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Carbenium ion trapping using sulfonamides: an acid-catalysed synthesis of pyrrolidines by intramolecular hydroamination

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ABSTRACT

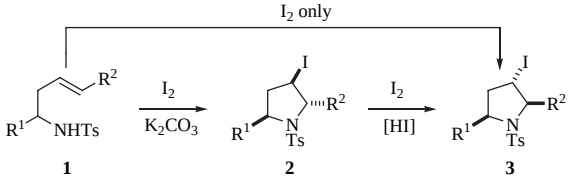
Cyclisations of homoallylic sulfonamides proceed smoothly via carbenium ion generation using trifluoromethanesulfonic (triflic) acid, the ease of cyclisation being directly related to the ion stability to give good to excellent yields of the corresponding pyrrolidines. Both toluene- and nitrophenyl-sulfonyl groups are suitable for all substrates tested whereas the corresponding carbamates are only useful in cases of tertiary and highly stabilised carbenium ions. Polyene-derived sulfonamides can also be cyclised to the corresponding polycyclic systems in remarkably high yields, in reactions reminiscent of related cascades encountered in terpene biosynthesis.

1. Introduction

The central importance of nitrogenous compounds to the manipulation of biological systems in general has meant that the development of methods for the efficient introduction of this element into organic compounds continues to occupy a pivotal position in synthetic methodology.[1] One only has to consider the impact that the Buchwald–Hartwig and related amination reactions[2] have had, especially in the Pharmaceutical sector, since their introduction. More generally, although a long established principle, new ways to carry out overall alkene hydroamination, the addition of the elements of nitrogen at the amine oxidation level and hydrogen to an alkene,[3] in a selective and mild manner have come to great prominence of late, by reason of the significant contribution that such methodology could have to this area.

In principle, one way to multiply the synthetic methods available to prepare a selected structural feature is to reverse the polarity associated with to a particular functional group.[4] The nucleophilicity inherent in a typical alkene bond can be reversed, for example, by epoxidation, which can allow it then to be attacked by various nucleophilic species. Closely related are more transient intermediates generated by the positioning of a halogen or selenium atom across the alkene, thereby achieving a similar reversal of polarity and hence intramolecular attack by a suitably positioned nucleophile such as an alcohol or attenuated amine group. These are, of course, the very familiar halo- or seleno-cyclisations processes for ring closure, which can operate in a number of modes, including 5- and 6-*exo* as well as 5-*endo* examples.[5] During our studies of such cyclisations,[6,7] we were stimulated to search for alternatives to both molecular iodine and selanyl halides for a number of reasons, not the least of which were the fact that a relatively large excess (3 equiv) of iodine is required and general limitations for scale up in both cases, especially when using the selenium-based reagents, where cost and disposal become limiting considerations. The idea to attempt to form pyrrolidines and perhaps *N*-heterocycles with other ring sizes using such chemistry but with alternative activating agents for the alkene arose from two observations.

Firstly, we found that overall 5-*endo-trig* iodocyclisations of homoallylic sulfonamides **1**, which give very largely the 2,5-*trans*-iodopyrrolidines **2** under basic conditions (Scheme 1), gave *only* the corresponding 2,5-*cis* diastereomers **3** if the base was omitted.[7] By starting with a single enantiomer of the precursor [**1**; R^1=Et; R^2=Bu], we were able to establish that formation of the latter most likely occurs by cycloreversion of the initially formed and hence kinetic isomers **2** back to precursor **1** and subsequent cyclisation to



1 **2** **3**

Scheme 1.

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eventually produce only the thermodynamically more stable 2,5-*cis*-isomers **3**. Presumably, the trigger for this is protonation of the *trans*-pyrrolidines at nitrogen by the hydrogen iodide formed as the cyclisation proceeds and which is now not removed as no base is present. A key implication is therefore that at least some of the regenerated starting material **1** remains unprotonated in the presence of this strong acid and hence is able to participate as a nucleophile in subsequent iodocyclisations.

A second significant observation was made during extensions of this methodology to the formation of highly substituted proline analogues **4**, which, in extreme cases, required prolonged exposure to excess iodine in order to achieve complete conversion into the desired iodopyrrolidines **5** (Fig. 1).[8] When such cyclisations were carried out in the absence of base, the products **5** were sometimes accompanied by small amounts of the de-iodopyrrolidines **6**. We were unsure as to how these were formed, but reasoned that one possibility was that direct acid-catalysed cyclisation was occurring to a limited extent. Therefore, when we began to investigate alternative electrophilic triggers for this type of cyclisation in general, the prospects for using protons, the simplest of electrophiles, for this purpose was one of the first to be investigated.

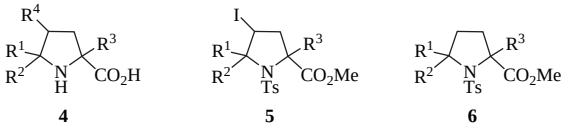
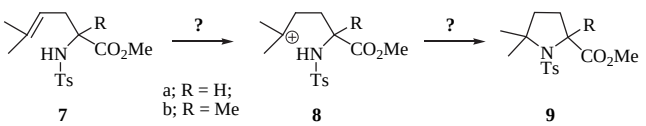


Figure 1.

Herein, we report in full on the successful outcome of this idea and on some of its key features. Although the initial concept of this methodology was that it was a pyrrolidine synthesis, it can of course also be viewed as an intramolecular hydroamination process, as will be discussed later, in which the amine is the nucleophile and the alkene in effect the electrophile.[9,10]

2. Results and dicussion

Our first experiments were focused not unnaturally on substrates, which were particularly well set up to undergo such cyclisations, on the grounds that if these could not be successfully transformed into pyrrolidines, then the whole idea was perhaps not a viable proposition (Scheme 2). We therefore chose the prenyl derivatives **7**, which were readily prepared using the convenient Stork procedure (see below),[11] along with the very stable *p*-toluenesulfonyl (tosyl) group to attenuate the reactivity of the amino group. Protonation of the prenyl group was expected to give the stabilised tertiary carbenium ions **8**, which looked well set up to be trapped by the nearby sulfonamide group at least some of which, as argued above, would not be protonated and hence would be available to trap the positive ion to give the desired pyrrolidines **9**. In addition, in the case of precursor **7b**, a helpful steric compression ('Thorpe–Ingold' effect) may also contribute.

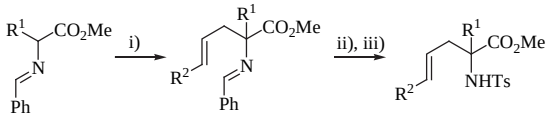


Scheme 2.

Initial trials met with success: when the sulfonamides **7** were refluxed with 1 equiv of *p*-toluenesulfonic (tosic) acid in chloroform, ethyl acetate or toluene, complete and reasonably clean conversions into the hoped-for pyrrolidines **9** were observed. Temperatures in excess of 70 °C were essential with this acid; in refluxing dichloromethane, no cyclisation occurred. Cyclisations were generally incomplete if less than 1 equiv of the acid was used. However, later trials using less substituted precursors such as those derived from cinnamyl or crotyl halides failed to produce such cyclisation products (see below). Other trials using acetic acid or trifluoroacetic acid also failed to produce any cyclisation products as did hydrogen chloride in methanol. It was only when we turned to a so-called super acid,[12] trifluoromethanesulfonic acid (triflic acid; TfOH, CF_3SO_3H) that success was achieved. This then became the reagent of choice for all subsequent experiments detailed below.

A brief optimisation study soon established that the two model substrates **7a**,**b** underwent very rapid and clean cyclisations to give the hoped-for pyrrolidines **9a**,**b** in essentially quantitative yields upon exposure to around half an equivalent of triflic acid in ice-cold chloroform for no more than 15 min. Using less acid (0.1 and 0.03 equiv) resulted in much lower conversions under the same conditions (28% and 8%, respectively). At a very low temperature (−78 °C), no cyclisation occurred using up to 1 equiv of acid while at −40 °C, conversions into pyrrolidines **9a**,**b** reached around 70% using 0.4 equiv of acid during up to 6 h. We therefore adopted the initial conditions of 0.4 equiv of triflic acid in chloroform or dichloromethane at 0 °C for around 15 min as our standard protocol for this type of substrate, which is expected to give relatively stabilised tertiary carbenium ions **8**.

We next tested the generality of this chemistry by using substituents that were somewhat less able to provide such stabilisation of a positive charge. All these and most subsequent substrates were synthesised using the Stork procedure featuring alkylation of the carbanion derived from the benzaldehyde Schiff's base of methyl glycinate or alaninate **10** (Scheme 3).[11] Yields of the intermediate imines **11** were generally excellent when using allylic bromides; use of the corresponding iodides was necessary in cases of less activated, non-allylic alkenyl halides.



10 a) R^1 = H
b) R^1 = Me

11 a) R^1 = H; R^2 = Ph
b) R^1 = Me; R^2 = Ph
c) R^1 = H; R^2 = Me
d) R^1 = R^2 = Me

12

Scheme 3. (i) LDA, THF, −78 °C, then add alkyl halide, −78 °C, 1 h then 20 °C, 1 h; (ii) 1 M HCl, Et_2O, 2 h, 20 °C; (iii) *p*-TsCl, Et_3N, DMAP (cat.), CH_2Cl_2, 20 °C, 16 h.

While the subsequent acid-catalysed imine hydrolysis was simple, we have great difficulty in obtaining decent yields of the final *N*-tosylated derivatives **12**, partly due to bis-tosylation.[13]

After some experimentation, we found conditions under which cyclisations of all four new precursors **12a**–**d** derived from combinations of glycine and alanine, together with cinnamyl and crotyl bromides, proceeded very smoothly to give excellent yields of the expected pyrrolidines **13a**–**d**. The results of these and the foregoing experiments using the prenyl derivatives **7a**,**b** are collected in Table 1. These initial cyclisations followed an approximate pattern expected from the likely carbenium ion stability [cf. ion **8**] in the sense that, while the prenyl derivatives **7a**,**b** underwent rapid cyclisation at 0 °C, the cinnamyl derivatives **12a**,**b** required reactions at ambient temperature and the crotyl analogues **12c**,**d** reflux temperature. This would seem to roughly equate to tertiary alkyl, benzylic and secondary alkyl carbenium ion stabilities. However, where relevant (see Experimental section), the reactions shown in Table 1 were not particularly stereoselective. We have briefly examined this feature and have obtained results, which suggest these initial products are best regarded as kinetic mixtures (Table 2).

Firstly, the stereochemical assignments shown in Table 2 were based upon our previous deductions made from both NMR and X-ray

Table 1
Acid-catalysed cyclisations of the prenyl, cinnamyl and crotyl precursors **7a**,**b** and **12a–d**

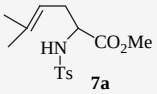
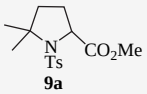
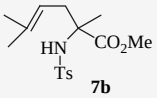
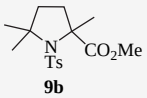
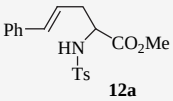
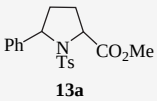
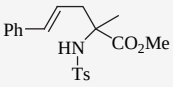
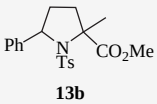
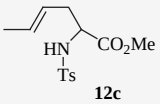
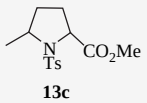
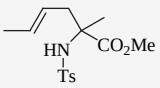
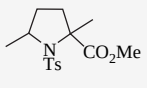
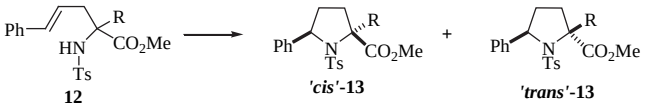
Precursor	Product	TfOH (equiv)	Time/temp (h/°C)	Convn	Yield (%)
 **7a**	 **9a**	0.4	0.25/0	100	97
 **7b**	 **9b**	0.4	0.25/0	100	95
 **12a**	 **13a**	0.6	4.5/25	100	95
 **12b**	 **13b**	0.4 0.4 0.6	2/0 6/25 4/25	0 74 100	— — 96
 **12c**	 **13c**	0.6	4/62	100	91
 **12d**	 **13d**	0.4 0.6	24/0–25 4/62	0 100	— 94

Table 2
Isomerisation characteristics of the cinnamyl derivatives **12**

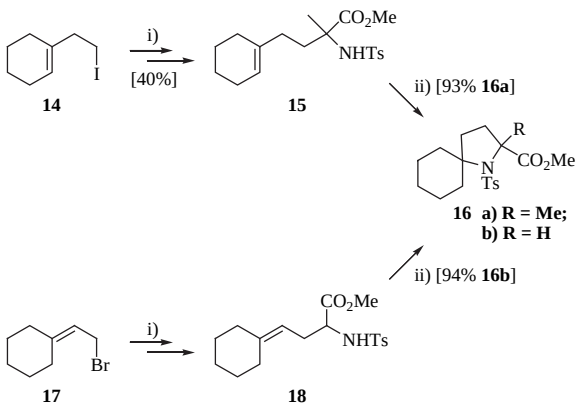


12a ⟶ **13a; R = H** **12b** ⟶ **13b; R = Me**

TfOH (equiv)	Time (h)	cis/trans	TfOH (equiv)	Time (h)	cis/trans
0.6	4.5	1.0:1	0.6	4.0	2.9:1
1.5	2.0	1.0:1	1.5	2.0	3.5:1
2.0	1.5	>20:1	2.0	1.5	4.0:1
5.0	1.0	>20:1	5.0	1.0	9.0:1

data of the corresponding iodocyclisation products and their deiodo derivatives.[7] As can be seen from Table 2, the key to inducing isomerisation towards what must be the more thermodynamically stable isomers is an increase in the amount of acid used rather than an increase in the reaction time. In the case of the glycine derivative **12a**, the thermodynamically more stable isomer has the 2,5-cis-stereochemistry, '*cis*'-**13a**, in which the two substituents adopt pseudoequatorial positions and is formed almost exclusively when an excess of acid is used, according to ^{1}H NMR analysis. Similarly, isomerisation of the pyrrolidines **13b** derived from the alanine derivative **12b** gave up to a 9:1 ratio in favour of '*cis*'-**13b**, which may well reflect the thermodynamically more stable ratio of the two isomers, given the closer similarity in size of the ester and methyl groups. In terms of the mechanism of isomerisation, there are two possibilities in the case of the glycine derivatives **13a**, either acid-catalysed enolisation and reprotonation or ring opening and reclosure, triggered presumably by protonation of the NTs group. While both could operate in the case of the glycine derivative **13a**, only the ring opening pathway can occur in the case of the alanine derivative **13b**, as enolisation is blocked. It therefore seems more likely that this type of cyclisation will often feature such ring openings on the way to the most thermodynamic isomer, which may not be the initial major product.

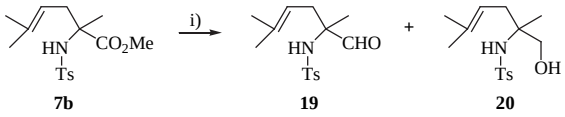
In view of the successful cyclisations of the prenyl derivatives **7a**,**b**, we reasoned that it might well be possible to apply this methodology to the synthesis of spiro-pyrrolidines, as this would also involve highly stabilised tertiary alkyl carbenium ions related to ion **8**. We therefore prepared two representative substrates **15** and **18**, using the same Stork methodology[11] (Scheme 4). The iodide **14** was necessary to efficiently alkylate the Schiff's base derived from alanine methyl ester; subsequent protecting group exchange then gave the desired precursor **15**. In contrast, the bromide **17** was a sufficiently reactive electrophile, which smoothly alkylated the corresponding glycinate carbanion to give, after the same protecting group exchange reactions, the exocyclic alkene isomer, the ylidenecyclohexane derivative **18**. We were delighted to find that both substrates behaved in essentially the same fashion as the prenyl derivatives **7** and led to the hoped-for spiro-compounds **16a**,**b** in excellent yields after only a brief exposure to ice-cold triflic acid. In addition to this being a useful synthetic approach to such spiro-pyrrolidines, the successful cyclisation of both precursors, presumably via a common tertiary carbe-



Scheme 4. (i) As Scheme 3; (ii) 0.4 equiv TfOH, $CHCl_3$, 0 °C, 0.25 h.

nium ion, gives this approach a potentially useful flexibility in the sense that either alkene positional isomer can be used.

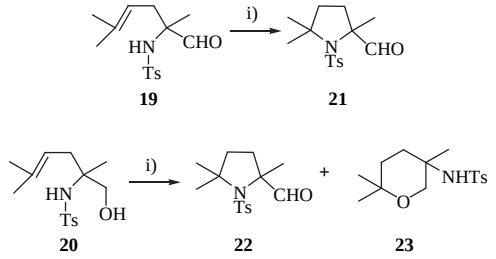
Having established the viability of this type of cyclisation, an immediate concern was the compatibility of this methodology with substrates containing acid-sensitive functional groups. As a small contribution to this aspect, we were fortunate to find that reduction of the hindered ester **7b** derived from alanine gave a separable mixture of the aldehyde **19** and the alcohol **20** (Scheme 5), both of which were exposed to triflic acid.



7b 19 20

Scheme 5. (i) 1 M Diisobutylaluminium hydride in ether, −78 °C, 4.5 h (39% and 50%).

The aldehyde **19** underwent smooth cyclisation to give the corresponding pyrrolidine **21** in excellent yield (Scheme 6). We suggest that this successful cyclisation will be limited to examples such as this, which do not have a proton α to the aldehyde group. Indeed, we could not even synthesise aldehyde precursors related to compound **7b**, which did not have such an α-substituent. The approximately 1:1 mixture of products **22** and **23** obtained from the alcohol **20** must reflect a similar reactivity in both nucleophiles, which is presumably composed of both their inherent nucleophilicity and the strength of the X–H bond, which is cleaved, i.e., their pK_a values.[14] Once again, we speculate that this type of cyclisation will be limited to such highly substituted examples, which do not allow simple alcohol dehydration to occur. Although not attempted during the present project, it may be possible to protect the hydroxyl group in such precursors, for example, by acetate formation as ester groups are stable to the present acidic conditions (Table 1), and thereby favouring pyrrolidine formation.



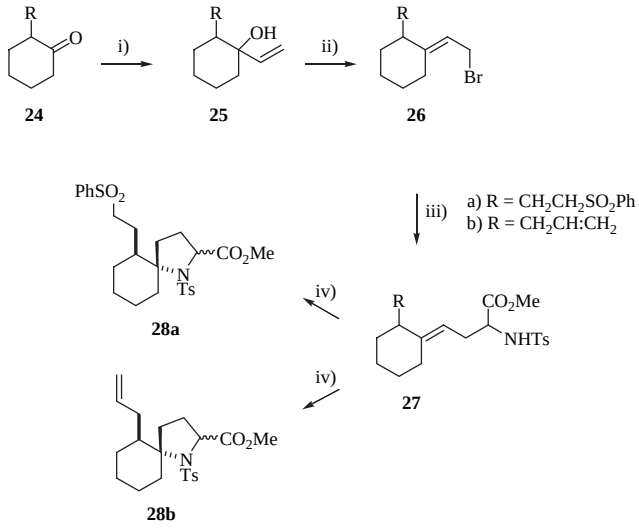
19 21

20 22 23

Scheme 6. (i) 0.4 equiv TfOH, $CHCl_3$, 0 °C, 0.25 h [**21**: 87%; **22**: 45%; **23**: 45%].

We also wished to demonstrate that some other useful functional groups beyond carboxylic acid esters (see Table 1) were compatible with this highly acidic methodology. To this end, we prepared the functionalised amino-ester precursors **27** using a similar approach for both compounds, starting with the corresponding 2-phenylsulfonylethyl- or 2-allyl-cyclohexanone **24** (Scheme 7). Each was condensed with vinylmagnesium bromide followed by brominative rearrangement of the resulting tertiary alcohols **25** to give the allylic bromides **26**, which were then used to alkylate the Schiff base **10a** derived from glycine.[11] We were delighted to find that both of the resulting substrates **27**, obtained using the usual protecting group exchange, underwent smooth cyclisation to give the hoped-for spiro-pyrrolidines upon exposure to sub-stoichiometric amounts of triflic acid in ice-cold chloroform. Unoptimised isolated yields were in the region of 70%. Both products **28** were isolated as 2–3:1 mixtures of only two diastereomers whose structures were tentatively assigned on steric grounds, arising from approach of the incoming sulfonamide nucleophile to the intermediate carbenium ion trans to the ring substituent, leaving a mixture at the carboxylic ester centre. Further studies will be necessary to confirm this.

