Short and Efficient Synthesis of Enantiomerically Pure 4-Substituted (1*E*,3*E*)-1[(*R*)-*p*-Tolylsulfinyl]-1,3-butadienes

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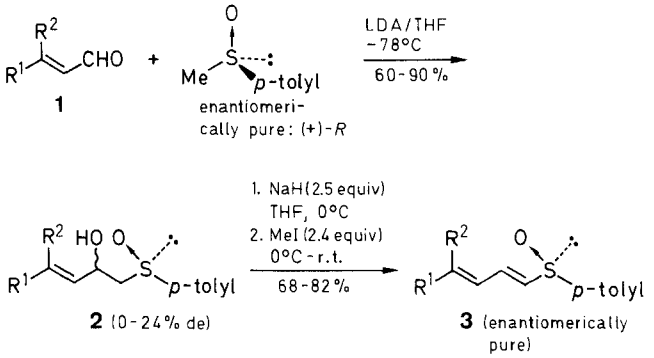
The title compounds were readily prepared in two steps by the condensation of (+)-methyl *p*-tolyl (*R*)-sulfoxide to α,β-unsaturated aldehydes followed by a one-pot dehydration of the resulting β-hydroxy sulfoxides.

Although optically active sulfinyl dienophiles[1-5] and very recently vinyl sulfoxonium salts[6] have been used in many asymmetric Diels–Alder reactions, very little has been done with sulfinyl dienes. The successful use of heterosubstituted 1,3-dienes, and particularly with a sulfinyl substituent, in cycloadditions was reported only in three papers[7-9] in which the sulfoxide group was racemic.

We report in this paper a short and efficient synthesis of optically active 4-substituted (1*E*,3*E*)-1-[(*R*)-*p*-tolylsulfinyl]-1,3-butadienes.

(+)-Methyl *p*-tolyl (*R*)-sulfoxide[10] was reacted in the presence of lithium diisopropylamide (LDA) with α,β-unsaturated aldehydes **1** to give the corresponding β-hydroxy sulfoxides **2** as a mixture of diastereoisomers (Table 1). Compounds **2** were easily dehydrated with an excess of sodium hydride and methyl iodide at room temperature leading to dienes **3** in high yield. The all-*trans* configuration was easily established from ^{1}H-NMR coupling constants. These new dienes are stable and most of them are crystalline solids (Table 2).



1–3	R^1	R^2	1–3	R^1	R^2
a	Me	H	**d**	Ph	H
b	Me	Me	**e**	2-$MeOC_6H_4$	H
c	Et	H			

Table 1. Compounds **2** Prepared

Product	Yield[a] (%)	Diastereoisomeric Ratio[b] I/II	^{1}H-NMR (200 MHz, $CDCl_3$/TMS) δ, *J* (Hz)[c]
2a	83	54 : 46	1.64 (pseudo td, 3H, =CHC$\underline{H}_3$), 2.39 (s, 3H, ArC$\underline{H}_3$), 2.84 (ABX system, 2H, diastereo- isomer II, J_{AB} = 13.3, J_{AX} = 9.8, J_{BX} = 2.5, $\Delta\nu$ = 50 Hz, CH_2S), 2.90 (ABX system, 2H, diastereoisomer I, J_{AB} = 13, J_{AX} = 8.6, J_{BX} = 4, $\Delta\nu$ = 65 Hz, CH_2S), 3.92 (br s, 0.46H, OH), 4.17 (br s, 0.54H, OH), 4.55–4.66 (m, 1H, H-2), 5.44–5.56 (m, 1H, H-3), 5.72–5.86 (m, 1H, H-4), 7.29–7.56 (2 AA'BB' systems, $4H_{arom}$)
2b	37	50 : 50	1.48, 1.66, 1.69, 1.71 [4d, 6H, *J* = 1.3, =C(CH_3)$_2$], 2.41 (s, 3H, ArC$\underline{H}_3$), 2.80 (ABX system, 2H, diastereoisomer I, J_{AB} = 13.5, J_{AX} = 9.2, J_{BX} = 2.3, $\Delta\nu$ = 92 Hz, CH_2S), 2.90 (ABX system, 2H, diastereoisomer II, J_{AB} = 13, J_{AX} = 7.3, J_{BX} = 3.9, $\Delta\nu$ = 82 Hz, CH_2S), 3.55 (br s, 0.5H, OH), 3.80 (br s, 0.5H, OH), 4.90–5.00 (m, 1H, H-2), 5.20 (H-3), 7.30–7.56 (2 AA'BB' systems, $4H_{arom}$)
2c	92	62 : 38	0.90–1.00 (2t, 3H, C$\underline{H}_3$CH$_2$), 1.93–2.10 (m, 2H, CH_2CH=C), 2.40 (s, 3H, ArC$\underline{H}_3$), 2.85 (ABX system, 0.76H, J_{AB} = 13.4, J_{AX} = 9.8, J_{BX} = 2.4, $\Delta\nu$ = 54 Hz, CH_2S), 2.90 (ABX system, 1.24H, J_{AB} = 13, J_{AX} = 8.8, J_{BX} = 3.7, $\Delta\nu$ = 63 Hz, CH_2S), 3.90 (br s, 1H, OH), 4.60–4.69 (m, 1H, H-2), 5.37–5.52 (m, 1H, H-3), 5.68–5.88 (m, 1H, H-4), 7.29–7.57 (2 AA'BB' systems, $4H_{arom}$)
2d	82	40 : 60	2.39 (s, 3H, ArC$\underline{H}_3$), 2.95 (ABX system, 2H, diastereoisomer I, J_{AB} = 13.3, J_{AX} = 9.8, J_{BX} = 2.5, $\Delta\nu$ = 43 Hz, CH_2S), 3.0 (ABX system, 2H, diastereoisomer II, J_{AB} = 13, J_{AX} = 8.5, J_{BX} = 4, $\Delta\nu$ = 62 Hz, CH_2S), 4.30 (br s, 0.4H, OH), 4.60 (br s, 0.6H, OH), 4.80–4.95 (m, 1H, H-2), 6.10–6.25 (m, 1H, H-3), 6.61–6.72 (m, 1H, H-4), 7.18–7.59 (m, $9H_{arom}$)
2e	64	42 : 58	2.38 (s, 3H, ArC$\underline{H}_3$), 2.95 (ABX system, 2H, diastereoisomer I, J_{AB} = 13.3, J_{AX} = 9.9, J_{BX} = 2.5, $\Delta\nu$ = 44 Hz, CH_2S), 3.0 (ABX system, 2H, diastereoisomer II, J_{AB} = 13, J_{AX} = 8.8, J_{BX} = 3.8, $\Delta\nu$ = 63 Hz, CH_2S), 3.77, 3.78 (2S, 3H each, OCH_3), 4.13 (br s, 0.58H, OH), 4.40 (br s, 0.42H, OH), 4.75–4.88 (m, 1H, H-2), 6.13–6.28 (m, 1H, H-3), 6.80–7.57 (m, $9H_{arom}$ + H-4)

