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OPTICALLY ACTIVE 2-*p*-TOLYLSULFINYLACRYLATE
—— A NOVEL CHIRAL DIENOPHILE WHICH EXHIBITS HIGH REACTIVITY AND DIASTEREOSELECTIVITY ——

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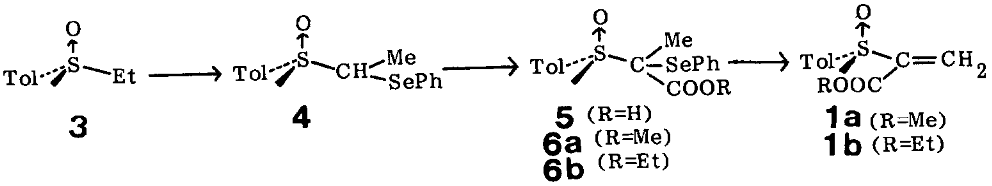
Summary The Diels-Alder reaction of a novel chiral dienophile, alkyl (*S*)-2-*p*-tolylsulfinylacrylates **1** with anthracene and cyclopentadiene showed high diastereoselectivity under the chelation controlled condition.

Optically active 3-*p*-tolylsulfinylacrylates[1] have currently received considerable attention as potential chiral dienophiles in the Diels-Alder (D-A) reaction: Our group[1a] and Maignan *et al*[1b] independently reported that the D-A reaction of optically active 3-*p*-tolylsulfinylacrylates with cyclopentadiene proceeded in highly diastereoselective manner giving cycloadducts which are useful for asymmetric organic synthesis[2] . In comparison, optically active alkyl 2-*p*-tolylsulfinylacrylates have neither been prepared nor utilized in the asymmetric D-A reaction[3] , although several literatures suggested the dienophilic reactivity of this class of compounds[4] . In this letter we would like to report the first synthesis of optically active 2-*p*-tolylsulfinylacrylates **1**, and also like to present that the dienophiles **1** having much higher reactivity than 3-*p*-tolylsulfinyl isomers are quite useful chiral dienophiles with high diastereoselectivity.

For the preparation of the optically active title compound 1[5] , we have designed the synthetic route which does not contain the possible racemization steps(Scheme 1)[6].
Optically pure ethyl *p*-tolyl sulfoxide 3[7] prepared from menthyl (*S*)-*p*-toluenesulfinate **2** was treated with 1.2 eq of *n*-butyllithium at -78 °C, followed by phenylselenenylation with phenylselenenyl chloride to afford 4 in 50 % yield. The (phenylselenenyl)sulfoxide 4 was treated with *n*-butyllithium at -78°C and the resulting anion was trapped with carbon dioxide to give the acid 5 in 82 % yield. Esterification of 5 afforded the methyl ester **6a** and the ethyl ester **6b** in fair yields, respectively[8] . The esters thus obtained were subjected

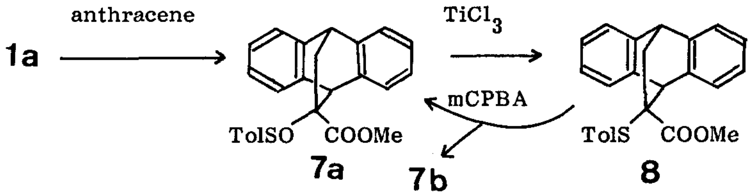
Scheme 1



to m-CPBA or $NaBrO_2$[9] oxidation to afford directly the alkyl 2-p-tolylsulfinylacrylates **1a** and **1b** in 70∿80 % yield[10]. The optical purities of both acrylates **1a,b** were determined as no less than 93 % by NMR shift reagent method using $Eu(\underline{tfmc})_3$ [11].

