

# Stereoselective synthesis of 2,4,5-trisubstituted piperidines by carbonyl ene and Prins cyclisations†

Claire A. M. Cariou, Benson M. Kariuki‡ and John S. Snaith\*

Received 21st May 2008, Accepted 13th June 2008

First published as an Advance Article on the web 28th July 2008

DOI: 10.1039/b808644c

An approach to 2,4,5-trisubstituted piperidines is reported, in which the key step is the Prins or carbonyl ene cyclisation of aldehydes of the type **1**. Prins cyclisation catalysed by concentrated hydrochloric acid in  $\text{CH}_2\text{Cl}_2$  at  $-78^\circ\text{C}$  afforded good yields of two of the four possible diastereomeric piperidines, with the 4,5-*cis* product **7** predominating in a diastereomeric ratio of up to 94 : 6. The diastereoselectivity of the cyclisation decreased as the 2-substituent increased in size, becoming unselective for very bulky 2-substituents. In contrast, cyclisation catalysed by  $\text{MeAlCl}_2$  in  $\text{CH}_2\text{Cl}_2$  or  $\text{CHCl}_3$  at temperatures of between  $20$ – $60^\circ\text{C}$ , favoured the 4,5-*trans* diastereomer **8**, in a diastereomeric ratio of up to 99 : 1. The low-temperature cyclisations catalysed by  $\text{HCl}$  proceed under kinetic control *via* a mechanism involving the development of significant carbocationic character, in which the 4,5-*cis* cation is more stable than the 4,5-*trans* cation as a result of overlap with the neighbouring oxygen. The cyclisations catalysed by  $\text{MeAlCl}_2$  proceed under thermodynamic control, affording the product in which both the 4- and 5-substituents are equatorial.

## Introduction

Functionalised piperidines occur widely in natural products<sup>1</sup> and feature in a number of successful pharmaceuticals, with the ring system being regarded as an important scaffold for drug discovery.<sup>2</sup> The biological importance of piperidines has led to the development of numerous synthetic approaches,<sup>3</sup> but the wide variety of functionality and substitution patterns present in piperidine targets continues to drive the search for new methodologies.<sup>4</sup>

We recently published an approach to 3,4-disubstituted piperidines using a carbonyl ene reaction as the key ring-closing step.<sup>5</sup> The Type I intramolecular carbonyl ene reaction is a very attractive method of ring closure, forming a carbon–carbon bond with the concomitant generation of two contiguous stereocentres.<sup>6</sup> In our case, the Brønsted acid-catalysed reaction at low temperatures strongly favoured a *cis* relationship between the two new stereocentres, while the Lewis acid-catalysed reaction at elevated temperatures gave the corresponding *trans* product, providing a useful stereocontrol feature.

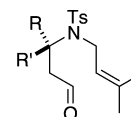
Extending our approach to 2,4,5-trisubstituted piperidines is an important goal, since they form the core of a number of important natural products, including the pseudodistomin family of anti-tumour compounds. These were isolated by Kobayashi *et al.* from

a tunicate,<sup>7</sup> with an ascidian later providing other members of the family,<sup>8</sup> and have recently been the focus of synthetic attention.<sup>9</sup>

We now describe in full our efforts towards the synthesis of 2,4,5-trisubstituted piperidines, using cyclisation precursors in the main derived from  $\alpha$ -amino acids.<sup>10</sup>

## Results and discussion

Our key cyclisation precursors were the aldehydes **1a–1g** (Fig. 1), and we envisaged that in most cases these could be prepared from the *N*-tosyl  $\beta$ -amino acids, obtained by homologation of the readily available  $\alpha$ -amino acids or the corresponding  $\alpha$ -amino alcohols. Given that 3-aminobutyric acid is commercially available, a simple *N*-tosylation of this material proved to be the most expeditious route to the *N*-tosyl  $\beta$ -amino acid, although nitrile **3a** was also prepared for later studies (*vide infra*). The preparation of **1g** used homoserine as a starting material (*vide infra*). Reduction of the corresponding amino acids according to the procedure of Meyers *et al.* afforded the  $\alpha$ -amino alcohols **2b–c** and **2e–f**,<sup>11</sup> we found reduction of alanine by this means to be low-yielding, and so commercially available alaninol was used. Bis-tosylation followed by treatment with  $\text{NaCN}$  in DMF gave



- 1a** R = Me, R' = H  
**1b** R = Bn, R' = H  
**1c** R = *i*-Pr, R' = H  
**1d** R = R' =  $-(\text{CH}_2)_5-$   
**1e** R = *t*-Bu, R' = H  
**1f** R = Ph, R' = H  
**1g** R =  $\text{CO}_2\text{Me}$ , R' = H

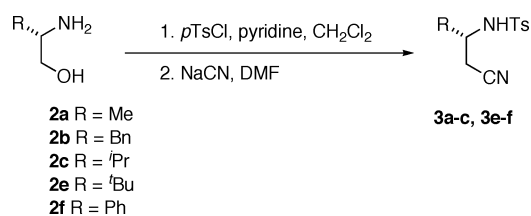
Fig. 1 Cyclisation precursors.

