*p*-tolylsufinylmethane (1.55 g, 82% yield) as a white solid, m.p. = 136–137°C, $[\alpha]_D = +317$ (*c* 1, acetone), lit.[25] m.p. = 137.5°C and $[\alpha]_D = +318$ (*c* 1, acetone).

3.2. (E)-γ-Hydroxy-α,β-unsaturated sulfoxides **1a–f**

The procedure described by Llera et al. was followed.[12]

3.2.1. General procedure for the lipase-mediated acylation of compounds **1a–f**

To a solution (50 mM) of the two isomers of (*E*)-γ-hydroxy-α,β-unsaturated sulfoxides **1a–f** in isopropyl ether was added sequentially 50 mg/mL of powdered molecular sieves (4 Å), (25 mg/mL) of enzyme and 5 equivalents of vinyl acetate. The resulting suspension was vigorously shaken at room temperature and monitored by TLC and ^{1}H NMR for the conversion. When 50% conversion was reached, the enzyme and the molecular sieves were filtered off and the solvent was evaporated to give a mixture of unreacted alcohol **1** and acetylated product **3**.

3.2.2. (R_s,S_c)-(E)-1-(p-Tolylsulfinyl)-1-buten-3-ol (R_s,S_c)-**1a** and (R_s,R_c)-(E)-3-acetoxy-1-(p-tolylsulfinyl)-1-butene (R_s,R_c)-**3a**

The general procedure was followed for the acylation of 220 mg (1.05 mmol) of **1a** for 12 h. Purification of the mixture by flash chromatography (ethyl acetate:hexane, 3:1) afforded 108 mg (49% yield) of (R_s,S_c)-**1a** as a viscous oil, and 140 mg (50% yield) of (R_s,R_c)-**3a** as a viscous oil.

Compound (R_s,S_c)-**1a**: d.e. 98%. $[\alpha]_D = +239.6$ (*c* 4.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (d, J = 6.6 Hz, 3H, CH_3-), 1.74 (br, 1H, OH), 2.42 (s, 3H, CH_3-Ar), 4.56 (m, 1H, CH(OH)), 6.46 (dd, $J_{anti} = 15.0$ Hz, $J_{1,3} = 1.6$ Hz, 1H, =CH-S(O)), 6.63 (dd, $J_{anti} = 15.0$ Hz, $J_{2,3} = 4.4$ Hz, 1H, CH=), 7.32–7.51 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (125.72 MHz, $CDCl_3$) δ 21.4, 23.0, 67.2, 124.8, 130.1, 133.7, 140.3, 141.6, 141.7. HRMS calcd *m*/*z* for $C_{11}H_{14}O_2S$: 210.0731. Found: 210.0714.

Compound (R_s,R_c) **3a**: d.e. 96%. $[\alpha]_D = +178$ (*c* 7.6, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (d, J = 6.6 Hz, 3H, CH_3), 2.03 (s, 3H, CH_3CO), 2.39 (s, 3H, CH_3-Ar), 5.48 (m, 1H, CH-($OCOCH_3$), 6.39 (dd, $J_{anti} = 15.1$ Hz, $J_{1,3} = 1.4$ Hz, 1H, =CH-S(O)), 6.53 (dd, $J_{anti} = 15.1$ Hz, $J_{2,3} = 5.2$ Hz, 1H, CH=), 7.31–7.49 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (125.72 MHz, $CDCl_3$) δ 19.7, 20.9, 21.2, 68.7, 124.7, 130.0, 135.5, 136.3, 139.8, 141.8, 169.7. HRMS calcd *m*/*z* for $C_{13}H_{16}O_3S$: 252.1632. Found: 252.1677.

3.2.3. (R_s,S_c)-(E)-1-(p-Tolylsulfinyl)-1-penten-3-ol (R_s,S_c)-**1b** and (R_s,R_c)-(E)-3-acetoxy-1-(p-tolylsulfinyl)-1-pentene (R_s,R_c)-**3b**

The general procedure was followed for the acylation of 473 mg (2.11 mmol) of **1b** for 48 h. Purification of the mixture by flash chromatography (ethyl acetate:hexane, 3:1) afforded 236 mg (49.9% yield) of (R_s,S_c)-**1b**, and 280 mg (49.6% yield) of (R_s,R_c)-**3b** as viscous oils.

