Synthesis of 2,5-Disubstituted 3-(Phenylsulfonyl)pyrrolidines via 5-*Endo*-Trig Cyclisation Reactions

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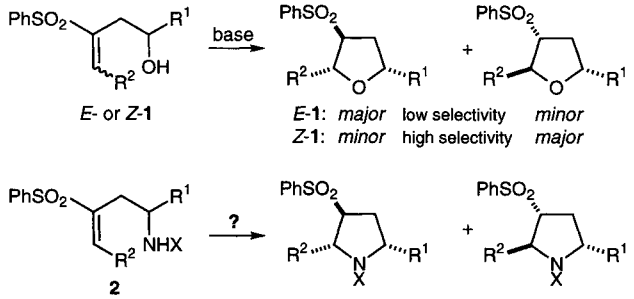
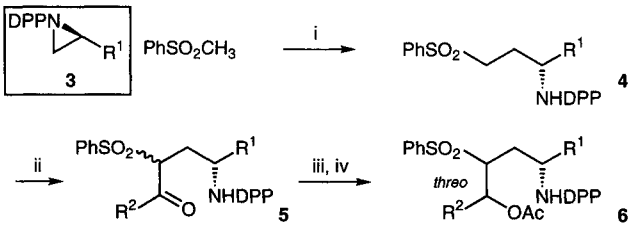
Abstract: Reaction of lithiated (phenylsulfonyl)methane with enantiomerically pure *N*-diphenylphosphinylaziridines gives adducts **4**, which may be acylated at the sulfone α-position by further lithiation and reaction with non-enolisable acid chlorides, giving ketones **5**. Reduction followed by acetylation gives substrates **6**, which undergo elimination and 5-*endo*-trig cyclisation to give 2,5-disubstituted 3-(phenylsulfonyl)pyrrolidines **7** in high yields and with excellent stereoselectivities. Some further reactions of the pyrrolidines are described.

Despite the disfavoured nature of the 5-*endo*-trig cyclisation mode,[1] reports of examples continue to appear in the literature.[2] In connection with our interest in synthetic methodologies underpinned by the diverse reactivity of the sulfone group,[3] we looked at 5-*endo*-trig cyclisations of vinylic sulfones **1** bearing a hydroxyl function appended to the α-position (Scheme 1).[4] The products of these reactions were tetrahydrofurans, and we demonstrated that the stereochemical outcome of ring-closure was profoundly affected by the geometry of the acceptor double bond.[5] As a natural extension of this work, we investigated the analogous formation of pyrrolidines. This appeared especially attractive, since we reasoned that by analogy with the tetrahydrofuran precursors, cyclisation substrates **2** would be available in enantiomerically pure form from α-aminoacid-derived aziridines. This Letter reports the results of these investigations.



Scheme 1

α-Aminoacids L-phenylalanine, L-leucine and L-valine were reduced to the corresponding aminoalcohols using sodium borohydride–iodine,[6] and converted into *N*-diphenylphosphinylaziridines **3** (DPP = diphenylphosphinyl) according to the method reported by Sweeney.[7] Addition of **3** to cold THF–TMEDA solutions of lithio(phenylsulfonyl)methane followed by warming to room temperature overnight gave adducts **4** in good yields. Exposure of **4** to two equivalents of strong base, and treatment of the resulting dianion solutions with benzoyl chlorides or pivaloyl chloride, followed by warming to room temperature and stoichiometric proton quench gave β-ketosulfones **5** as diastereomeric mixtures in mostly good yields.[8] Interestingly, it was observed that substantial C→N acyl transfer took place if the reaction mixtures were maintained at room temperature for excessive periods of time prior to quenching. Reduction of **5** with $NaBH_4$ and acetylation of the product alcohols gave two of the four possible diastereomeric β-acetoxysulfones **6**, to which we assign the *threo* stereochemistry in view of Julia's findings[9] and the Felkin–Anh model. The synthesis of **6** are summarised in Scheme 2 and Table 1.