School of Chemistry, The University of Birmingham, Edgbaston, Birmingham, UK B15 2TT. E-mail: j.s.snaith@bham.ac.uk

† Electronic supplementary information (ESI) available: Experimental procedures, NMR spectra and full characterisation for all compounds, as well as CIF files and ORTEP diagrams for the X-ray structures. CCDC reference numbers 689102–689105. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b808644c

‡ Author to whom correspondence regarding the X-ray crystallography should be addressed. Current address: School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff, UK, CF10 3AT. Email: KariukiB@cardiff.ac.uk

good yields of the *N*-tosyl  $\beta$ -amino nitriles **3a–c** and **3e–f** (Scheme 1).<sup>12</sup>



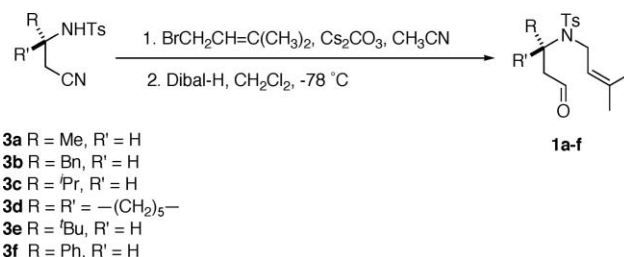
**Scheme 1** Synthesis of nitriles **3a–c** and **3e–f**.

Preparation of nitrile **3d** was achieved by a slightly modified route (Scheme 2). Reduction of 1-aminocyclohexane carboxylic acid by  $\text{BH}_3 \cdot \text{THF}$  in refluxing THF gave an excellent yield of the corresponding  $\beta$ -amino alcohol, but bis-tosylation was very low-yielding and gave a complex mixture of products. Instead, methyl ester formation, *N*-tosylation and subsequent  $\text{LiAlH}_4$  reduction gave the *N*-tosyl amino alcohol **2d**, which could be *O*-tosylated in near-quantitative yield; treatment with NaCN in DMF smoothly led to the desired nitrile **3d** in 97% yield.

With the nitriles in hand, we explored two different routes to the target aldehydes. Acid-catalysed hydrolysis of nitriles **3b–c** and **3e–f** to give the *N*-tosyl  $\beta$ -amino acids **4b–c** and **4e–f** (Scheme 3) proceeded smoothly for **3b–c** and **3e**, but for **3f** the inseparable elimination product **5** was visible in the  $^1\text{H}$  NMR spectrum.

Conversion of the *N*-tosyl  $\beta$ -amino acids **4a–c** into the cyclisation precursors was readily achieved by a three-step sequence (Scheme 4) involving *N,O*-alkylation by prenyl bromide,  $\text{LiAlH}_4$  reduction to alcohols **6a–c** and Swern oxidation to give **1a–c** in excellent overall yield.

Whilst the route was efficient for the preparation of **1a–c**, it was unsatisfactory for **1f**, and we believed that the same compounds should be accessible by a more direct route (Scheme 5). *N*-Alkylation of *N*-tosyl amino nitriles **3a–f** proceeded in excellent yield, and Dibal-H reduction of the products proceeded smoothly to afford the cyclisation precursors **1a–f**. Both routes to the



**Scheme 5** Route to cyclisation precursors from *N*-tosyl  $\beta$ -amino nitriles.

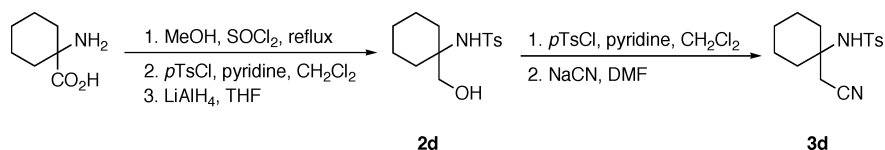
cyclisation precursors were used, although the Dibal-H reduction route was shorter and generally higher-yielding.

With a range of cyclisation precursors in hand, we turned our attention to their cyclisation. Initially, the cyclisation was catalysed by three equivalents of concentrated HCl in  $\text{CH}_2\text{Cl}_2$  at  $-78^\circ\text{C}$ . In our earlier work on 3,4-disubstituted piperidines,<sup>5</sup> these conditions had favoured formation of the kinetic product, in which there is a *cis* relationship between the hydroxyl and isopropenyl substituents. For aldehydes **1a–f** the results are summarised in Table 1.

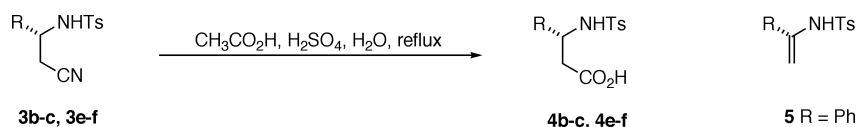
In all cases except **1f**, only two of the four possible stereoisomers were observed, in excellent combined yields. Small amounts (0–10%) of the HCl addition products **11** and **12** (*vide infra*) were often present; although generally separable from the alkene, it was also possible to treat the mixture with aqueous ammonia in THF to effect elimination of HCl and return the pure alkene. The identities of the *cis*, *cis* and *trans*, *trans* products were secured by X-ray diffraction on single crystals grown from **7c** and **8a** (Fig. S1 and S2 in the ESI†).