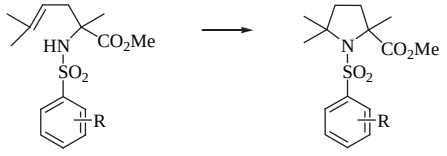
Another aspect that we were anxious to address was the nature of the nitrogen protecting group. Clearly the tosylated function had served



Scheme 7. (i) 1 M CH_2=CHMgBr in THF, −78 °C→20 °C, ~75–85%; (ii) PBr_3, pyridine 0 °C; (iii) as Scheme 3; (iv) 0.1–0.3 equiv TfOH, $CHCl_3$, 0 °C, 0.25 h (64–72%).

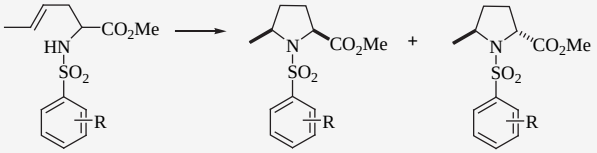
us very well, being able to prevent complete protonation of the amine group as well as proving to be perfectly stable to the acidic conditions. However, this very stability was a cause for concern, as it was likely to be a difficult group to remove. Although there are many methods known for achieving detosylation,[15] in our hands such reactions of representative pyrrolidines obtained during this project were not very efficient. This led us to test an alternative strategy that of using one of the three nitrophenylsulfonyl (nosyl) derivatives introduced by the Fukuyama group, which are so much easier to remove by *ipso* attack of a thiolate under very mild conditions.[16] However, the reduced nucleophilicity of the protonated nitrogen was a concern as was their overall stability to the acidic conditions. Such concerns proved unfounded when we found that all three such derivatives **29a–c** of alanine alkylated by a prenyl group, underwent very smooth and efficient cyclisations to provide the nosyl pyrrolidines **30a–c**, when exposed to the mildest set of conditions employed in this study: 0.5 equiv of triflic acid in ice-cold chloroform for 0.25 h. The results are collected in Table 3.[10]

Table 3
Acid-catalysed cyclisation of nitrophenylsulfonyl (nosyl) derivatives



29 30

R	TfOH (equiv)	Temp (°C)	Time (h)	Yield **30**
(a) 2-NO_2	0.5	0	0.25	89
(b) 4-NO_2	0.5	0	0.25	87
(c) 2,4-Di-NO_2	0.6	0	0.25	87



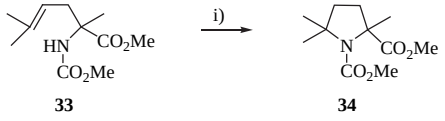
31 *cis*-32 *trans*-32

R	TfOH (equiv)	Temp (°C)	Time (h)	Yield **32** (cis/trans)
(a) 2-NO_2	1.0	62	4	86 (3:1)
(b) 4-NO_2	1.0	62	4	86 (3:1)
(c) 2,4-Di-NO_2	1.4	62	4	83 (3:1)

Overall, there was surprisingly little difference between the tosyl and nosyl derivatives **29**, all of which cyclised under much the same conditions; the returns from the nosyl derivatives were slightly lower and the 2,4-dinitro derivatives in particular responded slightly better when a little more triflic acid was used. Of course, the substrates **29** are the most easily cyclised and so we also tested the suitability of the nosyl groups in cyclisations of the corresponding crotyl derivatives, which are amongst the most difficult to cyclise, requiring relatively prolonged refluxing in chloroform to achieve complete conversions.

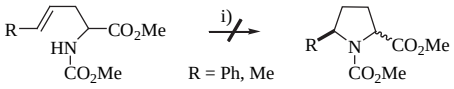
Once again, the results (Table 3) from these cyclisations were very comparable with those found for the related tosyl compounds; again, yields using the nosyl precursors were marginally lower but otherwise the overall outcomes were very similar. In terms of product stereochemistry, this too was similar in that there was a distinct preference for formation of the cis-diastereomers (see Table 2). Perhaps all of these results reflect a balance between the lower nucleophilicity of the nitrophenylsulfonyl groups and their lower pK_a values relative to the toluenesulfonyl group; the latter feature would facilitate the cyclisations on the assumption that N–H bond cleavage is a rate-determining step. In contrast, we found that carbamate derivatives were much less suited to this type of cyclisation. Again we first examined the prenyl derivative **33** of alanine now modified by a relatively acid-stable methoxycarbonyl function on nitrogen, as this was the most likely to undergo smooth cyclisation. However, this did not cyclise at ice temperature and only gave the anticipated pyrrolidine **34** in our hands in 69% yield when exposed to 2 equiv of triflic acid at ambient temperature.

As these were not the most extreme conditions, we pursued the use of this carbamate group by attempting to cyclise both the cinnamyl and crotyl derivatives **35**, but neither of these led to the formation of pyrrolidines **36**, even after very prolonged exposure to excess acid in refluxing chloroform (Scheme 9).



33 **34**

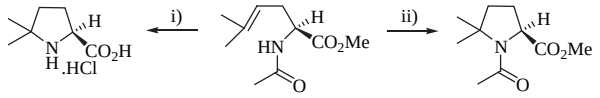
Scheme 8. (i) 2.0 equiv TfOH, $CHCl_3$, 25 °C, 2 h (69%).



35 **36**

Scheme 9. (i) 1.0–2.0 equiv TfOH, $CHCl_3$, 62 °C, 24 h (0%).

It would therefore appear that the inclusion of sulfonyl groups is generally necessary for achieving this type of cyclisation, with the exception of very acid-stable carbamates ($NHCO_2Me$ or acetamides) but only when the intermediate is a relatively favoured tertiary carbenium ion. The conversion of the prenyl derivative **33** into the pyrrolidines **34** (Scheme 8) is not strictly an original observation, as a very closely related conversion has recently been reported by Jackson et al. for the synthesis of 5,5-dimethylproline **38** from the acetylated precursor **37** (Scheme 10).[17] Quite forcing conditions were used to obtain the free acid **38** directly, while exposure to the much more vigorous conditions of triflic acid in hot toluene initially introduced by Schlummer and Hartwig[10] gave an excellent return of the fully protected proline derivative **39**. An additional and significant finding made by the Jackson group during this study is that the stereogenic centre adjacent to the ester group is not scrambled during such acid-induced cyclisations, despite the more demanding conditions used; both products **38** and **39** were obtained with undiminished levels of optical activity (Scheme 10). Similar methodology has also been applied successfully to examples of spiro-pyrrolidine synthesis, in much the same fashion as shown in Schemes 4 and 7, but again with carbonyl rather than sulfonyl groups protecting the amine function.[18]

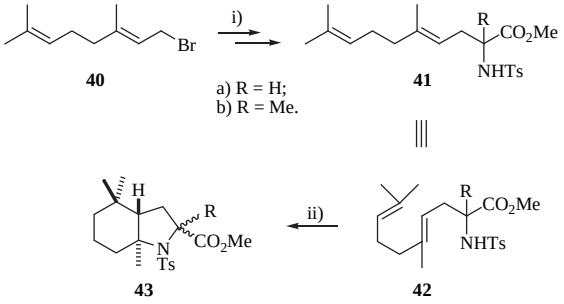


38 **37** **39**

Scheme 10. (i) 1 M HCl, reflux, 1.5 h (60%); (ii) 20% TfOH, toluene, 100 °C, 4 h (96%).

Repositioning the carbonyl group of such derivatives on the 'inside' of the precursor, as in *N*-aryl-4-pentenamides, has also been shown to be a viable and highly efficient tactic in a new approach to 2-pyrrolidinones but which requires rather brutal conditions (1 equiv TfOH, toluene, 100 °C, 5–30 h), reflecting the requirement for the generation of a secondary carbenium ion, at least in the examples reported.[10] Remarkably, an isolated but efficient example of an acid-catalysed intramolecular cyclisation of an isoxazolone, effectively an *O*-acyl hydroxylamine, onto a tertiary carbenium ion has been reported, although the fact that the nitrogen atom can also be regarded as being part of a vinylogous amide probably means it has considerable similarity to the foregoing examples.[14]

The seemingly clear intermediacy of carbenium ions in these types of cyclisation stimulated the thought that suitably placed sulfonamide groups could act as terminators to polyene cascade cyclisations, especially when the latter were similar to those encountered in terpene biosynthesis or related biomimetic syntheses.[19] Fortunately, this idea was relatively easy to test: using the Stork method (Scheme 3),[11] both Schiff's bases **10a**,**b** were smoothly alkylated using geranyl bromide **40**; following protecting group exchange, the first two test substrates **41a**,**b** were readily obtained (Scheme 11).



40 **41** **43** **42**

Scheme 11. (i) As Scheme 3, using Schiff's bases **10a** and **10b**; (ii) 0.4 equiv TfOH, $CHCl_3$, 0 °C, 0.25 h (~90%).

We were delighted and even surprised to find that both substrates **42a**,**b** were very readily transformed into the octahydroindoles **43a**,**b** using the mildest set of conditions, both in excellent yields and as 3:1 and 3:2 mixtures of diastereomers, respectively. Evidence for these complete cyclisations came from ^1H NMR analysis, which showed the complete disappearance of the two olefinic protons in precursors **42** and distinct upfield shifts of the three aliphatic methyl groups, together with separation of many of the high field protons into much more complex patterns, suggestive of cyclic structures. While all other spectroscopic and analytical data also supported the proposed structures **43a**,**b**, we were fortunate to be able to separate a sample of the major diastereoisomer **43a.maj** derived from glycine, which showed a key NOE enhancement between the proton α to the ester group and the methyl group at the new ring junction suggestive of conformation

44. Presumably, the isomer ratio is a balance of $A_{1,3}$ strain between the ester group and the ring junction proton when the former is axial as shown (**45**) and steric repulsion between the ester and tosyl groups if the former is equatorial. Evidently, the axial ester position is favoured in this substrate and most likely also in the product **43b** derived from alanine where the 3:2 ratio probably reflects the closer size similarity of the ester and methyl groups. The close similarity of the spectroscopic data supports these structural assignments (Fig. 2).

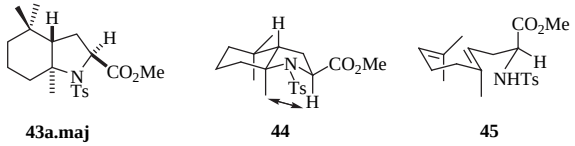
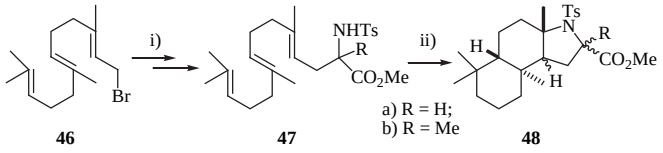


Figure 2. Likely three-dimensional shape **44** of the major diastereoisomer **43a.maj** derived from geranyl bromide and glycine and a likely transition state conformation **45**.

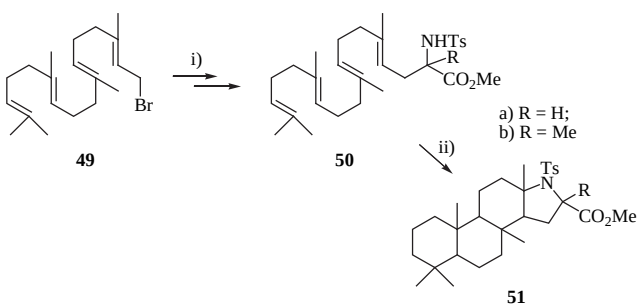
In no experiment did we observe any intermediate(s) arising from cyclisation onto only the central alkene group.[20] It would therefore seem that protonation takes place entirely at the distal alkene leading to complete cyclisation to the bicyclic systems **43**.

We then focussed on the more extended farnesyl derivatives **47a**,**b**, which were prepared in exactly the same manner from (*E*,*E*)-farnesyl bromide **46** (Scheme 12). This too underwent very smooth conversion into the completely cyclised tricyclic products **48a**,**b** under the mildest set of conditions and were both isolated as 3:3:1:1 mixtures of four stereoisomers in approximately 85% yields. The isomer ratios were determined from integrations of the methyl ester resonances in the ^{1}H NMR spectra. Although not proven, we speculate that there is a similar 3:1 ratio of epimers at the ester site, which then suggests that both trans- and cis-ring fusion were formed as shown, given the outcomes of such cyclisations of the related geranyl derivatives **42**.



Scheme 12. (i) and (ii) as Scheme 11 (85%).

In view of this success, we then went one step further and attempted to cyclise the geranylgeranyl derivatives **50**, again derived from the corresponding bromide **49**, prepared from natural geranylgeraniol. We were delighted to observe that, under the same set of conditions as those used in the foregoing cascades, the substrates **50a**,**b** were rapidly transformed into what appeared to be the azasteroid derivatives **51a**,**b** in 80% and 83% yields, respectively (Scheme 13). The proposed structures **51** are somewhat tentative. The complete disappearance of all olefinic resonances in the ^{1}H NMR spectra of the products provided good indications of



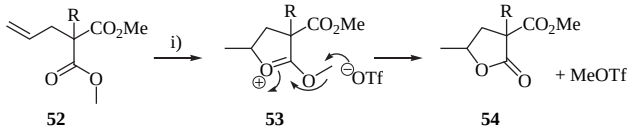
Scheme 13. (i) and (ii) as Scheme 11 (80–83%).

successful cascades, although the complexity of the spectra in which all resonances except those associated with the ester and tosyl functions appeared above δ_H 2.20 provided neither structural proof nor definite isomer ratios. The most compelling evidence for the structures **51a**,**b** came from very detailed analyses of the mass spectrometric fragmentation patterns and comparisons of these with those displayed by the lower homologues **43a**,**b** and **48a**,**b**, the full details of which have been published elsewhere.[21] Clearly, although arguably probably correct, this possible approach to the azasteroid skeleton requires more optimisation, especially to try and control the stereoselectivity as well as to carry out separation and more complete characterisation of those isomers, which are formed.

3. Conclusions

In conclusion, we suggest that this type of acid-catalysed intramolecular hydroamination will provide a valuable method for the synthesis of many substituted pyrrolidines in a very rapid and efficient manner. Of course, there will be limitations, especially associated with the presence of acid-sensitive functionalities. Current efforts are aimed at a much fuller definition of exactly what these are. For example, it is assumed that all acid-labile alcohol protecting groups will probably not survive the present acidic conditions, but this may not be entirely true. In addition, triflic acid is not a particularly attractive reagent, is expensive and very hygroscopic and hence requires very careful handling. Many of the conditions reported herein are considerably milder than those used by Schlummer and Hartwig for inducing very similar cyclisations, specifically heating in toluene at 100 °C for a number of hours.[10] Mostly, their examples consisted of cyclisations of sulfonamides onto benzylic carbenium ions unassisted by any substituents on the connecting chain, whereas all of the present substrates carry at least one, usually an ester group, which will provide assistance to the cyclisations by adding some steric compression. However, the difference between around an hour at ambient temperature and a few hours at 100 °C of otherwise relatively similar benzylic carbenium ions is considerable, even though the present cases are triggered by 40 mol % triflic acid, twice as much as was used in the Schlummer–Hartwig cases. In contrast and in line with the results published by Schlummer and Hartwig,[10] we have very recently examined the effectiveness of using concentrated sulfuric acid in its place. Preliminary findings suggest this may be a great improvement, obviating most if not all of the foregoing drawbacks associated with triflic acid. For example, a 2–3 M mixture of concentrated H_2SO_4 in dichloromethane is successful in cyclising the 'favourable' substrates **7a**,**b** (Scheme 2) at ice temperature with only a slight increase in reaction time; use of this reagent in such cases certainly does not require the much more brutal conditions of prolonged reflux in toluene as originally reported.[10,17] Subsequent to these initial reports of acid-catalysed intramolecular hydroamination, a number of groups have defined conditions for related acid-catalysed intermolecular hydroaminations of alkenes and alkynes.[3,22,23]

In an interesting caveat to the present work, Muñoz and Lloyd-Jones have very recently reported that triflic acid is capable of inducing dealkylative lactonisation in the formation of butyrolactones **54** from the unsaturated esters **52** and have even observed the oxonium intermediates **53** during ^{1}H NMR analysis (Scheme 14).[24]



Scheme 14. (i) 2.TfOH, $CHCl_3$, 20 °C, 24 h (79%; 1.7:1 ratio of diastereomers).

Evidently, in our examples, the sulfonamide group is much the more reactive with the initially formed carbenium ion as, in no cases, did we detect any lactone formation. However, this may not be the case if alternative esters, such as benzyl or 4-methoxybenzyl were used, which are much more reactive in a dealkylative sense.

This ability of the sulfonyl group to prevent complete protonation of the sulfonamides and hence allow cyclisation to occur, or at least to provide crucial assistance to proton transfer onto the alkene,[10] echoes the only other commonly encountered reaction wherein a nitrogen atom retains its nucleophilicity under acidic conditions, the Ritter reaction, which even today continues to attract attention, applications and further developments.[25]

4. Experimental section

4.1. General remarks

NMR spectra were recorded using a Bruker DPX spectrometer operating at 400 MHz for ^{1}H spectra and at 100.6 MHz for ^{13}C spectra, respectively. Unless stated otherwise, NMR spectra were measured using dilute solutions in deuteriochloroform. All NMR measurements were carried out at 30 °C and chemical shifts are reported as parts per million on the delta scale downfield from tetramethylsilane (TMS: δ=0.00) or relative to the resonances of $CHCl_3$ (δ_H=7.27 in proton spectra and δ_C=77.0 ppm for the central line of the triplet in carbon spectra, respectively). Coupling constants (J) are reported in hertz. Infrared spectra were recorded as thin films on sodium chloride plates for liquids and as KBr disks for solids, using a Perkin–Elmer 1600 series FTIR spectrophotometer and sodium chloride plates. Low resolution mass spectra were obtained using a VG Platform II Quadrupole spectrometer operating in the electron impact (EI; 70 eV) or atmospheric pressure chemical ionisation (ApcI) modes, as stated. High resolution mass spectrometric data was obtained from the EPSRC Mass Spectrometry Service, University College, Swansea, using the electrospray ionisation (ES) mode unless otherwise stated. Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Elemental analyses were obtained using a Perkin Elmer 240C Elemental Microanalyser.

All reactions were conducted in oven-dried apparatus under an atmosphere of dry nitrogen unless otherwise stated. All organic solutions from aqueous work-ups were dried by brief exposure to dried magnesium sulfate, followed by gravity filtration. The resulting dried solutions were evaporated using a Büchi rotary evaporator under water aspirator pressure and at ambient temperature unless otherwise stated. Column chromatography was carried out using Merck Silica Gel 60 (230–400 mesh). TLC analyses were carried out using Merck silica gel 60 F_{254} pre-coated, aluminium-backed plates, which were visualised using ultraviolet light or potassium permanganate or ammonium molybdenate sprays.

Ether refers to diethyl ether and petrol to the fraction boiling 60–80 °C unless stated otherwise.

4.2. Precursor synthesis

*4.2.1. Methyl (benzylideneamino)acetate (**10a**).* Glycine methyl ester hydrochloride (15.0 g, 120 mmol) and dried magnesium sulfate (14.0 g) were stirred together in dry dichloromethane (200 mL) at ambient temperature for 20 min then benzaldehyde (12.1 mL, 120 mmol) and dry triethylamine (26.8 mL, 220 mmol) were added sequentially and dropwise. The resulting mixture was stirred for 30 h at the same temperature then filtered and the solvent evaporated. The residue was dissolved in ether (100 mL) and water (100 mL) and the separated aqueous layer extracted with ether (2×100 mL). The combined ether solutions were washed with brine then dried, filtered and evaporated and finally dried under high vacuum at 0.1 mmHg to leave the *imine* **10a** (20.1 g, 95%) as a yellow oil. δ_H (400 MHz, $CDCl_3$) 8.22 (s, 1H, N=CH), 7.72–7.69 (m, 2H), 7.36–7.33 (m, 3H), 4.36 (s, 2H, CH_2), 3.70 (s, 3H, OMe).[11]

*4.2.2. Methyl 2-(benzylideneamino)propanoate (**10b**).* By the same procedure, reaction between alanine methyl ester hydrochloride (5.0 g, 36 mmol) and benzaldehyde (3.64 mL, 36 mmol) in dichloromethane (70 mL) gave the *imine* **10b** (6.6 g, 98%) also as a yellow oil. δ_H (400 MHz, $CDCl_3$) 8.25 (s, 1H, N=CH), 7.79–7.76 (m, 2H), 7.38–7.36 (m, 3H), 4.11 (q, J=6.8 Hz, 1H, H2), 3.67 (s, 3H, OMe), 1.45 (d, J=6.8 Hz, 3-Me).