Scheme 2. (i) *n*-BuLi (1 eq), THF–TMEDA (3:1, 0.4M), -78°C, add **3** (0.9 eq), -78°C→rt, 12 h; (ii) *n*-BuLi (2.1 eq), THF (0.05M), -78°C, add R^2COCl (1.3 eq), -78°C→rt, then AcOH–THF; (iii) excess $NaBH_4$, MeOH (0.1M), rt; (iv) DMAP (cat.), Et_3N (2.1 eq), Ac_2O (0.2M), rt, 2-12 h

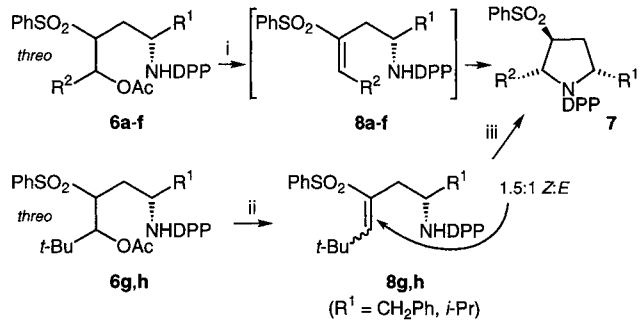
Table 1 Synthesis of cyclisation substrates **6**

Entry	R^1	R^2	yield of 4[a]	yield of 5	yield of 6[b]
a	CH_2Ph	Ph	68	82	77
b	*i*-Bu	Ph	91	60	81
c	*i*-Pr	Ph	78	70	83
d	CH_2Ph	Ar[c]	68	72	73
e	*i*-Bu	Ar[c]	91	69	92
f	*i*-Pr	Ar[c]	78	56	66
g	CH_2C_6H	*t*-Bu	68	62	41
h	*i*-Pr	*t*-Bu	78	50	71

[a]all yields are in %; [b]yields are for the two steps from **5**; [c]Ar = 3,4,5-$(MeO)_3C_6H_2$

Previous work in our laboratory[10] had shown that substrates analogous to **6** possessing *N*-tosyl groups undergo smooth elimination to *E*-vinylic sulfones on treatment with sodium hydroxide in 1,4-dioxane.[11] In the present investigation, exposure of **6a-f** to an excess of *freshly-powdered* NaOH in 1,4-dioxane led *directly* to the desired pyrrolidines **7** in good to excellent yields, and with complete selectivity. Interestingly, the use in these reactions of NaOH which had not been freshly prepared allowed isolation of the intermediate vinylic sulfones **8** exclusively as the the *E*-vinylic isomers, as evidenced by X-ray crystallographic analysis of **8f**; these could be converted into the same pyrrolidines **7** by further base treatment. Substrates **6g** and **6h** did not undergo efficient cyclisation under the conditions used for direct cyclisation of **6a-f**. Instead, treatment with potassium *tert*-butoxide in THF gave the vinylic sulfones **8g** and **8h** as mixtures of geometric isomers;[12] upon treatment with additional base under more forcing conditions these were converted respectively into pyrrolidines **7g** and **7h** in moderate and low yields respectively (Scheme 3, Table 2).

In all cases **7** were formed virtually exclusively as the 2,3-anti–2,5-syn isomers. This was inferred from the observation of characteristic n.O.e. effects, from H-5→H-2 and R^1 α-H→H-3,[13] and X-ray crystal structures of **7a**, **7b**, **7c** and **7g**.[14] The structures of **7c** and **7g** are shown in Figures 1 and 2.



Scheme 3. (i) *freshly-ground* NaOH (3 eq), 1,4-dioxane (0.1M), rt, 12 h; (ii) *t*-BuOK–THF (1M, 1 eq), THF (0.1M), rt, 12 h; (iii) *t*-BuOK–THF (1M,1 eq), THF (0.1M), reflux, 12 h

Table 2 Preparation of pyrrolidines **7**

Entry	R^1	R^2	yield of 7[a]	2,5-syn:anti ratio
a	CH_2Ph	Ph	78	>10:1
b	*i*-Bu	Ph	70	>20:1
c	*i*-Pr	Ph	95	>10:1
d	CH_2Ph	Ar[b]	67	10:0
e	*i*-Bu	Ar[b]	80	10:0
f	*i*-Pr	Ar[b]	86	10:0
g	CH_2Ph	*t*-Bu	53[c]	10:0
h	*i*-Pr	*t*-Bu	13[c]	10:0

[a]all yields are in %; [b]Ar = 3,4,5-$(MeO)_3C_6H_2$; [c]yields are for the two steps from **6**

