N-Alkenyl Nitrone Dipolar Cycloaddition Routes to Piperidines and Indolizidines. Part 5.† Preparation of a Gephyrotoxin Precursor

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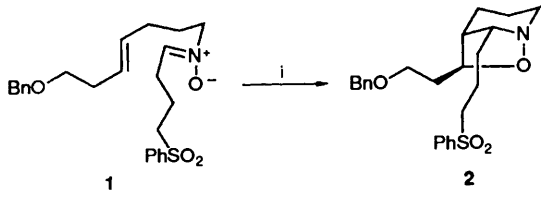
The synthesis of the B/C indolizidine ring skeleton of the alkaloid gephyrotoxin **3** is described. The route involved oxidative cleavage of the racemic bicyclic isoxazolidine **2** to form the nitrone **4** and its dipolar addition with methyl acrylate to give the adduct **7**. Reductive cleavage of **7** and cyclisation gave the lactam **21** which was deoxygenated and converted into the toluene-*p*-sulfonate **37**. Attempts to effect the intramolecular sulfone alkylation of **37** to form ring A of gephyrotoxin are summarised.

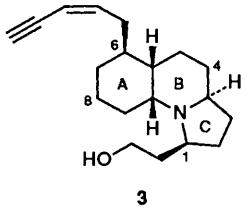
In a previous paper[3] we detailed the synthesis of the racemic isoxazolidine **2** by the intramolecular cycloaddition of the (*E*)-*N*-alkenyl nitrone **1** (Scheme 1). The isoxazolidine **2** is a key intermediate in our approach to the synthesis of the alkaloid gephyrotoxin **3**.



1 **2**

Scheme 1 *Reagents and conditions:* i, toluene, reflux, 15 h

In this paper we describe the conversion of the isoxazolidine **2** into the toluene-*p*-sulfonate **37** containing the B/C indolizidine ring portion of gephyrotoxin *via* an intermolecular nitrone cycloaddition. We also describe attempts to form the A-ring of gephyrotoxin by a stereoselective intramolecular sulfone alkylation.



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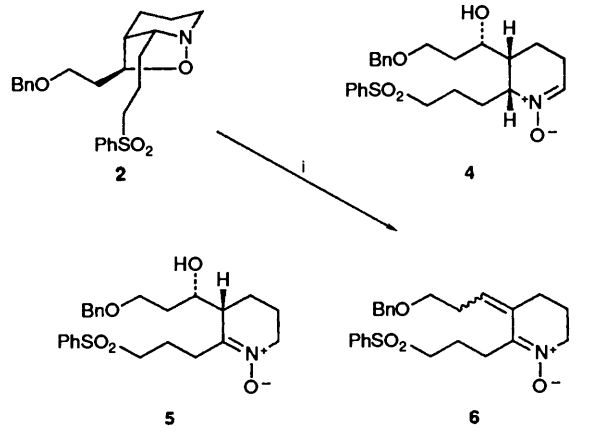
Results and Discussion

Our strategy called for dipolar addition of a suitable carbon fragment to the cyclic nitrone **4** which we expected to generate by oxidative cleavage of the isoxazolidine **2** (Scheme 2). We have previously communicated the results of a study on the oxidative cleavage of the isoxazolidine **2**, in which a variety of oxidants were employed.[5] The cleavage was complicated by production of the regioisomeric nitrone **5**. The reaction with *meta*-chloroperoxybenzoic acid (MCPBA) was found to give the nitrone **4**, although the regioselectivity was still highly variable.[6] As the nitrone **4** could be separated from the nitrone **5** by flash chromatography on silica, multigram quantities of pure material could be obtained. In contrast, use of magnesium monoperoxyphthalate (MMPP) as the oxidant resulted in only a moderate yield of the nitrone **5**. Other oxidants such as trifluoroperacetic acid and potassium monoperoxysulfate (Oxone®) also resulted in low yields of the nitrone **5**. Reaction with Oxone® resulted in dehydration of the nitrone **5** to give the unsaturated nitrone **6** for which the exocyclic double bond stereochemistry is unknown.

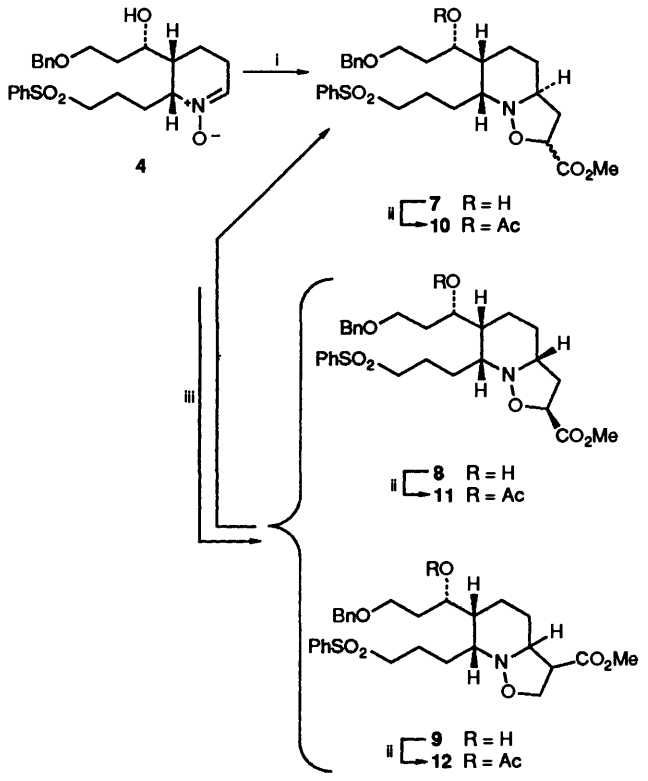


Scheme 2 *Reagents and conditions:* i, 85% MCPBA, CH_2Cl_2, room temp. For other oxidants see ref. 5 and Experimental section

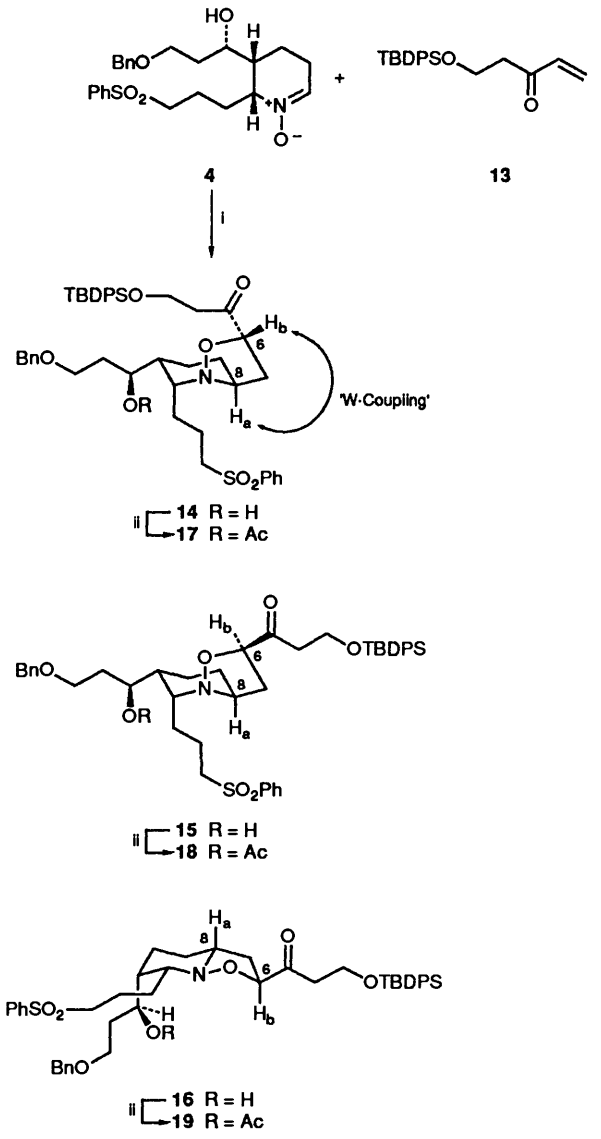
In order to introduce the remaining three carbon atoms required for indolizidine construction, the nitrone **4** was heated in refluxing benzene with methyl acrylate to give the three intermolecular cycloadducts **7**, **8** and **9** (Scheme 3). The minor product **9** (3%) was the regioisomer of adducts **7** and **8** in which the dipole oxygen had become attached to the β-carbon of the acrylate arising from the less favoured combination of HOMO (dipole)—LUMO (dipolarophile).[7] This was evident from the ^{1}H NMR spectra of the compound **9** and its acetate **12**. The other two adducts **7** (49%) and **8** (42%) were isolated in approximately a 1:1 ratio, indicating that there was essentially no preference for approach of the dipolarophile to either face of the nitrone during cycloaddition. The required adduct **7** was found to be a mixture of *endo*/*exo* diastereoisomers. However, this was of no consequence as the stereocentre carrying the methoxycarbonyl group was to be removed at a later stage in the synthesis.

The assignment of the ^{1}H NMR spectra of the adducts **7**–**9** was difficult, and the same problems were encountered in the ^{13}C NMR spectra. However, acetylation of the hydroxy groups greatly facilitated the structural elucidation. The key features of the ^{1}H NMR spectra of the mixture of acetates **10** and of **11** were very similar to those of the acetate esters **17**–**19** whose NMR spectra are described in some detail later. In particular, the proton alpha to the acetate in **10** appeared at δ 4.92 (t, *J* 8.3

† Part 1: Ref. 1. Part 2: Ref. 2. Part 3: Ref. 3. Part 4: Ref. 4.



Scheme 3 *Reagents and conditions:* i, methyl acrylate, benzene, reflux; ii, pyridine, Ac_2O, *N*, *N*-dimethyl-4-aminopyridine (DMAP); iii, methyl acrylate, toluene, reflux



Scheme 4 *Reagents and conditions:* i, benzene, reflux; ii, pyridine, Ac_2O, DMAP

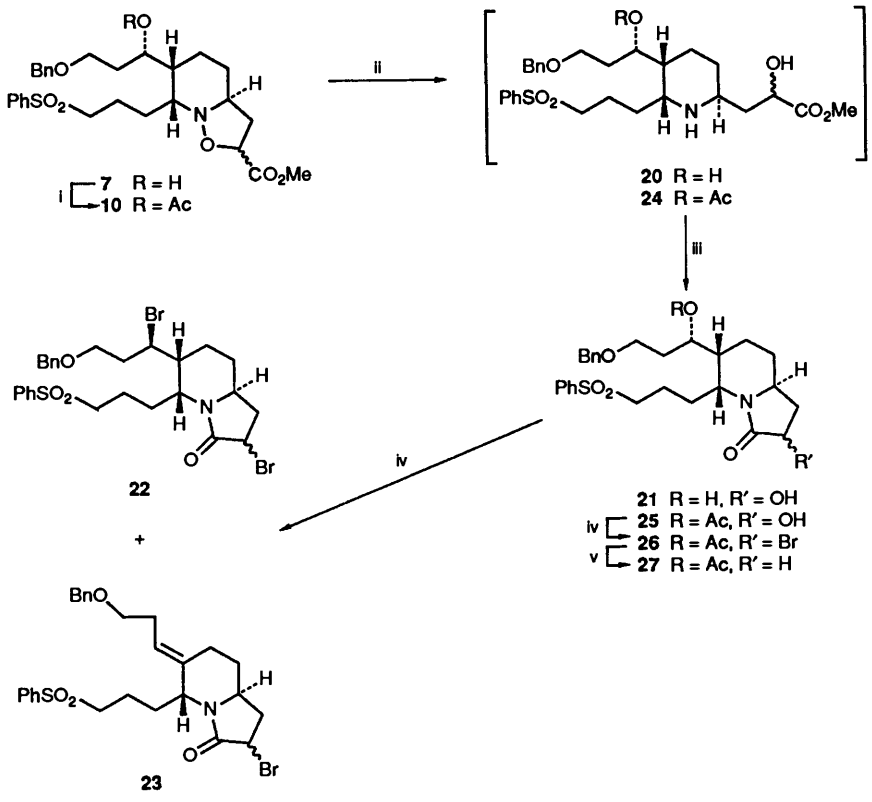
Hz) which resembled **17** and **18**, and similarly, the corresponding proton of the acetate **11** occurred as a broad singlet at δ 5.25, resembling **19**. This provides strong support for these compounds having the corresponding stereochemical relationships. Furthermore, adducts **7** were *proven* to be epimeric at the centre alpha to the isoxazolidine oxygen atom by their conversion into a single epimer upon removal of this chiral centre by deoxygenation (see Scheme 5). No information is available on the stereochemistry of the regioisomer **9** (which is a minor product), but the ^1H NMR signals at δ 3.98 and 3.84 in the acetate **12** clearly identify it as having a CH_2 group adjacent to oxygen.

