N-Alkenyl Nitrone Dipolar Cycloaddition Routes to Piperidines and Indolizidines. Part 3.† Approach to the Gephyrotoxin Ring System

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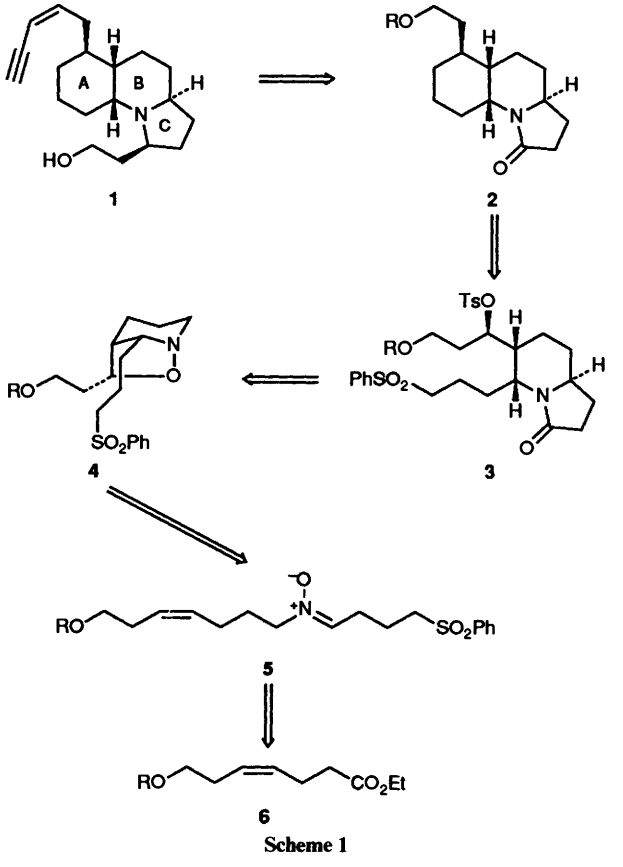
Intramolecular dipolar cycloaddition studies on the *N*-alkenyl nitrones **16**, **17**, **36** and **45** are reported. The regio- and stereo-chemistry of the product bicyclic isoxazolidines (precursors to ring B of gephyrotoxin **1**) are sensitive to the nature and geometry of the alkene dipolarophile.

Previously we have reported the use of the intramolecular thermal dipolar cycloaddition of (*Z*)-*N*-alkenyl nitrones in the synthesis of all-*cis*-2,3,6-trisubstituted piperidines[1] (and related indolizidines isolated from the Dendrobatidae family of neotropical frogs) as well as epimerisation of the C-3 substituent from *cis* to *trans*.[2–4] We considered that the methodology was amenable to more complex poison arrow alkaloids such as gephyrotoxin **1** which was one of the alkaloids isolated from skin extracts of the Colombian frog *Dendrobates histrionicus*.[5–7] It shows mild muscarinic,[8] and other interesting neurophysiological activity.[9] The structure and absolute configuration follow from X-ray crystallographic and chemical analysis,[10,11] although the rotation observed for **1** which had been synthesised by Kishi from L-glutamate was opposite to that reported for material assigned the absolute configuration **1**.[11,12] Other syntheses of gephyrotoxin have been reported by Hart[13,14] and Overman.[15]

Our planned synthesis of gephyrotoxin recognised the presence of the 2,3,6-trisubstituted piperidine ring B in which the substituent at the 6-position is *trans* to the remaining *cis* substituents at C-2 and C-3. This *cis*-relationship could be established by an intramolecular nitrone cycloaddition, while the *trans*-relationship could be established by an intermolecular cycloaddition of a suitable dipolarophile to a piperideine *N*-oxide derived from regioselective oxidation of a bicyclic isoxazolidine (Scheme 1). This strategy would establish four of the five stereocentres in gephyrotoxin and enhance the versatility of the nitrone cycloaddition strategy in alkaloid synthesis.

Our analysis (Scheme 1) showed that the A-ring might be formed by intramolecular alkylation of the anion of the indolizidinone sulfone **3** as employed by LeBel and Balasubramanian in their synthesis of pumiliotoxin C.[16] The indolizidinone could be elaborated according to Hart's formal synthesis of gephyrotoxin.[13] In the course of the preparation of compound **3** we have discovered some interesting chemistry which further delineates the mechanistic subtleties of nitrone cycloadditions. The transformation of the isoxazolidine **4** to the indolizidinone **3** and thence gephyrotoxin will be the subject of a future paper. The following discussion details our efforts to prepare the isoxazolidine **4** from nitrones of general structure **5** (in which it was hoped to use the dipolarophile's double bond geometry to control relative stereochemistry in ring B of **1**). Such nitrones **5** are available from enoates **6** by standard transformations.



Scheme 1

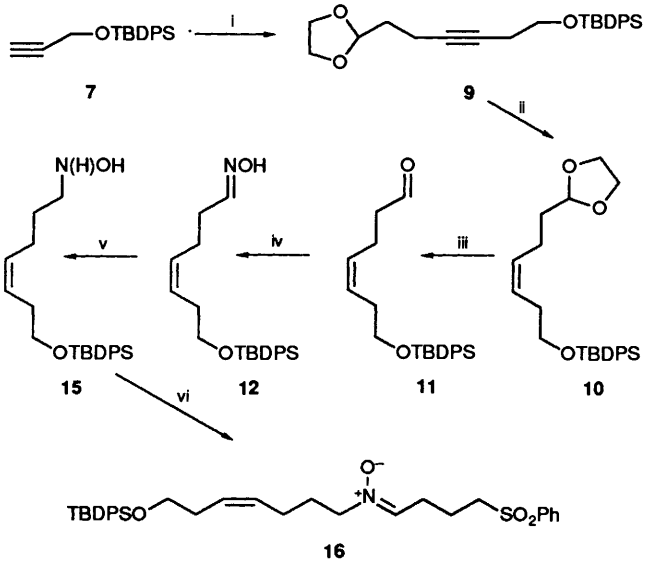
Results and Discussion

The preparation of the nitrone **5** is shown in Scheme 2. Alkylation of the butynol silyl ether **7** proceeded best by prolonged reflux in tetrahydrofuran (THF; 48 h, 56%). However, a shorter period of reflux, while resulting in a reduced yield of the dioxolane **9** (37%), did allow recovery of the starting material **7** (61%), which could then be recycled to provide a higher total conversion. Hydrogenation of the acetylene **9** over Lindlar catalyst was quantitative. The resulting (*Z*)-alkenyl dioxolane **10** (>95% *Z*-isomer as determined by ^{1}H NMR) was hydrolysed to give the crude aldehyde **11** which was stirred immediately with hydroxylamine to afford the oxime **12** as a 1:1 mixture of geometrical isomers in 61% yield from the dioxolane **10**.

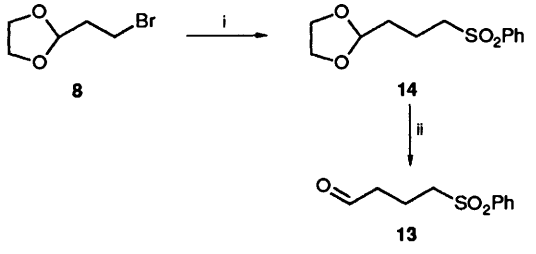
The γ-sulfonyl aldehyde **13** was also prepared from the dioxolane **8** (Scheme 3) by alkylation with the lithium anion of methyl phenyl sulfone over a long reaction time at −78 °C. However, it proved to be unstable, decomposing with time to give acrolein. It was therefore stored as the dioxolane **14** and converted into the aldehyde immediately before use.

The oxime **12** was reduced to the unstable[17,18] hydroxylamine **15** with sodium cyanoborohydride.[4] After a rapid work-up at 0 °C, a solution of the γ-sulfonyl aldehyde **13** was added. Stirring of the mixture at room temperature gave the nitrone **16**

† Part 1, ref. 2; Part 2, ref. 3.



Scheme 2 *Reagents and conditions:* i, BuLi, **8** THF, tetramethylethylenediamine (TMEDA), reflux; ii, Lindlar catalyst, H_2, EtOAc; iii, 2 mol dm^{-3} HCl, Et_2O; iv, NH_2OH·HCl, NaOAc; v, $NaCNBH_3$, aqueous MeOH, pH 3, 0 °C; vi, **13**, CH_2Cl_2, 0 °C to room temp., 12 h



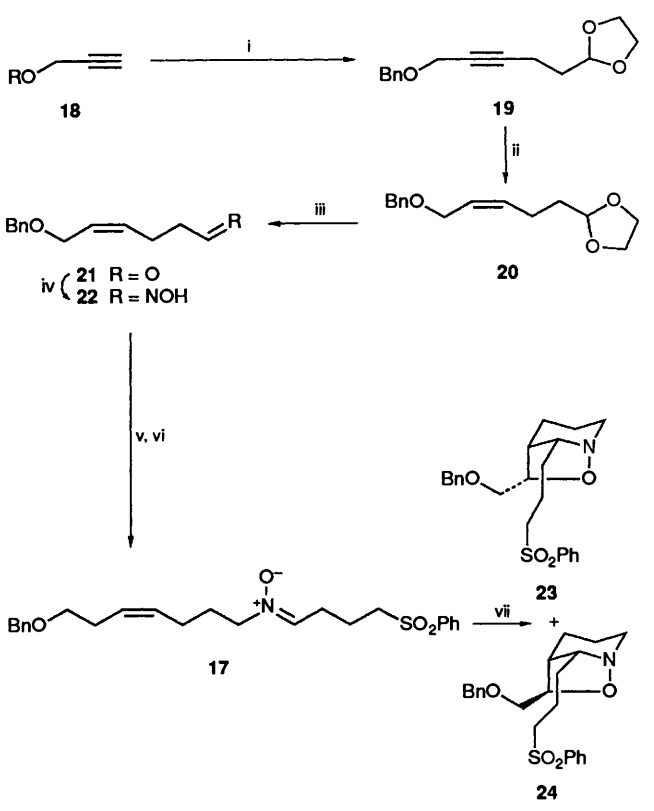
Scheme 3 *Reagents and conditions:* i, $MeSO_2Ph$, THF, BuLi, −78 °C, 6 h; ii, Et_2O, 2 mol dm^{-3} HCl

(85%). The nitrone **16** was chromatographed on silica before thermal cyclisation was attempted. However, when a solution of the purified nitrone **16** in toluene was heated at 90 °C no cyclisation or double bond isomerisation had occurred, while prolonged reaction at higher temperature (110 °C) caused decomposition. It was felt that the large active volume associated with the *tert*-butyldiphenylsilyl protecting group may prevent the nitrone **16** from folding into a reactive conformation. A reduction of this steric demand should facilitate the cycloaddition. To this end the nitrone **17** was prepared (Scheme 4).

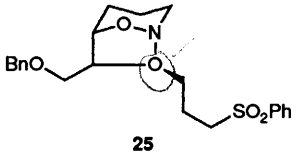
The benzyl ether **18**[19] was converted into the aldehyde **21** by an analogous method to that used to prepare the aldehyde **11**. The crude aldehyde afforded the unstable hydroxylamine by reduction of the oxime **22**. Conversion into the nitrone **17** and prolonged heating in toluene gave the isoxazolidines **23** and **24** in 20 and 13% yield respectively. However, none of the regiosomeric isoxazolidine **25** was isolated. This result, while showing that a dipolar cycloaddition was possible with these intermediates, raised some interesting mechanistic questions.

The assignment of the structure **23** follows by analogy with the results reported by LeBel.[16] The relative stereochemistry of the adduct **24** follows from the absence of vicinal coupling between the 5- and 6-H (δ_H 4.28, t, J 6) which is analogous to results obtained with the corresponding methyl analogues prepared in the synthesis of carpamic acid.[1]

It is appropriate at this point to discuss the factors affecting the nitrone cycloaddition in the light of the above result. Huisgen[20] has collated a considerable amount of chemical



Scheme 4 *Reagents and conditions:* i, BuLi, THF, 0 °C, 1.5 h, **8**, reflux; ii, Lindlar catalyst, H_2, EtOAc; iii, THF, H_2O, AcOH, 50 °C, 60 h; iv, NaOAc, NH_2OH·HCl; v, $NaCNBH_3$, aqueous MeOH, pH 3, 0 °C, vi, **13**, CH_2Cl_2, 0 °C to room temp., 2 h; vii, toluene, reflux



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evidence in support of the concertedness of dipolar cycloadditions in general. Nitrones and other dipoles are well known to provide excellent levels of stereoselectivity and predictable regiochemistry.[21] It is generally accepted that nitrone cycloadditions are concerted though asynchronous, the C–C bond being formed in advance of the C–O bond.[21a] In nitrone cycloadditions where electronic control predominates, FMO theory allows the prediction of reaction regiochemistry.[23] Intramolecular nitrone cycloadditions are not subject solely to electronic control. Other factors such as the length of the tether between the nitrone and the dipolarophile[18a] and steric considerations can play an important role in the regiochemistry of cycloaddition.[18]

There are, however, some examples of nitrone cycloadditions in which the electronic and stereochemical factors controlling the reaction are in opposition and mixtures are obtained. Oppolzer's work[18a] with intramolecular *N*-alkenylnitrone cycloadditions has demonstrated the reversal of regiochemistry achieved by placement of substituents with increasing steric bulk and differing electronic demand at specific points around the nitrone and the double bond.