The 2-p-tolylsulfinylacrylates thus obtained turned out to be excellent dienophiles, which react even with butadiene, piperylene, and anthracene[12] under the presence of Lewis acid catalyst. The methyl ester **1a** was subjected to the D-A reaction with anthracene in the presence of zinc chloride[13]. Surprisingly, the single diastereomeric cycloadduct **7a**[14] was found to form in the cycloaddition, which was confirmed as follows. The cycloadduct **7a** was reduced to the corresponding sulfide **8**[15], which was oxidized with m-CPBA to give two diastereomeric sulfoxides **7a** and **7b**, quantitatively[16]. The careful HPLC analysis of the crude cycloadduct[17] reveals that a trace amount(no more than 1 %) of **7b** was formed in the cycloaddition, indicating that the D-A reaction of **1** with anthracene proceeded in almost 100 % diastereoselection. (Scheme 2)

Scheme 2



Next, in order to elucidate the steric course of the cycloaddition as well as the role of the Lewis acid, we carried out the D-A reaction of the ethyl ester **1b** with cyclopentadiene with (or without) the Lewis acid catalyst. The reaction condition and the resulting diastereomeric ratios are shown in Table 1[18].

Table 1. D-A Reaction of 2-p-Tolylsulfinylacrylate **1b** with Cyclopentadiene

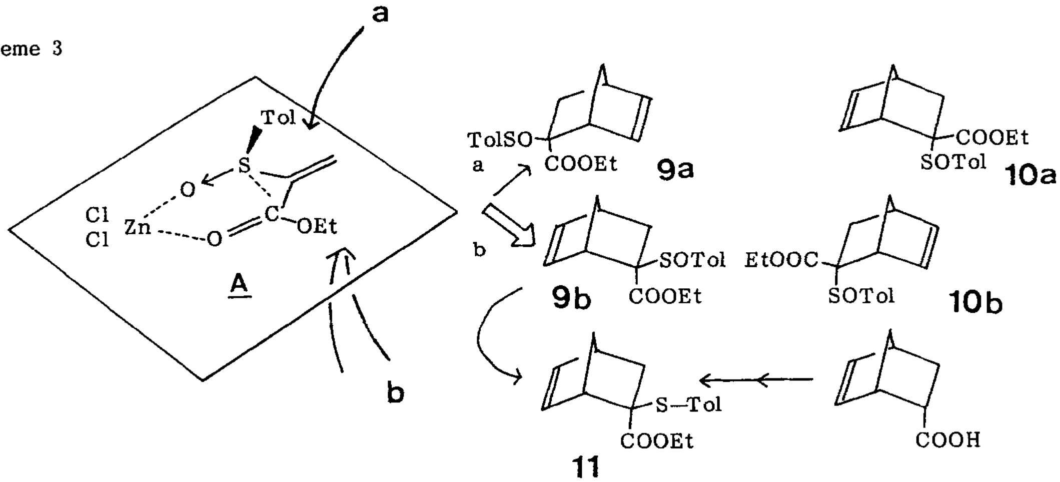
Reaction Conditions				Ratio of Diastereomeric Cycloadducts						
Lewis Acid	Temp.	hr.	Solvent	9 (endo COOEt)			10 (exo COOEt)			
				9a		**9b**	**10a**		**10b**	**9/10**
——	rt	6	PhH	64	:	11	23	:	2	3.0
$ZnCl_2$	0°	3	CH_2Cl_2	2	:	77	2	:	19	3.8

Clearly the dramatic change in the formation of the diastereomers was observed. Without $ZnCl_2$ catalyst, the endo cycloadduct **9a** and the exo cycloadduct **10a** were predominant. With the catalyst, the corresponding diastereomers **9b** and **10b** became the major adducts. The absolute configuration of the cycloadducts was determined by the following chemical correlation[19] (Scheme 3). The major cycloadduct **9b** formed under the chelation controlled condition was subjected to $TiCl_3$ reduction to give **11**[20] ($[\alpha]_D$ -94°) in 52 % yield. The compound **11** with the specific rotation of -55° was derived from (1S)-(-)-bicyclo[2.2.1]hept-5-ene-2-endo-carboxylic acid[21] ($[\alpha]_D$ -80°)by esterification followed by p-tolylsulfenylation reaction. The absolute configuration of **9b** is now established.