The dipolar cycloaddition of methyl acrylate to **4** is reversible and the mixture of adducts **8** and **9** could be equilibrated in refluxing toluene in the presence of methyl acrylate to afford a mixture of all three adducts. By this recycling procedure, the overall conversion of **4** into the diastereoisomers **7** was reproducibly 75–80%.

It is worth noting that the acrylate dipolarophile does not possess the two carbons of the gephyrotoxin C-1 hydroxyethyl sidechain. The silyloxypentenone **13** seemed to be an attractive dipolarophile for the intermolecular cycloaddition, as it would introduce the desired two carbon fragment in a suitable form for further elaboration. The pentenone **13** was readily prepared from propane-1,3-diol by monosilylation, Swern oxidation,[8] vinyl Grignard addition and a Jones oxidation.[10]

In practice, reaction of the nitrone **4** with the enone **13** (Scheme 4) was not straightforward. Three cycloadducts **14**, **15** and **16** were isolated in a 1:1:1 ratio (80% yield); however, the adducts were not separable by TLC and tentative assignment of their structures was only possible after the corresponding acetates **17**, **18** and **19** had been prepared. Based upon a careful examination of the ^1H NMR spectra of the three acetates the structures were assigned with reasonable confidence as shown in Scheme 4. All three acetates showed a single proton H_b alpha to the isoxazolidine oxygen, ruling out the presence of mixtures of regioadducts. Of the three acetates, only compound **17** showed a weak coupling between protons H_a and H_b. (Irradiation of the broad signal at δ 4.22 due to H_b resulted in slight sharpening of the broad signal at δ 2.50 due to H_a and *vice versa*. The coupling became obvious in the decoupled-difference spectra.) Furthermore, the corresponding signals for H_b in **18** and **19** were much sharper. Such a 'W-coupling' as observed for **17** would only be expected in a compound in which these two protons are *cis* to one another. Otherwise, the spectra of compounds **17** and **18** are very similar, and evidence will be presented that they are, in fact, epimeric at the isoxazolidine side chain. However, the spectrum of compound **19** is radically different from those of compounds **17** and **18**. In particular, the proton alpha to the acetate is markedly different; this appears at δ 4.96 (dt, *J* 2.9, 8.8) in compound **18** and δ 4.94 (t, *J* 6.2) in compound **17**, but as a broad singlet at δ 5.25 in compound **19**. This is consistent with the assumption that the side chain bearing the acetate will adopt an axial orientation in the *cis*-2,6-substituted piperidine **19**, but will prefer the equatorial orientation in the *trans*-2,6-substituted piperidines **17** and **18**, respectively.

No conclusive evidence is available that the *cis*- and *trans*-2,6-substituted piperidines have been correctly identified, but the circumstantial evidence is strong. Firstly, addition of the



Scheme 5 *Reagents and conditions:* i, pyridine, Ac_2O, DMAP; ii, Zn dust, AcOH, H_2O, heat, 2 h; iii, EtOAc, heat, 2 h; iv, CBr_4, PPh_3, CH_2Cl_2; v, Bu_3SnH, azoisobutyronitrile (AIBN) (cat.), toluene, reflux, 2 h

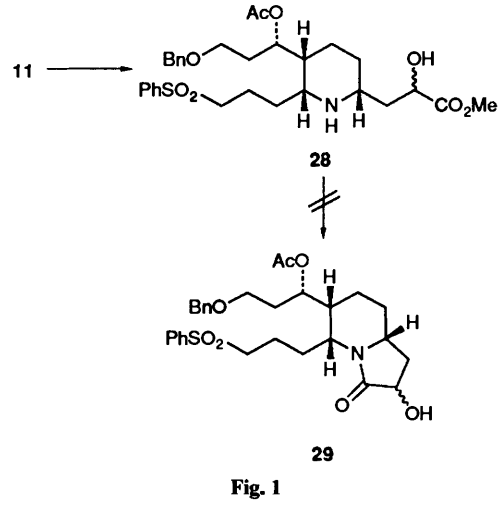


Fig. 1

dipolarophile from the less hindered face of the nitrone **4** would be expected to be favoured on steric grounds, giving rise mainly to the *trans* compound. Facial selectivity was observed here, although it was not very large (*ca.* 2:1) suggesting that the compounds **17** and **18** are indeed the *trans*-compounds. Secondly, of the four possible stereoisomers from the cycloaddition reaction, the one which is not observed is postulated to be the adduct resulting from addition to the more crowded face of the nitrone **4** *via* an *endo* transition state. Such a transition state would result in a severe steric interaction between the bulky *tert*-butyldiphenylsilyl group and the two pendant side chains of the nitrone **4**. The steric interaction of the *tert*-butyldiphenylsilyl group with the side chains of nitrone **4** is far less severe in the remaining three transition states. If this hypothesis is correct, then compound **19** must be the *cis*-2,6-substituted piperidine, and compounds **17** and **18** are the *trans*-2,6-substituted piperidines.

The assigned structures of the acetates revealed that stereocontrol in the cycloaddition was poor. The preference for the dipolarophile to approach the nitrone from the less hindered face, as determined from the configuration at C-6, was of the order 2:1 (the ratio of the sum of the adducts **14** and **15** to adduct **16**). However, there was no *endo*/*exo* selectivity, represented by the 1:1 ratio of the adducts **14** and **15**. In this cycloaddition, control of the configuration at C-8 is vital for obtaining the gephyrotoxin C-1 side chain in the correct relative orientation. Hence, of the three adducts isolated, only **14**, which was obtained in approximately 26% yield was synthetically useful. We therefore decided to continue the synthesis by pursuing the simpler intermolecular cycloaddition outlined in Scheme 3.

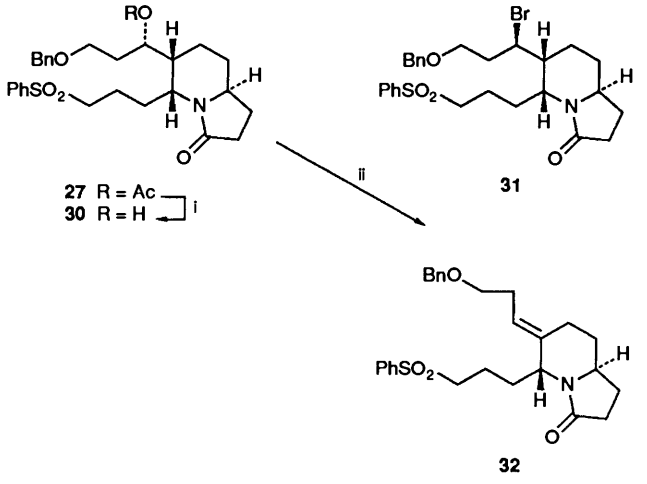
Reductive cleavage of the isoxazolidine **7** (Scheme 5) and cyclisation of the resulting intermediate amino diol **20** gave the hydroxy lactam **21**. Bromination of compound **21** with phosphorus tribromide resulted in decomposition, but use of carbon tetrabromide and triphenylphosphine gave the required dibromide **22** (57%) together with the dehydrobrominated derivative **23** (16%). The stereochemistry of the alkene double bond in **23** was not established, but is assumed to adopt the less crowded configuration. The low conversion into the dibromide **22** and the loss of material to the alkene **23** necessitated a less ambitious way to achieve the removal of the C-2 hydroxy and inversion of the sidechain hydroxy group.

The solution was to acetylate the cycloadduct **7** and then to proceed with formation of the lactam and removal of the hydroxy group. The acetate **10** (Scheme 5), prepared by standard conditions, was reductively cleaved with activated zinc dust in acetic acid, and the crude amino alcohol **24** was heated to reflux in ethyl acetate to afford the α-hydroxy lactam **25** in excellent yield (88%). Monobromination, using carbon tetrabromide and triphenylphosphine, gave the diastereoiso-

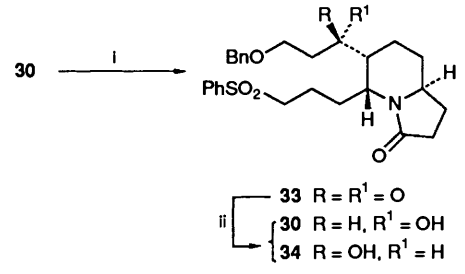
Table 1 Attempted intramolecular cyclisation of the sulfone **37** to the tricyclic lactam **38**

Entry	Base	Equiv.	Solvent	Additive	Temp. regime (°C)	Quench	Result
1	BuLi	1.2	THF	HMPA[b]	−100 → −78 → room temp.	—	NR[a]
2	BuLi	1.0	THF	HMPA	−100 → −78 → room temp.	$[^2H_4]$AcOH	NR
3	Bu^{s}Li	1.2	THF	HMPA	−100 → −78 → room temp.	$[^2H_4]$AcOH	NR
4	KHMDS[c]	2.2	THF	—	−100 → −78	—	Decomp.
5	BuLi Bu^{t}Li	1.0 2.0	THF	—	−94 → −78 → room temp.	$[^2H_4]$AcOH	Decomp.
6	LDA	2.0	THF	—	−78 → room temp.	H_2O	**39**

[a] NR refers to no reaction. [b] Hexamethylphosphoric triamide. [c] Potassium hexamethyldisilazide.



Scheme 6 *Reagents and conditions:* i, K_2CO_3, MeOH; ii, CBr_4, PPh_3



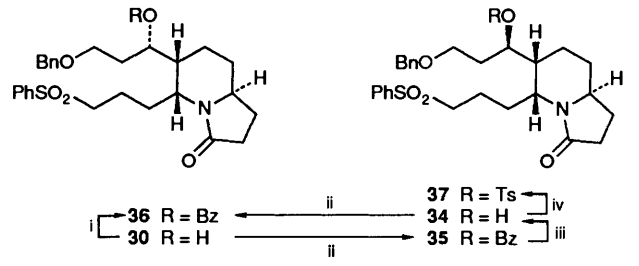
Scheme 7 *Reagents and conditions:* i, Jones' reagent, acetone; ii, $NaBH_4$, EtOH, 0 °C

meric bromides **26** (89%) which were debrominated with tributyltin hydride (Bu_3SnH)–AIBN to afford the lactam **27** (93%).

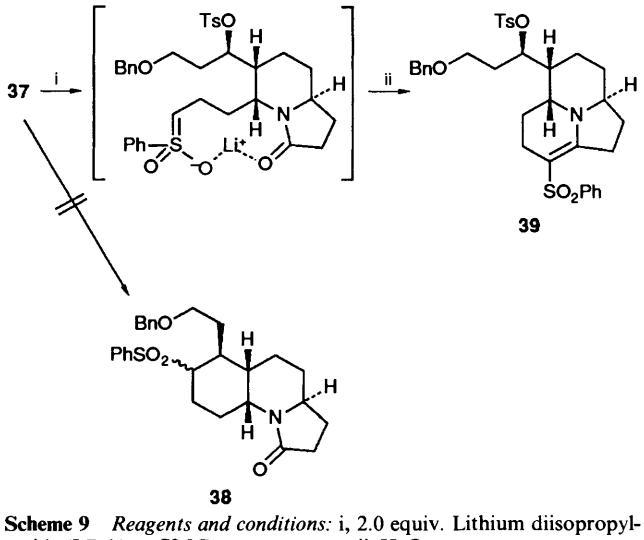
It is interesting to note that although cyclisation of **24** to the lactam **25** is straightforward, the corresponding epimeric amino alcohol **28** (Fig. 1) could not be cyclised to the hydroxy lactam **29** even after prolonged reflux in ethyl acetate, presumably owing to steric hindrance.

