Stereoselectivity in Electrophile-Mediated Cyclisations. Ag^{I}-Catalysed Synthesis of Disubstituted Pyrrolidines; Crystal Structure of *cis*-5-Phenyl-*N*-tosylpyrrolidin-2-ylmethyl 4-Bromobenzoate

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A series of phenyl-substituted allenic sulphonamides **5**, **6** and **7** have been prepared and shown to undergo Ag^{I}-catalysed cyclisation to give the corresponding 2,5-, 2,4- and 2,3-disubstituted *N*-sulphonylpyrrolidines **8**, **9**, and **10** respectively. The interactions between substituents in the ring-forming step play a key role in controlling the *cis*/*trans* selectivity observed in cyclisations involving **5** (*cis*-selective) and **7** (*trans*-selective). Ag^{I}-Catalysed cyclisation of **6** to give the 2,4-disubstituted pyrrolidine **9** was, however, nonselective.

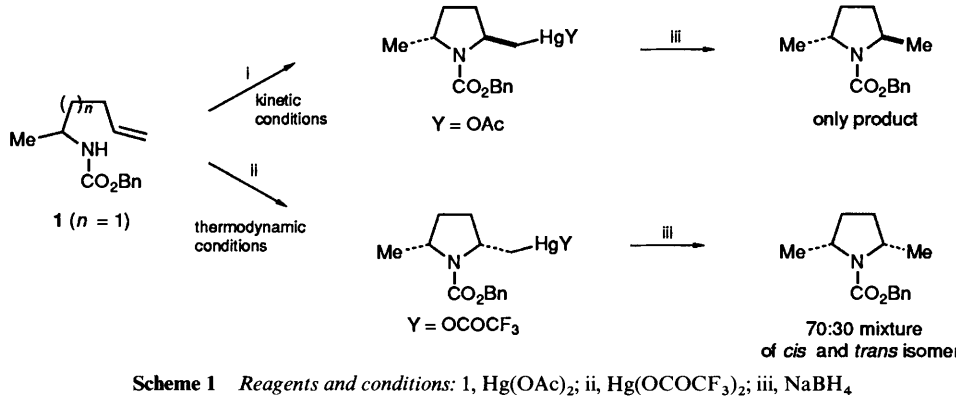
Electrophile-mediated cyclisations that lead to polysubstituted heterocycles have attracted considerable interest over recent years from synthetic chemists.[1] The principle advantages of this process are that the acyclic precursors are often readily assembled and the key cyclisation step may be carried out using a variety of electrophilic triggers, offering access to a range of functionalised products. The stereochemical consequences of the cyclisation step must also be given consideration and the task of controlling the relationship between the newly generated centre with respect to other substituent(s) on the ring has been the subject of intensive investigation. As a result, significant progress has been made towards understanding the factors that determine the stereochemistry of oxygen-containing heterocycles and valuable mechanistic rationale are now available for reactions of this type.[2,3]

Stereochemical studies relating to the corresponding nitrogen-containing systems are, however, more limited. Harding[4] and Danishefsky[5] have examined the cyclisation of alkenyl-based derivatives **1** (n = 1) as a stereoselective route to 2,5-dimethyl-substituted pyrrolidines (Scheme 1). These reactions utilize Hg^{II} as the electrophilic trigger and, in a series of elegant experiments, Harding established the importance of both kinetic and thermodynamic control in determining the distrubition of *cis*- and *trans*-pyrrolidine isomers.[4] Similar studies were also carried out on the corresponding cyclisation reaction leading to 2,6-dimethylpiperidines based on **1**(n = 2). Nevertheless, the situation remains clouded with a number of apparently inconsistent observations having also been reported. For example, Danishefsky[5b] reported that **1** (n = 1) underwent nonselective cyclisation using PhSeCl and, in an independent study, Barluenga[6] has described the synthesis of *cis*- and *trans*-*N*-substituted 2,5-dimethylpyrrolidines where the diastereoselectivity observed was dependent on both the nature of the *N*-substituent and the Hg^{II} salt used.

Although it is doubtful—given the diversity that exists in terms of the nitrogen nucleophile, the π-component and the electrophilic trigger used—that a single mechanistic model will evolve to account for these observations, the ability to make reliable predictions in this area would still be invaluable to the synthetic chemist.[7] However, it is also clear that before further progress in this direction is made, a much broader base of experimental data is required and the purpose of this paper is to describe our own recent results in this area.

Our efforts have focused primarily on substrates incorporating the allenic moiety as the reactive π-component.[8] Allene-based derivatives allow for the use of a wider range of electrophilic triggers and also impart a degree of functionality to the heterocyclic product that is not available with the corresponding alkenyl systems. However, there is very little known regarding the stereochemical outcome of allene-based cyclisations and one of our goals was to provide further insight into the stereoselectivity that is available with nitrogen-containing substrates in Ag^{I}-catalysed cyclisations leading to 2,5-, 2,4- and 2,3-disubstituted pyrrolidines.[9]

In earlier work we reported that the allenic α-amino ester **2** (R = SO_2Tol) underwent facile Ag^{I}-catalysed cyclisation to give the *cis*-2,5-disubstituted pyrrolidine **3** as the only observed product in essentially quantitative yield. Similar high levels of *cis*-selectivity were obtained for a series of other *N*-substituents, **2** (R = CO_2Bu^t, CO_2Me, CH_2Ph) although in the case of the corresponding primary amine **2** (R = H), cyclisation was nonselective and a 1:1 mixture of **3** and **4** was obtained (after reaction of the crude product with $TolSO_2Cl$–py).[10] In this latter case, and also possibly in the cyclisation reaction



Scheme 1 *Reagents and conditions:* 1, $Hg(OAc)_2$; ii, $Hg(OCOCF_3)_2$; iii, $NaBH_4$