Compound (R_s,S_c)-**1b**: d.e. 96%. $[\alpha]_D = +251$ (*c* 2.7, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 7.4 Hz, 3H, CH_3), 1.58 (m, 2H, -CH_2-), 2.37 (s, 3H, CH_3Ar), 3.38 (br, 1H, OH), 4.20 (m, 1H, CH(OH)), 6.41 (dd, $J_{anti} = 15.0$ Hz, $J_{1,3} = 0.9$ Hz, 1H, =CH-S(O)), 6.56 (dd, $J_{anti} = 15.0$ Hz, $J_{2,3} = 4.7$ Hz, 1H, CH=), 7.26–7.46 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (125.72 MHz, $CDCl_3$) δ 9.4, 21.3, 29.6, 71.9, 124.8, 129.7, 130.2, 133.8, 141.5, 141.6. HRMS calcd *m*/*z* for $C_{12}H_{16}O_2S$: 224.0876. Found: 224.0870.

Compound (R_s,R_c)-**3b**: d.e. 98%. $[\alpha]_D = +226.6$ (*c* 3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, J = 7.4 Hz, 3H, CH_3), 1.68 (m, 2H, -CH_2-), 2.02 (s, 3H, CH_3CO), 2.37 (s, 3H, CH_3-Ar), 5.34 (m, 1H, CH($OCOCH_3$)), 6.37 (dd, $J_{anti} = 15.0$ Hz, $J_{1,3} = 0.8$ Hz, 1H, =CH-S(O)), 6.48 (dd, $J_{anti} = 15.0$ Hz, $J_{2,3} = 5.7$ Hz, 1H, CH=), 7.28–7.46 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (125.72 MHz, $CDCl_3$) δ 9.0, 20.8, 21.4, 26.9, 73.4, 124.8, 130.0, 135.1, 136.2, 140.1, 141.8, 169.9.

HRMS calcd m/z for $C_{14}H_{18}O_3S$: 266.0971. Found: 266.0991. Anal. calcd for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81. Found: C, 62.92; H, 6.60.

*3.2.4. (R_s,S_c)-(E)-1-(p-Tolylsulfinyl)-1-hexen-3-ol (R_s,S_c)-**1c** and (R_s,R_c)-(E)-3-acetoxy-1-(p-tolylsulfinyl)-1-hexene (R_s,R_c)-**3c***

The general procedure was followed for the acylation of 392 mg (1.65 mmol) of **1c** for 24 h. Purification of the mixture by flash chromatography (ethyl acetate:hexane, 2:1) afforded 194 mg (49.5% yield) of (R_s,S_c)-**1c**, and 227 mg (49.3% yield) of (R_s,R_c)-**3c** as viscous oils.

Compound (R_s,S_c)-**1c**: d.e. 98%. $[\alpha]_D = +236$ (c 2.6, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H, CH_3), 1.31–1.40 (m, 2H, -CH_2-, 1.52 (m, 2H, -CH_2-), 2.36 (s, 3H, CH_3Ar), 3.43 (br, 1H, OH), 4.25 (m, 1H, CH(OH)), 6.38 (dd, $J_{anti} = 15.0$ Hz, $J_{1,3} = 1.4$ Hz, 1H, =CH-S(O)), 6.56 (dd, $J_{anti} = 15.0$ Hz, $J_{2,3} = 4.6$ Hz, 1H, CH=), 7.25–7.44 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (125.72 MHz, $CDCl_3$) δ 13.7, 18.4, 21.2, 38.6, 70.3, 124.7, 129.9, 133.1, 139.9, 141.6, 142.3. HRMS calcd m/z for $C_{13}H_{18}O_2S$: 238.1041. Found: 238.1027.

