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Asymmetric Diels-Alder Reactions of Enantiopure 1-Methoxy-3-(phenyl-2-hydroxyethylsulfinyl)-1,3-butadienes

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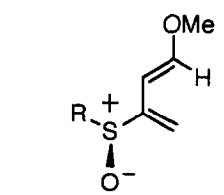
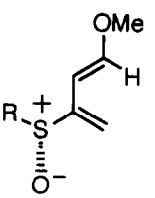
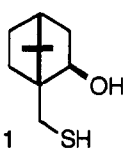
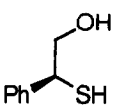
Abstract: Enantiopure 1-methoxy-3-(1-phenyl- and 2-phenyl-2-hydroxyethylsulfinyl)-1,3-butadienes were prepared from ethyl mandelate. Diels-Alder reactions with methyl acrylate proceeded with complete regioselectivity and high diastereoselectivity.

Diels-Alder reactions of acrylic acid derivatives have provided key intermediates for natural product synthesis.[1] For purposes of asymmetric synthesis high diastereofacial selectivities have been obtained in cycloadditions of prochiral 1,3-dienes with chiral acrylates,[2] but the combination of enantiopure dienes with prochiral acrylates has received less attention,[3,4] despite its potential advantages in extending the scope and usefulness of these asymmetric cycloadditions. Recently we reported that lithium perchlorate-catalysed cycloaddition of methyl acrylate to the enantiopure 1-methoxy-3-alkylsulfinyl-1,3-butadienes **4** was controlled by chirality at sulfur to engender very high endo/exo and diastereofacial selectivity, so providing ready access to enantiopure cycloadducts.[4] Further exploitation of these easy asymmetric cycloadditions is however hampered by difficulties in the mild removal of the chiral auxilliary, which was derived from 10-mercaptoisoborneol **1**.[5] In addressing this problem we have investigated the role of 2-hydroxy-1-phenylethanethiol **2** and 2-hydroxy-2-phenylethanethiol **3** as chiral control elements, encouraged by evidence that chiral auxilliaries derived from these









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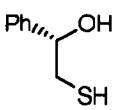


3

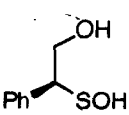
(RSH = 1) **4a** **4b**

(RSH = 2) **5a** **5b**

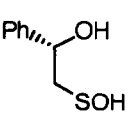
5c **5d** (H, OMe interchanged)

(RSH = 3) **6a** **6b**

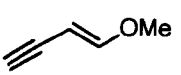
6c **6d** (H, OMe interchanged)



2a



3a



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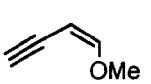
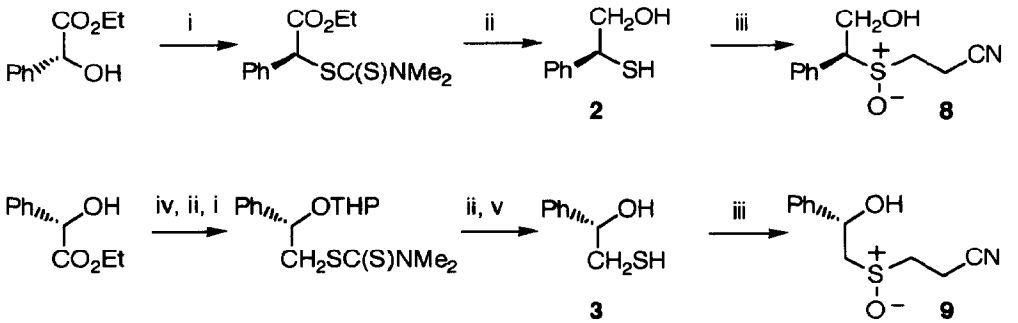


7a

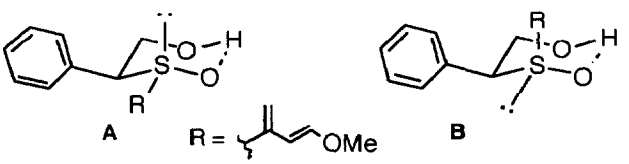
vicinal hydroxythiols may readily be removed by phenyloxiran formation.[6] These thiols were not previously described extensively in enantiopure form,[7,8] and for their preparation and conversion to the sulfinyl dienes **5** and **6** we exploited methods (cf. ref. 5) which involve the regioselective addition of sulfenic acids **2a** and **3a** to (E)- and (Z)-1-methoxy-1-buten-3-yne **7** and **7a**.

