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Directed addition of sulfur-stabilised carbanions to 1,2,3-trisubstituted aziridines

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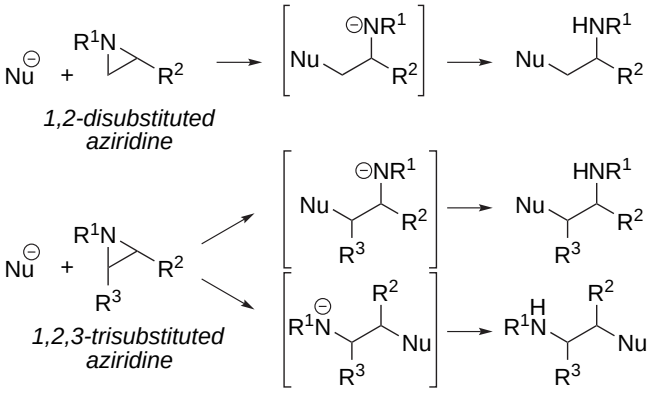
ABSTRACT

Thioether and sulfone-stabilised carbanions possessing varying functional groups enter into highly regioselective, stereospecific ring-opening reactions with vinyl- and hydroxymethyl-substituted aziridines. Some derivatisation reactions of the adducts are reported.

1. Introduction

Aziridines are valuable intermediates for the synthesis of nitrogen-containing molecules. Combining electrophilic reactivity with ease of synthesis, they are readily available from a variety of sources, most notably by cyclisation reactions of aminoalcohol derivatives, and by nitrenoid insertion into alkenes, and carbenoid insertion into the C—N double bonds of imines. Aziridine reactivity towards nucleophiles may be modified by variation of the *N*-substituent, and in general, aziridines substituted on nitrogen and on one of the ring carbon atoms suffer attack by anionic nucleophiles at the less substituted 3-position. When both carbon atoms are substituted, steric and electronic effects may compete, such that mixtures of products of attack at both electrophilic ring positions are obtained (Scheme 1).[1,2]

We reported recently[3] a series of reactions in which sulfur-stabilised (arylsulfenyl, arylsulfonyl) carbanions combined with 1,2,3-trisubstituted aziridines to give the products of stereospecific and completely regioselective ring-opening. These reactions proceeded with inversion of configuration at the aziridine carbon atom undergoing nucleophilic attack. We ascribed the observed complete regioselectivity in the vinylaziridine reactions to the directing effects of unsaturation, which causes selective weakening through $\pi-\sigma^*$ overlap of the breaking aziridine C—N bond. Aryl groups have been reported to show analogous directing effects, in ring-opening reactions of electron-rich arenes with arylaziridines involving S_EAr-type mechanisms.[4–9] The same regioselectivity has been reported for sulfur ylides[10,11] and organometallic reagents.[12] In contrast, reaction of vinylaziridines with organomagnesium[13] and organocopper[14–16] reagents frequently gives predominantly the products of S_N2'-type ring-opening. In the case of the hydroxyaziridine reactions, the directing group is the lithiated oxygen atom, through attractive interaction with the incoming lithiated carbanionic species (Scheme 2).[17] This paper describes further examples of these highly selective processes, and documents derivatisation reactions of the ring-opened products, which illustrate their potential in synthesis.



Scheme 1.

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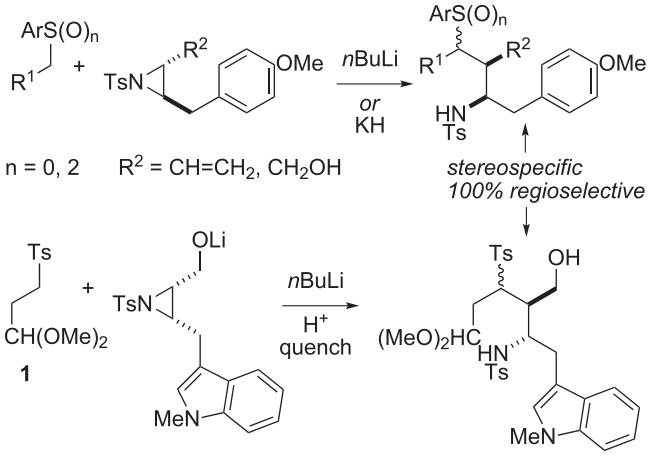
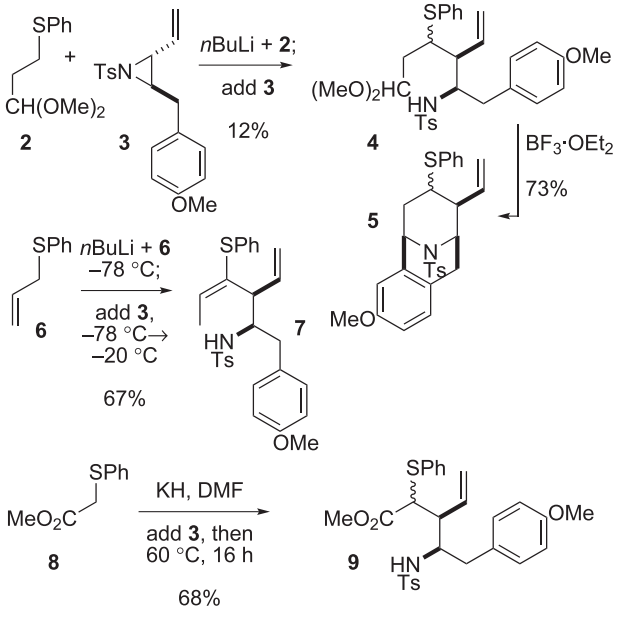


Scheme 2. Ref. 3.

2. Results and discussion

2.1. Olefin-directed nucleophilic ring-opening of a vinylaziridine: thioether-stabilised carbanions

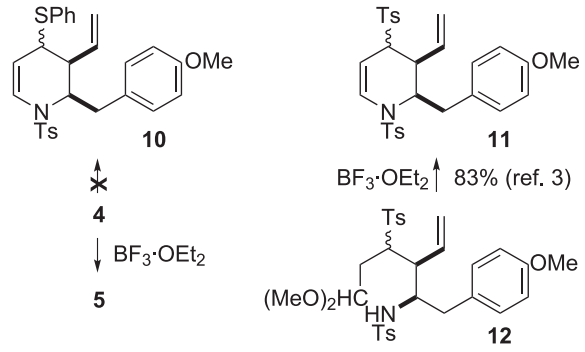
Our earlier work had established that both sulfone- and thioether-stabilised carbanions reacted with a *trans*-1,2,3-trisubstituted vinylaziridine in a highly selective manner. Further experimentation sought to extend the range of thioether-containing nucleophilic partners in these coupling reactions, and vinylaziridine **3**[3] was selected as the electrophile to enable valid comparisons to be made with the reactions studied previously. In contrast with the sulfone derivative **1** (Scheme 2), the lithio-anion of thioether–acetal **2** combined poorly with **3**, providing a 5:1 diastereoisomeric mixture of adducts **4** in just 12% yield; the structure of the major isomer was not assigned. Exposure of the isomeric mixture of **4** to $BF_3{\cdot}OEt_2$ resulted in cyclisation to give the benzo-fused 9-azabicyclo[3.3.1] nonane **5**, in good yield. Attempts to improve the yield of the ring-opening reaction of 1-phenylthio-2-propene **6** with **3** studied previously,[3] by raising the reaction temperature instead gave the vinylic thioether **7** in good yield, predominantly as the *E*-isomer. Presumably the N-centred anion formed on ring-opening of **3** is sufficiently basic to abstract reversibly the thioether α-proton in the adduct, thereby causing double bond migration to the thermodynamically favoured position. Finally, reaction of the potassium enolate of ester **8** with **3** gave in good yield a 3:1 diastereoisomeric mixture of adducts **9**. This behaviour again contrasted with that of the analogous sulfone-containing nucleophile, which in our earlier work had been shown to give the corresponding *N*-tosyl lactam, by spontaneous 5-*exo*-*trig* addition–elimination of the initially formed adduct. The reactions of **3** with thioether-stabilised carbanionic species are depicted in Scheme 3.



Scheme 3.