The synthesis of the lactam **27** represents the successful preparation of the B/C indolizidine ring skeleton of gephyrotoxin 3. Our strategy[3] then required inversion of stereochemistry at the carbon bearing the acetoxy substituent in order that the key intramolecular sulfone alkylation at this site would generate the correct sidechain stereochemistry of ring A of the gephyrotoxin ring skeleton. The acetate **27** was hydrolysed in near quantitative yield with potassium carbonate in methanol (Scheme 6). The resulting alcohol **30** was treated with carbon tetrabromide and triphenylphosphine to form the bromide **31**, but it was too readily dehydrobrominated under the reaction conditions and a 1:1 mixture of **31** and the alkene **32** was obtained. Again the stereochemistry of the double bond in **32** is unknown.

LeBel and Balasubramanian[9] had previously described an intramolecular sulfone alkylation of a toluene-*p*-sulfonate ester



Scheme 8 *Reagents and conditions:* i, pyridine, DMAP, BzCl; ii, $EtO_2CN{=}NCO_2Et$, PPh_3, BzOH, benzene, 0 °C, 1 h; iii, K_2CO_3, MeOH; iv, pyridine, DMAP, TsCl



Scheme 9 *Reagents and conditions:* i, 2.0 equiv. Lithium diisopropylamide (LDA), −78 °C → room temp.; ii, H_2O

to close ring A in the synthesis of pumiliotoxin C. We considered generating an analogous tosylate from the alcohol **30** by an oxidation to the ketone **33** and reduction to the required epimeric alcohol **34**. However, modelling of the ketone **33** suggested that hydride reduction would favour formation of the original alcohol **30**. Nevertheless, the alcohol **30** was oxidised with Jones' reagent[10] to give the ketone **33** (94%) (Scheme 7). Sodium borohydride reduction gave the two alcohols **30** (29%) and **34** (14%) together with unchanged ketone **33** (16%) thus confirming the modelling prediction.

Successful inversion was achieved, however, with a Mitsunobu reaction[11] to afford the benzoate **35** (81%) (Scheme 8). Confirmation of the inversion was possible by hydrolysis of the benzoate **35** to the alcohol **34** (89%) with potassium carbonate in methanol. The alcohol could then be re-inverted by the same Mitsunobu procedure to give the epimeric benzoate **36** (94%). This benzoate **36** was identical with material prepared by direct benzoylation of the alcohol **30** under standard conditions.

Tosylation of the alcohol **34** gave the required cyclisation substrate **37** (94%). Interestingly, the epimeric alcohol **30**, when

subjected to the same tosylating conditions failed to react and was recovered unchanged.

The tosylate **37** was subjected to the cyclisation conditions described by LeBel and Balasubramanian[9] (1.2 equiv. BuLi, HMPA, −78 °C → room temp.) in an effort to effect the key intramolecular sulfone alkylation to the tricycle **38** (Scheme 9). The tosylate **37** was recovered from this reaction. In an attempt to ascertain the site of anion formation the procedure was repeated, this time quenching the reaction with deuterioacetic acid. Again the tosylate **37** was re-isolated but no deuterium incorporation was evident. Several reactions were then performed in which the additive and the number of equivalents of base were changed systematically. The results of these reactions are summarised in Table 1. It was concluded from this study that treatment of the tosylate **37** with two equivalents of base resulted in decomposition. Milder conditions generally gave no reaction. Entry 6 (Table 1, Scheme 7) may provide a clue to the reason the cyclisation was unsuccessful. The product isolated from this reaction was unstable though it was possible to record a ^{1}H NMR spectrum which indicated the tosylate group was still present. There were also marked changes with respect to those signals attributed to the protons at C-2 and those alpha to the phenylsulfonyl group. This result suggested that compound **39** may have been formed. It may be that the lithium cation is being chelated by the α-phenylsulfonyl anion and the lactam carbonyl, thus holding the anion well away from the desired reaction site (Scheme 9).[12]

A possible solution to this problem is to replace the amide carbonyl group with the hydroxyethyl sidechain. Hart used an Eschenmoser sulfide contraction of a thioamide prepared from the corresponding amide, similar to structure **27**, to place the required sidechain in a synthesis of gephyrotoxin.[13] In our case this would require the preparation of a thio analogue of the lactam **27** not bearing the acetate protecting group. Such a compound might be prepared by treatment with the Heimgartner reagent.[14]

In summary, we have demonstrated that the intra/intermolecular nitrone cycloaddition strategy can indeed be applied to the stereoselective synthesis of the highly substituted racemic indolizidinone **27**. This indolizidinone is a key intermediate in our projected synthesis of gephyrotoxin **3** and its preparation is good evidence that similarly substituted indolizidine natural products might be efficiently synthesised by this method.

Experimental

NMR spectra were recorded using Varian EM390A, Bruker WM250 and WM400 instruments (*J* values are given in Hz). 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. 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 4Å molecular sieves. Ether refers to diethyl ether. Triethylamine was dried by distillation from calcium hydride, and stored over calcium hydride or potassium hydroxide.

(2R*,3R*)-3-[(1S*)3-*Benzyloxy*-1-*hydroxypropyl*]-2-(3-*phenylsulfonylpropyl*)-2,3,4,5-*tetrahydropyridine* 1-*Oxide* **4** *and* 3R*-[(1S*)-3-*Benzyloxy*-1-*hydroxypropyl*]-2-(3-*phenylsulfonylpropyl*)-3,4,5,6-*tetrahydropyridine* 1-*Oxide* **5**.—(a) A solution of the isoxazolidine **2** (216 mg, 0.50 mmol) in dry dichloromethane (5 cm^3) was cooled to −78 °C under an argon atmosphere and was treated with a solution of 3-chloroperoxybenzoic acid (MCPBA) (144 mg of a 60% sample, 0.50 mmol) in dry dichloromethane (5 cm^3). The solution was allowed to warm to 20 °C, poured into saturated aqueous sodium hydrogen carbonate (25 cm^3) and the aqueous phase was extracted with dichloromethane (3 × 25 cm^3). The combined extracts were dried (Na_2SO_4), filtered and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 15% methanol–ethyl acetate to give the *keto nitrone* **5** as a colourless gum (126 mg, 56%); $\nu_{max}(CDCl_3)$/cm^{-1} 3500m (OH), 3080m, 3030m, 1600m (Ar), 1440m (nitrone) and 1150s (SO_2); δ_H(250 MHz; $CDCl_3$) 7.80–7.76 (2 H, m, SO_2Ph), 7.54–7.39 (3 H, m, SO_2Ph), 7.27–7.13 (5 H, m, OCH_2Ph), 4.40 (2 H, s, OCH_2Ph), 4.40 (1 H, br s, OH), 3.97 (1 H, bt, *J* 7.3, C*H*OH), 3.70–3.46 (4 H, m, CH_2N and CH_2OBn), 3.05 (2 H, t, *J* 7.5, CH_2SO_2), 2.83–2.72 (1 H, m, C*H*HC=N), 2.61 (1 H, br s, CHC=N), 2.44–2.37 (1 H, m, CH*H*C=N) and 1.99–1.48 (8 H, m, methylene envelope); δ_C(100 MHz; $CDCl_3$) 146.9, 138.9, 138.0, 133.5, 129.1, 128.2, 127.8, 127.7, 127.5, 72.8, 71.5, 68.6, 58.9, 55.5, 44.1, 29.3, 24.1, 22.4, 21.2 and 19.0; *m*/*z* (CI, NH_3) 446 [(M^+ + H), 1%], 428 (9), 414 (16), 412 (21), 410 (34), 304 (56), 302 (28), 292 (14), 266 (100), 196 (14), 186 (7), 160 (31), 108 (19), 94 (13), 91 (7) and 78 (10) [Found: (CI, NH_3) (M^+ + H), 446.2001. $C_{24}H_{32}NO_5S$ requires *M*, 446.2001].

Further elution with 30% methanol–ethyl acetate afforded the *aldo nitrone* **4** as a colourless gum (47 mg, 21%); $\nu_{max}(CDCl_3)$/cm^{-1} 3500m (OH), 3080m, 3030m, 1600s (Ar), 1430m (nitrone) and 1150s (SO_2); δ_H(250 MHz; $CDCl_3$) 7.89–7.86 (2 H, m, SO_2Ph), 7.59–7.46 (3 H, m, SO_2Ph), 7.36–7.23 (5 H, m, OCH_2Ph), 6.95 (1 H, br s, 6-H), 4.50 (2 H, s, OCH_2Ph), 4.02 (1 H, br s, C*H*OH), 3.90–3.60 (3 H, m, CH_2OBn and 2-H), 3.30–3.24 (2 H, m, CH_2SO_2), 2.40 (2 H, br s, 5-H) and 2.18–1.23 (9 H, m, 3-H and methylene envelope); δ_C(100 MHz; $CDCl_3$) 139.2, 137.7, 135.2, 133.6, 129.2, 128.5, 128.0, 127.9, 127.8, 73.4, 70.7, 68.5, 67.6, 55.4, 43.9, 34.4, 28.0, 24.6, 21.1 and 16.2; *m*/*z* (CI, NH_3) 446 [(M^+ + H), 68%], 432 (38), 416 (10), 304 (45), 290 (25), 278 (12), 264 (23), 227 (12), 214 (23), 200 (16), 182 (100), 160 (78), 142 (13), 126 (12), 108 (57), 94 (13) and 78 (20).

(b) A solution of the isoxazolidine **2** (2.0 g, 4.66 mmol) in dry dichloromethane (40 cm^3) under an argon atmosphere was treated with a solution of MCPBA (1.07 g of a 75% sample, 4.66 mmol) in dichloromethane (50 cm^3). The reaction mixture was stirred for 5 min and work-up as above gave, after purification, the keto nitrone **5** (480 mg, 23%) as a colourless gum and the aldo nitrone **4** as a colourless foam (960 mg, 46%).

(c) A solution of the isoxazolidine **2** (513 mg, 1.2 mmol) in dry dichloromethane (10 cm^3) was treated with a solution of MCPBA (260 mg of an 80% sample, 1.2 mmol) in dichloromethane (5 cm^3). The reaction mixture was stirred for 5 min and work-up as above gave, after purification, the keto nitrone **5** as a colourless gum (63 mg, 12%) and the aldo nitrone **4** as a colourless gum (323 mg, 61%).

(d) A solution of the isoxazolidine **2** (4.3 g, 10 mmol) in dry dichloromethane (84 cm^3) under an argon atmosphere was treated with a solution of MCPBA (2.3 g of a 75% sample, 10 mmol) in dichloromethane (110 cm^3). The reaction mixture was stirred for 5 min and work-up as above gave, after purification, the aldo nitrone **4** as a light yellow oil (3.18 g, 71%).

(e) A solution of the isoxazolidine **2** (120 mg, 0.28 mmol) in dry dichloromethane (2.5 cm^3) was heated at 40 °C under an argon atmosphere and was treated with a solution of MCPBA (65 mg of a 75% sample, 0.28 mmol) in dichloromethane (3 cm^3). The reaction mixture was stirred for 5 min and work-up as above gave, after purification, the keto nitrone **5** as a colourless gum (22 mg, 18%) and the aldo nitrone **4** as a colourless foam (69 mg, 55%).

(f) A solution of the isoxazolidine **2** (97 mg, 0.23 mmol) in dry methanol (5 cm^3) was cooled to −78 °C under an argon atmosphere and was treated with a solution of magnesium monoperoxyphthalate (MMPP) (124 mg of a 90% sample, 0.23 mmol) in dry methanol (5 cm^3). The solution was warmed to 20 °C and work-up as above gave, after purification, the keto nitrone **5** as a colourless gum (62 mg, 62%).

(g) A solution of the isoxazolidine **2** (200 mg, 0.46 mmol) in dry methanol (10 cm^3) was titrated with a solution of magnesium monoperoxyphthalate (MMPP) (250 mg of a 90% sample, 0.46 mmol) in dry methanol (25 cm^3). The solution was stirred for 5 min and work-up as above gave, after purification, the keto nitrone **5** as a clear oil (140 mg, 68%).

