The synthesis and Diels–Alder reactions of (*E*)- and (*Z*)-1-methoxy-3-(phenylsulfinyl)buta-1,3-dienes

Harry Adams,[b] James C. Anderson,[a] Richard Bell,[c] D. Neville Jones,*[a] Michael R. Peel[a] and Nicholas C. O. Tomkinson[a]

[a] *Department of Chemistry, University of Sheffield, Sheffield, UK S3 7HF*
[b] *Crystallographic Department, University of Sheffield, Sheffield, UK S3 7HF*
[c] *Glaxo Wellcome Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, UK SG1 2NY*

Received (in Cambridge) 17th August 1998, Accepted 16th October 1998

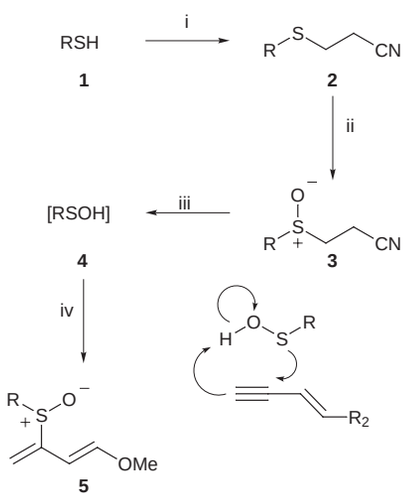
The mild and efficient generation of benzenesulfenic acid by the thermolysis of ethyl 2-ethoxycarbonyl-3-(phenylsulfinyl)butanoate **8** in refluxing dichloromethane, and its *in situ* trapping with (*E*)- and (*Z*)-1-methoxybut-2-en-3-yne to form (*E*)-1-methoxy-3-(phenylsulfinyl)buta-1,3-diene **10** and (*Z*)-1-methoxy-3-(phenylsulfinyl)buta-1,3-dienes **11** respectively proceeds in high yield. The lithium perchlorate catalysed Diels–Alder reaction of **10** with both symmetrical and unsymmetrical carbonyl activated dienophiles proceeds with complete regioselectivity and in some cases complete *endo*-selectivity.

Introduction

The Diels–Alder reaction has been developed to provide a valuable vehicle for the construction of enantiomerically enriched organic compounds.[1] An attractive feature of the reaction resides in the possibility, in principle, of generating up to four contiguous stereocentres in one step. The factors which determine the regioselectivity of the cycloaddition are quite well understood, and the remarkable stereoselectivity often displayed in cycloadditions is usually amenable to a satisfying mechanistic interpretation because of the cyclic nature of the transition state. This renders the Diels–Alder reaction eminently amenable to rational design, so providing a potentially powerful and attractive method for carbon–carbon bond formation in a predictable and controlled manner.

Over recent years there has been increased interest in the use of the sulfinyl group as a control element in the Diels–Alder reaction.[2] A number of useful synthetic methods have been reported for the introduction of a sulfinyl moiety to both the 1- and 2-positions of the diene partner, in both racemic and enantiomerically pure form.[3] The variety of dienophiles these systems have been reacted with, however, remains somewhat limited to mostly symmetrical systems, though much success has been observed with the lithium perchlorate catalysed cycloaddition of a number of optically pure 1-methoxy-3-alkylsulfinyl systems with methyl acrylate. These reactions proceed with complete regioselectivity, and high *endo*- and diastereofacial-selectivity.[4]

We have reported previously the synthesis of 2-sulfinyl dienes *via* the regioselective addition of sulfenic acids to enynes.[5] Although fundamentally much success has been achieved by this approach, there are problems inherent to the process. The synthesis involves three simple steps commencing with the base catalysed addition of a thiol **1** to acrylonitrile, followed by oxidation of the adduct **2** with *m*-chloroperoxybenzoic acid (*m*CPBA) to give the corresponding sulfoxide **3**. Thermolysis of the sulfoxide **3** gives a sulfenic acid **4**, which, in the presence of an enyne provides a sulfinyl diene **5** (Scheme 1). In the thermolysis step both a high temperature (>100 °C) and a large excess of the enyne is employed (neat, or greater than ten-fold molar excess). The diene product itself often proved to be thermally labile and the possibility of self-condensation, or cycloaddition with the acrylonitrile released by the thermolysis of the sulfenic acid precursor, led to diminished yields of the desired product. Herein we report a milder method for the generation of sulfenic acids from thiols, their *in situ* addition to enynes, and the scope and limitations of the dienophile partner in the Lewis acid catalysed cycloaddition of 1-methoxy-3-(phenylsulfinyl)-buta-1,3-dienes.



Scheme 1 *Reagents and conditions*: i, $Me_3BnN^+OH^-$, CH_2=CHCN, THF; ii, *m*CPBA, CH_2Cl_2; iii, toluene, Δ; iv, MeOCH=CHC≡CH (10 equiv.).

Results and discussion

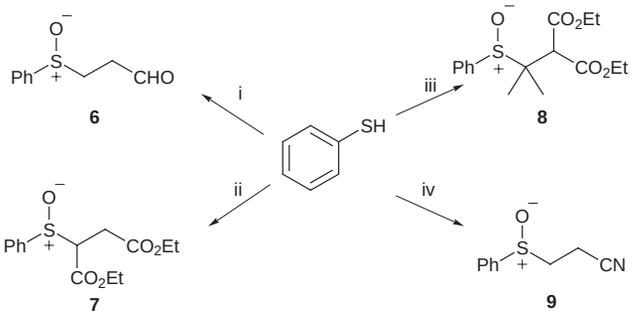
Preparation of 2-sulfinyl dienes

The thermolysis of sulfoxides to sulfenic acids is accelerated by increasing the acidity of the β-hydrogen by the presence of electron-withdrawing and alkyl substituents.[6] In seeking sulfenic acid precursors which might decompose at lower temperatures, and in doing so provide less reactive dienophiles, we prepared 3-(phenylsulfinyl)propanal **6**, diethyl phenylsulfinylsuccinate **7** and ethyl 2-ethoxycarbonyl-3-methyl-3-(phenylsulfinyl)butanoate **8** by conventional methods (Scheme 2).