2.2. Derivatisation reactions of vinylaziridine ring-opening adducts

One of the goals of this study was the identification of synthesis sequences, which would enable access to prepare thioether-substituted cyclic ene–sulfonamides, such as **10** (Scheme 4). These are less highly oxidised congeners of sulfones **11**, which we had demonstrated previously to be effective substrates for oxaphilic Lewis acid-mediated S_N1 and S_N1' C–C bond forming processes.[18,19] Scheme 3 shows an unsuccessful attempt to prepare **10** using the sequence **2**+**3**→**4**→**5**, which was unviable because of the low efficiency of combination of lithio-**2** and **3**, and the unwanted cyclisation of **4** to give **5** on treatment with $BF_3{\cdot}OEt_2$. Our earlier report[3] described the formation of **11** from the corresponding tosyl-substituted vinylaziridine ring-opened adduct **12** using the same conditions (Scheme 4).

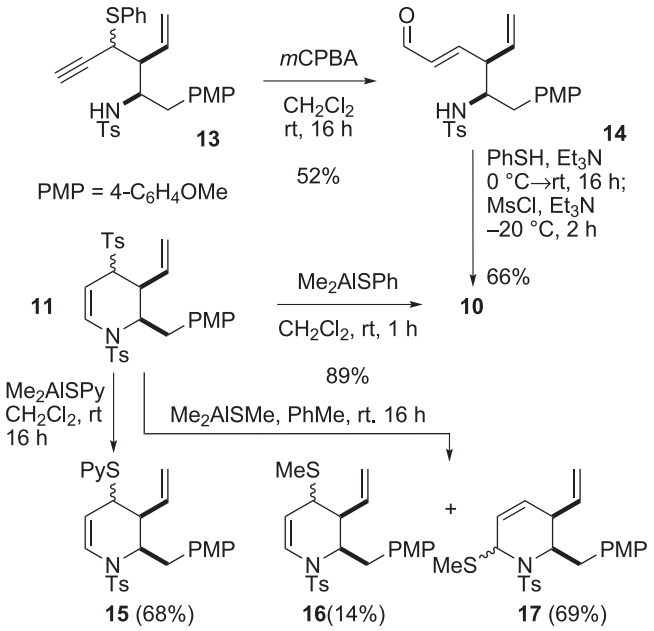


Scheme 4.

In the event, two routes to **10** were uncovered. The first of these employed thioether **13**, the ring-opened adduct of 1-phenylthio-2-propyne and **3**.[3] Treatment of **13** with *m*CPBA gave in 52% yield the *E*-enal **14**; likely this is formed by *S*-oxidation, followed by [2,3]-sigmatropic rearrangement of the propargylic sulfoxide[20] and hydrolysis of the resultant allenyl sulfenate. Reaction of **14** with thiophenol–Et_3N, and subsequent treatment of the resulting cyclic *N*-tosylhemiaminal with methanesulfonyl chloride in situ gave ene-sulfonamide **10** in 66% yield for the one-pot process starting from **14**.[21] Alternatively, simple exposure of **11** to Me_2AlSPh[22] gave **10** in 89% yield. This transformation was subsequently adapted to enable incorporation of 2-pyridylthio (from Me_2AlSPy,[23] to give **15**) and methylthio (from Me_2AlSMe,[24] to give **16**) groups into the ene–sulfonamide ring, although the latter reaction gave predominantly the allylically transposed product **17** (Scheme 5).

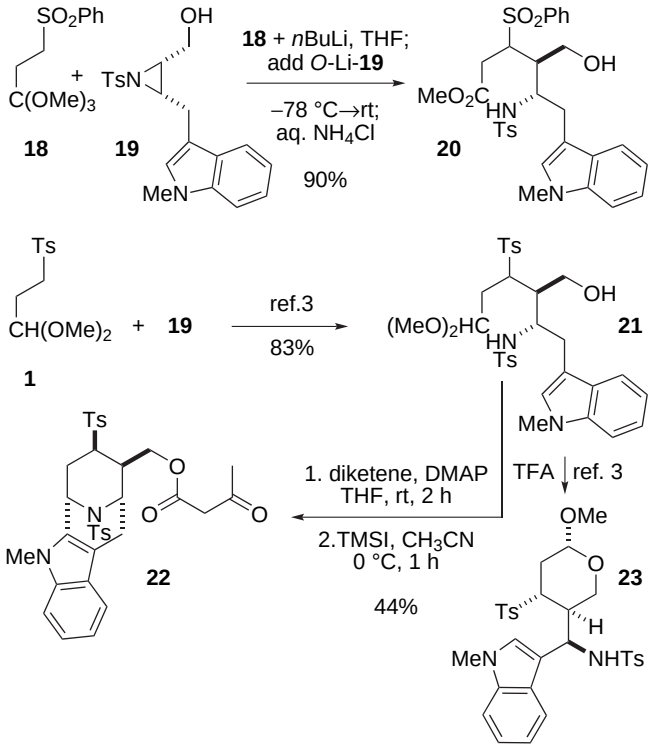
2.3. Alkoxide-directed nucleophilic ring-opening of hydroxyaziridines: sulfone-stabilised carbanions

The last part of this investigation focussed on hydroxyaziridines as electrophiles. Following the successful combination of sulfonylacetal **1** with the lithiated indolic hydroxyaziridine depicted in Scheme 1, we became interested in the analogous reaction of the



Scheme 5.

sulfonyl-substituted orthoester **18**. Compound **18** was best synthesised starting from commercially available phenylthioethene using the procedure of Parham and co-workers;[25] despite repeated attempts, we were unable to reproduce the method reported subsequently by Ghosez and co-workers.[26] Treatment of lithiated **18** with *O*-lithiated **19** again resulted in stereospecific, completely regioselective aziridine ring-opening to give the methyl ester **20** as a single diastereoisomer upon mildly acidic work-up. No products corresponding to aza-Payne rearrangement[27] of **19** were detected. In contrast, the analogous acetal-containing product **21** of the previously-reported[3] reaction of lithio-**1** with **19** underwent ready cyclisation on brief treatment with acid, giving lactol ether **23**.



Scheme 6.

However, this reactivity could be modified by functionalisation of the primary alcohol prior to acid treatment. Thus, reaction of adduct **21** with diketene, and treatment of the product with TMSI gave in 44% yield over two steps the tetracyclic β-ketoester **22**, as a single diastereoisomer (Scheme 6). We have reported previously[28] a related intramolecular Pictet–Spengler reaction of a structurally simpler indolic aziridine ring-opened adduct.

3. Conclusions

In conclusion, the results reported herein provide further demonstration of the powerful directing effects of the vinyl and lithiated hydroxymethyl groups on the regiochemistry of aziridine ring-opening reactions. These stereospecific transformations allow the rapid assembly of polyfunctionalised small molecules, which possess mutually reactive functional motifs, which may participate in subsequent transformations. We are presently applying some of the chemistry described above to the synthesis of piperidine and indole-containing natural products, and the results of these investigations will be reported in due course.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise stated) on either Jeol GX-270a, DRX 300, DRX 400 or Aspect 500 spectrometers, using residual isotopic solvents as internal reference. Infra-red spectra were measured on a Mattson 5000 FTIR spectrometer. Mass spectra were recorded using VG 707E or VG Autospec Q instruments. Accurate masses were determined using the Autospec Q instrument at Imperial College. Elemental combustion analyses were performed in the London Metropolitan University microanalytical laboratory. Melting points were measured on a Stuart Scientific SMP1 melting point apparatus and are uncorrected. Chromatography refers to flash chromatography on BDH (40–63 μM) silica gel. Analytical thin layer chromatography was performed using pre-coated aluminium-backed plates (Merck Kieselgel 60 F_{254}) and visualised with ultraviolet light and/or acidic ammonium molybdate (IV), acidic vanillin, ethanolic potassium permanganate or acidic 3,5-dinitrophenylhydrazine solutions. Standard solvents were distilled under nitrogen; Et_2O and THF from sodium–benzophenone ketyl, CH_2Cl_2 and MeCN from calcium hydride and PhMe from sodium. Petrol refers to petroleum ether bp 40–60 °C. Other solvents and reagents were used as received or purified before use according to standard procedures. All reactions were performed under an atmosphere of nitrogen unless stated otherwise.