As shown in the Table, it should be noted that the presence of Lewis acid($ZnCl_2$)[22] resulted in the dramatic change in the ratio of diastereomers: The ratio was almost completely reversed compared to that of the reaction without catalyst. Thus, the exclusive formation of **9b** with the determined absolute configuration is due to the initial complexation of the dienophile **1** with $ZnCl_2$ and the subsequent attack of the diene from the less hindered site (arrow b in Scheme 3) of the chelated structure **A**[23] . Accordingly, the absolute configurations of the other cycloaddducts, **9a** and **10a,b** should be assigned as shown in Scheme 3, respectively. The similar mechanistic consideration indicated that the absolute configuration of **7a** should be assigned as that shown in Scheme 2.

In conclusion, the new chiral dienophile **1** presented here has much higher dienophilic reactivity than 3-p-tolylsulfinylacrylates and also exhibits the satisfactory diastereoselection in the D-A reaction. The enhanced reactivity and the high diastereoselection particularly observed in the chelation controlled condition indicate that the compound **1** is potentially useful as a chiral dienophile. The wide range of application for the asymmetric synthesis is possible and is now in progress in this laboratory.

Scheme 3



References and Notes

1)a) T. Koizumi, I. Hakamada, and E. Yoshii, Tetrahedron Letters, **1984**, 25, 87.
b) C. Maignan, A. Guessous, F. Rouessac, ibid., **1984**, 25, 1727.
2)a) S. Danishefsky, T. Harayama, and R. K. Singh, J. Amer. Chem. Soc., **1979**, 101, 7008.
b) S. Ghersetti, H. Hogeveen, G. Maccagnani, F. Montanari, and F. Taddei, J. Chem. Soc., **1963**, 3718.
3) Racemic alkyl 2-arylsulfinylacrylates have been prepared and used as Michael acceptors. a)F. Leyendecker and M-T. Comte, Tetrahedron Lett., **1982**, 23, 5030. b) C. D. Foulds, A. A. Jaxa-Chamiec, A. C. O'Sullivan, and P. G. Sammes, J. Chem. Soc., Perkin Trans. I, **1984**, 21. c) P. J. Brown, D. N. Jones, M. A. Khan, N. A. Meanwell, and P. J. Richards, ibid., **1984**, 2049. Posner et al reported that optically active α-(methoxycarbonyl)alkenyl sulfoxides are useful as chiral Michael acceptors. G. H. Posner, J. P. Mallamo, and K. Miura, J. Am. Chem. Soc., **1981**, 103, 2886. However, these compounds were found in our laboratory to show little dienophilic reactivity, i.e., no cycloaddition was observed even in the D-A reaction with cyclopentadiene.

4)a) L. Stella, and J-L. Boucher, Tetrahedron Lett., **1982**, 23, 953. b) S. Knapp, R. Lis, and P. Michna, J. Org. Chem., **1981**, 46, 624.

5) All new compounds had satisfactory elemental analyses and spectral data. Optical rotations were taken in $CHCl_3$ at 23-25°C, unless otherwise described. The optical rotations were not measured in the case of diastereomeric mixture. All the yields are not optimized.

6) The most reasonable method is considered to use the Emmons-Horner reaction of optically active diethyl (p-tolylsulfinyl)ethoxycarbonylmethanephosphonate with formaldehyde. We at first undertook this route, but were unsuccessful to obtain almost completely racemized ethyl ester **1b**. The reaction of menthyl (S)-p-toluenesulfinate with sodium salt of triethyl phosphonoacetate afforded the corresponding diastereomeric mixture of (p-tolylsulfinyl)ethoxycarbonylmethanephosphonate. The Emmons-Horner reaction of the compound with paraformaldehyde gave the compound **1b** in 50 % yield. The optical rotation of **1b** was $[\alpha]_D$ +5.2°, which indicated almost complete racemization by the NMR shift reagent analysis using Eu(tfmc)$_3$. Probably the (p-tolylsulfinyl)ethoxycarbonylmethanephosphonate racemized during the preparation or the Emmons-Horner reaction condition.