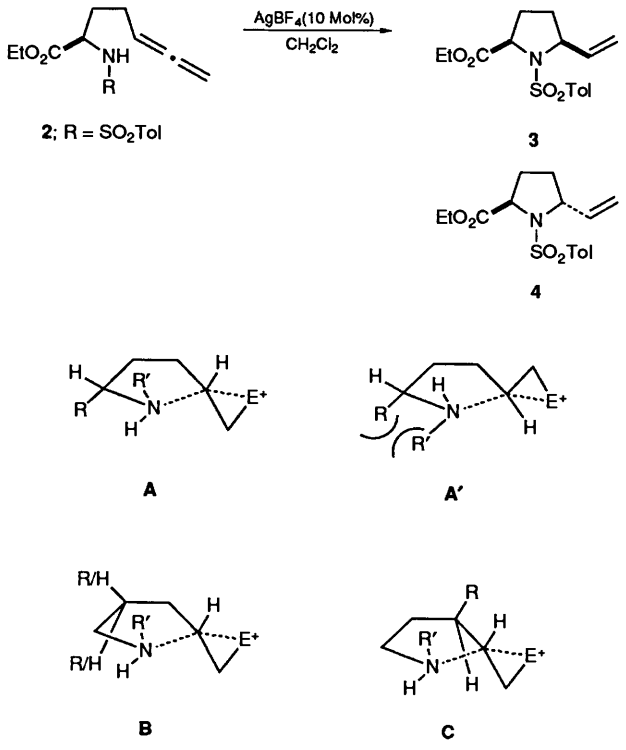


Fig. 1

involving the *N*-benzyl derivative, mechanistic interpretation is likely to be complicated by a direct interaction between the basic nitrogen and Ag^{I}. However, the *cis*-selectivity observed with nonbasic sulphonamide and carbamate nucleophiles, carrying a bulky substituent on nitrogen, bears close resemblance to the selectivity observed by Bartlett some years ago for the Lewis acid-mediated cyclisation of alkenyl ethers to give *cis*-2,5-disubstituted tetrahydrofurans.[2] In the mechanistic model proposed to account for *cis*-selectivity, Bartlett viewed the minimization of adjacent 1,2-interactions in the transition state for the cyclisation step involving an electrophile (E) as a key factor and the role of the temporary stereogenic heteroatom lay at the crux of this argument. This idea can also be used to explain the *cis*-selectivity observed with **2** (R = SO_2Tol) where cyclisation proceeds *via* transition state **A** rather than **A'** (Fig. 1). We were also interested to test the generality of this steric argument within the context of *N*-containing heterocycles and, in particular, with other substitution patterns. For example, a cyclisation leading to a 2,4-disubstituted pyrrolidine would, given the 1,3-relationship that exists between the C-4 residue and both the *N*-substituent and the developing alkenyl function (as in **B**), be expected to lead to a mixture of *cis*- and *trans*-products. Cyclisation would be predicted to be nonselective and although a *trans*-relationship would be expected between the substituent on N and that at C-2 in the transition state, this would not, of course, be apparent in the final product.* Finally, cyclisation to give a 2,3-disubstituted pyrrolidine would be expected to lead to a *trans*-relationship between the groups at C-2 and C-3 in the heterocyclic product *via* transition state **C**. This interaction would be important in its own right in the transition state and the influence of the stereocentre at N would not be crucial for overall stereocontrol.

Results and Discussion

Synthesis of Phenyl-substituted Allenic Sulphonamides **5**–**7**.—We chose, principally for reasons of synthetic accessibility, to examine three substrates carrying a phenyl substituent on each of the methylenes in the chain linking the allene and the nitrogen centre. The sulphonamide derivatives **5**–**7** were chosen, but the corresponding primary amines were also available (see below). The synthesis of all substrates is shown in Scheme 2 and although most of the yields were not optimised, the methods proved to be relatively efficient. The only significant problem encountered relates to the preparation of nitrile intermediate required for the synthesis of **7**. This involved cyanide displacement of the corresponding sulphonate ester and the highest yield for this step was 26% which was achieved using NaCN in hexamethylphosphoramide (HMPA). The major side reaction was presumed to result from competitive elimination and attempts to avoid HMPA by use of KCN–DMSO (dimethyl sulphoxide), KCN–MeCN/18-Crown-6, or NaCN–H_2O–hexane–benzyltrimethylammonium chloride were all unsuccessful.

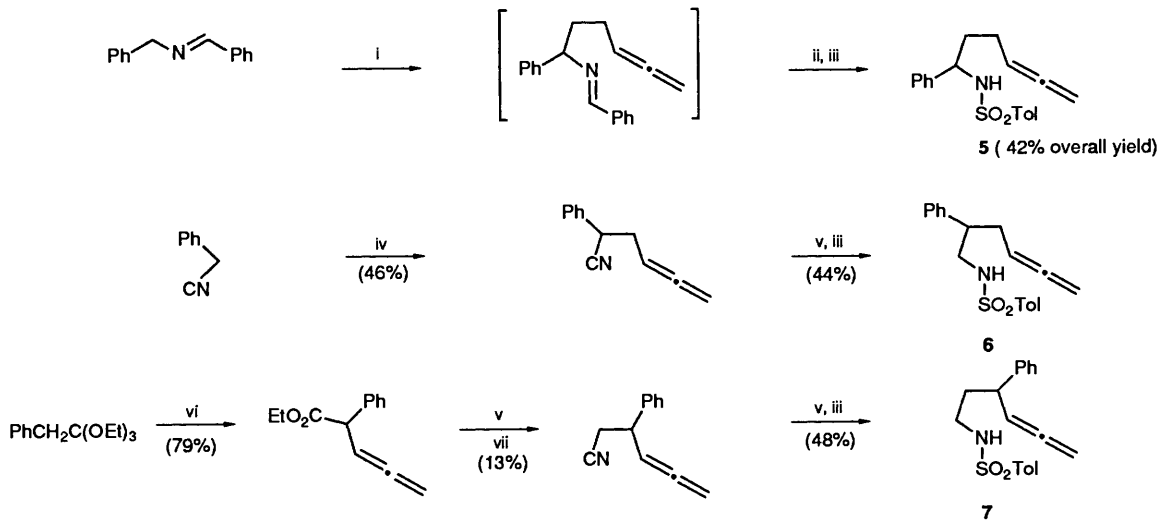
Ag^{I}-Catalysed Cyclisation of Phenyl-substituted Allenic Sulphonamides.—The cyclisation of the sulphonamide substrates was achieved using $AgBF_4$ (10–100 mol%) in CH_2Cl_2 at room temperature and the results of this study are shown in Table 1. Although reactions using a stoichiometric quantity of Ag^{I} proceeded more rapidly, control experiments established the amount of Ag^{I} used had no observable impact on either reaction yield or product distribution. The ratio of *cis*- and *trans*-isomers was then determined by ^1H NMR spectroscopic analysis of the crude reaction mixture, following a simple aqueous wash, and the yields cited were those then obtained following conventional work up–purification. Stereochemical assignment was, of course, vital to this study and a more complete discussion of this aspect of the work is given below.

