

**HIGH PRESSURE MEDIATED ASYMMETRIC DIELS-ALDER  
REACTION OF CHIRAL SULFINYLACRYLATE DERIVATIVES  
WITH FURAN AND 2-METHOXYFURAN<sup>†</sup>**

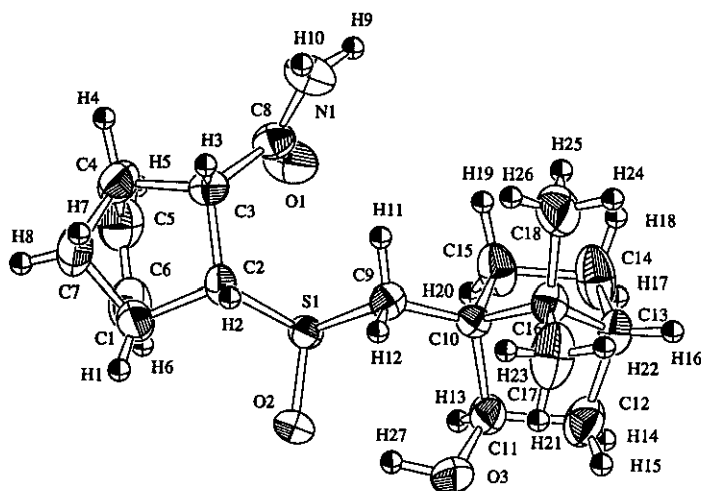
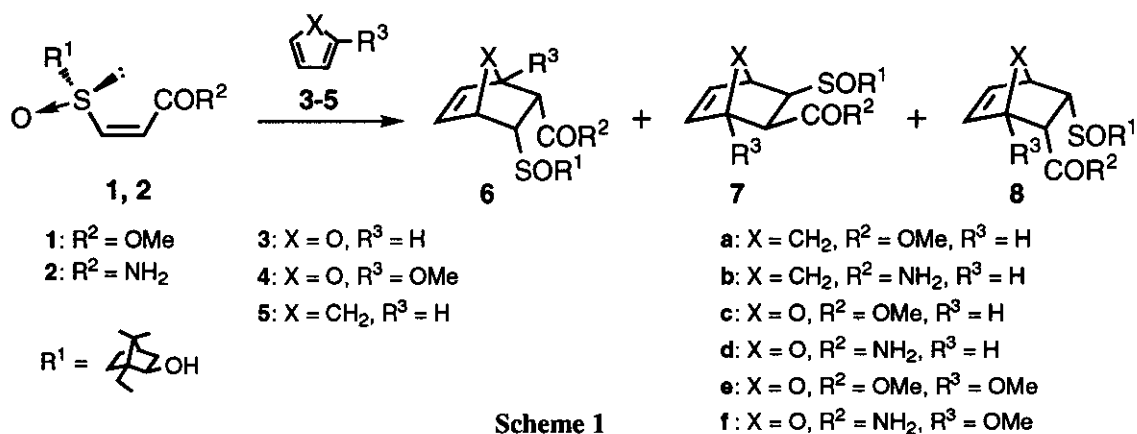
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**Abstract** -- Asymmetric Diels-Alder reaction of chiral sulfinylacrylate derivatives (**1** and **2**) with furan (**3**) and 2-methoxyfuran (**4**) proceeded under high pressure (1.2 GPa) conditions to give *endo* cycloadducts (**6c-f**). The absolute configuration of adduct (**6**) was confirmed by conversion of **6e** to (-)-COTC (**9**).

Optically pure 7-oxabicyclo[2.2.1]hept-5-ene derivatives are key intermediates in the chiral synthesis of biologically active and/or natural products.<sup>1</sup> Although this bicyclic framework is available by the asymmetric Diels-Alder (D-A) reaction of furans with more powerful chiral dienophiles under ordinary pressure, there are few examples of such efficient dienophiles.<sup>2</sup> This method can not be extended to the reactions giving acid-labile cycloadducts, because a Lewis acid is required to achieve high degree of diastereoselectivity in this reaction.<sup>2c</sup> (*S<sub>S</sub>*)(*Z*)-Menthyl 3-[2-(3-trifluoromethylpyridyl)sulfinyl]acrylate is the only dienophile which reacts with a substituted furan in a highly diastereoselective manner without a Lewis acid.<sup>2c</sup> Applying a high pressure technique, asymmetric D-A reaction would proceed without a Lewis acid between dienophiles with poor reactivity and furans,<sup>3</sup> and then this strategy could have wide application. We have recently exploited a practical method for diastereoselective preparation of a variety of chiral sulfinylethenes using 2-*exo*-hydroxy-10-bornyl group as a chiral auxiliary.<sup>4</sup> In this research setting, we applied chiral sulfinylacrylate derivatives (**1** and **2**), which were readily prepared but had poor D-A reactivity, to high pressure mediated asymmetric D-A reaction with furan (**3**) or 2-methoxyfuran (**4**). In the preliminary experiment, reactivity and steric course of the reaction were compared in the asymmetric

