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Highly Asymmetric Diels–Alder Cycloaddition of Menthyl (*Z*)-(*S*)$_S$-3-(2-Pyridylsulfinyl)propenoate with Cyclohexa-1,3-diene

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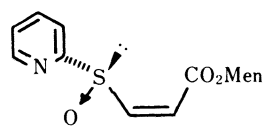
The Diels–Alder reaction of menthyl (*Z*)-(*S*)$_S$-3-(2-pyridylsulfinyl)propenoate with cyclohexa-1,3-diene in the presence of a Lewis acid, zinc bromide, afforded the *endo* cycloadduct in a highly diastereoselective manner in excellent yield. The absolute stereochemistry of the adduct was determined by transformation into (+)-bicyclo[2.2.2]oct-5-ene-2-*endo*-methanol with known absolute configuration.

Keywords——Diels–Alder reaction; high diastereoselectivity; menthyl (*Z*)-(*S*)$_S$-3-(2-pyridylsulfinyl)propenoate; chiral sulfoxide; cyclohexa-1,3-diene; bicyclo[2.2.2]oct-5-ene

Functionalized bicyclo[2.2.2]octane derivatives are known to be useful intermediates for natural products synthesis.[1] However, there are few reports concerning the chiral synthesis of these bicyclic compounds. To date, the chiral bicyclo[2.2.2] octane systems have been prepared by optical resolution of the racemic precursor[2] or by an asymmetric Diels–Alder reaction of menthyl acrylate.[3] In the latter case the diastereofacial selection in the Diels–Alder reaction was not reported.[3] In relation to the chiral synthesis of bicyclo[2.2.2]octane derivatives, we were intrigued by an asymmetric Diels–Alder reaction of (*Z*)-(*S*)$_S$-3-(2-pyridylsulfinyl)propenoate (**1**)[4] with cyclohexa-1,3-diene. We recently reported the highly asymmetric Diels–Alder reaction of **1** with 1,3-dienes such as cyclopentadiene and furan,[5] and we employed the cycloadducts for the enantioselective synthesis of natural products.[6] In this paper we describe the results of the Diels–Alder reaction of **1** with cyclohexa-1,3-diene and the determination of the absolute stereochemistry of the major cycloadduct.

Under the same conditions but in the absence of a Lewis acid at room temperature, no reaction took place between **1** and cyclohexa-1,3-diene. We chose diethyl aluminium chloride as a promoter in the reaction since the Lewis acid was remarkably effective in the asymmetric Diels–Alder reaction for cyclopentadiene.[6a] Unexpectedly, the use of Et_2AlCl for cyclohexa-1,3-diene resulted in only recovery of the starting material. The reasons for the unfavarable combination of **1** with the diene are not obvious. This difficulty was easily overcome by using zinc salts. It was found that zinc bromide was the most effective promoter in the cycloaddition. The reactions conducted in the presence of zinc chloride or zinc iodide were somewhat slower.

The Diels–Alder reaction of **1** with cyclohexa-1,3-diene in the presence of zinc bromide (1.2 eq used) in dichloromethane proceeded with high diastereoselectivity to give the cycloadduct (**2**). The high performance liquid chromatography (HPLC) and nuclear magnetic resonance (NMR) analyses of the reaction mixture showed the product to be almost a single diastereomer (quantitative yield).[7] The diastereomeric excess was proved to be no less than 96%. Although the stereochemistry of the cycloadduct (**2**) could not be



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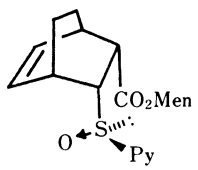

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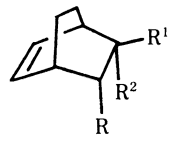
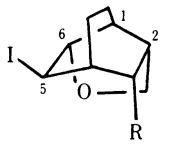
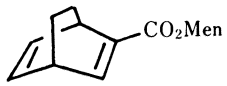


	R	R^1	R^2
3	SPy	H	CO_2Men
5	H	H	CH_2OH
7	H	H	CO_2Men
9	SO_2Py	H	CO_2Men
10	H	CH_2OH	H
11	H	H	CO_2H



4 : R=SPy
6 : R=H



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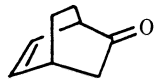

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Chart 1

ascertained at this stage, the following transformation proved that both the sulfinyl and the ester groups were located in the *endo* position. Reduction of **2** with $TiCl_3$ gave the sulfide **3** in 95% yield. Treatment of **3** with $LiAlH_4$ and subsequent iodoetherification (I_2–KI) gave the tricyclic ether **4** whose structure was characterized mainly by two signals (4.53 ppm due to the H-5 proton, d, $J=5.5$ Hz; 4.30 ppm due to the H-6 proton, dd, $J=5.5$, 1.5 Hz) in the NMR spectrum.

