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An Efficient Resolution of (±)-*p*-Tolylvinylsulfoxide Using (-)-Menthol.

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Abstract : The preparation of enantiopure (+)-(R)$_S$ and (-)-(S)$_S$-*p*-tolylvinylsulfoxide using (-)-menthol as a resolving agent is described. © 1998 Published by Elsevier Science Ltd. All rights reserved.

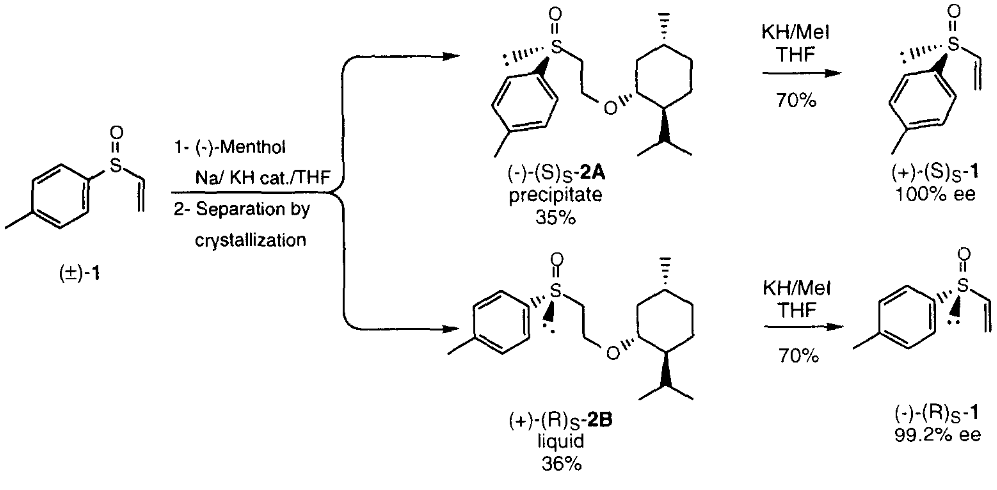
The use of sulfinyl group as chiral auxiliary is now well established in asymmetric syntheses.[1] In particular enantiopure α,β-unsaturated sulfoxides have been used in many stereoselective reactions and this methodology has been applied to the preparation of a number of natural products with high enantiomeric excess.[1b,2]

(R)$_S$ or (S)$_S$-*p*-tolylvinylsulfoxide was shown to be of great importance as synthetic intermediates in the obtention of other useful members of this class such as sulfinylhomo[3]- and hetero[4]-dienes.

The most popular approach is based on the S_N2 reaction[5] between vinylmagnesium chloride and (-)-menthylsulfinate.[6]

We wish to report an inexpensive, practical and efficient method for the resolution of readily available racemic *p*-tolylvinylsulfoxide[7] (±)-**1** using (-)-menthol as a chiral resolving agent.

Indeed, the conjugate heteroaddition of (-)-menthol onto (±)-*p*-tolylvinylsulfoxide was performed in THF at room temperature in the presence of NaH (1 equiv.) and a catalytic amount of KH and led to the crystalline (-)-2-menthoxyethyl-*p*-tolylsulfoxide **2A** and its liquid (+)-diastereomer **2B**.



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The adduct (-)-(S)$_S$-**2A**[8] was isolated in 72% yield after filtration of the precipitate appeared upon addition of diethyl ether onto the crude product and recrystallization in pentane/ether. Column chromatography on silica gel (ethylacetate-cyclohexane : 1-9) of the mother liquor residue afforded in order of elution the liquid diastereomer (+)-(R)$_S$-**2B**[8] in a 70% yield and the residual (-)-(S)$_S$-**2A** (10% yield).

Treatment of each diastereomer (-)-(S)$_S$-**2A** and (+)-(R)$_S$-**2B** with an excess of KH (2 equiv.) in THF at room temperature in the presence of methyliodide (2 equiv.) as a scavenger of the forming menthylate gave corresponding enantiopure (+)-(S)$_S$-**1**[9] and (-)-(R)$_S$-**1**[9] *p*-tolylvinylsulfoxide in 70% yield after chromatography on silica gel (ethylacetate-cyclohexane : 4-96).

The present work offers the only resolution method of (±)-*p*-tolylvinylsulfoxide and allows the obtention of each enantiomer in a very simple and practical way based on the easy separation of one crystalline diastereomer intermediate obtained from racemic *p*-tolylvinylsulfoxide and (-)-menthol.