*4.2.3. General procedure A: synthesis of unsaturated p-toluenesulfonamides (**7**, **12**, etc.)[11].* Lithium diisopropylamide was prepared by the dropwise addition of butyl lithium (1.2 equiv of a 2.5 M solution in hexanes) to a solution of diisopropylamine (1.2 equiv) in tetrahydrofuran (2 mL mmol^{-1} of diisopropylamine) maintained at 0 °C. After 0.5 h, the solution was cooled to −78 °C. A solution of an *N*-(benzylideneamino) ester **10** (1.0 equiv) in tetrahydrofuran (2 mL mmol^{-1}) was added dropwise by syringe and the resulting deep red solution stirred for 0.5 h at −78 °C. An allylic bromide or alkenyl iodide (1.1 equiv) in tetrahydrofuran (1 mL mmol^{-1}) was then added dropwise and the resulting solution stirred at −78 °C for 1 h, after which the now orange solution was allowed to warm to ambient temperature, stirred for an additional 1 h then quenched by the addition of saturated aqueous ammonium chloride (4 mL mmol^{-1}) and diluted with ether (2 mL mmol^{-1}). The layers were separated and the aqueous layer extracted with ether (3×4 mL mmol^{-1}). The combined organic solutions were dried, filtered and evaporated to leave the imine **11**, together with varying amounts of the hydrolysis products, the corresponding free amine and benzaldehyde.

Following brief characterisation by ^{1}H NMR, the crude imine **11** (1 equiv) was dissolved in ether (8 mL mmol^{-1}) and 1 M hydrochloric acid (8 mL mmol^{-1}) was added slowly to the resulting solution. The two-phase mixture was stirred vigorously at ambient temperature until TLC monitoring indicated complete hydrolysis of the imine (ca. 2 h). The organic layer was separated and discarded and the aqueous layer washed with ether (2×8 mL mmol^{-1}), then adjusted to pH 9 using 2 M aqueous sodium hydroxide and extracted with dichloromethane (3×4 mL mmol^{-1}). The combined extracts were dried, filtered and evaporated to leave the crude amine. After weighing, this was dissolved in dichloromethane (5 mL mmol^{-1}) at ambient temperature and treated with *p*-toluenesulfonyl chloride (1.2 equiv), triethylamine (1.2 equiv) and a few crystals of 4-(dimethylamino)pyridine. The resulting solution was stirred overnight at ambient temperature then quenched by the addition of 2 M hydrochloric acid (4 mL mmol^{-1}) and the phases separated. The aqueous phase was further extracted with dichloromethane (2×4 mL mmol^{-1}) and the combined dichloromethane extracts washed with brine, then dried, filtered and evaporated. The residue was either separated by column chromatography (EtOAc/petrol mixtures) or purified by crystallisation from ethyl acetate/hexanes mixtures to give the *sulfonamides* **12**.

*4.2.4. Methyl 5-methyl-2-(p-toluenesulfonylamino)hex-4-enoate (**7a**).* Methyl 2-(benzylideneamino)-acetate **10a** (4.00 g, 23 mmol) was alkylated using prenyl bromide according to general procedure A to give the *imine* **11a**: δ_H (400 MHz, $CDCl_3$) 8.12 (s, 1H, N=CH), 7.68–7.65 (m, 2H), 7.33–7.31 (m, 3H), 5.00 (t, J=7.5 Hz, 1H, H4), 3.89–3.87 (m, 1H, H2), 3.68 (s, 3H, OMe), 2.64 (ddd, J=14.8, 7.5, 6.4 Hz, 1H, $H3_a$), 2.47 (ddd, J=14.8, 7.5, 6.4 Hz, 1H, $H3_b$), 1.59 (s, 3H), 1.50 (s, 3H).

This was hydrolysed and tosylated to give the *sulfonamide* **7a** (2.60 g, 38%) as a colourless, crystalline solid, mp 97–99 °C; R_f 0.43 (40% EtOAc/petrol); $C_{15}H_{21}NO_4S$: calcd C 57.9, H 6.8, N 4.5; found: C 57.8, H 6.6, N 4.7%; δ_H (400 MHz, $CDCl_3$) 7.65 (d, J=8.2 Hz, 2H,

2×ArH), 7.20 (d, *J*=8.2 Hz, 2H, 2×ArH), 5.06 (d, *J*=8.6 Hz, 1H, NH), 4.86 (t, *J*=7.3 Hz, H4), 3.89 (td, 9.4, 8.6 Hz, 1H, H2), 3.44 (s, 3H, OMe), 2.38–2.35 (m, 2H, 3-CH_2), 2.36 (s, 3H, ArMe), 1.51 (s, 3H), 1.40 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 173.4 (CO), 143.4 (s), 139.6 (s), 139.0 (5-C), 129.7 (4-CH), 128.0 (2×d), 126.3 (2×d), 117.3 (5-CH), 67.3 (2-CH), 52.5 (OMe), 41.4 (3-CH_2), 29.3 (q), 28.2 (q), 27.7 (q); ν_{max} (KBr)/cm^{-1} 3253, 3241, 1734, 1430, 1328, 1254; HRMS: *m*/*z*: calcd for $C_{15}H_{22}NO_4S$: 312.1270; found: 312.1261 $[M+H]^+$.

*4.2.5. Methyl 2,5-dimethyl-2-(p-toluenesulfonylamino)hex-4-enoate (**7b**).* Methyl 2-(benzylideneamino)-propanoate **10b** (3.80 g, 20 mmol) was alkylated using prenyl bromide according to general procedure A to give the expected *imine*: δ_H (400 MHz, $CDCl_3$) 8.15 (s, 1H, N=CH), 7.69–7.67 (m, 2H), 7.36–7.34 (m, 3H), 5.03 (t, *J*=7.5 Hz, 1H, H4), 3.65 (s, 3H, OMe), 2.58–2.55 (m, 2H, 3-CH_2), 1.61 (s, 3H), 1.54 (s, 3H), 1.40 (s, 3H).

This was hydrolysed and tosylated to give the *sulfonamide* **7b** (2.40 g, 38%) as a colourless, crystalline solid, mp 84–87 °C; R_f 0.45 (40% EtOAc/petrol); $C_{16}H_{23}NO_4S$: calcd C 59.1, H 7.1, N 4.3; found: C 59.3, H 7.1, N 4.6%; δ_H (400 MHz, $CDCl_3$) 7.67 (d, *J*=8.2 Hz, 2H, 2×ArH), 7.19 (d, *J*=8.2 Hz, 2H, 2×ArH), 5.30 (br s, 1H, NH), 4.84 (t, *J*=7.8 Hz, H4), 3.52 (s, 3H, OMe), 2.32 (dd, *J*=14.4, 7.8 Hz, 1H, $H3_a$), 2.49 (dd, *J*=14.4, 7.8 Hz, 1H, $H3_b$), 2.32 (s, 3H, ArMe), 1.58 (s, 3H), 1.50 (s, 3H), 1.32 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 174.1 (CO), 143.5 (s), 139.9 (s), 137.4 (5-C), 129.8 (2×d), 127.4 (2×d), 117.1 (4-CH), 62.6 (2-C), 53.0 (OMe), 39.1 (3-CH_2), 26.4 (q), 21.9 (q), 21.4 (q), 14.6 (q); ν_{max} (KBr)/cm^{-1} 3253, 2942, 1733, 1463, 1377; HRMS: *m*/*z*: calcd for $C_{16}H_{24}NO_4S$: 326.1426; found: 326.1421 $[M+H]^+$.

*4.2.6. Methyl (E)-5-phenyl-2-(p-toluenesulfonylamino)pent-4-enoate (**12a**).* Cinnamyl bromide was used to alkylate methyl 2-(benzylideneamino)acetate **10a** (3.70 g, 21 mmol) according to general procedure A to give the *imine* **11a**: δ_H (400 MHz, $CDCl_3$) 8.13 (s, 1H, N=CH), 7.66–7.65 (m, 2H), 7.31–7.02 (m, 7H), 6.34 (d, *J*=15.8 Hz, 1H, H5), 6.08 (dt, *J*=15.8, 7.3 Hz, 1H, H4), 3.61 (s, 3H, OMe), 3.58–3.62 (obscured, 1H, H2), 2.70–2.68 (m, 2H, 3-CH_2), 1.41 (s, 3H).

This was hydrolysed and tosylated to give the *sulfonamide* **12a** (2.70 g, 36%) as a colourless, crystalline solid, mp 96–99 °C; $C_{19}H_{21}NO_4S$: calcd C 63.5, H 5.9, N 3.9; found: C 63.6, H 6.0, N 4.0%; δ_H (400 MHz, $CDCl_3$) 7.74 (d, *J*=8.2 Hz, 2H, 2×ArH), 7.34–7.23 (m, 7H), 6.40 (d, *J*=15.5 Hz, 1H, H5), 5.96 (dt, *J*=15.5, 7.6 Hz, 1H, H4), 5.10 (d, *J*=8.8 Hz, 1H, NH), 4.11 (dt, *J*=8.8, 5.9 Hz, 1H, H2), 3.57 (s, 3H, OMe), 2.70–2.64 (m, 2H, 3-CH_2), 2.41 (s, 3H, ArMe); δ_C (100.6 MHz, $CDCl_3$) 172.6 (CO), 144.1 (s), 135.6 (s), 134.9 (s), 130.1 (d), 128.9 (d), 128.1 (d), 127.6 (d), 126.7 (d), 126.3 (d), 122.9 (d), 55.9 (2-CH), 53.0 (OMe), 37.3 (3-CH_2), 22.0 (q); ν_{max} (KBr)/cm^{-1} 3274, 3031, 1734, 1597; HRMS: *m*/*z*: calcd for $C_{19}H_{22}NO_4S$: 360.1264; found: 360.1268 $[M+H]^+$.

*4.2.7. Methyl (E)-2-methyl-5-phenyl-2-(p-toluenesulfonylamino)pent-4-enoate (**12b**).* Cinnamyl bromide was used to alkylate methyl 2-(benzylideneamino)propanoate **10b** (1.90 g, 10 mmol) according to general procedure A to give the *imine* **11b**: δ_H (400 MHz, $CDCl_3$) 8.13 (s, 1H, N=CH), 7.66–7.64 (m, 2H), 7.31–7.02 (m, 8H), 6.34 (d, *J*=15.8 Hz, 1H, H5), 6.08 (dt, *J*=15.8, 7.3 Hz, 1H, H4), 3.61 (s, 3H, OMe), 2.69 (d, *J*=7.3 Hz, 2H, 3-CH_2), 1.41 (s, 3H, 2-Me).

This was hydrolysed and tosylated to give the *sulfonamide* **12b** (1.30 g, 33%) as a colourless, crystalline solid, mp 131–133 °C; R_f 0.33 (25% EtOAc/petrol); $C_{20}H_{23}NO_4S$: calcd C 64.3, H 6.2, N 3.8; found: C 64.0, H 6.3, N 3.7%; δ_H (400 MHz, $CDCl_3$) 7.72 (d, *J*=8.2 Hz, 2H, 2×ArH), 7.22–7.11 (m, 7H), 6.29 (d, *J*=15.8 Hz, 1H, H5), 5.87 (dt, *J*=15.8, 7.4 Hz, 1H, H4), 5.47 (br s, 1H, NH), 3.58 (s, 3H, OMe), 2.68 (dd, *J*=15.0, 7.4 Hz, 1H, $H3_a$), 2.55 (dd, *J*=15.0, 7.4 Hz, 1H, $H3_b$), 2.32 (s, 3H, ArMe), 1.39 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 174.6 (CO), 144.3 (s), 139.8 (s), 135.0 (s), 132.4 (d), 130.0 (2×d), 128.9 (2×d), 128.0 (d), 127.5 (2×d), 126.7 (2×d), 123.0 (d), 62.8 (2-C), 53.3 (OMe), 43.2 (3-CH_2), 23.0 (q), 21.9 (q); ν_{max} (KBr)/cm^{-1} 3354, 3055, 2990, 1738, 1598, 1421, 1370; HRMS: *m*/*z*: calcd for $C_{20}H_{24}NO_4S$: 374.1426; found: 374.1428 $[M+H]^+$.

*4.2.8. Methyl (E)-2-(p-toluenesulfonylamino)hex-4-enoate (**12c**).* Methyl 2-(benzylideneamino)acetate **10a** (1.50 g, 8.5 mmol) was alkylated using crotyl bromide according to general procedure A to give the *imine* **11c**: δ_H (400 MHz, $CDCl_3$) 8.12 (s, 1H, N=CH), 7.67–7.65 (m, 2H), 7.37–7.36 (m, 3H), 5.46 (dq, *J*=14.3, 6.2 Hz, 1H, H5), 5.18 (dt, *J*=14.3, 7.6 Hz, 1H, H4), 3.92–3.90 (m, 1H, H2), 3.64 (s, 3H, OMe), 2.64–2.58 (m, 2H, 3-CH_2), 1.59 (d, *J*=6.2 Hz, 3H, 5-Me).

This was hydrolysed and tosylated to give the *sulfonamide* **12c** (1.10 g, 51%) as a colourless, crystalline solid, mp 68–70 °C; R_f 0.33 (25% EtOAc/petrol); $C_{14}H_{19}NO_4S$: calcd C 56.6, H 6.4, N 4.7; found: C 56.5, H 6.3, N 4.9%; δ_H (400 MHz, $CDCl_3$) 7.68 (d, *J*=8.2 Hz, 2H, 2×ArH), 7.28 (d, *J*=8.2 Hz, 2H, 2×ArH), 5.45 (dq, *J*=15.2, 6.5 Hz, 1H, H5), 5.18 (ddd, *J*=15.2, 7.2, 7.0 Hz, 1H, H4), 5.10 (d, *J*=8.8 Hz, 1H, NH), 3.97–3.96 (m, 1H, H2), 3.53 (s, 3H, OMe), 2.39 (s, 3H, ArMe), 2.37–2.32 (m, 2H, 3-CH_2), 1.62 (d, *J*=6.5 Hz, 3H, 5-Me); δ_C (100.6 MHz, $CDCl_3$) 172.1 (CO), 143.7 (s), 137.1 (s), 136.3 (4(5)-CH), 129.4 (2×d), 127.7 (2×d), 122.4 (5(4)-CH), 57.5 (2-CH), 52.6 (OMe), 38.4 (3-CH_2), 22.3 (q), 19.7 (q); ν_{max} (KBr)/cm^{-1} 3261, 2955, 1743, 1431, 1331; HRMS: *m*/*z*: calcd for $C_{14}H_{20}NO_4S$: 298.1113; found: 298.1109 $[M+H]^+$.

*4.2.9. Methyl (E)-2-methyl-2-(p-toluenesulfonylamino)hex-4-enoate (**12d**).* Methyl 2-(benzylideneamino)propanoate **10b** (3.80 g, 20 mmol) was alkylated using crotyl bromide according to general procedure A to give the *imine* **11d**: δ_H (400 MHz, $CDCl_3$) 8.11 (s, 1H, N=CH), 7.67–7.64 (m, 2H), 7.40–7.38 (m, 3H), 5.41 (dq, *J*=13.5, 6.5 Hz, 1H, H5), 5.23 (ddd, *J*=13.5, 7.6, 7.1 Hz, 1H, H4), 3.61 (s, 3H, OMe), 2.54–2.40 (m, 2H, 3-CH_2), 1.55 (d, *J*=6.5 Hz, 3H, 5-Me), 1.36 (s, 3H).

This was hydrolysed and tosylated to give the *sulfonamide* **12d** (2.20 g, 36%) as a colourless, crystalline solid, mp 98–99 °C; R_f 0.35 (25% EtOAc/petrol); $C_{15}H_{21}NO_4S$: calcd C 57.9, H 6.8, N 4.5; found: C 57.5, H 7.0, N 4.6%; δ_H (400 MHz, $CDCl_3$) 7.97 (d, *J*=8.3 Hz, 2H, 2×ArH), 7.50 (d, *J*=8.3 Hz, 2H, 2×ArH), 5.75 (dq, *J*=13.2, 6.5 Hz, 1H, H5), 5.45 (br s, 1H NH), 5.43 (ddd, *J*=13.2, 7.6, 7.1 Hz, 1H, H4), 3.91 (s, 3H, OMe), 2.73–2.57 (m, 2H, 3-CH_2), 2.63 (s, 3H, ArMe), 1.86 (d, *J*=6.5 Hz, 3H, 5-Me), 1.62 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 173.4 (CO), 143.6 (s), 139.9 (s), 131.7 (4(5)-CH), 129.9 (2×d), 127.5 (2×d), 123.9 (5(4)-CH), 62.5 (2-C), 53.0 (OMe), 43.8 (3-CH_2), 22.4 (q), 21.9 (q), 18.5 (q); ν_{max} (KBr)/cm^{-1} 3350, 3032, 2953, 1734, 1597, 1431; *m*/*z* [APCI] 312 (M^++H, 100%), 252 (M^+-CO_2Me, 37); HRMS: *m*/*z*: calcd for $C_{15}H_{22}NO_4S$: 312.1270; found: 312.1262 $[M+H]^+$.

4.3. General procedure for acid-catalysed cyclisations

*4.3.1. General procedure B: acid-catalysed cyclisations of sulfonamides (**7**, **12**, etc.).* The sulfonamide was dissolved in dry, ethanol-free chloroform (2 mL $mmol^{-1}$) and the solution stirred and cooled to 0 °C. The desired amount of trifluoromethanesulfonic (triflic) acid was added as a 10% (v/v) solution in dry, ethanol-free chloroform [This is a 1 mmol solution; hence 1 ml contains 150 mg of triflic acid.]. The resulting solution was stirred at the desired temperature for the necessary length of time then cooled in ice, if heated, before being quenched with excess saturated aqueous sodium carbonate. The separated aqueous layer was extracted with dichloromethane (2×) and the combined organic solutions dried, filtered and evaporated. The crude product was purified usually by passage through a small plug of silica gel eluted with dichloromethane and/or by crystallisation from hexanes/ethyl acetate.

4.4. Model acid-catalysed cyclisations

*4.4.1. Methyl 5,5-dimethyl-1-(p-toluenesulfonyl)pyrrolidine-2-carboxylate (**9a**).* The sulfonamide **7a** (115 mg, 0.37 mmol) was treated with triflic acid (22 mg, 0.15 mmol) at 0 °C for 0.25 h according to

general procedure B and gave the *pyrrolidine* **9a** (105 mg, 91%) as a colourless, crystalline solid, mp 94–96 °C; $C_{15}H_{21}NO_4S$: calcd C 57.9, H 6.8, N 4.5; found: C 58.2, H 6.9, N 4.5%; δ_H (400 MHz, $CDCl_3$) 7.67 (d, *J*=8.2 Hz, 2H, 2×ArH), 7.24 (d, *J*=8.2 Hz, 2H, 2×ArH), 4.32 (dd, *J*=7.9, 2.4 Hz, 1H, H2), 3.49 (s, 3H, OMe), 2.30 (s, 3H, ArMe), 2.09–2.07 (m, 1H), 1.93–1.90 (m, 1H), 1.77–1.75 (m, 1H), 1.64–1.62 (m, 1H), 1.41 (s, 3H), 1.30 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 178.5 (CO), 144.1 (s), 139.8 (s), 130.2 (2×d), 128.9 (2×d), 68.8 (2-CH), 63.9 (5-C), 53.6 (OMe), 41.2 (t), 38.4 (t), 28.7 (q), 26.8 (q), 22.8 (q); ν_{max} (KBr)/cm^{-1} 2986, 1732, 1494; HRMS: *m*/*z*: calcd for $C_{15}H_{22}NO_4S$: 312.1270; found: 312.1272 $[M+H]^+$.