As will be seen from Table 1 cyclisation of **5** gave only the *cis*-2,5-disubstituted pyrrolidine *cis*-**8** in 92% yield. This result parallels our earlier observations with **2** (R = SO_2Tol) and is, in the same way, consistent with the Bartlett model, *i.e.* **A** *vs.* **A'** (Fig. 1). In the case of **6** there are two 1,3-interactions linking these three substituents across the developing pyrrolidine ring and cyclisation of **6** was predicted to be essentially nonselective (as in **B**, Fig. 1). This was borne out and a 1:1 mixture of *cis*- and *trans*-**9** was isolated in 86% combined yield. Finally, cyclisation of **7** showed complete selectivity for *trans*-**10** in 87% yield, with no trace of the corresponding *cis*-isomer being observed. This result provides support for the controlling influence of the steric interaction between the phenyl residue and the developing alkenyl function (as in **C**, Fig. 1) in determining product structure.

It is also appropriate at this stage to mention that cyclisation of the primary amines corresponding to **5**, **6** and **7** has been examined.† However, given the fundamentally different nature of the nitrogen nucleophile that is involved here, it would be misleading to interpret these results in relation to the sulphonamide series. Full details will be published when a more complete picture of the involvement of the amine nitrogen in the cyclisation mechanism is available.

* The formation of a fully-protonated sulphonamide as an intermediate in the cyclisation reaction is unlikely [$TolSO_2NH_2$: pK_B −3.2 ($MeCO_2H$)[13]]. However, the sulphonamide nitrogen, which is not trigonal, does still represent a stereocentre that is capable of interacting with adjacent substituents. After reaction is complete this nitrogen centre can invert so that any 'memory' of its role in the cyclisation step is lost.

† Cyclisation of the primary amine corresponding to **5** was nonselective but that corresponding to **7** underwent cyclisation to give the corresponding *trans*-2,3-disubstituted pyrrolidine cleanly. A 5:1 mixture of *cis*/*trans*-2,4-disubstituted products were isolated from the amine corresponding to **6** and the *cis* configuration has been tentatively assigned to the major isomer.

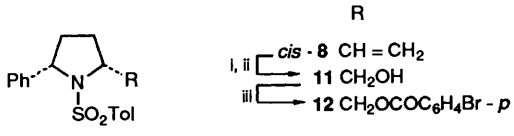


Scheme 2 *Reagents and conditions:* i, Lithium diisopropylamide(LDA),[11] 5-bromopenta-1,2-diene; ii, H_3O^+; iii, $TolSO_2Cl$, py; iv, Lithium isopropylcyclohexylamide(LiCA),[12] 4-bromobuta-1,2-diene; v, $LiAlH_4$, Et_2O; vi, $HC{\equiv}CCH_2OH$, H^+, heat; vii, $TolSO_2Cl$, py then KCN, HMPA.

Table 1

Allenic sulphonamide	Heterocyclic product (% yield)	
Ph NH SO_2Tol **5**	Ph NH SO_2Tol *cis* - **8**	92%
Ph NH SO_2Tol **6**	Ph N SO_2Tol *cis* and *trans* - **9** (1:1 mixture of diastereoisomers)	87%
Ph NH SO_2Tol **7**	Ph N SO_2Tol *trans* - **10**	86%

Stereochemical Assignment of Disubstituted Pyrrolidines.—The establishment of *cis*/*trans* stereochemistry was obviously vital to this work and is, within the context of substituted pyrrolidines, not always straightforward. We were unable to assign unambiguously the structure of *cis*-**8**, the sole product of cyclisation of **5**, following a series of NOE experiments. To overcome this difficulty *cis*-**8** was converted *via* ozonolysis–reduction into the alcohol **11** which was then esterified to give the 4-bromobenzoate **12** as shown in Scheme 3. The *cis*-configuration of **12** was confirmed by X-ray crystallographic



Scheme 3 *Reagents and conditions:* i, O_3, MeOH, −78 °C; ii, $NaBH_4$; iii, 4-bromobenzoyl chloride, DMAP, CH_2Cl_2

analysis (Fig. 2), but it is interesting to note the orientation of the N-SO_2Tol residue in **12** and the resemblance that this structure bears to transition state **A** (Fig. 1).

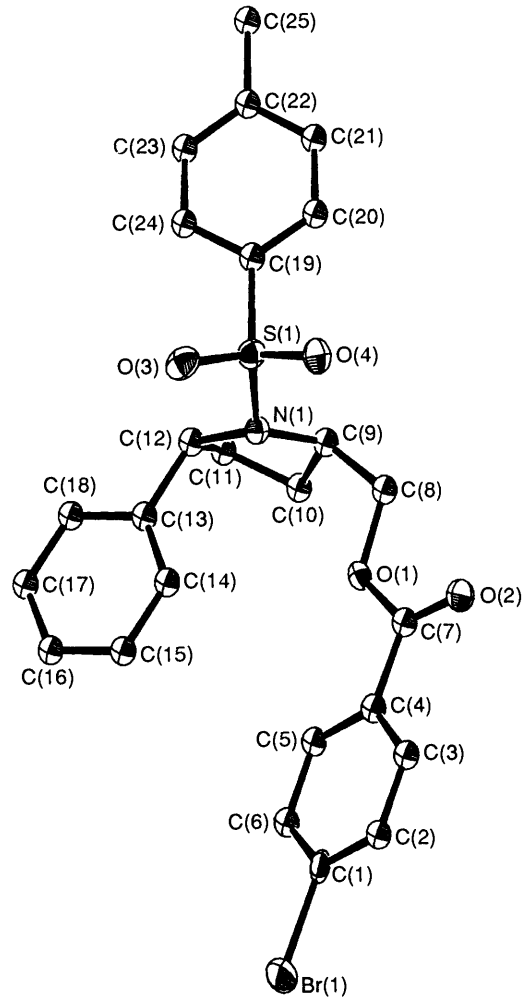


Fig. 2 ORTEP Diagram of bromobenzoate **12**

NOE experiments were, however, extremely useful in assigning *trans* stereochemistry to the 2,3-disubstituted system *trans*-**10**. A series of irradiation experiments were carried out to establish the relative stereochemistry of *trans*-**10** and these are indicated in Fig. 3; full details of proton assignment can be found in the Experimental section.