4.1.1. 3-(Phenylthio)propanal[29]. To a solution of thiophenol (2.20 g, 20.0 mmol, 1.0 equiv), Et_3N (0.28 mL, 2.0 mmol, 0.1 equiv) and CH_2Cl_2 (20 mL) at 0 °C was added acrolein (2.67 mL, 40 mmol, 2.0 equiv). After 30 min, concentration under reduced pressure and drying under high vacuum gave 3-(phenylthio)propanal (3.32 g, 100%) as a colourless oil; R_f 0.59 (50% EtOAc–petrol); δ_H (400 MHz) 9.79 (1H, s, CHO), 7.39–7.25 (5H, m, Ph), 3.21 (2H, t, *J* 7.0 Hz, CH_2CHO), 2.80 (2H, t, *J* 7.0 Hz, PhSCH_2); δ_C (125 MHz) 200.3 (CHO), 135.1 (*ipso* PhS), 130.0 (*ortho* PhS), 129.1 (*meta* PhS), 126.7 (*para* PhS), 43.3 (CH_2CHO), 26.4 (CH_2PhS); *m*/*z* (CI) 184 $[M+NH_4]^+$, 166, 52.

*4.1.2. ((3,3)-Dimethoxypropyl)(phenyl)sulfane (**2**)*[30]. A solution of 3-(phenylthio)propanal (2.90 g, 17.5 mmol, 1.0 equiv), $CH(MeO)_3$ (3.71 g, 34.9 mmol, 2.0 equiv), *p*-TsOH·H_2O (100 mg, 0.526 mmol, 0.03 equiv) and MeOH (35 mL) was heated to 50 °C. Then, EtOH (15 mL) was added to the crude, washed with satd aq $NaHCO_3$ (3×30 mL), H_2O (3×10 mL), brine (2×15 mL) and dried (Na_2SO_4).

Concentration under reduced pressure and column chromatography (5% EtOAc–petrol containing 1% Et_3N) gave ((3,3)-dimethoxypropyl)(phenyl)sulfone **2** (3.90 g, 96%) as a colourless oil; R_f 0.51 (23% Et_2O–petrol); ν_{max} (film) 3057, 2933, 2830, 1944, 1870, 1724, 1686, 1583, 1400, 1438, 1382, 1366, 1281, 1192, 1160, 1123, 1073 cm^{-1}; δ_H (400 MHz) 7.38–7.19 (5H, m, Ph), 4.53 (1H, t, *J* 5.0 Hz, CH), 3.35 (6H, s, OMe), 2.99 (2H, t, *J* 7.0 Hz, CH_2SPh), 1.96 (2H, dt, *J* 7.0, 5.0 Hz, CH_2CH); δ_C (125 MHz) 136.2 (*ipso* PhS), 129.2 (*ortho* PhS), 128.9 (*meta* PhS), 125.9 (*para* PhS), 103.2 (CH), 53.2 (OMe), 32.3 (*C*H_2PhS), 28.8 (*C*H_2CH).

4.1.3. N-((2R,3S*)-6,6-Dimethoxy-1-phenyl-4-(phenylthio)-3-vinylhexan-2-yl)-4-methylbenzenesulfonamide (**4**).* To a solution of acetal **2** (403 mg, 1.90 mmol, 1.3 equiv) in THF (0.7 mL) at −78 °C was added ^{n}BuLi (905 μL of a 2.1 M solution in hexanes, 1.90 mmol, 1.3 equiv). After 20 min, the mixture was warmed to 0 °C and stirred during 20 min. The mixture was re-cooled to −78 °C and a solution of vinylaziridine **3** (500 mg, 1.46 mmol, 1.0 equiv) in THF (0.7 mL) was added. The resulting solution was allowed to warm to rt. After 16 h, the reaction was quenched with satd aq $NaHCO_3$ (10 mL) and the aqueous phase extracted with EtOAc (3×7 mL). The combined organic layers were washed with brine (3×5 mL) and dried (Na_2SO_4). Concentration under reduced pressure and column chromatography (10%→25% EtOAc–petrol) gave a 5:1 diastereoisomeric mixture of *N*-[(2*R**,3*S**)-6,6-*dimethoxy-1*-(4-*methoxyphenyl*)-4-(*phenylthio*)-3-*vinylhexan-2-yl*]-4-*methylbenzenesulfonamide* **4** (100 mg, 12%) as a gum; data for major diastereomer only: R_f 0.21 (25% EtOAc–petrol); ν_{max} (film) 3277, 2938, 2833, 1161, 1583, 1513, 1439, 1324, 1302, 1248, 1178, 1157, 1124 cm^{-1}; δ_H (400 MHz) 7.69 (2H, d, *J* 8.0 Hz, *ortho* Ts), 7.65–7.14 (7H, m, SPh and *meta* Ts), 6.95 (2H, d, *J* 8.5 Hz, *meta* ArOMe), 6.73 (2H, d, *J* 8.5 Hz, *ortho* ArOMe), 5.47 (1H, dt, *J* 17.0, 10.0 Hz, C*H*=CH_2), 5.18 (1H, dd, *J* 10.0, 1.5 Hz, *trans* CH=C*H*H), 5.01 (1H, dd, *J* 17.0, 1.5 Hz, *cis* CH=CH*H*), 4.54 [1H, t, *J* 5.5 Hz, CH($OMe)_2$], 4.42 (1H, d, *J* 7.5 Hz, NH), 3.92–3.89 (1H, m, CHN), 3.79 (3H, s, ArO*Me*), 3.54 (1H, dt, *J* 7.0, 4.0 Hz, CHS), 3.25 (3H, s, *Me*OCHOMe), 3.23 (3H, s, MeOCHO*Me*), 2.76 (1H, dd, *J* 14.0, 6.0 Hz, C*H*HArOMe), 2.55 (1H, dd, *J* 14.0, 4.5 Hz, CH*H*ArOMe), 2.44 (3H, s, Me of Ts), 2.30–2.25 (1H, m, *CH*CH=CH_2), 1.85 (2H, dd, *J* 7.0, 5.5 Hz, *C*H_2CHS); δ_C (100.7 MHz) [158.3, 143.2, 137.6, 135.6 (q Ar)], 134.9 (3° Ar), [131.4, 130.9, 129.6, 128.9 (3° Ar)], 128.1 (q Ar), 127.2 (3° Ar), 126.9 (*C*H=CH_2), 120.8 (CH=*C*H_2), 113.8 (3° Ar), 102.5 [*C*H($OMe)_2$], 55.3 [CH(O*Me*)$_2$], 53.1 (ArO*Me*), 50.7 (CHN), 47.1 (*C*HSPh), [37.6, 37.4 (CH_2)], 23.9 (Me of Ts), 21.6 (*C*HCH=CH_2); *m*/*z* (ESI) 578 $[M+Na]^+$, 556 $[M+H]^+$, 554, 492 (found: $[M+NH_4]^+$, 578.1995. $C_{30}H_{37}NO_5S_2$ requires $[M+NH_4]^+$. 578.2011) (found: C, 65.00; H, 6.71; N, 2.58. $C_{30}H_{37}NO_5S_2$ requires C, 64.84; H, 6.71; N, 2.52%).