*4.4.2. Methyl 2,5,5-trimethyl-1-(p-toluenesulfonyl)pyrrolidine-2-carboxylate (**9b**).* The sulfonamide **7b** (92 mg, 0.28 mmol), derived from prenyl bromide, was exposed to triflic acid (17 mg, 0.11 mmol) in chloroform at 0 °C for 0.25 h according to general procedure B and gave the *pyrrolidine* **9b** (85 mg, 92%) as a colourless, crystalline solid, mp 87–89 °C; $C_{16}H_{23}NO_4S$: calcd C 59.1, H 7.1, N 4.3; found: C 59.4, H 6.8, N 4.0%; δ_H (400 MHz, $CDCl_3$) 7.69 (d, *J*=8.0 Hz, 2H, 2×ArH), 7.26 (d, *J*=8.0 Hz, 2H, 2×ArH), 3.70 (s, 3H, OMe), 2.34 (s, 3H, ArMe), 2.20 (ddd, *J*=11.4, 7.9, 5.0 Hz, 1H, $H3_a$), 1,79–1.77 (m, 3H, $H3_b$ and 4-CH_2), 1.70 (s, 3H), 1.33 (s, 3H), 1.21 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 177.3 (CO), 144.2 (s), 140.6 (s), 130.6 (2×d), 129.4 (2×d), 71.8 (s), 66.8 (s), 54.0 (OMe), 42.0 (t), 38.2 (t), 30.0 (q), 28.9 (q), 27.1 (q), 22.9 (q); ν_{max} (KBr)/cm^{-1} 1741, 1598, 1454, 1142; HRMS: *m*/*z*: calcd for $C_{16}H_{24}NO_4S$: 326.1426; found: 326.1428 $[M+H]^+$.

*4.4.3. Methyl (2RS,5RS)- and (2RS,5SR)-5-phenyl-1-(p-toluenesulfonyl)pyrrolidine-2-carboxylate (**13a**)*[26]. The sulfonamide **12a** (117 mg, 0.33 mmol), derived from cinnamyl bromide, was exposed to triflic acid (30 mg, 0.20 mmol) in chloroform at 20 °C for 4 h according to general procedure B and gave the *pyrrolidine* **13a** (111 mg, 95%) as a colourless, crystalline solid, in a ratio of 1.2:1 (2*RS*,5*SR*)/(2*RS*,5*RS*), mp 100–103 °C; $C_{19}H_{21}NO_4S$: calcd C 63.5, H 5.9, N 3.9; found: C 63.8, H 6.4, N 4.0%; δ_H (400 MHz, $CDCl_3$) (major cis-isomer) 7.53 (d, *J*=8.2 Hz, 2H, 2×ArH), 7.45–7.38 (m, 2H, 2×ArH), 7.24–7.10 (m, 5H), 4.77 (app. t, *J*=ca. 6.7 Hz, 1H, H5), 4.56 (app. t, *J*=ca. 6.5 Hz, 1H, H2), 3.78 (s, 3H, OMe), 2.36 (s, 3H, ArMe), 2.16–2.06 (m, 1H), 2.06–2.00 (m, 2H), 1.96–1.87 (m, 1H); δ_C (100.6 MHz, $CDCl_3$) 173.2 (CO), 143.9 (s), 141.7 (s), 135.9 (s), 129.7 (2×d), 128.6 (2×d), 128.1 (2×d), 127.6 (d), 127.4 (2×d), 65.3 (d), 62.4 (d), 52.9 (OMe), 36.2 (t), 29.8 (t), 21.9 (q); the minor trans-isomer could be identified and quantified by resonances at δ_H (400 MHz, $CDCl_3$) 5.11 (app. d, *J*=8.8 Hz, 1H, H2(5)), 4.58 (app. d, *J*=8.6 Hz, 1H, H5(2)), 3.73 (s, 3H, OMe), 2.66–2.55 (m, 1H), 2.31 (s, 3H, ArMe), 1.78–1.68 (m, 1H); ν_{max} (KBr)/cm^{-1} 1751, 1598, 1453; HRMS: *m*/*z*: calcd for $C_{19}H_{25}N_2O_4S$: 377.1535; found: 377.1532 $[M+NH_4]^+$.

*4.4.4. Methyl (2RS,5RS)- and (2RS,5SR)-2-methyl-5-phenyl-1-(p-toluenesulfonyl)pyrrolidine-2-carboxylate (**13b**).* The sulfonamide **12b** (134 mg, 0.36 mmol), derived from cinnamyl bromide, was exposed to triflic acid (33 mg, 0.22 mmol) in chloroform at 20 °C for 4 h according to general procedure B to give the *pyrrolidine* **13b** (129 mg, 96%) as a colourless, crystalline solid, in a ratio of 2:1 (2*RS*,5*SR*)/(2*RS*,5*RS*), mp 142–144 °C; $C_{20}H_{23}NO_4S$: calcd C 64.3, H 6.2, N 3.8; found: C 64.0, H 6.3, N 3.8%; δ_H (400 MHz, $CDCl_3$) (major isomer) 7.36 (d, *J*=8.2 Hz, 2H, 2×ArH), 7.11–7.09 (m, 2H, 2×ArH), 6.94–6.93 (m, 3H, 3×ArH), 6.85 (d, *J*=8.2 Hz, 2H, 2×ArH), 4.85 (dd, *J*=9.2, 1.5 Hz, 1H, H5), 3.82 (s, 3H, OMe), 2.60–2.48 (m, 1H), 2.37–2.28 (m, 1H), 2.16 (s, 3H, ArMe), 1.82–1.67 (m, 2H), 1.77 (s, 3H, 2-Me); δ_C (100.6 MHz, $CDCl_3$) 175.4 (CO), 142.8 (s), 142.2 (s), 139.2 (s), 129.1 (d), 128.6 (d), 127.5 (d), 127.3 (d), 126.9 (d), 70.4 (2-C), 65.9 (5-CH), 53.1 (OMe), 39.0 (t), 33.4 (t), 24.6 (q), 21.8 (q); δ_H (400 MHz, $CDCl_3$) (minor isomer) 7.12–6.79 (m, 9H), 5.22 (dd, *J*=9.1, 2.6 Hz, 1H, H5), 3.72 (s, 3H, OMe), 2.57–2.46 (m, 1H, $H3_a$), 2.21 (s, 3H, ArMe), 2.13–2.04 (m, 2H, $H3_b$, $H4_a$), 1.66–1.57 (m, 1H, $H4_b$), 1.80 (s, 3H, 2-Me); ν_{max} (KBr)/cm^{-1} 1732, 1598, 1451, 1151; HRMS: *m*/*z*: calcd for $C_{21}H_{24}NO_4S$: 374.1426; found: 374.1418 $[M+H]^+$.

*4.4.5. Methyl (2RS,5RS)- and (2RS,5SR)-5-methyl-1-(p-toluenesulfonyl)pyrrolidine-2-carboxylate (**13c**).* The sulfonamide **12c** (102 mg, 0.34 mmol), derived from crotyl bromide, was exposed to triflic acid (51 mg, 0.34 mmol) in chloroform at 62 °C for 4 h according to general procedure B and gave the *pyrrolidine* **13c** (93 mg, 91%) as a colourless, crystalline solid, in a ratio of 2.5:1 (2*RS*,5*SR*)/(2*RS*,5*RS*) of inseparable diastereoisomers, mp 130–132 °C; $C_{14}H_{19}NO_4S$: calcd C 56.6, H 6.4, N 4.7; found: C 56.8, H 6.6, N 4.6%; δ_H (400 MHz, $CDCl_3$) (major isomer) 7.68 (d, *J*=8.2 Hz, 2H, 2×ArH), 7.17 (d, *J*=8.2 Hz, 2H, 2×ArH), 4.30 (dd, *J*=7.8, 2.3 Hz, 1H, H2), 3.79–3.76 (m, 1H, H5), 3.72 (s, 3H, OMe), 2.35 (s, 3H, ArMe), 2.35–1.34 (m, 4H), 1.26 (d, *J*=6.5 Hz, 3H, 5-Me); δ_C (100.6 MHz, $CDCl_3$) 174.4 (CO), 148.7 (s), 142.6 (s), 128.8 (2×d), 127.0 (2×d), 66.5 (2-CH), 58.2 (5-CH), 52.7 (OMe), 38.6 (t), 31.2 (t), 24.3 (q), 21.9 (q); δ_H (400 MHz, $CDCl_3$) (minor isomer) 7.72 (d, *J*=8.2 Hz, 2H, 2×ArH), 7.12 (d, *J*=8.2 Hz, 2H, 2×ArH), 4.39 (dd, *J*=7.4, 2.8 Hz, 1H, H2), 4.07–4.05 (m, 1H, H5), 3.68 (s, 3H, OMe), 2.34 (s, 3H, ArMe), 2.27–1.31 (m, 4H), 1.12 (d, *J*=6.6 Hz, 3H, 5-Me); δ_C (100.6 MHz, $CDCl_3$) 174.8 (CO), 148.9 (s), 142.8 (s), 128.6 (2×d), 127.3 (2×d), 68.4 (2-CH), 57.6 (5-CH), 52.8 (OMe), 38.3 (t), 31.5 (t), 23.9 (q), 21.7 (q); ν_{max} (KBr)/cm^{-1} 2954, 1732, 1338, 1150; *m*/*z*: [APCI] 298 (100%, $[M+H]^+$).

*4.4.6. Methyl (2RS,5RS)- and (2RS,5SR)-2,5-dimethyl-1-(p-toluenesulfonyl)pyrrolidine-2-carboxylate (**13d**).* The sulfonamide **12d** (0.316 g, 1.00 mmol), derived from crotyl bromide, was exposed to triflic acid (0.151 g, 1.00 mmol) in chloroform at 62 °C for 4 h according to general procedure B and gave the *pyrrolidine* **13d** (0.297 g, 94%) as a colourless, crystalline solid, in a ratio of 1.3:1 (2*RS*,5*SR*)/(2*RS*,5*RS*) of inseparable diastereoisomers, mp 133–135 °C; $C_{15}H_{21}NO_4S$: calcd C 57.9, H 6.8, N 4.5; found: C 58.1, H 6.9, N 4.5%; δ_H (400 MHz, $CDCl_3$) (major isomer) 7.69 (d, *J*=8.2 Hz, 2H, 2×ArH), 7.12 (d, *J*=8.2 Hz, 2H, 2×ArH), 3.87–3.86 (m, 1H, H5), 3.74 (s, 3H, OMe), 2.34 (s, 3H, ArMe), 2.32–1.39 (m, 4H), 1.52 (s, 3H, 2-Me), 1.15 (d, *J*=6.5 Hz, 3H, 5-Me); δ_C (100.6 MHz, $CDCl_3$) 174.6 (CO), 149.2 (s), 143.9 (s), 129.8 (2×d), 127.9 (2×d), 67.4 (2-C), 57.8 (5-CH), 52.9 (OMe), 39.1 (t), 31.7 (t), 26.5 (q), 21.9 (q), 21.7 (q); δ_H (400 MHz, $CDCl_3$) (minor isomer) 7.72 (d, *J*=8.2 Hz, 2H, 2×ArH), 7.10 (d, *J*=8.2 Hz, 2H, 2×ArH), 4.07–4.06 (m, 1H, H5), 3.66 (s, 3H, OMe), 2.34 (s, 3H, ArMe), 2.21–1.27 (m, 4H), 1.70 (s, 3H, 2-Me), 1.03 (d, *J*=6.5 Hz, 3H, 5-Me); δ_C (100.6 MHz, $CDCl_3$) 175.2 (CO), 149.2 (s), 143.6 (s), 129.7 (2×d), 127.3 (2×d), 70.4 (2-C), 57.9 (5-CH), 52.8 (OMe), 38.3 (t), 32.0 (t), 27.3 (q), 22.2 (q), 21.8 (q); ν_{max} (KBr)/cm^{-1} 1727, 1326; HRMS: *m*/*z*: calcd for $C_{15}H_{22}NO_4S$: 312.1270; found: 312.1260 $[M+H]^+$.

4.5. Spiro-pyrrolidines

*4.5.1. Methyl 4-(cyclohex-1-en-1-yl)-2-methyl-2-(p-toluenesulfonylamino)butanoate (**15**).* Methyl 2-(benzylideneamino)propanoate **10b** (3.80 g, 20 mmol) was alkylated using 1-(2-iodoethyl)cyclohexene **14** [4.96 g, 21 mmol; δ_H (400 MHz, $CDCl_3$) 5.50 (br res., 1H,:CH), 3.22 (t, *J*=7.5 Hz, 2H, 1-CH_2), 2.51 (td, *J*=7.5 and ca. 1 Hz, 2H, 2-CH_2), 2.04–1.96 (m, 2H), 1.96–1.90 (m, 2H), 1.70–1.50 (m, 4H); δ_C (100.6 MHz, $CDCl_3$) 136.2 (s), 124.2 (d), 42.4 (t), 27.8 (t), 25.9 (t), 23.2 (t), 22.5 (t), 4.9 (t)][27] according to general procedure A to give an *imine*, which was immediately hydrolysed and tosylated to give the *sulfonamide* **15** (2.92 g, 40%) as an oil: δ_H (400 MHz, $CDCl_3$) 7.75 (d, *J*=8.1 Hz, 2H, 2×ArH), 7.22 (d, *J*=8.2 Hz, 2H, 2×ArH), 5.61 (s, 1H, NH), 5.28 (app. br s, 1H, =CH), 3.62 (s, 3H, OMe), 2.35 (s, 3H, ArMe), 1.98–1.44 (m, 12H), 1.42 (s, 3H, 2-Me); ν_{max} (film)/cm^{-1} 3240, 1730, 1460, 1380; HRMS: *m*/*z*: calcd for $C_{19}H_{28}NO_4S$: 366.1734; found: 366.1734 $[M+H]^+$.

*4.5.2. Methyl 1-aza-2-methyl-1-toluenesulfonyl-spiro-[4.5]decane-2-carboxylate (**16a**).* The foregoing sulfonamide **15** (182 mg, 0.50 mmol), derived from cyclohexenyl iodide **14**, was exposed to triflic acid

(34 mg, 0.22 mmol) in chloroform at 0 °C for 0.25 h according to general procedure B and gave the *spiro-pyrrolidine* **16a** (169 mg, 93%) as a pale yellow oil: δ_H (400 MHz, $CDCl_3$) 7.85 (d, J=8.3 Hz, 2H, 2×ArH), 7.23 (d, J=8.3 Hz, 2H, 2×ArH), 3.77 (s, 3H, OMe), 2.39 (s, 3H, ArMe), 2.27–1.03 (m, 14H), 1.77 (s, 3H, 2-Me); δ_C (100.6 MHz, $CDCl_3$) 175.8 (CO), 143.1 (s), 141.6 (s), 129.6 (2×d), 128.2 (2×d), 71.8 (s), 70.3 (s), 52.9 (OMe), 38.1 (t), 37.2 (t), 34.8 (t), 34.0 (t), 26.3 (q), 25.4 (t), 24.8 (t), 21.9 (q); ν_{max} (film)/cm^{-1} 1740, 1600, 1456, 1140; HRMS: m/z: calcd for $C_{19}H_{28}NO_4S$: 366.1734; found: 366.1739 $[M+H]^+$.

*4.5.3. Methyl 1-aza-1-toluenesulfonyl-spiro-[4.5]decane-2-carboxylate (**16b**).* Methyl 2-(*p*-toluenesulfonylamino)-4-cyclohexylidenebutanoate **18** was prepared using general procedure A from methyl 2-(benzylideneamino)-acetate **10a** and bromoethylidenecyclohexane **17**[28] on an 11 mmol scale. Subsequent exposure to triflic acid, in exactly the same manner and scale as in the foregoing reaction gave the *spiro-pyrrolidine* **16b** (165 mg, 94%) as a colourless solid, mp 121–124 °C; $C_{18}H_{25}NO_4S$: calcd C 62.8, H 6.9, N 3.9; found: C 62.7, H 7.0, N 4.1%; δ_H (400 MHz, $CDCl_3$) 7.76 (d, J=8.3 Hz, 2H, 2×ArH), 7.24 (d, J=8.3 Hz, 2H, 2×ArH), 4.38 (dd, J=8.6, 2.7 Hz, 1H, H2), 3.57 (s, 3H, OMe), 2.36 (s, 3H, ArMe), 2.43–1.14 (m, 14H); δ_C (100.6 MHz, $CDCl_3$) 173.5 (CO), 144.0 (s), 138.7 (s), 129.7 (2×d), 127.9 (2×d), 72.1 (5-C), 62.2 (2-CH), 52.6 (OMe), 38.4 (t), 35.0 (t), 34.8 (t), 28.3 (t), 25.5 (t), 25.4 (q), 25.0 (t), 21.9 (t); ν_{max} (KBr)/cm^{-1} 1749, 1588, 1458, 1376, 1140; m/z: [APCI] 352 (100%, $[M+H]^+$), 292 (49). HRMS: m/z: calcd for $C_{18}H_{26}NO_4S$: 352.1582; found: 352.1586 $[M+H]^+$.

4.6. Functionalised pyrrolidines

*4.6.1. 2,5-Dimethyl-2-(p-toluenesulfonylamino)hex-4-enal (**19**) and 2,5-dimethyl-2-(p-toluenesulfonylamino)hex-4-en-1-ol (**20**).* The sulfonamide **7b** (2.00 g, 7.19 mmol) was dissolved in dry ether (100 mL) and the resulting solution stirred and cooled to −78 °C. Diisobutylaluminium hydride (18.4 mL of a 1 M solution in hexanes, 18.4 mmol) was added dropwise and the resulting mixture stirred at the same temperature for 4.5 h, then allowed to warm to ambient temperature and quenched by the careful addition of saturated aqueous citric acid (100 mL). The resulting two layers were separated and the aqueous layer extracted with dichloromethane (2×50 mL). The combined organic solutions were dried, filtered and evaporated. Column chromatography (20% ethyl acetate/petrol) of the residue (1.8 g) gave:

(i) the *aldehyde* **19** (0.70 g, 39%) as a colourless solid, mp 83–86 °C; $C_{15}H_{21}NO_3S$: calcd C 61.0, H 7.2, N 4.7; found: C 61.2, H 7.0, N 4.7%; δ_H (400 MHz, $CDCl_3$) 9.32 (s, 1H, CHO), 7.68 (d, J=8.2 Hz, 2×ArH), 7.22 (d, J=8.2 Hz, 2×ArH), 5.15 (s, 1H, NH), 4.82 (t, J=7.5 Hz, 1H, H4), 2.34–2.31 (m, 5H, 3-CH_2, ArMe), 1.63 (s, 3H, Me), 1.56 (s, 3H, Me), 1.20 (s, 3H, 2-Me); δ_C (100.6 MHz, $CDCl_3$) 179.6 (CHO), 147.3 (s), 142.8 (s), 136.4 (5-C), 128.9 (2×d), 126.7 (2×d), 117.4 (4-CH), 66.4 (2-C), 36.8 (3-CH_2), 26.8 (q), 21.7 (q), 20.3 (q), 19.8 (q); ν_{max} (KBr)/cm^{-1} 2927, 1730, 1453, 1327; HRMS: m/z: calcd for $C_{15}H_{22}NO_3S$: 296.1320; found: 296.1322 $[M+H]^+$;

(ii) the *alcohol* **20** (0.90 g, 50%) as a colourless, crystalline solid, mp 91–93 °C; $C_{15}H_{23}NO_3S$: calcd C 60.6, H 7.7, N 4.8; found: C 60.6, H 7.6, N 4.9%; δ_H (400 MHz, $CDCl_3$) 7.80 (d, J=8.2 Hz, 2×ArH), 7.31 (d, J=8.2 Hz, 2×ArH), 5.07 (br t, J=ca. 7.6 Hz, 1H, H4), 4.75 (s, 1H, NH), 3.57 (dd, J=11.7, 6.2 Hz, 1H, $H1_a$), 3.50 (dd, J=11.7, 6.2 Hz, 1H, $H1_b$), 2.45 (s, 3H, ArMe), 2.30 (dd, J=14.3, 7.9 Hz, 1H, $H3_a$), 2.12 (dd, J=14.3, 7.4 Hz, 1H, $H3_b$), 1.73 (s, 3H, Me), 1.66 (br s, 1H, OH), 1.65 (s, 3H, Me), 1.13 (s, 3H, 2-Me); δ_C (100.6 MHz, $CDCl_3$) 143.7 (s), 140.1 (s), 137.2 (s, 5-C), 130.0 (2×d), 127.4 (2×d), 118.0 (d, 4-CH), 68.6 (t, 1-CH_2), 61.3 (s, 2-C), 37.1 (t, 3-CH_2), 26.5 (q), 21.9 (q), 21.5 (q), 18.4 (q); ν_{max} (KBr)/cm^{-1} 3277, 2926, 1598, 1483; m/z: [APCI] 298 (100%, $[M+H]^+$).