(h) A solution of the isoxazolidine **2** (250 mg, 0.58 mmol) in dry methanol (10 cm^3) under an argon atmosphere was treated with potassium monoperoxysulfate (Oxone®) (360 mg, 1.16 mmol). The reaction mixture was heated to 65 °C for 2 h and then work-up as above gave a crude mixture. Purification by flash chromatography on silica eluting with 15% methanol–ethyl acetate gave the isoxazolidine **2** (56 mg, 22%). The second fraction eluted was the *dehydro nitrone* **6** (80 mg, 32%); ν_{max}(thin film)/cm^{-1} 3060m, 3030m, 3000–2760s, 2220w, 1588w (conj. C=N), 1535m, 1445s (nitrone), 1310s (SO_2) and 1145s (SO_2); δ_H(250 MHz; $CDCl_3$) 7.85–7.81 (2 H, m, $PhSO_2$), 7.59–7.43 (3 H, m, SO_2Ph), 7.31–7.22 (5 H, m, CH_2Ph), 5.79 (1 H, br t, *J* 7.1, CH=), 4.47 (2 H, s, CH_2Ph), 3.77 (2 H, t, *J* 5.9, 2-H), 3.50 (2 H, t, *J* 6.5, CH_2OBn), 3.16 (2 H, br t, *J* 7.7, CH_2SO_2), 2.79 (2 H, t, *J* 7.6, $CH_2C{=}N$), 2.44–2.32 (4 H, m, $CH_2CH{=}CCH_2$) and 1.97–1.83 (4 H, m, 5-H and $CH_2CH_2SO_2$); *m/z* (CI) 428 (28%), 412 (86), 304 (100), 292 (4), 266 (11), 244 (3) and 160 (15). Further elution afforded the keto nitrone **5** (40 mg, 15%).

(i) A solution of the isoxazolidine **2** (200 mg, 0.46 mmol) in dry dichloromethane (10 cm^3) was cooled to 0 °C under an argon atmosphere and was treated with a solution of trifluoroperacetic acid in dichloromethane (0.3 cm^3 of a 1.61 mol dm^{-3} solution, 0.46 mmol). [The solution of trifluoroperacetic acid was made by the addition of trifluoroacetic acid (9.5 cm^3, 67.5 mmol) to a vigorously stirred suspension of 84% hydrogen peroxide (1.5 cm^3) in dry dichloromethane (20 cm^3). The suspension became clear after stirring for 30 min at room temp. and was then ready for use.] The reaction mixture was stirred for 5 min at room temp. and worked-up as above. Purification of the crude mixture by flash chromatography on silica eluting with 15% methanol–ethyl acetate gave, firstly, the isoxazolidine **2** (80 mg, 39%). The next fraction to be eluted was the keto nitrone **5** as a clear film (89 mg, 43%). Further elution provided the aldo nitrone **4** as a clear oil (28 mg, 14%).

(j) A solution of the isoxazolidine **2** (200 mg, 0.47 mmol) in dry dichloromethane (10 cm^3) was treated with a sample of the Davis oxaziridine[15] (120 mg, 0.47 mmol) in dichloromethane (5 cm^3). The reaction mixture was stirred for 16 h and then evaporated to dryness under reduced pressure. Work-up as above gave, after purification, the keto nitrone **5** as a colourless gum (60 mg, 28%) and the aldo nitrone **4** as a colourless film (80 mg, 38%).

Methyl [2R*,3R*,6S*,8(R,S)]-3-[(1S*)-3-*Benzyloxy*-1-*hydroxypropyl*]-2-(3-*phenylsulfonylpropyl*)-9-*oxa*-1-*azabicyclo*[4.3.0]*nonane*-8-*carboxylate* **7** *and Methyl* [2R*,3R*,6R*,8S*]-3-[(1S*)-3-*Benzyloxy*-1-*hydroxypropyl*]-2-(3-*phenylsulfonylpropyl*)-9-*oxa*-1-*azabicyclo*[4.3.0]*nonane*-8-*carboxylate* **8** *and Methyl* (2R*,3R*)-3-[(1S*)-3-*Benzyloxy*)-1-*hydroxypropyl*]-2-(3-*phenylsulfonylpropyl*)-9-*oxa*-1-*azabicyclo*[4.3.0]*nonane*-7-*carboxylate* **9**.—(a) A solution of the aldo nitrone **4** (1.15 g, 2.58 mmol) in dry benzene (50 cm^3) and methyl acrylate (10 cm^3) was heated to reflux under an argon atmosphere using a Dean–Stark distillation head for 24 h. The reaction mixture was evaporated to dryness under reduced pressure and the residue was purified by flash chromatography on silica eluting with 50–60% ethyl acetate–hexane to give, firstly, a minor fraction identified as the adduct **9** as a colourless gum (42 mg, 3%); ν_{max}(CCl_4)/cm^{-1} 3520s (OH), 3060m, and 3020m (CH), 1740s (CO), 1440s and 1150s (SO_2); δ_H(250 MHz; $CDCl_3$) 7.89–7.86 (2 H, m, SO_2Ph), 7.64–7.49 (3 H, m, SO_2Ph), 7.37–7.25 (5 H, m, OCH_2Ph), 4.49 (2 H, s, OCH_2Ph), 4.14–3.88 (2 H, m, CHOH and 7-H), 3.70 (3 H, s, CO_2Me), 3.66–3.54 (2 H, m, CH_2OBn), 3.08 (2 H, t, *J* 7.7, CH_2SO_2), 3.08–3.00 (1 H, m, 2-H or 6-H), 2.66 (1 H, m, 6-H or 2-H), 2.42 (1 H, br t, *J* 9.3, 3-H) and 2.03–1.39 (12 H, m, methylene envelope); *m/z* (CI, NH_3) 532 [(M + H), 71%], 430 (100), 290 (21), 266 (10), 234 (18), 182 (22), 160 (15), 108 (19) and 55 (61) [Found: (M^+ + H), 532.2369. $C_{28}H_{38}NO_7S$ requires *M*, 532.2369]. Further elution afforded the adduct **8** as a colourless gum (572 mg, 42%); ν_{max}(CCl_4)/cm^{-1} 3520br s (OH), 3060m and 3020m (CH), 1740s (CO), 1440s and 1150 (SO_2); δ_H(250 MHz; $CDCl_3$) 7.89–7.85 (2 H, m, SO_2Ph), 7.62–7.48 (3 H, m, SO_2Ph), 7.36–7.23 (5 H, m, OCH_2Ph), 4.48 (2 H, s, OCH_2Ph), 4.39 (1 H, dd, *J* 9.6 and 3.4, 8-H), 4.01–3.90 (1 H, m, CHOH), 3.71 (3 H, s, CO_2Me), 3.65–3.53 (2 H, m, CH_2OBn), 3.10 (1 H, br s, 2-H or 6-H), 3.09 (2 H, br t, *J* 6.5, CH_2SO_2), 2.75 (1 H, br s, 6-H or 2-H) and 2.50–1.34 (13 H, m, 3-H and methylene envelope); *m/z* (FAB) 532 [(M + H), 90%], 440 (11), 348 (49), 149 (30) and 91 (100) [Found: (M^+ + H), 532.2369. $C_{28}H_{38}NO_7S$ requires *M*, 532.2369]. Further elution provided the adducts **7** (as a 1:1 mixture) as a colourless gum (672 mg, 49%); ν_{max}(CCl_4)/cm^{-1} 3520s (OH), 3070m and 3030m (CH), 1740s (CO), 1440s and 1150s (SO_2); δ_H(250 MHz; $CDCl_3$) 7.90–7.86 (2 H, m, SO_2Ph), 7.62–7.46 (3 H, m, SO_2Ph), 7.36–7.23 (5 H, m, OCH_2Ph), 4.49 (2 H, s, OCH_2Ph), 4.45–4.34 (1 H, m, 8-H), 3.72 (3 H, s, CO_2Me), 3.75–3.52 (3 H, m, CH_2OBn and OH), 3.23–3.13 (2 H, m, CH_2SO_2), 3.10–2.96 (1 H, br s, 2-H or 6-H), 2.57–2.45 (1 H, m, 6-H or 2-H) and 2.22–1.10 (13 H, m, 3-H and methylene envelope); *m/z* (CI, NH_3) 532 [(M^+ + H), 8%], 430 (50), 282 (38), 266 (33), 182 (100), 160 (73), 108 (40) and 55 (68) [Found: (M^+ + H), 532.2369. $C_{28}H_{38}NO_7S$ requires *M*, 532.2369].

(b) *Equilibration of adducts* **7**, **8** *and* **9**.—A solution of the isoxazolidines **8** and **9** (572 mg, 1.08 mmol) in dry toluene (50 cm^3) and methyl acrylate (10 cm^3) were heated to reflux under an argon atmosphere with a Dean–Stark distillation head for 24 h. TLC analysis of the reaction mixture and isolation of the products indicated that equilibration had occurred. The solution was evaporated under reduced pressure and the residue was purified by flash chromatography as described above to give the adduct **9** (17 mg, 3%), followed by the isoxazolidine **8** (227 mg, 40%) and, finally, the isoxazolidines **7** (281 mg, 49%); all as colourless gums identical with the materials characterised above.

Methyl[2R*,3R*,6S*,8*(R,S)]-3-[(1S*)-1-*Acetoxy*-3-*benzyloxypropyl*]-2-(3-*phenylsulfonylpropyl*]-9-*oxa*-1-*azabicyclo*-[4.3.0]*nonane*-8-*carboxylate* **10**.—A solution of the adducts **7** (56.3 mg, 0.106 mmol) in dry pyridine (1.0 cm^3) was treated with acetic anhydride (0.2 cm^3) and DMAP (*ca.* 10 mg, cat.). The solution was stirred for 1 h at 20 °C, poured into saturated aqueous sodium hydrogen carbonate (25 cm^3) and extracted with dichloromethane (3 × 25 cm^3). The combined organic

extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 50% ethyl acetate–hexane to give the *acetates* **10** as a colourless gum (57.7 mg, 95%); ν_{max}(CCl_4)/cm^{-1} 3080m and 3020m (CH), 1740s (CO), 1440s and 1150s (SO_2); δ_H(250 MHz; $CDCl_3$) 7.90–7.86 (2 H, m, SO_2Ph), 7.66–7.48 (3 H, m, SO_2Ph), 7.39–7.21 (5 H, m, CH_2*Ph*), 4.92 (1 H, t, *J* 8.3, C*H*OAc), 4.42 (2 H, s, CH_2Ph), 4.51–4.36 (1 H, m, 8-H), 3.74 (3 H, s, OMe), 3.51–3.35 (2 H, m, CH_2OBn), 3.19–3.05 (2 H, m, CH_2SO_2), 2.57–2.49 (1 H, m, 2-H or 6-H), 2.25–2.12 (1 H, m, 6-H or 2-H), 1.90 (3 H, s, OAc) and 2.04–1.16 (13 H, m, 3-H and methylene envelope); *m*/*z* (CI, NH_3) 574 [(M^+ + H), 38%], 472 (34), 304 (18), 202 (5), 160 (18), 104 (49) and 55 (100) [Found: (CI, NH_3) (M^+ + H), 574.2475. $C_{30}H_{40}NO_8S$ requires *M*, 574.2475].