The hydroxythiols (S)-**2** and (S)-**3**, prepared from (R)- and (S)-ethyl mandelate respectively (Scheme 1),[9] gave the cyanosulfoxides **8** and **9** respectively on treatment in sequence with acrylonitrile and 3-chloroperbenzoic acid.[10] The hydroxy thiol **2** was formed from (R)-ethyl mandelate with complete inversion of configuration,[11] and none of the reactions in Scheme 1 was attended by detectable racemization despite the presence of potentially sensitive benzylic centres.[12]



Scheme 1. Reagents: i, $Zn[SC(S)NMe_2]_2$, DEAD, Ph_3P; ii, $LiAlH_4$; iii, (a) CH_2=CHCN, THF, Triton B; (b), mCPBA; iv, dihydropyran, PPTS; v, EtOH, PPTS.

Thermolysis of the cyanosulfoxide **8** in the presence of (E)-1-methoxy-1-buten-3-yne **7** provided transiently the sulfenic acid **2a**, which added to **7** to give a mixture of two sulfoxides, isolated in 33% and 12% yield after easy chromatographic separation. The major, chromatographically more mobile isomer was allocated the (S_S)-configuration **5a**, on the basis that an intramolecularly hydrogen bonded conformation **A** of the (S_S)-sulfoxide **5a** is apparently more readily accesible than that **B** for the (R_S)-sulfoxide **5b**. There is sound evidence that chromatographic mobility is directly related to the extent of intramolecular hydrogen bonding in hydroxy sulfoxides.[4,5]

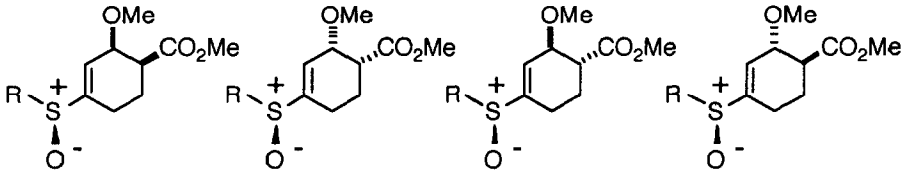


On heating the cyanosulfoxide **9** with the enyne **7**, two sulfinyl dienes **6a** and **6b** were obtained (25% combined yield). They were formed in approximately equal amounts, according to tlc and nmr analysis. Allocations of configuration at sulfur, which rested on relative chromatographic mobility, is less secure in this case because the epimers at sulfur had similar chromatographic characteristics, and were difficult to separate. This suggests that the extent of intramolecular hydrogen bonding in **6a** is similar to that in **6b**, although the reasons for this are not immediately apparent from examination of models.

The (Z)-1-methoxy-3-alkylsulfinyl-1,3-butadienes **5c** and **5d**, and **6c** and **6d** were prepared similarly by heating the cyanosulfoxides **8** and **9** respectively with (Z)-1-methoxy-1-buten-3-yne **7a**. The relative yields and chromatographic characteristics reflected those of the corresponding (E)-isomers. The predominant and

more mobile isomer **5c** was easy to separate from **5d**, whereas **6c** and **6d** were formed in equal amounts and were difficult to separate because of chromatographic similarities.

Cycloadditions with methyl acrylate in dichloromethane were investigated only for the (E)-sulfinyldienes **5a** and **6a**, in order to obtain a comparison with the behaviour of the sulfinyl dienes **4**. The products are indicated in Scheme 2, and the results are collected in the Table. Both uncatalysed and catalysed cycloadditions occurred completely regioselectively, and catalysis of the cycloaddition by zinc chloride or lithium perchlorate was attended by complete endo-selectivity and very high diastereoface selectivity. The major adducts **10** and **14** were easily obtained pure by chromatography, and their absolute configurations were assigned by analogy with related cycloadducts, the structures of which were firmly anchored by X-ray crystallographic analysis.[4]



10 [RSH = 2] **11** [RSH = 2] **12** [RSH = 2] **13** [RSH = 2]
14 [RSH = 3] **15** [RSH = 3] **16** [RSH = 3] **17** [RSH = 3]

Scheme 2

Table

Cycloadditions of dienes **5a** and **6a** with methyl acrylate [13]

Diene	Catalyst	Time	Isomer ratio
			10 : 11 : 12 : 13
5a	None	42 h	56 : 22 : 16 : 6
5a	$ZnCl_2$	17 h	81 : 13 : 0 : 0
5a	$LiClO_4$	16 h	90 : 6 : 0 : 0
			14 : 15 : 16 : 17
6a	None	6 days	44 : 26 : 19 : 11
6a	$ZnCl_2$	5 days	92 : 2 : 0 : 0
6a	$LiClO_4$	3 days	93 : 2 : 0 : 0

Taken in conjunction with previous results,[4] it is apparent that asymmetric induction in Diels-Alder reactions of 2-sulfinyldienes with methyl acrylate is influenced overwhelmingly by chirality at sulfur, and that other chiral elements present in the chiral auxilliary have no significant effect. This conclusion is important in relation to the design of other auxilliaries based on sulfoxides. It also appears that sulfoxides derived from 2-hydroxy-1-phenylethanethiol **2** are superior to those from its isomer **3** because of greater ease of preparation and separation. It now remains to establish easy methods for the removal of the chiral auxilliaries from cycloadducts such as **10**.