The formation of the sulfinyl dienes involved addition of a concentrated solution of the sulfenic acid precursor to a boiling

Table 1 Preparation of (*E*)-1-methoxy-3-(phenylsulfinyl)buta-1,3-diene **10** by addition of benzenesulfenic acid to (*E*)-1-methoxybut-1-en-3-yne

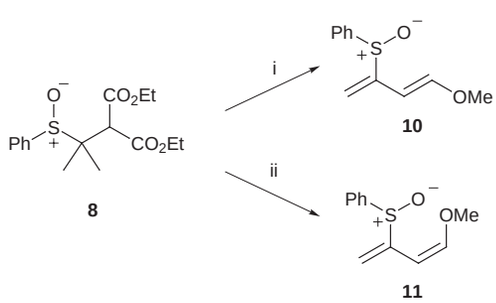
Entry	Sulfenic acid precursor	Solvent	*T*/°C	Time	Yield (%) of diene **10**
1	**9**	Toluene	110	7 h	15
2	**6**	Toluene	110	3 h	35
3	**7**	Benzene	80	5 min	82
4	**8**	Dichloromethane	40	6 h	89



Scheme 2 *Reagents*: i, (a) CH_2=CHCHO, $Me_3BnN^+OH^-$, THF, (b) *m*CPBA, CH_2Cl_2; ii, (a) $EtCO_2CH$=$CHCO_2Et$, NEt_3, THF, (b) *m*CPBA, CH_2Cl_2; iii, (a) $(CH_3)_2C$=$C(CO_2Et)_2$, $Me_3BnN^+OH^-$, THF, (b) *m*CPBA, CH_2Cl_2; iv, (a) CH_2=CHCN, $Me_3BnN^+OH^-$, THF, (b) *m*CPBA, CH_2Cl_2.

solution of three molar equivalents of (*E*)-1-methoxybut-1-en-3-yne in an appropriate solvent (chosen according to the suitability of its boiling point). The effectiveness of **6**, **7** and **8**, compared with that of 3-(phenylsulfinyl)propionitrile **9**, is shown in Table 1.

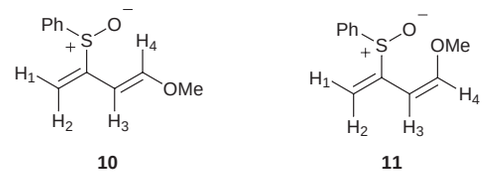
The greater yield obtained by the use of the sulfinyl aldehyde **6** (entry 2) over that from the sulfinyl cyanide **9** (entry 1) at the same temperature may be attributed to the greater competition from Diels–Alder reaction associated with acrylonitrile over that from crotonaldehyde. The presence of two electron-withdrawing groups greatly increased the facility with which the thermolysis proceeded (entry 3), and the further introduction of alkyl substituents into the sulfenic acid precursor gave the desired (*E*)-1-methoxy-3-(phenylsulfinyl)buta-1,3-diene **10** (Scheme 3) in excellent yield (89%) (entry 4) at an acceptable



Scheme 3 *Reagents and conditions*: i, (*E*)-1-methoxybuten-3-yne, CH_2Cl_2, Δ; ii, (*Z*)-1-methoxybuten-3-yne, CH_2Cl_2, Δ.

temperature. The related (*Z*)-1-methoxy-3-(phenylsulfinyl)-buta-1,3-diene **11** was also prepared by the reaction of benzenesulfenic acid with (*Z*)-1-methoxybut-1-en-3-yne under conditions which accorded to entry 4 in Table 1.

The structure of the dienes **10** and **11** was confirmed by ^{1}H NMR ($CDCl_3$) spectroscopy, the salient spectral data of which are presented in Fig. 1.



	10	**11**
H_1	5.81, s	6.15, s
H_2	5.55, s	6.11, s
H_3	5.18, d, *J* = 13 Hz	4.68, d, *J* = 7 Hz
H_4	6.83, d, *J* = 13 Hz	6.14, d, *J* = 7 Hz
OMe	3.47, s	3.63, s

Fig. 1 Selected chemical shifts and coupling constants in the 250 MHz ^{1}H NMR of dienes **10** and **11** in $CDCl_3$.

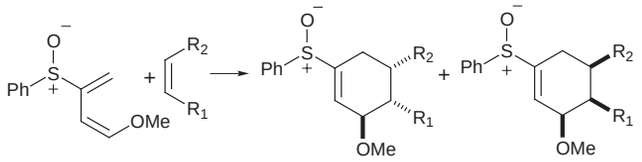
Diels–Alder reactions of 2-sulfinyl dienes

Grieco first reported that concentrated homogeneous solutions of lithium perchlorate in diethyl ether (5 M), catalysed the addition of allyl stannanes to chiral α-hydroxy aldehydes with excellent degrees of chelation control.[7] More recently, Reetz has shown that a suspension of 3–5 mol% of lithium perchlorate in dichloromethane is a much more reactive catalytic system in Mukaiyama aldol reactions,[8] as well as hetero Diels–Alder cycloadditions and 1,3-Claisen rearrangements.[9] We have reported that a suspension of lithium perchlorate in dichloromethane was an excellent catalyst for the stereoselective cycloadditions of methyl acrylate to 2-sulfinyl dienes derived from 10-mercaptoisoborneol.[10] This catalyst therefore presented itself as a promising candidate for promoting stereoselective Diels–Alder reactions of other sulfinyl dienes with a range of dienophiles.

Diels–Alder reaction of (*Z*)-1-methoxy-3-(phenylsulfinyl)-buta-1,3-diene **11** with methyl acrylate proceeded at 80 °C in the absence of a catalyst to give the *endo* and *exo* adducts in the ratio of 3.3 : 1 by ^{1}H NMR ($CDCl_3$) spectroscopy (Table 2, entry 1) (*endo*/*exo* stereochemistry was assigned by analogy with adducts previously reported[4] and by comparison to adduct **12**, whose stereochemistry was proven by X-ray crystallographic analysis). The use of Lewis acids markedly increased the rate of reaction and, more significantly, dramatically influenced the stereoselectivity. Whilst magnesium bromide (entry 2) and zinc chloride (entry 3) increased the proportion of *endo* addition, relative to the uncatalysed reaction, boron trifluoride reversed the stereoselectivity. Use of zinc chloride as a Lewis acid greatly increased the rate of reaction at 80 °C, and furnished the adducts in the ratio 10 : 1 (entry 3). The predominance of *endo* addition may be rationalised in terms of mutual co-ordination of the metal with both the sulfinyl and carbonyl oxygens in the transition state (*cf.* Fig. 3). The reversal of selectivity observed with boron trifluoride (entry 4) may be due to the availability of only one co-ordination site on this complex. The boron may co-ordinate to either sulfinyl oxygen or the carbonyl oxygen such that the *endo* transition state would be disfavoured due to steric effects.