X-Ray Structure Determination of Compound **12**.—*Crystal*

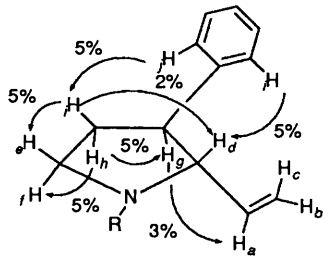


Fig. 3

Table 2 Fractional atomic coordinates (Å) for the 4-bromobenzoate **12**

Atom	*x*	*y*	*z*
Br-1	0.239 28(14)	0.008 73(7)	0.698 88(11)
S-1	−0.563 0(3)	0.239 5(1)	0.924 1(2)
O-1	−0.261 4(6)	0.077 4(3)	0.973 6(5)
O-2	−0.333 7(7)	−0.037 6(4)	0.917 2(6)
O-3	−0.547 4(7)	0.296 0(4)	0.850 8(5)
O-4	−0.624 3(7)	0.168 3(4)	0.889 9(5)
N-1	−0.409 9(7)	0.222 4(4)	0.986 2(5)
C-1	0.089 7(10)	0.009 8(5)	0.770 9(7)
C-2	−0.012 5(11)	−0.044 1(5)	0.749 0(8)
C-3	−0.121 1(10)	−0.043 2(5)	0.802 9(8)
C-4	−0.128 3(9)	0.012 9(5)	0.872 2(6)
C-5	−0.023 6(9)	0.067 1(5)	0.893 0(7)
C-6	0.087 2(10)	0.065 7(6)	0.841 0(7)
C-7	−0.250 6(10)	0.012 2(6)	0.923 8(7)
C-8	−0.382 4(9)	0.082 4(5)	1.020 6(7)
C-9	−0.390 1(9)	0.161 3(5)	1.063 9(7)
C-10	−0.258 3(11)	0.186 2(6)	1.134 5(8)
C-11	−0.266 7(12)	0.271 7(6)	1.132 7(8)
C-12	−0.325 1(10)	0.291 0(5)	1.024 1(7)
C-13	−0.217 5(9)	0.308 8(5)	0.959 4(7)
C-14	−0.167 7(11)	0.259 3(6)	0.899 0(8)
C-15	−0.065 6(12)	0.276 9(7)	0.843 7(9)
C-16	−0.014 3(12)	0.350 6(7)	0.850 0(9)
C-17	−0.064 2(12)	0.402 1(7)	0.908 2(9)
C-18	−0.166 8(10)	0.383 2(6)	0.963 3(8)
C-19	−0.662 8(10)	0.277 4(5)	1.007 1(7)
C-20	−0.741 4(10)	0.233 2(6)	1.058 3(7)
C-21	−0.817 4(11)	0.264 3(6)	1.123 5(8)
C-22	−0.816 1(11)	0.343 2(6)	1.141 3(8)
C-23	−0.736 3(11)	0.386 6(7)	1.090 2(8)
C-24	−0.660 7(10)	0.357 5(6)	1.023 0(8)
C-25	−0.902 8(11)	0.376 0(6)	1.211 1(8)

data. A blocky crystal of **12** of dimensions *ca.* 0.3 × 0.3 × 0.25 mm was selected for data collection. The crystals were not of a particularly high quality. $C_{25}H_{24}BrNO_4S$, M = 514.4, monoclinic, a = 9.809(2), b = 17.696(4), c = 13.582(4) Å, β = 100.32(3)°, U = 2319.3 Å^3, space group $P2_1/n$, Z = 4, D_c = 1.47 gcm^{-3}, μ(Mo-Kα) = 18.23 cm^{-1}, F(000) = 1056. Data were measured at room temperature on a Hilger and Watts Y290 four-circle diffractometer in the range 2 < θ < 22°. 3171 Reflections were collected of which 1842 were unique with $I \geq 3\sigma(I)$. Data were corrected for Lorentz and polarization effects but not for absorption.

Structure solution and refinement. The structure was solved by conventional Patterson methods and refined using the SHELX suite of programs.[14] Thermal parameters of the oxygen and also C-1, C-2 and C-3 atoms were larger than those of the rest of the atoms in the molecule, hence anisotropic refinement was carried out. The bromine and sulphur atoms were allowed to vibrate anisotropically in the final stages of convergence. Hydrogens were included at calculated positions. Final residuals after 10 cycles of full-matrix least squares were $R = R_w = 0.0666$ for unit weights. The total number of parameters varied was 179. Max. final shift/esd was 0.004, and the max. and min. residual densities were 0.26 and −0.25 eA^{-3} respectively. Final fractional atomic coordinates are shown in Table 2. Isotropic thermal parameters, bond distances and angles and tables of anisotropic temperature factors and hydrogen atom positions have been deposited at the Cambridge Crystallographic Data Centre.*

* For full details of the CCDC deposition scheme see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1991, issue 1.

Experimental

IR spectra were recorded using a Perkin-Elmer 1310 grating spectrophotometer. Routine mass spectra from electron ionisation (E.I.70eV), chemical ionisation (CI, iso-butane) and high resolution accurate mass determination were recorded with a VG Analytical 7070E instrument with a VG2000 data system. ^{1}H NMR spectra were recorded in $CDCl_3$ at 270 MHz on a JEOL GNM GX FT 270 spectrometer, unless otherwise stated, J values are given in Hz. Elemental microanalyses were carried out using a Carlo Erba 1106 Elemental Analyser. Ether is diethyl ether and light-petroleum is the fraction of b.p. 60–80 °C.