D-A reaction of methyl 3-(2-*exo*-hydroxy-10-bornyl)propenoate (**1**)<sup>5</sup> or 3-(2-*exo*-hydroxy-10-bornyl)propenamide (**2**)<sup>6,7</sup> with cyclopentadiene (**5**) under both atmospheric and high pressure conditions (Scheme 1). Reactions of **1** with **5** in CH<sub>2</sub>Cl<sub>2</sub> at room temperature under both atmospheric and high pressure (1.2 GPa) conditions gave *endo* cycloadduct (**6a**) as a single diastereomer in 92% and 88% yield, respectively. The structure of **6a** was confirmed by comparison of its spectral data with those in the literature.<sup>5</sup> Similar reactions of **2** with **5** in CH<sub>2</sub>Cl<sub>2</sub> / MeOH (1:1) proceeded under atmospheric or high pressure conditions to give *endo* cycloadduct (**6b**) and *exo* cycloadduct (**7b**) in 87% and 5% yield or 81% and 9% yield, respectively. All these reactions proceeded with high diastereoselectivity and regioselectivity. The absolute configuration of product (**6b**) was determined by X-ray diffraction analysis (Figure 1).<sup>9</sup> From these results, the same steric course was suggested as shown in Figure 2 for the reaction of **1** or **2** with cyclopentadiene (**5**).



**Figure 1.** Perspective Structure of Compound (**6b**).

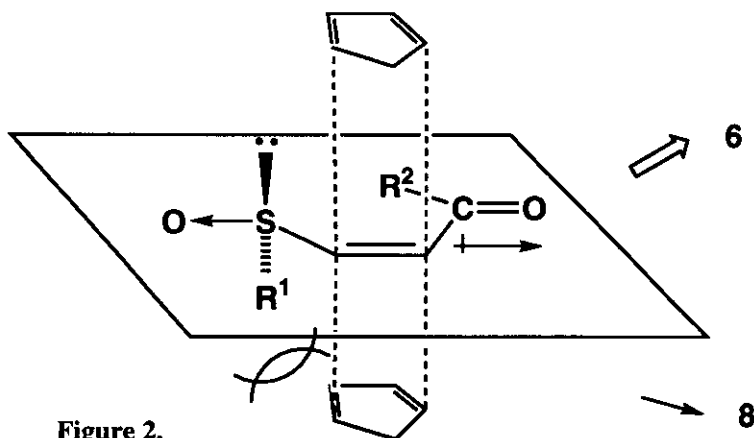


Figure 2.

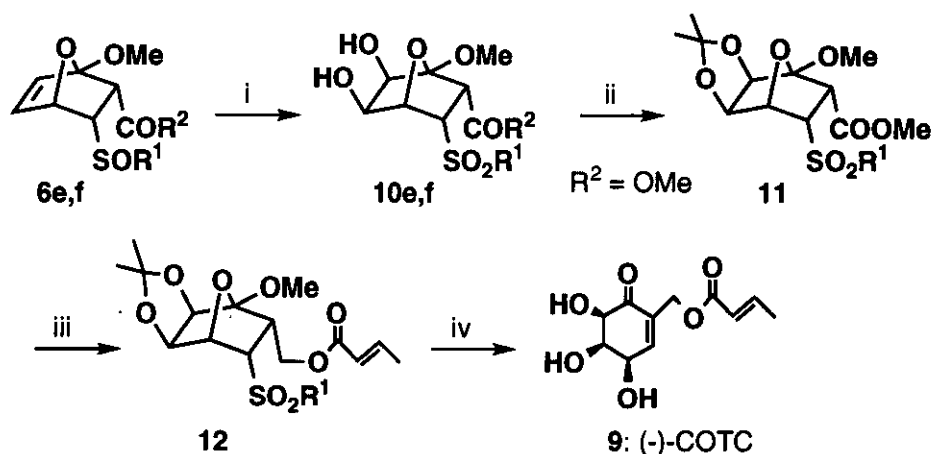
**Table 1.** Diels-Alder Reactions of Chiral Sulfinylacrylate Derivatives (**1** and **2**) with Furans (**3** and **4**)<sup>a</sup>