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8. To a stirred suspension of NaH (2 g ; 50 mmol) in THF (25 mL) was added dropwise a solution of (-)-menthol (7.81 g ; 50 mmol) in THF (75 mL) at room temperature. After 30 min., a solution of (±)-**1** (8.32 g ; 50 mmol) in THF (25 mL) was added dropwise. Then a small piece of KH was added to the mixture, and the reaction was stirred for 3 hrs, terminated by the addition of moist ether (50 mL). The mixture was washed (water), extracted (CH_2Cl_2, 3 x 50), dried ($MgSO_4$) and concentrated to give an oil. After addition of ether, the precipitate of (-)-(S)$_S$-**2A** was filtered off. Recrystallization of the precipitate from ether/pentane gave 4.77 g of (-)-(S)$_S$-**2A** in 72% yield. The mother liquid was chromatographed on silicagel using cyclohexane/ethyl acetate as the eluent afforing 5.73 g of liquid (+)-(R)$_S$-**2B** (70% yield) and 0,99 g of the residual (-)-(S)$_S$-**2A** (10% yield). (-)-(S)$_S$-**2A** : mp 109-110 °C (pentane-ether) ; $[\alpha]_D$ - 186.6 (c 0.56, acetone). ^{1}H NMR δ 0.76 (d, J = 7 Hz, 3H, 0.90 (d, J = 7 Hz, 3H, 0.92 (2d, J = 6.6 Hz, 3H, 0.80-1.03 (m, 2H), 1.20-1.40 (2m, 2H), 1.65 (m, 3H), 2.17 (m, 2H), 2.42 (s, 3H), 2.96 (m, 2H), 3.06 (td, J = 10.6 et 4.1 Hz, 1H), 3.56 (td, J = 10.2 and 4.7 Hz, 1H), 4.07 (m, 1H), 7.32 and 7.44 (2d, AB system, J = 8 Hz, 4H). ^{13}C NMR δ 15.17 (q), 16.20 (q), 20.86 (q), 21.30 (q), 22.17 (q), 23.15 (t), 25.41 (d), 31.40 (d), 34.34 (t), 40.05 (t), 47.97 (d), 58.92 (t), 61.26 (t), 79.58 (d), 123.90 (d), 129.82 (d), 140.95 (s), 141.28 (s). (+)-(R)$_S$-**2B** : $[\alpha]_D$ + 60.5 (c 0.83, acetone). ^{1}H NMR δ 0.81 (d, J = 7 Hz, 3H), 0.92 (2d, J = 7 Hz, 6H), 0.90-1.06 (m, 2H), 1.20-1.40 (2m, 2H), 1.65 (m, 3H), 2.10-2.31 (m, 2H), 2.41 (s, 3H), 2.96 (m, 2H), 3.19 (td, J = 10.6 and 4.1 Hz, 1H), 3.79 (m, 1H), 3.91 (td, J = 10.2 and 4.7 Hz, 1H), 7.34 and 7.55 (2d, AB system, J = 8 Hz, 4H). ^{13}C NMR δ 16.29 (q), 20.97 (q), 21.41 (q), 22.32 (q), 23.29 (t), 25.65 (d), 31.42 (d), 34.53 (t), 40.23 (t), 48.30 (d), 59.27 (t), 61.11 (t), 80.09 (d), 123.92 (d), 129.92 (d), 141.18 (s), 141.30 (s). ; (Found : C, 70.09 ; H, 9.15 ; S, 10.39%. $C_{19}H_{30}O_2S$ requires C, 70.14 ; H, 9.05 ; S, 10.45%.)
9. To a solution of KH (2.29 g ; 20 mmol) in THF (100 mL) was added dropwise (+)-(R)$_S$-**2B** (3.22 g ; 10 mmol) in THF (50 mL) at room temperature. After 5 min., methyl iodide (1.26 mL ; 20 mmol) in THF (50 mL) was added dropwise. The reaction was stirred for 3 hrs, terminated by addition of ether (100 mL) and quenched by addition of aqueous NaCl solution (100 mL). Extractive work-up with ether (3 x 30 mL) gave 1 g of (-)-(R)$_S$-**1** (70% yield) after chromatography on silicagel using cyclohexane/ethyl acetate as the eluent. (+)-(R)$_S$-**1** : $[\alpha]_D$ + 400 (c 1.0, ethanol) ; (-)-(S)$_S$-**1** : $[\alpha]_D$ - 402 (c 0.87, ethanol). An enantiomeric excess of 100% for (+)-(S)$_S$-**1** and 99.2 % for (-)-(R)$_S$-**1** was determinated by chiral GL on CP-chirasil-DEX CB.