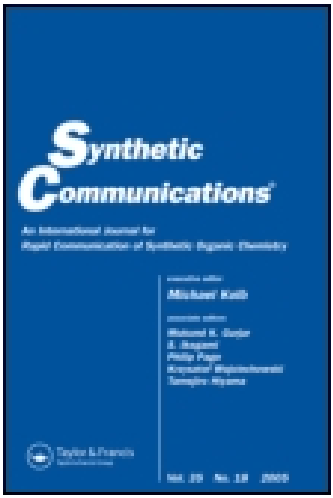

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Complete Diastereofacial Selective Cycloaddition of New Sulfinyl Dienophiles (Ss)- and (Rs)-(-)Menthyl α-(2-Methoxyphenylsulfoxyl)acylate with Anthracene Under Chelation Control

Tay-Yuan Chau [a] , Hsaio-Chi Lin [a] & Wenhao Hu [b]
[a] Department of Chemistry , National Chung-Hsing University , Taichung, Taiwan, 40227, Republic of China
[b] Union Laboratory of Asymmetric Synthesis , Chengdu Institute of Organic Chemistry , Chengdu, 610041
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COMPLETE DIASTEREOFACIAL SELECTIVE CYCLOADDITION OF NEW SULFINYL DIENOPHILES (Ss)-AND (Rs)-(-)MENTHYL α-(2-METHOXYPHENYLSULFOXYL)ACYLATE WITH ANTHRACENE UNDER CHELATION CONTROL

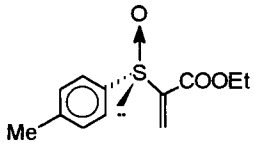
Tay-Yuan Chau*[a], Hsaio-Chi Lin[a], Wenhao Hu[b]

[a] Department of Chemistry, National Chung-Hsing University,Taichung, Taiwan 40227, Republic of China

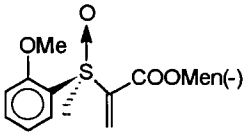
[b] Union Laboratory of Asymmetric Synthesis, Chengdu Institute of Organic Chemistry, Chengdu 610041

Abstract: New sulfinyldienophiles (Ss)- and (Rs)- (-)menthyl α-(2-methoxyphenylsulfoxyl)acylate were prepared. Cycloadditions with anthracene in dichloromethane proceeded with complete diastereoselectivity under chelation control. Chirality at sulfur controlled diastereofacial selectivity.

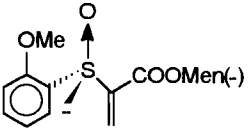
Sulfoxides as chiral auxiliaries in Diels-Alder cycloaddition have met with notable success[1]. The preparation of optically pure sulfoxides is still of great interest[2]. Most of the dienophiles in the cycloadditions have been treated with reactive Diels-Alder dienes, but are slow to react with low reactivity dienes such as furan. Enhanced reactivity and high diastereofacial selectivity have been obtained in cycloadditions under chelation controlled conditions[3]. For example, 2-p-tolylsulfinylacrylate 1 reported by Koizumi showed higher reactivity and



1



2a



2b

provided the cycloadducts with completely opposite absolute stereochemistry under the chelation controlled condition compared to the uncatalyzed reaction[4].

Because of the important influence of chelation state on the cycloaddition, we designed the new sulfinyldienophiles **2a** and **2b**, which are tridentate to make the chelation more stable, and expected that the chelated comformation would block one face of the dienophile **2a** or **2b** to improve the facial selectivity. On the other hand, the tridentate chelation makes the dienophiles **2a** and **2b** more reactive than dienophile **1**. We found that **2a** and **2b** could even react with furan smoothly at 0℃ in the presence of $TiCl_4$.