As can be seen from Table 1, the diastereoselectivities were generally good, and the reaction favoured the *cis*, *cis* product **7** for small- and medium-sized 2-substituents, although the reaction became unselective for very bulky 2-substituents (entries 5 and 6).

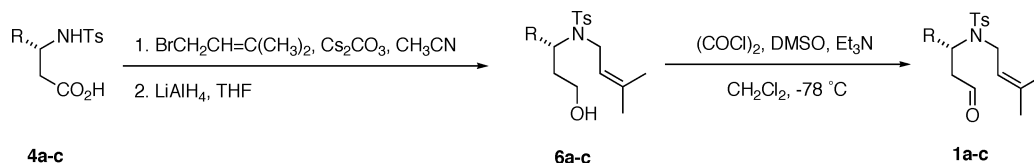
The stereoselectivities can be rationalised by considering two factors. Firstly, there is a strong preference for the 2-substituent to adopt an axial disposition in the chair-like transition state, thus avoiding the pseudo  $A^{1,3}$  strain with the sulfonamide



**Scheme 2** Preparation of nitrile **3d**.

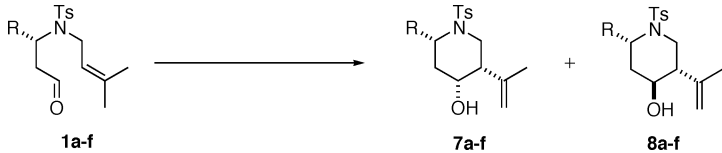


**Scheme 3** Hydrolysis of nitriles.



**Scheme 4** Route to cyclisation precursors from *N*-tosyl  $\beta$ -amino acids.

**Table 1** Cyclisations of aldehydes **1a–f** with concentrated hydrochloric acid

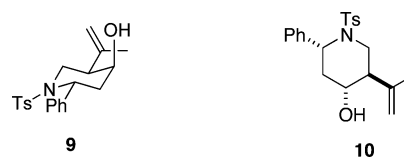
|  |           |                                    |                      |                        |
|------------------------------------------------------------------------------------|-----------|------------------------------------|----------------------|------------------------|
| Entry                                                                              | Aldehyde  | R                                  | 7 : 8 <sup>a</sup>   | Yield (%) <sup>b</sup> |
| 1                                                                                  | <b>1a</b> | Me                                 | 78 : 22              | 70 (22)                |
| 2                                                                                  | <b>1b</b> | Bn                                 | 94 : 6               | 81 (0)                 |
| 3                                                                                  | <b>1c</b> | <sup>i</sup> Pr                    | 89 : 11              | 75 (5)                 |
| 4                                                                                  | <b>1d</b> | –(CH <sub>2</sub> ) <sub>5</sub> – | 89 : 11              | 68 (11)                |
| 5                                                                                  | <b>1e</b> | <sup>t</sup> Bu                    | 47 : 53              | 42 (37)                |
| 6                                                                                  | <b>1f</b> | Ph                                 | 54 : 46 <sup>c</sup> | 41 (40)                |

<sup>a</sup> Ratio was determined by integration of crude <sup>1</sup>H NMR spectra. <sup>b</sup> Isolated yield of major (minor) isomers after chromatography. <sup>c</sup> Traces of two other isomers were observed—see main text.

(Scheme 6); this stereochemical preference in *N*-acyl and *N*-sulfonamido piperidines has been shown to be pronounced in a number of cases.<sup>13</sup> The second factor is the kinetic preference for the ene component and the aldehyde to adopt a *cis* relationship in the cyclisation transition state, as observed in our earlier work.<sup>5</sup> According to our proposal, any carbocationic character developed on the 5-substituent in the transition state (or a carbocationic intermediate formed during cyclisation through a fully stepwise mechanism) can be stabilised by interaction with the lone pair of the oxygen when these two substituents adopt a *cis* relationship. This *cis* relationship is achieved with the aldehyde lying in an axial position in the transition state, and the more bulky ene component lying equatorial. More bulky 2-substituents lead to a lowering of the diastereoselectivity as a result of increased 1,3-diaxial interactions with the aldehyde, forcing the aldehyde into an equatorial position to give **8**.

The rather modest selectivity observed for **1a** appears to be a result of equilibration of the initially formed kinetic isomer **7a** to the thermodynamic product **8a** due to the fact that the reaction required 48 h to reach completion, compared with around 18 h for the other examples. Later studies (*vide infra*) supported the fact that Brønsted acid-catalysed isomerisation to the thermodynamically more stable *trans, trans* piperidine occurred readily for these compounds. This contrasts with our previous work where Brønsted acid-catalysed isomerisation was very slow for 3,4-disubstituted piperidines, reflecting the much smaller 1,3-diaxial interactions with the hydroxyl group that are present in these molecules.