In order to determine the absolute configuration of **2**, we planned to transform the adduct **2** into the known alcohol **5**.[8] Several attempts to convert **4** into **6** were unsuccessful. Treatment of **3** with Raney Ni (W-4) in refluxing ethanol for 3.5 d gave the ester **7**, but in capricious yields. We sought another route to **5** involving desulfenylation and subsequent selective reduction. Although it was difficult to convert **2** into the α,β-unsaturated ester **8** by heating or by base treatment, the sulfone **9** obtained from **2** was smoothly converted into **8** by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in 97% yield. Reduction of **8** with $LiAlH_4$ in ether gave the alcohols **5** and **10** in a 1 : 1 mixture, in 64% combined yield. The mixture of **5** and **10**[9] was subjected to iodoetherification to afford the iodo ether **6** (39%), along with recovery of **10** (15%). Exposure of **6** to zinc in acetic acid gave the isomerically pure **5** in 78% yield. The spectral data (NMR, infrared(IR)) were in good agreement with those reported previously.[8] The positive sign in the specific rotation ($[\alpha]_D^{25}$ +5.73° ($c=0.38$, EtOH)) showed the *endo* alcohol **5** derived from **2** have 1*R*,4*R* configuration. An authentic sample, which was independently prepared from the known carboxylic acid **11** ($[\alpha]_D^{25}$ +35.8°, 71% ee),[10] showed $[\alpha]_D^{25}$ +8.4° ($c=2.7$, EtOH).

From the above results, the absolute configuration of the major cycloadduct **2** was established and it was found that the cycloaddition proceeded in a highly diastereoselective manner. The absolute stereochemistry of **2** supports the Diels–Alder reaction mechanism which we have proposed.[11] Namely, the sulfoxide **1** would exist predominantly in the conformation where the zinc metal could co-ordinate with the sulfoxide oxygen and with nitrogen in the pyridine ring (Chart 2). Thus, the cycloaddition might take place from the less hindered side (route a) to afford the cycloadduct **2**. Compounds **2**, **5** and **8** might provide useful intermediates in the synthesis of natural products. For example, the ketone **12**,[12] which could be derived from **5**, has been employed as a feasible optically active building block in the synthesis of polycyclopentanoids.[13] The utility of the chiron **2** for the synthesis of natural products is under investigation.