4.2. Cyclisation of acetal 4

To a solution of tosamide **4** (16.0 mg, 0.029 mmol, 1.0 equiv) in CH_2Cl_2 (0.6 mL) at −78 °C was added $BF_3{\cdot}Et_2O$ (0.06 mL, 0.44 mmol, 15.0 equiv). The solution was warmed to rt slowly. After 16 h, satd aq $NaHCO_3$ (1.0 mL) was added. The mixture was extracted with CH_2Cl_2 (2×2 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Concentration under reduced pressure and purification by preparative TLC gave the major diastereomer of the tricycle **5** (10.0 mg, 73%) as a gum; R_f 0.74 (30% EtOAc–petrol); δ_H (400 MHz) 7.50 (2H, d, *J* 8.5 Hz, *ortho* Ts), 7.26–7.23 (5H, m, SPh), 7.05 (2H, d, *J* 8.5 Hz, *meta* Ts), 6.75 (1H, d, *J* 8.5 Hz, *meta* ArOMe), 6.67 (1H, dd, *J* 8.5, 2.5 Hz, *ortho* MeOAr), 6.50 (1H, d, *J* 2.5 Hz, *ortho* MeOAr), 5.76 (1H, ddd, *J* 17.0, 10.5, 8.5 Hz, C*H*=CH_2), 5.34–5.27 (2H, m, CH=CH_2), 5.07 (1H, m, ArC*H*N), 4.29–4.27 (1H, m, CHC*H*N), 3.79 (3H, s, OMe), 2.91–2.84 (1H, m, C*H*SPh), 2.69–2.56 (3H, m, CH_2ArOMe and *CH*CH=CH), 2.33 (3H, s, Me of Ts), 2.07–2.00 (2H, m, CH_2CHS); δ_C (100.7 MHz) [157.9, 143.0 (q Ar)], 137.7 (3°), [137.2, 135.9 (q Ar)], 133.6 (3°), 131.8 (q Ar), [129.1, 129.0 (3°)], 128.8 (3°), 127.7 (3°), 126.9 (3°), 125.5 (q Ar), 119.2 (CH=*C*H_2), 113.5, 110.5, 55.4 (OMe), [53.8, 53.6 (CHNCH)], 50.1 (PhS*C*H), 41.1 (*C*HCH=CH_2), 40.4 (*C*H_2ArOMe), 25.4 (*C*H_2CHS), 21.4 (Me of Ts); *m*/*z* (EI) 491 $[M]^+$, 382, 314, 227, 160, 91 (found: $[M]^+$, 491.1583. $C_{28}H_{29}NO_3S_2$ requires $[M]^+$, 491.1589).

4.2.1. 4-Methyl-N-((2R,3S*,E)-1-(4-methoxyphenyl)-4-(phenylthio)-3-vinylhex-4-en-2-yl)benzenesulfonamide (**7**).* To a solution of thioether **6** (81.4 mg, 0.542 mmol, 1.4 equiv) in THF (0.3 ml) at −78 °C was added ^{n}BuLi (62 μL of a 9.4 M solution in hexanes, 0.581 mmol, 1.5 equiv). After 15 min, the mixture was warmed to −30 °C, and then to 0 °C. After 15 min, it was re-cooled to −20 °C then a solution of aziridine **3** (100 mg, 0.387 mmol, 1.0 equiv) in THF (0.2 ml) was added. The resulting solution was warmed to rt. After 16 h the solution was quenched with satd aq NH_4Cl (2 mL), diluted with H_2O (5 mL) and the aqueous phase extracted with EtOAc (2×5 ml). The combined organic layers were washed with brine (2×5 ml) and dried (Na_2SO_4). Concentration under reduced pressure and column chromatography (5→15% EtOAc–petrol) gave a 12:1 *E*/*Z* mixture of 4-*methyl*-N-[(2*R**,3*S**)-1-(4-*methoxyphenyl*)-4-(*phenylthio*)-3-*vinylhex*-4-*en*-2-*yl*]-4-*methylbenzenesulfonamide* **7** (97.0 mg, 67%) as a solid; data for *E*-isomer only: R_f 0.33 (15% EtOAc–petrol); ν_{max} (film) 3287, 1612, 1513, 1439, 1326, 1247, 1158, 1093, 1036, 813, 741, 690, 663 cm^{-1}; δ_H (400 MHz) 7.66 (2H, d, *J* 8.5 Hz, *ortho* Ts), 7.30 (2H, d, *J* 8.5 Hz, *meta* Ts), 7.25 (2H, d, *J* 8.0 Hz, *ortho* PhS), 7.13–7.09 (1H, m, *para* PhS), 6.98–6.96 (2H, m, *meta* PhS), 6.85 (2H, d, *J* 8.5 Hz, *meta* ArOMe), 6.63 (2H, d, *J* 8.5 Hz, *ortho* ArOMe), 6.03 (1H, q, *J* 6.5 Hz, CH_3*CH*=C), 5.75 (1H, ddd, *J* 17.0, 10.0, 8.5 Hz, CH_2=C*H*), 5.16 (1H, dd, *J* 10.0, 1.5 Hz, *trans CH*H=CH), 4.91 (1H, dd, *J* 17.0, 1.5 Hz, *cis* CH*H*=CH), 4.44 (1H, d, *J* 8.0 Hz, NH), 3.80–3.78 (4H, m, OMe and NCH), 2.85–2.81 (1H, m, *CH*CH=CH_2), 2.74 (1H, dd, *J* 14.0, 5.0 Hz, CH*H*), 2.63–2.58 (1H, m, *CH*H), 2.43 (3H, s, Me of Ts), 1.79 (3H, d, *J* 6.5 Hz, *CH*$_3$CH=C); δ_C (125 MHz) [158.0, 143.1, 137.5 (q Ar)], [134.9, 134.8, 133.8 (CH=C and *para* PhS)], [129.9, 129.6 (q Ar)], [130.1, 129.5, 128.9, 128.7, 127.2 (*ortho* and *meta* Ar)], 125.8 (*C*H=CH_2), 119.2 (CH=*C*H_2), 113.6 (*ortho* or *meta* Ar), 56.9, 55.1, 52.1, 38.5, 21.5, 15.9; *m*/*z* (ESI) 516 $[M+Na]^+$, 494 $[M+H]^+$, 304, 214 (found: $[M+Na]^+$, 516.1642. $C_{28}H_{31}NO_3S_2$ requires $[M+Na]^+$, 516.1643).

4.2.2. (R)-Methyl 3-[(S)*-2-(4-methoxyphenyl)-1-(4-methylphenylsulfonamido)ethyl]-2-(phenylthio)pent-4-enoate (**9**).* A solution of thioether **8** (64.0 mg, 0.35 mmol, 1.3 equiv) in DMF (0.2 mL) was added dropwise to KH (27 mg, from a 35% mixture in oil washed with petrol three times, 0.673 mmol, 2.6 equiv) at 0 °C. After 30 min, a solution of aziridine **3** in DMF (0.8 mL) was added. After 2 h at that temperature, the reaction mixture was heated to 60 °C. After 16 h, the reaction was quenched with MeOH (2 mL). The resulting mixture was concentrated under reduced pressure to remove the excess MeOH, then diluted with EtOAc (3 mL) and brine (5 mL). The organic phase was separated and aqueous phase extracted with EtOAc (2×5 mL). The combined organic layers were washed with brine (3×5 mL) and dried ($MgSO_4$). Concentration under reduced pressure and column chromatography (10→25% EtOAc–petrol) gave a separable 3:1 diastereomeric of (*R**)-*methyl* 3-[(*S*)*-2-(4-*methoxyphenyl*)-1-(4-*methylphenylsulfonamido*)*ethyl*]-2-(*phenylthio*)*pent*-4-*enoate* **9** (93.0 mg, 68%) as gums.

Data for minor diastereoisomer: 22 mg, 16%; R_f 0.73 (40% EtOAc–petrol); ν_{max} (film) 3522, 3275, 3061, 2988, 2958, 2836, 1728, 1612, 1584, 1513, 1438, 1326, 1248, 1159, 1091, 1036, 998, 928, 814, 738, 665 cm^{-1}; δ_H (400 MHz) 7.55 (2H, d, *J* 8.0 Hz, *ortho* Ts), 7.38–7.36 (2H, m, *meta* SPh), 7.27–7.25 (3H, m, *ortho* and *para* SPh), 7.17 (2H, d, *J* 8.0 Hz, *meta* Ts), 6.81 (2H, d, *J* 8.5 Hz, *meta* ArOMe), 6.67 (2H, d, *J* 8.5 Hz, *ortho* ArOMe), 5.66 (1H, td, *J* 17.0, 10.0 Hz, C*H*=CH_2), 5.40 (1H, dd, *J* 10.0, 1.5 Hz, *trans* CH=C*H*H), 5.14 (1H, dd, *J* 17.0, 1.5 Hz, *cis* CH=CH*H*), 4.57 (1H, d, *J* 8.5 Hz, NH), 3.96 (1H, d, *J* 11.0 Hz,

C*H*SPh), 3.77 (3H, s, CH_3OOC), 3.70 (1H, m, NCH), 3.64 (3H, s, CH_3OAr), 2.66 (1H, ddd, *J* 11.5, 11.5, 2.0 Hz, C*H*CH=CH_2), 2.55 (1H, dd, *J* 14.0, 8.5 Hz, C*H*HArOMe), 2.42–2.37 (4H, m, Me of Ts and CH*H*ArOMe); δ_C (125 MHz) 171.9 (COO), [158.3, 143.2, 137.3 (q Ar)], [133.2, 133.0 (3°)], 132.9 (q Ar), [130.1, 129.9, 128.8 (3°)], 128.4(q Ar), [127.9, 126.9 (3°)], 121.7 (CH=*C*H_2), 113.8 (3°), 55.3, 55.1, 52.1, 51.2, 47.0, 39.2 (CH_2), 21.5; *m*/*z* (ESI) 548.1555 $[M+Na]^+$, 526.1734 $[M+H]^+$, 469.3163, 208.0410 (found: $[M+Na]^+$, 526.1734. $C_{28}H_{31}O_5S_2$ requires $[M+Na]^+$, 526.1722).