N-1-*Phenyl*-N-*tosylhexa*-4,5-*dienylamine* **5**.—A solution of *N*-benzylidenebenzylamine (3.0 g, 15 mmol) in THF (tetrahydrofuran) (50 cm^3) was cooled to −78 °C and treated with LDA (lithium diisopropylamide) [prepared from BuLi (1.6 mol dm^{-3} in hexane; 10.6 cm^3, 16.9 mmol), diisopropylamine (2.4 cm^3, 1.71 g, 16.9 mmol) in THF (15 cm^3)] according to the procedure of Kauffmann *et al.*[11] The resulting deep red solution was stirred for 2 h after which 5-iodopenta-1,2-diene (3.28 g, 16 mmol) was added and the solution was allowed to warm to room temperature. Saturated aqueous NH_4Cl (10 cm^3) was added together with sufficient water to dissolve the solids and the product was extracted with ether (5 × 30 cm^3). The combined extracts were then stirred vigorously with aqueous HCl (50 cm^3; 2 mol dm^{-3}) for 0.5 h (reaction complete by TLC) to effect imine hydrolysis. The ether layer was then extracted with aqueous HCl (2 mol dm^{-3}; 2 × 10 cm^3) and the combined aqueous extracts were treated with concentrated aqueous NaOH until basic. The product was then extracted with ether (5 × 30 cm^3) and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give 1-phenylhexa-4,5-dienylamine (1.55 g, 60%) as a pale yellow oil which was used without further purification; ν_{max}(thin film)/cm^{-1} 3350 and 1960; δ(60 MHz) 7.40–7.20 (5 H, m), 5.15 (1 H, m), 4.90–4.75 (2 H, m), 3.90 (1 H, t, *J* 7), 2.30–1.65 (4 H, m) and 1.60 (2 H, s).

The crude amine prepared above was dissolved in pyridine (5 cm^3), cooled to 0 °C and treated with tosyl chloride (1.9 g, 10 mmol). After the mixture had been stored at −10 °C overnight, the solvent was removed under reduced pressure and ethyl acetate (50 cm^3) was added. The resulting mixture was washed with HCl (2 mol dm^{-3}; 20 cm^3) and the organic phase was separated, dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the residue by flash chromatography gave the *sulphonamide* **5** (2.13 g, 42% overall yield) as colourless crystals, m.p. 72 °C (diethyl ether–petroleum) (Found: C, 69.5; H, 6.5; N, 4.25%. $C_{19}H_{21}NO_2S$ requires C, 69.69; H, 6.47; N, 4.28%); $\nu_{max.}$($CHCl_3$)/cm^{-1} 3260, 1950 and 1590; δ 7.65 (2 H, d, *J* 7, part of AA′BB′), 7.19–6.80 (7 H, m), 5.05 (1 H, m), 4.80 (1 H, br d, *J* 7, NH), 4.70–4.63 (2 H, m), 4.35 (1 H, m), 2.38 (3 H, s) and 1.98–1.78 (4 H, m); *m*/*z* (CI) 328 ($M^+ + 1$).

2-*Phenylhexa*-4,5-*dienenitrile*.—To a solution of lithium isopropylcyclohexylamide [prepared from BuLi (1.6 mol dm^{-3} in hexane; 9.21 cm^3, 14.7 mmol) and isopropylcyclohexylamine (2.4 cm^3, 2.08 g, 14.7 mmol) in THF (20 cm^3) at −78 °C] was added a solution of benzyl cyanide (1.71 cm^3, 1.73 g, 14.7 mmol)

in THF (3 cm^3). After 15 min a solution of 4-bromobuta-1,2-diene (2.06 g, 15 mmol) in THF (3 cm^3) was slowly added. After a further 15 min saturated aqueous ammonium chloride (5 cm^3) and water (15 cm^3) were added. The reaction mixture was extracted with ether (4 × 20 cm^3) and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Removal of solvent and purification of the residue by flash chromatography (ether–light petroleum) gave 3-*phenylhexa*-4,5-*dienenitrile* (1.14 g, 46%) as a colourless oil, b.p. 90–91 °C (0.2 mmHg) (Found M^+, 169.089. $C_{12}H_{11}N$ requires *M*, 169.089); $\nu_{max}(CCl_4)/cm^{-1}$ 2240, 1960 and 1600; δ 7.50–7.30 (5 H, m), 5.14 (1 H, pent, *J* 7), 4.82–4.76 (2 H, m), 3.87 (1 H, dd, *J* 8, 6.5) and 2.63–2.53 (2 H, m).

2-*Phenyl*-N-*tosylhexa*-4,5-*dienylamine* **6**.—A solution of 2-phenylhexa-4,5-dienenitrile (1.14 g, 6.7 mmol) in ether (10 cm^3) was added slowly to an ice cold solution of $LiAlH_4$ (256 mg, 6.7 mmol) in ether (100 cm^3). After 1.5 h the mixture was quenched by addition of water, the aluminium salts were filtered off and the filtrate was dried (Na_2SO_4), and evaporated. Distillation of the residue gave 2-phenylhexa-4,5-dienylamine (1.03 g, 88%) as a colourless oil, b.p. (bulb-to-bulb) 130 °C (0.1 mmHg) (Found M^+, 173.118. $C_{12}H_{15}N$ requires *M*, 173.120); ν_{max}(thin film)/cm^{-1} 3370, 1955 and 1600; δ 7.40–7.10 (5 H, m), 4.98 (1 H, pentet, *J* 7), 4.64–4.56 (2 H, m), 3.00 (1 H, dd, *J* 12.5, 5), 2.86 (1 H, dd, *J* 12.5, 8), 2.70 (1 H, m), 2.38–2.28 (2 H, m) and 1.30 (2 H, br s, NH_2); *m*/*z* (CI) 174 ($M^+ + 1$).

A solution of this amine (500 mg, 2.9 mmol) in pyridine (6 cm^3) was cooled to 0 °C and treated with tosyl chloride (665 mg, 3.5 mmol). The mixture was allowed to stand at −5 °C overnight, concentrated, and then aqueous HCl (2 mol dm^{-3}; 5 cm^3) was added. The mixture was extracted with ethyl acetate (3 × 10 cm^3) and the extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give an oil which crystallised. Recrystallisation of this from ether–light petroleum gave the *sulphonamide* **6** (416 mg, 44%) as colourless needles, m.p. 85–86 °C (Found: C, 70.0; H, 6.5; N, 4.4. $C_{19}H_{21}NO_2S$ requires C, 69.69; H, 6.47; N, 4.28%); $\nu_{max}(CCl_4)/cm^{-1}$ 3590, 3390 and 1960; δ 7.65 (2 H, d, *J* 7, part of AA′BB′), 7.32–7.20 (5 H, m), 7.04 (2 H, d, *J* 7, part of AA′BB′), 4.90 (1 H, m), 4.60 (2 H, m), 4.16 (1 H, m, NH), 3.36 (1 H, ddd, *J* 13, 8.5, 5.5), 3.02 (1 H, ddd, *J* 13, 9, 4), 2.80 (1 H, m), 2.42 (3 H, s) and 2.33–2.23 (2 H, m); *m*/*z* (CI) 328 ($M^+ + 1$).

