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AN EFFICIENT SYNTHESIS OF CHIRAL 2-(*p*-TOLYLSULFINYL)-2-BUTENOLIDES

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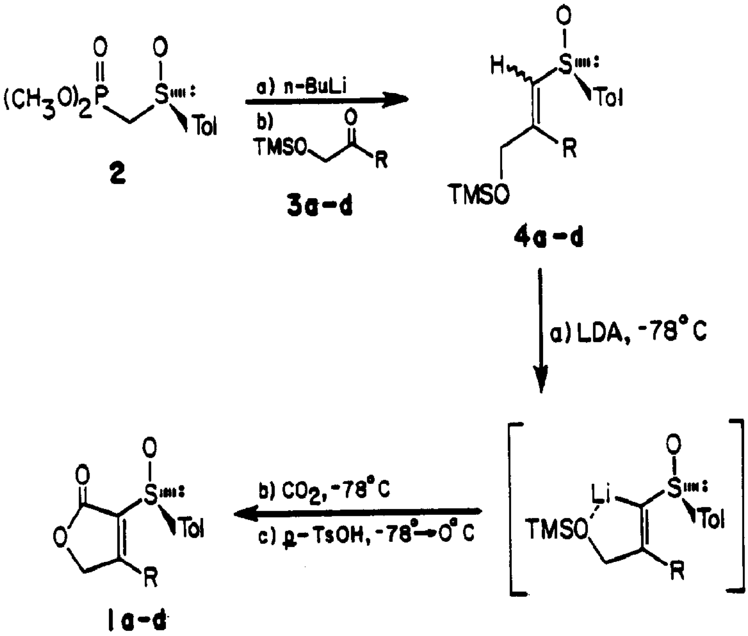
Summary: A high yield, two-step synthesis of enantiomerically pure 2-(*p*-tolylsulfinyl)-2-butenolides has been developed. The method is applicable to the preparation of butenolides having a variety of substituents in the 3-position.

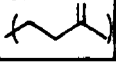
Chiral α-sulfinyl α,β-unsaturated carbonyl compounds have recently attracted much interest due to their ability to direct the conjugate addition of organocopper or magnesium reagents with a high degree of stereocontrol. Futhermore, the sulfinyl group may be subsequently removed, thereby providing convenient preparations of a variety of 3-alkyl cycloalkanes of high optical purity.[2]

This methodology has recently been extended to include the conversion of S-(+)-2-(*p*-tolylsulfinyl)-2-buten-4-olide (**1a**) to the lignan lactone (-)-podorhizon.[3] For this purpose, the preparation of **1a** in five steps and 20% overall yield from *E*-3-iodo-2-propen-1-ol was developed.[3,4]

Due to our interest in studying the stereochemical course of the Michael addition[5] and its application to the synthesis of various natural products, we sought a more efficient method for the construction of **1a** which would also be of sufficient generality to provide access to a variety of β-alkyl substituted 2-(*p*-tolylsulfinyl)-2-butenolides. We now report the realization of this goal in a short (two step), efficient synthesis of sulfinyl butenolides **1a**-**d** having extremely high optical purity.

The Wittig-Horner reaction[6] of the lithio derivative of (+)-(R)-dimethylphosphorylmethyl *p*-tolyl sulfoxide (**2**)[7] with trimethylsiloxy carbonyl compounds **3a**-**d**[8] gave optically active (R) vinyl sulfoxides **4a**-**d**. The vinyl sulfoxide mixtures 4a-d isomerized[9,7b] to provide predominantly the *E* lithio derivatives (E/Z>>10)[10] upon treatment with LDA (1.2 equiv) in THF solution at -78°C (-95°C for 3a) for 15 min. These solutions were quenched by the introduction of gaseous CO_2 at -78°C, followed by the introduction of *p*-toluenesulfonic acid at -78°C, with subsequent warming to 0°C to allow desilylation and cyclization to 2-(*p*-tolylsulfinyl)butenolides 1a-d. The overall yields for the conversion of 4a-d to 1a-d are 50-65%,[11] and the optical purities of 1a-d are all greater than 98% ee.[12]



	4		1		
	YIELD, %	Z/E	YIELD, %	m.p., °C	$[\alpha]_D^{24.6°}$
a, R=H	70	1/1	70	115-118	+242
b, R=CH_3	84	1/1	67	79-82	+169
c, R=n-Bu	82	3/2	78	61-63	+156
d, R= 	82	3/2	75	56-58	+150

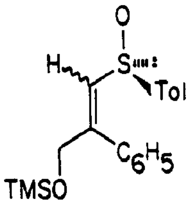
The following is an experimental procedure for the conversion of 4 to 1. Workup A is for 1b, 1c, and 1d and workup B is for 1a, differing due to the relative acid and base sensitivity and water solubility of the compounds.