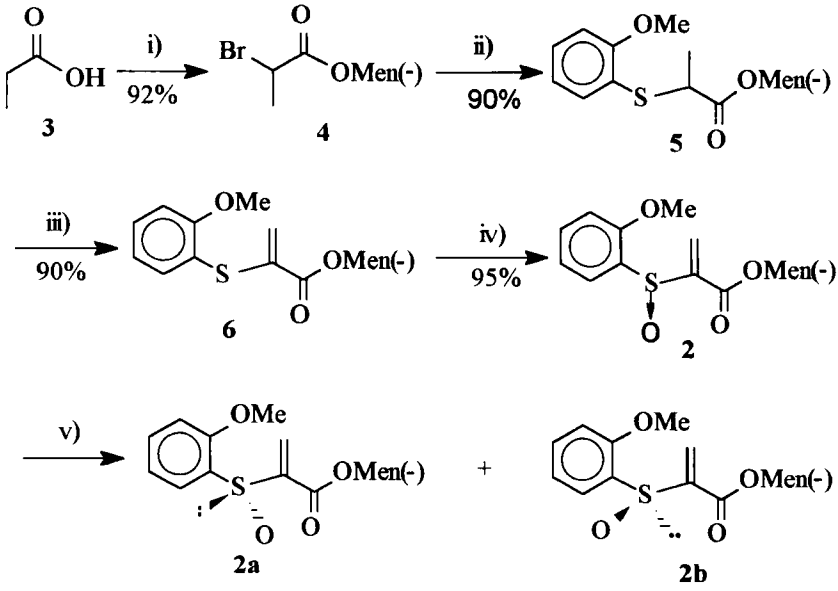
Herein we reported the preparation of optically pure **2a** and **2b** by using (-)-menthol as a convenient chiral auxiliary and the cycloaddition of **2a** and **2b** with anthracene catalyzed by zinc chloride. Sulfinyldienophile **2** was prepared by the route shown in Scheme 1. (Ss)-Sulfinyldienophile **2a** and (Rs)-sulfinyldienophile **2b** were easily separated by column chromatography on silica-gel using n-hexane:ethyl acetate (83:17) as eluent. The ratio of **2a**: **2b** was determined as 55:45 by 300 MHz ^{1}H NMR.

Cycloaddition of **2a** with anthracene in dichloromethane at 0°C for 18h proceeded smoothly in the presence of zinc chloride to give the single diastereomeric cycloadduct **7a** (Scheme 2). Interestingly, cycloaddition of **2b** with anthracene also gave the single diastereomeric adduct **7b** with the opposite absolute configuration at C-15. This indicated that the chirality at sulfur in both **2a** and **2b** controlled diastereofacial selectivity[5].

The absolute configuration of **7a** was confirmed by x-ray crystallographic analysis[6] (Figure 1). This result also unequivocally shows that the absolute configurations of compounds **2a**, **2b** and **7b** are correct.

The stereochemical control of cycloaddition exerted by configuration at sulfur in the dienophiles **2a** and **2b** may be rationalized by complete chelation control. The adducts **7a** and **7b** result from the approach of anthracene from the less hindered face (the one containing the lone pair at sulfur) of conformations **A** and **B** respectively (Figure 2).

In conclusion, the new chiral dienophiles **2a** and **2b** were prepared, which presented here high dienophilic reactivity[7] and satisfactory diastereoselectivity in the Diels-Alder reaction under chelation controlled conditions. The cycloadditions of **2a** and **2b** with other dienes are now in progress in our laboratory.



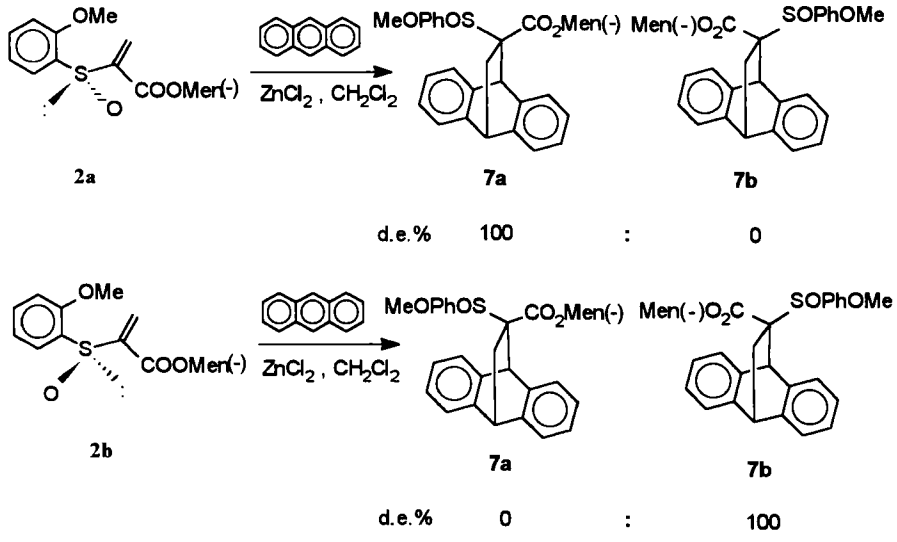
i) 1. $SOCl_2$ reflux 2h; 2. Br_2 reflux 2h; 3. (-)Menthol/CH_2Cl_2 rt. 10h
ii) 2-Methoxybenzenethiol, NEt_3 /CH_2Cl_2;0-5℃ 12h
iii) 1.SO_2Cl_2/CH_2Cl_2; 2. Toluene, reflux
iv) MCPBA/CH_2Cl_2, 0℃
v) Column chromatography (n-hexane:ethyl acetate=83:17)