entry	dienophile	diene	reaction conditions				products (ratio) <sup>c</sup>	yield (%)
			pressure (GPa)	temp.	solv. <sup>b</sup>	time (h)		
1	<b>1</b>	<b>3</b>	d	50 °C	A	120	—	—
2	<b>1</b>	<b>3</b>	1.2	r.t. <sup>e</sup>	A	67	<b>6c</b> / <b>7c</b> / <b>8c</b> (82:14:4)	94
3	<b>2</b>	<b>3</b>	d	100 °C	B	72	—	—
4	<b>2</b>	<b>3</b>	1.2	r.t. <sup>e</sup>	B	72	<b>6d</b> (100)	81
5	<b>1</b>	<b>4</b>	1.2	r.t. <sup>e</sup>	A	72	<b>6e</b> / <b>7e</b> (71:29)	f
6	<b>2</b>	<b>4</b>	1.2	r.t. <sup>e</sup>	B	72	<b>6f</b> / <b>7f</b> (92:8)	g

a) Atmospheric pressure conditions: a dienophile (0.2 mmol) and a diene (20 equiv.) in a solvent (3 ml) were used for the reaction; High pressure conditions: a dienophile (0.2-0.74 mmol) and a diene (3.6-22 equiv.) in a solvent (10 ml) were used for the reaction. b) A: CH<sub>2</sub>Cl<sub>2</sub>; B: CH<sub>2</sub>Cl<sub>2</sub> / MeOH (1:1). c) Ratio was determined by <sup>1</sup>H nmr spectroscopy. d) Atmospheric pressure. e) room temperature. f) Diol (**10e**) was obtained from **6e** after dihydroxylation in 53% yield from **1**. g) Diol (**10f**) was obtained from **6f** after dihydroxylation in 63% yield from **2**.

With these preliminary results in hand, we started to examine high pressure mediated asymmetric D-A reaction of **1** or **2** with furan (**3**) or 2-methoxyfuran (**4**) (Scheme 1 and Table 1). Starting material was recovered unchanged in the reaction of **1** or **2** with furan (**3**) under atmospheric pressure conditions. Under high pressure (1.2 GPa) conditions, the reaction of **1** with furan (**3**) gave major *endo* adduct (**6c**) (77% yield), *exo* adduct (**7c**) (13% yield), and minor *endo* adduct (**8c**) (4% yield). Diastereoselectivity (ds) of *endo* adducts (**6c** / **8c**) was 95:5. Similar reaction of **2** with **3** afforded *endo* adduct (**6d**) (81% yield) as a single diastereomer. So high pressure reaction system was proved to be very effective to asymmetric D-A reaction of **1** or **2** with furan (**3**) in respect of chemical yield, diastereoselectivity, and regioselectivity (86:14 for **6c**+**8c** / **7c** and 100:0 for **6d** / **7d**). High pressure mediated D-A reaction of **1** with 2-methoxyfuran (**4**)