7) K. K. Andersen, Tetrahedron Lett., **1962**, 93.

8) **6a** was obtained as a diastereomeric mixture in 80 % yield after the methylation with diazomethane and similarly, **6b** in 66 % yield after the ethylation with EtOH-DCC-DMAP.

9) $NaBrO_2$ was kindly provided by Nihon Silica Ind. Co., Ltd.

10) **1a**:$[\alpha]_D$ +263°(c 0.68). **1b**:$[\alpha]_D$ +238°(c 0.12). Other spectral data were completely identical with those of the racemates.

11) In NMR, one of the olefinic protons of racemic **1** was separated to a pair of singlets by the addition of Eu(tfmc)$_3$.

12) The corresponding 3-p-tolylsulfinyl isomers hardly reacted with these dienes. The cycloadducts of **1** with butadiene and piperylene are rather unstable to afford the desulfenylation product, and the diastereoselection could not be estimated.

13) In the presence of 1 eq. of $ZnCl_2$, **1a** and 1-2 eq. of anthracene in CH_2Cl_2 was kept at rt for 51 hr. The adduct was obtained in 82 % yield.

14) **7a**: mp 171-173°C(n-hexane-AcOEt);$[\alpha]_D$ +40°(c 0.35).

15) **8**:$[\alpha]_D$ +24.0°(c 1.7).

16) m-CPBA oxidation of **8** at 0°C afforded a mixture of **7a** and **7b** in a ratio of 1:1. **7b**: mp 131-133 °C(n-hexane-AcOEt).

17) HPLC: μ-Porasil; n-hexane-AcOEt(20:1); **7a**: R_t 34.5 min; **7b**: R_t 23.4 min.

18) The cycloaddition proceeded almost quantitatively. All cycloadducts were decomposed on the attempted distillation. The ratio of diastereomer was estimated by HPLC analysis. HPLC of **9** and **10**: μ-Porasil; n-hexane-AcOEt- i-PrOH (200:20:1); R_t : **9a**, 11.0 min; **9b**, 34.8 min; **10a**, 47.4 min; **10b**, 53.6 min. The stereochemistry of each adduct was determined by the NMR analysis and by the halolactonization of **11** after the alkaline hydrolysis. The diastereomeric relationship of **9a** and **9b** was confirmed by the fact that the $TiCl_3$ reduction of each diastereomer afforded the same sulfide **11**. The $TiCl_3$ reduction of **10a** and **10b** gave a single sulfide, which is different from **11**. **9a**:$[\alpha]_D$ +130°(c 0.2); **9b**:$[\alpha]_D$ -62°(c 2); **10a**:$[\alpha]_D$ +69.4°(c 0.53); **10b**:$[\alpha]_D$ -30.0°(c 0.1).

19) The 2-endo-carboxylic acid was esterified with HCl-EtOH to give the ethyl ester, which was further treated with LDA followed by di-p-tolyl disulfide to give **11**,$[\alpha]_D$ -55.7°(c 0.27, ee 54 %) in 50 % yield.

20) **11** from **9b**: bp 130°/0.8 torr; $[\alpha]_D$ -94°(c 1).

21) The optically active 2-endo-carboxylic acid{$[\alpha]_D$ -80°(EtOH, c 1); ee 55 %} was obtained according to the resolution method by Berson et al. (J. A. Berson and D. A. Ben-Efraim, J. Am. Chem. Soc., **1959**, 81, 4083.)

22) Similar chelation controlled diastereoselection was reported by Posner et al (reference 3) and Kosugi et al. (H. Kosugi, H. Konta, and H. Uda, J. Chem. Soc. Chem. Commun., **1985**, 211.)

23) Without the Lewis acid the dienophile **1** should react in the structure in which the S→O and C=C groups should be in the s-cis conformation. In this case the attack of the diene from the less hindered side afforded the cycloadducts **9a** and **10a**.

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