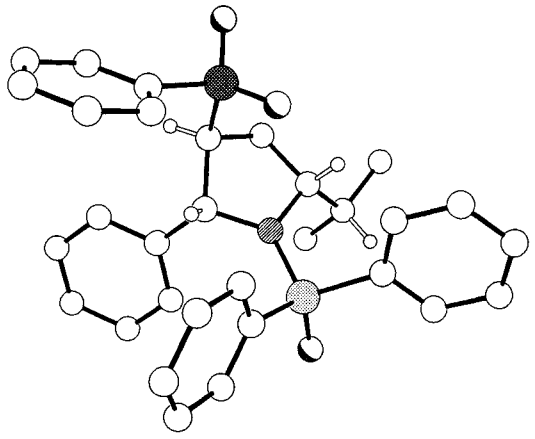


Figure 1. X-ray structure of **7c**

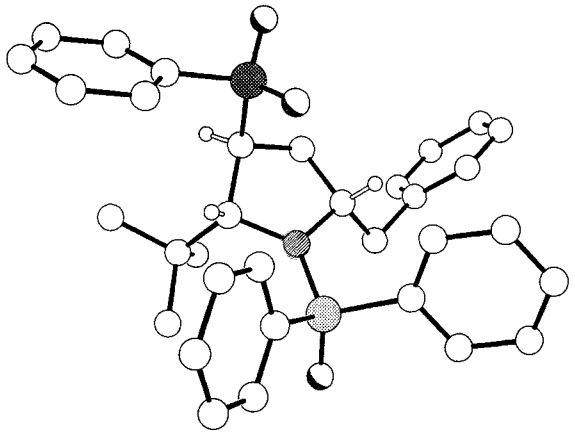
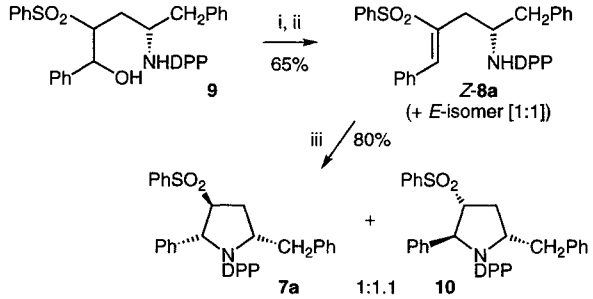


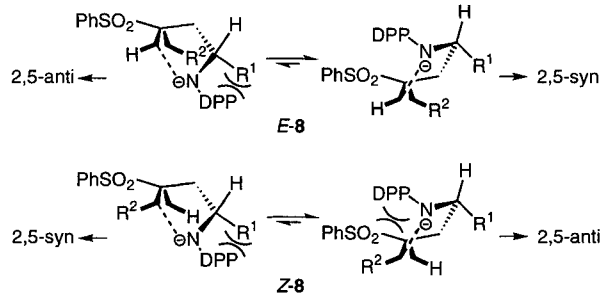
Figure 2. X-ray structure of **7g**

In view of the differing selectivities observed in the cyclisations of the different geometric isomers of oxygen analogues **1** (Scheme 1), we were keen to probe further the effect of double bond geometry on the stereochemical outcome of the pyrrolidine-forming reactions. It was already established that *E*-**8a-f** gave only 2,5-syn pyrrolidines on base-mediated cyclisation, and that *E*/*Z* mixtures of the *tert*-butyl-substituted substrates **8g,h** behaved similarly (Scheme 3), although the forcing conditions used for the latter reactions might have caused *Z*→*E* isomerisation prior to cyclisation, and the low yields obtained of **7g,h** might imply that only the *E*-isomers react. Treatment with *n*-butyllithium–tosyl chloride of the alcohols **9** - which were intermediates in the preparation of **6a** - followed by exposure of the resulting tosylates to sodium ethoxide[9] gave a separable 1:1 mixture of *E*- and *Z*-**8a**. Subjection of *Z*-**8a** to the standard cyclisation conditions gave a virtually 1:1 mixture of **7a** and the 2,3-anti–2,5-anti compound **10** clearly demonstrating the kinetically-controlled nature of the cyclisations (Scheme 4).