Compound (R_s,R_c)-**3c**: d.e. 98%. $[\alpha]_D = +154.8$ (c 6.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, J = 7.4 Hz, 3H, CH_3), 1.28–1.34 (m, 2H, -CH_2-), 1.59–1.66 (m, 2H, -CH_2-), 2.01 (s, 3H, CH_3CO), 2.37 (s, 3H, CH_3Ar), 5.40 (m, 1H, CH($OCOCH_3$)), 6.35 (dd, $J_{anti} = 15.1$ Hz, $J_{1,3} = 1.2$ Hz, 1H, =CH-S(O)), 6.48 (dd, $J_{anti} = 15.1$ Hz, $J_{2,3} = 5.7$ Hz, 1H, CH=), 7.26–7.45 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (125.72 MHz, $CDCl_3$) δ 13.4, 17.8, 20.6, 21.7, 35.7, 71.9, 124.6, 129.8, 135.1, 135.6, 139.8, 141.5, 169.6. HRMS calcd m/z for $C_{15}H_{20}O_3S$: 280.1115. Found: 280.1056. Anal. calcd for $C_{15}H_{20}O_3S$: C, 64.25; H, 7.19. Found: C, 64.56; H, 7.23.

*3.2.5. (R_s,S_c)-(E)-1-(p-Tolylsulfinyl)-1-octen-3-ol (R_s,S_c)-**1d** and (R_s,R_c)-(E)-3-acetoxy-1-(p-tolylsulfinyl)-1-octene (R_s,R_c)-**3d***

The general procedure was followed for the acylation of 685 mg (2.57 mmol) of **1d** for 3 h. Purification of the mixture by flash chromatography (ethyl acetate:hexane, 2:1) afforded 336 mg (49.0% yield) of (R_s,S_c)-**1d**, and 390 mg (49.2% yield) of (R_s,R_c)-**3d** as viscous oils.

Compound (R_s,S_c)-**1d**: d.e. 96%. $[\alpha]_D = +294$ (c 2.8, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.9 Hz, 3H, CH_3), 1.26–1.42 (m, 6H, $(CH_2)_3$), 1.61 (m, 2H, -CH_2-), 2.23 (br, 1H, OH), 2.40 (s, 3H, CH_3Ar), 4.33 (m, 1H, CH(OH)), 6.44 (dd, $J_{anti} = 15.0$ Hz, $J_{1,3} = 1.6$ Hz, 1H, =CH-S(O)), 6.60 (dd, $J_{anti} = 15.0$ Hz, $J_{2,3} = 4.6$ Hz, 1H, CH=), 7.30–7.49 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (125.72 MHz, $CDCl_3$) δ 13.8, 21.4, 22.54, 24.88, 31.5, 36.2, 70.8, 124.6, 129.9, 133.5, 140.3, 141.4, 141.9. HRMS calcd m/z for $C_{15}H_{22}O_2S$: 266.1361. Found: 266.1340.

Compound (R_s,R_c)-**3d**: d.e. 98%. $[\alpha]_D = +223$ (c 3.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, J = 7.4 Hz, 3H, CH_3), 1.19–1.38 (m, 6H, $(CH_2)_3$), 1.63–1.69 (m, 2H, –CH_2–), 2.05 (s, 3H, CH_3CO), 2.40 (s, 3H, CH_3Ar), 5.40 (m, 1H, CH($OCOCH_3$)), 6.37 (dd, $J_{anti} = 15.1$ Hz, $J_{1,3} = 1.2$ Hz, 1H, =CH-S(O)), 6.51 (dd, $J_{anti} = 15.1$ Hz, $J_{2,3} = 5.7$ Hz, 1H, CH=), 7.30–7.48 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (125.72 MHz, $CDCl_3$) δ 13.8, 21.1, 21.3, 22.3, 24.4, 31.3, 33.8, 72.4, 124.9, 130.1, 135.4, 135.9, 140.0, 141.9, 169.9. HRMS calcd m/z for $C_{17}H_{24}O_3S$: 308.1446. Found: 308.1446. Anal. calcd for $C_{17}H_{24}O_3S$: C, 66.20; H, 7.84. Found: C, 65.96; H, 7.71.