We did not believe it to be practicable to pursue the use of lithium perchlorate with the diene **11** due to the high temperatures required to bring about cycloaddition, so we turned our attention to the diene **10**. The results for the cycloaddition of (*E*)-1-methoxy-3-(phenylsulfinyl)buta-1,3-diene **10** to various electron-deficient dienophiles are recorded in Table 3. As observed with (*Z*)-1-methoxy-3-(phenylsulfinyl)buta-1,3-diene **11**, in the absence of a Lewis acid catalyst, reactions were slow, requiring a large excess of dienophile and proceeded with low stereoselectivity (entries 1, 6, 8, 10 and 12). The use of magnesium bromide, zinc chloride and boron trifluoride as Lewis acid catalysts led to a marked increase in rate and yield (Table 3, entries 2, 3 and 4). Lithium perchlorate in dichloromethane had a dramatic effect in accelerating the cycloadditions and in increasing the yields, but only for the dienophiles which contained a carbonyl group (entries 5, 7, 9 and 11). In these cases, the reaction proceeded smoothly at room temperature in the presence of just three equivalents of dienophile, and the reac-

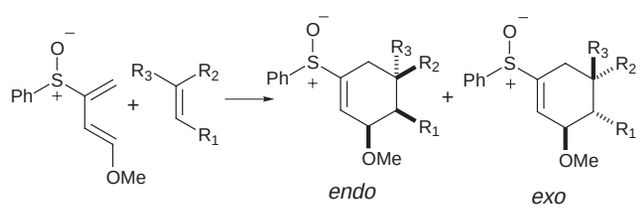
Table 2 Diels–Alder reaction of (*Z*)-1-methoxy-3-(phenylsulfinyl)buta-1,3-diene **11** with electron-deficient dienophiles



Entry	R_1	R_2	Catalyst	Yield (%)	Ratio[a] *endo*:*exo*	Reaction conditions	Dienophile (equiv.)
1	CO_2Me	H	none	73	3.3:1.0	80 °C, 8 d	60
2	CO_2Me	H	$MgBr_2{\cdot}Et_2O$	43	7.5:1.0	80 °C, 18 h	60
3	CO_2Me	H	$ZnCl_2$	54	10:1.0	80 °C, 48 h	60
4	CO_2Me	H	$BF_3{\cdot}Et_2O$	11	1:2.4	80 °C, 1.5 h	60
5	CN	H	none	64	1.5:1.0	80 °C, 4 d	60
6	CO_2Et	CO_2Et	none	46	1.5:1.0	80 °C, 7 d	60

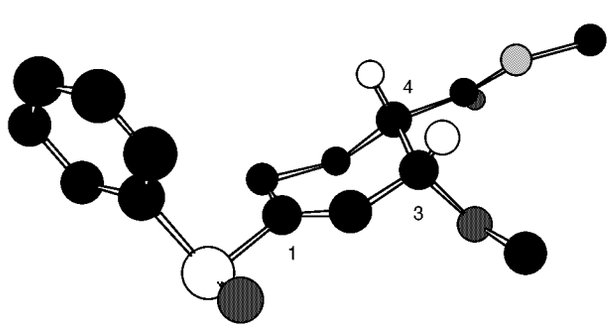
[a] Ratios determined by ^1H NMR integration of the crude reaction mixture.

Table 3 Diels–Alder reactions of (*E*)-1-methoxy-3-(phenylsulfinyl)buta-1,3-diene **10** with electron-deficient dienophiles



Entry	R_1	R_2	R_3	Catalyst	Yield (%)	Ratio[a] *endo*:*exo*	Reaction conditions	Dienophile (equiv.)
1	CO_2Me	H	H	none	72	2:1	r.t., 2 d	60
2	CO_2Me	H	H	$MgBr_2{\cdot}Et_2O$	80	2.5:1	r.t., 10 h	60
3	CO_2Me	H	H	$ZnCl_2$	82	4:1	r.t., 10 h	60
4	CO_2Me	H	H	$BF_3{\cdot}Et_2O$	70	1:1	r.t., 10 h	60
5	CO_2Me	H	H	$LiClO_4$	96	1:0	r.t., 8 h	3
6	COMe	H	H	none	52	3:2	r.t., 4 d	60
7	COMe	H	H	$LiClO_4$	91	1:0	r.t., 8 h	3
8	CO_2Et	H	CO_2Et	none	52	2:1	r.t., 2 d	10
9	CO_2Et	H	CO_2Et	$LiClO_4$	97	1:0	r.t., 8 h	3
10	CO_2Et	CO_2Et	H	none	35	3:2	r.t., 4 d	10
11	CO_2Et	CO_2Et	H	$LiClO_4$	90	10:1	r.t., 18 h	3
12	CN	H	H	none	23	1:1	r.t., 4 d	60
13	CN	H	H	$LiClO_4$	66	1:1	r.t., 4 d	3

[a] Ratios determined by ^1H NMR integration of the crude reaction mixture.



12

Fig. 2 X-Ray crystal structure of the lithium perchlorate catalysed Diels–Alder adduct of *rel*-(3*R*,4*R*)-3-methoxy-4-methoxycarbonyl-1-(phenylsulfinyl)cyclohex-1-ene **12** with methyl acrylate.

tions proceeded with very high *endo* selectivity. The *endo*-stereochemistry of the adduct **12** obtained from methyl acrylate was confirmed by single crystal X-ray crystallographic analysis (Fig. 2). The relative stereochemistry at sulfur and C_3 strongly suggests the geometry of the transition state is as shown in Fig. 3, with mutual co-ordination of sulfinyl and carbonyl oxygens to the metal. At this stage we have yet to ascertain if this diastereofacial selectivity exists for all of the *endo* adducts reported.

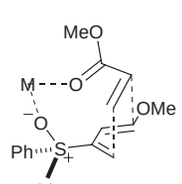


Fig. 3 Transition state model for reaction of (*E*)-1-methoxy-3-(phenylsulfinyl)buta-1,3-diene **10** with methyl acrylate.

In the absence of catalyst, a large excess of dienophile had to be employed in order for the reaction to proceed at an acceptable rate, and there was poor *endo*/*exo* selectivity. For acrylonitrile as dienophile, this also applied even in the presence of lithium perchlorate, which denotes the significant role played by the carbonyl group in the mechanism of catalysis and stereochemical control, substantiating the depiction of the transition state proposed (Fig. 3).