*4.6.2. 1-(p-Toluenesulfonyl)-2,5,5-trimethylpyrrolidine-2-carboxaldehyde (**21**).* The aldehyde **19** (0.324 g, 1.1 mol) was cyclised according to general procedure B using triflic acid (66 mg, 0.44 mmol) for 0.25 h at 0 °C, to give an oily solid. Crystallisation from ethyl acetate/hexanes gave the *pyrrolidine-2-carboxaldehyde* **21** (0.283 g, 87%) as a colourless, crystalline solid, mp 86–88 °C; $C_{15}H_{21}NO_3S$: calcd C 61.0, H 7.2, N 4.7; found: C 61.2, H 7.2, N 4.7%; δ_H (400 MHz, $CDCl_3$) 9.51 (s, 1H, CHO), 7.69 (d, J=8.2 Hz, 2H, 2×ArH), 7.18 (d, J=8.2 Hz, 2H, 2×ArH), 2.32 (s, 3H, ArMe), 2.00 (ddd, J=10.5, 6.8, 2.1 Hz, 1H, $H3_a$), 1.83 (ddd, J=10.5, 6.4, 2.3 Hz, 1H, $H3_b$), 1.68 (ddd, J=10.3, 6.8, 2.3 Hz, 1H, $H4_a$), 1.47 (ddd, J=10.3, 6.4, 2.1 Hz, 1H, $H4_b$), 1.45 (s, 3H), 1.36 (s, 3H), 1.28 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 179.6 (CHO), 142.8 (s), 140.6 (s), 129.4 (2×d), 128.6 (2×d), 70.2 (s), 66.9 (s), 40.3 (t), 39.4 (t), 28.7 (q), 24.2 (q), 23.6 (q), 21.8 (q); ν_{max} (KBr)/cm^{-1} 2972, 1731, 1600, 1454, 1322; HRMS: m/z: calcd for $C_{15}H_{22}NO_3S$: 296.1320; found: 296.1318 $[M+H]^+$.

*4.6.3. 1-(p-Toluenesulfonyl)-2,5,5-trimethylpyrrolidine-2-methanol (**22**) and 5-(p-toluenesulfonylamino)-2,2,5-trimethyltetrahydropyran (**23**).* The sulfonamide alcohol **20** (0.276 g, 0.93 mmol) when treated with triflic acid (56 mg, 0.37 mmol) for 0.25 h at 0 °C as described in general procedure B, followed by column chromatography (20% ethyl acetate/petrol) gave:

(i) the *pyrrolidine-2-methanol* **22** (0.121 g, 45%) as a colourless, crystalline solid, mp 92–95 °C; $C_{15}H_{23}NO_3S$: calcd C 60.6, H 7.8, N 4.7; found: C 60.9, H 8.0, N 4.9%; δ_H (400 MHz, $CDCl_3$) 7.72 (d, J=8.2 Hz, 2H, 2×ArH), 7.25 (d, J=8.2 Hz, 2H, 2×ArH), 3.26 (s, 2H, CH_2OH), 2.42 (s, 1H, OH), 2.34 (s, 3H, ArMe), 1.61–1.33 (m, 4H), 1.17 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 142.9 (s), 140.6 (s), 129.5 (2×d), 126.8 (2×d), 71.6 (s), 70.3 (CH_2OH), 67.8 (s), 31.8 (t), 31.4 (t), 28.6 (q), 23.3 (q), 22.5 (q), 22.2 (q); ν_{max} (KBr)/cm^{-1} 3527, 2972, 1496, 1368; HRMS: m/z: calcd for $C_{15}H_{24}NO_3S$: 298.1477; found: 298.1476 $[M+H]^+$;

(ii) the *tetrahydropyran* **23** (0.123 g, 45%) as a colourless, crystalline solid, mp 89–94 °C; δ_H (400 MHz, $CDCl_3$) 7.72 (d, J=8.2 Hz, 2H, 2×ArH), 7.26 (d, J=8.2 Hz, 2H, 2×ArH), 5.17 (s, 1H, NH), 3.80 (d, J=12.2 Hz, 1H, $H6_a$), 3.32 (d, J=12.2 Hz, 1H, $H6_b$), 2.34 (s, 3H, ArMe), 1.80–1.34 (m, 4H), 1.49 (s, 3H), 1.42 (s, 3H), 0.87 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 143.0 (s), 140.6 (s), 129.5 (2×d), 127.6 (2×d), 70.6 (s), 68.6 (t), 54.0 (s), 39.2 (t), 34.4 (t), 29.5 (q), 28.9 (q), 22.2 (q), 21.5 (q); ν_{max} (KBr)/cm^{-1} 3279, 2970, 1598, 1457; HRMS: m/z: calcd for $C_{15}H_{24}NO_3S$: 298.1477; found: 298.1473 $[M+H]^+$.

*4.6.4. 2-(2-Benzenesulfonylethyl)cyclohexanone (**24a**)*[29]. Toluene (20 mL), cyclohexanone (10.3 mL, 100 mmol), morpholine (11.5 mL, 130 mmol) and *p*-toluenesulfonic acid (0.10 g) were refluxed together under a Dean and Stark water separator for 1 h then cooled to ambient temperature. Phenyl vinyl sulfone (16.8 g, 100 mmol) was then added and the resulting mixture refluxed for a further 4 h after which the toluene was evaporated to leave a crude enamine as a brown oil.

This was added to a stirred mixture of glacial acetic acid (48 mL), sodium acetate (16 g) and water (48 mL), which was then refluxed for 2 h. The cooled mixture was then neutralised using aqueous ammonia and filtered through Celite. The brown filtrate was extracted with dichloromethane (3×100 mL) and the combined organic extracts dried, filtered and evaporated. The residue was separated by column chromatography (25% EtOAc/petrol) to give the *keto-sulfone* **24a** (12.2 g, 46%) as an off-white solid, mp 87–90 °C [lit.[29] mp 71–71 °C]; δ_H (400 MHz, $CDCl_3$) 7.88–7.80 (m, 2H), 7.64–7.50 (m, 3H), 3.46 (t, J=7.0 Hz, 2H, 2′-CH_2), 3.10–3.00 (m, 1H, H2), 2.45–1.20 (m, 10H); δ_C (100.6 MHz, $CDCl_3$) 193.2 (CO), 140.5 (s), 134.1 (d), 129.6 (d), 128.4 (d), 52.1 (d), 49.3 (t), 42.6 (t), 34.8 (t), 28.3

(t), 25.5 (t), 23.5 (t); ν_{max} (KBr)/cm^{-1} 1700, 1350, 1310; *m*/*z*: [APCI] 267 (100%; M+H)$^+$.

*4.6.5. (E)-1-(2-Benzenesulfonylethyl)-2-(2-bromoethylidene)cyclohexane (**26a**).* The foregoing sulfone **24a** (2.60 g, 10 mmol) was dissolved in dry tetrahydrofuran (50 mL) and the solution cooled to −78 °C. Vinylmagnesium bromide (20 mL of a 1 M solution in tetrahydrofuran, 20 mmol) was added dropwise and the solution allowed to warm slowly to ambient temperature then stirred overnight. Saturated aqueous ammonium chloride (50 mL) and ether (50 mL) were then carefully added, the two layers separated and the aqueous layer extracted with ether (50 mL). The combined ether extracts were dried, filtered and evaporated to leave *2-(2-benzenesulfonylethyl)-1-ethenylcyclohexanol* **25a** (2.5 g, 87%) as a pale yellow oil: δ_H (400 MHz, $CDCl_3$) 7.89–7.80 (m, 3H), 7.50–7.40 (m, 2H), 5.68 (dd, *J*=17.2, 10.7 Hz, 1H, =CH), 5.09 (app. d, *J*=17.2 Hz, 1H, =CH), 4.99 (app. d, *J*=10.7 Hz, 1H, =CH), 3.08–2.89 (m, 2H), 1.80–1.15 (m, 11H); ν_{max} (film)/cm^{-1} 3400, 2936, 1447, 1304; *m*/*z*: [APCI] 295 (100%; M+H)$^+$, 278 (54; M$^+$−OH).

The alcohol **25a** (2.5 g, 8.5 mmol) was dissolved in pyridine (1 mL) and the resulting solution added dropwise to phosphorus tribromide (0.32 mL, 3.4 mmol), protected from light. After stirring for 5 min, excess reagents were removed under reduced pressure to leave the crude *bromide* **26a** (2.5 g, 82%) as a pale yellow oil, which was separated from solid products using a pipette and used immediately in the next step: δ_H (400 MHz, $CDCl_3$) 7.70–7.60 (m, 2H), 7.55–7.48 (m, 3H), 5.31 (t, *J*=7.2 Hz, 1H, =CH), 4.12 (d, *J*=7.2 Hz, 2H, CH_2Br), 3.00–2.95 (m, 2H), 2.10–1.22 (m, 11H).

*4.6.6. Methyl (E)-4-[2-(2-benzenesulfonylethyl)cyclohexylidene]-2-(p-toluenesulfonylamino)butanoate (**27a**).* Methyl 2-(benzylideneamino)acetate **10a** (2.00 g, 11.3 mmol) was alkylated using the foregoing bromide **26a** according to general procedure A to give an *imine*: δ_H (400 MHz, $CDCl_3$) 8.17 (s, 1H, N=CH), 7.75–7.60 (m, 4H), 7.55–7.50 (m, 3H), 7.40–7.33 (m, 3H), 4.43 (dd, *J*=7.2, 6.8 Hz, 1H, H4), 3.72 (dd, *J*=7.3, 6.9 Hz, 1H, H2), 3.58 (s, 3H, OMe), 3.02–2.97 (m, 2H), 2.45–2.40 (m, 2H), 2.10–1.25 (m, 11H). This imine was hydrolysed and tosylated and the crude product purified by column chromatography (20% EtOAc/petrol) to give the *sulfonamide* **27a** (1.41 g, 24%) as a colourless solid, mp 67–69 °C; $C_{26}H_{33}NO_6S_2$: calcd C 60.1, H 6.4, N 2.7; found: C 60.1, H 6.4, N 2.6%; δ_H (400 MHz, $CDCl_3$) 7.86 (d, *J*=8.2 Hz, 2H), 7.65–7.61 (m, 3H), 7.52–7.48 (m, 2H), 7.23 (d, *J*=8.2 Hz, 2H), 5.17 (t, *J*=9.4 Hz, 1H, H4), 4.82 (br res., 1H, NH), 3.86 (ddd, *J*=9.4, 7.4, 6.8 Hz, 1H, H2), 3.42 (s, 3H, OMe), 2.81–2.95 (m, 2H, CH_2SO_2), 2.37–2.32 (m, 5H, including 2.33, s, Me), 1.98–1.20 (m, 10H); δ_C (100.6 MHz, $CDCl_3$) 171.6 (CO), 144.8 (s), 143.7 (s), 139.2 (s), 136.7 (s), 133.7 (d), 129.7 (2×d), 129.3 (2×d), 128.1 (2×d), 127.2 (2×d), 114.9 (d), 55.6 (d), 54.5 (t), 52.6 (OMe), 43.5 (d), 33.6 (t), 31.1 (t), 27.8 (t), 25.9 (t), 24.3 (t), 22.8 (t) 21.6 (q); ν_{max} (KBr)/cm^{-1} 2928, 1743, 1598, 1447; *m*/*z*: [APCI] 519 (25%; M+H)$^+$, 256 (100); HRMS: *m*/*z*: calcd for $C_{26}H_{37}N_2O_6S_2$: 537.2088; found: 537.2092 [M+NH$_4$]$^+$.

*4.6.7. Methyl 6-(2-benzenesulfonylethyl)-1-(p-toluenesulfonyl)-1-azaspiro[4.5]decane-2-carboxylate (**28a**).* Sulfonamide **27a** (0.40 g, 0.80 mmol) was cyclised for 0.25 h at 0 °C using triflic acid (46 mg, 0.30 mmol) according to general procedure B to give the *spiro-pyrrolidine* **28a** (0.34 g, 84%) as a colourless, crystalline solid as a 3:1 ratio of diastereoisomers, mp 127–129 °C (EtOAc/hexane); $C_{26}H_{33}NO_6S_2$: calcd C 60.1, H 6.4, N 2.7; found: C 60.0, H 6.3, N 2.9%; δ_H (400 MHz, $CDCl_3$) (major isomer) 7.70–7.62 (m, 4H), 7.48–7.42 (m, 3H), 7.22 (d, *J*=8.2 Hz, 2H), 4.12–4.08 (m, 1H, H2), 3.82–3.76 (m, 2H), 3.68 (s, 3H, OMe), 2.33 (s, 3H, ArMe), 2.05–2.00 (m, 2H), 1.95–1.88 (m, 4H), 1.74–1.05 (m, 9H); δ_C (100.6 MHz, $CDCl_3$) 172.0 (CO), 140.9 (s), 138.5 (s), 136.3 (s), 133.5 (d), 129.5 (d), 128.7 (d), 126.6 (d), 125.4 (d), 68.1 (s), 62.4 (d), 53.8 (OMe), 52.7 (t), 36.7 (d), 31.0 (t), 27.2 (t), 25.2 (t), 24.5 (t), 20.9 (q), 20.4 (t), 18.9 (t), 17.8 (t); δ_H (400 MHz, $CDCl_3$) (minor isomer) 7.70–7.62 (m, 4H), 7.54–7.50 (m, 3H), 7.25 (d, *J*=8.2 Hz, 2H), 4.15–4.11 (m, 1H, H2), 3.82–3.76 (m, 2H), 3.61 (s, 3H, OMe), 2.34 (s, 3H, ArMe), 2.08–2.03 (m, 2H), 1.95–1.88 (m, 4H), 1.74–1.00 (m, 9H); δ_C (100.6 MHz, $CDCl_3$) 174.1 (CO), 141.1 (s), 138.8 (s), 136.2 (s), 133.5 (d), 130.1 (d), 129.6 (d), 126.3 (d), 124.2 (d), 66.5 (s), 63.2 (d), 53.7 (OMe), 52.9 (t), 35.8 (d), 31.0 (t), 26.8 (t), 25.5 (t), 24.7 (t), 21.1 (q), 20.4 (t), 18.3 (t), 17.6 (t); ν_{max} (KBr)/cm^{-1} 1740; *m*/*z*: [APCI] 520 (100%; M+H)$^+$; HRMS: *m*/*z*: calcd for $C_{26}H_{34}NO_6S_2$: 520.1822; found: 520.1822 [M+H]$^+$.

*4.6.8. 2-Allyl-1-ethenylcyclohexanol (**25b**).* Vinylmagnesium bromide (40 mL of a 1 M solution in tetrahydrofuran, 40 mmol) was added dropwise to a solution of 2-allylcyclohexanone **24b** (3.0 g, 22 mmol) in dry tetrahydrofuran (100 mL), stirred and cooled in an ice-water bath. The resulting mixture was stirred overnight without further cooling then carefully diluted with saturated aqueous ammonium chloride (100 mL) and ether (50 mL). The separated aqueous layer was extracted with ether (100 mL) and the combined organic solutions dried, filtered and evaporated to leave the *alcohol* **25b** (2.6 g, 72%) as a pale yellow oil: δ_H (400 MHz, $CDCl_3$) 5.68–5.63 (m, 2H), 5.05–4.95 (m, 4H), 2.33–2.28 (m, 2H), 1.90–1.84 (m, 3H), 1.80–1.10 (m, 6H); δ_C (100.6 MHz, $CDCl_3$) 140.0 (d), 138.3 (d), 115.5 (t), 113.5 (t), 74.9 (s), 46.8 (d), 40.4 (t), 34.7 (t), 28.4 (t), 25.2 (t), 23.3 (t); ν_{max} (film)/cm^{-1} 3364, 2923, 1346; *m*/*z*: [APCI] 167 (53%; M+H)$^+$, 149 [100; M−OH]$^+$.

*4.6.9. Methyl (E)-4-(2-allylcyclohexylidene)-2-(p-toluenesulfonylamino)butanoate (**27b**).* A solution of the foregoing alcohol **25b** (1.0 g, 6.1 mmol) and pyridine (0.07 mL) in tetrahydrofuran was added dropwise to a stirred mixture of phosphorus tribromide (0.23 mL) containing pyridine (one drop) and protected from light. After 5 min, the solvent was evaporated to leave the crude *bromide* **26b** (0.98 g, 71%), after separation from solid products by removal by pipette: δ_H (400 MHz, $CDCl_3$) 5.64–5.61 (m, 1H), 5.41 (t, *J*=8.5 Hz, 1H), 5.01 (d, *J*=17.6 Hz, 1H), 4.98 (d, *J*=10.6 Hz, 1H), 3.98 (d, *J*=8.5 Hz, 2H), 2.30–1.25 (m, 11H).

Methyl 2-(benzylideneamino)acetate **10a** (0.6 g, 3.5 mmol) was alkylated using the foregoing bromide **26b** according to general procedure A to give an *imine*, which was hydrolysed and tosylated and the crude product purified by column chromatography (20% EtOAc/petrol) to give the *sulfonamide* **27b** (0.36 g, 27%) as a colourless solid in a 1.2:1 ratio of diastereoisomers, mp 91–94 °C; $C_{21}H_{29}NO_4S$: calcd C 64.5, H 7.4, N 3.6; found: C 64.3, H 7.6, N 3.7%; δ_H (400 MHz, $CDCl_3$) (major isomer) 7.62 (d, *J*=8.2 Hz, 2H), 7.22 (d, *J*=8.2 Hz, 2H), 5.67–5.58 (m, 1H), 5.10–4.75 (m, 4H), 3.95–3.88 (m, 1H), 3.45 (s, 3H, OMe), 2.45–2.35 (m, 5H), 2.25–2.20 (m, 2H), 2.00–1.30 (m, 9H); δ_C (100.6 MHz, $CDCl_3$) 171.2 (CO), 147.3 (s), 143.6 (s), 138.0 (d), 137.7 (d), 136.3 (s), 129.6 (2×d), 127.2 (2×d), 115.5 (t), 112.8 (d), 112.6 (d), 55.6 (d), 52.4 (OMe), 44.4 (d), 36.6 (t), 33.1 (t), 30.9 (t), 28.0 (t), 27.3 (t), 23.5 (t), 21.6 (q); δ_H (400 MHz, $CDCl_3$) (minor isomer) 7.63 (d, *J*=8.2 Hz, 2H), 7.21 (d, *J*=8.2 Hz, 2H), 5.67–5.58 (m, 1H), 5.10–4.75 (m, 4H), 3.95–3.88 (m, 1H), 3.44 (s, 3H, OMe), 2.45–2.35 (m, 5H), 2.25–2.20 (m, 2H), 2.00–1.30 (m, 9H); ν_{max} (KBr)/cm^{-1} 2928, 1744, 1446, 1162; *m*/*z*: [APCI] 392 (100%; M+H)$^+$; HRMS: *m*/*z*: calcd for $C_{21}H_{30}NO_4S$: 392.1895; found: 392.1898 [M+H]$^+$.

*4.6.10. Methyl 6-allyl-1-(p-toluenesulfonyl)-1-azaspiro[4.5]decane-2-carboxylate (**28b**).* Sulfonamide **27b** (0.27 g, 0.69 mmol) was cyclised for 0.25 h at 0 °C using triflic acid (24 μL, 0.28 mmol) according to general procedure B to give the *spiro-pyrrolidine* **28b** (0.34 g, 84%) as a colourless, crystalline solid in a 3:1 ratio of diastereoisomers, mp 81–84 °C (EtOAc/hexane); $C_{21}H_{29}NO_4S$: calcd C 64.5, H 7.4, N 3.6; found: C 64.4, H 7.6, N 3.7%; δ_H (400 MHz, $CDCl_3$) (major isomer) 7.67 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* 8.2 Hz, 2H), 5.70−5.66 (m, 1H), 5.06 (app. d, *J* 17.3 Hz, 1H; H3$_c$), 4.98 (app. d, *J* 10.2 Hz, 1H; H3$_t$), 3.74–3.71 (m, 1H; H2), 3.65 (s, 3H; OMe), 2.34 (s, 3H; ArMe), 2.00–1.97 (m, 2H), 1.95–1.91 (m, 2H), 1.85–1.00 ppm (m, 11H);

d_C (100 MHz, $CDCl_3$) 173.3 (CO), 143.1 (s), 138.4 (s), 137.2 (d), 129.3 (2 × d), 128.2 (2 × d), 127.0 (d), 116.2 (t), 76.1 (s), 62.1 (d), 52.1 (OMe), 43.0 (d), 40.4 (t), 35.8 (t), 32.4 (t), 30.1 (t), 28.8 (t), 25.5 (t), 21.5 ppm (q); d_H (400 MHz, $CDCl_3$) (minor isomer) 7.64 (d, J = 8.2 Hz, 2H), 7.21 (d, J 8.2 Hz, 2H), 5.66–5.62 (m, 1H; 2'-:CH), 5.02 (app. d, J 17.3 Hz, 1H; $H3_c$), 4.91 (app. d, J 10.2 Hz, 1H; $3H_t$), 3.69-3.66 (m, 1H; H2), 3.57 (s, 3H; OMe), 2.34 (s, 3H; ArMe), 2.00–1.97 (m, 2H), 1.95–1.91 (m, 2H), 1.85–1.00 ppm (m, 11H); δ_C (100.6 MHz, $CDCl_3$) 172.8 (CO), 143.2 (s), 138.4 (s), 137.2 (d), 129.6 (2×d), 127.9 (2×d), 127.6 (d), 116.2 (t), 76.1 (s), 61.4 (d), 52.0 (OMe), 45.7 (d), 42.0 (t), 35.1 (t), 29.9 (t), 28.3 (t), 27.6 (t), 25.2 (t), 21.5 (q); ν_{max} (KBr)/cm^{-1} 1742; m/z: [APCI] 392 (100%; M+H)$^+$; HRMS: m/z: calcd for $C_{21}H_{30}NO_4S$: 392.1895; found: 392.1898 $[M+H]^+$.

