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## Thermal and Lewis Acid-promoted Novel Asymmetric Hetero Diels–Alder Reactions of a 1-Thiabuta-1,3-diene System (Thiochalcones) with (—)-Dimethyl Fumarate

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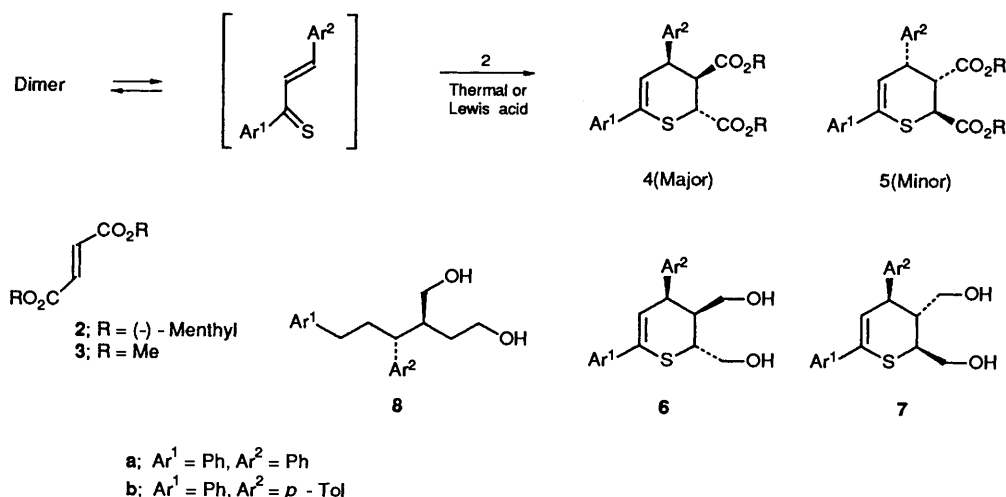
Thermal and Lewis acid-promoted reactions of thiochalcones with (—)-dimethyl fumarate gave two 3,4-*cis*-cycloadducts, **4** and **5**, in good yields with 100% *endo*-diastereoselectivity and with a high level of diastereofacial selectivity. The major product **4** could be obtained stereochemically pure by recrystallization and this, when reduced with LiAlH<sub>4</sub>, gave the optically active diol **6**. The latter was converted into the acyclic diol **8** by Raney-Ni desulphurization.

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Since the pioneering studies of Walborsky and other workers,<sup>1</sup> great progress in the asymmetric Diels–Alder reaction has been made, and increasing attention is being paid to the asymmetric hetero Diels–Alder (AHDA) reaction using heterodienes or heterodienophiles.<sup>2–4</sup> However, the use of hetero atom cycloaddends has been limited, in most cases, to oxa- or azadienophiles.<sup>3,4</sup> Recently Vedejs *et al.* and Bonini *et al.* reported that thioaldehydes and a silyl thioketone, participated as

heterodienophiles in AHDA reactions.<sup>5</sup> There has been no report, however, of a 1-thiabuta-1,3-diene system, taking part in an AHDA reaction although unsaturated thiocarbonyls are sufficiently reactive to undergo cycloadditions with a variety of dienophiles under mild conditions.<sup>4,6</sup> Here we describe the first example of an AHDA reaction of a thiabutadiene with a chiral dienophile.

The reaction of the thiochalcone **1a**, generated by thermolysis



Scheme 1

**Table 1** Thermal asymmetric Diels-Alder reaction of thiochalcones **1** with (-)-dimethyl fumarate **2**<sup>a</sup>

Entry	Thio-ketone	Solvent	Cyclo-adduct	Yield (%)	$\pi$ -Facial d.e. (%) <sup>b</sup>	(6/7) e.e. (%) <sup>c</sup>
1	<b>1a</b>	CH <sub>2</sub> Cl <sub>2</sub>	<b>4a</b> + <b>5a</b>	99	28	26
2	<b>1a</b>	CH <sub>2</sub> Cl <sub>2</sub> <sup>d</sup>	<b>4a</b> + <b>5a</b>	93	35	37
3	<b>1a</b>	CCl <sub>4</sub>	<b>4a</b> + <b>5a</b>	92	22	22
4	<b>1a</b>	Et <sub>2</sub> O <sup>e</sup>	<b>4a</b> + <b>5a</b>	94	19	— <sup>f</sup>
5	<b>1a</b>	Benzene	<b>4a</b> + <b>5a</b>	82	— <sup>f</sup>	9
6	<b>1a</b>	Toluene	<b>4a</b> + <b>5a</b>	92	16	15
7	<b>1a</b>	CHCl <sub>3</sub>	<b>4a</b> + <b>5a</b>	95	48	43
8	<b>1b</b>	CH <sub>2</sub> Cl <sub>2</sub>	<b>4b</b> + <b>5b</b>	98	26	— <sup>f</sup>
9	<b>1b</b>	CCl <sub>4</sub>	<b>4b</b> + <b>5b</b>	99	16	— <sup>f</sup>
10	<b>1b</b>	Toluene	<b>4b</b> + <b>5b</b>	83	10	— <sup>f</sup>
11	<b>1b</b>	CHCl <sub>3</sub>	<b>4b</b> + <b>5b</b>	86	40	— <sup>f</sup>