N-Alkenyl nitrone cycloadditions are well precedented to occur suprafacially on the double bond of the dipolarophile.[21b] Yet it is noted that the adduct **24** is formally the product of dipolar cycloaddition to the (*E*)-double bond isomer of the nitrone **17**. It is notable that the nitrone **17** represents, to the best of our knowledge, only the second example of the use of a

(*Z*)-disubstituted dipolarophile in an intramolecular nitrone cycloaddition. The other example is the (*Z*)-hex-4-enyl side chain used in LeBel and Balasubramanian's synthesis of pumiliotoxin C.[16] Evidently the difference between that example, in which the dipolarophile bears a (*Z*)-methyl substituent, and **17** is the increased $A_{1,3}$-strain[22] which is introduced by the presence of a bulkier substituent in the transition state for the cyclisation of the nitrone **17** to the adduct **23**.

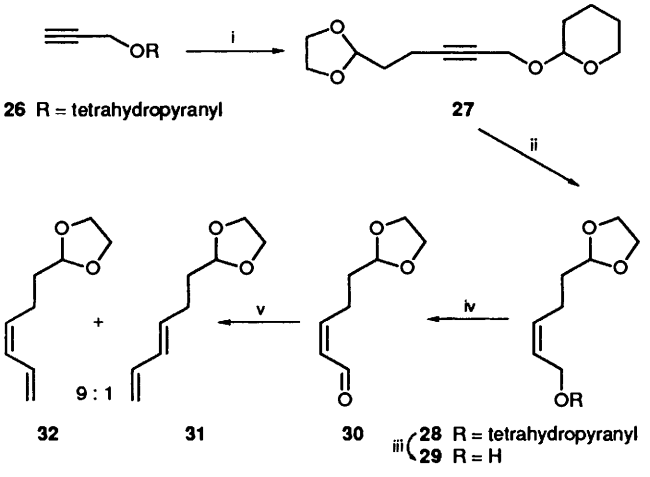
The second product **24** is formally the product of double bond isomerisation. As such, it may represent evidence of a stepwise mechanism for a nitrone cycloaddition.[24] It is also feasible that isomerisation may occur before or after concerted cycloaddition.[25] That neither of the pathways giving the isoxazolidines **23** and **24** is particularly favourable is shown by their low chemical yields (20 and 13% respectively) after prolonged reaction.

It was, therefore, apparent that a (*Z*)-substituent of even lower steric demand than the benzyloxymethyl group was required in order to facilitate the cycloaddition. The (*Z*)-dienyl nitrone **36** was, therefore, selected as the next target.

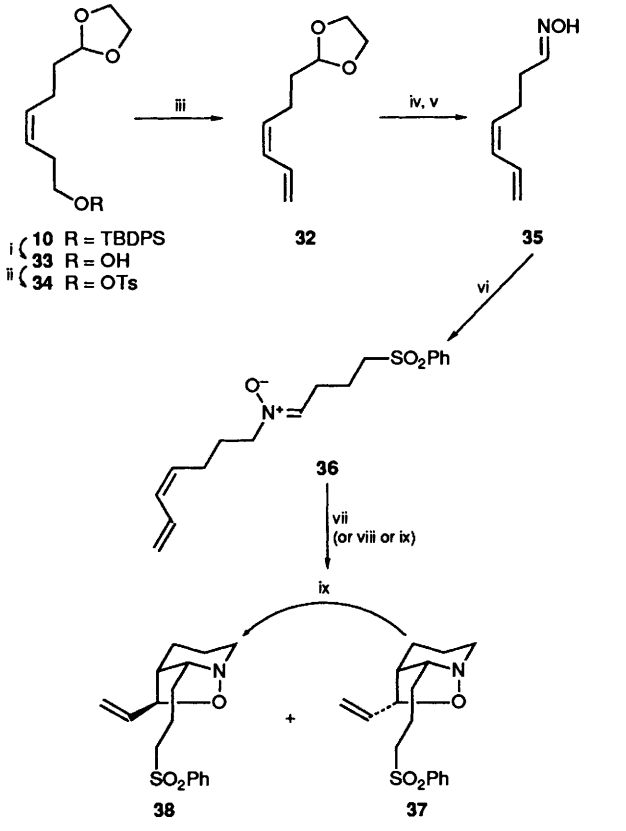
The diene **32** was prepared from prop-2-ynyl alcohol (Scheme 5). Alkylation of the THP ether **26** with the bromodioxolane **8** gave a moderate yield (52%) of the disubstituted acetylene **27**. Following Lindlar hydrogenation to give the (*Z*)-alkene **28** (98%), the THP ether could be selectively removed by transketalisation with toluene-*p*-sulfonic acid and dry methanol in 74% yield. Oxidation of the allylic alcohol **29** with activated manganese dioxide gave the unstable aldehyde **30** as a mixture of (*Z*)/(*E*)-enals. The enals **30** were methylenated by a Wittig reaction to give the dienes **31** and **32** in 95% yield in a ratio of 1:9 (^{1}H NMR) respectively. The loss of (*Z*)-double bond integrity and the instability of the enal **30** necessitated an alternative route to the (*Z*)-diene **32** that avoided the aldehyde.

Thus, the (*Z*)-alkenyl silyl ether **10** was desilylated (88%) (Scheme 6) with tetrabutylammonium fluoride (TBAF) and the resulting alcohol **33** was converted into the tosylate **34** (79%). Treatment of the tosylate **34** with potassium *tert*-butoxide in dry dimethyl sulfoxide caused elimination to afford the dienes **32** and **31** in 90% yield as a 97:3 (*Z*)/(*E*)-mixture as shown by ^{1}H NMR and GC analysis. Careful hydrolysis of the THP group of the (*Z*)-diene **32** gave the aldehyde which was not isolated but was converted as usual *via* the corresponding oxime **35** (80%; mixture of geometric isomers) into the required nitrone **36** in 82% yield from the oxime.

The cycloaddition of the nitrone **36** could be effected in refluxing benzene, toluene or xylene. In each of these solvents



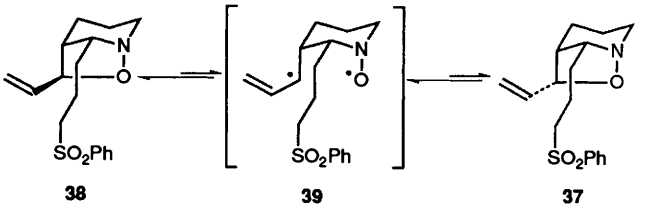
Scheme 5 *Reagents and conditions:* i, BuLi, TMEDA, THF, **8**, 0 °C to reflux, 48 h; ii, Lindlar, H_2, EtOAc; iii, TsOH, MeOH; iv, MnO_2, CH_2Cl_2, room temp., 1 h; v, CH_2=PPh_3, THF, −78 °C, 1 h



Scheme 6 *Reagents and conditions:* i, $Bu_4N^+F^-$, THF, 0 °C, 30 min; ii, pyridine, TsCl, 20 °C, 16 h; iii, KOBu^t, DMSO, 20 °C, 2 h; iv, 2 mol dm^{-3} HCl, Et_2O, 20 °C, 36 h; v, $NaHCO_3$, NaOAc, NH_2OH·HCl, H_2O, EtOH, 20 °C, 14 h; vi, $NaCNBH_3$, 6 mol dm^{-3} HCl, H_2O, MeOH; vii, benzene, reflux, 24 h; viii toluene, reflux, 24 h; ix, xylene, reflux

two C-6 epimeric isoxazolidines **37** and **38** were isolated in similar total chemical yields although in different ratios. In refluxing benzene the ratio was 7:1 in favour of the isoxazolidine **38**. This ratio was reduced to 3:1 in toluene and approached equality (1.8:1) in xylene. In one experiment the 7:1 mixture of isoxazolidines produced from a reaction in refluxing benzene was reheated to reflux in xylene. On reisolation the ratio of products had changed to that observed for the reaction of the nitrone **36** in xylene (1.8:1).

The ratio of compounds **37** and **38** obtained by equilibration in xylene is presumably a true thermodynamic ratio. The adduct **38** is formally the product of suprafacial cycloaddition to the (*E*)-isomer of the nitrone **36**. It is sterically less congested than the isomer **37**. The fact that **37** and **38** are interconvertible in refluxing xylene suggests that they are related by a pathway involving the intermediate **39** (Scheme 7). The intermediate **39** is a stabilised allyl radical which may form readily under thermolytic conditions. However, an alternative heterolytic cleavage cannot be ruled out. It is also tempting to suggest that the production of the adduct **39** is consistent with initial C–C bond formation from the nitrone **36** which may be viewed as a diradical species as proposed by Kahn, Hehre and Pople.[26] It would follow from this argument that the partitioning of the



Scheme 7

first formed intermediate **39** is kinetically controlled in benzene and toluene and only reflects thermodynamic control when sufficient activation energy is provided in refluxing xylene. Of course, it is impossible to exclude an alternative explanation in which kinetic concerted formation of **37** from the nitrone **36** is followed by equilibration between adducts **38** and **37** *via* the intermediate **39**. The least likely explanation for the formation of adduct **38** is *via* the isomerised (*E*)-isomer of the diene **36**.

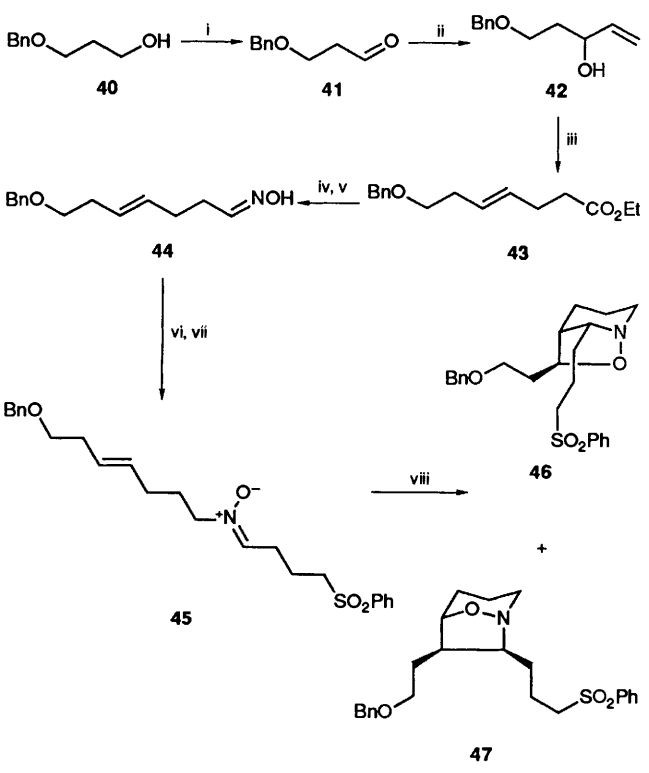
Given the difficulty of introducing the required stereocentre in the gephyrotoxin precursor **4** from a (*Z*)-alkene and the relatively facile cycloaddition possibilities with (*E*)-alkenes, it was recognised that the configuration of C-6 of the isoxazolidines (*e.g.* **37**) might be inverted to that required by, for example, a Mitsunobu reaction.[27] Furthermore, the *E*-double bond could be substituted with a functional group serving as a latent enyne sidechain. The nitrone **45** (Scheme 8) was selected for this purpose.

The required unsaturated oxime **44** was obtained from the ester **43** which was synthesised by the Johnson modification of the Claisen rearrangement.[28] The allylic alcohol **42** was prepared by cerium(III) chloride[29] mediated addition of vinylmagnesium bromide to the aldehyde **41**. This suppressed enolisation of aldehyde **41**.