In the case of **1f**, two other isomers were isolated in very small amounts: **9** in 4% yield and **10** in 2% yield. Compound **9** was confirmed by single-crystal X-ray analysis as the *trans, cis* piperidine in which the 2-substituent is equatorial, Fig. 2 and Fig. S3 in the ESI.† Compound **10** is presumed to be the fourth diastereomer, although there was insufficient material for a full

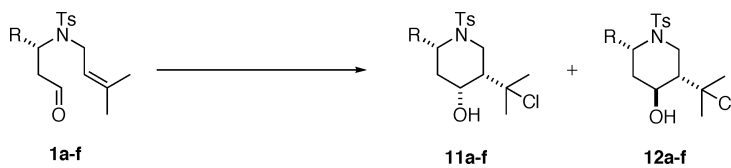
**Fig. 2** The two additional diastereomers isolated from cyclisation of **1f**.

structural analysis. The equatorial 2-substituent in **9** is interesting. Normally there is a very strong preference for the 2-substituent of *N*-tosyl and *N*-acyl piperidines to lie in an axial position to minimise the pseudo A<sup>1,3</sup> strain with the nitrogen substituent. It would appear that in this example the energetic penalty of placing both the phenyl and the isopropenyl groups axial is greater than the pseudo A<sup>1,3</sup> strain, meaning that this conformer is not observed for **9**.

The successful results achieved with concentrated hydrochloric acid led us to explore the cyclisation of **1a–f** in dichloromethane saturated with hydrogen chloride gas. Typically, hydrogen chloride gas was bubbled through a solution of the aldehyde in dichloromethane at –78 °C for 1 h and the reaction mixture was stirred for a further 4 h at –78 °C to complete the cyclisation. The reaction mixture was then stirred for 24 h at room temperature to ensure complete addition of HCl across the double bond in the product. The results are presented in Table 2.

The *cis/trans* selectivities are broadly in line with those obtained using concentrated hydrochloric acid, although the reactions are slightly less *cis* selective. Although the cyclisations were more rapid than those with concentrated hydrochloric acid, with starting material consumed within 2–4 h rather than 18 h, the reactions had to be left for around 24 h to get complete addition of HCl across the double bond, and it appeared that this prolonged contact with acid led to some equilibration to the *trans, trans* isomer. For example, cyclisation of **1b** to a mixture of alkenes and chlorides

**Scheme 6** Stereocontrol model for Brønsted acid-catalysed cyclisations.

**Table 2** Cyclisations of aldehydes **1a–f** in CH<sub>2</sub>Cl<sub>2</sub> saturated with HCl


| Entry | Aldehyde  | R                                  | <b>11</b> : <b>12</b> <sup>a</sup> | Yield (%) <sup>a</sup> |
|-------|-----------|------------------------------------|------------------------------------|------------------------|
| 1     | <b>1a</b> | Me                                 | 72 : 28                            | 55 (20)                |
| 2     | <b>1b</b> | Bn                                 | 88 : 12                            | 83 (11)                |
| 3     | <b>1c</b> | <sup>i</sup> Pr                    | 81 : 19                            | 68 (12)                |
| 4     | <b>1d</b> | –(CH <sub>2</sub> ) <sub>5</sub> – | 87 : 13                            | 65 (10)                |
| 5     | <b>1e</b> | <sup>t</sup> Bu                    | 46 : 54                            | 28 (36)                |
| 6     | <b>1f</b> | Ph                                 | 57 : 43 <sup>c</sup>               | 42 (34)                |

<sup>a</sup> Ratio was determined by integration of crude <sup>1</sup>H NMR spectra. <sup>b</sup> Isolated yield of major (minor) isomers after chromatography. <sup>c</sup> Traces of two other isomers were observed in the crude NMR spectra, but were not isolated—see main text.

was complete after 3 h with an overall *cis* : *trans* ratio of 93 : 7. After 24 h, conversion to the chlorides was complete, but the *cis* : *trans* ratio had dropped to 88 : 12.

Addition of HCl to the 4,5-*trans* alkenes was noticeably slower than addition to the 4,5-*cis* alkenes, supporting our assertion that overlap between the oxygen lone pair of the hydroxyl and the empty p-orbital of the cationic centre stabilises the 4,5-*cis* cation but not the 4,5-*trans* cation, in which such overlap is geometrically unfavourable.

Turning to the Lewis acid-catalysed reaction, aldehydes **1a–f** were treated with one equivalent of methylaluminium dichloride, which had been found to be the optimal Lewis acid in our earlier studies;<sup>5</sup> the results are summarised in Table 3.