*3.2.6. (R_s,S_c)-(E)-4-Methyl-1-(p-tolylsulfinyl)-1-penten-3-ol (R_s,S_c)-**1e** and (R_s,R_c)-(E)-3-acetoxy-4-methyl-1-(p-tolylsulfinyl)-1-pentene (R_s,R_c)-**3e***

The general procedure was followed for the acylation of 304 mg (1.27 mmol) of **1e** for 10 days. Purification of the mixture by flash chromatography (ethyl acetate:hexane:ether, 6:3:1) afforded 147 mg (48.4% yield) of (R_s,S_c)-**1e** as a viscous oil, and 175 mg (49.2% yield) of (R_s,R_c)-**3e** as a viscous oil.

Compound (R_s,S_c)-**1e**: d.e. 96%. $[\alpha]_D = +225$ (*c* 4.7, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, J = 6.7 Hz, 6H, $(CH_3)_2$), 1.25 (s, 1H, OH), 1.83 (oct, J = 6.7 Hz, 1H, CH), 2.39 (s, 3H, CH_3Ar), 4.12 (m, 1H, CH(OH)), 6.44 (dd, $J_{anti} = 15.0$ Hz, $J_{1,3} = 1.5$ Hz, 1H, =CH-S(O)), 6.60 (dd, $J_{anti} = 15.0$ Hz, $J_{2,3} = 4.8$ Hz, 1H, CH=), 7.29–7.49 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (125.72 MHz, $CDCl_3$) δ 17.7, 18.2, 21.3, 33.5, 75.9, 124.5, 130.2, 134.7, 139.9, 141.3, 141.8. HRMS calcd *m*/*z* for $C_{13}H_{18}O_2S$: 238.1028. Found: 238.1027.

Compound (R_s,R_c)-**3e**: d.e. 98%. $[\alpha]_D = +195$ (*c* 4.1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (d, J = 6.8 Hz, 6H, $(CH_3)_2$), 1.95 (m, 1H, CH), 2.04 (s, 3H, CH_3CO), 2.38 (s, 3H, CH_3Ar), 5.24 (m, 1H, $CH(OCOCH_3)$), 6.37 (dd, $J_{anti} = 15.1$ Hz, $J_{1,3} = 1.2$ Hz, 1H, =CH–(O)), 6.50 (dd, $J_{anti} = 15.1$ Hz, $J_{2,3} = 5.8$ Hz, 1H, CH=), 7.29–7.47 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (125.72 MHz, $CDCl_3$) δ 17.6, 17.8, 20.8, 21.3, 31.9, 76.7, 124.9, 130.0, 134.0, 136.4, 139.7, 141.9, 169.9. HRMS calcd *m*/*z* for $C_{15}H_{20}O_3S$: 280.1116. Found: 280.1176. Anal. calcd for $C_{15}H_{20}O_3S$: C, 64.25; H, 7.19. Found: C, 63.77; H, 6.97.

*3.2.7. (R$_s$,R$_c$)-(E)-3-Acetoxy-4,4-dimethyl-1-(p-tolylsulfinyl)-1-pentene (R$_s$,R$_c$)-**3f***

The general procedure was followed for the acylation of 330 mg (1.19 mmol) of **1f** for 12 days. Purification of mixture by flash chromatography (ethyl acetate:hexane, 3:2) afforded 13 mg (7.4% yield) of (R_s,R_c)-**3f** as a viscous oil.