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9 We also synthesized thiol **3** from (S)-phenyloxirane by the Lalancette and Frêche procedure (ref. 7) but, in our hands, the procedure outlined in Scheme 1 was more convenient and efficient.

10 All new compounds were characterized by IR, ^1H and ^{13}C NMR, MS or elemental analysis. Selected data (specific rotations in $CHCl_3$; ^1H NMR at 300 MHz and ^{13}C NMR at 75 MHz in $CDCl_3$): *(S)-2-mercapto-2-phenylethanol* **2**, m.p. 46-48 °C, $[\alpha]_D$ +90 (c 0.022); δ 7.4-7.2 (5H, m, Ph), 4.07 (1H, q, $J_{1A,2}$ 6.5, $J_{1B,2}$ 7.6, $J_{2,SH}$ 6.7 Hz, H-2), 3.90 (1H, AB dd, J_{gem} 11.0 Hz, H_A-1), 3.78 (1H, AB dd, H_B-1), 1.97 (1H, d, SH), 140.42, 128.85, 127.84, and 127.39 (Ph), 68.31 (C-1), 46.35 (C-2); *(S)-2-mercapto-1-phenylethanol* **3**, oil, $[\alpha]_D$ +50 (c 0.009); δ 7.4-7.2 (5H, m, Ph), 4.71 (1H, dd, $J_{1,2A}$ 4.1, $J_{1,2B}$ 8.2 Hz, H-1), 2.86 (1H, AB ddd, J_{gem} 13.8, $J_{2A,SH}$ 9.0 Hz, H_A-2), 2.79 (1H, AB ddd, $J_{2B,SH}$ 8.2 Hz, H_B-2), 1.44 (1H, t, SH), 141.99, 128.42, 127.86, and 125.79 (Ph), 74.61 (C-1), 33.54 (C-2); *(S,S$_S$,E)-3-(2-hydroxy-1-phenylethylsulfinyl)-1-methoxy-1,3-butadiene* **5a**, oil, $[\alpha]_D$ +127 (c 0.004); δ 7.5-7.1 (5H, m, Ph), 6.79 (1H, d, $J_{1,2}$ 12.9 Hz, H-1), 5.45 and 5.29 (2H, two s, H_2-4), 5.36 (1H, d, H-2), 4.7-4.1 (3H, m, CH_2CH), 3.52 (3H, s, Me); *(S,S$_S$,Z)-3-(2-hydroxy-1-phenylethylsulfinyl)-1-methoxy-1,3-butadiene* **5c**, oil, $[\alpha]_D$ +119 (c 0.003); δ 7.4-7.3 (5H, m, Ph), 6.27 (1H, d, $J_{1,2}$ 6.8 Hz, H-1), 5.97 and 5.54 (2H, two s, H_2-4), 5.03 (1H, d, H-2), 4.54 and 4.16 (2H, split AB system, Jgem 12.4, J_{vic} 8.0 and 3.4 Hz, C*H*$_2$CH), 4.01 (1H, dd, CH_2CH), 3.72 (3H, s, Me); *(S,S$_S$,E)-3-(2-hydroxy-2-phenylethylsulfinyl)-1-methoxy-1,3-butadiene* **6a**, oil, $[\alpha]_D$ +83 (c 0.001); δ 7.4-7.3 (5H, m, Ph), 6.84 (1H, d, $J_{1,2}$ 13.1 Hz, H-1), 5.80 and 5.72 (2H, two s, H_2-4), 5.45 (1H, d, H-2), 5.33 (1H, dd, J_{vic} 10.1 and 2.1 Hz, PhC*H*), 3.64 (3H, s, Me), 3.26 and 2.79 (2H, split AB system, J_{gem} 13.7 Hz, CHC*H*$_2$); *(S,R$_S$,E)-3-(2-hydroxy-2-phenylethylsulfinyl)-1-methoxy-1,3-butadiene* **6b**, oil, $[\alpha]_D$ -58 (c 0.002); δ 7.4-7.3 (5H, m, Ph), 6.85 (1H, d, $J_{1,2}$ 13.1 Hz, H-1), 5.70 and 5.59 (2H, two s, H_2-4), 5.43 (1H, d, H-2), 5.39 (1H, dd, J_{vic} 8.8 and 3.5 Hz, PhC*H*), 3.63 (3H, s, Me), 3.3-2.7 (2H, m, CHC*H*$_2$); *(S,S$_S$,Z)-3-(2-hydroxy-2-phenylethylsulfinyl)-1-methoxy-1,3-butadiene* **6c**, oil, $[\alpha]_D$ +100 (c 0.008); δ 7.4-7.3 (5H, m, Ph), 6.16 (1H, d, $J_{1,2}$ 6.8 Hz, H-1), 6.06 (2H, s, H_2-4), 5.34 (1H, dd, J_{vic} 10.0 and 1.7 Hz, PhC*H*), 5.03 (1H, d, H-2), 