Scheme 1

EXPERIMENTAL

I.R. spectra were recorded on a Hitachi model 270-30 spectrophotometer and MS analyses were performed on a Jms-D 100 mass spectrometer. ^{1}H-NMR spectra were recorded on a Varian Vxr-300 MHz instrument in $CDCl_3$ solution.

(-)-Menthyl α-bromopropionate 4. A mixture of propanoic acid (30g, 405.3mmol) and thionyl chloride (32ml, 450mmol) was refluxed for about 2h. The bromine (23.15ml, 450mmol) was added dropwise to the above solution under refluxing. After 2h, the reaction mixture was allowed to cool to the r.t., then



Scheme 2

a solution of (-)-menthol (60.84g, 390mmol) in CH_2Cl_2 (50ml) was added. After stirring at this temperature for 10h, the reaction mixture was hydrolyzed with H_2O (100ml). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 200ml). The combined organic layers were dried (Na_2SO_4) and after evaporation of the solvent, the crude product was purified by distillation (102°C, 0.5 mmHg) to afford 4 as an colourless oil (104g, 92%). ^{1}H-NMR δ 0.6-2.1 (m, 21H), 4.3 (q, J=6.6Hz, 1H), 4.7 (dd, J_1=10Hz, J_2=2.4Hz, 1H); IR (neat)ν_{max} : 2964, 1738, 1452, 1272, 1226, 1164, 1164, 1100 cm-1; MS m/z 289 (M^+).

(-)-Menthyl α-(2-methoxyphenylsulfenyl)propionate 5. To a stirred suspension of 2-methoxybenethiol (10g, 71.3mmol) in CH_2Cl_2 (50ml) was added Et_3N (11.91ml, 85mmol) and the reaction mixture was cooled to 0°C. CH_2Cl_2 solution of 4 (20.61g, 70.82mmol) was added dropwise to the above mixture. The reaction mixture was allowed to warm to r.t. and was stirred for another 12h. H_2O (50ml) was added and the organic layer was separated. After extraction with CH_2Cl_2