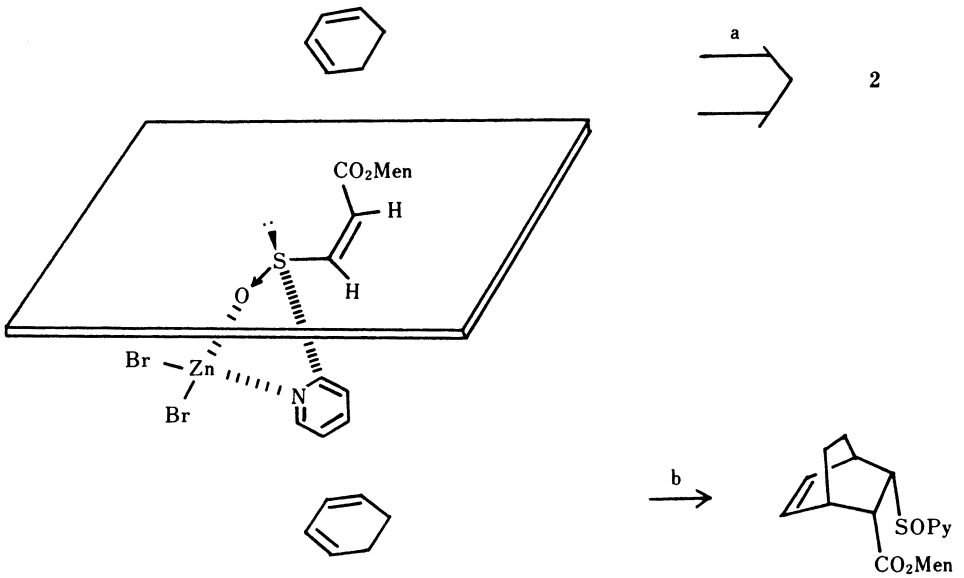

Chart 2

Experimental

All melting points and boiling points are uncorrected. IR spectra were recorded with a JASCO A102 infrared spectrophotometer. ^{1}H-NMR spectra were measured with a JEOL PMX-60 (60 MHz) spectrometer or a JEOL GX-270 (270 MHz) spectrometer. ^{13}C-NMR spectra were recorded on a Varian XL-200 (50 MHz) spectrometer. Tetramethylsilane was used as internal standard. Mass spectra (MS) were recorded with a JEOL JMS-D 200 spectrometer. Optical rotations were measured on a JASCO DIP-140 digital polarimeter. Analytical HPLC was carried out on a Shimadzu LC-6A pump by using a μ-Bondapak-NH_2. Commercially available anhydrous zinc bromide was used without purification.

Menthyl (1*R*,4*S*)-(+)-(*S*)$_s$-*endo*-3-(2-Pyridylsulfinyl)bicyclo[2.2.2]oct-5-ene-*endo*-2-carboxylate (2)——Anhydrous $ZnBr_2$ (202 mg, 0.9 mmol) was added to a solution of (*Z*)-(*S*)$_s$-3-(2-pyridylsulfinyl)propenoate (**1**)[5a] (251 mg, 0.75 mmol) in dry CH_2Cl_2 (5 ml) and the mixture was stirred at room temperature for 30 min. Cyclohexa-1,3-diene (0.7 ml, 7.3 mmol) was added to the suspension *via* a syringe and the suspension was stirred vigorously for 4 d. The mixture was diluted with ether (10 ml) and the organic layer was washed with 5% hydrochloric acid, saturated sodium hydrogen carbonate, and saturated brine, and dried ($MgSO_4$). The solvent and excess of the diene were removed under reduced pressure and the residue was chromatographed on silica gel with ethyl acetate to give **2** (310 mg, quantitative yield). mp 130—131 °C (hexane–ether). $[\alpha]_D^{24}$ +60.6° (*c*=0.39, $CHCl_3$). IR (KBr) cm^{-1}: 1720 (CO), 1030 (SO). ^{1}H-NMR ($CDCl_3$) δ: 0.732 (3H, d, *J*=6.5 Hz, CH_3), 0.899 (3H, d, *J*=7 Hz, CH_3), 0.96—1.91 (13H, m), 2.983 (1H, d, *J*=4.5 Hz, H-1), 3.174 (1H, dd, *J*=9.5, 2 Hz, H-2), 3.302 (1H, d, *J*=5.5 Hz, H-4), 3.721 (1H, dd, *J*=10, 2 Hz, H-3), 4.491 (1H, dt, *J*=10, 4 Hz, OCH), 6.275 (1H, t, *J*=7 Hz, H-5 or H-6), 6.557 (1H, t, *J*=7 Hz, H-6 or H-5), 7.33—8.59 (4H, m, ArH). *Anal.* Calcd for $C_{24}H_{33}NO_3S$: C, 69.32; H, 8.01; N, 3.37. Found: C, 69.52; H, 8.01; N, 3.21. *Rf* 0.35 (EtOAc).