Conclusions

In summary, we have devised an improved, reliable method for the synthesis of 2-sulfinyl dienes, which involved the use of a new precursor, ethyl 2-ethoxycarbonyl-3-methyl-3-(phenylsulfinyl)butanoate **8**, for the generation of sulfenic acids under mild and convenient conditions. A suspension of lithium perchlorate in dichloromethane is an excellent catalyst for cycloadditions of 2-sulfinyl dienes to electron-deficient dienophiles that bear a carbonyl substituent, the reactions proceeding with high and in some cases complete *endo*-selectivity. We are currently investigating this protocol with a series of 2-sulfinyl dienes homochiral at sulfur to discover if any diastereofacial selectivity pertains for these reactions, and will report our findings in due course.

Experimental

Proton magnetic resonance spectra were recorded on a Bruker ACF-250. Mass spectra were obtained on a Kratos MS 25 instrument operating in E.I., C.I. mode. Melting points were determined on a Kofler hot stage micro melting point apparatus and are uncorrected. Elemental microanalyses were carried out using a Perkin-Elmer 2400 elemental analyser CHN. Sulfur content was determined by oxygen combustion followed by wet titration. Infrared spectra were recorded in the range 4000–600 cm^{-1} using a Perkin-Elmer 157G grating infrared spectrophotometer. Thin layer chromatography (TLC) was performed on Merck 5554 60F silica gel coated aluminium plates and detection was effected with a solution of 10% ceric sulfate in 10% sulfuric acid, followed by heating the plates. Purification of compounds was achieved by medium pressure chromatography using Merck 9385 60 silica gel. Ether refers to diethyl ether.

Dimethoxybut-2-yne

Crushed sodium hydroxide pellets (20 × 2 g, 1.8 mol) and dimethyl sulfate (20 × 12.8 g, 1.8 mol) were added alternately to a solution of but-2-yne-1,4-diol (70 g, 0.8 mol) in water (130 ml) with the temperature being kept below 40 °C by means of an ice bath. After the addition was complete the mixture was heated at 90 °C for 3 hours. Ice water (120 ml) was added and the mixture was cooled to 20 °C. The aqueous phase was extracted with ether (5 × 250 ml) and the combined organic fractions were dried with magnesium sulfate. The ether was distilled through a 40 cm Vigreux column and the crude product was purified by vacuum distillation to give the product (64.5 g, 70%) 62 °C, 25 mmHg (Lit., 54 °C, 12 mmHg)[11] as a colourless oil.

(*E*)-1-Methoxybut-1-en-3-yne

Sodium (1 g, 43 mmol) was added to liquid ammonia (700 ml) and the mixture was stirred until a deep blue colour persisted. Ferric nitrate (0.5 g, 1 mmol) was added and stirring was continued until a uniformly brown colour was obtained. Sodium (25 g, 1.08 mol) was added to the solution in 1 g portions over 1 hour. 1,4-Dimethoxybut-2-yne (50 g, 0.44 mol) was added slowly over 1 hour and the mixture was stirred for a further 1 hour. Ether (130 ml) was carefully added and the ammonia was evaporated by means of a water bath. When only a trace of ammonia remained a further 130 ml of ether was added and the water bath was warmed until no more ammonia was detectable. Ice water (200 ml) was added very carefully over 15 minutes and the mixture was stirred vigorously until no solid material remained. The organic layer was separated and the aqueous layer was extracted with ether (5 × 200 ml). The combined ether extracts were dried with magnesium sulfate and the solvent was distilled off through a 60 cm Vigreux column (ensuring the oil bath temperature was kept below 80 °C). The crude product was purified by distillation under argon at reduced pressure to afford the product (32.5 g, 91%) 48–50 °C, 70 mmHg (Lit., 48–50 °C, 70 mmHg).[11]

(*Z*)-1-Methoxybut-1-en-3-yne

To a solution of (*Z*)-1-methoxybut-1-en-3-yne in a 40% mixture of methanol and water (50 ml), was added saturated sodium chloride solution (20 ml), and the resulting solution was continuously extracted with ether (150 ml) for 18 hours. The ether was dried ($MgSO_4$), and removed *in vacuo*, to give a brown oil which was distilled under argon at reduced pressure (72 mmHg), into a vessel maintained at −78 °C, to afford the product (18 g, 90%) as a white solid, which decolourised rapidly at room temperature.

3-(Phenylthio)propionitrile

Trimethyl(benzyl)ammonium hydroxide (0.1 ml, 40% solution in methanol) was added to a stirred solution of thiophenol (1 g, 9 mmol) in dry tetrahydrofuran (20 ml) at −78 °C. After 15 minutes acrylonitrile (0.9 ml, 13.5 mmol) was added and the reaction mixture was allowed to warm up to room temperature over 1 hour. After a further 12 hours at this temperature the solvent was removed *in vacuo* leaving a yellow oil which was separated between ether (50 ml) and water (50 ml). The ethereal layer was washed with water (30 ml), brine (30 ml) before being dried ($MgSO_4$) and reduced. Purification by flash column chromatography on silica eluting with ether–light petroleum (5%) gave the product (0.89 g, 64%) as a colourless oil; ν_{max}/cm^{-1} ($CHCl_3$) 2240 (CN), 1600 (Ar); δ_H($CDCl_3$) 2.97 (2H, t, *J* 7, C*H*$_2$SPh), 3.38 (2H, t, *J* 7, C*H*$_2$CN), 7.4–7.6 (5H, m, Ph-*H*) (Found: C, 66.3; H, 5.7; S, 19.8%; *m*/*z* 164. C_9H_9NS requires C, 66.2; H, 5.5; S, 19.6%; M^+ 164).

3-(Phenylsulfinyl)propionitrile 9

A solution of *m*-chloroperbenzoic acid (0.32 g, 2.1 mmol) in dry dichloromethane (5 ml) was added to a stirred solution of phenylthiopropionitrile (0.5 g, 1.9 mmol) in dry dichloromethane (5 ml) at 0 °C. After 1 hour the reaction mixture was washed with sodium hydrogen carbonate solution (2 × 10 ml). The organic phase was dried ($MgSO_4$) and the solvent was removed *in vacuo* to give the product **9** (0.542 g) as a colourless oil which was used directly without further purification; ν_{max}/cm^{-1} ($CHCl_3$) 2240 (CN), 1600 (Ar), 1046 (SO); δ_H($CDCl_3$) 3.04 (2H, t, *J* 7, C*H*$_2$SO), 3.58 (2H, t, *J* 7, C*H*$_2$CN), 7.4–7.6 (5H, m, Ph-*H*) (Found: C, 60.5; H, 4.9; S, 18.0%; *m*/*z* 180. C_9H_9NOS requires C, 60.3; H, 5.0; S, 17.9%; M^+ 180).