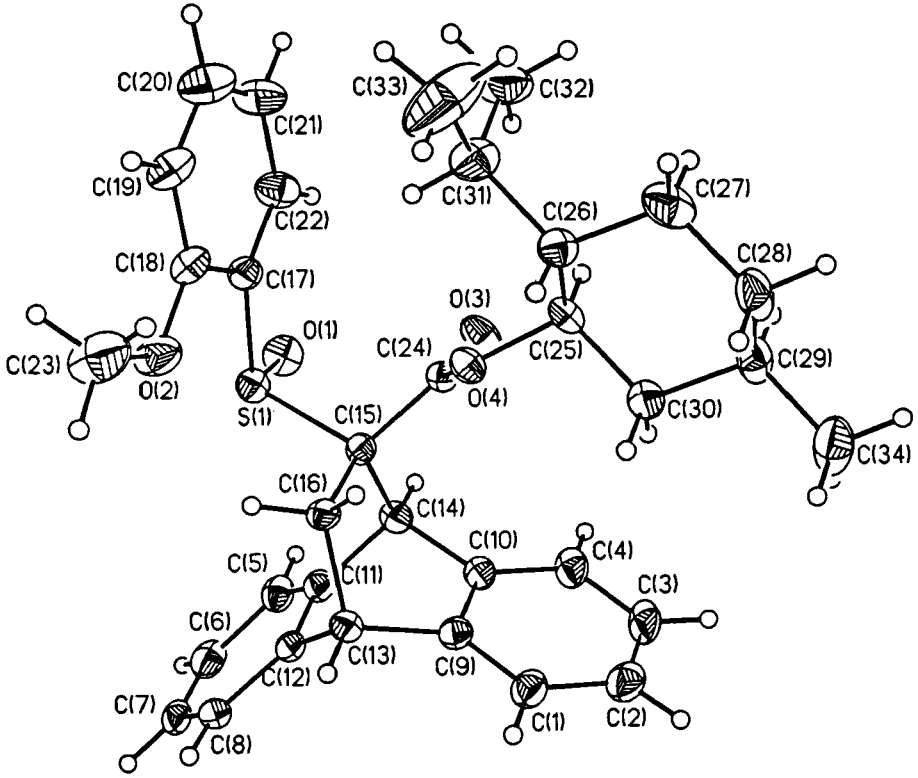


Figure 1: X-ray crystal structure of **7a**

(50ml x 3), the combined organic fractions were dried (Na_2SO_4), filtered and the solvent was evaporated. The resulting yellow oil was purified by chromatography (ethyl acetate : hexane = 7 : 93) to afford a colourless oil **5** (22.13g, 90%). ^{1}H-NMR δ 0.6-2.0 (m, 22H), 3.9 (s, 3H), 4.1 (t, 3H), 4.6 (td, J_1=10Hz, J_2=2.4Hz, 1H), 6.8 (m, 2H), 7.3 (m, 1H), 7.4 (m, 1H); IR ν_{max} 3076, 2960, 1734, 1480, 1436, 1252, 1072 cm^{-1}; MS m/z 350 (M^+).

(-)-Menthyl α-(2-methoxyphenylsulfenyl)acrylate 6. SO_2Cl_2 (3.94g, 21.19mmol) was added dropwise to a CH_2Cl_2 (10ml) solution of **5** (8.52g, 24.3mmol) at 0°C and the reaction mixture was stirred for another 10 min. EtOAc

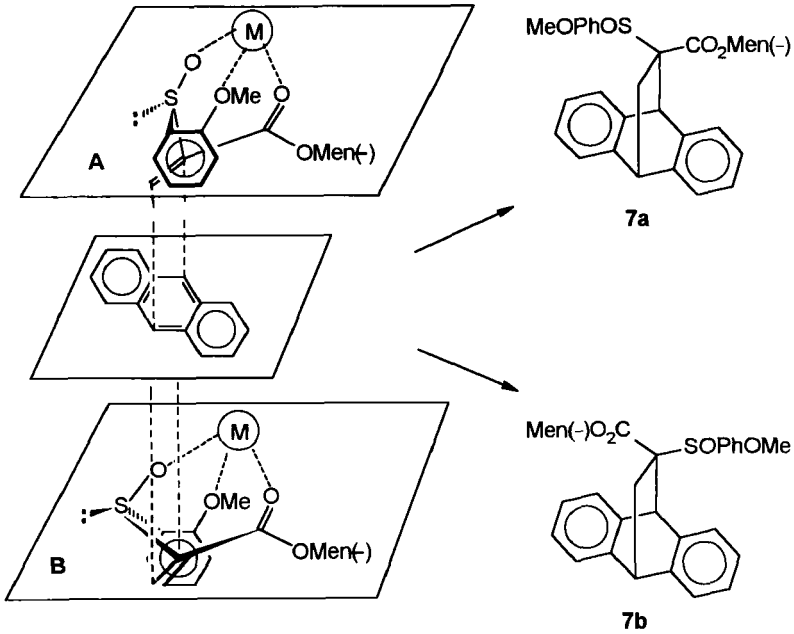


Figure 2

(100ml) and ice water were added and the organic solution was washed with 5% $NaHCO_3$ (100ml), with brine (100ml) and dried over Na_2SO_4. After removal of solvent, the crude compound was dissolved in toluene (20ml) and refluxed for 1 h. After evaporation of toluene in vacuo, the crude product was purified by column chromatography (ethyl acetate : hexane = 10 : 90) to afford **6** (8.67g, 90%). ^{1}H-NMR δ 0.6-2.0 (m, 19H), 3.9 (s, 3H), 4.7 (t, 1H), 5.2 (s, 1H), 6.3 (m, 1H), 7.3 (m, 4H); IR ν_{max} 3076, 2096, 1734, 1580, 1480, 1072 cm^{-1}; MS m/z 348 (M^+).

(-)-Menthyl α-(2-methoxyphenylsulfoxyl)acrylate 2a and 2b. To a stirred solution of **6** (5.48g, 15.75mmol) in CH_2Cl_2 (10ml) was added MCPBA (3.54g, 20.48mmol) in CH_2Cl_2 (20ml) at 0°C. The reaction mixture was stirred for another 10 min and was hydrolyzed with water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (50ml x 2). The combined organic layers were washed with 5% $NaHCO_3$ (50ml), with brine (50ml) and dried over Na_2SO_4.