<sup>a</sup> The reactions were carried out at 40 °C for 24–26 h. <sup>b</sup> Determined by HPLC and 500 MHz <sup>1</sup>H NMR. <sup>c</sup> Determined by comparison with the specific rotation of pure **6a** ( $[\alpha]_D^{27} + 237$  in benzene). <sup>d</sup> At 20 °C for 11 d. <sup>e</sup> At 35 °C for 36 h. <sup>f</sup> Not determined.

of its dimer **6** with (-)-dimethyl fumarate **2** at 40 °C in dichloromethane for 25 h (Entry 1, Table 1) gave cycloadducts (99% yield), which, of four possible diastereoisomers, were found to be a mixture of two diastereoisomers (**4a** + **5a**) in a ratio of 64:36 (28% d.e.) by HPLC and/or 500 MHz <sup>1</sup>H NMR spectroscopic analysis. The <sup>1</sup>H NMR spectra confirmed that both products were 3,4-*cis*-adducts (*endo*),<sup>†</sup> no 3,4-*trans*-adducts (*exo*) being detected. Such complete *endo*-selectivity was also observed in the reaction of **1a** with dimethyl fumarate **3**. The  $\pi$ -face differentiation-related d.e. was further confirmed by determining that the d.e. value (e.g. 28%, Entry 1) was parallel to the e.e. value (e.g. 26%, Entry 1) of the diols (**6** + **7**), formed in each case after removal of the chiral auxiliary by LiAlH<sub>4</sub> reduction. The best result was obtained when the reaction was carried out in chloroform at 40 °C (95% yield, 48% d.e., Entry 7). Although the d.e. was not high, the major *endo*-adduct **4a** could be obtained stereochemically pure by preparative TLC and/or several recrystallizations to give the

\* The thiopyran-type dimer **T** is used in all cases in Table 1. We assumed that influence of the dimer structure alteration to the d.e.'s was negligible because the d.e.'s are consistent with those obtained when the dithiin-type dimer **D** was used.

<sup>†</sup> *Endo* refers to *cis*-relationship between the substituents at 3- and 4-positions of the dihydrothiopyran ring formed.

<sup>‡</sup> Details will be published elsewhere.

**Table 2** The Lewis acid-promoted asymmetric hetero Diels-Alder reaction of the thiochalcone **1a** with (-)-dimethyl fumarate **2**<sup>a</sup>

Entry	Lewis acid (equiv.)	Time (h)	Yield (%)	$\pi$ -Facial d.e. (%) <sup>b</sup>
1	None	36	94	19
2	AlCl <sub>3</sub> (1.0)	7	58	59
3	AlCl <sub>3</sub> (2.0)	5	73	64
4	AlCl <sub>3</sub> (3.0)	5	76	71
5	AlCl <sub>3</sub> (4.0)	4	55	64
6	EtAlCl <sub>2</sub> (3.0)	8	79	54
7	EtAlCl <sub>2</sub> (4.0)	7	87	56
8	Pr <sup>i</sup> OAlCl <sub>2</sub> (4.0)	5	89	54
9	BF <sub>3</sub> (4.0)	18	75	19
10	ZnCl <sub>2</sub> (4.0)	20	95	28
11	SnCl <sub>4</sub> (4.0)	10	36	34

<sup>a</sup> The reactions were carried out in diethyl ether at 35 °C. <sup>b</sup> Determined by HPLC and 500 MHz <sup>1</sup>H NMR spectroscopy.

optically pure diols **6** and **8** by LiAlH<sub>4</sub> and Raney Ni reduction, respectively. Reactions at <40 °C in the appropriate solvent were impractical owing to the slowness of the thermolysis, whilst higher temperatures caused lower  $\pi$ -facial selectivity. Solvent and thermal effects on the d.e.'s were also observed in the reaction of **1b** with **2** and gave the corresponding 3,4-*cis*-adducts **4b** + **5b** (Entries 8–11).