4.7. Nitrophenylsulfonyl (nosyl) derivatives

*4.7.1. General procedure C: synthesis of nitrosulfonamides (nosyl derivatives) (**29** and **31**)*[16]. Crude amines were prepared as described in general procedure A. The crude amine was weighed and immediately dissolved in dry, ethanol-free chloroform (4 mL mmol^{-1}) at ambient temperature and treated with nitrobenzenesulfonyl chloride (1.2 equiv), dry pyridine (1.2 equiv) and a few crystals of 4-(dimethylamino)pyridine. The resulting solution was stirred at ambient temperature overnight then quenched by the addition of 2 M aqueous hydrochloric acid (4 mL mmol^{-1}). The resulting two layers were separated and the aqueous layer extracted with dichloromethane (2×2 mL mmol^{-1}). The combined organic solution was washed with brine, then dried, filtered and evaporated. The residue was purified by column chromatography (EtOAc/petrol) or crystallisation (EtOAc/hexanes).

All of the following preparations of nosyl derivatives were carried out on 2.0–3.5 mmol scales.

*4.7.2. Methyl 2,5-dimethyl-2-(2-nitrobenzenesulfonylamino)hex-4-enoate (**29a**).* Colourless solid (0.521 g, 61%), mp 88–90 °C; $C_{15}H_{20}N_2O_6S$: calcd C 50.6, H 5.7, N 7.9; found: C 50.4, H 5.7, N 7.7%; δ_H (400 MHz, $CDCl_3$) 8.03 (dd, J=6.5, 1.8 Hz, 1H), 7.82 (dd, J=6.5, 2.1 Hz, 1H), 7.70–7.60 (m, 2H), 6.06 (s, 1H, NH), 4.93 (t, J=7.6 Hz, 1H, H4), 3.75 (s, 3H, OMe), 2.61–2.47 (m, 3-CH_2), 1.79 (s, 3H), 1.74 (s, 3H), 1.71 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 174.2 (CO), 148.8 (s), 138.1 (5-C), 136.6 (s), 133.7 (d), 130.6 (d), 129.4 (d), 123.6 (d), 118.1 (4-CH), 60.8 (2-C), 52.8 (OMe), 40.4 (3-CH_2), 25.7 (q), 21.6 (q), 18.9 (q); ν_{max} (KBr)/cm^{-1} 3334, 2951, 1738, 1539, 1441, 1344; m/z [APCI] 357 (80%), 155 (100); HRMS: m/z: calcd for $C_{15}H_{21}N_2O_6S$: 357.1114; found: 357.1117 $[M+H]^+$.

*4.7.3. Methyl 2,5-dimethyl-2-(4-nitrobenzenesulfonylamino)hex-4-enoate (**29b**).* Colourless solid (0.750 g, 63%), mp 97–100 °C; δ_H (400 MHz, $CDCl_3$) 8.45 (d, J=8.2 Hz, 2H, 2×ArH), 8.17 (d, J=8.2 Hz, 2H, 2×ArH), 5.60 (s, 1H, NH), 5.01 (dd, J=7.6, 7.2 Hz, 1H, H4), 3.81 (s, 3H, OMe), 2.68 (dd, J=14.5, 7.6 Hz, 1H, $H3_a$), 2.55 (dd, J=14.5, 7.2 Hz, 1H, $H3_b$), 1.78 (s, 3H), 1.70 (s, 3H), 1.54 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 173.2 (CO), 149.5 (s), 149.1 (s), 137.6 (5-C), 129.1 (d), 123.6 (d), 117.4 (4-CH), 61.9 (2-C), 52.7 (OMe), 38.9 (3-CH_2), 26.2 (q), 20.8 (q), 18.5 (q); ν_{max} (KBr)/cm^{-1} 3288, 2954, 1738, 1607, 1537, 1435; m/z [APCI] 357 (85%), 297 (100); HRMS: m/z: calcd for $C_{15}H_{21}N_2O_6S$: 357.1114; found: 357.1115 $[M+H]^+$.

*4.7.4. Methyl 2,5-dimethyl-2-(2,4-dinitrobenzenesulfonylamino)hex-4-enoate (**29c**).* Colourless solid (0.598 g, 52%), mp 75–78 °C; $C_{15}H_{19}N_3O_8S$: calcd C 44.9, H 4.8, N 10.5; found: C 44.5, H 4.7, N 11.0%; δ_H (400 MHz, $CDCl_3$) 8.65 (s, 1H, ArH), 8.48 (d, J=8.6 Hz, 1H, ArH), 8.26 (d, J=8.6 Hz, 1H, ArH), 6.10 (s, 1H, NH), 4.85 (app. t, J=ca. 7.3 Hz, 1H, H4), 3.61 (s, 3H, OMe), 2.18 (dd, J=7.3, 6.7 Hz, 1H, $H3_a$), 2.07 (dd, J=7.3, 6.7 Hz, 1H, $H3_b$), 1.59 (s, 3H), 1.55 (s, 3H), 1.50 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 172.5 (CO), 149.4 (s), 146.5 (s), 140.0 (s), 138.5 (5-C), 132.2 (d), 132.0 (d), 127.2 (d), 119.3 (4-CH), 60.4 (2-C), 52.7 (OMe), 39.6 (3-CH_2), 25.6 (q), 21.1 (q), 18.0 (q); ν_{max} (KBr)/cm^{-1} 3371, 3106, 1738, 1595, 1442, 1348; m/z [APCI] 402 (100%, $[M+H]^+$).

*4.7.5. Methyl (E)-2-(2-nitrobenzenesulfonylamino)hex-4-enoate (**31a**).* Colourless solid (0.37 g, 56%), mp 83–85 °C; $C_{13}H_{16}N_2O_6S$: calcd C 47.6, H 4.9, N 8.5; found: C 47.4, H 4.9, N 8.3%; δ_H (400 MHz, $CDCl_3$) 7.97–7.96 (m, 1H), 7.83–7.82 (m, 1H), 7.66–7.65 (m, 2H), 5.95 (d, J=8.7 Hz, 1H, NH), 5.46 (dt, J=15.2, 7.5 Hz, 1H, H4), 5.15 (dq, J=15.2, 6.5 Hz, 1H, H5), 4.17 (dt, J=8.7, 7.5 Hz, 1H, H2), 3.43 (s, 3H, OMe), 2.40 (t, J=7.5 Hz, 2H, 3-CH_2), 1.53 (d, J=6.5 Hz, 3H, 5-Me); δ_C (100.6 MHz, $CDCl_3$) 172.5 (CO), 147.9 (s), 135.2 (s), 133.7 (d), 133.5 (d), 131.6 (d), 131.3 (d), 130.9 (d), 124.1 (d), 62.8 (2-CH), 52.6 (OMe), 32.0 (3-CH_2), 21.0 (5-Me); ν_{max} (KBr)/cm^{-1} 3291, 2955, 1737, 1586, 1437; m/z [APCI] 327 (100%), 269 (52); HRMS: m/z: calcd for $C_{13}H_{17}N_2O_6S$: 329.0799; found: 329.0802 $[M+H]^+$.

*4.7.6. Methyl (E)-2-(4-nitrobenzenesulfonylamino)hex-4-enoate (**31b**).* Colourless solid (0.583 g, 61%), mp 81–85 °C; δ_H (400 MHz, $CDCl_3$) 8.28 (d, J=8.0 Hz, 2H, 2×ArH), 8.04 (d, J=8.0 Hz, 2H, 2×ArH), 5.45 (dq, J=15.0, 6.6 Hz, 1H, H5), 5.36 (d, J=8.4 Hz, 1H, NH), 5.11 (dt, J=15.0, 6.5 Hz, 1H, H4), 4.02–4.00 (m, 1H, H2), 3.51 (s, 3H, OMe), 2.37 (t, J=6.5 Hz, 2H, 3-CH_2), 1.55 (d, J=6.6 Hz, 3H, 5-Me); δ_C (100.6 MHz, $CDCl_3$) 172.8 (CO), 150.3 (s), 146.7 (s), 129.2 (d), 128.9 (2×d), 124.9 (d), 124.4 (2×d), 62.2 (2-CH), 58.3 (OMe), 32.4 (3-CH_2), 21.9 (q); ν_{max} (KBr)/cm^{-1} 3274, 2957, 1736, 1538, 1442; m/z [APCI] 329 (56%, M+H$^+$), 269 (100); HRMS: m/z: calcd for $C_{13}H_{20}N_3O_6S$: 346.1067; found: 346.1065 $[M+NH_4]^+$.

*4.7.7. Methyl (E)-2-(2,4-dinitrobenzenesulfonylamino)hex-4-enoate (**31c**).* Colourless solid (0.612 g, 47%), mp 78–79 °C; δ_H (400 MHz, $CDCl_3$) 8.65 (d, J=2.0 Hz, 1H), 8.44 (dd, J=8.6, 2.0 Hz, 1H), 7.87 (d, J=8.6 Hz, 1H), 6.03 (br d, J=7.8 Hz, 1H, NH), 5.56–5.54 (m, 1H, H4), 5.15–5.12 (m, 1H, H5), 4.23–4.21 (m, 1H, H2), 3.49 (s, 3H, OMe), 2.49–2.47 (m, 2H, 3-CH_2), 1.34 (d, J=7.2 Hz, 3H, 5-Me); δ_C (100.6 MHz, $CDCl_3$) 171.1 (CO), 149.6 (s), 147.7 (s), 140.1 (s), 132.2 (d), 132.0 (d), 127.1 (d), 122.9 (d), 121.0 (d), 56.4 (2-CH), 52.7 (OMe), 35.9 (3-CH_2), 18.0 (q); ν_{max} (KBr)/cm^{-1} 3112, 2928, 1743, 1606, 1539, 1429, 1350; m/z [APCI] 374 (83%, M+H$^+$), 314 (100); HRMS: m/z: calcd for $C_{13}H_{16}N_3O_8S$: 374.0658; found: 374.0654 $[M+H]^+$.

*4.7.8. Methyl 1-(2-nitrobenzenesulfonyl)-2,5,5-trimethylpyrrolidine-2-carboxylate (**30a**).* The sulfonamide **29a** (67 mg, 0.19 mmol) was cyclised at 0 °C for 0.25 h using triflic acid (14 mg, 0.10 mmol) according to general procedure B to yield the *pyrrolidine* **30a** (58 mg, 87%) as a colourless, crystalline solid, mp 123–126 °C; $C_{15}H_{20}N_2O_6S$: calcd C 50.6, H 5.6, N 7.9; found: C 50.4, H 5.7, N 7.6%; δ_H (400 MHz, $CDCl_3$) 8.00–7.99 (m, 1H), 7.55–7.54 (m, 2H), 7.43–7.42 (m, 1H), 3.68 (s, 3H, OMe), 2.28–2.26 (m, 1H, $H3_a$), 1.87–1.85 (m, 3H, $H3_b$ and 4-CH_2), 1.71 (s, 3H), 1.40 (s, 3H), 1.17 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 174.5 (CO), 148.9 (s), 136.2 (s), 133.1 (d), 130.9 (d), 129.6 (d), 123.9 (d), 71.2 (2(5)-C), 68.1 (5(2)-C), 40.4 (3(4)-CH_2), 36.9 (4(3)-CH_2), 27.8 (q), 27.3 (q), 25.8 (q); ν_{max} (KBr)/cm^{-1} 1742, 1554, 1441, 1346; HRMS: m/z: [APCI] 357 (M+H$^+$).

*4.7.9. Methyl 1-(4-nitrobenzenesulfonyl)-2,5,5-trimethylpyrrolidine-2-carboxylate (**30b**).* The sulfonamide **29b** (60 mg, 0.17 mmol) was cyclised at 0 °C for 0.25 h using triflic acid (13 mg, 0.09 mmol) according to general procedure B to yield the *pyrrolidine* **30b** (53 mg, 89%) as a colourless, crystalline solid, mp 126–128 °C; $C_{15}H_{20}N_2O_6S$: calcd C 50.6, H 5.6, N 7.9; found: C 50.8, H 5.8, N 7.5%; δ_H (400 MHz, $CDCl_3$) 8.24 (d, J=8.0 Hz, 2×ArH), 8.07 (d, J=8.0 Hz, 2×ArH), 3.69 (s, 3H, OMe), 2.22 (ddd, J=10.8, 7.2, 4.4 Hz, 1H, $H3_a$), 1.83–1.80 (m, 3H, $H3_b$ and 4-CH_2), 1.69 (s, 3H), 1.66 (s, 3H), 1.22 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 174.1 (CO), 143.5 (s), 139.9 (s), 130.0 (2×d), 127.4 (2×d), 62.6 (s), 60.4 (s), 53.0 (OMe), 39.1 (3(4)-CH_2), 32.3 (4(3)-CH_2), 26.4 (q), 22.3 (q), 21.9 (q); ν_{max} (KBr)/

cm^{-1} 1739, 1529, 1348, 1143; *m/z* [APCI] 357 (100%, $M+H^+$), 297 (42); HRMS: *m/z*: calcd for $C_{15}H_{21}N_2O_6S$ 357.1120; found: 357.1115 $[M+H]^+$.

*4.7.10. Methyl 1-(2,4-dinitrobenzenesulfonyl)-2,5,5-trimethylpyrrolidine-2-carboxylate (**30c**).* The sulfonamide **29c** (88 mg, 0.22 mmol) was cyclised at 0 °C for 0.25 h using triflic acid (20 mg, 0.13 mmol) according to general procedure B to yield the *pyrrolidine* **30c** (77 mg, 87%) as a colourless, crystalline solid, mp 118–120 °C; δ_H (400 MHz, $CDCl_3$) 8.63 (s, 1H), 8.46 (d, *J*=8.4 Hz, 1H), 7.88 (d, *J*=8.4 Hz, 1H), 3.68 (s, 3H, OMe), 2.29–2.26 (m, 2H), 2.14–2.11 (m, 2H), 1.51 (s, 3H), 1.48 (s, 3H), 1.46 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 175.2 (CO), 149.2 (s), 146.5 (s), 139.8 (s), 132.4 (d), 132.1 (d), 127.4 (d), 63.0 (s), 60.9 (s), 52.8 (OMe), 39.6 (t), 32.1 (t), 26.6 (q), 22.8 (q), 18.9 (q); ν_{max} (KBr)/cm^{-1} 2956, 1738, 1606, 1538, 1462, 1350; *m/z* [APCI] 402 (100%, $M+H^+$); HRMS: *m/z*: calcd for $C_{15}H_{23}N_4O_8S$ 419.1237; found: 419.1236 $[M+NH_4]^+$.

*4.7.11. Methyl (2RS,5RS)- and (2SR,5RS)-5-methyl-1-(2-nitrobenzenesulfonyl)pyrrolidine-2-carboxylate (**32a**).* The sulfonamide **31a** (86 mg, 0.25 mmol), derived from crotyl chloride, was cyclised for 4 h in gently refluxing chloroform using triflic acid (22 mg, 0.15 mmol) according to general procedure B to give the *pyrrolidine* **32a** (74 mg, 86%) as a colourless, crystalline solid, in a 3:1 ratio of (2*SR*,5*RS*) and (2*RS*,5*RS*) diastereoisomers, as an inseparable mixture, mp 99–104 °C; δ_H (400 MHz, $CDCl_3$) (major isomer) 8.06–8.05 (m, 1H), 7.63–7.61 (m, 2H), 7.55–7.54 (m, 1H), 4.52 (app. d, *J*=9.2 Hz, 1H, H2), 4.31–4.28 (m, 1H, H5), 3.58 (s, 3H, OMe), 2.40–1.63 (m, 4H, 2×CH_2), 1.02 (d, *J*=6.4 Hz, 3H, 5-Me); δ_C (100.6 MHz, $CDCl_3$) 175.6 (CO), 148.6 (s), 135.9 (s), 132.8 (d), 131.0 (d), 129.5 (d), 123.7 (d), 66.5 (d), 57.8 (d), 52.8 (OMe), 38.1 (t), 30.8 (t), 20.3 (q); δ_H (400 MHz, $CDCl_3$) (minor isomer) 8.07–8.06 (m, 1H), 7.64–7.62 (m, 2H), 7.55–7.53 (m, 1H), 4.51–4.47 (m, 1H, H2), 4.01 (dq, *J*=8.9, 6.4 Hz, 1H, H5), 3.68 (s, 3H, OMe), 2.40–1.63 (m, 4H, 2×CH_2), 1.32 (d, *J*=6.4 Hz, 3H, 5-Me); δ_C (100.6 MHz, $CDCl_3$) 174.8 (CO), 148.9 (s), 136.1 (s), 133.0 (d), 130.9 (d), 129.6 (d), 123.8 (d), 67.7 (d), 56.6 (d), 52.9 (OMe), 38.8 (t), 30.2 (t), 20.7 (q); ν_{max} (KBr)/cm^{-1} 1740, 1552, 1444, 1359, 1148; *m/z* [APCI] 329 (100%, $M+H^+$), 269 (84); HRMS: *m/z*: calcd for $C_{13}H_{17}N_2O_6S$ 329.0807; found: 329.0806 $[M+H]^+$.

*4.7.12. Methyl (2RS,5RS)- and (2SR,5RS)-5-methyl-1-(4-nitrobenzenesulfonyl)pyrrolidine-2-carboxylate (**32b**).* The sulfonamide **31b** (44 mg, 0.13 mmol), derived from crotyl chloride, was cyclised for 4 h in gently refluxing chloroform using triflic acid (11 mg, 0.075 mmol) according to general procedure B to give the *pyrrolidine* **32b** (38 mg, 86%) as a colourless, crystalline solid, in a 3:1 ratio of (2*SR*,5*RS*) and (2*RS*,5*RS*) diastereoisomers, as an inseparable mixture, mp 87–93 °C; $C_{13}H_{16}N_2O_6S$: calcd C 47.6, H 4.9, N 8.5; found: C 47.3, H 5.0, N 8.6%; δ_H (400 MHz, $CDCl_3$) (major isomer) 8.34 (d, *J*=7.9 Hz, 2H, 2×ArH), 8.06 (d, *J*=7.9 Hz, 2H, 2×ArH), 4.54 (dd, *J*=8.6, 1.3 Hz, 1H, H2), 4.08 (app. pent., *J*=6.4 Hz, 1H, H5), 3.68 (s, 3H, OMe), 2.40–1.60 (m, 4H, 2×CH_2), 1.27 (d, *J*=6.4 Hz, 3H, 5-Me); δ_C (100.6 MHz, $CDCl_3$) 174.4 (CO), 148.7 (s), 142.6 (s), 128.8 (2×d), 127.0 (2×d), 66.5 (d), 58.2 (d), 52.7 (OMe), 38.6 (t), 31.2 (t), 20.3 (q); δ_H (400 MHz, $CDCl_3$) (minor isomer) 8.36 (d, *J*=7.9 Hz, 2H, 2×ArH), 8.11 (d, *J*=7.9 Hz, 2H, 2×ArH), 4.41 (dd, *J*=7.7, 5.7 Hz, 1H, H2), 3.97–3.90 (m, 1H, H5), 3.76 (s, 3H, OMe), 2.40–1.60 (m, 4H, 2×CH_2), 1.30 (d, *J*=6.4 Hz, 3H, 5-Me); δ_C (100.6 MHz, $CDCl_3$) 174.6 (CO), 143.7 (s), 140.1 (s), 129.7 (2×d), 127.3 (2×d), 68.1 (d), 59.2 (d), 53.0 (OMe), 37.9 (t), 32.4 (t), 19.8 (q); ν_{max} (KBr)/cm^{-1} 1737, 1533, 1344, 1150; *m/z* [APCI] 329 (100%, $M+H^+$); HRMS: *m/z*: calcd for $C_{13}H_{17}N_2O_6S$ 329.0807; found: 329.0810 $[M+H]^+$.