(*E*)-1-Methoxy-3-(phenylsulfinyl)buta-1,3-diene 10

A solution of phenylsulfinylpropionitrile, prepared from 0.5 g of phenylthiopropionitrile as above, and (*E*)-1-methoxybut-1-en-3-yne (0.32 g, 3.5 mmol) in dry toluene (10 ml) was heated at 110 °C under argon for 7 hours, after which time the mixture was cooled in ice. The crude reaction mixture was purified by column chromatography on silica eluting with light petroleum followed by ether–light petroleum (50%) to furnish the product **10** (95 mg, 15%); ν_{max}/cm^{-1} (thin film) 1630 (C=C), 1040 (SO); δ_H($CDCl_3$) 3.47 (3H, s, OC*H*$_3$), 5.55 (1H, s, H*H*C=C), 5.18 (1H, d, *J* 13, CH=C*H*OMe), 5.81 (1H, s, *H*HC=C), 6.83 (1H, d, *J* 13, C*H*=CHOMe), 7.4–7.5 (5H, m, Ph-*H*) (Found: *m*/*z* 208.0551. $C_{11}H_{12}O_2S$ requires M^+ 208.0558).

3-(Phenylthio)propanal

Trimethyl(benzyl)ammonium hydroxide (0.1 ml, 40% solution in methanol) was added to a stirred solution of thiophenol (1 g, 9 mmol) in dry tetrahydrofuran (20 ml) at −78 °C. After 15 minutes crotonaldehyde (3.18 g, 45 mmol) was added and the reaction mixture was allowed to warm up to room temperature over 1 hour. After a further 36 hours at this temperature the solvent was removed *in vacuo* leaving a yellow oil which was separated between ether (50 ml) and water (50 ml). The ethereal layer was washed with water (30 ml), brine (30 ml), dried

($MgSO_4$) and reduced. Purification of the residue by column chromatography on silica eluting with ether–light petroleum (8%) gave the product (1.096 g, 67%) as a colourless oil; ν_{max}/cm^{-1} (thin film) 1736 (CO), 1600 (Ar); $\delta_H(CDCl_3)$ 1.28 (3H, d, *J* 5, C*H*$_3$), 2.84 (1H, dm, *J* 5, C*H*CH_3), 3.16 (2H, m, C*H*$_2$CHO), 7.4–7.65 (5H, m, Ph-*H*), 9.7 (1H, t, *J* 2, C*H*O) (Found: C, 66.9; H, 6.7; S, 17.9%; *m*/*z* 180. $C_{10}H_{12}OS$ requires C, 66.6; H, 6.7; S, 17.8%; M^+ 180).

3-(Phenylsulfinyl)propanal 6

A solution of *m*-chloroperbenzoic acid (1.102 g, 6.26 mmol) in dry dichloromethane (8 ml) was added to a stirred solution of 3-(phenylthio)propanal (0.94 g, 5.2 mmol) in dry dichloromethane (8 ml) at 0 °C. After 1 hour the reaction mixture was washed with sodium hydrogen carbonate solution (2 × 10 ml). The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo* to give the product **6** (0.97 g) as a colourless oil which was used directly without further purification.

(*E*)-1-Methoxy-3-(phenylsulfinyl)buta-1,3-diene 10

A solution of 3-methyl-3-(phenylsulfinyl)propionaldehyde, prepared from 0.94 g of 3-methyl-3-(phenylthio)propionaldehyde as above, and (*E*)-1-methoxybut-1-en-3-yne (0.32 g, 3.5 mmol) in dry toluene (10 ml) was heated at 110 °C under argon for 3 hours, after which time the mixture was immediately cooled in ice. The crude reaction mixture was purified by column chromatography on silica eluting with light petroleum followed by ether–light petroleum (50%) to furnish the product **10** (404 mg, 35%), which was identical to an authentic sample.

Diethyl phenylthiosuccinate

Diethyl fumarate (5.5 g, 32 mmol) was added slowly to a solution of thiophenol (1.15 g, 11 mmol) and triethylamine (0.1 g, 1 mmol) in dry benzene (15 ml) ensuring that the temperature remained below 60 °C. After the addition was complete the mixture was heated at reflux for 1 hour. The excess diethyl fumarate and solvent were removed under reduced pressure and the crude product was purified by vacuum distillation to give the product (2.63 g, 89%) (134 °C, 0.04 mmHg); ν_{max}/cm^{-1} ($CHCl_3$) 1742 (CO), 1600 (Ar); $\delta_H(CDCl_3)$ 1.14 (6H, 2 × t, *J* 6, $CO_2CH_2CH_3$), 3.47 (2H, m, CH_2CO_2Et), 3.64 (1H, m, $CHCO_2Et$), 4.23 (4H, 2 × q, *J* 7, $CO_2CH_2CH_3$), 7.4–7.6 (5H, m, Ph-*H*) (Found: C, 59.8; H, 6.7; S, 11.3%; *m*/*z* 282. $C_{14}H_{18}O_4S$ requires C, 59.6; H, 6.4; S, 11.3%; M^+ 282).

Diethyl phenylsulfinylsuccinate 7

A solution of *m*-chloroperbenzoic acid (0.67 g, 4.6 mmol) in dry dichloromethane (10 ml) was added to a stirred solution of diethyl phenylthiosuccinate (1 g, 3.5 mmol) in dry dichloromethane (10 ml) at 0 °C. After 15 minutes the reaction mixture was washed rapidly with sodium hydrogen carbonate solution (2 × 10 ml). The organic phase was dried ($MgSO_4$) and the solvent was removed *in vacuo* at room temperature to give the product **7** (1.23 g) as a colourless oil which was used immediately without further purification.

(*E*)-1-Methoxy-3-(phenylsulfinyl)buta-1,3-diene 10

A solution of diethyl phenylsulfinylsuccinate, prepared from 1 g of diethyl phenylthiosuccinate as above, and (*E*)-1-methoxybut-1-en-3-yne (0.6 g, 7 mmol) in dry benzene (10 ml) was heated at 80 °C under argon for 5 minutes, after which time the mixture was immediately cooled in ice. The crude reaction mixture was purified by flash column chromatography on silica eluting with light petroleum followed by ether–light petroleum (50%) to furnish the product **10** (1.202 g, 82%), which was identical to an authentic sample.