Data for major diastereoisomer: 71 mg, 52%; R_f 0.65 (40% EtOAc–petrol); ν_{max} (film) 3510, 3273, 3060, 2951, 2837,1732, 1612, 1513, 1439, 1326, 1248, 1159, 1048, 1035, 931, 815, 737, 664 cm^{-1}; δ_H (400 MHz) 7.78 (2H, d, *J* 8.0 Hz, *ortho* Ts), 7.29–7.19 (7H, SPh and *meta* Ts), 6.87 (2H, d, *J* 8.5 Hz, *meta* ArOMe), 6.76 (2H, d, *J* 8.5 Hz, *ortho* ArOMe), 5.70 (1H, td, *J* 17.0, 10.0 Hz, C*H*=CH_2), 5.29 (1H, dd, *J* 10.5, 1.0 Hz, *trans* CH=C*H*H), 5.14 (1H, dd, *J* 17.0, 1.0 Hz, *cis* CH=CH*H*), 4.81 (1H, d, *J* 9.0 Hz, NH), 4.27–4.21 (1H, m, NCH), 3.99 (1H, d, *J* 11.0 Hz, C*H*SPh), 3.80 (3H, s, CH_3OOC), 3.48 (3H, s, CH_3OAr), 2.51–2.39 (6H, m, C*H*CH=CH_2 and CH_2ArOMe and Me of Ts); δ_C (125 MHz) 171.7 (COO), [158.4, 143.5, 137.3 (q Ar)], [133.5, 132.6 (3°)], 131.9 (q Ar), [130.1, 129.7 (3°)], 129.4 (q Ar), [128.7, 128.1, 127.2 (3°)], 121.8 (CH=*C*H_2), 114.1 (3°), 55.2, 54.6, 52.0, 51.7, 45.6, 39.2 (CH_2), 21.5; *m*/*z* (ESI) 548.1540 $[M+Na]^+$, 526.1730 $[M+H]^+$, 494.1479, 344.1046 (found: $[M+Na]^+$, 526.1730. $C_{28}H_{31}O_5S_2$ requires $[M+Na]^+$, 526.1722).

4.2.3. N-((2R,3R*,E)-1-(4-Methoxyphenyl)-6-oxo-3-vinylhex-4-en-2-yl)-4-methylbenzenesulfonamide (**14**).* To a solution of thioethers **13**[3] (1.47 g, 2.99 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) at rt was added a solution of *m*CPBA (1.07 g of a 53% mixture of *m*-chlorobenzoic acid and H_2O, 3.29 mmol, 1.1 equiv) in CH_2Cl_2 (5 mL). After 16 h, Concentration under reduced pressure and column chromatography (20% EtOAc–petrol) gave *N*-[(2*R**,3*R**,*E*)-1-(4-*methoxyphenyl*)-6-*oxo*-3-*vinylhex*-4-*en*-2-*yl*]-4-*methylbenzene-sulfonamide* **14** (622 mg, 52%) as a gum; R_f 0.21 (25% EtOAc–petrol); ν_{max} (film) 3275, 2923, 1687, 1612, 1513, 1442, 1324, 1303, 1248, 1158, 1093, 1034, 814 cm^{-1}; δ_H (400 MHz) 9.37 (1H, d, *J* 8.0 Hz, CHO), 7.60 (2H, d, *J* 8.0 Hz, *ortho* Ts), 7.23 (2H, d, *J* 8.0 Hz, *meta* Ts), 6.89 (2H, d, *J* 8.5 Hz, *meta* ArOMe), 6.75–6.69 (3H, m, *ortho* ArOMe and CHOCH=C*H*), 6.03 (1H, ddd, *J* 16.0, 8.0, 1.5 Hz, CHOC*H*=CH), 5.77 (1H, ddd, *J* 17.0, 10.5, 8.0 Hz, C*H*=CH_2), 5.37 (1H, d, *J* 10.5 Hz, *trans* CH=C*H*H), 5.21 (1H, d, *J* 17.0 Hz, *cis* CH=CH*H*), 4.43 (1H, d, *J* 8.0 Hz, NH), 3.80 (3H, s, OMe), 3.59–3.53 (1H, m, NCH), 3.28–3.24 (1H, m, C*H*CH=CH_2), 2.73 (1H, dd, *J* 14.0, 7.5 Hz, C*H*HArOMe), 2.54 (1H, dd, *J* 14.0, 7.0 Hz, CH*H*ArOMe), 2.44 (3H, s, Me of Ts); δ_C (125 MHz) 193.4 (CHO), 158.6 (q Ar), 155.7, [143.6, 139.9 (q Ar)], 134.1, 132.9, 129.9, 129.6, 128.2 (q Ar), 128.1, 121.3 (CH=*C*H_2), 114.1, 58.5, 55.1, 48.9, 37.9 (CH_2), 21.5, 15.3; *m*/*z* (ESI) 422.1422 $[M+Na]^+$, 417.1865, 400.1585 $[M+H]^+$, 382.1478, 338.3427, 245.0269 (found: $[M+H]^+$, 400.1585. $C_{22}H_{25}NO_4S$ requires $[M+H]^+$, 400.1583) (found: C, 66.20; H, 6.30; N, 3.50. $C_{22}H_{25}NO_4S$ requires C, 66.14; H, 6.31; N, 3.51%).