Menthyl (1*R*,4*S*)-(+)-*endo*-3-(2-Pyridylthio)bicyclo[2.2.2]oct-5-ene-*endo*-2-carboxylate (3)——*Ca.* 25% $TiCl_3$ aqueous solution (0.1 ml, 0.16 mmol) was added dropwise to a solution of **2** (51 mg, 0.12 mmol) in ethanol (5 ml). After an additional 20 min, water (5 ml) was added to the mixture. Most of the ethanol was evaporated off and the aqueous layer was extracted with ether (5 × 6 ml). The extracts were washed with saturated brine, dried ($MgSO_4$), and concentrated to give a crystalline product **3** (47 mg, 95%). mp 120 °C (hexane). $[\alpha]_D^{25}$ +77.8° (*c*=2, $CHCl_3$). IR (KBr) cm^{-1}: 1730 (CO). ^{1}H-NMR ($CDCl_3$) δ: 0.257 (1H, q, *J*=12 Hz, CH), 0.701 (3H, d, *J*=7 Hz, CH_3), 0.727 (3H, d, *J*=7 Hz, CH_3), 0.851 (3H, d, *J*=7 Hz, CH_3), 0.9—1.9 (12 H, m), 2.87 (1H, br, H-1 or H-4), 2.931 (1H, br s, H-4 or H-1), 3.292 (1H, d, *J*=9.5 Hz, H-2), 4.545 (1H, td, *J*=11, 4.5 Hz, OCH), 4.739 (1H, dd, *J*=9.5, 3 Hz, H-3), 6.349 (1H, t, *J*=7.5 Hz, H-5 or H-6), 6.547 (1H, t, *J*=7.5 Hz, H-6 or H-5), 6.95—8.42 (4H, m, ArH). ^{13}C-NMR ($CDCl_3$) 16.22, 20.85, 21.94, 23.10, 24.19, 25.25, 25.95, 31.14, 33.00, 34.13, 37.00, 40.04, 45.07, 46.83, 51.25, 74.19, 94.18, 119.07, 122.16, 131.55, 148.97, 159.51, 172.11. *Anal.* Calcd for $C_{24}H_{33}NO_2S$: C, 72.15; H, 8.33; N, 3.51. Found: C, 72.40; H, 8.37; N, 3.50. *Rf* 0.60 (EtOAc).

Menthyl (1*R*,4*S*)-(−)-*endo*-3-(2-Pyridylsulfonyl)bicyclo[2.2.2]oct-5-ene-*endo*-2-carboxylate (9)——A solution of

m-chloroperoxybenzoic acid (MCPBA, 80% purity, 258 mg, 1.2 mmol) in dry CH_2Cl_2 (10 ml) was added dropwise to a stirred solution of **2** (453 mg, 1.1 mmol) in dry CH_2Cl_2 (5 ml) at −80 °C. After the addition the temperature was allowed to rise slowly to room temperature and the mixture was stirred for 5 h. The mixture was diluted with ether (30 ml) and the organic layer was washed with diluted sodium hydrogen sulfite (2 × 5 ml), diluted sodium hydrogen carbonate (2 × 5 ml), and saturated brine, dried ($MgSO_4$) and concentrated. The residue was crystallized from hexane–ether to give **9** (400 mg, 85%). mp 120—121 °C. $[\alpha]_D^{25}$ −3.9° (*c*=0.4, $CHCl_3$). IR (KBr) cm^{-1}: 1740 (CO), 1320 (SO). ^{1}H-NMR ($CDCl_3$) δ: 0.748 (3H, d, *J*=7 Hz, CH_3), 0.848 (3H, d, *J*=6.5 Hz, CH_3), 0.883 (3H, d, *J*=7 Hz, CH_3), 0.9—2.0 (13H, m), 2.97 (1H, br s, H-7 or H-8), 3.19 (1H, m, H-8 or H-7, overlapping with H-2), 3.214 (1H, dd, *J*=10, 2 Hz, H-2), 4.562 (1H, td, *J*=11, 4 Hz, OCH), 4.574 (1H, d, *J*=10 Hz, H-3), 6.40 (2H, m, 2 × CH=), 7.5—8.7 (4H, m, ArH). *Anal.* Calcd for $C_{24}H_{33}NO_4S$: C, 66.80; H, 7.71; N, 3.25. Found: C, 66.86; H, 7.76; N, 3.14.

Menthyl (1*R*,4*S*)-(−)-Bicyclo[2.2.2]octa-2,5-diene-2-carboxylate (8)——Dry DBU (0.27 ml, 1.8 mmol) was added dropwise to a solution of **9** (390 mg, 0.9 mmol) in dry acetonitrile (5 ml) at 0 °C. After the addition the reaction mixture was stirred at room temperature for 4 h. Most of the solvent was evaporated off and the residue was diluted with ether (*ca.* 20 ml). The organic layer was washed with 5% hydrochloric acid (5 ml) and brine (5 ml), dried ($MgSO_4$) and concentrated. The residue was purified by chromatography with EtOAc to give **8** (252 mg, 97%) as an oil. $[\alpha]_D^{25}$ −128° (*c*=0.5, $CHCl_3$). IR (neat) cm^{-1}: 1700 (CO). ^{1}H-NMR ($CDCl_3$) δ: 0.768 (3H, d, *J*=7 Hz, CH_3), 0.891 (3H, d, *J*=6.5 Hz, CH_3), 0.897 (3H, d, *J*=7 Hz, CH_3), 0.9—1.6 (9H, m), 1.7 (2H, m), 1.9 (1H, m), 2.05 (1H, br d, *J*=11 Hz), 3.75 (1H, br, H-1 or H-4), 4.19 (1H, br, H-4 or H-1), 4.717 (1H, dt, *J*=11, 4.5 Hz, OCH), 6.265 (1H, dt, *J*=6, 1.5 Hz, H-5 or H-6), 6.374 (1H, dt, *J*=6, 1.5 Hz, H-6 or H-5), 7.242 (1H, dd, *J*=6.5, 2 Hz, H-3). High-resolution MS *m/z*: Calcd for $C_{19}H_{28}O_2$: 288.2089. Found: 288.2134. *Rf* 0.68 (EtOAc).