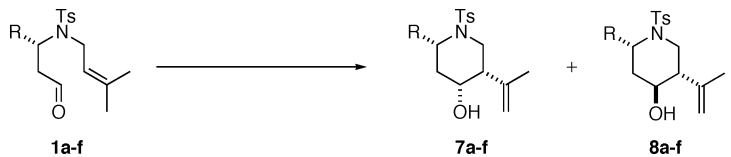
The stereoselectivities for the Lewis acid-catalysed cyclisation ranged from good to excellent (up to 99 : 1), with good overall yields (typically over 70% of the major isomer was isolated after chromatography). Generally 40–60 °C afforded the best

stereoselectivities, although in some cases, a small loss in stereoselectivity occurred on switching from dichloromethane at 40 °C to chloroform at 60 °C.

Under these Lewis acid conditions, equilibration to the thermodynamic *trans*, *trans* product is favoured to minimise the large 1,3-diaxial interactions that result in the transition state between the axial 2-substituent and the Lewis acid-coordinated oxygen, Scheme 7. This accounts for the increased preference for the *trans*, *trans* isomer as the 2-substituent becomes larger.

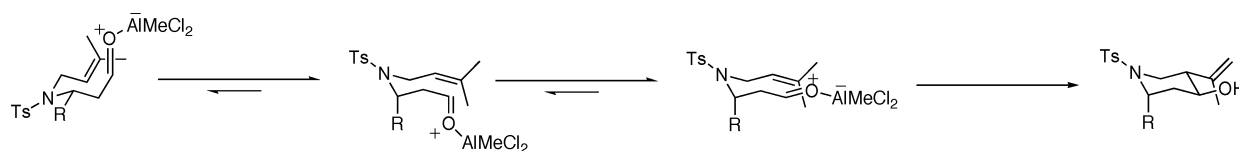
### Pipecolic acid derivatives

Pipecolic acid (piperidine 2-carboxylic acid) is an important non-proteinogenic amino acid and one of the constituents of a variety of natural products such as rapamycin and FK506. A variety of substituted pipecolic acids feature in natural products, as well as

**Table 3** Cyclisations of aldehydes **1a–f** with MeAlCl<sub>2</sub>


| Entry | Aldehyde  | R                                  | Temp/°C <sup>a</sup> | <b>7</b> : <b>8</b> <sup>b</sup> | Yield (%) <sup>c</sup> |
|-------|-----------|------------------------------------|----------------------|----------------------------------|------------------------|
| 1     | <b>1a</b> | Me                                 | 20                   | 12 : 88                          | 76 (5)                 |
| 2     | <b>1a</b> | Me                                 | 40                   | 7 : 93                           | 60 (4)                 |
| 3     | <b>1a</b> | Me                                 | 60                   | 4 : 96                           | 71 (4)                 |
| 4     | <b>1b</b> | Bn                                 | 20                   | 10 : 90                          | 61 (10)                |
| 5     | <b>1b</b> | Bn                                 | 40                   | 5 : 95                           | 64 (5)                 |
| 6     | <b>1b</b> | Bn                                 | 60                   | 9 : 91                           | 73 (9)                 |
| 7     | <b>1c</b> | <sup>i</sup> Pr                    | 20                   | 4 : 96                           | 74 (2)                 |
| 8     | <b>1c</b> | <sup>i</sup> Pr                    | 40                   | 2 : 98                           | 82 (2)                 |
| 9     | <b>1c</b> | <sup>i</sup> Pr                    | 60                   | 3 : 97                           | 83 (0)                 |
| 10    | <b>1d</b> | –(CH <sub>2</sub> ) <sub>5</sub> – | 20 <sup>d</sup>      | 3 : 97                           | 76 (3)                 |
| 11    | <b>1e</b> | <sup>t</sup> Bu                    | 60                   | 1 : 99                           | 88 (1)                 |
| 12    | <b>1f</b> | Ph                                 | 60                   | 2 : 98 <sup>e</sup>              | 80 (2)                 |

<sup>a</sup> Reactions were carried out in dichloromethane (20 °C and 40 °C) or chloroform (60 °C). <sup>b</sup> Ratio was determined by integration of crude <sup>1</sup>H NMR spectra. <sup>c</sup> Isolated yield of major (minor) isomers after chromatography. <sup>d</sup> Carrying out the reaction in refluxing chloroform resulted in very low yields of product. <sup>e</sup> Traces of two other isomers were observed—see main text.



Scheme 7 Stereocontrol model for Lewis acid-catalysed cyclisations.

in pharmaceuticals such as the HIV protease inhibitor Palinavir, and synthetic work in this area continues apace.<sup>14</sup> We believed that substituted pipercolic acids or their derivatives should be accessible using our chemistry, starting from the readily available amino acid homoserine.

*O*-*tert*-Butyldimethylsilylhomoserine methyl ester **13**, prepared in two steps from homoserine by the method of Kline *et al.*,<sup>15</sup> was *N*-tosylated and *N*-alkylated using prenyl bromide to give **14** in 80% overall yield (Scheme 8). Removal of the TBDMS group by pyridinium *p*-toluenesulfonate in methanol and subsequent Swern oxidation gave the aldehyde cyclisation precursor **1g** in near-quantitative yield.