Ethyl 2-ethoxycarbonyl-3-methyl-3-(phenylthio)butanoate

Trimethyl(benzyl)ammonium hydroxide (0.1 ml, 40% solution in methanol) was added to a stirred solution of thiophenol (1 g, 9 mmol) in dry tetrahydrofuran (10 ml) at −78 °C. After 15 minutes diethyl isopropylidenemalonate (9.09 g, 45 mmol) was added and the reaction mixture was allowed to warm up to room temperature over 1 hour. After a further 48 hours at this temperature the solvent was removed *in vacuo* leaving a yellow oil which was separated between ether (50 ml) and water (50 ml). The ethereal layer was washed with water (30 ml), brine (30 ml), dried ($MgSO_4$) and reduced. Purification of the residue by column chromatography on silica eluting with ether–light petroleum (3%) gave the product (2.59 g, 92%) as a colourless oil; ν_{max}/cm^{-1} ($CHCl_3$) 1738 (CO), 1600 (Ar); $\delta_H(CDCl_3)$ 1.16 (6H, 2 × t, *J* 7, $CO_2CH_2CH_3$), 1.41 (6H, s, $C(CH_3)_2$), 3.52 (1H, s, $CH(CO_2Et)_2$), 4.08 (4H, 2 × q, *J* 7, $CO_2CH_2CH_3$), 7.4–7.6 (5H, m, Ph-*H*) (Found: C, 62.1; H, 7.2; S, 10.5%; *m*/*z* 310. $C_{16}H_{22}O_4S$ requires C, 61.9; H, 7.1; S, 10.3%; M^+ 310).

Ethyl 2-ethoxycarbonyl-3-methyl-3-(phenylsulfinyl)butanoate 8

A solution of *m*-chloroperbenzoic acid (0.624 g, 3.52 mmol) in dry dichloromethane (10 ml) was added to a stirred solution of ethyl 2-ethoxycarbonyl-3-methyl-3-(phenylthio)butanoate (1 g, 3.2 mmol) in dry dichloromethane (10 ml) at 0 °C. After 1 hour potassium fluoride (0.56 g) was added and stirring was continued at 0 °C for a further hour. The reaction mixture was filtered through a pad of Celite and the resulting clear solution was reduced *in vacuo* at room temperature to give the product **8** (1.05 g) as a colourless oil which was used directly without further purification.

(*E*)-1-Methoxy-3-(phenylsulfinyl)buta-1,3-diene 10

A solution of ethyl 2-ethoxycarbonyl-3-methyl-3-(phenylsulfinyl)butanoate, prepared from 1 g of ethyl 2-ethoxycarbonyl-3-methyl-3-(phenylthio)butanoate malonate as above, and (*E*)-1-methoxybut-1-en-3-yne (1.32 g, 16.13 mmol) in dry dichloromethane (5 ml) was heated at 40 °C under argon for 6 hours, after which time the mixture was cooled in ice. The crude reaction mixture was purified by column chromatography on silica eluting with ether–light petroleum (50%) to furnish the product **10** (0.597 g, 89%), which was identical to an authentic sample.

(*Z*)-1-Methoxy-3-(phenylsulfinyl)buta-1,3-diene 11

A solution of ethyl 2-ethoxycarbonyl-3-methyl-3-(phenylsulfinyl)butanoate, prepared from 1 g of ethyl 2-ethoxycarbonyl-3-methyl-3-(phenylthio)butanoate as above, and (*Z*)-1-methoxybut-1-en-3-yne (1.32 g, 16.13 mmol) in dry dichloromethane (5 ml) was heated at 40 °C under argon for 6 hours, after which time the mixture was cooled in ice. The crude reaction mixture was purified by column chromatography on silica eluting with ether–light petroleum (60%) to furnish the product **1** (0.617 g, 92%); ν_{max}/cm^{-1} (thin film) 1630 (C=C), 1045 (SO); $\delta_H(CDCl_3)$ 3.63 (3H, s, OCH_3), 4.68 (1H, d, *J* 7, CH=C*H*OMe), 6.11 (1H, s, H*H*C=C), 6.14 (1H, d, *J* 7, C*H*=CHOMe), 6.15 (1H, s, *H*HC=C), 7.4–7.7 (5H, m, Ph-*H*) (Found: *m*/*z* 208.0551. $C_{11}H_{12}O_2S$ requires M^+ 208.0558).

rel-(3*R*,4*S*)-3-Methoxy-4-methoxycarbonyl-1-(phenylsulfinyl)-cyclohex-1-ene and *rel*-(3*R*,4*R*)-3-methoxy-4-methoxycarbonyl-1-(phenylsulfinyl)cyclohex-1-ene

Anhydrous zinc chloride (80 mg, 0.6 mmol) was added to a mixture of (*Z*)-1-methoxy-3-(phenylsulfinyl)buta-1,3-diene (0.321 g, 1.5 mmol) and methyl acrylate (6.5 g, 72 mmol) and the mixture was heated at 80 °C under argon for 48 hours. The excess methyl acrylate was evaporated and the residue was purified by chromatography on silica eluting with ether–light

petroleum (50%) to give the title compounds (0.239 g, 54%); ν_{max}/cm^{-1} ($CHCl_3$) 1725 (CO) and 1310 (SO); δ_H($CDCl_3$) 3.49 (3H, s, OCH_3), 3.71 (3H, s, CO_2CH_3), 4.35 (1H, m, C*H*OMe), 6.77 (1H, s, C=C*H*), 7.45–7.65 (5H, m, Ph-*H*) and 3.46 (3H, s, CO_2CH_3), 3.73 (3H, s, OCH_3), 4.25 (1H, m, C*H*OMe), 6.92 (1H, s, C=C*H*), 7.45–7.65 (5H, m, Ph-*H*) (Found: C, 61.5; H, 6.3; S, 10.8%; *m*/*z* 296. $C_{15}H_{18}O_4S$ requires C, 61.2; H, 6.2; S, 10.9%; (M + H)$^+$ 296).

rel-(3*R*,4*S*)-3-Methoxy-4-cyano-1-(phenylsulfinyl)cyclohex-1-ene and *rel*-(3*R*,4*R*)-3-methoxy-4-cyano-1-(phenylsulfinyl)-cyclohex-1-ene

A mixture of (*Z*)-1-methoxy-3-(phenylsulfinyl)buta-1,3-diene (0.175 g, 0.8 mmol) and acrylonitrile (4 g, 76 mmol) was heated at 80 °C for 48 hours under argon. The excess acrylonitrile was removed under reduced pressure and the residue was purified on silica eluting with ether–light petroleum (50%) to give the title compounds (82 mg, 64%); ν_{max}/cm^{-1} ($CHCl_3$) 2240 (CN), 1040 (SO); δ_H($CDCl_3$) 2.8 (1H, m, C*H*CN), 3.55 (3H, s, OCH_3), 4.05 (1H, m, C*H*OMe), 6.68 (1H, m, C=C*H*), 7.5–7.6 (5H, m, Ph-*H*) and 3.1 (1H, m, C*H*CN), 3.56 (3H, s, OCH_3), 4.1 (1H, m, C*H*OMe), 6.75 (1H, m, C=C*H*), 7.45–7.65 (5H, m, Ph-*H*) (Found: C, 64.6; H, 5.8; N, 5.4; S, 11.8%; *m*/*z* 261. $C_{15}H_{18}O_4S$ requires C, 64.3; H, 5.8; N, 5.4; S, 12.2%; (M + H)$^+$ 261).