After removal of solvent, the crude product was separated by MPLC (ethyl acetate : hexane = 17 : 83) to give **2a** (3.01g) and **2b** (2.81g) in overall yield of 95%.**2a:** ^{1}H-NMR δ 0.5-2.0 (m, 19H), 3.9 (s, 3H), 4.6 (m, 1H), 6.7 (s, 1H), 6.9 (s, 1H), 6.9-7.1 (m, 2H), 7.5 (m, 2H); ^{13}C-NMR (300MHz) δ 161.62, 157.88, 147.30, 131.02, 129.30, 127.64, 127.47, 111.72, 75.82, 55.94, 46.79, 40.09, 34.05, 31.14, 26.23, 23.37, 21.81, 20.52, 16.20; IR ν_{max} 2960, 1724, 1588, 1278, 1252, 1050 cm-1; MS m/z 365 (M^++1). **2b:** 0.5-2.0 (m, 19H), 3.9 (s, 3H), 4.7 (m, 1H), 6.8 (s, 1H), 7.0 (s, 1H), 6.9-7.1 (m, 2H), 7.4-7.6 (m, 2H); ^{13}C-NMR (300MHz) δ 161.52, 157.86, 146.62, 146.59, 133.51, 131.03, 130.57, 127.43, 121.51, 111.78, 75.83, 55.95, 46.78, 40.46, 33.94, 31.24, 25.34, 22.72, 21.80, 20.86, 15.49; IR ν_{max} 2960, 1724, 1588, 1278, 1252, 1050 cm^{-1} ; MS m/z 365 (M^++1).

General procedure for cycloaddition of 2 with anthracene: $ZnCl_2$ (409mg, 3mmol) was added to a CH_2Cl_2 solution of **2a** (364 mg, 1 mmol). After being stirred at 0°C for 0.5h, a solution of anthracene (534 mg, 3 mmol) in dry CH_2Cl_2 (10 ml) was added dropwise. The reaction mixture was stirred at 0°C for another 18h. The mixture was extracted with CH_2Cl_2 (30 ml×3), washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4. After removal of the solvent, the crude compound was purified by column chromatography to give **7a** (444 mg, 82%). The reaction was performed using the same conditions by using **2b** (364 mg, 1 mmol) as starting material to give **7b** (439 mg, 81%). Selected data for **7a**: IR(CCl_4) 3076, 2956, 1714, 1582, 1370 cm^{-1}; ^{1}H NMRδ 0.2-1.6 (m, 18H), 2.4 (dd, J_1=14.1Hz, J_2=2.4Hz, 1H), 2.6 (dd, J_1=14.1Hz, J_2=2.4Hz, 1H), 3.8 (s, 3H), 4.2 (m, 1H), 4.4 (t, J=2.4Hz, 1H), 5.4 (s, 1H), 6.7-7.9 (m, 12H); MS m/z 543 (M^++1); HRMS: m/e for $C_{34}H_{38}O_4S$ calcd. 542.2491, measured 542.2487; Anal.calcd for $C_{34}H_{38}O_4S$: C 75.25, H 7.06. Found: C 75.51, H 7.01. **7b** IR(CCl_4) 3076, 2956, 1714, 1528, 1480,1390, 1370, 1330 cm^{-1}; ^{1}H NMRδ 0.2-1.3 (m, 18H), 2.3 (dd, J_1=14.8Hz, J_2=2.7Hz, 1H), 2.7 (dd, J_1=14.8Hz, J_2=2.7Hz, 1H), 3.7 (s, 3H), 4.2 (m, 1H), 4.4 (t, J=2.7Hz, 1H), 5.2 (s, 1H), 6.8-7.9 (m, 12H); MS m/z 543 (M^++1); HRMS: m/e for $C_{34}H_{38}O_4S$ calcd. 542.2491, measured 542.2489; Anal.calcd for $C_{34}H_{38}O_4S$: C 75.25, H 7.06. Found: C 75.51, H 7.01.

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5. Similar conclusion was obtained by Jones, D.N. (see ref. 3a).
6. Crystal data for **7a** ($C_{34}H_{38}O_4S$): monoclinic, space group $P2_1$, a=12.993(6) b=18.070(4) c=13.245(4)A, β=105.93(3)°, V=299.3(17)A^3, Z=4, Dc=1.205g cm^{-3}, 3107 independent observed reflections, 702 refined parameters, R_{obs}=0,0358.
7. Compared to the cycloaddition of **1** with anthracene which proceeded at r.t. for 51 hr. under the presence of $ZnCl_2$ reported by Koizumi (see ref.4a).

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