[a] Yield of isolated products. The oily products are purified by column chromatography and are not distilled.
[b] Determined by ^{1}H-NMR spectra.
[c] Chemical shift values and coupling constants for CH_2S and OH groups of both the stereoisomers are given.

Table 2. Compounds **3** Prepared

Product	Reaction Time (h)	Yield (%)[a]	mp (°C)	$[\alpha]_D^{r.t.}$ (*c*, acetone)	Molecular Formular[b]	^{1}H-NMR (200 MHz, $CDCl_3$/TMS), δ, *J* (Hz)	^{13}C-NMR (50.3 MHz, $CDCl_3$/TMS)
3a	24	68	73–74	+224.5 (0.37)	$C_{12}H_{14}OS$ (206.3)	1.81 (d, 3H, *J* = 5.4, =CHC$\underline{H}_3$), 2.38 (s, 3H, ArC$\underline{H}_3$), 6.04–6.11 (m, 2H, H-3, 4), 6.18 (d, 1H, *J* = 15.2, H-1), 6.86–6.99 (m, 1H, H-2), 7.25–7.51 (AA'BB' system, 4H_{arom})	18.4 (C-5), 21.3 (Ar$\underline{C}H_3$), 124.6, 128.2, 129.9, 133.1, 137.0, 137.5 (C-1, 2, 4 and CH_{arom}), 141.0, 141.3 ($CH_3\underline{C}_{arom}$ and $S\underline{C}_{arom}$)
3b	24	69	55	+216.1 (0.74)	$C_{13}H_{16}OS$ (220.3)	1.85, 1.90 (2s, 3H each, 2CH_3), 2.40 (s, 3H, ArC$\underline{H}_3$), 5.91 (dm, 1H, *J* = 11.3, H-3), 6.19 (d, 1H, *J* = 14.8, H-1), 7.22 (dd, 1H, *J* = 14.8, 11.3, H-2), 7.27–7.53 (AA'BB' system, 4H_{arom})	18.7, 21.3, 26.3 [=C($\underline{C}H_3$)$_2$ and Ar$\underline{C}H_3$), 124.6, 129.9 (CH_{arom}), 122.1 (C-3), 132.9 (C-2), 133.7 (C-1), 141.2, 144.5 ($CH_3\underline{C}_{arom}$ and $S\underline{C}_{arom}$)
3c	12	72	45	+269.3 (1.88)	$C_{13}H_{16}OS$ (220.3)	0.99 (t, 3H, *J* = 7.4, $C\underline{H}_3CH_2$), 2.13 (qd, 2H, *J* = 7.4, 4.6, $CH_3C\underline{H}_2$), 2.36 (s, 3H, ArC$\underline{H}_3$), 6.05–6.10 (m, 2H, H-3, 4), 6.19 (d, 1H, *J* = 14.7, H-1), 6.92 (ddd, 1H, *J* = 14.7, 6.4, 3.6, H-2), 7.24–7.50 (AA'BB' system, 4H_{arom})	12.7 (C-6), 21.2 (Ar$\underline{C}H_3$), 25.7 (C-5), 124.5, 125.8, 129.8, 133.3, 137.1, 144.2 (C-1, 2, 3, 4 and CH_{arom}), 141.0, 141.2 ($CH_3\underline{C}_{arom}$ and $S\underline{C}_{arom}$)
3d	12	82	102.3	+225.1 (0.82)	$C_{17}H_{16}OS$ (268.4)	2.42 (s, 3H, ArC$\underline{H}_3$), 6.44 (d, 1H, *J* = 14.7, H-1), 6.81–6.85 (m, 2H, H-3, 4), 7.15 (ddd, 1H, *J* = 14.7, 8.2, 1.8, H-2), 7.29–7.58 (m, 9H_{arom})	21.4 (Ar$\underline{C}H_3$), 124.7, 124.8, 127.0, 128.7, 128.8, 130.0, 135.6, 135.9, 136.2, 138.8 (C-1, 2, 3, 4 and CH_{arom}), 135.6 (=$C\underline{C}_{arom}$), 140.8, 141.6 ($CH_3\underline{C}_{arom}$ and $S\underline{C}_{arom}$)