Claisen rearrangement of the alcohol **42** gave the (*E*)-heptenoate **43** (89%). Reduction of the ester **43** to the corresponding aldehyde with diisobutylaluminium hydride (DIBAL) and condensation with hydroxylamine hydrochloride afforded the oxime **44**. However, for convenience, a brief work-up of the DIBAL reduction and immediate condensation of the crude aldehyde with hydroxylamine hydrochloride was at least as efficient.

The oxime **44** was converted, *via* the usual sequence, into the nitrone **45** in 91% yield. This could be cyclised in refluxing benzene to give the required isoxazolidine **46** as the sole product (54%). However, a better yield (76%) could be obtained by performing the cycloaddition in refluxing toluene. Under these conditions a second compound, the regioisomeric isoxazolidine **47** was also isolated (14%). The two isoxazolidines were not interconvertible.[30] Evidently the homoallylic benzyloxy substituent in the nitrone **45** does not encourage this equilibrium. The isoxazolidine **46** has the correct configuration at C-6 for Mitsunobu inversion[26] later in the synthesis.

In summary then, we have succeeded in preparing the isoxazolidine **46** in 46% yield over six steps from the benzyl ether **40**. In the course of the study a remarkable sensitivity to substitution at the furthest allylic centre from the nitrone function was found in a variety of intramolecular *N*-alkenyl nitrone dipolar cycloadditions. In particular, one product **24**, was isolated which may represent experimental evidence for a stepwise mechanism in a nitrone cycloaddition. Further studies toward the synthesis of gephyrotoxin **1** using the methodology introduced in this paper will be reported later.



Scheme 8 *Reagents and conditions:* i, Swern; ii, $CeCl_3$, vinyl MgBr, THF, −78 °C to −65 °C, 6 h; iii, $MeC(OEt)_3$, $EtCO_2H$ (cat.), 125 °C; iv, DIBAL, THF, −100 °C, 3 h; v, EtOH, NH_2OH·HCl, NaOAc, 30 min; vi, $NaCNBH_3$, EtOH, pH 3, −10 °C; vii, **13**, CH_2Cl_2, Na_2SO_4, 1 h; viii, toluene, reflux, 15 h

Experimental

NMR spectra were recorded using Varian EM390A, Bruker WM250 and WM400 instruments. Low and high resolution electron impact mass spectra were determined on AEI MS902 and MS30 instruments respectively. Chemical ionisation mass spectra were recorded by Dr. J. Ballantine and co-workers at the SERC Mass Spectrometry Service, Swansea. IR spectra were recorded on a Perkin-Elmer 1310 spectrophotometer, calibrated relative to polystyrene. *J* Values are recorded in Hz. Microanalyses were performed by Mr. D. Flory and staff at the Department of Chemistry, Cambridge. Melting points were determined on a Büchi 510 apparatus. Flash chromatography was carried out on Merck Kieselgel 60 (230–400 mesh). Thin layer chromatography was carried out on Merck Kieselgel 60 GF254 plates, coated to a thickness of 0.25 mm. Gas chromatography (GC) was carried out using a Carlo Erba 4130 instrument, [S.G.E. BP5 (5% phenylmethylsiloxane as stationary phase) 25 m column, diameter 0.33 mm, carrier gas flow rate 2.0 cm^3 min^{-1}]. THF refers to tetrahydrofuran distilled from potassium in a recycling still. Dimethyl sulfoxide (DMSO) was dried by distillation from calcium hydride, and stored over 4 Å molecular sieves. Ether refers to diethyl ether. Triethylamine and *N,N,N′,N′*-tetramethylenediamine (TMEDA) were dried by distillation from calcium hydride, and stored over calcium hydride or potassium hydroxide.

1-(*tert*-*Butyldiphenylsilyloxy*)*but*-3-*yne* **7**.—A solution of but-3-yn-1-ol (2.00 g, 28.6 mmol) in dry dichloromethane (40 cm^3) was treated with imidazole (4.28 g, 62.9 mmol) and *tert*-butyldiphenylsilyl chloride (8.16 cm^3, 31.5 mmol) at 0 °C. The solution was stirred at 20 °C for 2 h, poured into saturated aqueous sodium hydrogen carbonate (100 cm^3) and extracted with dichloromethane (3 × 100 cm^3). The combined organic extracts were dried (Na_2SO_4), evaporated under reduced pressure and the residue was purified by flash chromatography on silica eluting with 10% ethyl acetate–hexane to give the pure *silyl ether* **7** as a colourless liquid (8.80 g, 100%) (Found: C, 77.6; H, 7.7. $C_{20}H_{24}SiO$ requires C, 77.9; H, 7.8%); $\nu_{max}(CCl_4)/cm^{-1}$ 3300s (C≡CH) and 2120m (C≡C); δ_H(250 MHz; $CDCl_3$) 7.78–7.73 (4 H, m, ArH), 7.48–7.40 (6 H, m, ArH), 3.85 (2 H, t, *J* 7.1, CH_2O), 2.51 (2 H, dt, *J* 7.1 and 2.6, $CH_2C{\equiv}C$), 1.99 (1 H, t, *J* 2.6, C≡CH) and 1.13 (9 H, s, Bu^t); δ_C(100 MHz; $CDCl_3$) 135.5, 133.5, 129.7, 127.7, 81.4, 69.3, 62.3, 26.8, 22.6 and 19.2; *m/z* (EI) 308 (M^+, 5%), 269 (44), 251 (100), 221 (76), 211 (17) and 105 (37) (Found: M^+, 308.1622. $C_{20}H_{24}SiO$ requires *M*, 308.1597).

2-[6-(*tert*-*Butyldiphenylsilyloxy*)*hex*-3-*ynyl*]-1,3-*dioxolane* **9**.—(a) A solution of the acetylene **7** (8.00 g, 26.0 mmol) in dry

THF (50 cm^3) was treated with TMEDA (3.92 cm^3, 26.0 mmol) and butyllithium (1.60 mol dm^{-3} solution in hexane; 16.25 cm^3, 26.0 mmol) at 0 °C and the mixture was stirred for 1 h. 2-(2-Bromoethyl)-1,3-dioxolane **8** (3.66 cm^3, 31.2 mmol) was added and the solution was heated at reflux for 22 h. The solution was poured into saturated aqueous sodium hydrogen carbonate (500 cm^3) and extracted with dichloromethane (3 × 200 cm^3). The combined organic extracts were dried (Na_2SO_4), evaporated under reduced pressure and the residue was purified by flash chromatography on silica eluting with 20% ethyl acetate–hexane to afford the starting material **7** (4.86 g, 61%). Further elution gave the *acetylene* **9** (3.97 g, 37%); $\nu_{max}(CCl_4)/cm^{-1}$ 3020w (CH) and 3000w (CH); δ_H(250 MHz; $CDCl_3$) 7.71–7.68 (4 H, m, ArH), 7.44–7.35 (6 H, m, ArH), 4.96 (1 H, t, *J* 4.7, OCHO), 3.97–3.80 (4 H, m, OCH_2CH_2O), 3.75 (2 H, t, *J* 7.1, CH_2OSi), 2.47–2.39 (2 H, m, $CH_2C{\equiv}C$), 2.32–2.24 (2 H, m, $CH_2C{\equiv}C$), 1.87–1.79 (2 H, dt, *J* 7.5 and 4.8, CH_2) and 1.07 (9 H, s, Bu^t); δ_C(100 MHz; $CDCl_3$) 135.5, 133.7, 129.6, 127.6, 103.2, 80.1, 77.3, 64.8, 62.8, 33.1, 26.7, 22.9 and 19.1; *m/z* (EI) 407 (M^+ − H, 30%), 351 (45), 307 (100), 277 (28), 229 (42), 199 (100) and 183 (45) [Found: (M^+ − H), 407.2019. $C_{25}H_{31}SiO_3$ requires *M*, 407.2042].

(b) To a stirred solution of 4-(*tert*-butyldiphenylsilyloxy)but-1-yne **7** (6.0 g, 19.48 mmol) in dry THF (120 cm^3) at −5 °C was added butyllithium (1.6 mol dm^{-3} solution in hexane; 12.17 cm^3, 19.47 mmol). The resulting solution was stirred for 1.5 h and then allowed to warm to room temperature. TMEDA (2.27 g, 19.53 mmol) was added and the solution was stirred for 10 min. 2-(2-Bromoethyl)-1,3-dioxolane **8** (3.8 g, 21 mmol) was added and the solution was heated at reflux for 48 h. Saturated aqueous sodium hydrogen carbonate was added and the mixture extracted with ether (3 × 150 cm^3). The combined organic phases were dried ($MgSO_4$), filtered and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 10 ⟶ 40% ether–hexane to give the acetylene **9** as a colourless oil (4.48 g, 56%) identical with material prepared above.

2-[6-(tert-*Butyldiphenylsilyloxy*)-(Z)-*hex*-3-*enyl*]-1,3-*dioxolane* **10**.—A solution of the acetylene **9** (3.63 g, 8.90 mmol) in ethyl acetate (100 cm^3) was treated with Lindlar catalyst (500 mg, Kataly Sator type C) and stirred under a hydrogen atmosphere (1 atm) for 3 h. The solution was filtered, the filtrate evaporated under reduced pressure, and the residue was purified by flash chromatography on silica eluting with 20% ethyl acetate–hexane to give the pure *alkene* **10** as a colourless liquid (3.64 g, 100%); $\nu_{max}(CCl_4)/cm^{-1}$ 3080s (CH), 3060m (CH) and 700s (*Z*-CH=CH); δ_H(250 MHz; $CDCl_3$) 7.72–7.64 (4 H, m, ArH), 7.45–7.33 (6 H, m, ArH), 5.46–5.40 (2 H, m, CH=CH), 4.83 (1 H, t, *J* 4.8, OCHO), 3.97–3.79 (4 H, m, OCH_2CH_2O), 3.65 (2 H, t, *J* 6.9, CH_2OSi), 2.37–2.29 (2 H, m, $CH_2C{=}C$), 1.71–1.64 (2 H, m, CH_2) and 1.04 (9 H, s, Bu^t); δ_C(100 MHz; $CDCl_3$) 135.5, 133.9, 130.4, 129.5, 127.6, 126.5, 104.1, 64.8, 63.7, 33.7, 30.7, 26.8, 22.0 and 19.2; *m/z* (EI) 410 (M^+, 2%), 409 (20), 353 (15), 309 (30), 243 (40), 225 (22), 199 (92), 183 (25), 165 (38), 139 (28), 135 (22), 111 (100), 93 (40), 73 (30) and 67 (40) (Found: M^+, 410.2252. $C_{25}H_{34}SiO_3$ requires *M*, 410.227).

7-(tert-*Butyldiphenylsilyloxy*)-(Z)-*hept*-4-*enal Oxime* **12**.—A solution of the dioxolane **10** (70 mg, 0.171 mmol) and concentrated hydrochloric acid (0.3 cm^3, 2.5 mol%) in wet acetone (20 cm^3) was stirred for 30 min. Saturated aqueous sodium hydrogen carbonate was added and the mixture was extracted with ether (3 × 30 cm^3). The combined organic phases were dried ($MgSO_4$) and filtered and the filtrate was evaporated under reduced pressure. Sodium acetate (28 mg, 0.342 mmol) was added to a stirred solution of the crude aldehyde in methanol (15 cm^3) at room temperature, followed by hydroxylamine hydrochloride (24 mg, 0.345 mmol). The mixture was stirred for 12 h and then evaporated under reduced pressure. Saturated aqueous sodium hydrogen carbonate (25 cm^3) was added to the residue and the aqueous phase was extracted with dichloromethane (3 × 20 cm^3). The combined organic phases were dried ($MgSO_4$) and filtered and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 10 ⟶ 33% ether–hexane to give the *oxime* **12** as a colourless oil (1:1 mixture of geometrical isomers) (39.7 mg, 61%) (Found: C, 72.1; H, 8.3; N, 3.5. $C_{23}H_{31}NO_2Si$ requires C, 72.4; H, 8.2; N, 3.7%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3580m (OH) 3300br s (OH), 2920s (CH) and 2840s (CH); δ_H(250 MHz; $CDCl_3$) 7.68–7.64 and 7.42–7.34 (10.5 H, 2 × m, ArH and C*H*NOH), 6.75–6.65 (0.5 H, m, C*H*NOH), 5.44–5.42 (2 H, m, CH=CH), 3.65 and 3.64 (2 H, t, *J* 6.9, CH_2OSi), 2.30–2.17 (6 H, m, $CH_2CH{=}CHCH_2CH_2$) and 1.03 (9 H, s, Bu^t); *m/z* (EI) 324 (M^+ + Bu^t, 5%), 308 (11), 307 (13), 306 (54), 246 (31), 222 (12), 200 (21), 299 (100), 197 (13), 183 (14), 181 (17), 139 (15), 135 (10) and 81 (9) (Found: M^+ − Bu^t, 324.1407. $C_{19}H_{22}NO_2Si$ requires *M*, 324.1420).