Methyl [2R*,3R*,6R*,8S*]-3-[(1S*)-1-*Acetoxy*-3-*benzyloxypropyl*]-2-(3-*phenylsulfonylpropyl*)-9-*oxa*-1-*azabicyclo*[4.3.0]*nonane*-8-*carboxylate* **11**.—A solution of the adduct **8** (76.8 mg, 0.145 mmol) in dry pyridine (1.0 cm^3) was treated with acetic anhydride (0.2 cm^3) and DMAP (*ca.* 10 mg, cat.). The solution was stirred for 1 h at 20 °C, poured into saturated aqueous sodium hydrogen carbonate (25 cm^3) and the aqueous phase was extracted with dichloromethane (3 × 25 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 50% ethyl acetate–hexane to give the *acetate* **11** as a colourless gum (78.6 mg, 95%); ν_{max}(CCl_4)/cm^{-1} 3070w and 3030w (CH), 1740s (CO), 1440s and 1150s (SO_2); δ_H(250 MHz; $CDCl_3$) 7.91–7.88 (2 H, m, SO_2Ph), 7.63–7.51 (3 H, m, SO_2Ph), 7.32–7.27 (5 H, m, OCH_2*Ph*), 5.25 (1 H, br s, C*H*OAc), 4.46 and 4.42 (2 H, 2 × d, J_{AB} 11.6, CH_2Ph), 4.40–4.30 (1 H, br s, 8-H), 3.72 (3 H, s, OMe), 3.47–3.33 (2 H, m, CH_2OBn), 3.09–3.03 (2 H, m, CH_2SO_2), 2.79–2.63 (1 H, br s, 2-H or 6-H) and 2.40–1.24 (14 H, m, 3-H, methylene envelope and 6-H or 2-H); *m*/*z* (CI, NH_3) 574 [(M^+ + H), 40%], 472 (35), 306 (20), 202 (5), 160 (20), 104 (50) and 55 (100) [Found: (M^+ + H), 574.2475. $C_{30}H_{40}NO_8S$ requires *M*, 574.2475].

Methyl (2R*,3R*)-3-[(1S*)-1-*Acetoxy*-3-*benzyloxypropyl*]-2-(3-*phenylsulfonylpropyl*)-9-*oxa*-1-*azabicyclo*[4.3.0]*nonane*-7-*carboxylate* **12**.—A solution of the alcohol **9** (47.6 mg, 90 μmol) in dry pyridine (1 cm^3) was treated with acetic anhydride (0.2 mm^3) and DMAP (*ca.* 10 mg, cat.). The solution was stirred for 30 min, poured into saturated aqueous sodium hyrogen carbonate (20 cm^3) and extracted with dichloromethane (3 × 20 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 50% ethyl acetate–hexane to give the pure *acetate* **12** as a colourless oil (49 mg, 96%); ν_{max}(CCl_4)/cm^{-1} 1740s (CO); δ_H(250 MHz; $CDCl_3$) 7.88 (2 H, dd, *J* 8.5 and 1.5, SO_2Ph), 7.65–7.50 (3 H, m, SO_2Ph), 7.35–7.23 (5 H, m, CH_2*Ph*), 5.27 (1 H, br s, C*H*OAc), 4.45 and 4.41 (2 H, 2 × d, J_{AB} 11.7, CH_2Ph), 3.98 (1 H, dd, *J* 7.9 and 5.1, 8-H), 3.84 (1 H, t, *J* 7.9, 8-H), 3.69 (3 H, s, OMe), 3.44–3.36 (2 H, m, CH_2OBn), 3.06–2.95 (3 H, m, CH_2SO_2 and 2-H or 6-H), 2.59 (1 H, br s, 6-H or 2-H), 2.42–2.19 (2 H, m, 3-H and 7-H), 1.93 (3 H, s, OAc) and 2.16–1.33 (10 H, m, methylene envelope); *m*/*z* (CI, NH_3) 574 [(M^+ + H), 100%] [Found: (M^+ + H), 574.2475. $C_{30}H_{40}NO_8S$ requires *M*, 574.2475].

Preparation of 5-(tert-*Butyldiphenylsilyloxy*)*pent*-1-*en*-3-*one* **13**.—(a) 3-(tert-*Butyldiphenylsilyloxy*)*propan*-1-*ol*. To a suspension of sodium hydride (2.00 g of a 60% dispersion in oil, 50 mmol) in dry THF (60 cm^3) was added propane-1,3-diol (3.6 cm^3, 50 mmol) dropwise at 0 °C. The reaction mixture was stirred for 1 h at room temp. and was then cooled to 0 °C and treated with *tert*-butyldiphenylsilyl chloride (13.0 cm^3, 50 mmol). The solution was allowed to warm to room temperature over 2 h and was then quenched with saturated aqueous sodium hydrogen carbonate (100 cm^3). The aqueous mixture was extracted with dichloromethane (4 × 50 cm^3) and the combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by flash chromatography on silica eluting with 0–50% ethyl acetate–hexane to afford 3-(tert-*butyldiphenylsilyloxy*)*propan*-1-*ol* as a colourless solid (11.67 g, 74%), m.p. 39–41 °C (Found: C, 72.6; H, 8.4. $C_{19}H_{26}O_2Si$ requires C, 72.6; H, 8.3%); ν_{max}($CHCl_3$)/cm^{-1} 3520br s (OH), 2930s and 2850s (CH); δ_H(250 MHz; $CDCl_3$) 7.72–7.68 (4 H, m, Ph), 7.47–7.36 (6 H, m, Ph), 3.85 (4 H, 2 t, *J* 5.7, 1-H and 3-H), 2.43 (1 H, br s, OH), 1.82 (2 H, quintet, *J* 5.7, 2-H) and 1.07 (9 H, s, Bu^t); δ_C(100 MHz; $CDCl_3$) 135.5, 133.2, 129.7, 127.7, 63.2, 34.2, 26.8 and 19.0; *m*/*z* (CI, NH_3) 315 [(M^+ + H), 100%], 257 (6), 237 (27), 216 (12), 196 (28), 176 (11) and 135 (5) [Found: (M − Bu^t), 257.1080. $C_{15}H_{17}O_2Si$ requires *M*, 257.1078].

(b) 3-(tert-*Butyldiphenylsilyloxy*)*propanal*. A solution of oxalyl chloride (1.66 cm^3, 19.1 mmol) in dry dichloromethane (50 cm^3) was cooled to −78 °C under a nitrogen atmosphere. DMSO (2.71 cm^3, 38.2 mmol) in dry dichloromethane (50 cm^3) was added dropwise, stirring was continued for 20 min, and then a solution of 3-(*tert*-butyldiphenylsilyloxy)propan-1-ol (5.00 g, 15.9 mmol) in dry dichloromethane (50 cm^3) was added dropwise. Stirring was continued for a further 20 min and then triethylamine (13.3 cm^3, 95.4 mmol) was added. After a further 10 min at −78 °C, the solution was allowed to warm to room temp. over 1 h and was poured into saturated aqueous sodium hydrogen carbonate (200 cm^3). The aqueous phase was extracted with dichloromethane (3 × 100 cm^3). The combined organic layers were 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 3-(tert-*butyldiphenylsilyloxy*)*propanal* as a colourless solid (4.72 g, 95%), m.p. 46–48 °C (Found: C, 73.3; H, 7.9. $C_{19}H_{24}O_2Si$ requires C, 73.0; H, 7.7%); ν_{max}($CHCl_3$)/cm^{-1} 2920s and 2850s (CH), 2720w (CHO) and 1720s (CO); δ_H(250 MHz; $CDCl_3$) 9.82 (1 H, t, *J* 2.1, CHO), 7.70–7.65 (4 H, m, Ph), 7.45–7.36 (6 H, m, Ph), 4.03 (2 H, t, *J* 6, 3-H), 2.61 (2 H, dt, *J* 6 and 2.2, 2-H) and 1.05 (9 H, s, Bu^t); δ_C(100 MHz; $CDCl_3$) 201.8, 135.5, 133.2, 129.8, 127.7, 58.2, 46.3, 26.7 and 19.1; *m*/*z* (EI) 255 [(M − Bu^t), 100%], 225 (88), 199 (41), 183 (61), 177 (40) and 117 (55) [Found: (M − Bu^t), 255.0836. $C_{15}H_{15}O_2Si$ requires *M*, 255.0842].

(c) (3R,S)-1-(tert-*Butyldiphenylsilyloxy*)*pent*-4-*en*-3-*ol*. Vinylmagnesium bromide (17.3 cm^3 of a 1.00 mol dm^{-3} solution in THF, 17.3 mmol) was added slowly to a stirred solution of 3-(*tert*-butyldiphenylsiloxy)propanal (4.5 g, 14.42 mmol) in dry THF (150 cm^3) at −78 °C. The mixture was allowed to warm to room temp. over 1 h and was quenched with saturated aqueous ammonium chloride. The organic phase was separated and the aqueous phase was extracted with ether (3 × 100 cm^3). The combined organic layers 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% ether–hexane to give (3R,S)-1-(tert-*butyldiphenylsilyloxy*)*pent*-4-*en*-3-*ol* as a colourless oil (3.75 g, 77%) (Found: C, 74.0; H, 8.2. $C_{21}H_{28}O_2Si$ requires C, 74.1; H, 8.3%); ν_{max}(thin film)/cm^{-1} 3420br (OH), 3060m and 3040m (CH), 2940s, 2920s and 2840s (CH), 990m and 910m (CH); δ_H(250 MHz; $CDCl_3$) 7.70–7.65 (4 H, m, Ph), 7.44–7.35 (6 H, m, Ph), 5.88 (1 H, ddd, *J* 17.1, 10.4 and 5.5, 4-H), 5.30 (1 H, dt, *J* 17.1 and 1.5, 5*E*-H), 5.11 (1 H, dt, *J* 10.4 and 1.5, 5*Z*-H), 4.45–4.42 (1 H, m, 3-H), 3.91–3.80 (3 H, m, 1-H and OH), 1.82–1.74 (2 H, m, 2-H) and 1.05 (9 H, s, Bu^t); δ_C(100 MHz; $CDCl_3$) 140.60, 135.55, 133.01, 129.82, 127.77, 114.28, 72.18, 62.65, 38.30, 26.78 and 19.03; *m*/*z* 283 [(M − Bu^t),

5%], 230 (10), 229 (47), 200 (19), 199 (100), 91 (6) and 77 (8) [Found: (M − Bu^t), 283.1156. $C_{17}H_{19}O_2Si$ requires *M*, 283.1154].

(d) 5-(tert-*Butyldiphenylsilyloxy*)*pent*-1-*en*-3-*one* **13**. A solution of (3R,S)-1-(*tert*-butyldiphenylsilyloxy)pent-4-en-3-ol (685 mg, 2.01 mmol) in acetone (20 cm^3) at 0 °C was treated dropwise with a 2 mol dm^{-3} solution of Jones' reagent until an orange colouration persisted. The reaction mixture was quenched by the addition of isopropyl alcohol. The green mixture was poured into saturated brine (100 cm^3) and extracted with ethyl acetate (3 × 100 cm^3). The combined organic extracts were filtered through a Florisil column and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 10–20% ethyl acetate–hexane to afford the *enone* **13** as a colourless oil (604 mg, 89%) (Found: C, 74.5; H, 7.9. $C_{21}H_{26}O_2Si$ requires C, 74.5; H, 7.7%); $\nu_{max}(CCl_4)$/cm^{-1} 3080s, 3060s and 3040m (CH), 1680s (CO) and 1620m (C=C); δ_H(250 MHz; $CDCl_3$) 7.70–7.65 (4 H, m, Ph), 7.47–7.35 (6 H, m, Ph), 6.38 (1 H, dd, *J* 17.7 and 10.3, 2-H), 6.20 (1 H, dd, *J* 17.7 and 1.3, 1*E*-H), 5.85 (1 H, dd, *J* 17.7 and 10.3, 1*Z*-H), 4.00 (2 H, t, *J* 6.4, 5-H), 2.83 (2 H, t, *J* 6.4, 4-H) and 1.03 (9 H, s, Bu^t); δ_C(100 MHz; $CDCl_3$) 199.5, 137.0, 135.5, 133.4, 129.7, 128.5, 127.7, 59.8, 42.1, 26.7 and 19.1; *m*/*z* (EI) 281 [(M − Bu^t), 100%], 251 (20), 203 (50), 199 (62) and 173 (40) [Found: (M − Bu^t), 281.1012. $C_{17}H_{17}O_2Si$ requires *M*, 281.1998].