Ethyl 2-*Phenylpenta*-3,4-*dienoate*.—A solution of prop-2-ynyl alcohol (1.40 cm^3, 1.35 g, 24 mmol), triethyl orthophenylacetate (7.14 g, 30 mmol) and pivalic acid (1 crystal) was heated at 115 °C for 9 h. The mixture was then directly distilled to give *ethyl* 2-*phenylpenta*-3,4-*dienoate* (3.30 g, 79%) as a colourless liquid, b.p. 85–88 °C (0.05 mmHg) (Found: C, 77.1; H, 7.1. $C_{13}H_{14}O_2$ requires C, 77.2; H, 6.98%); ν_{max}(thin film)/cm^{-1} 1960 and 1720; δ (60 MHz) 7.35–7.10 (5 H, br s), 5.55 (1 H, m), 4.90–4.63 (2 H, m), 4.30–3.90 (3 H, m) and 1.18 (3 H, t, *J* 7).

2-*Phenylpenta*-3,4-*dien*-1-*ol*.—A solution of ethyl 2-phenylpenta-3,4-dienoate (4.62 g, 23 mmol) in ether (30 cm^3) was slowly added to a cold (−10 °C) solution of $LiAlH_4$ (2.41 g, 64 mmol) in ether (50 cm^3). After 5 min saturated aqueous sodium sulphate (20 cm^3) was added and the ether layer was separated. The aqueous phase was extracted with ether (4 × 20 cm^3) and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by flash chromatography (ethyl acetate–light petroleum) gave 2-phenylpenta-3,4-dien-1-ol (2.15 g, 58%) as a colourless oil (Found, M^+, 160.087. $C_{11}H_{12}O$ requires *M*, 160.088); ν_{max}(thin film)/cm^{-1} 3550, 1950 and 1600; δ 7.35–7.20 (5 H, m), 5.33 (1 H, q, *J* 5), 4.82 (1 H, d, *J* 5), 4.81 (1 H, d, *J* 5), 3.85 (1 H, dd, *J* 16, 8), 3.70 (1 H, dd, *J* 16, 8), 3.49 (1 H, m) and 2.00 (1 H, s, OH); *m*/*z* (EI) 160 (M^+).

3-*Phenylhexa*-4,5-*dienenitrile*.—Tosyl chloride (178 mg, 0.93 mmol) was added to a solution of 2-phenylpenta-3,4-dien-1-ol (124 mg, 0.78 mmol) in pyridine (2 cm^3) at 0 °C. After 1.5 h an additional quantity of tosyl chloride (118 mg) was added and the mixture was stirred at room temperature overnight. After solvent removal under reduced pressure and addition of CH_2Cl_2 (20 cm^3) the mixture was washed with aqueous HCl (2 mol dm^{-3}; 10 cm^3), dried (Na_2SO_4) and concentrated. The product was purified by flash chromatography to give the corresponding tosylate (215 mg, 87%) as a colourless oil (Found: C, 69.0; H, 5.77. $C_{18}H_{18}O_3S$ requires C, 68.76; H, 5.77%); ν_{max}(thin film)/cm^{-1} 1950 and 1600; δ 7.65 (2 H, d, *J* 7, part of AA′BB′), 7.40–7.20 (5 H, m), 7.15 (2 H, d, *J* 7, part of AA′BB′), 5.27 (1 H, q, *J* 6.5), 4.80 (1 H, d, *J* 6.5), 4.75 (1 H, d, *J* 6.5), 4.26 (1 H, dd, *J* 10, 7), 4.12 (1 H, dd. *J* 10, 7), 3.67 (1 H, m) and 2.40 (3 H, s); *m*/*z* (CI) 315 ($M^+ + 1$).

A solution of the above tosylate (1.947 g, 6.2 mmol) in HMPA (10 cm^3) was treated with NaCN (607 mg, 12 mmol) and stirred at room temperature for 6 d. After this time ethyl acetate (30 cm^3) was added and the mixture was washed with brine (4 × 20 cm^3). The organic phase was dried (Na_2SO_4), concentrated under reduced pressure and the residue was purified by flash chromatography to give 3-phenylhexa-4,5-dienenitrile (275 mg, 26%) as a colourless oil which was used without further purification: $\nu_{max}(CHCl_3)/cm^{-1}$ 2240, 1950 and 1600; δ 7.40–7.20 (5 H, m), 5.41 (1 H, q, *J* 6.5), 5.00–5.02 (2 H, m), 3.70 (1 H, m), 2.76 (1 H, dd, *J* 16, 7) and 2.65 (1 H, dd, *J* 16, 7); *m*/*z* (CI) 170 ($M^+ + 1$).

3-*Phenyl*-N-*tosylhexa*-4,5-*dienylamine* **7**.—3-Phenylhexa-4,5-dienenitrile (252 mg, 1.5 mmol) in ether (5 cm^3) was added to a mixture of $LiAlH_4$ (57 mg, 1.5 mmol) in ether (30 cm^3). After 30 min, water was added and the solids removed by filtration. The filtrate was dried ($NaSO_4$) and concentrated to give 3-phenylhexa-4,5-dienylamine (228 mg, 88%) as a pale yellow oil which was used immediately: ν_{max}(thin film)/cm^{-1} 3380 and 1940; δ 7.40–7.20 (5 H, m), 5.30 (1 H, q, *J* 6.5), 4.78–4.77 (2 H, m), 3.28 (1 H, m), 2.77–2.62 (2 H, m), 1.95–1.75 (2 H, m) and 1.20 (2 H, br s, NH_2); *m*/*z* (EI) 173 (M^+).