rel-(3*R*,4*S*,5*S*)-3-Methoxy-4,5-di(ethoxycarbonyl)-1-(phenylsulfinyl)cyclohex-1-ene and *rel*-(3*R*,4*R*,5*R*)-3-methoxy-4,5-di(ethoxycarbonyl)-1-(phenylsulfinyl)cyclohex-1-ene

A mixture of (*Z*)-1-methoxy-3-(phenylsulfinyl)buta-1,3-diene (0.249 g, 1.2 mmol) and diethyl maleate (4.7 g, 27 mmol) was heated at 80 °C for 7 days under argon. The excess diethyl maleate was evaporated under reduced pressure and the residue was purified by chromatography on silica eluting with ether to afford a mixture of the title compounds (0.21 g, 46%); ν_{max}/cm^{-1} ($CHCl_3$) 1720 (CO), 1040 (SO); δ_H($CDCl_3$) 1.1–1.35 (6H, m, CH_3CH$_2$), 3.45 (3H, s, OCH_3), 4.0–4.4 (5H, m, CH_2CH$_3$ and C*H*OMe), 6.76 and 6.95 (1H, 2 × br s, C=C*H*), 7.4–7.8 (5H, m, Ph-*H*) (Found: C, 60.0; H, 6.4; S, 8.7%; *m*/*z* 381. $C_{15}H_{18}O_4S$ requires C, 59.9; H, 6.4; S, 8.4%; (M + H)$^+$ 381).

rel-(3*R*,4*R*)-3-Methoxy-4-methoxycarbonyl-1-(phenylsulfinyl)-cyclohex-1-ene 12

Anhydrous lithium perchlorate (103 mg, 0.8 equiv.) was added to a stirred solution of methyl acrylate (315 mg) and (*E*)-1-methoxy-3-(phenylsulfinyl)buta-1,3-diene (254 mg, 1.22 mmol) in dry dichloromethane (5 ml), and the mixture was stirred at room temperature for 8 hours. The reaction mixture was loaded directly onto silica and was eluted with ethyl acetate–light petroleum (90%) to give the product **12** (344 mg, 96%); mp 87 °C (ethyl acetate–light petroleum); ν_{max}/cm^{-1} ($CHCl_3$) 1725 (CO), 1030 (SO); δ_H($CDCl_3$) 3.46 (3H, s, CO_2CH_3), 3.72 (3H, s, OCH_3), 4.25 (1H, m, C*H*OMe), 6.92 (1H, m, C=C*H*), 7.45–7.65 (5H, m, Ph-*H*) (Found: C, 61.5; H, 6.3; S, 10.8%; *m*/*z* 296. $C_{15}H_{18}O_4S$ requires C, 61.2; H, 6.2; S, 10.9%; (M + H)$^+$ 296).

Crystal data. $C_{15}H_{18}O_4S$, M = 294.35, crystallises from ethyl acetate as colourless blocks; crystal dimensions: 0.54 × 0.34 × 0.26 mm. Monoclinic, a = 6.279(3), b = 29.250(5), c = 8.340(4) Å, β = 108.95(4)°, U = 1448.7(10) Å^3, Z = 4, D_c = 1.350 Mg m^{-3}, space group: $P2_1/n$ (a non-standard setting of $P2_1/c$ C^5_{2h}, No. 14), Mo-Kα radiation: ($\bar{\lambda}$ = 0.71073 Å), μ(Mo-Kα) = 0.234 mm^{-1}, F(000) = 624.

Three dimensional, room temperature X-ray data were collected in the range $3.5 < 2\theta < 45°$ on a Siemens P4 diffractometer by the omega scan method. The 1267 independent reflections (of 2523 measured) for which $|F|/\sigma(|F|) > 4.0$ were corrected for Lorentz and polarisation effects, but not for absorption. The structure was solved by direct methods and refined by full-matrix least-squares on F^2. Hydrogen atoms were included in calculated positions and refined in riding mode. Refinement converged at a final R = 0.0802 (wR_2 = 0.3967, for all 1804 data, 181 parameters, mean and maximum δ/σ 0.000, 0.000), with allowance for the thermal anisotropy of all non-hydrogen atoms. Minimum and maximum final electron density −0.572 and 0.551 e Å^{-3}. A weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.1425P)^2 + 6.4818P]$ where $P = (F_o^2 + 2F_c^2)/3$ was used in the latter stages of refinement. Complex scattering factors were taken from the program package SHELXTL 93[12] as implemented on the Viglen 486DX computer.

Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/272.

rel-(3*R*,4*R*,5*R*)-3-Methoxy-4,5-di(ethoxycarbonyl)-1-(phenylsulfinyl)cyclohex-1-ene

Anhydrous lithium perchlorate (87 mg, 0.8 equiv.) was added to a stirred solution of diethyl maleate (530 mg) and (*E*)-1-methoxy-3-(phenylsulfinyl)buta-1,3-diene (214 mg, 1.03 mmol) in dry dichloromethane (5 ml), and the mixture was stirred at room temperature for 8 hours. The reaction mixture was loaded directly onto silica and was eluted with ethyl acetate–light petroleum (95%) to give the product (355 mg, 91%); ν_{max}/cm^{-1} ($CHCl_3$) 1725 (CO), 1600 (Ar), 1040 (SO); δ_H($CDCl_3$) 1.07 (3H, t, *J* 7, $CO_2CH_2CH_3$), 1.16 (3H, t, *J* 7, $CO_2CH_2CH_3$), 2.65 (1H, m, C*H*CO_2Et), 3.51 (3H, s, OCH_3), 4.05 (4H, 2 × q, *J* 7, $CO_2CH_2CH_3$), 4.25 (1H, m, C*H*OMe), 6.64 (1H, m, C=C*H*), 7.4–7.6 (5H, m, Ph-*H*) (Found: C, 60.0; H, 6.4; S, 8.7%; *m*/*z* 381. $C_{19}H_{24}O_6S$ requires C, 59.9; H, 6.4; S, 8.4%; (M + H)$^+$ 381).