(2R*,3R*,6S*,8S*)-3-[(1S*)-1-*Acetoxy*-3-*benzyloxypropyl*]-8-[3-(tert-*butyldiphenylsilyloxy*)-1-*oxopropyl*]-2-(3-*phenylsulfonylpropyl*)-9-*oxa*-1-*azabicyclo*[4.3.0]*nonane* **17** *and* (2R*,3R*,6S*,8R*)-3-[(1S*)-1-*Acetoxy*-3-*benzyloxypropyl*]-8-[3-(tert-*butyldiphenylsilyloxy*)-1-*oxopropyl*]-2-(3-*phenylsulfonylpropyl*)-9-*oxa*-1-*azabicyclo*[4.3.0]*nonane* **18** *and* (2R*,3R*,6R*,8S*)-3-[(1S*)-1-*Acetoxy*-3-*benzyloxypropyl*]-8-[3-(tert-*butyldiphenylsilyloxy*)-1-*oxopropyl*]-2-(3-*phenylsulfonylpropyl*)-9-*oxa*-1-*azabicyclo*[4.3.0]*nonane* **19**.—To a solution of the nitrone **4** (47 mg, 0.106 mmol) in dry benzene (10 cm^3) under an argon atmosphere was added the enone **13** (46.5 mg, 0.127 mmol) and the mixture was heated to reflux for 16 h. The solution was evaporated to dryness under reduced pressure and the residue was purified by flash chromatography on silica to afford an inseparable mixture of product isoxazolidines **14**, **15** and **16** (66 mg, 80%) (in the approximate ratio 1:1:1 as judged by ^{1}H NMR spectroscopy) as a colourless gum.

The mixture was taken up in dry pyridine (1.0 cm^3) and the solution was treated with acetic anhydride (0.2 cm^3) and DMAP (*ca.* 10 mg, cat.). The solution was stirred for 1 h at 20 °C and then poured into saturated aqueous sodium hydrogen carbonate (25 cm^3). The aqueous phase was extracted with dichloromethane (3 × 25 cm^3) and the combined extracts were dried (Na_2SO_4), filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 50% ethyl acetate–hexane to afford the title *acetates* **17**, **18** and **19** (72 mg, 99%). Subsequent repeated chromatography provided purified samples (in the order of elution) of the *acetate* **19** R_f 0.5 (50% ethyl acetate–hexane); $\nu_{max}(CCl_4)$/cm^{-1} 3080m (CH), 1740s (CO), 1440m and 1150s (SO_2); δ_H(250 MHz; $CDCl_3$) 7.90–7.84 (2 H, m, SO_2Ph), 7.66–7.62 (3 H, m, SO_2Ph), 7.61–7.22 (15 H, m, ArH), 5.25 (1 H, br s, C*H*OAc), 4.44 (2 H, dd, *J* 14.6 and 11.7, OC*H*$_2$Ph), 4.34–4.27 (1 H, m, 8-H), 3.92 (2 H, br s, CH_2OSi), 3.46–3.38 (2 H, m, C*H*$_2$OBn), 3.04 (2 H, t, *J* 7.2, CH_2SO_2), 2.72–2.58 (3 H, m, CH_2CO and 6-H), 2.35–2.19 (1 H, m, 2-H), 2.15–1.20 (13 H, m, 3-H and methylene envelope), 1.95 (3 H, s, OAc) and 1.00 (9 H, s, Bu^t); *m*/*z* (FAB) 826 [(M$^+$ + H), 39%], 488 (11), 199 (22), 197 (29), 154 (16), 149 (12), 139 (11), 135 (63), 121 (13), 107 (14) and 105 (15) [Found: (M + H), 826.3816. $C_{47}H_{60}NO_8SSi$ requires *M*, 826.3809].

The second fraction was identified as the *acetate* **18** R_f 0.45 (ethyl acetate–hexane); $\nu_{max}(CCl_4)$/cm^{-1} 3080m (CH), 1740s (CO), 1440m and 1150s (SO_2); δ_H(400 MHz; $CDCl_3$) 7.82 (2 H, d, *J* 7.4, SO_2Ph), 7.68–7.66 (3 H, m, SO_2Ph), 7.56–7.25 (15 H, m, ArH), 4.96 (1 H, dt, *J* 8.8 and 2.9, C*H*OAc), 4.45 (2 H, s, OC*H*$_2$Ph), 4.27 (1 H, dd, *J* 9.0 and 5.9, 8-H), 3.95–3.89 (2 H, m, CH_2OSi), 3.51–3.39 (3 H, m, C*H*$_2$OBn and 6-H), 3.28 (1 H, br s, 2-H), 3.18–3.00 (2 H, m, CH_2SO_2), 3.00–2.92 (1 H, m, C*H*HCO), 2.72–2.63 (1 H, m, CH*H*CO), 1.97 (3 H, s, OAc), 1.01 (9 H, s, Bu^t) and 2.50–0.80 (13 H, m, 3-H and methylene envelope); *m*/*z* (FAB) 826 [(M$^+$ + H), 56%], 582 (10), 199 (20), 197 (36) and 135 (70) [Found: (M$^+$ + H), 826. 3808. $C_{47}H_{60}NO_8SSi$ requires *M*, 826.3809].

The last fraction to be eluted was the *acetate* **17** R_f 0.43 (50% ethyl acetate–hexane); $\nu_{max}(CCl_4)$/cm^{-1} 3080w (CH), 1740s (CO), 1440m and 1150 (SO_2); δ_H(400 MHz; $CDCl_3$) 7.91–7.89 (2 H, m, SO_2Ph), 7.69–7.66 (3 H, m, SO_2Ph), 7.65–7.25 (15 H, m, ArH), 4.94 (1 H, t, *J* 6.2, C*H*OAc), 4.44 (2 H, s, C*H*$_2$Ph), 4.22 (1 H, br s, 8-H), 3.95 (2 H, m, CH_2OSi), 3.45 (2 H, m, C*H*$_2$OBn), 3.10 (2 H, m, CH_2SO_2), 2.95–2.78 (2 H, m, CH_2CO), 2.50 (1 H, br s, 2-H or 6-H), 2.20 (1 H, br s, 6-H or 2-H), 1.93 (3 H, s, OAc), 1.03 (9 H, s, Bu^t) and 2.30–0.80 (13 H, m, 3-H and methylene envelope); *m*/*z* (FAB) 826 [(M$^+$ + H), 38%], 488 (11), 199 (15), 197 (28) and 135 (68) [Found: (M$^+$ + H), 826.3808. $C_{47}H_{59}NO_8SSi$ requires *M*, 826.3809].

[2(R,S),5R*,6R*,8aS*]-6-[(1S*)-3-*Benzyloxy*-1-*hydroxy*]-2-*hydroxy*-5-(3-*phenylsulfonylpropyl*)*octahydroindolizine*-3-*one* **21**.—A solution of the isoxazolidines **7** (38.2 mg, 71.9 μmol) in acetic acid–water (1:1; 5 cm^3) was treated with activated Zn dust (100 mg, 1.54 mg atom) and heated under a nitrogen atmosphere to 80 °C for 2 h. The solution was cooled, basified with sodium hydroxide (2 mol dm^{-3} solution) and extracted with dichloromethane (4 × 25 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was dissolved in ethyl acetate (25 cm^3) and the solution was heated at reflux under an argon atmosphere for 16 h. The cooled solution was evaporated under reduced pressure and the residue was purified by flash chromatography on silica eluting with ethyl acetate to give the *lactams* **21** (27.96 mg, 78%); $\nu_{max}(CDCl_3)$/cm^{-1} 3600–3100br s (OH), 3070w and 3030w (CH), 2980–2820s (CH), 1670s (CO), 1430m, 1300s and 1140s (SO_2); δ_H(250 MHz; $CDCl_3$) 7.92–7.85 (2 H, m, SO_2Ph), 7.65–7.49 (3 H, m, SO_2Ph), 7.40–7.27 (5 H, m, CH_2Ph), 4.49 (2 H, s, OC*H*$_2$Ph), 4.45–4.44 (1 H, m, 2-H), 4.36–4.18 (1 H, m, C*H*OH), 3.79–3.01 (8 H, m, C*H*$_2$OBn, OH × 2, CH_2SO_2, 2-H and 5-H or 8a-H), 2.62–2.50 (1 H, m, 8a-H or 5-H) and 2.14–1.14 (13 H, m, 6-H and methylene envelope); *m*/*z* (FAB) 502 [(M$^+$ + H), 48%], 411 (88), 363 (15), 327 (14), 301 (77), 286 (17), 213 (26), 154 (18), 133 (100), 91 (50), 81 (24), 69 (48) and 55 (49).

[2(R,S),5R*,6R*,8aS*]-6-[(1R*)-3-*Benzyloxy*-1-*bromopropyl*]-2-*bromo*-5-(3-*phenylsulfonylpropyl*)*octahydroindolizin*-3-*one* **22**.—A solution of the diols **21** (24.5 mg, 49 μmol) in dry dichloromethane (1 cm^3) under an argon atmosphere was treated with a solution of carbon tetrabromide (65 mg, 0.2 mmol) in dry dichloromethane (1 cm^3) followed by triphenylphosphine (51.4 mg). The reaction mixture was stirred for 24 h, poured into saturated aqueous sodium hydrogen carbonate (25 cm^3) and extracted with dichloromethane (3 × 25 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was triturated with ethyl acetate and the organic solution was filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 66% ethyl acetate–hexane to give the bromides **22** (8.96 mg, 29%) (contaminated with the dehydrobromo

derivative **23**); $\nu_{max}(CCl_4)/cm^{-1}$ 3080w, 3040m and 3000–2800s (CH), 1740s (CO), 1430s, 1370w, 1310s and 1150s; *m/z* (FAB) 626/628/630 [1:2:1, (M^+ + H), 18%/45%/25%], 570 (23), 548 (100), 440 (23), 419 (65), 293 (30), 133 (26) and 91 (100).

Repeated chromatography allowed partial separation of the two compounds.

22: δ_H(250 MHz; $CDCl_3$) 7.87–7.82 (2 H, m, SO_2Ph), 7.64–7.46 (3 H, m, SO_2Ph), 7.33–7.21 (5 H, m, CH_2Ph), 5.31 (0.5 H, t, *J* 6.7, 2-H of 1 isomer), 4.84 (0.5 H, t, *J* 7.2, 2-H of 1 isomer), 4.50–4.47 (2 H, m, CH_2Ph), 4.38–4.25 (2 H, m, 5-H and CHBr), 3.79–3.62 (1 H, m, 8a-H), 3.46 (2 H, t, *J* 6.5, CH_2OBn), 3.24–3.02 (2 H, m, CH_2SO_2) and 2.53–1.43 (13 H, m, 6-H and methylene envelope).

23: The compound was not pure. The spectrum was similar to and was contaminated with the dibromide **22**. The 250 MHz ^1H NMR spectrum had a diagnostic resonance at δ_H 5.61.

[2(R,S),5R*,6R*,8aS*]-6-[(1S*)-1-*Acetoxy*-3-*benzyloxypropyl*]-2-*hydroxy*-5-(3-*phenylsulfonylpropyl*)*octahydroindolizin*-3-*one* **25**.—A solution of the isoxazolidines **10** (800 mg, 1.40 mmol) in acetic acid–water (1:1; 40 cm^3) was treated with activated Zn dust (1.10 g, 16.94 mg atom) and heated under a nitrogen atmosphere to 80 °C for 2 h. The solution was cooled, neutralised with solid sodium hydrogen carbonate, diluted with distilled water (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. The residue was dissolved in ethyl acetate (65 cm^3) and the solution was heated at reflux under an argon atmosphere for 14 h. The cooled solution was evaporated under reduced pressure and the residue was purified by flash chromatography on silica eluting with ethyl acetate to give the lactams **25** (670 mg, 88%); $\nu_{max}(CCl_4)/cm^{-1}$ 3600–3100 br s (OH), 3070w and 3030w (CH), 3000–2820s (CH), 1740s (CO), 1680s (CO), 1440s and 1150s (SO_2); δ_H(250 MHz; $CDCl_3$) 7.90–7.84 (2 H, m, SO_2Ph), 7.63–7.50 (3 H, m, SO_2Ph), 7.35–7.22 (5 H, m, CH_2Ph), 4.98–4.87 (1 H, m, CHOAc), 4.41 (2 H, s, OCH_2Ph), 4.36–4.05 (3 H, m, 2-H, 5-H and 8a-H), 3.61–3.24 (4 H, m, CH_2OBn, OH, $CHHSO_2$), 3.03–2.85 (1 H, m, $CHHSO_2$), 2.66–2.51 (1 H, m, 6-H), 1.97 (3 H, s, OAc) and 2.15–1.05 (12 H, m, methylene envelope); *m/z* (FAB) 544 [(M^+ + H), 48%], 411 (42), 327 (45), 301 (52), 281 (56), 221 (42), 207 (77), 91 (84), 73 (100) and 55 (100) [Found: (M^+ + H), 544.2369. $C_{29}H_{38}NO_7S$ requires *M*, 544.2369].