4.2.4. (2R,3S*)-2-(4-Methoxybenzyl)-4-(phenylthio)-1-tosyl-3-vinyl-1,2,3,4-tetrahydropyridine (**10**).* To a solution of enal **14** (244 mg, 0.561 mmol, 1.0 equiv) in CH_2Cl_2 (2.3 mL) at 0 °C were added thiophenol (173 μL, 1.68 mmol, 3.0 equiv) and Et_3N (391 μL, 2.80 mmol, 5.0 equiv). The solution was then warmed to rt gradually. After 16 h, TLC analysis showed complete consumption of **14**. The mixture was cooled to −20 °C followed by addition of Et_3N (391 μL, 2.80 mmol, 5.0 equiv) and mesyl chloride (434 μL, 5.61 mmol, 10.0 equiv). After 2 h, Concentration under reduced pressure and column chromatography (5% EtOAc–petrol) gave a 2:1 diastereomeric mixture of (2*R**,3*S**)-2-(4-*methoxybenzyl*)-4-(*phenylthio*)-1-*tosyl*-3-*vinyl*-1,2,3,4-*tetrahydropyridine* **10** (182 mg, 66%) as a solid; R_f 0.47 (18% EtOAc–petrol); ν_{max} (film) 2930, 1721, 1640, 1612, 1512, 1440, 1353, 1302, 1247, 1165, 1091, 1035, 991, 927, 815, 749, 675 cm^{-1}; δ_H (400 MHz) 7.57 (2H, d, *J* 8.5 Hz, *ortho* Ts, minor diast.), 7.48 (2H, d, *J* 8.5 Hz, *ortho* Ts, major diast.), 7.41–7.24 [(2×5H, m, SPh, 2×diast.) and (2H, *meta* Ts, minor diast.)], 7.19 (2H, d, *J* 8.5 Hz, *meta* Ts, major diast.), 7.14 (2H, d, *J* 8.5 Hz, *meta* ArOMe, minor diast.), 7.08 (2H, d, *J* 8.5 Hz, *meta* ArOMe, major diast.), 6.88–6.82 (2×2H, d, *J* 8.5 Hz, *ortho* ArOMe, 2×diast.), 6.65–6.12 (2×1H, m, CH=C*H*NTs, 2×diast.), 5.70 (1H, ddd, *J* 17.5, 10.5, 8.0 Hz, C*H*=CH_2, major diast.), 5.49–5.43 (1H, m, C*H*=CH_2, minor diast.), 5.28–5.22 [(2×1H, m, CH=CHNTs, 2×diast.) and (1H, m, *trans* CH=C*H*H, major diast.)], 5.16 (1H, dd, *J* 10.5, 1.5 Hz, *trans* CH=C*H*H, minor diast.), 4.99–4.92 (2×1H, m, *cis* CH=CH*H*, 2×diast.), 4.09–4.03 (2×1H, m, NTsCHCH_2, 2×diast.), 3.83 (3H, s, OMe, minor diast.), 3.82 (3H, s, OMe, major diast.), 3.55–3.48 (2×1H, m, C*H*SPh, 2×diast.), [2.98–2.85 and 2.78–2.65 (2×2H, m, CH_2ArOMe, 2×diast.), 2.44 (3H, s, Me of Ts, major diast.), 2.43 (3H, s, Me of Ts, minor diast.), 1.73–1.68 (2×1H, m, C*H*CH=CH_2, 2×diast.); δ_C (125 MHz) (major diast.) [158.3, 143.4 (q Ar)], 137.4, 135.7 (q Ar), 133.7 (3° Ar), 132.0 (q Ar), [130.6, 129.7 (3° Ar)], 129.6 (q Ar), 128.7 (3° Ar), 127.7, 126.8 (3° Ar), 124.2, 118.7 (CH=*C*H_2), 113.6 (3° Ar), 112.1, 60.9, 55.1, 43.9, 42.9, 32.4 (*C*H_2ArOMe), 21.6; *m*/*z* (ESI) 555.1768, 530.1248, 514.1501 $[M+Na]^+$, 509.1948, 492.1668 $[M+H]^+$, 382.1476 (found: $[M+H]^+$, 514.1668. $C_{28}H_{29}NO_3S_2$ requires $[M+H]^+$, 492.1667).

4.3. Preparation of 10 from 11

To a solution of PhSH (924 mg, 8.38 mmol, 4.5 equiv) in CH_2Cl_2 at rt was added $AlMe_3$ (4.20 mL of a 3 M solution in hexanes, 8.38 mmol, 4.5 equiv). After 30 min, the resulting solution was added to a solution of tetrahydropyridines **11** in CH_2Cl_2 via cannula. After 1 h, the solution was cooled to 0 °C and satd Na/K aq tartrate (15 mL) added dropwise, followed by H_2O (10 mL) and EtOAc (10 mL). The organic phase was separated and aqueous phase extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (2×10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (5→10% EtOAc–petrol) followed by recrystallisation gave a 2:1 diastereoisomeric mixture of **11** (810 mg, 89%) as a solid; data were in agreement with those listed above.

4.3.1. 2-[(2R,3S*)-2-(4-Methoxybenzyl)-1-tosyl-3-vinyl-1,2,3,4-tetrahydropyridin-4-ylthio]pyridine (**15**).* To a solution of 2-mercaptopyridine (207 mg, 1.86 mmol, 5.0 equiv) in CH_2Cl_2 (2 mL) at rt was added $AlMe_3$ (930 μL of a 2 M solution in hexane, 1.86 mmol, 5.0 equiv). After 45 min, it was added to a solution of a 2:1 diastereoisomeric mixture of tetrahydropyridines **11** (200 mg, 0.372 mmol, 1.0 equiv) in CH_2Cl_2 (0.7 mL) at rt. After 16 h, the reaction was quenched with satd Na/K aq tartrate and stirred for 5 min. The organic phase was separated and the aqueous phase extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (2×10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (5→10% EtOAc–petrol) followed by recrystallisation gave a 2.5:1 diastereoisomeric mixture of 2-[(2*R**,3*S**)-2-(4-*methoxybenzyl*)-1-*tosyl*-3-*vinyl*-1,2,3,4-*tetrahydropyridin*-4-*ylthio*]*pyridine* **15** (125 mg, 68%) as a solid; R_f 0.69 (30% EtOAc–petrol); ν_{max} (film) 3044, 2922, 2850, 1637, 1613, 1597, 1577, 1558, 1512, 1453, 1416, 1354, 1302, 1247, 1165, 1122, 1091, 1035, 986, 927, 891, 815, 760, 684 cm^{-1}; δ_H (400 MHz) 8.42 (1H, ddd, *J* 4.0, 1.5, 1.0 Hz, 2-pyH, minor diast.), 8.35 (1H, ddd, *J* 4.0, 1.5, 1.0 Hz, 2-pyH, major diast.), 7.61–7.57 (2×2H, m, *ortho* Ts, 2×diast.), 7.48–7.43 (2×1H, m, 6-pyH, 2×diast.), 7.29–7.26 (2×2H, m, *meta* Ts, 2×diast.), 7.16–7.09 (2×3H, m, *meta* ArOMe and 1-pyH, both diast.), 6.98–6.95 (2×1H, m, 5-pyH, 2×diast.), 6.86–6.82 (2×2H, m, *ortho* ArOMe, 2×diast.), 6.67 (1H, ddd, *J* 6.5, 1.5, 1.0 Hz, CH=C*H*NTs, major diast.), 6.60 (1H, ddd, *J* 6.5, 1.5, 1.0 Hz, minor diast.), 5.99 (1H, ddd, *J* 14.0, 8.5, 6.0 Hz, C*H*=CH_2, major

diast.), 5.63 (1H, ddd, *J* 14.5, 8.5, 6.5 Hz, C*H*=CH_2, minor diast.), 5.46 (1H, dd, *J* 6.5, 4.0 Hz, CH=C*H*H, major diast.), 5.38–5.36 (1H, dd, *J* 6.5, 2.0 Hz, CH=C*H*H, minor diast.), 5.11–5.09 (1H, m, CH=CH*H*, minor diast.), 5.06–5.04 (1H, m, CH=CH*H*, major diast.), 4.97–4.92 (2×1H, m, C*H*=CHNTs, 2×diast.), 4.83–4.81 (1H, m, C*H*NTs, major diast.), 4.62–4.59 (1H, m, C*H*NTs, minor diast.), [3.80, 3.79 (2×3H, 2×s, OMe, 2×diast.)], 2.88–2.76 (2×2H, m, CH_2ArOMe, 2×diast.), [2.43, 2.42 (2×3H, 2×s, Me of Ts, 2×diast.)], 2.39–2.36 (1H, m, C*H*CH=CH_2, major diast.), 2.87–2.82 (1H, m, C*H*CH=CH_2, minor diast.); δ_C (100 MHz) 157.9, 157.9, 149.6, 149.4, 149.1, 143.7, 137.4, 137.1, 136.1, 135.9, 135.8, 130.8, 130.6, 130.5, 130.4, 129.8, 129.7, 129.7, 127.0, 126.9, 123.9, 123.6, 122.8, 122.6, 121.1, 119.7, 118.5, 117.5, 113.8, 113.6, 113.3, 60.9, 59.9, 55.1, 44.4, 38.6, 38.2, 33.7, 31.9, 29.7, 21.6; *m*/*z* (ESI) 531.1200, 515.1447, 493.1632 $[M+Na]^+$, 382.1485, 221.0214 (found: $[M+Na]^+$, 493.1632. $C_{27}H_{28}N_2O_3S_2$ requires $[M+Na]^+$, 493.1620).