Scheme 4. (i) *n*-BuLi (1.05 eq), THF–TMEDA (3:1, 0.2M), -78°C, add TsCl (1.05 eq), -78°C, 10 min; (ii) EtONa (1 eq), EtOH (0.1M), rt, 20 min; (iii) NaOH (3 eq), 1,4-dioxane (0.1M), rt, 7 h

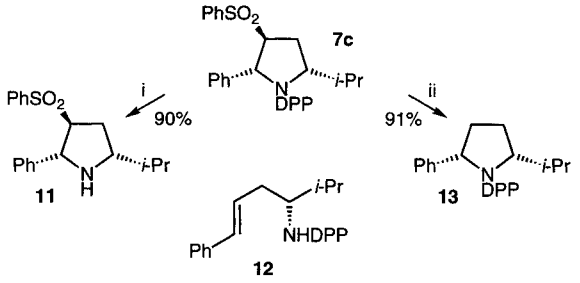
In the tetrahydrofuran-forming reactions depicted in Scheme 1, *E*-**1** give tetrahydrofuran products with poor 2,5-syn selectivity, whereas *Z*-**1** show high selectivity for the 2,5-anti products. In contrast, *E*-**8** give almost exclusively 2,5-syn pyrrolidines, and *Z*-**8** give mixtures, such that cyclisations giving pyrrolidines appear to have an inherent 2,5-syn bias. We speculate that this may be attributed to steric repulsion between the bulky diphenylphosphinyl group and either the C-2 or C-5 substituents; in *E*-**8** this is avoided if the 2,5-syn compounds are formed, whereas for the *Z*-isomers this interaction is possible for the 2,5-syn and 2,5-anti transition-states alike, and a non-selective reaction results (Scheme 5).



Scheme 5

Finally, we explored briefly some further reactions on one of the pyrrolidine products. Compound **7c** was dephosphinylated by both Lewis acid-catalysed[7(i)] and Brønsted acid-catalysed[15] methanolysis, giving the free pyrrolidine **11** in excellent yields (Scheme 6). Alternatively, **7c** could smoothly be desulfonylated to give **13** using samarium(II) iodide in THF–DMPU *in the presence of methanol*;

reactions carried out without methanol cleanly gave the product **12** of reductive ring-opening.[16]



Scheme 6. (i) HCl, MeOH, rt, 72 h, or $BF_3{\cdot}OEt_2$ (10 eq), CH_2Cl_2–MeOH (1:1, 0.09M), rt, 24 h; (ii) SmI_2 (5 eq), THF–MeOH–DMPU (12:8:1, 0.012M), -20°C, 1.5 h

In summary, we have defined a short route for the efficient, stereoselective synthesis of enantiomerically pure 2,5-disubstituted pyrrolidines.[17] The application of this chemistry to the synthesis of pyrrolidine-containing natural products will be the subject of further contributions from this laboratory.

Acknowledgements

We thank SERC/EPSRC and Roche Discovery Welwyn (CASE Studentship to G. J. R.) for financial support of this research.