Since there is no precedent for Lewis acid-promoted thio-carbonyl Diels-Alder reactions, we investigated the reaction of **1** with a variety of achiral carbonyl-activated dienophiles, such as methyl acrylate, methyl vinyl ketone, acrolein and dimethyl fumarate (**3**), only to find that the thiopyran type dimer **T**<sup>7</sup> was largely decomposed by the action of the Lewis acid before completion of the Diels-Alder reaction. The use of the dithiin-type dimer **D**<sup>7</sup> in diethyl ether, however, gave satisfactory yields and stereoselectivities.<sup>‡</sup> The AHDA reactions of **1** (from its precursor **D**) in the presence of various Lewis acids were examined, and the results are summarized in Table 2. Of the various conditions, the best  $\pi$ -facial d.e. (71%) with a 100% *endo*-selectivity was obtained with AlCl<sub>3</sub> (3.0 equiv.) in diethyl ether at 35 °C (Entry 4, Table 2).

Both the thermal and Lewis acid-promoted AHDA reactions, gave, preferentially, the 3,4-*cis*-adduct **4** with the same configuration. Although the absolute configurations of the adducts were not determined, the major isomer **4** was tentatively assigned as 2*R*,3*S*,4*S* on the basis of the Prelog-model consideration that **1** would preferentially attack the less hindered *re-re* face of **2**.<sup>1</sup>

**Experimental\***

**Hetero Diels–Alder Reaction of the Thiochalcone 1a with (–)-Dimethyl Fumarate 2 to afford (2R\*,3S\*,4S\*)-2,3-trans-3,4-cis-2,3-Bis[(–)-menthoxy carbonyl]-3,4-diphenyl-3,4-dihydro-2H-thiopyrans 4a and 5a.**—Typical procedure (Entry 7 in Table 1). A stirred mixture of 1a-dimer (T) (112 mg, 0.50 mmol as the monomer) and 2 (235 mg, 0.60 mmol) was heated at 40 °C in chloroform (15 ml) for 25 h under a nitrogen atmosphere. Evaporation of the solvent and column chromatography of the residue [silica gel, benzene–hexane (1:4)] gave the adducts 4a + 5a (297 mg, 95%). The HPLC analysis (Shiseido Capcell pack C<sub>18</sub>, CH<sub>3</sub>CN) showed a ratio of 74:26 (48% d.e.) of the diastereoisomers. The major isomer 4a was obtained pure by recrystallization (×3) from benzene–ethanol (1:4) (10–30% yield) as colourless fluffy needles, m.p. 128.7–129.7 °C (Found: C, 75.6; H, 8.8. C<sub>39</sub>H<sub>52</sub>O<sub>4</sub>S requires C, 75.9; H, 8.5%);  $[\alpha]_D^{27} +237$  (c, 2.0 in benzene);  $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$  1734;  $\delta_{\text{H}}(\text{CDCl}_3)$  0.40–2.28 (36 H, m, Menthyl), 3.39 (1 H, dd, J 4.5 and 11.1, 3-H), 4.16 (1 H, dd, J 4.5 and 6.7, 4-H), 4.23 (1 H, d, J 11.1, 2-H), 4.35–4.85 (2 H, m, Menthyl), 6.20 (1 H, d, J 6.7, 5-H) and 7.00–7.60 (10 H, m, ArH);  $\delta_{\text{C}}(\text{CDCl}_3)$  15.8 (Me), 16.0 (Me), 21.0 (Me), 22.1 (2 Me), 22.8, 23.2, 25.7, 25.9, 31.4, 34.3, 40.3, 40.7, 42.7, 46.0, 47.1, 75.5, 76.0, 120.7–138.9, 170.2 and 171.4;  $m/z$  616 (M<sup>+</sup>, 0.4%), 477 (M<sup>+</sup> – Menthyl, 29), 339 (65), 321 (32), 223 (53) and 83 (100). The minor isomer 5a showed small differences in its <sup>1</sup>H and <sup>13</sup>C NMR spectra:  $\delta_{\text{H}}$  0.52–2.16 (36 H, m), 3.64 (1 H, dd, J 4.8 and 12.2, 3-H), 4.20 (1 H, dd, J 4.8 and 6.8, 4-H), 4.23 (1 H, d, J 12.2, 2-H), 4.37–4.89 (2 H, m), 6.19 (1 H, d, J 6.8, 5-H), and 7.02–7.58 (10 H, m, ArH);  $\delta_{\text{C}}$  169.9 and 170.9.