4.3.2. (2R,3S*)-2-(4-Methoxybenzyl)-4-(methylthio)-1-tosyl-3-vinyl-1,2,3,4-tetrahydropyridine (**16**) and (2R*,3R*)-2-(4-methoxybenzyl)-6-(methylthio)-1-tosyl-3-vinyl-1,2,3,6-tetrahydropyridine (**17**).* To a mixture of sulfur powder (27.0 mg, 0.842 mmol, 4.5 equiv) in toluene (1.3 mL) at rt was added $AlMe_3$ (373 μL of a 2 M solution in hexanes, 0.745 mmol, 4.0 equiv). The mixture was heated to reflux for 2 h then cooled to rt. To the resulting mixture was added via cannula a solution of 2:1 diastereoisomeric mixture of tetrahydropyridines **11** (100 mg, 0.186 mmol, 1.0 equiv) in toluene (0.6 mL). After 16 h, it was quenched with H_2O (5 mL), diluted with satd aq Na/K tartrate (5 mL) and EtOAc (5 mL). After stirring for 5 min, the organic phase was separated and the aqueous phase extracted with EtOAc (2×5 mL). The combined organic layers were washed with brine (3×5 mL) and dried (Na_2SO_4). Concentration under reduced pressure and column chromatography (5→10% EtOAc–petrol) gave a 2:1 diastereomeric mixture of (2*R**,3*S**)-2-(4-*methoxybenzyl*)-4-(*methylthio*)-1-*tosyl*-3-*vinyl*-1,2,3,4-*tetrahydropyridine* **16** (11.1 mg, 14%) as a gum and a 1.2:1 diastereomeric mixture of (2*R**,3*R**)-2-(4-*methoxybenzyl*)-6-(*methylthio*)-1-*tosyl*-3-*vinyl*-1,2,3,6-*tetrahydropyridine* **17** (55.1 mg, 69%) as a gum.

Data for 2:1 diastereoisomeric mixture of (2*R**,3*S**)-2-(4-methoxybenzyl)-4-(methylthio)-1-tosyl-3-vinyl-1,2,3,4-tetrahydropyridine **16**: R_f 0.71 (30% EtOAc–petrol); ν_{max} (film) 3034, 2920, 2835, 1636, 1611, 1598, 1584, 1513, 1464, 1440, 1420, 1347, 1303, 1247, 1161, 1092, 1036, 913, 814 cm^{-1}; δ_H (400 MHz) 7.61 (2H, d, *J* 8.0 Hz, *ortho* Ts, major diast.), 7.57 (2H, d, *J* 8.0 Hz, *ortho* Ts, minor diast.), 7.30–7.26 (2×2H, m, *meta* Ts, 2×diast.), 7.12–7.09 (2×2H, m, *meta* ArOMe, 2×diast.), 6.87–6.84 (2×2H, m, *ortho* ArOMe, 2×diast.), 6.69 (1H, d, *J* 8.0 Hz, NC*H*=CH, major diast.), 6.62 (1H, d, *J* 8.0 Hz, NC*H*=CH, minor diast.), 6.18 (1H, ddd, *J* 17.5, 10.0, 8.0 Hz, C*H*=CHH, minor diast.), 5.66 (1H, ddd, *J* 17.5, 10.0, 8.0 Hz, C*H*=CHH, major diast.), 5.47 (1H, dd, *J* 8.0, 4.5 Hz, NCH=C*H*, minor diast.), 5.28–5.15 (2×1H, m, CH=C*H*H, 2×diast. and 1H, m, NCH=C*H*, major diast.), 5.01–4.94 (2×1H, m, CH=CH*H*, 2×diast), 4.14–4.07 (2×1H, m, NC*H*CH_2, 2×diast), 3.83 (2×3H, s, OMe, 2×diast), 3.14–3.11 (1H, m, C*H*SMe, major diast.), 3.03–3.00 (1H, m, C*H*SMe, minor diast.), 2.92 (1H, dd, *J* 14.0, 4.0 Hz, C*H*HArOMe, minor diast.), 2.84 (1H, dd, *J* 14.0, 10.0 Hz, CH*H*ArOMe, minor diast.), 2.72 (1H, dd, *J* 14.0, 4.0 Hz, C*H*HArOMe, major diast.), 2.65 (1H, dd, *J* 14.0, 10.0 Hz, CH*H*ArOMe, major diast.), 2.43 (3H, s, Me of Ts, major diast.), 2.25–2.20 (1H, m, C*H*CH=CH_2, minor diast.), 2.18 (3H, s, Me of Ts, minor diast.), 1.77–1.72 (1H, m, C*H*CH=CH_2, major diast.), 1.59 (3H, s, SMe, minor diast.), 1.56 (3H, s, SMe, major diast.); δ_C (100 MHz) 158.3, 158.1, 143.8, 143.6, 137.6, 136.5, 136.1, 135.6, 130.7, 130.5, 129.7, 129.6, 127.1, 127.0, 125.5, 125.4, 123.2, 118.4, 117.9, 113.7, 113.6, 113.1, 60.8, 60.1, 55.2, 45.7, 44.3,42.6, 39.5, 33.8, 32.1, 31.8, 29.7, 21.5, 18.4, 9.7; *m*/*z* (ESI) 452.1334 $[M+Na]^+$, 447.1773, 430.1506 $[M+H]^+$, 382.1479, 242.1179, 227.1312 (found: $[M+Na]^+$, 452.1334. $C_{23}H_{27}NO_3S_2$ requires $[M+Na]^+$, 452.1330).

Data for 1.2:1 diastereoisomeric mixture of (2*R**,3*R**)-2-(4-methoxybenzyl)-6-(methylthio)-1-tosyl-3-vinyl-1,2,3,6-tetrahydropyridine **17**: R_f 0.76 (30% EtOAc–petrol); ν_{max} (film) 3035, 2922, 2837, 1609, 1512, 1442, 1339, 1247, 1159, 1094, 1036, 914, 816 cm^{-1}; δ_H (400 MHz) 7.60 (2H, d, *J* 8.0 Hz, *ortho* Ts, major diast.), 7.55 (2H, d, *J* 8.0 Hz, *ortho* Ts, minor diast.), 7.28–7.19 (2×4H, m, *meta* Ts and *meta* ArOMe, 2×diast.), 6.87 (2H, d, *J* 8.5 Hz, *ortho* ArOMe, major diast.), 6.77 (2H, d, *J* 8.5 Hz, *ortho* ArOMe, minor diast.), 5.89–5.63 (2×3H, m, C*H*=CH_2 and C*H*=C*H*, 2×diast.), 5.19–5.02 (2×2H, m, CH=CH_2, 2×diast.), 4.57–4.52 (1H, m, NC*H*SMe, minor diast.), 4.39–4.34 (1H, m, NC*H*SMe, major diast.), 3.83 (3H, s, OMe, minor diast.), 3.81 (3H, s, OMe, major diast.), 3.51–3.44 (1H, m, NC*H*CH_2, major diast.), 3.22 (1H, dd, *J* 15.0, 10.0 Hz, C*H*HArOMe, major diast.), 3.09 (1H, dd, *J* 14.5, 9.0 Hz, C*H*HArOMe, minor diast.), 2.76–2.68 (2×1H, m, C*H*HArOMe, 2×diast. and 1H, m, NC*H*CH_2, minor diast.), 2.44–2.39 (2×4H, m, Me of Ts and C*H*CH=CH_2, 2×diast.), 2.14 (3H, s, SMe, major diast.), 1.66 (3H, s, SMe, minor diast.); δ_C (100 MHz) 158.2, 157.8, 143.6, 143.4, 137.3, 136.9, 134.8, 130.9, 130.8, 130.6, 130.5, 130.2, 129.6, 129.4, 129.3, 128.1, 127.7, 127.3, 125.3, 124.8, 118.4, 117.1, 113.8, 113.3, 64.0, 59.8, 58.8, 57.7, 57.1, 56.5, 55.3, 55.2, 43.8, 40.2, 35.2, 32.5, 21.5, 15.5; *m*/*z* (ESI) 425.1346 $[M+Na]^+$, 382.1488 $[M+H]^+$, 318.0591, 253.5798, 227.1316 (found: $[M+Na]^+$, 452.1346. $C_{23}H_{27}NO_3S_2$ requires $[M+Na]^+$, 452.1330).