Stirring **1g** at  $-78^{\circ}\text{C}$  in dichloromethane saturated with hydrogen chloride gas (Scheme 9) resulted in a completely stereoselective reaction and afforded a mixture of four products, all of which had the *cis, cis* stereochemistry: the expected carbonyl ene product **7g** and the HCl addition product **11g**, along with lactones **15** and **16**. None of the corresponding *trans* products was detected. In contrast, treating **1g** with one equivalent of  $\text{MeAlCl}_2$  at room temperature gave solely the lactone **15** in 79% yield after chromatography; the structure of **15** was confirmed by single crystal X-ray diffraction (Fig. S4, ESI†).

Although the two lactones **15** and **16** could be separated from the two esters **7g** and **11g**, these pairs of compounds were inseparable from one another, and so we attempted to convert the two mixtures entirely to the corresponding chlorides. Stirring the mixture of esters in dichloromethane saturated with hydrogen chloride gas resulted in complete HCl addition and partial lactonisation to afford a separable mixture of **11g** and **16** in roughly equal

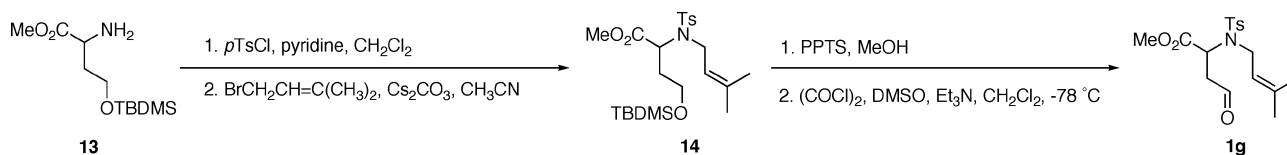
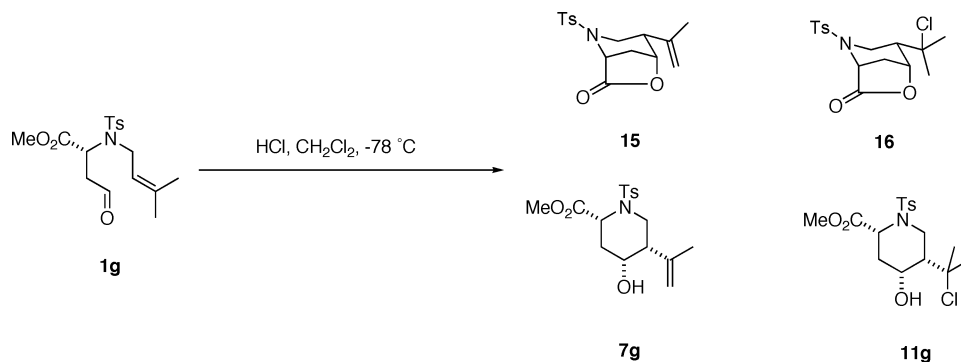
amounts, allowing us to confirm the structure of **11g** by X-ray diffraction (Fig. S5, ESI†). In contrast, lactone **15** proved to be completely unreactive towards HCl addition, so that an unchanged mixture of **15** and **16** was returned after stirring for two days in dichloromethane saturated with hydrogen chloride gas.

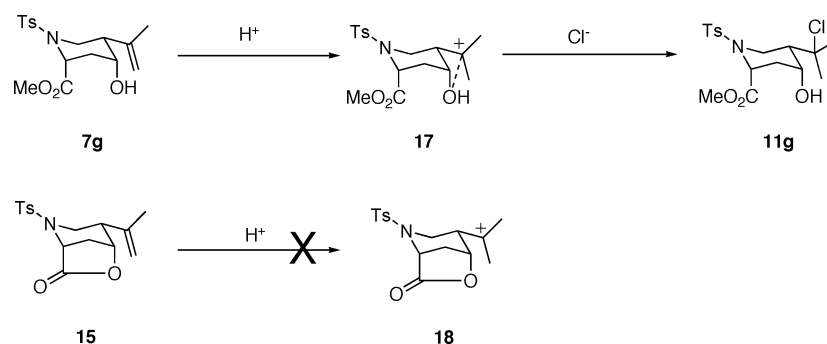
Given that alkene **7g** readily underwent HCl addition, and that chlorolactone **16** appeared to be completely stable, the failure of lactone **15** to add HCl is interesting. Addition of HCl to both compounds would be considered to proceed through a carbocation (Scheme 10).

In the case of **7g**, addition of HCl will proceed *via* cation **17**, in which the lone pair of the hydroxyl provides a stabilising interaction with the empty p-orbital. In contrast, the delocalised oxygen lone pair in **18** will have little, if any, overlap with the empty p-orbital, and it would appear that without this stabilisation, **18** does not form.