*4.7.13. Methyl (2RS,5RS)- and (2SR,5RS)-1-(2,4-dinitrobenzenesulfonyl)-5-methylpyrrolidine-2-carboxylate (**32c**).* The sulfonamide **31c** (59 mg, 0.16 mmol), derived from crotyl chloride, was cyclised for 4 h in gently refluxing chloroform using triflic acid (20 mg, 0.13 mmol) according to general procedure B to give the *pyrrolidine* **32c** (48 mg, 83%) as a colourless, crystalline solid, in a 3:1 ratio of (2*SR*,5*RS*) and (2*RS*,5*RS*) diastereoisomers, as an inseparable mixture, mp 80–86 °C; $C_{13}H_{16}N_3O_8S$: calcd C 41.7, H 4.3, N 11.2; found: C 41.6, H 4.4, N 11.4%; δ_H (400 MHz, $CDCl_3$) (major isomer) 8.65 (d, *J*=2.1 Hz, 1H, ArH3), 8.39 (dd, *J*=8.6, 2.1 Hz, 1H, ArH5), 8.23 (d, *J*=8.6 Hz, 1H, ArH6), 4.52 (app. d, *J*=8.5 Hz, 1H, H2), 4.31–4.27 (m, 1H, H5), 3.58 (s, 3H, OMe), 2.29–2.25 (m, 1H, $3H_a$), 2.16–2.12 (m, 1H, $3H_b$), 1.96 (ddd, *J*=12.0, 6.7, 1.3 Hz, 1H, $H4_a$), 1.59–1.56 (m, 1H, $H4_b$), 1.10 (d, *J*=6.4 Hz, 3H, 5-Me); δ_C (100.6 MHz, $CDCl_3$) 174.8 (CO), 149.2 (s), 146.4 (s), 139.6 (s), 132.3 (d), 132.1 (d), 129.3 (d), 68.6 (d), 59.0 (d), 52.9 (OMe), 38.9 (t), 31.3 (t), 20.2 (q); δ_H (400 MHz, $CDCl_3$) (minor isomer) 8.65 (d, *J*=2.1 Hz, 1H, ArH3), 8.40 (dd, *J*=8.6, 2.1 Hz, 1H, ArH5), 8.24 (d, *J*=8.4 Hz, 1H, ArH6), 4.56 (dd, *J*=8.2, 4.4 Hz, 1H, H2), 4.10–4.07 (m, 1H, H5), 3.66 (s, 3H, OMe), 2.34–2.29 (m, 1H, $3H_a$), 2.14–2.11 (m, 1H, $3H_b$), 2.04–2.00 (m, 1H, $H4_a$), 1.61–1.58 (m, 1H, $H4_b$), 1.28 (d, *J*=6.3 Hz, 3H, 5-Me); δ_C (100.6 MHz, $CDCl_3$) 174.7 (CO), 149.2 (s), 146.3 (s), 139.5 (s), 132.3 (d), 132.1 (d), 129.6 (d), 68.6 (d), 59.0 (d), 52.9 (OMe), 38.9 (t), 31.3 (t), 20.2 (q); ν_{max} (KBr)/cm^{-1} 2956, 1747, 1538, 1462, 1352; *m/z* [APCI] 374 (100%, $M+H^+$), 314 (64); HRMS: *m/z*: calcd for $C_{13}H_{19}N_4O_8S$ 391.0924; found: 391.0921 $[M+NH_4]^+$.

4.8. Carbamates

*4.8.1. Methyl 2,5-dimethyl-2-(methoxycarbonylamino)hex-4-enoate (**33**).* Methyl 2-amino-2,5-dimethylhex-4-enoate (2.30 g, 13 mmol; see Schemes 2 and 3), prepared according to general procedure A, was immediately dissolved in methanol (10 mL) containing anhydrous potassium carbonate (2.48 g, 18 mmol) and methyl chloroformate (1.25 mL, 16 mmol) added dropwise. The resulting solution was refluxed for 2 h then cooled and evaporated. The residue was dissolved in ether (30 mL) and water (20 mL) and the separated organic solution washed with water (50 mL) and brine (50 mL), then dried, filtered and evaporated. Crystallisation of the residue from ethyl acetate/hexanes then gave the *carbamate* **33** (2.20 g, 64%) as a yellowish solid, mp 64–66 °C; δ_H (400 MHz, $CDCl_3$) 5.33 (s, 1H, NH), 4.91 (t, *J*=7.4 Hz, 1H, H4), 3.68 (s, 3H, OMe), 3.58 (s, 3H, OMe), 2.64 (dd, *J*=14.4, 7.4 Hz, 1H, $H3_a$), 2.43 (dd, *J*=14.4, 7.4 Hz, 1H, $H3_b$), 1.64 (s, 3H), 1.54 (s, 3H), 1.46 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 174.6 (CO), 164.2 (NCO), 136.6 (5-C), 117.4 (4-CH), 59.8 (2-C), 52.6 (OMe), 51.9 (OMe), 36.0 (3-CH_2), 26.1 (q), 23.0 (q), 17.9 (q); ν_{max} (KBr)/cm^{-1} 3354, 2952, 1728, 1724, 1524, 1453, 1376; *m/z* [APCI] 230 (69%, $M+H^+$), 170 (100, M^+-CO_2Me); HRMS: *m/z*: calcd for $C_{11}H_{20}NO_4$: 230.1387; found: 230.1387 $[M+H]^+$.

*4.8.2. Dimethyl 2,5,5-trimethylpyrrolidine-1,2-dicarboxylate (**34**).* The carbamate **33** (140 mg, 0.61 mmol) was cyclised at ambient temperature for 2 h using triflic acid (174 mg, 1.22 mmol, 2 equiv) according to general procedure B to give the *pyrrolidine* **34** (96 mg, 69%) as a colourless, crystalline solid, mp 88–91 °C; $C_{11}H_{19}NO_4$: calcd C 57.6, H 8.3, N 6.1; found: C 57.5, H 8.0, N 6.3%; δ_H (400 MHz, $CDCl_3$) 3.60 (s, 3H, OMe), 3.50 (s, 3H, OMe), 2.05 (ddd, *J*=11.6, 7.8, 4.6 Hz, 1H, $H3_a$), 1.76–1.73 (m, 3H, $H3_b$ and 4-CH_2), 1.42 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 175.3 (CO), 153.6 (CO), 67.3 (s), 63.4 (s), 52.6 (OMe), 51.9 (OMe), 39.3 (t), 36.0 (t), 27.8 (q), 24.5 (q), 23.5 (q); ν_{max} (KBr)/cm^{-1} 2955, 1745, 1694, 1442, 1360; *m/z* [APCI] 230 (33%, $M+H^+$), 170 (100; M^+-CO_2Me); HRMS: *m/z*: calcd for $C_{11}H_{20}NO_4$ 230.1387; found: 230.1384 $[M+H]^+$.

*4.8.3. Methyl (E)-2-(methoxycarbonylamino)-5-phenylpent-4-enoate (**35a**).* By the foregoing procedure, reaction between methyl (*E*)-2-amino-5-phenylpent-4-enoate (1.30 g, 6.1 mmol) and methyl chloroformate (0.57 mL, 7.3 mmol) gave, after crystallisation from ethyl acetate/hexanes, the *carbamate* **35a** (0.96 g, 51%) as

a yellowish solid, mp 99–105 °C; δ_H (400 MHz, $CDCl_3$) 7.29–7.27 (m, 2H), 7.15–7.12 (m, 3H), 6.32 (d, *J*=15.3 Hz, 1H, H5), 5.97 (dt, *J*=15.3, 7.5 Hz, 1H, H4), 5.34 (d, *J*=9.0 Hz, 1H, NH), 4.24–4.22 (m, 1H, H2), 3.65 (s, 3H, OMe), 3.62 (s, 3H, OMe), 2.56–2.53 (m, 2H, 3-CH_2); δ_C (100.6 MHz, $CDCl_3$) 174.3 (CO), 160.0 (NCO), 136.7 (s), 130.5 (d), 127.9 (d), 127.2 (d), 125.8 (d), 123.2 (d), 56.5 (2-CH), 52.7 (OMe), 51.8 (OMe), 35.9 (3-CH_2); ν_{max} (KBr)/cm^{-1} 3299, 2967, 1729, 1726, 1537, 1150; *m*/*z* [APCI] 264 (100%, $M+H^+$), 206 (92, M^+-CO_2Me).

*4.8.4. Methyl (E)-2-(methoxycarbonylamino)hex-4-enoate (**35b**).* By the foregoing procedure, reaction between methyl (*E*)-2-amino-hex-4-enoate (0.70 g, 4.9 mmol) and methyl chloroformate (0.46 mL, 5.9 mmol) gave, after crystallisation from ethyl acetate/hexanes, the *carbamate* **35b** (0.712 g, 58%) as an off-white solid, mp 57–59 °C; $C_9H_{15}NO_4$: calcd C 53.7, H 7.5, N 7.0; found: C 53.7, H 7.8, N 6.6%; δ_H (400 MHz, $CDCl_3$) 5.36 (d, *J*=8.8 Hz, 1H, NH), 5.32 (dq, *J*=14.8, 6.5 Hz, 1H, H5), 4.98 (ddd, *J*=14.8, 7.6, 7.4 Hz, 1H, H4), 4.36–4.35 (m, 1H, H2), 3.67 (s, 3H, OMe), 3.58 (s, 3H, OMe), 2.59 (dt, *J*=14.5, 7.4 Hz, $H3_a$), 2.47 (ddd, *J*=14.5, 7.6, 7.4 Hz, 1H, $H3_b$), 1.52 (d, *J*=6.5 Hz, 3H, 5-Me); δ_C (100.6 MHz, $CDCl_3$) 175.2 (CO), 162.3 (NCO), 121.4 (d), 117.4 (d), 57.5 (2-CH), 51.8 (OMe), 50.7 (OMe), 35.1 (3-CH_2), 19.9 (q); ν_{max} (KBr)/cm^{-1} 3353, 2956, 1732, 1728, 1554, 1432; *m*/*z* [APCI] 202 (88%, $M+H^+$), 142 (100, M^+-CO_2Me).

4.9. Cascade cyclisations

*4.9.1. Methyl (E)-5,9-dimethyl-2-(p-toluenesulfonylamino)deca-4,8-dienoate (**41a**).* Geranyl bromide **40** (3.2 mL, 16 mmol) was used to alkylate methyl 2-(benzylideneamino)acetate **10a** (2.50 g, 14 mmol) according to general procedure A to give an intermediate imine: δ_H (400 MHz, $CDCl_3$) 8.07 (s, 1H, N=CH), 7.65–7.60 (m, 2H), 7.30–7.26 (m, 3H), 4.95–4.90 (m, 2H), 3.83 (dd, *J*=8.3, 5.4 Hz, 1H, H2), 3.63 (s, 3H, OMe), 2.52–2.48 (m, 2H), 1.90–1.80 (m, 4H), 1.52 (s, 3H), 1.46 (s, 3H), 1.42 (s, 3H).

The crude imine was hydrolysed and tosylated followed by column chromatography (25% ethyl acetate/petrol) to give the *geranyl sulfonamide* **41a** (1.72 g, 39%) as a pale yellow oil; R_f 0.40 (25% EtOAc/petrol); δ_H (400 MHz, $CDCl_3$) 7.62 (d, *J*=8.2 Hz, 2H), 7.22 (d, *J*=8.2 Hz, 2H), 5.01 (d, *J*=9.3 Hz, 1H, NH), 4.97 (t, *J*=6.7 Hz, 1H), 4.88 (t, *J*=6.9 Hz, 1H), 3.92 (dt, *J*=9.3, 5.7 Hz, 1H, H2), 3.56 (s, 3H, OMe), 2.35–2.31 (m, 2H), 2.32 (s, 3H, ArMe), 1.95–1.85 (m, 4H), 1.53 (s, 3H), 1.51 (s, 3H), 1.49 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 172.7 (CO), 143.6 (s), 143.1 (s), 139.4 (s), 137.3 (s), 129.7 (2×d), 129.0 (2×d), 127.4 (d), 118.1 (d), 59.2 (d), 51.3 (OMe), 42.0 (t), 40.9 (t), 39.2 (t), 28.2 (q), 21.1 (q), 19.6 (q), 14.8 (q); ν_{max} (film)/cm^{-1} 3526, 3259, 2939, 1737; *m*/*z*: [APCI] 380 (100%; $M+H)^+$; HRMS: *m*/*z*: calcd for $C_{20}H_{29}NO_4S$: 379.1817; found: 379.1813 $[M]^+$.

*4.9.2. Methyl (2RS/SR,3aRS,7aRS)-4,4,7a-trimethyl-1-(p-toluenesulfonyl)octahydroindole-2-carboxylate (**43a**).* The foregoing sulfonamide **41a** (0.55 g, 1.8 mmol) was cyclised for 0.25 h at 0 °C using triflic acid (0.11 g, 0.77 mmol) as described in general procedure B followed by crystallisation from EtOAc/hexanes gave the *octahydroindole* **43a** (0.48 g, 88%) as a colourless solid and a mixture of two diastereoisomers in a 3:1 ratio, mp 92–94 °C; $C_{20}H_{29}NO_4S$: calcd C 63.3, H 7.7, N 3.6; found: C 63.3, H 7.7, N 3.8%; δ_H (400 MHz, $CDCl_3$) (major isomer) 7.76 (d, *J*=8.2 Hz, 2H), 7.19 (d, *J*=8.2 Hz, 2H), 4.34 (app. d, *J*=9.3 Hz, 1H, H2), 3.53 (s, 3H, OMe), 2.34 (s, 3H, ArMe), 2.30–1.10 (m, 9H), 1.55 (s, 3H), 1.22 (s, 3H), 0.80 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 173.4 (CO), 143.2 (s), 138.9 (s), 129.2 (2×d), 128.1 (2×d), 67.8 (s), 58.2 (d), 55.0 (d), 52.2 (OMe), 40.2 (t), 38.3 (t), 32.8 (q), 28.1 (t), 21.6 (q), 20.6 (q), 20.4 (t), 19.2 (q); δ_H (400 MHz, $CDCl_3$) (minor isomer) 7.71 (d, *J*=8.2 Hz, 2H), 7.19 (d, *J*=8.2 Hz, 2H), 4.29 (app. d, *J*=8.9 Hz, 1H, H2), 3.73 (s, 3H, OMe), 2.35 (s, 3H, ArMe), 2.30–0.90 (m, 9H), 1.52 (s, 3H), 1.25 (s, 3H), 0.76 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 172.7 (CO), 143.2 (s), 138.8 (s), 129.4 (2×d), 127.8 (2×d), 65.9 (s), 58.4 (d), 55.0 (d), 51.9 (OMe), 40.3 (t), 38.0 (t), 32.9 (q), 28.6 (t), 21.7 (q), 20.5 (q), 20.3 (t), 19.5 (q); ν_{max} (KBr)/cm^{-1} 2942, 1752, 1459, 1322, 1152; *m*/*z*: [APCI] 380 (100%; $M+H)^+$; HRMS: *m*/*z*: calcd for $C_{20}H_{29}NO_4S$: 379.1800; found: 379.1802 $[M]^+$.

Careful column chromatography (silica gel, 20% EtOAc in petrol) separated a fraction enriched in the major isomer **43a.maj**, crystallisation of which from EtOAc/hexane gave prisms, mp 132–135 °C, of approximately 90% purity in terms of isomer ratio.

*4.9.3. Methyl (E)-2-(p-toluenesulfonylamino)-2,5,9-trimethyldeca-4,8-dienoate (**41b**).* Geranyl bromide **40** (2.9 mL, 14 mmol) was used to alkylate methyl 2-(benzylideneamino)propanoate **10b** (2.50 g, 13 mmol) according to general procedure A to give an intermediate imine: δ_H (400 MHz, $CDCl_3$) 8.12 (s, 1H, N=CH), 7.71–7.66 (m, 2H), 7.38–7.35 (m, 3H), 5.46 (t, *J*=8.5 Hz, 1H), 5.05–5.00 (m, 1H), 3.66 (s, 3H, OMe), 2.57 (t, *J*=7.8 Hz, 2H), 2.00–1.95 (m, 4H), 1.66 (s, 3H), 1.53 (s, 3H), 1.41 (s, 3H), 1.36 (s, 3H).

The crude imine was hydrolysed and tosylated followed by column chromatography (25% ethyl acetate/petrol) to give the *geranyl sulfonamide* **41b** (1.90 g, 44%) as a pale yellow oil; R_f 0.38 (25% EtOAc/petrol); δ_H (400 MHz, $CDCl_3$) 7.68 (d, *J*=8.2 Hz, 2H), 7.24 (d, *J*=8.2 Hz, 2H), 5.22 (s, 1H, NH), 5.00 (t, *J*=8.1 Hz, 1H), 4.86 (t, *J*=7.5 Hz, 1H), 3.56 (s, 3H, OMe), 2.44 (dd, *J*=14.3, 8.1 Hz, 1H, $H3_a$), 2.34 (dd, *J*=14.3, 7.5 Hz, 1H, $H3_b$), 2.34 (s, 3H, ArMe), 1.98–1.90 (m, 4H), 1.62 (s, 3H), 1.53 (s, 3H), 1.51 (s, 3H), 1.35 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 174.2 (CO), 143.7 (s), 142.9 (s), 139.6 (s), 137.2 (s), 129.8 (2×d), 129.0 (2×d), 127.1 (d), 118.5 (d), 60.0 (s), 48.2 (OMe), 42.0 (t), 40.6 (t), 39.6 (t), 28.9 (q), 21.5 (q), 20.7 (q), 19.8 (q), 14.1 (q); ν_{max} (film)/cm^{-1} 3518, 3272, 2950, 1738, 1598; *m*/*z*: [APCI] 394 (100%; $M+H)^+$; HRMS: *m*/*z*: calcd for $C_{21}H_{31}NO_4S$: 393.1974; found: 393.1976 $[M]^+$.

*4.9.4. Methyl (2RS/SR,3aRS,7aRS)-2,4,4,7a-tetramethyl-1-(p-toluenesulfonyl)octahydroindole-2-carbxylate (**43b**).* The foregoing sulfonamide **41b** (0.63 g, 1.9 mmol) was cyclised for 0.25 h at 0 °C using triflic acid (0.11 g, 0.77 mmol) as described in general procedure B followed by crystallisation from dichloromethane gave the *octahydroindole* **43b** (0.57 g, 91%) as a colourless solid and a mixture of two diastereoisomers in a 3:2 ratio, mp 87–89 °C; $C_{21}H_{31}NO_4S$: calcd C 64.1, H 7.7, N 3.6; found: C 64.2, H 7.9, N 3.7%; δ_H (400 MHz, $CDCl_3$) (major isomer) 7.65 (d, *J*=8.2 Hz, 2H), 7.18 (d, *J*=8.2 Hz, 2H), 3.78 (s, 3H, OMe), 2.34 (s, 3H, ArMe), 2.15–2.10 (m, 2H), 1.80–1.74 (m, 5H), 1.71 (s, 3H), 1.32 (s, 3H), 0.80 (s, 3H), 0.75 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 174.7 (CO), 141.8 (s), 141.4 (s), 128.1 (2×d), 126.5 (2×d), 67.7 (s), 65.7 (s), 54.7 (d), 51.6 (OMe), 39.3 (d), 37.2 (t), 36.6 (t), 31.7 (q), 24.7 (t), 20.5 (q), 19.5 (q), 19.4 (q), 13.1 (q); δ_H (400 MHz, $CDCl_3$) (minor isomer) 7.80 (d, *J*=8.2 Hz, 2H), 7.18 (d, *J*=8.2 Hz, 2H), 3.71 (s, 3H, OMe), 2.34 (s, 3H, ArMe), 2.15–2.10 (m, 2H), 1.80–1.74 (m, 5H), 1.32 (s, 3H), 1.11 (s, 3H), 0.77 (s, 3H), 0.73 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 174.1 (CO), 140.8 (s), 139.7 (s), 127.3 (2×d), 126.0 (2×d), 66.9 (s), 66.8 (s), 53.8 (d), 51.6 (OMe), 41.0 (t), 39.1 (t), 37.1 (t), 31.8 (q), 26.2 (t), 20.4 (q), 19.8 (q), 19.4 (q), 19.0 (q); ν_{max} (KBr)/cm^{-1} 2950, 1740, 1598, 1459, 1092; *m*/*z*: [APCI] 394 (100%; $M+H)^+$; HRMS: *m*/*z*: calcd for $C_{21}H_{31}NO_4S$: 393.1974; found: 393.1978 $[M]^+$.