**Reduction of 4a with LiAlH<sub>4</sub> to Afford 6a.**—A solution of 4a (308 mg, 0.50 mmol) in dry diethyl ether (20 ml) was added to a suspension of LiAlH<sub>4</sub> (95 mg, 2.5 mmol) in dry ether (50 ml) at 0 °C under nitrogen atmosphere. After being stirred for 3 h at 0 °C, the reaction mixture was quenched with saturated aq. NH<sub>4</sub>Cl solution. The organic layer was separated, washed with brine and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was evaporated and the residue was chromatographed [silica gel, ethyl acetate–hexane (1:4)] and recrystallized from ethyl acetate–hexane to give the diol 6a, (137 mg, 88%), m.p. 205–206 °C (Found: C, 72.95; H, 6.7%. C<sub>19</sub>H<sub>20</sub>O<sub>2</sub>S requires C, 73.0; H, 6.45%);  $[\alpha]_D^{26} +24.4$  (c, 1.0 in ethanol);  $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$  3256 (OH), 1028 and 1016;  $\delta_{\text{H}}(\text{CDCl}_3)$  1.84–2.24 (2 H, m), 2.76–3.20 (1 H, m), 3.28–3.64 (3 H, m), 3.64–4.00 (3 H, m), 6.11 (1 H, d, J 4.0, 5-H) and 7.00–7.64 (10 H, m, ArH);  $\delta_{\text{C}}(\text{CDCl}_3)$  40.1 (C-3), 40.9 (C-4), 43.7

(C-2), 62.2 (CH<sub>2</sub>) and 120.7–133.7;  $m/z$  312 (M<sup>+</sup>, 12%), 294 (7), 276 (16), 236 (41) and 223 (100).

**Reduction of 6a with Raney Ni to Afford (2S\*, 1'R\*)-2-(1,3-Diphenylpropyl)butane-1,4-diol 8.**—A mixture of 6a (312 mg, 1.0 mmol) and Raney Ni (W-2; 5 g) in ethanol (30 ml) was stirred overnight at room temperature. The mixture was filtered and evaporated. Chromatography [silica gel, ethyl acetate–hexane (1:8)] of the residue gave 8 (200 mg, 70%) as a colourless oil (Found: M<sup>+</sup>, 284.1784. C<sub>19</sub>H<sub>24</sub>O<sub>2</sub> requires M, 284.1777);  $[\alpha]_D^{27} +0.58$  (c, 2.0 in ethanol);  $\nu_{\max}(\text{CCl}_4)/\text{cm}^{-1}$  3356 and 1043;  $\delta_{\text{H}}(\text{CDCl}_3)$  0.60–4.00 (14 H, m) and 6.88–7.50 (10 H, m);  $\delta_{\text{C}}(\text{CDCl}_3)$  33.2, 33.9, 34.7, 44.4, 46.5, 60.9, 63.9 and 125.7–143.0;  $m/z$  284 (M<sup>+</sup>, 1%), 266 (6), 220 (5), 117 (34) and 91 (100).

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**References**

- H. M. Walborsky, L. Barash and T. C. Davis, *J. Org. Chem.*, 1961, **26**, 4778; H. M. Walborsky, L. Barash and T. C. Davis, *Tetrahedron*, 1963, **19**, 2333; W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 876; L. A. Paquette, *Asymmetric Synthesis*, ed. by J. D. Morrison, Academic Press, New York, 1984, vol. 3, p. 455.
- J. Jurczak and A. Zamojsky, *Tetrahedron*, 1972, **28**, 1505; J. Jurczak and M. Tkacz, *J. Org. Chem.*, 1979, **44**, 3347; S. W. Remiszewsky, J. Yang and S. M. Weinreb, *Tetrahedron Lett.*, 1986, **27**, 1853.
- M. J. Taschner, *Asymmetric Diels–Alder Reactions*, in *Organic Synthesis, Theory and Applications*, ed. by T. Hudlicky, Jal Press, London, 1989, vol. 1, p. 1.
- D. L. Boger and S. M. Weinreb, *Hetero Diels–Alder Methodology in Organic Syntheses*, Academic Press, New York, 1987.
- E. Vedejs, J. S. Stults and R. G. Wilde, *J. Am. Chem. Soc.*, 1988, **110**, 5452; B. F. Bonini, G. Mazzanti, P. Zani and G. Maccagnani, *J. Chem. Soc., Chem. Commun.*, 1988, 365.
- T. Karakasa and S. Motoki, *J. Org. Chem.*, 1978, **43**, 4147; T. Karakasa and S. Motoki, *J. Org. Chem.*, 1979, **44**, 4151; T. Karakasa, H. Yamaguchi and S. Motoki, *J. Org. Chem.*, 1980, **45**, 927.
- T. Karakasa, *Nippon Shika Daigaku Kiyo, Ippan Kyoiku-kei*, 1987, **16**, 115. (*Chem. Abstr.*, 1989, **111**, 039314r); T. Karakasa, S. Satsumabayashi and H. Kurihara, *Nippon Shika Daigaku Kiyo, Ippan Kyoiku-kei*, 1991, **20**, 65; J.-P. Guemas and H. Quiniou, *Sulfur Lett.*, 1984, **2**, 121.

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\* *J* Values in Hz,  $[\alpha]_D$  values in 10<sup>-1</sup> deg cm<sup>2</sup> g<sup>-1</sup>.