[2(R,S),5R*,6R*,8aS*]-6-[(1S*)-1-*Acetoxy*-3-*benzyloxypropyl*]-2-*bromo*-5-(3-*phenylsulfonylpropyl*)*octahydroindolizin*-3-*one* **26**.—A solution of the alcohols **25** (538 mg, 0.991 mmol) in dry dichloromethane (2 cm^3) at 0 °C under an argon atmosphere was treated with a solution of carbon tetrabromide (1.22 g, 3.96 mmol) in dry dichloromethane (1 cm^3) followed by a solution of triphenylphosphine (0.97 g, 3.96 mmol) in dry dichloromethane (1 cm^3). The reaction mixture was stirred at 0 °C for 2 h, poured into saturated aqueous sodium hydrogen carbonate (25 cm^3) and extracted with dichloromethane (3 × 25 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was triturated with ethyl acetate and the organic solution was filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 66% ethyl acetate–hexane to give the *bromides* **26** (538 mg, 89%); $\nu_{max}(CCl_4)/cm^{-1}$ 3060m, 3020m and 3000–2800s (CH), 1730s (CO), 1690s (CO), 1440s, 1370s and 1140s; *m/z* (CI, NH_3) 608/606 [1:1, (M^+ + H), 5%], 528 (100), 386 (8) and 160 (5) [Found: (M^+ + H), 606.1525. $C_{29}H_{37}{}^{79}BrNO_6S$ requires *M*, 606.1525].

Repeated chromatography allowed separation of the epimers.

[2(R* *or* S*),5R*,6R*,8aS*]-6-[(1S*)-1-*Acetoxy*-3-*benzyloxypropyl*]-2-*bromo*-5-(3-*phenylsulfonylpropyl*)*octahydroindolizin*-3-*one* **26a**. R_f = 0.24 (66% ethyl acetate–hexane); δ_H(250 MHz; $CDCl_3$) 7.89–7.85 (2 H, m, SO_2Ph), 7.67–7.52 (3 H, m, SO_2Ph), 7.36–7.25 (5 H, m, CH_2Ph), 4.95 (1 H, dt, *J* 7.8 and 3.3, CHOAc), 4.43 (2 H, s, CH_2Ph), 4.34 (1 H, dd, *J* 8.8 and 5.1, 2-H), 4.29 (1 H, dt, *J* 12.1 and 3, 5-H), 3.57–3.50 (1 H, m, 8a-H), 3.50–3.42 (2 H, m, CH_2OBn), 3.37–3.24 (1 H, m, $CHHSO_2$), 2.99–2.88 (1 H, m, $CHHSO_2$), 2.88–2.78 (1 H, m, 6-H), 1.99 (3 H, s, OAc) and 2.08–1.37 (12 H, m, methylene envelope).

[2(S* *or* R*),5R*,6R*,8aS*]-6-[(1S*)-1-*Acetoxy*-3-*benzyloxypropyl*]-2-*bromo*-5-[3-(*phenylsulfonyl*)*propyl*]*octahydroindolizin*-3-*one* **26b**. R_f = 0.17 (66% ethyl acetate–hexane); δ_H(250 MHz; $CDCl_3$) 7.89–7.86 (2 H, m, SO_2Ph), 7.64–7.49 (3 H, m, SO_2Ph), 7.36–7.29 (5 H, m, CH_2Ph), 4.97 (1 H, dt, *J* 8.6 and 3.3, CHOAc), 4.43 (2 H, s, CH_2Ph), 4.29 (1 H, dd, *J* 7.1 and 0.9, 2-H), 4.26 (1 H, dt, *J* 10.5 and 2.3, 5-H), 3.72–3.58 (1 H, m, 8a-H), 3.53–3.38 (2 H, m, CH_2OBn), 3.38–3.25 (1 H, m, $CHHSO_2$), 3.07–2.97 (1 H, m, $CHHSO_2$), 2.48 (1 H, dd, *J* 14.1 and 6.1, 6-H), 2.02 (3 H, s, OAc) and 2.09–1.39 (12 H, m, methylene envelope).

[5R*,6R*,8aS*]-6-[(1S*)-1-*Acetoxy*-3-*benzyloxypropyl*]-5-(3-*phenylsulfonylpropyl*)*octahydroindolizin*-3-*one* **27**.—A solution of the bromides **26** (533 mg, 0.88 mmol) in toluene (25 cm^3) was treated with tributyltin hydride (0.71 cm^3, 2.64 mmol) and AIBN (*ca.* 10 mg, cat.), and the reaction mixture was heated at reflux under an argon atmosphere for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate (25 cm^3) and extracted with ethyl acetate (3 × 25 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica eluting with ethyl acetate to give the *lactam* **27** (431 mg, 93%) as a colourless gum; $\nu_{max}(CCl_4)/cm^{-1}$ 3060m, 3020m and 3000–2800s (CH), 1735s (CO), 1680s (CO), 1440s, 1420s, 1360s, 1300s and 1140s; δ_H(250 MHz; $CDCl_3$) 7.91–7.86 (2 H, m, SO_2Ph), 7.66–7.51 (3 H, m, SO_2Ph), 7.36–7.22 (5 H, m, CH_2Ph), 4.93 (1 H, dt, *J* 9.0 and 3.3, CHOAc), 4.43 (2 H, s, CH_2Ph), 4.24 (1 H, dt, *J* 11.9 and 3.9, 5-H), 3.54–3.38 (3 H, m, CH_2OBn and 8a-H), 3.38–3.28 (1 H, m, $CHHSO_2$), 2.99–2.87 (1 H, m, $CHHSO_2$), 2.39–2.25 (1 H, m, 6-H), 1.98 (3 H, s, OAc) and 2.15–1.06 (14 H, m, methylene envelope); *m/z* (CI, NH_3) 528 [(M^+ + H), 100%] and 386 (12) [Found: (M^+ + H), 528.2420. $C_{29}H_{38}NO_6S$ requires *M*, 528.2420].

(2R*,3R*,6R*)-3-[(1S*)-1-*Acetoxy*-3-*benzyloxypropyl*]-6-[(2R* *or* S*)-2-*hydroxy*-2-*methoxycarbonylethyl*]-2-(3-*phenylsulfonylpropyl*)*piperidine* **28**.—A solution of the isoxazolidine **11** (78.6 mg, 0.137 mmol) in acetic acid–water (1:1, 5 cm^3) was treated with activated zinc dust (100 mg) and heated to 80 °C for 2 h under a nitrogen atmosphere. The solution was cooled, basified with aqueous sodium hydroxide (2 mol dm^{-3}) and poured into saturated aqueous sodium hydrogen carbonate (25 cm^3). The aqueous phase was extracted with dichloromethane (3 × 25 cm^3) and the combined extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was dissolved in ethyl acetate (25 cm^3) and the solution was heated to reflux under a nitrogen atmosphere for 16 h. TLC analysis indicated no cyclisation to the lactam **29** had occurred. The reaction mixture was evaporated under reduced pressure and the residue was purified by flash chromatography on silica eluting with 1% aqueous ammonia–ethyl acetate to give the *piperidines* **28** (44.6 mg, 57%) as a colourless oil; $\nu_{max}(CCl_4)/cm^{-1}$ 3540br w and 3300br w (OH and NH), 3080w and 3040w (CH), 1735s (CO), 1440s and 1150s (SO_2); δ_H(250 MHz; $CDCl_3$) 7.91–7.87 (2 H, m, SO_2Ph), 7.67–7.51 (3 H, m, SO_2Ph), 7.35–7.23 (5 H, m, OCH_2Ph), 5.32 (1 H, dt, *J* 8.4 and 2.9,

CHOAc), 4.44 (2 H, s, OCH_2Ph), 4.38 (1 H, t, *J* 5.1, CHOH), 3.74 (3 H, s, OMe), 3.48–3.41 (2 H, m, CH_2OBn), 3.11–2.97 (2 H, m, CH_2SO_2), 2.94–2.60 (4 H, m, 2-H, 6-H, OH and NH), 1.94 (3 H, s, OAc) and 2.09–1.16 (13 H, m, 3-H and methylene envelope); δ_C(100 MHz; $CDCl_3$) 175.2, 170.8, 139.1, 138.2, 133.6, 129.3, 128.4, 128.0, 127.7 127.6, 73.2, 70.2, 69.8, 66.6, 59.7, 56.0, 55.4, 52.2, 39.0, 38.4, 33.2, 32.7, 28.2, 27.7, 21.4 and 20.7; *m/z* (FAB) 576 [(M^+ + H), 55%], 279 (15), 205 (16), 149 (100) and 91 (42) [Found: (M^+ + H), 576.2631. $C_{30}H_{42}NO_8S$ requires *M*, 576.2631].

(5R*,6R*,8aS*)-6-[(1S*)-3-*Benzyloxy*-1-*hydroxypropyl*]-5-(3-*phenylsulfonylpropyl*)*octahydroindolizin*-3-*one* **30**.—A solution of the acetate **27** (431 mg, 0.82 mmol) in methanol (10 cm^3) was treated with potassium carbonate (100 mg) and stirred under an argon atmosphere for 48 h. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate (50 cm^3) and extracted with dichloromethane (4 × 50 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica eluting with ethyl acetate to give the *alcohol* **30** (381 mg, 96%) as a colourless gum; $\nu_{max}(CCl_4)/cm^{-1}$ 3600–3200br m (OH), 3060w and 3020w (CH), 1670s (CO), 1440m, 1420m, 1300s and 1150s (SO_2); δ_H(400 MHz; $CDCl_3$) 7.90–7.88 (2 H, m, SO_2Ph), 7.63–7.51 (3 H, m, SO_2Ph), 7.36–7.26 (5 H, m, CH_2Ph), 4.50 and 4.48 (2 H, dd, *J* 11.9, CH_2Ph), 4.52–4.43 (1 H, m, 5-H or 8a-H), 3.73–3.69 (1 H, m, CHOBn), 3.65–3.60 (1 H, m, CHOBn), 3.54 (1 H, t, *J* 9, CHOH), 3.48–3.43 (1 H, m, 8a-H or 5-H), 3.40–3.33 (1 H, m, $CHHSO_2$), 3.13–3.06 (1 H, m, $CHHSO_2$), 2.34–2.28 (2 H, m, 2-H), 2.16–2.12 (1 H, m, 6-H) and 1.88–1.11 (12 H, m, methylene envelope); δ_C(100 MHz; $CDCl_3$) 173.6, 139.1, 137.6, 133.5, 129.1, 128.4, 128.0, 127.7, 127.7, 73.3, 71.5, 68.7, 55.0, 52.2, 47.4, 44.4, 34.1, 33.3, 30.1, 24.4, 23.0, 22.1 and 18.8; *m/z* (CI, NH_3) 486 [(M^+ + H), 100%] and 344 (28) [Found: (M^+ + H), 486.2305. $C_{27}H_{36}NO_5S$ requires *M*, 486.2315].