The sulphonamide **7** was obtained in 55% yield from 3-phenylhexa-4,5-dienylamine using the procedure described above for **6**, m.p. 68 °C (ethyl acetate–light petroleum) (Found: C, 69.4; H, 6.5; N, 4.25. $C_{19}H_{21}NO_2S$ requires C, 69.69; H, 6.47; N, 4.28%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3380, 1950 and 1600; δ 7.70 (2 H, d, *J* 7, part of AA′BB′) 7.30–7.10 (5 H, m), 7.10 (2 H, d, *J* 7 Hz, part of AA′BB′), 5.22 (1 H, q, *J* 6.5 Hz), 4.76–4.74 (2 H, m), 4.62 (1 H, br t, *J* 6, NH), 3.30 (1 H, m), 2.92 (2 H, m), 2.40 (3 H, s) and 2.00–1.72 (2 H, m); *m*/*z* (CI) 328 ($M^+ + 1$).

Ag^I-*Catalysed Cyclisations*.—*General Procedure*. A CH_2Cl_2 solution of allenic sulphonamide **5**–**7** (0.1 mmol cm^{-3}) was treated with $AgBF_4$ (10–100 mol%). After completion of reaction (TLC, 12–24 h) the mixture was diluted with an equal volume of CH_2Cl_2 and washed with water. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were dried (Na_2CO_3), concentrated under reduced pressure and the products were purified by flash chromatography (ethyl acetate–hexane). Yields and product distribution are shown in Table 1 and physical and spectroscopic data for **8**–**10** are provided below.

cis-5-*Phenyl*-N-*tosyl*-2-*vinylpyrrolidine*(cis-**8**). Isolated as *colourless crystals*, m.p. 79 °C (ether–light petroleum) (Found: C, 69.3; H, 6.4; N, 4.25. $C_{19}H_{21}NO_2S$ requires C, 69.69; H, 6.47; N, 4.28%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1620; δ 7.63 (2 H, d, *J* 7, part of AA′BB), 7.38–7.08 (7 H, m), 6.00 (1 H, m), 5.36 (1 H, dt, *J* 17,

1.5), 5.20 (1 H, dt, *J* 10, 1.5), 4.82 (1 H, t, *J* 6), 4.33 (1 H, qt, *J* 6, 1), 2.41 (3 H, s) and 2.00–1.62 (4 H, m); *m/z* (CI) 328 ($M^+ + 1$).

cis- *and trans-4-Phenyl-N-tosyl-2-vinylpyrrolidines* (cis- *and* trans-**9**). Obtained as an *inseparable mixture.* (Found: C, 69.4; H, 6.45; N, 4.15. $C_{19}H_{21}NO_2S$ requires C, 69.69; H, 6.47; N, 4.28%); $\nu_{max}(CCl_4)/cm^{-1}$ 1640 and 1600; δ (Tentative stereochemical assignments have been made using a combination of NOE and 2D-COSY experiments and individual signals attributed to *cis*-**9** and *trans*-**9** are indicated) 7.76 (2 H, d, *J* 7, part of AA′BB′, both isomers), 7.38–7.08 (7 H, m, both isomers), 5.93 (1 H, ddd, *J* 16, 10.5, 7, both isomers), 5.40 (1 H, dt, *J* 16, 1, *trans*), 5.22 (1 H, dt, *J* 10, 1, *trans*) 5.28 (1 H, dt, *J* 15, 1, *cis*), 5.14 (1 H, dt, *J* 10, 1 H, *cis*), 4.41 (1 H, m, 2-H *trans*), 4.18 (1 H, m, 5-H *cis*), 3.94 (1 H, ddd, *J* 10.5, 8, 1, 5-H *trans*), 3.82 (1 H, ddd, *J* 10.5, 8, 1, 5-H *cis*), 3.52-3.34 (2 H, m, 5-H *cis* and 4-H *trans*), 3.12 (1 H, dd, *J* 10.5, 9.5, 5-H *trans*), 2.85 (1 H, m, 4-H *cis*), 2.48–2.30 (4 H, m, CH_3, 3-H both isomers) 2.02 (1 H, m, 3-H *trans*), 1.86 (1 H, m, 3-H *cis*); *m/z* (EI) 327 (M^+).

trans-3-*Phenyl*-N-*tosyl*-2-*vinylpyrrolidine* (trans-**10**). Isolated as *colourless crystals*, m.p. 108 °C (methanol) (Found: C, 69.4; H, 6.5; N, 4.25. $C_{19}H_{21}NO_2S$ requires C, 69.69; H, 6.47; N, 4.28%), $\nu_{max}(CHCl_3)/cm^{-1}$ 1600; δ 7.75 (2 H, d, *J* 7, part of AA′BB′), 7.35–7.17 (5 H, m), 6.92 (2 H, m, H_j), 5.85 (1 H, ddd, *J* 17, 10.5, 7, H_a) 5.08 (1 H, dt, *J* 10.5, 1, H_b), 5.05 (1 H, dt, *J* 17, 1, H_c), 4.16 (1 H, t, *J* 7, H_d), 3.68 (1 H, ddd, *J* 11, 8, 4, H_e), 3.53 (1 H, ddd, *J* 11, 9, 6.5, H_f), 3.07 (1 H, dt, *J* 9.5, 7, H_g), 2.45 (3 H, s), 2.10 (1 H, m, H_h) and 1.70 (1 H, m, H_i); *m/z* (EI) 327 (M^+).

For NOE correlations and ^1H assignments, see Fig. 3.

cis-2-*Hydroxymethyl*-5-*phenyl*-N-*tosylpyrrolidine* **11**.—A solution of **8** (160 mg, 0.49 mmol) in MeOH (10 cm^3) at −78 °C was treated with a stream of ozone until all starting material was consumed (TLC). An excess of $NaBH_4$, was then added and the reaction mixture was allowed to warm to room temperature. The solvent was then removed under reduced pressure and the residue partioned between CH_2Cl_2 and water. The organic phase was separated, dried (Na_2SO_4) and concentrated under reduced pressure. Recrystallisation of the residue gave alcohol **11** (143 mg, 88%) as colourless crystals, m.p. 125–126 °C (benzene–petroleum) (Found: C, 65.5; H, 6.4; N, 4.2. $C_{18}H_{21}NO_3S$ requires C, 65.22; H, 6.39; N, 4.22%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500; δ 7.75 (2 H, d, *J* 7, part of AA′BB′), 7.40–7.21 (7 H, m), 4.77 (1 H, t, *J* 7), 3.38–3.71 (3 H, m), 2.80 (1 H, br, OH), 2.44 (3 H, s) and 1.94–1.64 (4 H, m); *m/z* (CI) 332 ($M^+ + 1$).