gave a mixture containing *endo* and *exo* adducts, (**6e** and **7e**) (71:29). These products were so unstable that we could not separate them. Dihydroxylation of the mixture afforded diol (**10e**) deriving from **6e** in 53% yield from **1**. Similar D-A reaction of **2** with **4** yielded a mixture containing *endo* and *exo* adducts, (**6f** and **7f**) (92:8), which gave diol (**10f**) deriving from **6f** in 63% yield from **2**. The configuration of *endo* and *exo* cycloadducts (**6-8**) was deduced by  $^1\text{H}$  nmr spectra and mechanistic consideration.<sup>2b-e</sup> To make sure the absolute configuration of major *endo* adduct (**6**), adduct (**6e**) was converted to (-)-COTC (**9**)<sup>2c,10</sup> (Scheme 2). Dihydroxylation of **6e** gave diol (**10e**), mp 189-191 °C,  $[\alpha]_{\text{D}}^{25} +5.9^\circ$  ( $c = 4.15$ ,  $\text{CHCl}_3$ ), in 53% yield from **1**. Acetonide formation of **10e** afforded acetonide (**11**), mp 164-167 °C,  $[\alpha]_{\text{D}}^{26} -6.7^\circ$  ( $c = 5.21$ ,  $\text{CHCl}_3$ ), in 64% yield. Ester (**11**) was converted to crotonate ester (**12**), mp 162-164 °C,  $[\alpha]_{\text{D}}^{28} -74.3^\circ$  ( $c = 2.72$ ,  $\text{CHCl}_3$ ), by successive reduction with  $\text{LiAlH}_4$  and esterification with crotonic anhydride in 43% yield. Treatment of **12** with trifluoroacetic acid afforded (-)-COTC (**9**), mp 176-178 °C,  $[\alpha]_{\text{D}}^{28} -109.7^\circ$  ( $c = 0.23$ ,  $\text{MeOH}$ ), [lit.,<sup>10</sup> mp 181 °C,  $[\alpha]_{\text{D}}^{24} -109^\circ$  ( $c = 1.5$ ,  $\text{MeOH}$ ), and lit.,<sup>2c</sup> mp 179-181 °C,  $[\alpha]_{\text{D}} -108^\circ$  ( $c = 0.23$ ,  $\text{MeOH}$ )], in 29% yield.  $^1\text{H}$  Nmr and ir spectra of **9** were identical with those reported.<sup>2c,10</sup> From these results, the absolute configuration of **6e** was determined as shown in Schemes 1 and 2. Accordingly, steric course of the reaction was confirmed to be the same in all these asymmetric cycloadditions under atmospheric and high pressure conditions.



i) cat.  $\text{OsO}_4$ ,  $\text{Me}_3\text{NO}$ , acetone, 0 °C then room temperature, **10e**: 53% from **1**, **10f**: 63% from **2**; ii) 2,2-dimethoxypropane, cat. *p*-TsOH, acetone, reflux, 64%; iii)  $\text{LiAlH}_4$ , THF, room temperature; crotonic anhydride, pyridine, DMAP, benzene, room temperature, 43% from **11**; iv) 80% aqueous TFA, -20 °C, 29%.

Scheme 2

Thus, we developed high pressure mediated asymmetric D-A reaction of sulfinylacrylate derivatives (**1** and **2**) with furan (**3**) or 2-methoxyfuran (**4**), and obtained major *endo* adduct (**6**) in good to high yield. Transformation of major *endo* adduct (**6e**) to (-)-COTC provided not only determination of the absolute configuration of **6e** but also a new strategy for practical chiral synthesis of natural polyoxygenated cyclohexane derivatives. Further investigation is now in progress in our group for transformation of adducts (**6c-f**) to biologically active and/or natural products (gabosine C *etc.*).

## REFERENCES AND NOTES

- † Dedicated to the memory of the late Dr. Yoshio Ban, Professor Emeritus Hokkaido University.
- †† Fellow of the Science and Technology Agency of Japan, on leave from National Institute of Health Sciences.
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  6. Satisfactory analytical (combustion) and spectral (ir, <sup>1</sup>H nmr, mass) data were obtained for all new isolable compounds.
  7. Dienophile (**2**) was obtained by successive Michael addition of 10-mercapto-2-*exo*-borneol<sup>5</sup> to propiolamide<sup>8</sup> and oxidation with *m*-chloroperbenzoic acid in 43% overall yield.
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  9. Crystallographic data for **6b**: monoclinic, space group, *P*2<sub>1</sub> with *a* = 10.971(3) Å, *b* = 7.338(2) Å, *c* = 12.159(3) Å, β = 116.08(2)°, *V* = 879.1(4) Å<sup>3</sup>, and *Z* = 2 (*d*<sub>calcd</sub> = 1.275 g cm<sup>-3</sup>), μ(MoKα) = 2.98 cm<sup>-1</sup> absorption corrected by ω scans; 2290 unique reflections; 2181 with *I* > 3.00σ(*I*) were used in refinement; *R* = 4.3%, *R*<sub>w</sub> = 4.4%. The authors have deposited atomic coordinates for **6b** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
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