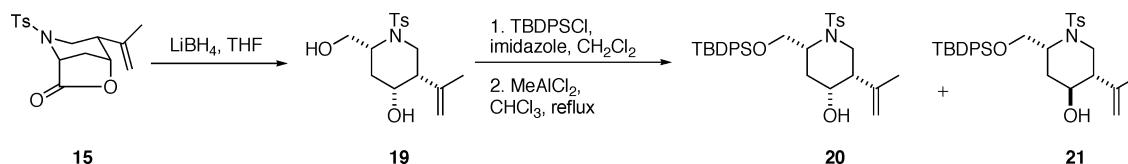
The facile lactonisation of **1g** on treatment with  $\text{MeAlCl}_2$  meant that isomerisation to the *trans, trans* isomer would not be possible under these conditions. Instead, lactone **15** was reduced to diol **19** by  $\text{LiBH}_4$ , but this proved resistant to isomerisation by  $\text{MeAlCl}_2$  in refluxing  $\text{CHCl}_3$ , presumably due to chelation of the Lewis acid by the two hydroxyl groups. Protection of the primary hydroxyl as a TBDPS ether overcame this problem, and treatment of the *cis, cis* silyl ether **20** with one equivalent of  $\text{MeAlCl}_2$  in refluxing  $\text{CHCl}_3$  afforded an 86 : 14 ratio of **21** : **20** after 1 h, from which **21** was isolated in 61% yield (Scheme 11). Longer reaction times resulted in a lower recovery of **21**, along with unidentified side-products.

The success of the cyclisations of the substrates containing a prenyl ene moiety led us to investigate the corresponding crotyl

Scheme 8 Preparation of cyclisation precursor **1g**.Scheme 9 Brønsted acid-catalysed cyclisation of **1g**.



Scheme 10 Proposed HCl addition pathway.

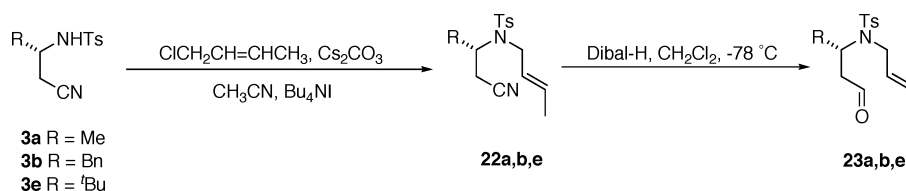


Scheme 11 Lactone opening and isomerisation.

compounds **23a,b,e**. These were prepared *via* nitriles **22a,b,e** (Scheme 12) using commercial crotyl chloride, which afforded the products as roughly 5 : 1 mixtures of *E* : *Z* isomers. In our earlier work on the synthesis of 3,4-disubstituted piperidines, we found that the geometry of the crotyl double bond did not influence the stereochemical outcome of the reaction, with both the *E* and *Z* crotyl compounds giving the *cis* piperidine on cyclisation with  $\text{MeAlCl}_2$  at room temperature.<sup>5</sup> Aldehydes **23a,b,e**, chosen to provide a range of steric demands at the 2-position, were treated

with three equivalents of  $\text{MeAlCl}_2$  in  $\text{CH}_2\text{Cl}_2$  at room temperature; the results are summarised in Table 4.

The major product was identified by NOE studies as the *trans*, *cis* piperidine **26**, and this was subsequently confirmed by X-ray diffraction in the case of **26b** (Fig. S6, ESI†). The other two products, formed in roughly equal amounts, were the *cis*, *cis* and *trans*, *trans* products **24** and **25**, respectively. Small amounts of the product of  $\beta$ -elimination **27** were also observed, as well as some trace products from dimerisation (*vide infra*).

Scheme 12 Preparation of crotyl cyclisation precursors **23a,b,e**.Table 4 Cyclisations of aldehydes **23a,b,e** with  $\text{MeAlCl}_2$ 

| Entry | Aldehyde   | R               | Temp/°C <sup>a</sup> | Time/h | <b>24</b> <sup>b</sup> | <b>25</b> <sup>b</sup> | <b>26</b> <sup>b</sup> |
|-------|------------|-----------------|----------------------|--------|------------------------|------------------------|------------------------|
| 1     | <b>23a</b> | Me              | −78                  | 16     | 10                     | 8                      | 22                     |
| 2     | <b>23a</b> | Me              | 20                   | 3      | 8                      | 11                     | 35                     |
| 3     | <b>23a</b> | Me              | 20                   | 16     | 12                     | 10                     | 33                     |
| 4     | <b>23a</b> | Me              | 20 <sup>c</sup>      | 22     | 8                      | 8                      | 25                     |
| 5     | <b>23a</b> | Me              | 40                   | 3      | 8                      | 11                     | 33                     |
| 6     | <b>23b</b> | Bn              | 20                   | 16     | 18                     | 16                     | 44                     |
| 7     | <b>23e</b> | <sup>t</sup> Bu | 20                   | 16     | 7                      | 27                     | 18                     |

<sup>a</sup> Reactions were carried out in dichloromethane with 3 equiv of  $\text{MeAlCl}_2$  unless otherwise stated. <sup>b</sup> Isolated yield after chromatography. <sup>c</sup> Reaction carried out with 1 equiv of  $\text{MeAlCl}_2$ .