*4.9.5. (2E,6E)-1-Bromo-3,7,11-trimethyldodeca-2,6,10-trienoate (farnesyl bromide)[30] (**46**).* (*E*,*E*)-Farnesol (2.50 g, 8.6 mmol) was dissolved in ether (30 mL) and the solution cooled in ice-water and protected from light. Pyridine (4.3 mL, 66 mmol) was added followed by phosphorus tribromide (1.0 mL, 14 mmol). The resulting mixture was then stirred for 3 h without further cooling and the solvent evaporated. The bromide **46** (6.2 g, 72%), a pale yellow oil, was removed by pipette from the solid residue and used immediately in the next step: δ_H (400 MHz, $CDCl_3$) 5.47 (t, *J*=7.8 Hz, 1H), 5.05–5.00 (m, 2H), 3.94 (br d, *J*=7 Hz, 2H, CH_2Br), 2.10–1.90 (m, 8H), 1.61 (s, 6H), 1.53 (s, 6H); δ_C (100.6 MHz, $CDCl_3$) 144.0 (s), 136.0 (s),

131.8 (s), 124.7 (d), 123.8 (d), 120.9 (d), 40.2 (t), 32.4 (t), 30.1 (t), 27.1 (t), 26.5 (t), 26.1 (q), 23.8 (q), 18.1 (q).[30]

*4.9.6. Methyl (4E,8E)-5,9,13-trimethyl-2-(p-toluenesulfonylamino)-tetradeca-4,8,12-trienoate (**47a**).* Farnesyl bromide **46** (see above; 1.8 g, 6.2 mmol) was used to alkylate methyl 2-(benzylideneamino)acetate **10a** (1.0 g, 5.6 mmol) according to general procedure A to give the expected imine: δ_H (400 MHz, $CDCl_3$) 8.13 (s, 1H, N=CH), 7.86–7.82 (m, 2H), 7.35–7.30 (m, 3H), 5.35 (t, J=7.6 Hz, 1H), 5.04–5.00 (m, 2H), 3.88 (dd, J=8.3, 5.5 Hz, 1H, H2), 3.69 (s, 3H, OMe), 2.66 (dd, J=14.2, 5.5 Hz, 1H, $H3_a$), 2.51 (dd, J=14.2, 8.3 Hz, 1H, $H3_b$), 2.10–1.90 (m, 8H), 1.60 (s, 6H), 1.52 (s, 6H). This crude imine was hydrolysed and tosylated as usual and the crude product purified by column chromatography (25% ethyl acetate/petrol) to give the *farnesyl sulfonamide* **47a** (0.78 g, 36%) as a pale yellow oil; R_f 0.38 (25% EtOAc/petrol); δ_H (400 MHz, $CDCl_3$) 7.82 (d, J=8.2 Hz, 2H), 7.39 (d, J=8.2 Hz, 2H), 5.21 (d, J=8.8 Hz, 1H, NH), 5.20–5.16 (m, 2H), 5.06 (t, J=7.1 Hz, 1H), 4.10–4.07 (m, 1H, H2), 3.62 (s, 3H, OMe), 2.67–2.51 (m, 2H), 2.51 (s, 3H, ArMe), 2.20–2.00 (m, 8H), 1.78 (s, 6H), 1.72 (s, 6H); δ_C (100.6 MHz, $CDCl_3$) 173.2 (CO), 143.5 (s), 143.0 (s), 139.8 (s), 138.6 (s), 137.7 (s), 129.5 (2×d), 128.6 (2×d), 126.3 (d), 118.9 (d), 115.2 (d), 61.4 (2-CH), 52.0 (OMe), 43.1 (t), 42.7 (t), 41.3 (t), 40.8 (t), 39.4 (t), 28.6 (q), 21.7 (q), 20.4 (q), 19.3 (q), 15.8 (q); ν_{max} (film)/cm^{-1} 3278, 2975, 1735, 1451, 1273; m/z: [APCI] 448 (100%; $M+H)^+$; HRMS: m/z: calcd for $C_{25}H_{37}NO_4S$: 447.2443; found: 447.2452 $[M]^+$.

*4.9.7. Methyl 3a,6,6,9a-tetramethyl-3-(p-toluenesulfonyl)dodecahydro-1H-benzo[e]indole-2-carboxylate (**48a**).* The foregoing farnesyl sulfonamide **47a** (0.60 g, 1.60 mmol) was cyclised for 0.25 h at 0 °C by the general procedure B using triflic acid (95 mg, 0.60 mmol). The crude product was purified by column chromatography (dichloromethane) to give the *tricycle* **48a** (0.52 g, 86%) as a pale yellow oil: δ_H (400 MHz, $CDCl_3$) (whole sample) 7.80–7.60 (m, 2H), 7.15–7.05 (m, 2H), 4.32–4.25 (m, 1H), 3.68–3.60 (m, 1H), 3.47, 3.45, 3.44, 3.42 (all s, total 3H, OMe), 2.33–2.27 (m, 3H, ArMe), 2.10–0.70 (m, 14H), 1.55, 1.53 1.48, 1.46, 1.33, 1.24, 0.92, 0.90, 0.88, 0.77, 0.75, 0.74 (all s, total 12H, Me); δ_C (100.6 MHz, $CDCl_3$) (whole sample) 174.5 (CO), 172.3 (CO), 172.1 (CO), 170.9 (CO), 145.6 (s), 144.2 (s), 143.7 (s), 139.9 (s), 139.8 (s), 131.0 (d), 130.5 (d), 130.4 (d), 129.9 (d), 129.1 (d), 128.7 (d), 69.9 (d), 68.9 (d), 68.1 (d), 67.2 (s), 66.5 (s), 66.4 (s), 52.4 (OMe), 52.2 (OMe), 39.8 (d), 39.6 (d), 38.7 (d), 36.2 (t), 36.0 (t), 35.7 (t), 35.0 (t), 34.8 (t), 34.6 (t), 34.5 (t), 32.3 (s), 31.8 (s), 29.8 (t), 29.6 (t), 29.4 (t), 28.7 (t), 28.3 (t), 27.2 (t), 27.0 (t), 26.9 (t), 26.5 (q), 26.3 (q), 26.2 (q), 25.9 (q), 24.6 (s), 24.0 (s), 23.3 (s), 23.3 (q), 22.9 (q), 22.4 (q), 21.8 (q), 21.2 (t), 20.7 (t), 20.6 (t), 19.9 (q), 19.5 (q), 19.2 (q), 18.8 (q), 18.4 (q), 17.9 (q); ν_{max} (film)/cm^{-1} 2928, 1743, 1598, 1477; m/z: [APCI] 448 (100%; $M+H)^+$; HRMS: m/z: calcd for $C_{25}H_{37}NO_4S$: 447.2443; found: 447.2450 $[M]^+$.

*4.9.8. Methyl (4E,8E)-2,5,9,13-tetramethyl-2-(p-toluenesulfonylamino)tetradeca-4,8,12-trienoate (**47b**).* The foregoing bromide **46** (2.5 g, 8.6 mmol) was used to alkylate methyl 2-(benzylideneamino)propanoate **10b** (1.5 g, 7.9 mmol) according to general procedure A to give the expected imine: δ_H (400 MHz, $CDCl_3$) 8.14 (s, 1H, N=CH), 7.70–7.65 (m, 2H), 7.30–7.25 (m, 3H), 5.35–5.30 (m, 1H), 5.02–4.95 (m, 2H), 3.73 (s, 3H, OMe), 2.50–2.40 (m, 2H), 2.00–1.85 (m, 4H), 1.60 (s, 3H), 1.57 (s, 3H), 1.39 (s, 3H), 1.35 (s, 3H), 1.21 (s, 3H). This crude imine was hydrolysed and tosylated as usual and the crude product purified by column chromatography (25% ethyl acetate/petrol) to give the *farnesyl sulfonamide* **47b** (0.95 g, 31%) as a pale yellow oil; R_f 0.38 (25% EtOAc/petrol); δ_H (400 MHz, $CDCl_3$) 7.79 (d, J=8.2 Hz, 2H), 7.28 (d, J=8.2 Hz, 2H), 5.25 (s, 1H, NH), 5.20–5.15 (m, 2H), 5.05–5.00 (m, 1H), 3.69 (s, 3H, OMe), 2.65–2.50 (m, 2H), 2.41 (s, 3H, ArMe), 2.20–2.00 (m, 8H), 1.68 (s, 3H), 1.61 (s, 3H), 1.52 (s, 6H), 1.22 (s, 3H); ν_{max} (film)/cm^{-1} 3162, 2984, 1721, 1398; m/z: [APCI] 462 (100%; $M+H)^+$; HRMS: m/z: calcd for $C_{26}H_{39}NO_4S$: 461.2600; found: 461.2622 $[M]^+$.

*4.9.9. Methyl 2,3a,6,6,9a-pentamethyl-3-(p-toluenesulfonyl)dodecahydro-1H-benzo[e]indole-2-carboxylate (**48b**).* The foregoing farnesyl sulfonamide **47b** (0.39 g, 0.85 mmol) was cyclised for 0.25 h at 0 °C by the general procedure B using triflic acid (51 mg, 0.34 mmol). The crude product was purified by column chromatography (dichloromethane) to give the *tricycle* **48b** (0.33 g, 86%) as a pale yellow oil and as a 1:1:3:3 mixture of diastereoisomers. δ_H (400 MHz, $CDCl_3$) (major isomers) 7.78 (d, J=8.2 Hz, 2H), 7.19 (d, J=8.2 Hz, 2H), 3.75 (s, 3H, OMe), 3.63 (s, 3H, OMe), 2.34 (s, 3H, ArMe), 2.33 (s, 3H, ArMe), 2.20–0.90 (m, 14H), 1.80 (s, 3H), 1.79 (s, 3H), 1.62 (s, 3H), 1.56 (s, 3H), 1.54 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H); δ_H (400 MHz, $CDCl_3$) (minor isomers) 7.76 (d, J=8.2 Hz, 2H), 7.72 (d, J=8.2 Hz, 2H), 7.20 (d, J=8.2 Hz, 2H), 7.18 (d, J=8.2 Hz, 2H), 3.77 (s, 3H, OMe), 3.50 (s, 3H, OMe), 2.34 (s, 3H, ArMe), 2.20–0.90 (m, 14H), 1.68 (s, 3H), 1.61 (s, 3H), 1.59 (s, 3H), 1.51 (s, 3H), 1.48 (s, 3H), 1.21 (s, 3H), 1.09 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) (whole sample) 173.5 (CO), 171.2 (CO), 170.8 (CO), 143.7 (s), 143.6 (s), 139.3 (s), 139.1 (s), 139.0 (s), 130.6 (d), 129.6 (d), 129.5 (d), 128.7 (d), 128.6 (d), 127.5 (d), 71.0 (s), 69.4 (s), 68.2 (s), 66.7 (s), 66.1 (s), 52.4 (OMe), 52.2 (OMe), 52.1 (OMe), 41.2 (d), 39.7 (d), 39.3 (t), 39.2 (t), 39.0 (t), 38.6 (d), 38.4 (d), 38.1 (t), 37.9 (t), 37.6 (t), 37.4 (t), 36.9 (t), 36.7 (t), 35.8 (t), 35.2 (t), 31.6 (t), 31.3 (t), 25.6 (q), 25.0 (t), 24.9 (t), 21.2 (t), 20.9 (t), 20.5 (s), 20.1 (s), 20.0 (s), 19.9 (t), 19.8 (t), 19.8 (s), 19.6 (s), 19.5 (q), 19.4 (q), 19.2 (q), 19.1 (q), 18.8 (q), 18.4 (q), 18.3 (q), 18.0 (q), 17.9 (q), 17.5 (q), 17.2 (q); ν_{max} (film)/cm^{-1} 2923, 2852, 1744, 1462, 1262; m/z: [APCI] 462 (100%; $M+H)^+$; HRMS: m/z: calcd for $C_{26}H_{39}NO_4S$: 461.2600; found: 461.2609 $[M]^+$.

*4.9.10. (2E,6E,10E)-1-Bromo-2,6,10,14-tetramethylhexadeca-2,6,10,14-tetraene[31] (**49**).* Geranylgeraniol (0.88 g, 3 mmol) was dissolved in dry ether (5 mL) and the solution stirred, protected from light and cooled in an ice-water bath. Pyridine (0.48 mL, 6 mmol) was added followed by phosphorus tribromide (0.11 mL, 1.1 mmol). The resulting solution was allowed to warm to ambient temperature for 3 h then passed through a plug of silica gel and the filtrate evaporated. The crude geranylgeranyl bromide **49** (0.68 g, 64%) was used immediately: δ_H (400 MHz, $CDCl_3$) 5.47 (t, J=8.4 Hz, 1H), 5.05–4.95 (m, 3H), 4.09 (d, J=6.9 Hz, 2H, 1-CH_2), 2.15–1.85 (m, 12H), 1.74 (s, 3H), 1.69 (s, 3H), 1.53 (s, 9H).[31]

*4.9.11. Methyl (4E,8E,12E)-5,9,13,17-tetramethyl-2-(p-toluenesulfonylamino)octadeca-4,8,12,16-tetraenoate (**50a**).* Geranylgeranyl bromide **49** was used to alkylate methyl 2-(benzylideneamino)acetate **10a** (0.34 g, 1.9 mmol) according to general procedure A to give the expected imine: δ_H (400 MHz, $CDCl_3$) 8.12 (s, 1H, N=CH), 7.70–7.66 (m, 2H), 7.38–7.33 (m, 3H), 5.00–4.95 (m, 4H), 3.91 (dd, J=7.3, 5.6 Hz, 1H, H2), 3.63 (s, 3H, OMe), 2.65 (dd, J=14.1, 5.6 Hz, 1H, $H3_a$), 2.51 (dd, J=14.1, 7.3 Hz, 1H, $H3_b$), 2.05–1.85 (m, 12H), 1.60 (s, 3H), 1.52 (s, 9H), 1.48 (s, 3H). This crude imine was hydrolysed and tosylated as usual and the crude product purified by column chromatography (25% ethyl acetate/petrol) to give the *geranylgeranyl sulfonamide* **50a** (1.50 g, 28%) as a pale yellow oil: δ_H (400 MHz, $CDCl_3$) 7.69 (d, J=8.2 Hz, 2H), 7.23 (d, J=8.2 Hz, 2H), 5.11 (d, J=9.1 Hz, 1H, NH), 5.05–4.95 (m, 4H), 4.91 (t, J=7.0 Hz, 1H, H4), 3.95–3.90 (m, 1H, H2), 3.48 (s, 3H, OMe), 2.42–2.33 (m, 2H), 2.35 (s, 3H, ArMe), 2.00–1.82 (m, 12H), 1.61 (s, 3H), 1.53 (s, 9H), 1.49 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 172.1 (CO), 144.0 (s), 141.0 (s), 137.2 (s), 135.8 (s), 135.4 (s), 131.7 (s), 129.9 (2×d), 127.6 (2×d), 124.8 (d), 124.6 (d), 124.2 (d), 116.9 (d), 55.9 (d), 52.7 (OMe), 40.1 (t), 40.0 (t), 35.6 (t), 32.2 (t), 27.1 (t), 27.0 (t), 26.9 (t), 26.1 (q), 21.9 (q), 20.1 (q), 18.2 (q), 16.7 (q), 16.4 (q); ν_{max} (film)/cm^{-1} 3508, 3276,

2921, 1743, 1481; *m/z*: [APCI] 516 (100%; M+H)$^+$; HRMS: *m/z*: calcd for $C_{30}H_{45}NO_4S$: 515.1976; found: 515.1987 [M]$^+$.

*4.9.12. Methyl 17-aza-4,4,8,10,13,-pentamethyl-17-(p-toluenesulfonyl)hexadecahydrocyclopenta[a]-phenanthrene-16-carboxylate (**51a**).* The foregoing geranylgeranyl sulfonamide **50a** (0.101 g, 0.20 mmol) was cyclised for 0.25 h at 0 °C using triflic acid (12 mg, 0.08 mmol) as described in general procedure B. The crude product was purified by column chromatography (dichloromethane) to give the *cyclised product* **51a** (0.083 g, 83%) as a pale yellow oil: δ_H (400 MHz, $CDCl_3$) 7.80–7.65 (m, 2H), 7.25–7.15 (m, 2H), 4.38–4.27 (m, 1H, H16), 3.70–3.67 (m, OMe), 2.38–2.30 (m, 3H, ArMe), 2.20–0.65 (m, 34H); ν_{max} (film)/cm^{-1} 2964, 2891, 1742, 1477; *m/z*: [APCI] 516 (100%; M+H)$^+$; HRMS: *m/z*: calcd for $C_{30}H_{45}NO_4S$: 515.1976; found: 515.1990 [M]$^+$.

*4.9.13. Methyl (4E,8E,12E)-2,5,9,13,17-pentamethyl-2-(p-toluenesulfonylamino)octadeca-4,8,12,16-tetraenoate (**50b**).* The foregoing bromide **49** was used to alkylate methyl 2-(benzylideneamino)-propanoate **10b** (0.27 g, 1.4 mmol) according to general procedure A to give the expected imine: δ_H (400 MHz, $CDCl_3$) 8.21 (s, 1H, N=CH), 7.75–7.68 (m, 2H), 7.30–7.22 (m, 3H), 5.05–4.95 (m, 4H), 3.69 (s, 3H,OMe), 2.68 (dd, *J*=14.2, 7.4 Hz, 1H, $H3_a$), 2.61 (dd, *J*=14.2, 7.6 Hz, 1H, $H3_b$), 2.10–1.80 (m, 12H), 1.61 (s, 3H), 1.56 (s, 3H), 1.53 (s, 3H), 1.51 (s, 6H), 1.40 (s, 3H). This crude imine was hydrolysed and tosylated as usual and the crude product purified by column chromatography (25% ethyl acetate/petrol) to give the *geranylgeranyl sulfonamide* **50b** (0.25 g, 32%) as a pale yellow oil: δ_H (400 MHz, $CDCl_3$) 7.68 (d, *J*=8.2 Hz, 2H), 7.20 (d, *J*=8.2 Hz, 2H), 5.22 (s, 1H, NH), 5.05–5.00 (m, 3H), 4.89 (t, *J*=7.6 Hz, 1H), 3.64 (s, 3H, OMe), 2.45 (dd, *J*=14.4, 7.6 Hz, 1H, $H3_a$), 2.35 (dd, *J*=14.4, 7.6 Hz, 1H, $H3_b$), 2.34 (s, 3H, ArMe), 2.05–1.90 (m, 12H), 1.61 (s, 3H), 1.54 (s, 6H), 1.53 (s, 3H), 1.52 (s, 3H), 1.35 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 174.2 (CO), 143.7 (s), 142.5 (s), 141.6 (s), 139.8 (s), 139.6 (s), 138.2 (s), 129.8 (2×d), 127.9 (2×d), 126.3 (d), 124.4 (d), 122.3 (d), 117.2 (d), 60.8 (d), 53.4 (OMe), 43.0 (t), 42.1 (t), 41.8 (t), 41.3 (t), 40.7 (t), 40.0 (t), 39.6 (t), 27.5 (q), 26.2 (q), 24.3 (q), 21.8 (q), 19.9 (q), 18.1 (q); ν_{max} (film)/cm^{-1} 1730; *m/z*: [APCI] 530 (100%; M+H)$^+$; HRMS: *m/z*: calcd for $C_{31}H_{47}NO_4S$: 529.1366; found: 529.1382 [M]$^+$.

*4.9.14. Methyl 17-aza-4,4,8,10,13,16-hexamethyl-17-(p-toluenesulfonyl)hexadecahydrocyclopenta[a]-phenanthrene-16-carboxylate (**51b**).* The foregoing geranylgeranyl sulfonamide **50b** (0.118 g, 0.22 mmol) was cyclised for 0.25 h at 0 °C using triflic acid (13 mg, 0.10 mmol) as described in general procedure B. The crude product was purified by column chromatography (dichloromethane) to give the *cyclised product* **51b** (0.095 g, 80%) as a pale yellow oil: δ_H (400 MHz, $CDCl_3$) 7.80–7.60 (m, 2H), 7.30–7.15 (m, 2H), 3.70–3.58 (m, OMe), 2.45–2.30 (m, 3H, ArMe), 2.20–0.65 (m, 37H); ν_{max} (film)/cm^{-1} 2936, 2945, 1746, 1448; *m/z*: [APCI] 530 (100%; M+H)$^+$; HRMS: *m/z*: calcd for $C_{31}H_{47}NO_4S$: 529.1366; found: 529.1374 [M]$^+$.

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