cis-5-*Phenyl*-N-*tosylpyrrolidin*-2-*ylmethyl* 4-Bromobenzoate **12**.—A solution of the alcohol **11** (50 mg, 0.15 mmol) in CH_2Cl_2 (2 cm^3) containing 4-(dimethylamino)pyridine (DMAP) (18 mg) was treated with a solution of 4-bromobenzoyl chloride (33 mg, 0.15 mmol) in CH_2Cl_2 (2 cm^3). After 30 min the solution was diluted with CH_2Cl_2 (5 cm^3) and washed with aqueous HCl (2 mol dm^{-3}; 5 cm^3) and the organic phase was separated, dried (Na_2SO_4) and concentrated under reduced pressure. Removal of solvent gave the 4-*bromobenzoate* **12** (462 mg, 90%) as colourless crystals, m.p. (MeOH) 175–176 °C (Found $M^+ + 1$, 516.066. $C_{25}H_{25}{}^{81}BrNO_4S$ requires *M*, 516.066); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720; δ 7.83 (2 H, br d, *J* 5), 7.70 (2 H, d, *J* 8), 7.55 (2 H, d, *J* 7), 7.42–7.22 (7 H, m), 4.73 (1 H, t, *J* 7), 4.63–4.49 (2 H, m), 4.25 (1 H, m), 2.42 (3 H, s) and 2.02–1.70 (4 H, m); (CI) 514/516 ($M^+ + 1$).

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References

1 P. A. Bartlett in *Asymmetric Synthesis*, ed. J. D. Morrison, vol 3, Academic Press, New York, 1984, p. 411; L. S. Hegedus, *Tetrahedron*, 1984, **40**, 2415; M. B. Gasc, A. Lattes, J. J. Perier, *Tetrahedron*, 1983, **39**, 703; G. Cardillo and M. Orena, *Tetrahedron*, 1990, **46**, 3321.

2 S. C. Rychnovsky and P. A. Bartlett, *J. Am. Chem. Soc.*, 1981, **103**, 3963. For the application of this model to the stereochemical outcome of the cyclisation of allenic silyl enol ethers, see R. D. Walkup and G. Park, *Tetrahedron Lett.*, 1987, **28**, 1023; R. D. Walkup and G. Park, *Tetrahedron Lett.*, 1988, **29**, 5505.

3 Transition state models have also been developed to account for allylic asymmetric induction, see M. Labelle and Y. Guindon, *J. Am. Chem. Soc.*, 1989, **111**, 2204 and refs. therein.

4 K. E. Harding and T. H. Marman, *J. Org. Chem.*, 1984, **49**, 2838; K. E. Harding and S. R. Burkes, *J. Org. Chem.*, 1981, **46**, 3920.

5 (*a*) R. R. Webb and S. Danishefsky, *Tetrahedron Lett.*, 1983, **24**, 1357; (*b*) S. Danishefsky, E. Taniyama and R. R. Webb, *Tetrahedron Lett.*, 1983, **24**, 11.

6 J. Barluenga, C. Jiménez, C. Nájera and M. Yus, *J. Chem. Soc., Perkin Trans. 1*, 1984, 721; J. Barluenga, C. Jiménez, C. Nájera and M. Yus, *J. Heterocycl. Chem.*, 1984, 1733; J. Barluenga, C. Nájera and M. Yus, *J. Heterocycl. Chem.*, 1981, 1297.

7 For other stereochemical studies in this area leading to substituted pyrrolidines, see D. L. J. Clive, V. Farina, A. Singh, C. K. Wong, W. A. Kiel and S. M. Menchen, *J. Org. Chem.*, 1980, **45**, 2120; Y. Tamura, S. Kawamura, K. Tanaka and Z. Yoshida, *Tetrahedron Lett.*, 1984, **24**, 1063; A. Toshimitsu, K. Terao and S. Uemura, *J. Org. Chem.*, 1986, **51**, 1724; M. Tokuda, Y. Yamada and H. Suginome, *Chem. Lett.*, 1988, 1289; D. R. Williams, M. H. Osterhout and J. M. McGill, *Tetrahedron Lett.*, 1989, **30**, 1327; N. X. Hu, Y. Aso, T. Otsubo and F. Ogura, *J. Org. Chem.*, 1989, **54**, 4398; H. Takahata, T. Takamatsu and T. Yamazaki, *J. Org. Chem.*, 1989, **54**, 4812; H. Takahata, T. Takamatsu, Y.-S. Chen, N. Ohkubo, T. Yamazaki, T. Momose and T. Date, *J. Org. Chem.*, 1990, **55**, 3792.

8 For an overview of the reactivity of allenes towards electrophiles, including a discussion of possible mechanistic pathways, see T. L. Jacobs in *The Chemistry of the Allenes*, ed. S. R. Landor, Academic Press, 1982, vol 2, p. 349–510; W. Smadja, *Chem. Rev.*, 1983, **83**, 263.

9 For the first examples of the use of Ag^I-catalysis in the cyclisation of both allenic amines and alcohols, see A. Claesson, C. Sahlberg and K. Luthman, *Acta Chem. Scand., Ser. B*, 1979, **33**, 309; L.-I. Olsson and A. Claesson, *Synthesis*, 1979, 743.

10 R. Kinsman, D. Lathbury, P. Vernon and T. Gallagher, *J. Chem. Soc., Chem. Commun.*, 1987, 243; N. J. S. Huby, R. G. Kinsman, D. Lathbury, P. G. Vernon and T. Gallagher, *J. Chem. Soc., Perkin Trans. 1*, 1991, 145.

11 For the metallation of *N*-benzylidenebenzylamine, see T. Kauffmann, K. Habersaat and E. Köppelmann, *Chem. Ber.*, 1977, **110**, 638.

12 D. S. Watt, *Tetrahedron Lett.*, 1974, 707.

13 E. M. Arnett, *Progr. Phy. Org. Chem.*, 1963, **1**, 223.

14 SHELX86, G. M. Sheldrick, University of Gottingen, W. Germany, 1986; SHELX76, G. M. Sheldrick, University of Cambridge, England, 1976.

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