rel-(3*R*,4*R*)-3-Methoxy-4-methylcarbonyl-1-(phenylsulfinyl)-cyclohex-1-ene

Anhydrous lithium perchlorate (115 mg, 0.8 equiv.) was added to a stirred solution of methyl vinyl ketone (285 mg) and (*E*)-1-methoxy-3-(phenylsulfinyl)buta-1,3-diene (284 mg, 1.36 mmol) in dry dichloromethane (5 ml), and the mixture was stirred at room temperature for 8 hours. The reaction mixture was loaded directly onto silica and was eluted with ethyl acetate–light petroleum (90%) to give the product (365 mg, 97%); ν_{max}/cm^{-1} ($CHCl_3$) 1720 (CO), 1600 (Ar), 1035 (SO); δ_H($CDCl_3$) 1.6–2.1 (4H, m, ring protons), 2.12 (3H, s, CHCOCH_3), 2.41 (1H, dm, *J* 7, C*H*COCH$_3$), 3.37 (3H, s, OCH_3), 4.24 (1H, t, *J* 7, 7, C*H*OMe), 6.67 (1H, br d, *J* 6, C=C*H*), 7.4–7.6 (5H, m, Ph-*H*) (Found: C, 64.6; H, 6.5; S, 11.7%; *m*/*z* 278. $C_{15}H_{18}O_3S$ requires C, 64.7; H, 6.5; S, 11.5%; M$^+$ 278).

rel-(3*R*,4*R*,5*S*)-3-Methoxy-4,5-di(ethoxycarbonyl)-1-(phenylsulfinyl)cyclohex-1-ene and *rel*-(3*R*,4*S*,5*R*)-3-methoxy-4,5-di(ethoxycarbonyl)-1-(phenylsulfinyl)cyclohex-1-ene

Anhydrous lithium perchlorate (72 mg, 0.8 equiv.) was added to a stirred solution of diethyl fumarate (440 mg) and (*E*)-1-methoxy-3-(phenylsulfinyl)buta-1,3-diene (176 mg, 0.85 mmol) in dry dichloromethane (3 ml), and the mixture was stirred at room temperature for 8 hours. The reaction mixture was loaded directly onto silica eluting with ethyl acetate to give the products (285 mg, 90%) as an inseparable mixture of diastereoisomers; ν_{max}/cm^{-1} ($CHCl_3$) 1725 (CO), 1600 (Ar), 1040 (SO); δ_H($CDCl_3$) 1.15 (6H, 2 × t, *J* 7, $CO_2CH_2CH_3$), 3.36 (3H, s, OCH_3), 4.07 (4H, 2 × q, *J* 7, $CO_2CH_2CH_3$), 4.23 (1H, t, C*H*OMe), 6.85 (1H, br s, C=C*H*), 7.4–7.6 (5H, m, Ph-*H*) (Found: *m*/*z* 380.4614. $C_{19}H_{24}O_6S$ requires M$^+$ 380.4616).

***rel*-(3*R*,4*R*)-3-Methoxy-4-cyano-1-(phenylsulfinyl)cyclohex-1-ene and *rel*-(3*R*,4*S*)-3-methoxy-4-cyano-1-(phenylsulfinyl)cyclohex-1-ene**

Anhydrous lithium perchlorate (78 mg, 0.8 equiv.) was added to a stirred solution of acrylonitrile (150 mg) and (*E*)-1-methoxy-3-(phenylsulfinyl)buta-1,3-diene (192 mg, 0.92 mmol) in dry dichloromethane (3 ml), and the mixture was stirred at room temperature for 4 days. The reaction mixture was loaded directly onto silica and was eluted with ethyl acetate–light petroleum (70%) to give the title compounds (52 mg, 23%) as a mixture of diastereoisomers; ν_{max}/cm^{-1} ($CHCl_3$) 2240 (CN), 1040 (SO); $\delta_H(CDCl_3)$ 3.37 (3H, s, $CHOCH_3$), 4.13 (1H, m, C*H*OMe), 6.6–6.72 (1H, 2 × br s, C=C*H*), 7.4–7.6 (5H, m, Ph-*H*) (Found: C, 64.6; H, 5.8; N, 5.4; S, 11.8%; *m*/*z* 261. $C_{14}H_{15}NOS$ requires C, 64.3; H, 5.8; N, 5.4; S, 12.2%; M^+ 261).

Acknowledgements

We wish to thank Glaxo Wellcome for a research studentship (N. C. O. T.), and the SERC (M. R. P.) for financial support.

References

1 W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Oxford, 1990.
2 M. C. Aversa, A. Barattucci, P. Bonaccorsi and P. Giannetto, *Tetrahedron: Asymmetry*, 1997, **8**, 1339; M. C. Carreno, *Chem. Rev.*, 1995, **95**, 1717.
3 R. S. Paley, A. de Dios, L. A. Estroff, J. A. Lafontaine, C. Montero, D. J. McCulley, M. B. Rubio, M. P. Ventura, H. L. Weers, R. F. de la Predilla, S. Castro, R. Dorado and M. Morente, *J. Org. Chem.*, 1997, **62**, 6326; M. C. Carreno, M. B. Cid and J. L. Garcia Ruano, *Tetrahedron: Asymmetry*, 1996, **7**, 2151; P. Gosselin, E. Bonfand, C. Maignan, *J. Org. Chem.*, 1996, **61**, 9049.
4 M. C. Aversa, A. Barattucci, P. Bonaccorsi, P. Giannetto and D. N. Jones, *J. Org. Chem.*, 1997, **62**, 4376.
5 R. Bell, D. Cottam, J. Davis and D. N. Jones, *J. Chem. Soc.*, *Perkin Trans. 1*, 1981, 2106.
6 J. R. Shelton and K. E. Davis, *Int. J. Sulfur Chem.*, 1973, **8**, 205.
7 K. J. Henry Jr., P. A. Grieco and C. T. Jagoe, *Tetrahedron Lett.*, 1992, **33**, 1817.
8 M. T. Reetz and D. N. A. Fox, *Tetrahedron Lett.*, 1993, **34**, 1119.
9 M. T. Reetz and A. Gansaiver, *Tetrahedron*, 1993, **49**, 6025.
10 M. C. Aversa, P. Bonacorsci, P. Giannetto and D. N. Jones, *Tetrahedron: Asymmetry*, 1994, **5**, 805.
11 L. Brandsma, *Preparative Acetylenic Chemistry*, Elsevier, Amsterdam, 1971.
12 G. M. Sheldrick, University of Göttingen, Germany, 1993. SHELXL93. An integrated system for solving and refining crystal structures from diffraction data (Revision 5.1).

Paper 8/06470I