3e	12	70	oil	+121.2 (1.74)	$C_{18}H_{18}O_2S$ (298.4)	2.40 (s, 3H, ArC$\underline{H}_3$), 3.86 (s, 3H, CH_3O), 6.41 (d, 1H, *J* = 14.6, H-1), 6.78–6.96 (m, 3H, H-2, 3, 4), 7.10–7.57 (m, 8H_{arom})	21.2 (Ar$\underline{C}H_3$), 55.3 ($\underline{O}CH_3$), 110.9, 120.6, 124.5, 124.6, 124.7, 125.3, 127.2, 129.9, 134.2, 134.8, 137.6 (C-1, 2, 3, 4 and CH_{arom}), 141.0, 141.3 ($CH_3\underline{C}_{arom}$ and $S\underline{C}_{arom}$), 157.2 ($CH_3O\underline{C}_{arom}$)

[a] Yield of isolated products.

[b] Satisfactory microanalyses obtained: C ±0.29, H ±0.30.

In summary, we have presented an easy and short route to enantiomerically pure toluenesulfinyl butadiene derivatives, which are useful for the synthesis of chiral compounds.

Condensation of (+)-Methyl *p*-Tolyl (*R*)-Sulfoxide to α,β-Unsaturated Aldehydes 1; General Procedure:

To a solution of diisopropylamine (115 μL, 0.818 mmol) in dry THF (1 mL) cooled to −50 °C, is added slowly a solution of BuLi in hexane (1.55 M, 520 μL, 0.779 mmol) under an Ar atmosphere. The mixture is stirred at −50 °C for 30 min. Then a solution of (+)-methyl *p*-tolyl (*R*)-sulfoxide (100 mg, 0.649 mmol) in THF (6.5 mL) cooled to −50 °C, is added slowly and the resulting mixture stirred at the same temperature for 30 min. Then after cooling down to −78 °C, the corresponding aldehyde **1** (1.298 mmol) is added. The resulting solution is stirred at −78 °C and the progress of the reaction was monitored by TLC (hexane/EtOAc, 3:7). The mixture is hydrolyzed by addition of a sat. aq NH_4Cl solution (10 ml), extracted with CH_2Cl_2 (3 × 10 mL), dried (Na_2SO_4) and the solvent evaporated. The product is purified by flash chromatography (hexane/EtOAc, 3:7) (Table 1).

4-Substituted (1*E*,3*E*)-1-[(*R*)-*p*-Tolylsulfinyl]-1,3-butadienes 3; General Procedure:

A solution of the corresponding diasteromeric mixture of β-hydroxy sulfoxides **2a–e** in dry THF (10 mL per mmol) is slowly added to a cold (0 °C) slurry of NaH (2.5 equiv) in THF (2.4 mL per mmol). The resulting mixture is stirred for 20 min. Then MeI (2.4 equiv) is added via a syringe and after 30 min at 0 °C, the mixture is allowed to reach r.t. and stirred till the total conversion of the starting product is achieved (TLC, hexane/EtOAc, 7:3). The mixture is diluted with Et_2O and filtered through Celite. The resulting solution is washed twice with a sat. solution of $NaHCO_3$ (2 × 10 mL), dried (Na_2SO_4) and the solvents evaporated. The product is purified by flash chromatography (hexane/EtOAc, 8:2) (Table 2).

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