(1*R*,4*R*)-Bicyclo[2.2.2]oct-5-ene-*endo*/*exo*-2-methanol (5 and 10)——A solution of **8** (390 mg, 1.35 mmol) in dry ether (3 ml) was added dropwise to a suspension of lithium aluminium hydride (257 mg, 6.77 mmol) in dry ether (4 ml) *via* a syringe at 0 °C. After addition, the reaction mixture was stirred at room temperature for 4 h. After dilution with ether (10 ml), excess of reagent was destroyed by addition of a minimal amount of water under cooling. Anhydrous magnesium sulfate (*ca.* 0.5 g) was added to the suspension and the mixture was stirred for 2—3 min. Filtration was done through a short pad of Celite and the filtrate was concentrated to give the crude product (454 mg). The residue was purified by chromatography with hexane–ethyl acetate (4:1) to give a mixture of **5** and **10** (119 mg, 64%). Without further purification, a solution of iodine (436 mg, 1.7 mmol) and potassium iodide (856 mg, 5.2 mmol) in water (2 ml) was added to a stirred solution of the product obtained above (119 mg, 0.86 mmol) in 0.5 M sodium hydrogen carbonate (1.5 ml). The reaction mixture was stirred in the dark for 36 h. The reaction mixture was diluted with ether (10 ml) and the organic layer was washed with 1% aqueous sodium thiosulfate (3 × 8 ml), saturated sodium hydrogen carbonate (8 ml) and brine (8 ml), dried ($MgSO_4$) and concentrated to give a yellow oil (248 mg). The residue was purified by chromatography with hexane–ethyl acetate (4:1) to give the iodo ether **6** (91 mg, 39%) and **10** (19 mg, 15%). **6**: mp 37—38 °C. $[\alpha]_D^{25}$ −62.6° (*c*=0.3, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 2950, 1200. ^{1}H-NMR ($CDCl_3$) δ: 1.24—2.24 (9H, m), 3.492 (1H, d, *J*=7.5 Hz, OCHH), 3.693 (1H, dd, *J*=7.5, 3.5 Hz, OCHH), 4.079 (1H, dt, *J*=3, 1 Hz, CHI), 4.518 (1H, d, *J*=5.5 Hz, OCH). High-resolution MS *m/z*: Calcd for $C_9H_{13}IO$: 264,0013. Found: 264.0048. **10**: A colorless oil. IR ($CHCl_3$) 3400 (OH). ^{1}H-NMR ($CDCl_3$) δ: 0.867 (1H, ddd, *J*=12.5, 5, 2 Hz), 1—1.8 (7H, m), 2.4 (1H, m, H-1 or H-4), 2.55 (1H, m, H-4 or H-1), 3.540 (1H, dd, *J*=10.5, 8.5 Hz, HCHO), 3.673 (1H, *J*=10.5, 6.5 Hz, HCHO), 6.259 (1H, t, *J*=7 Hz, CH=), 6.377 (1H, t, *J*=7 Hz, CH=). MS *m/z*: 138 (M^+), 120, 80.