Compound (R_s,R_c)-**3f**: d.e. 98%. $[\alpha]_D = +118$ (*c* 1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 0.9 (s, 9H, $(CH_3)_3$), 2.02 (s, 3H, CH_3CO), 2.37 (s, 3H, CH_3Ar), 5.14 (dd, $J_{2,3} = 6.1$ Hz, $J_{1,3} = 1.1$ Hz, 1H, $CH(OCOCH_3)$), 6.31 (dd, $J_{anti} = 15.1$ Hz, $J_{1,3} = 1.1$ Hz, 1H, =CH-S(O)), 6.55 (dd, $J_{anti} = 15.1$ Hz, $J_{2,3} = 6.1$ Hz, 1H, CH=), 7.27–7.45 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (125.72 MHz, $CDCl_3$) δ 20.9, 21.4, 25.7, 34.9, 79.3, 125.0, 130.1, 133.3, 137.3, 140.0, 141.9, 170.0. HRMS calcd *m*/*z* for $C_{16}H_{22}O_3S$: 294.1289. Found: 294.1345.

*3.3. (S)-(+)-(E)-3-Hydroxy-1-(p-tolylsulfones) (**4c** and **4d**)*

Derivatives **4c** and **4d** were prepared by oxidation of optically pure sulfoxides (R_s,S_c)-**1c** and (R_s,S_c)-**1d** according to the procedure described by Trost et al.[20]

*3.4. (R)-(+)-(E)-3-Acetoxy-1-(p-tolylsulfonyl)-1-hexenene **5c***

A solution of (R_s,R_c)-**3c** (42 mg, 0.38 mmol) in 4 mL of methanol was treated with 93 mg (0.15 mmol) of Oxone® in 2 mL of water. The reaction mixture was stirred at room temperature for 3 h. The aqueous phase was extracted with CH_2Cl_2 (15 mL). The combined extracts were dried (Na_2SO_4), filtered, and evaporated under reduced pressure to afford 44 mg (98% yield) of (*R*)-**5c** as a viscous oil; e.e. 98%. $[\alpha]_D = +12.8$ (*c* 4.4, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 0.84 (t, J = 7.1 Hz, 3H, CH_3), 1.18–1.33 (m, 2H, -CH_2-), 1.53–1.65 (m, 2H, -CH_2-, 1.99 (s, 3H, CH_3CO), 2.37 (s, 3H, CH_3Ar), 5.38 (m, 1H, $CH(OCOCH_3)$), 6.37 (dd, $J_{anti} = 15.1$ Hz, $J_{1,3} = 1.6$ Hz, 1H, =CH-SO_2), 6.81 (dd, $J_{anti} = 15.1$ Hz, $J_{2,3} = 4.6$ Hz, 1H, CH=), 7.27–7.68 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (125.72 MHz, $CDCl_3$) δ 13.6, 18.0, 21.5, 22.6, 35.6, 71.2, 127.7, 129.9, 130.8, 136.9, 143.0, 144.5, 169.7. HRMS calcd *m*/*z* for $C_{15}H_{20}O_4S$: 296.1081. Found: 296.1085.

*3.5. (R)-(+)-(E)-3-Acetoxy-1-(p-tolylsulfonyl)-1-octenene **5d***

A solution of (R_s,R_c)-**3d** (50 mg, 0.16 mmol) in 5 mL of methanol was treated with 100 mg (0.16 mmol) of Oxone® in 3 mL of water. The reaction mixture was stirred at room temperature

for 3 h. The aqueous phase was extracted with CH_2Cl_2 (15 mL). The combined extracts were dried (Na_2SO_4), filtered, and evaporated under reduced pressure to afford 51 mg (95% yield) of (*R*)-**5d** as a viscous oil; e.e. 98%. $[\alpha]_D = +7.8$ (*c* 1.6, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 0.75 (t, J = 6.2 Hz, 3H, CH_3), 1.12–1.23 (m, 6H, $(CH_2)_3$), 1.51–1.62 (m, 2H, -CH_2-), 1.95 (s, 3H, CH_3CO), 2.32 (s, 3H, CH_3Ar), 5.30–5.40 (m, 1H, $CH(OCOCH_3)$), 6.36 (dd, $J_{anti} = 15.1$ Hz, $J_{1,3} = 1.6$ Hz, 1H, =CH-SO_2), 6.79 (dd, $J_{anti} = 15.1$ Hz, $J_{2,3} = 4.6$ Hz, 1H, CH=), 7.23–7.65 (AA′BB′ system, 4H, aromatic). ^{13}C NMR (125.72 MHz, $CDCl_3$) δ 13.6, 20.6, 21.3, 22.1, 24.1, 31.0, 33.2, 71.1, 127.4, 129.7, 130.7, 136.8, 142.9, 144.3, 169.5. HRMS calcd *m*/*z* for $C_{17}H_{24}O_4S$: 324.1393. Found: 324.1397.