(5R*,6R*,8aS*)-6-(3-*Benzyloxy*-1-*oxopropyl*)-5-(3-*phenylsulfonylpropyl*)*octahydroindolizin*-3-*one* **33**.—A solution of the alcohol **30** (18.5 mg, 38.1 μmol) in acetone (1 cm^3) at 0 °C was treated with Jones' reagent (2 mol dm^{-3}; 2 drops) and the mixture stirred for 15 min. The reaction mixture was quenched with isopropyl alcohol and poured into brine (20 cm^3). The aqueous phase was extracted with ethyl acetate (3 × 20 cm^3) and the combined organic fractions were dried ($MgSO_4$), filtered through a Florisil plug and evaporated under reduced pressure to give the *ketone* **33** (17.4 mg, 94%) as a colourless oil; $\nu_{max}(CCl_4)/cm^{-1}$ 1720m (CO) and 1690s (CO); δ_H(250 MHz; $CDCl_3$) 7.83 (2 H, d, *J* 7.7, SO_2Ph), 7.65–7.50 (3 H, m, SO_2Ph), 7.30–7.23 (5 H, m, CH_2Ph), 4.59 (1 H, dt, *J* 4.5 and 1.3, 5-H or 8a-H), 4.44 (2 H, s, CH_2Ph), 3.84–3.75 (1 H, m, CHOBn), 3.70–3.62 (1 H, m, CHOBn), 3.48–3.44 (1 H, m, 8a-H or 5-H), 3.15–3.03 (1 H, m, $CHHSO_2$), 2.89–2.73 (2 H, m, $CHHSO_2$ and 6-H), 2.65–2.52 (2 H, m, CH_2CO), 2.38–2.29 (2 H, m, CH_2CO) and 2.22–0.95 (10 H, m, methylene envelope); *m/z* (CI, NH_3) 484 [(M^+ + H), 100%], 394 (2) and 376 (18) [Found: (M^+ + H), 484.2158. $C_{27}H_{34}NO_5S$ requires *M*, 484.2158].

Reduction of the Ketone **33**.—A solution of the ketone **33** (17.4 mg, 36 μmol) in dry ethanol (1 cm^3) was treated with sodium borohydride (*ca.* 10 mg) and the mixture was stirred at 0 °C for 15 min. The mixture was poured into saturated aqueous sodium hydrogen carbonate (20 cm^3) and extracted with dichloromethane (3 × 20 cm^3). The combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography eluting five times with ethyl acetate to give three close running fractions. The least polar band was identified as the ketone **33** (2.8 mg, 16%). The middle band was spectroscopically identical with the alcohol **30** (5 mg, 29%). The lowest running fraction was identified as the inverted alcohol **34** (2.6 mg, 14%) and was identical with the alcohol obtained by hydrolysis of the benzoate **35**.

(5R*,6R*,8aS*)-6-[(1R*)-3-*Benzyloxy*-1-*hydroxypropyl*]-5-(3-*phenylsulfonylpropyl*)*octahydroindolizin*-3-*one* **34**.—A solution of the benzoate **35** (220 mg, 0.37 mmol) in dry methanol (20 cm^3) was treated with potassium carbonate (300 mg) and the mixture was stirred at room temperature for 72 h. 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 ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 0–2% methanol–ethyl acetate to give the *alcohol* **34** (160 mg, 89%); $\nu_{max}(CCl_4)/cm^{-1}$ 3500br m (OH) and 1680s (CO); δ_H(250 MHz; $CDCl_3$) 7.89–7.85 (2 H, m, SO_2Ph), 7.66–7.50 (3 H, m, SO_2Ph), 7.37–7.24 (5 H, m, CH_2Ph), 4.50 (2 H, s, CH_2Ph), 4.14 (1 H, br d, *J* 12, 5-H or 8a-H), 3.81–3.73 (1 H, m, CHOBn), 3.70–3.63 (1 H, m, CHOBn), 3.61–3.54 (1 H, m, CHOH), 3.52–3.40 (1 H, m, 8a-H or 5-H), 3.33–3.19 (2 H, m, $CHHSO_2$ and OH), 3.09–2.97 (1 H, m, $CHHSO_2$), 2.40–2.26 (2 H, m, 2-H), 2.22–2.04 (1 H, m, 6-H) and 2.01–1.10 (12 H, m, methylene envelope); δ_C(100 MHz; $CDCl_3$) 173.73, 139.22, 137.59, 133.56, 129.20, 128.48, 128.01, 127.84, 127.66, 73.43, 72.01, 69.30, 54.99, 52.60, 48.82, 44.84, 33.78, 33.48, 30.07, 24.46, 23.58, 20.76 and 16.96; *m/z* (CI, NH_3) 486 [(M^+ + H), 100%], 344 (8) and 138 (2) [Found: (M^+ + H), 486.2314. $C_{27}H_{36}NO_5S$ requires *M*, 486.2314].

(5R*,6R*,8aS*)-6-[(1R*)-1-*Benzoyloxy*-3-*benzyloxypropyl*]-5-(3-*phenylsulfonylpropyl*)*octahydroindolizin*-3-*one* **35**.—The alcohol **30** (222 mg, 0.458 mmol) in dry benzene (1 cm^3) was treated with a solution of triphenylphosphine (601 mg, 2.3 mmol) and benzoic acid (168 mg, 1.37 mmol) in dry benzene (5 cm^3). The mixture was cooled in an ice bath and DEAD (361 mm^3, 2.3 mmol) was added dropwise. The solution was stirred for 1 h, poured into saturated aqueous sodium hydrogen carbonate (50 cm^3) and extracted with dichloromethane (3 × 50 cm^3). The combined extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 66% toluene–acetone to give the *benzoate* **35** (220 mg, 81%) as a colourless gum; $\nu_{max}(CCl_4)/cm^{-1}$ 1725s (CO) and 1685s (CO); δ_H(250 MHz; $CDCl_3$) 8.00–7.97 (2 H, m, COPh), 7.88–7.85 (2 H, m, SO_2Ph), 7.66–7.40 (6 H, m, COPh and SO_2Ph), 7.25–7.17 (5 H, m, CH_2Ph), 5.22 (1 H, dt, *J* 9.1 and 2.8, CHOBz), 4.40 (2 H, s, CH_2Ph), 4.27 (1 H, dt, *J* 12.4 and 4.0, 5-H or 8a-H), 3.55–3.41 (3 H, m, CH_2OBn and 8a-H or 5-H), 3.31–3.20 (1 H, m, $CHHSO_2$), 2.98–2.87 (1 H, m, $CHHSO_2$), 2.37–2.29 (2 H, m, 2-H), 2.25–2.00 (1 H, m, 6-H) and 1.93–1.08 (12 H, m, methylene envelope); δ_C(100 MHz; $CDCl_3$) 173.67, 166.05, 139.07, 138.15, 133.61, 133.13, 129.90, 129.60, 129.22, 128.44, 128.25, 128.04, 127.65, 127.48, 73.13, 72.15, 66.25, 54.93, 52.27, 48.21, 42.94, 33.12, 32.53, 30.00, 24.37, 23.29, 21.66 and 16.78; *m/z* (CI, NH_3) 590 [(M^+ + H), 100%], 468 (5) and 448 (5) [Found: (M^+ + H), 590.2576. $C_{34}H_{40}NO_6S$ requires *M*, 590.2576].

(5R*,6R*,8aS*)-6-[(1S*)-1-*Benzoyloxy*-3-*benzyloxypropyl*]-5-(3-*phenylsulfonylpropyl*)*octahydroindolizin*-3-*one* **36**.—(a) The alcohol **30** (12 mg, 25 μmol) in dry pyridine (1 cm^3) was treated with benzoyl chloride (0.2 cm^3) and DMAP (*ca.* 10 mg) and the mixture was stirred for 1 h. The solution was poured into saturated aqueous sodium hydrogen carbonate (20 cm^3) and extracted with dichloromethane (3 × 20 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash

chromatography on silica eluting with 50–100% ethyl acetate–hexane to give the *benzoate* **36** (11 mg, 75%) as a colourless oil; $\nu_{max}(CCl_4)/cm^{-1}$ 1725s (CO) and 1685s (CO); δ_H(250 MHz; $CDCl_3$) 8.00–7.96 (2 H, m, COPh), 7.80–7.77 (2 H, m, SO_2Ph), 7.63–7.38 (6 H, m, SO_2Ph and COPh), 7.27–7.21 (5 H, m, CH_2Ph), 5.22 (1 H, dt, *J* 8 and 3.6, C*H*OBz), 4.40 (2 H, s, CH_2Ph), 4.33 (1 H, dt, *J* 13.5 and 3.7, 5-H), 3.56–3.43 (3 H, m, CH_2OBn and 8a-H), 3.34–3.23 (1 H, m, C*H*HSO_2), 2.83–2.72 (1 H, m, CH*H*SO_2), 2.36–2.26 (2 H, m, 2-H) and 2.22–1.14 (13 H, m, 6-H and methylene envelope); δ_C(100 MHz; $CDCl_3$) 173.58, 166.67, 139.15, 138.06, 133.44, 133.24, 133.01, 132.13, 132.03, 131.95, 131.92, 129.69, 129.64, 129.12, 128.56, 128.43, 128.29, 127.96, 127.73, 127.54, 73.20, 72.70, 66.32, 54.98, 52.06, 47.41, 42.60, 33.33, 32.64, 30.08, 24.48, 23.78, 22.31 and 18.68; *m/z* (CI, NH_3) 590 [(M^+ + H), 100%] and 448 (3) [Found: (M^+ + H), 590.2576. $C_{34}H_{40}NO_6S$ requires *M*, 590.2576].

(b) The alcohol **34** (20 mg, 0.04 mmol) in dry benzene (1 cm^3) was treated with triphenylphosphine (52 mg, 0.2 mmol) and benzoic acid (15 mg, 0.12 mmol) and the solution was cooled to 0 °C. The mixture was treated with DEAD (35 mm^3) and the mixture was stirred at room temperature for 1 h. The mixture was evaporated under reduced pressure and the residue was purified by preparative thin layer chromatography on silica eluting with ethyl acetate to give the benzoate **36** (24 mg, 94%) as a colourless film.

(5R*,6R*,8aS*)-6-[(1R*)-3-*Benzyloxy*-1-(*toluene*-p-*sulfonyloxy*)*propyl*]-5-(3-*phenylsulfonylpropyl*)*octahydroindolizin*-3-*one* **37**.—A solution of the alcohol **34** (154 mg, 0.318 mmol) in dry pyridine (3 cm^3) was treated with DMAP (50 mg) and toluene-*p*-sulfonyl chloride (606 mg, 3.5 mmol) and the mixture was stirred under a nitrogen atmosphere for 48 h. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate (50 cm^3) and extracted with dichloromethane (3 × 50 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica eluting with 50–100% ethyl acetate–hexane to give the *tosylate* **37** (191 mg, 94%) as a colourless gum; $\nu_{max}(CCl_4)/cm^{-1}$ 1685s (CO); δ_H(400 MHz; $CDCl_3$) 7.85 (2 H, dd, *J* 8.6 and 1.4, SO_2Ph), 7.73 (2 H, d, *J* 8.3, CH_3Ph), 7.63 (1 H, t, *J* 7.2, SO_2Ph), 7.53 (2 H, t, *J* 7.3, SO_2Ph), 7.33–7.26 (7 H, m, CH_3Ph and CH_2Ph), 4.66 (1 H, dt, *J* 7.3 and 3.3, C*H*OTs), 4.36 and 4.30 (2 H, dd, J_{AB} 11.6, CH_2Ph), 4.19 (1 H, dt, *J* 12.1 and 3.4, 5-H), 3.42–3.37 (2 H, m, 8a-H and C*H*HOBn), 3.29–3.25 (1 H, m, CH*H*OBn), 3.19–3.13 (1 H, m, C*H*HSO_2), 2.91–2.85 (1 H, m, CH*H*SO_2), 2.43 (3 H, s, CH_3Ph), 2.33–2.26 (2 H, m, 2-H), 2.15–2.10 (1 H, m, 6-H) and 1.99–1.07 (12 H, m, methylene envelope); δ_C(100 MHz; $CDCl_3$) 173.68, 144.72, 139.13, 138.19, 134.46, 133.60, 129.75, 129.21, 128.35, 128.03, 127.56, 81.96, 72.89, 65.17, 54.84, 52.19, 47.97, 42.66, 33.09, 32.48, 29.98, 24.39, 23.18, 22.12 and 18.67; *m/z* (EI) 559 (M − 80, 5%), 469 (80), 285 (100), 178 (60), 150 (30) and 91 (100) [Found: (FAB) (M^+ + H), 640.2403. $C_{34}H_{42}NO_7S_2$ requires *M*, 640.2403].

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