References and Notes

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2. For examples of 5-*endo*-trig reactions giving rise to pyrrolidines, see: Padwa, A.; Norman, B. H. *J. Org. Chem.* **1990**, *55*, 4801-4807. For a recent report describing iodonium ion-mediated cyclisations which give pyrrolidines via overall 5-*endo*-trig cyclisation processes, see: Jones, A. D.; Knight, D. W. *Chem. Commun.* **1996**, 915-916.
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7. (i) Osborn, H. M. I.; Sweeney, J. B.; Howson, W. *Synlett* **1994**, 145-147; (ii) Osborn, H. M. I.; Cantrill, A. A.; Sweeney, J. B.; Howson, W. *Tetrahedron Lett.* **1994**, *35*, 3159-3162.
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12. Treatment of **6a-f** with potassium *tert*-butoxide–THF gave mixtures of pyrrolidines **7** and vinylic sulfones *E*-**8** in low yields.
13. We thank Mr Dick Sheppard and Mr Paul Hammerton of this department for these determinations.
14. We thank Professor David J. Williams and Dr Andrew J. P. White of this department for these determinations.
Crystal data for **7c**: $C_{31}H_{32}NO_3PS$, M = 529.6, orthorhombic, space group $P2_12_12_1$ (no. 19), a = 9.283(2), b = 15.985(2), c = 18.788(3) Å V = 2788.0(9) Å^3, Z = 4, D_c = 1.262 g cm^{-3} μ(Cu-K$_\alpha$) = 18.3 cm^{-1}, F(000) = 1120. A clear block of dimensions 0.50 x 0.40 x 0.33 mm was used. 4389 Independent reflections were measured on a Siemens P4/PC diffractometer with Cu-K$_\alpha$ radiation (graphite monochromator) using ω-scans. The structure was solved by direct methods and all the non-hydrogen atoms were refined anisotropically using full-matrix least-squares based on F^2 to give R_1 = 0.042, wR_2 = 0.109 for 4191 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 124°$] and 287 parameters. The absolute polarity was determined by use of the Flack parameter which refined to a value of -0.01(2).
Crystal data for **7g**: $C_{33}H_{36}NO_3PS{\bullet}CH_2Cl_2$, M = 642.6, orthorhombic, space group $P2_12_12_1$ (no. 19), a = 8.662(3), b = 10.842(3), c = 35.337(13) Å V = 3319(2) Å^3, Z = 4, D_c = 1.286 g cm^{-3}, μ(Cu-K$_\alpha$) = 30.7 cm^{-1}, F(000) = 1352. A clear plate of dimensions 0.27 x 0.22 x 0.04 mm was used. 2991 Independent reflections were measured on a Siemens P4/RA diffractometer with Cu-K$_\alpha$ radiation (graphite monochromator) using ω-scans. The structure was solved by direct methods and all the non-hydrogen atoms were refined anisotropically using full-matrix least-squares based on F^2 to give R_1 = 0.066, wR_2 = 0.160 for 2360 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 124°$] and 356 parameters. The absolute polarity was determined by use of the Flack parameter which refined to a value of lengths and angles, and thermal parameters for **7c** and **7g** have been deposited at the Cambridge Crystallographic Data Centre.
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17. Experimental procedure for preparation of **7c**
To a solution of (1*RS*,2*RS*,4*R*)-1-acetoxy-4-[(diphenylphosphinyl)amino]-5-methyl-1-phenyl-2-(phenylsulfonyl)hexane **6c** (2.68 g, 4.55 mmol, 1 eq) in 1,4-dioxane (46 ml, 0.1M) under a nitrogen atmosphere was added fresh, finely-ground NaOH (0.55 g, 13.66 mmol, 3 eq) with stirring. The resulting bright yellow solution was stirred at room temperature overnight. Acetic acid (9.10 ml of a 1M solution in THF, 9.10 mmol, 2 eq) was added, causing the coloration to fade. The solvent was removed under reduced pressure and the colourless, semi-solid residue adsorbed on silica gel. Chromatography (SiO_2, 20% Et_2O–CH_2Cl_2) yielded (2*R*,3*S*,5*R*)-1-diphenylphosphinyl-5-(1-methylethyl)-2-phenyl-3-(phenylsulfonyl)pyrrolidine **7c** (2.29 g, 95%) as a crystalline solid, mp 160°C; $[\alpha]_D^{27}$ -104.46 (*c* 0.87, $CHCl_3$); ν_{max} (film) 2956, 2924, 1439, 1304, 1201, 1148, 1119, 1084, 753, 726 and 699 cm^{-1}; δ_H (500 MHz) 8.10-6.83 (20H, m, Ar-H), 4.92 (1H, dd, J 6.0, 4.0 Hz, H-2), 3.94 (1H, qd, J 7.0, 4.5 Hz, H-5), 3.60 (1H, ddd, J 8.5, 5.0, 5.0 Hz, H-3), 2.44 (1H, ddd, J 13.5, 6.5, 6.0 Hz, H-4), 2.18 (1H, ddd, J 14.5, 7.5, 7.5 Hz, H-4), 1.94-1.88 (1H, m, H-1'), 1.03 (3H, d, J 6.5 Hz, Me), 0.82 (3H, d, J 6.5 Hz, Me); δ_C (75 MHz) 142.7, 137.9, 134.1, 133.1, 132.3, 132.1, 131.7, 131.4, 129.4, 128.7, 128.6, 128.2, 128.0, 127.8, 127.2, 126.3, 71.6, 66.0, 64.8, 31.4, 28.1, 20.8, 17.3; *m/z* (CI) 530 $[M+H]^+$, 486 $[M-Pr]^+$, 422, 390 $[M+2H-PhSO_2]^+$, 344, 272, 218 $[DPPNH_3]^+$, 201 $[DPP]^+$, 188, 160, 125, 78 $[PhH]^+$ (Found C, 70.58; H, 5.93; N, 2.73. $C_{31}H_{33}NO_3PS$ requires C, 70.32; H, 6.23; N, 2.65%).