3.6. (R)-(–)-(E)-1-(p-*Tolylsulfonyl*)-1-hexen-3-ol **6c**

A solution of **5c** (26 mg, 0.08 mmol) in 4.5 mL of methanol:H_2O:Et_3N (1:1:1) was stirred at room temperature for 8 h. The reaction was quenched by the addition of 10% hydrochloric acid (5 mL), and the aqueous phase was extracted with CH_2Cl_2 (15 mL). The combined extracts were washed successively with saturated aqueous $NaHCO_3$ solution (5 mL) and saturated aqueous NaCl solution (5 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford 19 mg (86.4% yield) of (*R*)-**6c** as a white solid; m.p. 89–90°C. $[\alpha]_D = -43.6$ (*c* 1.8, $CHCl_3$); e.e. 98%. ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, J = 7.1 Hz, 3H, CH_3), 1.56–1.28 (m, 4H, $(CH_2)_2$), 2.38 (s, 3H, CH_3Ar), 2.48 (br, 1H, OH), 4.27–4.32 (m, 1H, CH(OH)), 6.52 (dd, $J_{anti} = 14.9$ Hz, $J_{1,3} = 1.8$ Hz, 1H, =CH-SO_2), 6.89 (dd, $J_{anti} = 14.9$ Hz, $J_{2,3} = 3.8$ Hz, 1H, CH=), 7.28–7.69 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (125.72 MHz, $CDCl_3$) δ 13.7, 18.3, 21.5, 38.2, 69.8, 127.5, 129.8, 137.1, 144.3, 148.0. HRMS calcd *m*/*z* for $C_{13}H_{18}O_3S$: 254.0982. Found: 254.0963.

3.7. (R)-(–)-(E)-1-(p-*Tolylsulfonyl*)-1-octen-3-ol **6d**

A solution of **5d** (46 mg, 0.14 mmol) in 9 mL of methanol:H_2O:Et_3N (1:1:1) was stirred at room temperature for 8 h. The reaction was quenched by addition of 10% hydrochloric acid (10 mL), and the aqueous phase was extracted with CH_2Cl_2 (25 mL). The combined extracts were washed successively with a saturated aqueous $NaHCO_3$ solution (10 mL) and saturated aqueous NaCl solution (10 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford 35 mg (87.5% yield) of (*R*)-**6d** as a white solid; m.p. 103–105°C. $[\alpha]_D = -39.5$ (*c* 2.4, $CHCl_3$); e.e. 98%. ^1H NMR (500 MHz, $CDCl_3$) δ 0.78 (t, J = 7.1 Hz, 3H, CH_3), 1.17–1.41 (m, 6H, $(CH_2)_3$), 1.40–1.48 (m, 2H, -CH_2-), 2.34 (s, 3H, CH_3Ar), 3.02 (br, 1H, OH), 4.23 (m, 1H, CH(OH)), 6.48 (dd, $J_{anti} = 14.9$ Hz, $J_{1,3} = 1.7$ Hz, 1H, =CH-SO_2), 6.85 (dd, $J_{anti} = 14.9$ Hz, $J_{2,3} = 3.8$ Hz, 1H, CH=), 7.23–7.65 (AA′BB′ system, 4H, aromatics). ^{13}C NMR (125.72 MHz, $CDCl_3$) δ 13.7, 21.3, 22.2, 24.6, 31.3, 36.0, 69.8, 127.3, 129.7, 137.0, 144.2, 148.2. HRMS calcd *m*/*z* for $C_{15}H_{22}O_3S$: 282,1290. Found: 282,1274.

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