3.73 (3H, s, Me), 3.27 and 2.74 (2H, split AB system, J_{gem} 13.7 Hz, CHC*H*$_2$); *(S,R$_S$,Z)-3-(2-hydroxy-2-phenylethylsulfinyl)-1-methoxy-1,3-butadiene* **6d** oil, $[\alpha]_D$ -71 (c 0.002); δ 7.4-7.3 (5H, m, Ph), 6.16 (1H, d, $J_{1,2}$ 6.7 Hz, H-1), 5.94 and 5.92 (2H, two s, H_2-4), 5.41 (1H, dd, J_{vic} 9.6 and 2.2 Hz, PhC*H*), 5.04 (1H, d, H-2), 3.72 (3H, s, Me), 3.06 and 2.95 (2H, split AB system, J_{gem} 13.2 Hz, CHC*H*$_2$); *(3S,4S)-1-[(S,S$_S$)-2-hydroxy-1-phenylethylsulfinyl]-3-methoxy-4-methoxycarbonylcyclohexene* **10**, oil, $[\alpha]_D$ +200 (c 0.001); δ 7.4-7.2 (5H, m, Ph), 6.23 (1H, d, $J_{2,3}$ 4.8 Hz, H-2), 4.6-4.0 (4H, m, H-3 and HOC*H*$_2$C*H*), 3.72 (3H, s, 3-OMe), 3.09 (3H, s, CO_2Me), 2.9-1.9 (5H, m, H-4, H_2-5, H_2-6), 172.27 (CO), 145.57 (C-1), 132.36, 129.11, 129.01, and 128.83 (Ph), 128.55 (C-2), 72.02 (C-3), 68.38 (CHSO), 64.62 (CH_2OH), 57.19 (3-OMe), 51.83 (CO_2*Me*), 44.45 (C-4), 21.90 (C-6), 19.13 (C-5); *(3S,4S)-1-[(S,S$_S$)-2-hydroxy-2-phenylethylsulfinyl]-3-methoxy-4-methoxycarbonylcyclohexene* **14**, oil, $[\alpha]_D$ +53 (c 0.002); δ 7.4-7.3 (5H, m, Ph), 6.82 (1H, d, $J_{2,3}$ 4.4 Hz, H-2), 5.28 (1H, dd, $J_{1'A,2'}$ 10.1, $J_{1'B,2'}$ 2.1 Hz, PhC*H*), 4.24 (1H, t, $J_{3,4}$ 4.4 Hz, H-3), 3.75 (3H, s, 3-OMe), 3.43 (3H, s, CO_2Me), 3.19 and 2.75 (2H, split AB system, J_{gem} 13.6, CH_2SO), 2.7 (1H, m, H-4), 2.3-2.0 (4H, m, H_2-5, H_2-6), 172.21 (CO), 144.82 (C-1), 141.84, 128.78, 128.19, and 125.63 (Ph), 127.41 (C-2), 72.32 (C-3), 69.05 (CHOH), 57.73 (3-OMe), 56.77 (CH_2SO), 51.84 (CO_2*Me*), 44.99 (C-4), 22.85 (C-6), 19.37 (C-5).

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12 The optical purity of hydroxythiols **2** and **3** was checked by ^1H NMR analysis using the chiral shift reagent Eu(tfc)$_3$ in CD_3CN solution (L.M. Sweeting, D.C. Crans, and G.M. Whitesides, *J. Org. Chem.*, 1987, **52**, 2273). The same procedure was used to establish that the dienes **5** and **6** were enantiopure.

13 Cycloadditions were performed at RT in CH_2Cl_2 solution, using 0.8 mol equiv. of Lewis acids. Yields were moderate to good. Isomer ratios were determined by ^1H NMR at 300 MHz: relative proportions of the adducts **10** - **13** were easily established from the relative intensities of the vinyl proton signals in CD_3CN, while for the adducts **14** - **17** we integrated the well separated PhC**H** signals in C_6D_6. The assignment of absolute stereochemistry for the various Diels-Alder adducts is based on comparison of ^1H NMR data and the established relationship between chirality at sulfur and diastereofacial selectivity (ref. 4).

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