2-(3-*Phenylsulfonylpropyl*)-1,3-*dioxolane* **14**.—A solution of methyl (phenyl) sulfone (11.70 g, 75 mmol) in dry THF (100 cm^3) was cooled to 0 °C under a dry nitrogen atmosphere and treated with butyllithium (1.60 mol dm^{-3} solution in hexane; 45 cm^3, 72 mmol). The resulting white suspension was stirred for 15 min at 0 °C, and then cooled to −78 °C. 2-(2-Bromoethyl)-1,3-dioxolane **8** (4.40 cm^3, 37.5 mmol) was added dropwise, and the solution was maintained at −78 °C for 6 h; it was then allowed to warm to room temperature slowly over 15 h. The reaction mixture was quenched with saturated aqueous ammonium chloride and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure; the residue was purified by flash chromatography on silica eluting with 25 ⟶ 50% ethyl acetate–hexane to give the pure 1,3-*dioxolane* **14** as a colourless liquid (7.83 g, 81%) (Found: C, 56.3; H, 6.5; S, 12.2. $C_{12}H_{16}SO_4$ requires C, 56.2; H, 6.3; S, 12.5%); ν_{max}(neat)/cm^{-1} 3060m (CH), 1300s (SO_2) and 1140s (SO_2); δ_H(250 MHz; $CDCl_3$) 7.97–7.86 (2 H, m, Ph), 7.69–7.52 (3 H, m, Ph), 4.81 (1 H, t, *J* 4.1, OCHO), 3.94–3.72 (4 H, m, OCH_2CH_2O), 3.17 (2 H, t, *J* 7.7, CH_2SO_2) and 1.99–1.61 (4 H, m, CH_2CH_2); *m/z* (EI) 255 (M^+ − H, 4%), 222 (3), 181 (3), 179 (5), 81 (6), 77 (7), 73 (100) and 67 (7).

4-*Phenylsulfonylbutanal* **13**.—A solution of the 1,3-dioxolane **14** (5.44 g, 21.2 mmol) in ether (50 cm^3) was treated with 2 mol dm^{-3} hydrochloric acid (50 cm^3) and stirred at 20 °C for 1 h. The solution was neutralised with solid sodium hydrogen carbonate, diluted with sufficient water to dissolve the salts, and then extracted with dichloromethane (1 × 200 cm^3, 3 × 100 cm^3). The combined organic extracts were dried (Na_2SO_4), evaporated under reduced pressure, and the resulting residue was subjected to the above conditions twice more to completely hydrolyse the acetal **14**. The combined organic extracts were dried (Na_2SO_4), evaporated under reduced pressure, and the residue was purified by flash chromatography on silica eluting with 50% ethyl acetate–hexane to give the pure *aldehyde* **13** as a colourless liquid (4.19 g, 93%) (Found: C, 56.3; H, 5.7; S, 15.2. $C_{10}H_{12}SO_3$ requires C, 56.6; H, 5.7; S, 15.1%); ν_{max}(neat)/cm^{-1} 3060m (CH), 2730s (CHO), 1300s (SO_2) and 1140s (SO_2); δ_H(250 MHz; $CDCl_3$) 9.72 (1 H, s, CHO), 7.92–7.84 (2 H, m, Ph), 7.70–7.52 (3 H, m, Ph), 3.14 (2 H, t, *J* 7.6, CH_2SO_2), 2.67 (2 H, t, *J* 7.2, CH_2CHO) and 2.02 (2 H, m, CH_2); *m/z* (EI) 184 (12%), 182 (5), 142 (11), 94 (11), 91 (34), 78 (72), 77 (100), 73 (16), 71 (83) and 64 (21).

(Z)-1-(tert-*Butyldiphenylsilyloxy*)-7-[N-(4-*phenylsulfonylbutylidene*)*amino*]-(Z)-*hept*-3-*ene* N-*Oxide* **16**.—A solution of

sodium cyanoborohydride (60 mg, 0.955 mmol) in methanol (4 cm^3) was added dropwise to a stirred solution of the oxime **12** (240 mg, 0.63 mmol) in methanol (20 cm^3) containing Methyl Orange indicator (3 mg) at 0 °C. Concurrently, a solution of hydrochloric acid in aqueous methanol (6 mol dm^{-3}) was added dropwise so as to maintain pH 3. After 30 min, the solution was basified with 6 mol dm^{-3} potassium hydroxide and the aqueous phase was extracted at 0 °C with dichloromethane (3 × 30 cm^3). The combined organic phases were dried ($MgSO_4$) and filtered. To the filtrate at 0 °C was added anhydrous Na_2SO_4 (2.0 g) followed by a solution of 4-phenylsulfonylbutanal **13** (267 mg, 1.26 mmol) in dry dichloromethane (2 cm^3). After 12 h the mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography on silica eluting with ethyl acetate to give the *nitrone* **16** as a colourless oil (310 mg, 85%); ν_{max}(neat)/cm^{-1} 3060m (=CH), 3000m (CH), 2920s (CH), 2840s (CH), 1590m (nitrone), 1440s (nitrone), 1300s (SO_2), 1150s (SO_2) and 700s (*Z*-CH=CH); δ_H(250 MHz; $CDCl_3$) 7.91–7.34 (15 H, m, ArH), 6.60 (1 H, t, *J* 6.0, N=CH), 5.44–5.29 (2 H, m, CH=CH), 3.74–3.62 (4 H, m, CH_2OSi and CH_2N^+), 3.15–3.07 (2 H, m, CH_2SO_2), 2.55–1.89 (10 H, m, methylene envelope) and 1.03 (9 H, s, Bu^t); *m/z* (EI) 520 ($M^+ - Bu^t$, 5%), 504 (12), 378 (8), 310 (8), 255 (12), 225 (14), 200 (21), 199 (100), 197 (12), 183 (20) and 181 (14) [Found: ($M^+ - Bu^t$), 520.2004. $C_{29}H_{34}NO_4SSi$ requires *M*, 520.1978].

Attempted Thermal Cyclisation of the Nitrone **16**.—A solution of the nitrone **16** (270 mg, 0.47 mmol) in toluene (250 cm^3) was heated under an argon atmosphere at 90 °C for 12 h. Thin layer chromatographic analysis (TLC) indicated no reaction. The temperature was raised to 110 °C and the reaction was stirred for a further 12 h. TLC indicated decomposition of the nitrone **16** and the reaction was abandoned.

5-*Benzyloxypent*-3-*ynyl*-1,3-*dioxolane* **19**.—To a stirred solution of 3-benzyloxyprop-1-yne **18** (14.9 g, 102.1 mmol) in dry THF (300 cm^3) was added butyllithium (1.60 mol dm^{-3} in hexane; 64 cm^3, 102.4 mmol) at 0 °C. The solution was stirred for 1.5 h and then allowed to warm to room temperature. TMEDA (11.85 g, 102 mmol) was added and the solution was stirred for 10 min. 2-(2-Bromoethyl)-1,3-dioxolane **8** (18.44 g, 102.2 mmol) was added and the solution was heated at reflux for 48 h. Water (100 cm^3) was added, the organic phase was separated and the aqueous phase extracted with ether (3 × 100 cm^3). The combined organic layers were dried ($MgSO_4$) and filtered and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 10 ⟶ 25% ether–hexane to give the *dioxolane* **19** as a colourless liquid (17.26 g, 69%); ν_{max}(neat)/cm^{-1} 3060w (CH), 3020m (CH), 2920s (CH) and 2860s (CH); δ_H(250 MHz; $CDCl_3$) 7.35–7.26 (5 H, m, ArH), 4.97 (1 H, t, *J* 4.7, OCHO), 4.57 (2 H, s, CH_2Ph), 4.14 (2 H, t, *J* 2.2, $CCCH_2O$), 3.99–3.82 (4 H, 2 × m, OCH_2CH_2O), 2.41–2.34 (2 H, m, $CCCH_2$) and 1.93–1.85 (2 H, m, CH_2CHO_2); δ_C(100 MHz; $CDCl_3$) 137.52, 128.27, 127.95, 127.65, 103.03, 85.98, 76.03, 71.25, 64.84, 57.55, 32.75 and 13.55; *m/z* (EI) 158 ($M^+ - C_4H_8O_2$, 4%), 155 (7), 105 (12), 92 (15), 91 (46), 86 (13), 84 (19), 77 (13), 73 (100), 70 (8) and 65 (11) [Found: ($M^+ - C_4H_8O_2$), 158.0738. $C_{11}H_{10}O$ requires *M*, 158.0732].

5-*Benzyloxy*-(Z)-*pent*-3-*enyl*-1,3-*dioxolane* **20**.—A solution of the dioxolane **19** (15.00 g, 60.98 mmol) in dry ethyl acetate (250 cm^3) was stirred with Lindlar catalyst (Kataly Sator type C, 1.5 g) at room temperature under a hydrogen atmosphere (1 atm) for 3 h. The suspension was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 10 ⟶ 25% ether–hexane to give the *dioxolane* **20** as a colourless liquid (13.8 g, 91%) (Found: C, 72.5; H, 8.0. $C_{15}H_{20}O_3$ requires C, 72.6; H, 8.1%); ν_{max}(neat)/cm^{-1} 3060w (CH), 3020m (CH), 2940s (CH), 2850s (CH) and 700m (*Z*-CH=CH); δ_H(250 MHz; $CDCl_3$) 7.35–7.25 (5 H, m, ArH), 5.74–5.59 (2 H, m, CH=CH), 4.85 (1 H, t, *J* 4.7, OCHO), 4.50 (2 H, s, CH_2Ph), 4.10–4.08 (2 H, m, OCH_2CH=CH), 4.00–3.80 (4 H, m, OCH_2CH_2O), 2.23–2.15 (2 H, m, CH=$CHCH_2$) and 1.79–1.70 (2 H, m, CH_2CHO_2); *m/z* (EI) 160 ($M^+ - C_4H_8O_2$, 6%), 157 (18), 99 (14), 92 (12), 91 (74), 80 (16) and 73 (100) [Found: ($M^+ - C_4H_8O_2$), 160.0294. $C_{11}H_{12}O$ requires *M*, 160.0288].

6-*Benzyloxy*-(Z)-*hex*-4-*enal Oxime* **22**.—A solution of the dioxolane **20** (5.00 g, 20.2 mmol) in THF–water–acetic acid (1:1:3; 25 cm^3) was stirred at 50 °C for 60 h, diluted with toluene (100 cm^3), and then evaporated to dryness under reduced pressure. The residue was diluted with saturated aqueous sodium hydrogen carbonate and the aqueous phase was extracted with dichloromethane (3 × 50 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual crude aldehyde **21** was taken up in methanol (100 cm^3) and treated with sodium acetate (3.2 g, 39 mmol). This mixture was then treated with hydroxylamine hydrochloride (2.73 g, 39.3 mmol) and stirred for 12 h at room temperature, after which the solution was evaporated under reduced pressure. Saturated aqueous sodium hydrogen carbonate (100 cm^3) was added and the aqueous phase was extracted with dichloromethane (3 × 100 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 25% ether–hexane to give the *oxime* **22** (1:1 mixture of geometrical isomers) as a colourless liquid (3.29 g, 74%); ν_{max}(neat)/cm^{-1} 3300br s (OH), 3080m (CH), 3020m (CH), 2900s (CH), 2860s (CH) and 700s (*Z*-CH=CH); δ_H(250 MHz; $CDCl_3$) 7.45–7.24 (5.5 H, m, ArH and *CH*NOH), 6.70 (0.5 H, t, *J* 5.4, *CH*NOH), 5.74–5.53 (2 H, m, CH=CH), 4.51 and 4.50 (2 H, 2 × s, CH_2Ph), 4.09–4.05 (2 H, m, OCH_2CH=CH) and 2.53–2.16 (4 H, m, CH_2-CH_2CHNOH); δ_C(100 MHz; $CDCl_3$) 151.53, 151.06, 138.12, 131.73, 131.38, 128.34, 127.60, 127.54, 127.47, 72.16, 65.49, 29.31, 24.76, 24.62 and 24.01; *m/z* (EI) 202 (M^+ − OH, 2%), 112 (23), 107 (23), 107 (12), 92 (17), 91 (100), 79 (10) and 65 (11) [Found: (M^+ − OH), 202.1236. $C_{13}H_{16}NO$ requires *M*, 202.1232].