Zinc powder (48 mg, 0.7 mg atom) was added in portions to a cold solution of **6** (39 mg, 0.15 mmol) in glacial acetic acid (3 ml). The reaction mixture was stirred at room temperature for 3 d, then diluted with ether (20 ml). The mixture was filtered and the filtrate was washed with brine (3 × 5 ml), dried ($MgSO_4$) and concentrated to give the crude product (34 mg). The residue was purified by chromatography with hexane–ethyl acetate (4:1) to give **5** (16 mg, 78%) as an oil. $[\alpha]_D^{25}$ +5.73° (*c*=0.38, EtOH). IR ($CHCl_3$) cm^{-1}: 3450 (OH). ^{1}H-NMR ($CDCl_3$) δ: 0.759 (1H, ddt, *J*=12.5, 5.0, 2.5 Hz), 1.15—1.7 (7H, m), 1.9 (1H, m), 2.5 (1H, br, H-1 or H-4), 2.6 (1H, br, H-4 or H-1), 3.25 (2H, m, CH_2O), 6.133 (1H, t, *J*=7.5 Hz, CH=), 6.276 (1H, t, *J*=7.5 Hz, CH=). High-resolution MS *m/z*: Calcd for $C_9H_{14}O$: 138.1045. Found: 138.1072.

An authentic sample independently prepared from (+)-**11** ($[\alpha]_D^{25}$ +35.8°, 71% ee) showed $[\alpha]_D^{25}$ +8.4° (*c*=2.7, EtOH).

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References and Notes

1) For example, see: J. ApSimon, "The Total Synthesis of Natural Products," Vol. 5, Wiley, New York, 1983, pp. 461—469.
2) M. Nakazaki, K. Naemura, and S. Nakahara, *J. Org. Chem.*, **43**, 4745 (1978), and references contained therein.
3) Červinka reported the Diels–Alder reaction of (−)-menthyl acrylate with cyclohexa-1,3-diene. Judging from the

reported value of the optical rotation ($[\alpha]_D^{20}$ +0.30° (EtOH)) of **5** derived from the cycloadduct, the optical purity of the cycloadduct seemed to be very low. See: O. Červinka and O. Kříž, *Collect. Czech. Chem. Commun.*, **33**, 2342 (1968).

4) The symbol $(S)_s$ used in the text expresses that the chirality at sulfur is *S*.

5) *a*) H. Takayama, A. Iyobe, and T. Koizumi, *J. Chem. Soc., Chem. Commun.*, **1986**, 771; *b*) H. Takayama, K. Hayashi, Y. Takeuchi, and T. Koizumi, *Heterocycles*, **24**, 2137 (1986).

6) *a*) Y. Arai, Y. Hayashi, M. Yamamoto, H. Takayama, and T. Koizumi, *Chem. Lett.*, **1987**, 185; *b*) H. Takayama, K. Hayashi, and T. Koizumi, *Tetrahedron Lett.*, **27**, 5509 (1986); H. Takayama, A. Iyobe, and T. Koizumi, *Chem. Pharm. Bull.*, **35**, 433 (1987).

7) The sulfide **3** was oxidized with MCPBA to give **2** and its diastereomer in 45 and 16% yields, respectively. Each peak could be easily separated by HPLC. In a preliminary experiment using racemic ethyl (*Z*)-3-(2-pyridylsulfinyl)propenoate (i), the Diels–Alder reaction with cyclohexa-1,3-diene proceeded in a highly diastereoselective manner. The sulfide derived from (i) by treatment with $TiCl_3$ appeared to be a single diastereomer by NMR analysis. Oxidation of the sulfide with MCPBA gave a mixture of (i) and its diastereomeric sulfoxide. The structures of the isomers could be easily ascertained from the differences in their NMR spectra.

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9) For the spectral data of (±)-**10**, see: A. B. Smith, III and W. C. Agosta, *J. Org. Chem.*, **37**, 1259 (1972); E. Pretsch, H. Immer, C. Pascual, K. Schaffner, and W. Simon, *Helv. Chim. Acta*, **50**, 105 (1967).

10) Nakazaki *et al.* reported (ref. 8) the conversion of (+)-**11** ($[\alpha]_D^{26}$ +31.8° (EtOH) into **5** ($[\alpha]_D^{25}$ +4.5° (*c*=1.1, MeOH). Tichý reported that the optical purity of **11** ($[\alpha]_D^{20}$ +50.9° (*c*=0.450, MeOH) was 95% (*Tetrahedron Lett.*, **1972**, 2001). From these results, the rotation value of **5** would be expected to be +7.58° in MeOH solution.

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13) For example, see: M. Demuth, S. Chandrasekhar, and K. Schaffner, *J. Am. Chem. Soc.*, **106**, 1092 (1984).