To a solution of LDA (1.2 mmol) in 6 mL of THF at -78°C (-95°C for 1a under a nitrogen atmosphere was added a solution of 4 (1 mmol) in 2 mL of THF down the side of the flask. The mixture was stirred at -78°C (-95°C for **1a**) for 15 min, CO_2 gas was bubbled into the mixture for 30 min at -78°C, *p*-toluenesulfonic acid monohydrate (2.7 mmol) was added and the mixture was slowly warmed to 0°C.

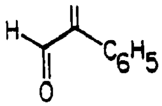
Workup A (for **1b**, **1c** and **1d**): After stirring for 10 min at 0°C, the reaction mixture was diluted with 30 mL of CH_2Cl_2, washed with cold water, washed three times with cold saturated aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated below 10°C. Recrystallization from ether-pentane provided colorless crystals of **1b**, **1c**, or **1d**.

Workup B (for **1a**): After stirring for 5 min at 0°C, the turbid reaction mixture was filtered through an anhydrous magnesium sulfate pad which was then washed with 10 mL of ethyl acetate. The combined filtrate was concentrated below 10°C and the residue was dissolved in 20 mL of chloroform. The chloroform solution was allowed to stand for 2h at 25°C, then washed with 20 mL of water, dried over anhydrous magnesium sulfate, and concentrated to provide a pale yellow solid. Recrystallization from ethyl acetate-hexane gave colorless crystals of **1a**.

Attempts to prepare 3-phenyl-2-(*p*-tolylsulfinyl)-2-butenolide (**5**) were unsuccessful. In this case, treatment of vinyl sulfoxide **6** with LDA provided a small amount of aldehyde **7**, presumably formed from olefin isomerization and [2.3] sigmatropic rearrangement, along with unchanged **6**.



6



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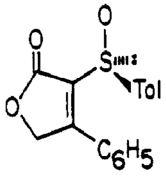

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We have described here an efficient and general new procedure for the two step preparation of 2-(*p*-tolylsulfinyl)-2-butenolides of high optical purity. Since both enantiomers of **2** are readily available,[7] either S-(+) or R-(-)-2-(*p*-tolylsulfinyl)-2-butenolides may be easily prepared by this route.

We are actively intestigating the utility of **1a-d** as Michael acceptors as well as their possible role as intermediates in natural product synthesis.

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References and Notes

(1) A portion of this work was carried out at Virginia Polytechnic Institute and State University.

(2) (a) Posner, G. H.; Asirvatham, E. J. Org. Chem. 1985, 50, 2589; (b) Posner, G. H.; Frye, L. L.; Hulce, M. Tetrahedron 1984, 40, 1401, and references contained therein; (c) For a review, see Posner, G. H. in "Asymmetric Syntheses," Morrison, J. D., Ed., Academic Press, N. Y., 1983, Vol. II, p. 225.

(3) Posner, G. H.; Kogan, T. P.; Haines, S. R.; Frye, L. L. Tetrahedron Lett. 1984, 25, 2627.

(4) Synthesis of racemic 1a: (a) Barbier, P.; Benezra, C. Ibid. 1982, 23, 3511; (b) Watanabe, M.; Shirai, K.; Kumamoto, T. Chem. Lett. 1975, 855; (c) Iwai, K.; Kosugi, H.; Uda, H. Ibid. 1974, 1237.

(5) Krafft, M.E.; Kennedy, R. M.; Holton, R. A. Tetrahedron Lett. submitted.

(6) Mikolajczyk, M.; Grezejszczak, J.; Zatorski, A. J. Org. Chem. 1975, 40, 1979.

(7) (a) Mikolajczyk, M.; Midura, W.; Grzejszczak, S.; Zatorski, A.; Chefczynska, A. Ibid. 1978, 43, 473; (b) Solladie, G.; Moine, G. J. Am. Chem. Soc. 1984, 106, 6097; (c) Solladie, G. Synthesis 1981, 185.

(8) (a) Aldehyde 3a was prepared by ozonolysis of 1-trimethylsiloxy-3-methyl-2-butene; (b) Ketones 3b-d were prepared by the method of Rubottom: Rubottom, G. M.; Gruber, J. M. J. Org. Chem. 1978, 43, 1599.

(9) Okamura, H.; Mitsuhira, Y.; Miura, M.; Takei, H. Chem. Lett. 1978, 517.

(10) E/Z ratios were determined by ^{1}H NMR. The chemical shift of the α vinylic protons of 4a-d was ca. δ6.33 for the E isomers and ca. δ6.00 for the Z isomers.

(11) All yields refer to chromatographically and spectrally homogeneous substances (except for E/Z isomers).

(12) Determined by ^{1}H NMR in the presence of tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato], europium (III) derivative, Aldrich catalog # 16,474-7, in $CDCl_3$ solution.

(13) Melting points were recorded on a hot stage and are uncorrected. The reported melting point for 1a is 121-125°C.[3]

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