(Z)-1-*Benzyloxy*-7-(4-*phenylsulfonylbutylideneamino*)-(Z)-*hept*-2-*ene* N-*Oxide* **17**.—A solution of the oxime **22** (300 mg, 1.37 mmol) in methanol (25 cm^3) containing Methyl Orange indicator (3 mg) at 0 °C was treated dropwise with a solution of sodium cyanoborohydride (129 mg, 2.05 mmol) in methanol (4 cm^3). The reaction mixture was also treated dropwise with a solution of hydrochloric acid in aqueous methanol (6 mol dm^{-3}) so as to maintain pH 3 during the course of the reaction. After 30 min, the solution was basified with 6 mol dm^{-3} aqueous potassium hydroxide and extracted at 0 °C with dichloromethane (3 × 50 cm^3). The combined organic phases were dried ($MgSO_4$) and filtered. To the filtrate, maintained at 0 °C, a solution of 4-phenylsulfonylbutanal **13** (435 mg, 2.05 mmol) in dry dichloromethane (4 cm^3) and anhydrous sodium sulfate (3.0 g) were added. After being stirred for 2 h the reaction mixture was evaporated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 0 ⟶ 6% methanol–dichloromethane to give the *nitrone* **17** as a colourless oil (370 mg, 65%); ν_{max}($CHCl_3$)/cm^{-1} 2930s (CH), 2840s (CH), 1590m (nitrone), 1450 m (nitrone), 1300s (SO_2) and 1140s (SO_2); δ_H(250 MHz; $CDCl_3$) 7.91–7.86 (2 H, m, SO_2Ph), 7.69–7.53 (3 H, m, $PhSO_2$), 7.34–7.25 (5 H, m, *Ph*CH_2), 6.64 (1 H, t, *J* 6.0, CH=N^+), 5.67–5.56 (2 H, m, CH=CH), 4.50 (2 H, s, $PhCH_2$), 4.07–4.01 (2 H, m, OCH_2CH=CH), 3.72–3.67 (2 H, m,

CH_2N^+), 3.16–3.04 (2 H, m, CH_2SO_2), 2.57–2.48 and 2.13–1.90 (8 H, m, methylene envelope); *m/z* (EI) 324 ($M^+ - C_7H_7$, 11%), 159 (11), 130 (10), 127 (10), 122 (10), 115 (13), 112 (12), 110 (11), 108 (13), 107 (16), 105 (11), 97 (12), 96 (13), 92 (13), 91 (100), 82 (12), 81 (13), 79 (22), 78 (22), 77 (38), 75 (13), 70 (12), 65 (13), 57 (18) and 55 (15) [Found: ($M^+ - C_7H_7$), 324.1279. $C_{16}H_{22}NO_4S$ requires *M*, 324.1269].

(5R*,6R*,8R*)-6-*Benzyloxymethyl*-8-[3-(*phenylsulfonyl*)*propyl*]-7-*oxa*-1-*azabicyclo*[3.2.1]*octane* **23** *and* (5R*,6S*,8R*)-6-*Benzyloxymethyl*-8-[3-(*phenylsulfonyl*)*propyl*]-7-*oxa*-1-*azabicyclo*[3.2.1]*octane* **24**.—A solution of the nitrone **17** (300 mg, 0.72 mmol) in toluene (50 cm^3) was heated at reflux for 5 days, cooled and then evaporated to dryness under reduced pressure. The residue was purified by flash chromatography on silica eluting with 66–100% ethyl acetate–hexane to give the *isoxazolidine* **24** as a colourless oil (40 mg, 13%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2920s (CH), 2860s (CH), 1440m, 1290s and 1130s (SO_2); δ_H(400 MHz; $CDCl_3$) 7.90–7.53 (5 H, m, $PhSO_2$), 7.34–7.24 (5 H, m, *Ph*CH_2), 4.55 and 4.46 (2 H, s × d, J_{AB} 12.1, PhCH_2), 4.28 (1 H, t, *J* 6.2, HCO), 3.46 (1 H, dd, *J* 9.8 and 6.6, OC*H*HCH), 3.38 (1 H, dd, *J* 9.8 and 5.8, OCH*H*CH), 3.31 (1 H, dd, *J* 14.2 and 6.5, 2-H_{eq}), 3.15 (1H, ddd, *J* 15.8, 10.3 and 5.5, C*H*HSO_2), 2.99 (1 H, ddd, *J* 15.8, 10.2 and 5.5, CH*H*SO_2), 2.78–2.70 (2 H, m, 2-H_{ax} and 8-H), 2.33 (1 H, br s, 5-H) and 1.94–1.24 (8 H, m, methylene envelope); δ_C(100 MHz; $CDCl_3$) 139.19, 137.93, 133.58, 129.21, 128.33, 127.95, 127.73, 127.69, 127.64, 83.44, 73.19, 72.38, 56.86, 55.91, 44.71, 31.39, 30.40, 21.00 and 18.62; *m/z* (EI) 415 (M^+, 2%), 324 (21), 274 (14), 232 (12), 126 (13), 124 (12), 98 (11), 97 (13), 96 (12), 91 (100), 82 (13), 81 11), 80 (11), 79 (12), 78 (13), 77 (23) and 65 (12) (Found: M^+, 415.1779. $C_{23}H_{29}NO_4S$ requires *M*, 415.1817). Further elution afforded the more polar *isoxazolidine* **23** as a colourless oil (60 mg, 20%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2920s (CH), 2860s (CH), 1440m, 1290s and 1130s (SO_2); δ_H(250 MHz; $CDCl_3$) 7.92–7.86 (2 H, m, SO_2Ph), 7.68–7.51 (3 H, m, $PhSO_2$), 7.34–7.23 (5 H, m, *Ph*CH_2), 4.63 and 4.52 (2 H, 2 × d, J_{AB} 12.0, PhCH_2), 4.25–4.17 (1 H, m, 6-H), 3.91–3.75 (2 H, m, OCH_2CH), 3.51–2.70 (5 H, m, 2-H_{ax}, 2-H_{eq}, 7-H and CH_2SO_2), 2.23–2.21 (1 H, m, 5-H) and 1.96–1.33 (8 H, m, methylene envelope); *m/z* (EI) 415 (M^+, 2%), 324 (26), 274 (17), 232 (15), 126 (13), 124 (11), 98 (11), 97 (13), 96 (15), 92 (11), 91 (100), 82 (12), 81 (11), 80 (10), 79 (11), 78 (11) and 77 (19) (Found: M^+, 415.1795. $C_{23}H_{29}NO_4S$ requires *M*, 415.1818).

2-*Prop*-2-*ynyloxytetrahydro*-2H-*pyran* **26**.—Prop-2-ynyl alcohol (10.0 g, 178 mmol) and dihydropyran (15.0 g, 178 mmol) were dissolved in dry dichloromethane (200 cm^3), cooled to 0 °C and treated with a catalytic amount of toluene-*p*-sulfonic acid. After 2 h, the solution was washed with saturated aqueous sodium hydrogen carbonate (200 cm^3) and the aqueous washing was extracted with dichloromethane (2 × 100 cm^3). The combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give a yellow oil which was distilled under reduced pressure to give the THP-ether **26** as a colourless liquid (21.27 g, 85%) (b.p. 82–86 °C; 30 mmHg); $\nu_{max}(CCl_4)/cm^{-1}$ 3300s (C≡CH); δ_H(400 MHz; $CDCl_3$) 4.77 (1 H, t, *J* 3.3, OCHO), 4.21 (2 H, ddd, *J* 26.1, 15.8 and 2.4, C≡C–CH_2), 3.79 (1 H, dt, *J* 9.3 and 3.1, OC*H*H), 3.51–3.46 (1 H, m, OCH*H*), 2.37 (1 H, t, *J* 2.3, C≡CH) and 1.83–1.45 (6 H, m, methylene envelope); δ_C(100 MHz; $CDCl_3$) 96.7, 79.7, 76.7, 73.9, 61.9, 53.9, 30.1, 25.2 and 18.9; *m/z* (EI) 139 ($M^+ - H$, 17%), 101 (10), 85 (100) and 56 (55) [Found: ($M^+ - H$), 139.0758. $C_8H_{11}O_2$ requires *M*, 139.0759].

2-(5-*Tetrahydro*-2H-*pyranyloxypent*-3-*ynyl*)-1,3-*dioxolane* **27**.—A solution of the THP ether **26** (6.00 g, 42.9 mmol) in dry THF (100 cm^3) at 0 °C under an argon atmosphere was treated with TMEDA (6.41 cm^3) and butyllithium (1.6 mol dm^{-3} solution in hexane; 26.8 cm^3, 42.9 mmol). The solution was stirred at 0 °C for 15 min after which 2-(2-bromoethyl)-1,3-dioxolane (6.0 cm^3, 51.5 mmol) was added, and the solution was heated at reflux for 48 h. The resulting black solution was poured into saturated aqueous sodium hydrogen carbonate (100 cm^3) and the mixture extracted with ether (3 × 100 cm^3). The combined organic layers were dried ($MgSO_4$), decolourised (charcoal), filtered and evaporated under reduced pressure to give a pale yellow oil. The residue was purified by flash chromatography on silica eluting with 9 ⟶ 20% ethyl acetate–hexane to give the pure *alkylated product* **27** as a colourless liquid (5.36 g, 52%); $\nu_{max}(CCl_4)/cm^{-1}$ 3940s (CH); δ_H(400 MHz; $CDCl_3$) 4.91 [1 H, t, *J* 4.6, OCHO (THP)], 4.75 (1 H, t, *J* 3.4, OCHO), 4.18 (2 H, ddt, *J* 36.4, 15.2 and 2.1, CH_2OTHP), 3.94–3.76 [5 H, m, OCH_2CH_2O and OC*H*H (THP)], 3.50–3.45 [1 H, m, OCH*H* (THP)], 2.35–2.29 (2 H, tt, *J* 7.6 and 2.1, CH_2C≡C) and 1.88–1.45 (8 H, m, methylene envelope); δ_C(100 MHz; $CDCl_3$) 103.1, 96.6, 85.4, 76.0, 64.9, 61.9, 54.5, 32.8, 30.2, 25.3, 19.0 and 13.6; *m/z* (EI) 155 (8%), 139 (32), 85 (30), 73 (100), 67 (20) and 55 (15) [Found (CI, NH_3): M + NH_4, 258.1712. $C_{33}H_{24}NO_4$ requires *M*, 258.1719].

2-(5-*Tetrahydro*-2H-*pyranyloxy*-(Z)-*pent*-3-*enyl*)-1,3-*dioxolane* **28**.—A solution of the acetylene **27** (4.17 g, 17.38 mmol) in ethyl acetate (50 cm^3) was treated with Lindlar catalyst (50 mg, Kataly Sator type C) and stirred under an atmosphere of hydrogen (1 atm) for 3.5 h. After that time 1 equiv. of hydrogen had been taken up and GC analysis indicated that the reaction was complete. The solution was filtered, evaporated under reduced pressure and the residue was purified by flash chromatography on silica eluting with 20% ethyl acetate–hexane to give the pure *allylic ether* **28** as a colourless liquid (4.10 g, 98%) (Found: C, 64.2; H, 9.3. $C_{13}H_{22}O_4$ requires C, 64.4; H, 9.2%); $\nu_{max}(CCl_4)/cm^{-1}$ 1655w (C=C); δ_H(400 MHz; $CDCl_3$) 5.60–5.52 (2 H, m, CH=CH), 4.82 [1 H, t, *J* 4.7, OCHO (THP)], 4.59 (1 H, t, *J*, 3.6, OCHO), 4.26–4.21 and 4.07–4.03 (2 H, 2 × m, C=CCH_2O), 3.96–3.78 [5 H, m, OCH_2CH_2O and OC*H*H (THP)], 3.50–3.44 [1 H, m, OCH*H* (THP)], 2.21–2.16 (2 H, 2 × m, CH_2C=C) and 1.82–1.46 (1 H, m, methylene envelope); δ_C(100 MHz; $CDCl_3$) 132.2, 126.5, 103.9, 97.9, 64.8, 62.6, 62.1, 33.6, 30.6, 25.4, 22.1 and 19.4; *m/z* (EI) 242 (M^+, 1%), 198 (1), 173 (2), 157 (10), 141 (20), 99 (29), 85 (45), 74 (100) and 55 (27) (Found: M^+, 242.1495. $C_{13}H_{22}O_4$ requires *M*, 242.1518).