4.3.3. (4R,5S*)-Methyl 4-(hydroxymethyl)-6-(1-methyl-1H-indol-3-yl)-5-(4-methylphenylsul-fonamido)-3-(phenylsulfonyl)hexanoate (**20**).* To a solution of sulfonylorthoester **18** (108 mg, 0.39 mmol, 1.5 equiv) in THF (0.5 mL) at −78 °C was added ^{n}BuLi (150 μL of a 2.6 M solution in hexanes, 0.39 mmol, 1.5 equiv [1 equiv with respect to **18**]). The mixture was stirred for 30 min, and a solution of *O*-lithio-**19** (made by ^{n}BuLi (1 equiv) treatment of **19** (100 mg, 0.26 mmol, 1.0 equiv)) in THF (0.6 mL) at −78 °C added dropwise. The mixture was warmed to rt during 16 h, quenched with satd aq NH_4Cl (10 mL) and the aqueous layer extracted with EtOAc (3×15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (50% EtOAc–petrol) gave (4*R**,5*S**)-*methyl* 4-(*hydroxymethyl*)-6-(1-*methyl*-1*H*-*indol*-3-*yl*)-5-(4-*methylphenylsulfonamido*)-3-(*phenylsulfonyl*)*hexanoate* **20** as an off-white solid (140 mg, 90%); R_f 0.35 (66% EtOAc–petrol); mp 90–92 °C; ν_{max} (film) 3301, 2924, 1739, 1601, 1475, 1427, 1305, 1155, 1090, 1072, 954, 726 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.94 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.69 (1H, m, ArH), 7.59 (3H, m, *meta*-Ts+ArH), 7.25 (2H, m, 2×ArH), 7.20 (2H, d, *J* 7.5 Hz, 2×ArH) 7.10 (2H, d, *J* 7.5 Hz, 2×ArH), 7.04 (1H, m, ArH), 6.80 (1H, s, C*H*NMe), 5.84 (1H, d, *J* 9.0 Hz, N*H*Ts), 4.32 (1H, dt, *J* 3.0, 6.0 Hz, $PhSO_2CH$), 4.10 (1H, dt, *J* 8.5 Hz, TsNHC*H*), 4.01 (2H, ddd, *J* 6.5 Hz, CH_2OH), 3.64 (3H, s, NMe), 3.42 (3H, s, OMe), 3.10–2.90 (2H, dd, *J* 7.0 Hz, CH_2CHNHTs), 2.36 (2H, d, *J* 5.0 Hz, CH_2CO_2Me), 2.52 (1H, m, C*H*CH_2OH), 2.93 (3H, s, CH_3Ts); δ_C (100 MHz, $CDCl_3$); 170.7 (CO), 142.9 (CSO_2), 137.8 (CSO_2), 137.6 (CH_3C-Ts), 134.2 (*para*-$PhSO_2$), 129.8 (Ar*C*), 129.2 (*ortho*-Ts), 129.3 (*ortho*-$PhSO_2$), 129.0 (*meta*-Ts), 128.8 (Ar*C*), 127.7 (*meta*-$PhSO_2$), 126.8 (*meta*-$PhSO_2$), 121.7 (ArH), 119.1 (ArH), 118.5 (ArH), 109.0 (ArCH), 107.5 (*C*CHNCH_3), 60.1 (CH_2OH), 59.2 (OCH_3), 53.2 ($PhSO_2CH$), 52.2 (TsNHC*H*), 46.8 (C*H*CH_2OH), 34.1 ($CH_2CO_2CH_3$), 32.5 (NCH_3), 29.0 (CH_2C), 21.6 (TsCH_3); *m*/*z* (ESI): 621.1710 [M+Na], 589.1450 [M+Na−$HOCH_3$], 567.1626 [M−OCH_3], 479.1616 [M+Na−HSO_2Ph]$^+$, 457.1797 [M−SO_2Ph]$^+$ (found $[M]^+$, 599.1890. $C_{30}H_{34}N_2O_7S_2$ requires $[M]^+$, 599.1886.) (found: C, 60.20; H, 5.74; N, 4.64. $C_{30}H_{34}N_2O_7S_2$ requires C, 60.18; H, 5.72; N, 4.68%).

4.3.4. (1R,12R*,13S*,14S*)-14,16-Ditosyl-3-methyl-3,16-diazatetracyclo[10.3.1.0^{2,10}.0^{4,9}]hexa-deca-2(10),4,6,8-tetraen-13-yl 3-oxobutanoate (**22**).* To a solution of alcohol **21**[3] (88 mg, 0.14 mmol, 1 equiv) and DMAP (1.7 mg, 0.0014 mmol, 10 mol %) in THF (1 mL) at rt was added diketene (14 μL, 15 mg, 0.18 mmol, 1.26 equiv, freshly distilled under vacuum). The reaction mixture was heated under

reflux with stirring for 2 h, and then cooled and concentrated under reduced pressure. Chromatography using gradient elution (50%→75%→90% Et_2O–petrol, then Et_2O, then 10% acetone–Et_2O) gave the intermediate β-ketoester (51 mg, 0.072 mmol, 51%). This was dissolved in MeCN (0.73 mL) and NaI (60 mg, 0.43 mmol, 6 equiv) followed by TMSCl (55 μL, 49 mg, 0.43 mmol, 6 equiv) were added at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, satd aq $NaHCO_3$ (5 ml) was added and the aqueous layer extracted with CH_2Cl_2 (3×10 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography using gradient elution (50%→75%→90% Et_2O–petrol, then Et_2O, then 10% acetone–Et_2O) gave (1*R**,12*R**,13*S**,14*S**)-14,16-*ditosyl*-3-*methyl*-3,16-*diazatetra*-*cyclo*[10.3.1.$0^{2,10}$.$0^{4,9}$]*hexadeca*-2(10),4,6,8-*tetraen*-13-*yl* 3-*oxobutanoate* **22** (40 mg, 0.062 mmol, 86%) as a colourless oil; R_f 0.27 (Et_2O); ν_{max} (film) 1743, 1716, 1468, 1316, 1163, 1148, 674 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.65 (2H, d, *J* 8.0 Hz, 2×TsH), 7.28 (4H, d, *J* 8.0 Hz, 4×TsH), 7.22–7.15 (2H, m, 2×ArH), 7.07 (1H, d, *J* 8.0 Hz, ArH), 7.01 (1H, t, *J* 7.0 Hz, ArH), 6.72 (2H, d, *J* 8.0 Hz, 2×TsH), 5.43 (1H, app s, NCHCNMe), 4.94 (1H, dd, *J* 11.5, 4.0 Hz, C*H*$_A$H$_B$O), 4.66 (1H, d, *J* 8.0 Hz, NC*H*CH), 4.54 (1H, t, *J* 11.0, 3.5 Hz, CH$_A$*H*$_B$O), 3.58 (3H, s, NCH_3), 3.56 (2H, d, *J* 5.5 Hz, $CH_2C{=}O$), 3.38 (1H, dt, *J* 13.0, 4.0, CHTs), 2.87 (1H, dd, *J* 17.0, 8.5 Hz, C*H*$_A$H$_B$C), 2.57 (1H, td, *J* 13.0, 4.5 Hz, C*H*$_A$H$_B$CHTs), 2.48–2.27 (1H, m, C*H*CHN), 2.40 (3H, s, $TsCH_3$), 2.36 (3H, s, $TsCH_3$), 2.18 (1H, d, *J* 17.0 Hz, CH$_A$*H*$_B$C), 2.02–1.99 (1H, m, CH$_A$*H*$_B$CHTs), 1.93 (3H, s, $CH_3C{=}O$); δ_C (100 MHz, $CDCl_3$) 201.1 (C=O), 166.7 (C=O), 145.4 (TsC), 143.8 (TsC), 136.8 (ArC), 135.4 (TsC), 134.1 (TsC), 131.1 (ArC), 130.2 (2×TsCH), 128.8 (2×TsCH), 128.7 (2×TsCH), 126.4 (2×TsCH), 125.7 (ArC), 122.1 (ArCH), 119.4 (ArCH), 118.0 (ArCH), 109.1 (ArCH), 107.1 (ArC), 61.0 (CH_2O), 57.2 (CHTs), 50.1 ($CH_2C{=}O$), 48.8 (NCHCH$_2$C), 47.2 (NCHCNMe), 41.1 (CHCHN), 30.4 ($CH_3C{=}O$), 29.2 (NCH_3), 26.4 (CH_2CHTs), 24.2 (CH_2C), 21.7 ($TsCH_3$), 21.1 ($TsCH_3$); *m*/*z* (FAB) 648 ([M]$^+$), 391, 149, 71, 57 (found: [M]$^+$, 648.1976. $C_{34}H_{36}N_2O_7S_2$ requires [M]$^+$, 648.1964).

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.04.096.

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