2-[5-*Hydroxy*-(Z)-*pent*-3-*enyl*]-1,3-*dioxolane* **29**.—The allylic ether **28** (2.0 g, 8.26 mmol) in dry methanol (50 cm^3) was treated with toluene-*p*-sulfonic acid (*ca.* 10 mg) and stirred for 16 h under an argon atmosphere. The solution was poured into saturated aqueous sodium hydrogen carbonate (100 cm^3) and extracted with dichloromethane (3 × 50 cm^3). The combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure. Purification of the residue by flash chromatography on silica eluting with 50% ethyl acetate–hexane gave the pure *allylic alcohol* **29** as a colourless liquid (964 mg, 74%); $\nu_{max}(CCl_4)/cm^{-1}$ 3620m (OH), 3500br m (OH) and 1655w (C=C); δ_H(250 MHz; $CDCl_3$) 5.73–5.50 (2 H, m, CH=CH), 4.87 (1 H, t, *J* 4.9, OCHO), 4.17 (2 H, d, *J* 6.5, OCH_2C=C), 3.99–3.81 (4 H, m, OCH_2CH_2O), 2.28–2.11 (2 H, m, CH_2C=C), 1.84–1.69 (2 H, m, CH_2) and 1.66 (1 H, br s, OH); δ_C(100 MHz; $CDCl_3$) 313.3, 129.3, 103.8, 64.8, 57.9, 33.3 and 21.9; *m/z* (EI) 158 (M^+, 1%), 157 (2), 141 (3), 129 (6), 99 (23), 86 (10) and 73 (100) (Found: M^+, 158.0928. $C_8H_{14}O_3$ requires *M*, 158.0943).

2-[4-*Formyl*-(Z)-*but*-3-*enyl*]-1,3-*dioxolane* **30**.—A solution of the allylic alcohol **29** (200 mg, 1.27 mmol) in dry dichloromethane (10 cm^3) was treated with activated manganese(IV)

oxide (Aldrich Co., *ca.* 3 g) and stirred at 25 °C for 1 h. The solution was filtered, evaporated under reduced pressure, and the residue was purified by flash chromatography on silica eluting with 33% ethyl acetate–hexane to give the *unstable aldehyde* **30** (99 mg, 50%) (as a mixture of the *Z*/*E*-enals in the ratio 9:1 as determined by ^{1}H NMR of the dienes from Wittig olefination); $\nu_{max}(CCl_4)/cm^{-1}$ 1685s (C=O) and 1640w (C=C–C=O); *E*-isomer δ_H(250 MHz; $CDCl_3$) 9.49 (1 H, d, *J* 7.9, CHO), 6.88 (1 H, dt, *J* 15.6 and 6.7, CHCCO), 6.12 (1 H, ddt, *J* 15.6, 7.9 and 1.5, C=CHCO), 4.91 (1 H, t, *J* 4.4, OCHO), 4.01–3.79 (4 H, m, OCH_2CH_2O), 2.52–2.38 (2 H, m, CH_2C=C) and 1.90–1.83 (2 H, m, CH_2); *Z*-isomer δ_H(250 MHz; $CDCl_3$) 10.09 (1 H, d, *J* 8.0, CHO), 6.64 (1 H, dt, *J* 11.2 and 8.2, CH=CCO), 5.94 (1 H, ddt, *J* 11.2, 8.1 and 1.6, C=CHCO), 4.91 (1 H, t, *J* 4.4, OCHO), 4.01–3.79 (4 H, m, OCH_2CH_2O), 2.79–2.68 (2 H, m, CH_2C=C) and 1.90–1.83 (2 H, m, CH_2).

2-[(3Z)-*Hexa*-3,5-*dienyl*]-1,3-*dioxolane* **32**.—(a) A suspension of methyl(triphenyl)phosphonium bromide (502 mg, 1.40 mmol) in dry THF (6 cm^3) was treated with butyllithium (1.6 mol dm^{-3} solution in hexane, 0.8 cm^3, 1.31 mmol) under argon at 25 °C. The yellow ylide solution was stirred for 1 h prior to use. The aldehyde **30** (99 mg, 0.64 mmol) in dry THF (10 cm^3) was cooled to −78 °C under an argon atmosphere and treated dropwise with the ylide solution until a permanent yellow colour developed. The solution was stirred for 1 h at −78 °C, allowed to warm to 25 °C and the poured into saturated aqueous sodium hydrogen carbonate (25 cm^3). The mixture was extracted with dichloromethane (3 × 25 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure and the residue purified by flash chromatography on silica eluting with 20 ⟶ 50% ethyl acetate–hexane to give the *diene* **32** as a colourless liquid (94 mg, 95%). Ratio of *Z*/*E*-isomers 9:1 as determined by ^{1}H NMR.

(b) A solution of the tosylate **34** (1.05 g, 3.23 mmol) in dry DMSO (15 cm^3) was treated with potassium *tert*-butoxide (726 mg, 6.46 mmol) and stirred at 20 °C for 2 h. The solution was diluted with saturated aqueous ammonium chloride (200 cm^3) and extracted with ethyl acetate (3 × 100 cm^3). The combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure to afford a mixture of the *dienes* **31** and **32** as a colourless liquid (450 mg, 90%) (^{1}H NMR and GC analysis indicated a *Z*/*E* ratio of 97:3); $\nu_{max}(CCl_4)/cm^{-1}$ 3090m (C=CH) and 1640w (C=C); δ_H(250 MHz; $CDCl_3$) 6.65 (1 H, ddt *J* 16.8, 10.2 and 1.1, CH_2=C*H*–C=C), 6.01 (1 H, t, *J* 11.4, CH_2=CC*H*=C), 5.46 (1 H, dt, *J* 10.0 and 7.7, CH_2CH=C), 5.18 (1 H, dd, *J* 6.9 and 2.0, C*H*H=CC=C), 5.09 (1 H, d, *J* 10.2, CH*H*=CC=C), 4.86 (1 H, t, *J* 4.7, OCHO), 3.99–3.81 (4 H, m, OCH_2CH_2O), 2.37–2.20 (2 H, m, CH_2C=C) and 1.79–1.63 (2 H, m, CH_2); δ_H(100 MHz; $CDCl_3$) 132.0, 131.4, 129.6, 117.1, 103.9, 64.8, 33.6 and 22.2; *m*/*z* (EI) 154 (M^+, 4%) 153 (19), 125 (18), 112 (20), 107 (20), 99 (81), 73 (100), 67 (18) and 55 (10) (Found: M^+, 154.0994. $C_9H_{14}O_2$ requires *M*, 154.0994).

2-[(2E)-*Hexa*-2,5-*dienyl*]-1,3-*dioxolane* **31**; δ_H(250 MHz; $CDCl_3$) 6.30 (1 H, dt, *J* 16.8 and 10.2, CH_2=C*H*C=C), 6.12–6.00 (1 H, m, CH_2=CC*H*=C), 5.71 (1 H, dt, *J* 14.6 and 6.8, CH_2CH=C), 5.08 (1 H, d, *J* 15.1, C*H*H=CHCC=C), 4.96 (1 H, dd, *J* 9.6 and 1.0, CH*H*=CHC=C), 4.86 (1 H, t, *J* 4.7, OCHO), 3.99–3.81 (4 H, m, OCH_2CH_2O), 2.37–2.20 (2 H, m, CH_2C=C) and 1.79–1.63 (2 H, m, CH_2).

2-[6-*Hydroxy*-(Z)-*hex*-3-*enyl*]-1,3-*dioxolane* **33**.—A solution of the silyl ether **10** (3.26 g, 7.95 mmol) in dry THF (40 cm^3) at 0 °C was treated with tetrabutyl ammonium fluoride (1.0 mol dm^{-3} solution in THF; 8.35 cm^3, 8.35 mmol) and stirred for 30 min. The solution was poured into saturated aqueous sodium hydrogen carbonate (200 cm^3) and extracted with dichloromethane (3 × 100 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure, and the residue was purified by flash chromatography on silica eluting with 20 ⟶ 50% ethyl acetate–hexane to give the pure *alcohol* **33** as a colourless liquid (1.2 g, 88%); $\nu_{max}(CCl_4)/cm^{-1}$ 3640m (OH) and 3600m (OH); δ_H(250 MHz; $CDCl_3$) 5.57–5.46 (1 H, m, C=CH), 5.42–5.31 (1 H, m, C=CH), 4.83 (1 H, t, *J* 4.8, OCHO), 3.96–3.77 (4 H, m, OCH_2CH_2O), 3.59 (2 H, q, *J* 6.0, CH_2O), 2.34–2.26 (2 H, m, CH_2C=C), 2.22–2.13 (2 H, m, CH_2C=C), 2.02 (1 H, t, *J* 5.8, OH) and 1.73–1.64 (2 H, m, CH_2); δ_C(100 MHz; $CDCl_3$) 131.7, 126.0, 104.0, 64.8, 62.1, 33.5, 30.7 and 21.9; *m*/*z* (EI) 172 (M^+, 3%), 171 (6), 141 (33), 129 (12), 113 (20), 110 (30), 99 (23) and 73 (100) (Found: M^+, 172.1098. $C_9H_{16}O_3$ requires *M*, 172.1099).

2-[6-(p-*Tolylsulfonyloxy*)-(Z)-*hex*-3-*enyl*]-1,3-*dioxolane* **34**.—A solution of the alcohol **33** (706 mg, 4.10 mmol) in dry pyridine (10 cm^3) was treated with toluene-*p*-sulfonyl chloride (1.17 g, 6.15 mmol) and stirred at 20 °C for 16 h. The solution was poured into saturated aqueous sodium hydrogen carbonate (100 cm^3) and extracted with dichloromethane (3 × 100 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered, evaporated under reduced pressure, and the residue was purified by flash chromatography on silica eluting with 20% ethyl acetate–hexane to give the pure *tosylate* **34** as a colourless liquid (1.05 g, 79%) (Found: C, 59.1; H, 6.8. $C_{16}H_{22}SO_5$ requires C, 58.9; H, 6.8%); $\nu_{max}(CCl_4)/cm^{-1}$ 1360s (OTs), 1170s (OTs) and 675s (CH=CH); δ_H(250 MHz; $CDCl_3$) 7.75 and 7.31 (4 H, AA′BB′, *J* 8.2, OTs), 5.52–5.42 (1 H, m, C=CH), 5.28–5.17 (1 H, m, C=CH), 4.79 (1 H, t, *J* 4.7, OCHO), 3.98 (2 H, t, *J* 6.8, CH_2OTs), 4.02–3.77 (4 H, m, OCH_2CH_2O), 2.42 (3 H, s, $ArCH_3$), 2.42–2.33 (2 H, m, CH_2C=C), 2.13–2.04 (2 H, m, CH_2C=C) and 1.67–1.60 (2 H, m, CH_2); δ_C(100 MHz; $CDCl_3$) 144.7, 133.1, 132.5, 129.8, 127.8, 123.5, 103.8, 69.7, 64.8, 33.3, 26.9, 21.9 and 21.6; *m*/*z* (EI) 326 (M^+, 17%), 171 (15) and 73 (100) (Found: M^+, 326.1178. $C_{16}H_{22}SO_5$ requires *M*, 326.1188).

(4Z)-*Hepta*-4,6-*dienal Oxime* **35**.—A solution of the 1,3-dioxolane **32** (450 mg, 2.92 mmol) in ether/2 mol dm^{-3} hydrochloric acid (40 cm^3 of a 1:1 mixture) was stirred at 20 °C for 36 h. The solution was neutralised with solid sodium hydrogen carbonate. Hydroxylamine hydrochloride (609 mg, 8.76 mmol) and sodium acetate trihydrate (1.19 g, 8.76 mmol) in water (5 cm^3) were combined, and sufficient ethanol was added to give a homogeneous solution. The solution was stirred for 14 h at 20 °C and then poured into saturated aqueous sodium hydrogen carbonate (500 cm^3) and extracted with dichloromethane (3 × 200 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered, evaporated under reduced pressure and the residue purified by flash chromatography on silica eluting with 20% ethyl acetate–hexane to give recovered 1,3-dioxolane **32** (89 mg, 20%). Further elution gave the pure *oxime* **35** as a colourless liquid (292 mg, 80%) (1:1 mixture of geometrical isomers); $\nu_{max}(CCl_4)/cm^{-1}$ 3600s (OH), 3500–3100br s (OH) and 910s (vinyl CH); δ_H(250 MHz; $CDCl_3$) 9.7–9.3 and 9.3–8.9 (1 H, 2 × br s, OH), 7.42 and 6.72 (1 H, 2 × t, *J* 5.7 and 5.1, CH=N), 6.69–6.51 (1 H, m, CH_2=C*H*C=C), 6.09–5.99 (1 H, m, CH_2=CC*H*=C), 5.46–5.36 (1 H, m, CH_2CH=C), 5.24–5.10 (2 H, m, CH_2=CC=C) and 2.52–2.24 (4 H, m, CH_2CH_2); δ_C(100 MHz; $CDCl_3$) 151.7 151.3, 131.8, 130.5, 130.4, 130.0, 117.9, 29.5, 24.9, 24.8 and 24.1; *m*/*z* (EI) 125 (M^+, 10%), 108 (12), 80 (32) and 67 (100) (Found: M^+, 125.0834. $C_7H_{11}NO$ requires *M*, 125.0840).

(Z)-N-(4-*Phenylsulfonylbutylidene*)-(4Z)-*hepta*-4,6-*dienylamine* N-*Oxide* **36**.—A solution of the oxime **35** (243 mg, 1.94 mmol) in methanol (10 cm^3) under an argon atmosphere was treated with Methyl Orange indicator (5 drops), cooled to

−10 °C, and treated with sodium cyanoborohydride (200 mg, 3.2 mmol). A solution of 6 mol dm^{-3} hydrochloric acid in water/methanol was added dropwise to maintain a pink colour until the reduction was complete by TLC (*ca.* 30 min). The reaction mixture was poured into ice–brine (100 cm^3), made strongly alkaline (20% NaOH) and extracted with dichloromethane (3 × 50 cm^3). The organic extracts were added directly to a solution of 4-phenylsulfonylbutanal **13** (500 mg, 2.36 mmol) in dichloromethane (20 cm^3) containing anhydrous $MgSO_4$. The solution was stirred under argon for 2 h and filtered with the aid of Celite. The filtrate was evaporated under reduced pressure and the residue was purified by flash chromatography on silica eluting with 10% methanol–ethyl acetate to give the pure *nitrone* **36** as a viscous colourless oil (513 mg, 82%); $\nu_{max}(CCl_4)/cm^{-1}$ 3080m (CH), 1640w (diene), 1600m (diene), 1440s (nitrone), 1140s (SO_2) and 690s (*Z* − CH=CH); δ_H(250 MHz; $CDCl_3$) 7.88–7.84 (2 H, m, SO_2Ph), 7.66–7.50 (3 H, m, SO_2Ph), 6.62 (1 H, t, *J* 6.0, CH=N), 6.58–6.46 (1 H, m, CH_2CCH=C), 6.01 (1 H, t, *J* 10.9, CH_2CCH=C), 5.39–5.26 (1 H, m, CH_2CH=C), 5.16 (1 H, dd, *J* 16.8 and 1.3, CHH=CC=C), 5.07 (1 H, d, *J* 10.2, CHH=CC=C), 3.69 (2 H, t, *J* 6.8, CH_2N), 3.14–3.07 (2 H, m, CH_2SO_2), 2.56–2.48 (2 H, m, CH_2C=N), 2.23–2.14 (2 H, m, CH_2C=C) and 2.00–1.87 (2 H, m, CH_2); δ_C(100 MHz; $CDCl_3$) 138.9, 136.7, 133.8, 131.6, 130.7, 130.2, 129.4, 128.0, 118.0, 64.3, 55.7, 26.7, 25.1, 24.2 and 19.0; *m/z* (EI) 321 (M^+, 12%), 224 (30), 138 (100), 122 (28), 96 (60), 79 (92), 67 (40) and 55 (47) (Found: M^+, 321.1393. $C_{17}H_{23}NSO_3$ requires *M*, 321.1398).

(5R*,6S*,8R*)-8-(3-*Phenylsulfonylpropyl*)-6-*vinyl*-7-*oxa*-1-*azabicyclo*[3.2.1]*octane* **37**. (5R*,6R*,8R*)-8-[3-*Phenylsulfonylpropyl*]-6-*vinyl*-7-*oxa*-1-*azabicyclo*[3.2.1]*octane* **38**.—(a) A solution of the nitrone **36** (93.5 mg, 0.29 mmol) in dry benzene (20 cm^3) was heated at reflux under an argon atmosphere for 24 h using a Dean–Stark distillation head. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica eluting with 50% ethyl acetate–hexane to afford an inseparable mixture of the *cycloadducts* **37** and **38** (60.4 mg, 65%) as a colourless gum (in the ratio 1:7 by ^1H NMR); $\nu_{max}(CCl_4)/cm^{-1}$ 3040w (CH), 1430s, 1310s (SO_2), 1140s (SO_2), 1070s (C–O), 910s (vinyl CH) and 675s (Aryl CH); δ_H(250 MHz; $CDCl_3$; **37**/**38** 1:3) 7.87–7.83 (2 H + 0.6 H, m, SO_2Ph, **37** + **38**), 7.64–7.48 (1 H + 3 H, m, SO_2Ph, **37** + **38**), 6.18–6.03 (0.33 H, m, CH=CH_2, **37**), 5.86–5.72 (1 H, m, CH=CH_2, **38**), 5.33 (0.33 H, d, *J* 17.1, CHH=CH, **37**), 5.25 (0.33 H, d, *J* 10.3, CHH=CH, **37**), 5.14 (1 H, d, *J* 17.1, CHH=C, **38**), 4.99 (1 H, d, *J* 10.3, CHH=C, **38**), 4.50 (1 H, d, *J* 5.9, CH–O, **38**), 4.39 (0.33 H, t, *J* 5.6, CH–O, **37**), 3.31–2.95 (1 H + 3 H, m, CH_2SO_2 and CHN, **37** + **38**), 2.89–2.82 (0.33 H, m, CHHN, **37**), 2.78–2.70 (2 H + 0.33 H, m, CH_2N **38** + CHHN **37**), 2.33 (1 H, br s, bridgehead H, **38**), 2.16 (0.33 H, br s, bridgehead H, **37**) and 2.00–1.24 (8 H + 2.66 H, m, methylene envelope, **38** + **37**); δ_C(100 MHz; $CDCl_3$; **37**/**38** 1:3) 139.1, 138.9, 133.6, 132.4, 129.3, 128.0, 119.2, 115.8, 84.7, 82.7, 72.3, 72.1, 56.8, 56.5, 56.0, 53.5, 47.2, 45.0, 31.1, 30.4, 30.1, 25.9, 20.7, 20.3, 18.8 and 18.0; *m/z* (EI) 321 (M^+, 20%), 224 (30), 180 (11), 138 (100), 96 (58), 79 (81), 67 (28) and 55 (40) (Found: M^+, 321.1392. $C_{17}H_{23}NSO_3$ requires *M*, 321.1399).

(b) A solution of the nitrone **36** (260 mg, 0.81 mmol) in dry toluene (20 cm^3) was subjected to the same procedure as above to give an inseparable mixture of the cycloadducts **37** and **38** as a colourless gum (161 mg, 62%) (ratio 1:3 by ^1H NMR).

(c) A solution of the nitrone **36** (61.2 mg, 0.81 mmol) in dry xylene (20 cm^3) was subjected to the same procedure as above to give an inseparable mixture of the cycloadducts **37** and **38** (33.2 mg, 54%) as a colourless gum (ratio 1:1.8 by ^1H NMR).

(d) *Equilibration of the cycloadducts* **37** *and* **38**. A solution of the adducts **37** and **38** (50 mg, 0.16 mmol) (in the ratio 1:7) in dry xylene (20 cm^3) was heated at reflux under an argon atmosphere with a Dean–Stark distillation head for 24 h. The solvent was removed under reduced pressure and ^1H NMR of the residue indicated the adducts were present in the ratio 1:1.8.

3-*Benzyloxypropanal* **41**.—A solution of oxalyl chloride (3.01 cm^3, 34.4 mmol) in dry dichloromethane (100 cm^3) was cooled to −78 °C under a nitrogen atmosphere, and a solution of dry dimethyl sulfoxide (5.39 g, 68.9 mmol) in dry dichloromethane (50 cm^3) was added dropwise. The solution was stirred at −78 °C for 15 min, after which the alcohol **40**[31] (4.76 g, 28.7 mmol) in dry dichloromethane (50 cm^3) was added dropwise. Stirring was continued at −78 °C for a further 15 min, after which additional dry triethylamine (24 cm^3, 172 mmol) was added. After a further 10 min at −78 °C, the solution was allowed to warm to 20 °C and stirred at that temperature for a further 30 min. The solution was poured into saturated aqueous sodium hydrogen carbonate (200 cm^3) and the aqueous layer was extracted with dichloromethane (3 × 100 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered, evaporated under reduced pressure, and the residue was purified by flash chromatography on silica eluting with 25% ethyl acetate–hexane to give the pure *aldehyde* **41** as a colourless liquid (3.99 g, 85%); $\nu_{max}(CCl_4)/cm^{-1}$ 3080w (CH), 3060w (CH), 3030m, 2720m (CHO) and 1725s (C=O); δ_H(250 MHz; $CDCl_3$) 9.77 (1 H, t, *J* 1.9, CHO), 7.39–7.25 (5 H, m, Ph), 4.52 (2 H, s, OCH_2Ph), 3.80 (2 H, t, *J* 6.0, CH_2O) and 2.67 (2 H, dt, *J* 6.0 and 1.9, CH_2CO); δ_C(100 MHz; $CDCl_3$) 201.2 (CO), 137.9, 128.5, 127.8, 127.7, 73.2, 63.9 and 43.9; *m/z* (EI) 164 (M^+, 8%), 120 (28), 107 (100), 91 (80), 79 (22) and 65 (12) (Found: M^+, 164.0833. $C_{10}H_{12}O_2$ requires *M*, 164.0837).

1-*Benzyloxypent*-4-*en*-3-*ol* **42**.—Cerium(III) chloride heptahydrate (38.8 g, 104 mmol) was heated to 140 °C and stirred for 2 h under reduced pressure to give the anhydrous compound as a white powder. The flask was allowed to cool, dry nitrogen was admitted, and dry THF (550 cm^3) was added. The suspension was stirred for 1 h at 20 °C, cooled to −78 °C, and vinylmagnesium bromide (1.0 mol dm^{-3} solution in THF; 97 cm^3, 97.5 mmol) was added. Stirring was continued for a further 1 h, and the aldehyde **41** (10.66 g, 65 mmol) in dry THF (270 cm^3) was added dropwise. After a further 4 h at −78 °C, the reaction was allowed to warm to −65 °C for 2 h. The reaction mixture was quenched by the addition of water, allowed to warm to room temperature, poured into dilute acetic acid solution and extracted with dichloromethane (3 × 300 cm^3). The combined organic extracts were washed sequentially with brine (1 × 150 cm^3), saturated aqueous sodium hydrogen carbonate (1 × 150 cm^3) and brine (1 × 150 cm^3), dried (Na_2SO_4), filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 20% ethyl acetate–hexane to give the *allylic alcohol* **42** as a colourless oil (11.31 g, 91%); $\nu_{max}(CCl_4)/cm^{-1}$ 3620m (OH), 3520s (OH), 3080m (=CH), 3060m (=CH) and 3020s (CH); δ_H(400 MHz; $CDCl_3$) 7.42–7.29 (5 H, m, Ph), 5.96–5.88 (1 H, m, $CHCH_2$), 5.32 (1 H, dt, *J* 15.7 and 1.5, CHH=C), 5.12 (1 H, dt, *J* 10.5 and 1.5, CHH=C), 5.12 (1 H, dt, *J* 10.5 and 1.5, CHH=C), 4.56 (2 H, s, OCH_2Ph), 4.40–4.36 (1 H, m, CH–O), 3.78–3.65 (2 H, m, CH_2–O), 3.10–2.95 (1 H, br s, OH) and 1.96–1.82 (2 H, m, CH_2); δ_C(100 MHz; $CDCl_3$) 140.6, 138.0, 128.5, 127.7, 127.7, 114.4, 73.3, 71.7, 66.2 and 36.4; *m/z* (EI) 192 (M^+, 10%), 174 (23), 120 (12), 107 (43), 91 (100), 79 (17) and 68 (56) (Found: M^+, 192.1159. $C_{12}H_{16}O_2$ requires *M*, 192.1150).

Ethyl 7-*benzyloxy*-(E)-*hept*-4-*enoate* **43**.—A solution of the allylic alcohol **42** (3.14 g, 16.4 mmol) in triethyl orthoacetate (20 cm^3, 115 mmol) was treated with propionic acid (20 drops) and heated under an argon atmosphere to 125 °C, with removal of

ethanol by distillation, for 2 h. The solution was cooled and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica eluting with 5% ethyl acetate–hexane to give the pure ester **43** as a colourless liquid (3.82 g, 89%); $\nu_{max}(CCl_4)/cm^{-1}$ 1730s (C=O); δ_H(250 MHz; $CDCl_3$) 7.34–7.30 (5 H, m, Ph), 5.50–5.47 (2 H, m, CH=CH), 4.50 (2 H, s, OCH_2Ph), 4.11 (2 H, q, *J* 7.1, CO_2CH_2), 3.46 (2 H, t, *J* 6.8, CH_2O), 2.35–2.30 (6 H, m, methylene envelope) and 1.23 (3 H, t, *J* 7.1, CH_3); δ_C(100 MHz; $CDCl_3$) 173.1, 138.5, 130.2, 128.3, 127.7, 127.6, 127.5, 72.8, 70.0, 60.2, 34.2, 33.0, 28.0 and 14.2; *m/z* (EI) 262 (M^+, 10%), 216 (20), 188 (20), 175 (28), 141 (68), 113 (29), 99 (47) and 91 (100) (Found: M^+, 262.1568. $C_{16}H_{22}O_3$ requires *M*, 262.1569).

7-Benzyloxy-(E)-hept-4-enal Oxime **44**.—A solution of the ester **43** (4.07 g, 15.55 mmol) in dry THF (100 cm^3) was cooled to −100 °C under a nitrogen atmosphere, and diisobutylaluminium hydride (1.5 mol dm^{-3} solution in toluene; 31 cm^3, 46.5 mmol) was added dropwise. Stirring was continued for 3 h after which the reaction was quenched at −100 °C by the dropwise addition of saturated aqueous ammonium chloride (20 cm^3). The solution was allowed to warm to 20 °C and saturated aqueous Rochelle's salt (50 cm^3) was added. Stirring was continued for 1 h, by which time the aluminium salts had dissolved. The solution was diluted with saturated brine (100 cm^3) and extracted with ethyl acetate (4 × 100 cm^3). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give crude *heptenal* as a colourless oil (3.39 g, 100%); $\nu_{max}(CCl_4)/cm^{-1}$ 3080m (=CH), 3060m (=CH), 3030s (CH), 2800s, 2710s (CHO) and 1725s (C=O); δ_H(250 MHz; $CDCl_3$) 9.75 (1 H, t, *J* 1.6, CHO), 7.39–7.25 (5 H, m, Ph), 5.52–5.45 (2 H, m, CH=CH), 4.51 (2 H, s, OCH_2Ph), 3.48 (2 H, t, *J* 6.8, CH_2O), 2.37–2.28 (4 H, m, 2 × CH_2) and 2.15–2.07 (2 H, m, CH_2CO); δ_C(100 MHz; $CDCl_3$) 202.3, 138.5, 129.9, 128.4, 128.0, 127.6, 72.9, 69.9, 33.9, 33.0 and 26.6; *m/z* (EI) 218 (M^+, 18%), 173 (48), 107 (58), 97 (38) and 91 (100) (Found: M^+, 218.1295. $C_{14}H_{18}O_2$ requires *M*, 218.1307).

The crude aldehyde was dissolved in ethanol (50 cm^3), and a solution of hydroxylamine hydrochloride (3.04 g, 46.5 mmol) and sodium acetate trihydrate (5.95 g, 46.5 mmol) in water (50 cm^3) was added. The resulting solution was stirred at 20 °C for 30 min. The ethanol was removed under reduced pressure, and the aqueous solution was extracted with dichloromethane (3 × 50 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure and the residue was purified by flash chromatography on silica eluting with 33% ethyl acetate–hexane to give the pure *oxime* **44** as a colourless liquid (1:1 mixture of geometrical isomers) (3.50 g, 97%); $\nu_{max}(CCl_4)/cm^{-1}$ 3600s (OH), 3500–3100br s (OH), 3080w (=CH), 3060m (=CH) and 3030s (CH); δ_H(250 MHz; $CDCl_3$) 7.41 and 6.72 (1 H, 2 × t, *J* 5.3, CH=N), 7.35–7.25 (5 H, m, Ph), 5.52–5.49 (2 H, m, CH=CH), 4.51 (2 H, s, OCH_2Ph), 3.48 (2 H, t, *J* 6.8, OCH_2) and 2.49–2.16 (6 H, m, methylene envelope) (Found: M^+, 233.1429. $C_{14}H_{19}NO_2$ requires *M*, 233.1415).

(Z)-1-Benzyloxy-7-(4-phenylsulfonylbutylideneamino)-(Z)-hept-3-ene N-Oxide **45**.—A solution of the oxime **44** (3.46 g, 14.8 mmol) in ethanol (80 cm^3) was cooled to −10 °C under a nitrogen atmosphere and treated with Methyl Orange indicator (10 drops) and sodium cyanoborohydride (1.89 g, 30 mmol). Aqueous HCl (6 mol dm^{-3}) was added to maintain a light pink colouration until the reduction was complete as judged by TLC (*ca.* 30 min). The reaction mixture was treated with an excess of dilute aqueous sodium hydroxide and then filtered with the aid of Celite. The filtrate was extracted with cold dichloromethane and the cold combined organic extracts were washed with brine, dried (Na_2SO_4) and filtered into a solution of freshly prepared and purified aldehyde **13** (3.37 g, 15.9 mmol) in dichloromethane (140 cm^3) containing anhydrous Na_2SO_4. The solution was stirred under an argon atmosphere for 1 h at room temperature. Filtration of the reaction mixture and evaporation of the filtrate under reduced pressure gave an oil which was purified by flash chromatography on silica eluting with 10% methanol–ethyl acetate to afford the *nitrone* **45** as a colourless oil (5.78 g, 91%); $\nu_{max}(CCl_4)/cm^{-1}$ 3060m (=CH), 3030m (CH), 1440s (nitrone) and 1145s (SO_2); δ_H(250 MHz; $CDCl_3$) 7.91–7.84 (2 H, m, SO_2Ph), 7.67–7.49 (3 H, m, SO_2Ph), 7.36–7.23 (5 H, m, OCH_2Ph), 6.60 (1 H, t, *J* 5.9, CH=N), 5.49–5.37 (2 H, m, CH=CH), 4.48 (2 H, s, OCH_2Ph), 3.67 (2 H, t, *J* 6.7, CH_2N), 3.47 (2 H, t, *J* 6.6, CH_2O), 3.15–3.06 (2 H, m, CH_2SO_2), 2.55–2.47 (2 H, m, CH_2C=N), 2.33–2.23 (2 H, m, CH_2C=C) and 2.06–1.85 (6 H, m, methylene envelope); δ_C(100 MHz; $CDCl_3$) 138.9, 138.3, 136.5, 133.8, 131.8, 130.1, 129.3, 128.4, 128.3, 127.9, 127.6, 72.8, 69.9, 64.4, 55.6, 32.9, 29.1, 26.5, 24.9 and 18.9; *m/z* (EI) 429 (M^+, 12%), 412 (18), 338 (25), 246 (18) and 91 (100) (Found: M^+, 429.1976. $C_{24}H_{31}NSO_4$ requires *M*, 429.1974).

(5R,6S*,8R*)-6-[2-Benzyloxyethyl]-8-(3-phenylsulfonylpropyl)-7-oxa-1-azabicyclo[3.2.1]octaine* **46** *and (5S*,6R*,7S*)-6-(2-Benzyloxyethyl)-7-(3-phenylsulfonylpropyl)-8-oxa-1-azabicyclo[3.2.1]octane* **47**.—(a) A solution of the nitrone **45** (108 mg, 0.252 mmol) in dry benzene (20 cm^3) was refluxed under an argon atmosphere for 48 h using a Dean–Stark distillation head. The solution was evaporated under reduced pressure and the residue was purified by flash chromatography on silica eluting with 50–66% ethyl acetate–hexane to give, as the sole product, the *adduct* **46** as a pale yellow oil (58.7 mg, 54%); $\nu_{max}(CCl_4)/cm^{-1}$ 3060m (CH), 3030m (CH), 1440s and 1150s (SO_2); δ_H(250 MHz; $CDCl_3$) 7.89–7.85 (2 H, m, SO_2Ph), 7.65–7.49 (3 H, m, SO_2Ph), 7.31–7.24 (5 H, m, CH_2Ph), 4.47 and 4.44 (2 H, 2 × d, J_{AB} 12.0, OCH_2Ph), 4.17 (1 H, t, *J* 7.0, CH–O), 3.50 (2 H, t, *J* 6.4, CH_2OBn), 3.31–3.04 (3 H, m, CH_2SO_2 and CHN), 2.79–2.68 (2 H, m, CH_2N), 2.27 (1 H, br s, 5-H), 1.91–1.75 (6 H, m, methylene envelope), 1.73–1.54 (2 H, m, CH_2) and 1.44–1.36 (2 H, m, CH_2); δ_C(100 MHz; $CDCl_3$) 139.0, 138.2, 133.5, 129.2, 128.2, 127.9, 127.5, 127.5, 81.8, 73.0, 72.2, 67.5, 56.8, 55.9, 46.5, 35.9, 31.5, 30.3, 21.2 and 18.6; *m/z* (EI) 429 (M^+, 30%), 412 (20), 338 (52), 288 (18), 246 (35), 140 (38) and 91 (100) (Found: M^+, 429.1977. $C_{24}H_{31}NSO_4$ requires *M*, 429.1973).

(b) A solution of the nitrone **45** (7.39 g, 17.2 mmol) in dry toluene (500 cm^3) was refluxed under an argon atmosphere for 15 h using a Dean–Stark distillation head. The solution was concentrated under reduced pressure and the residue purified by flash chromatography on silica eluting with 50% ethyl acetate–hexane to give pure adduct **46** as a pale yellow oil (5.6 g, 76%). Further elution with ethyl acetate gave the more polar *title compound* **47** as a pale yellow oil (1.00 g, 14%); $\nu_{max}(CCl_4)/cm^{-1}$ 3060w (CH), 3030w (CH), 1440m and 1150s (SO_2); δ_H(250 MHz; $CDCl_3$) 7.92–7.86 (2 H, m, SO_2Ph), 7.68–7.51 (3 H, m, SO_2Ph), 7.38–7.23 (5 H, m, CH_2Ph), 4.50 and 4.45 (2 H, 2 × d, J_{AB} 11.9, OCH_2Ph), 4.36 (1 H, t, *J* 5.8, CH–O), 3.55 (2 H, t, *J* 6.8, CH_2OCH_2Ph), 3.17 (2 H, br t, *J* 7.1, CH_2SO_2), 3.10 (1 H, br s, CHN), 3.05–2.96 (1 H, m, CHH–N), 2.89–2.77 (1 H, m, CHH–N), 2.06 (1 H, br s, CHCH–O), 1.96–1.66 (8 H, m, methylene envelope) and 1.44–1.34 (2 H, m, CH_2); δ_C(100 MHz; $CDCl_3$) 138.9, 138.3, 133.7, 129.3, 128.3, 128.0, 127.6, 127.5, 81.9, 73.1, 67.1, 63.3, 55.9, 47.7, 43.1, 35.8, 25.2, 21.3, 20.9 and 17.9; *m/z* (EI) 429 (M^+, 15%), 428 (21), 412 (11), 352 (18), 338 (48), 308 (22), 246 (73), 140 (38), 124 (39), 107 (31) and 91 (100) (Found: M^+, 429.1949. $C_{24}H_{31}NSO_4$ requires *M*, 429.1974); hydrogen oxalate salt, m.p. 129–130 °C (Found: C, 59.9; H, 6.5; N, 2.6. $C_{26}H_{33}NSO_8$ requires C, 60.1; H, 6.4; N, 2.7%).

(c) A solution of the adduct **47** (895 mg, 2.09 mmol) in dry

toluene (500 cm^3) was heated at reflux under an argon atmosphere for 24 h using a Dean–Stark head. TLC analysis of the reaction mixture indicated that isomerisation had not taken place.

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