It is interesting that the cyclisation of **23** should favour formation of the previously unobserved **26**. Assuming cyclisation *via* a cationic mechanism (although the arguments hold for a more concerted mechanism in which partial cationic character is generated), in intermediate **28** (leading to **24**) and intermediate **29** (leading to **26**) the hydroxyl can stabilise the carbocation (Fig. 3). However, in **29** the relatively sterically undemanding ethyl cation can adopt an axial disposition, allowing the *cis* relationship to be maintained with the Lewis acid-coordinated oxygen, which now lies in an equatorial position to avoid the 1,3-diaxial interaction with the 2-substituent.



Fig. 3 Stabilising interactions in intermediates **28** and **29**.

The product ratio was rather insensitive to reaction time, temperature and the amount of Lewis acid used. The three products were separated and re-subjected to  $\text{MeAlCl}_2$  at room temperature

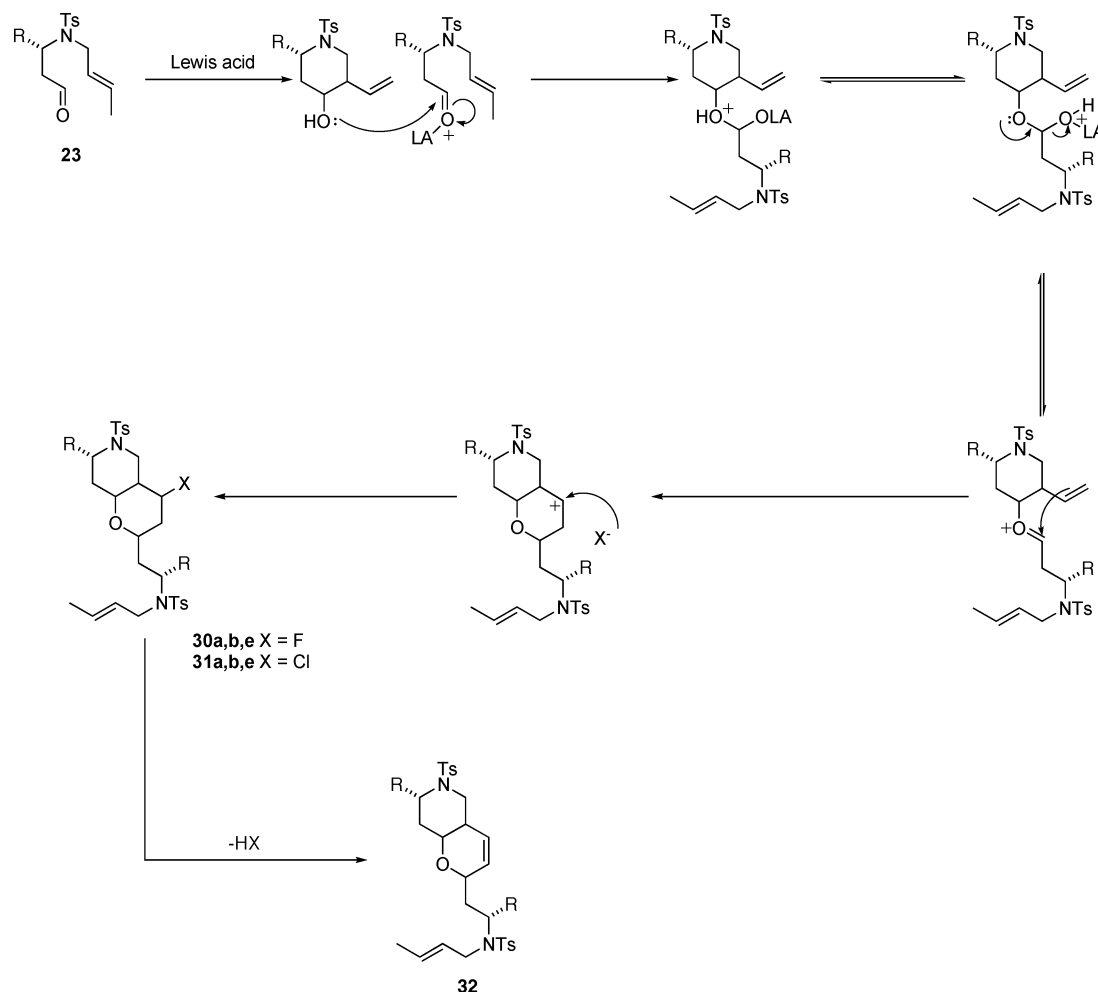
for four days; only in the case of **24** did any isomerisation occur, with small amounts of **25** (4%) and **26** (9%) produced, along with recovered starting material (60%) and decomposition products (accounting for the remaining mass).

The cyclisation of **23a,b,e** was also screened using the Lewis acids  $\text{AlCl}_3$ ,  $\text{Me}_2\text{AlCl}$ ,  $\text{TiCl}_4$ ,  $\text{SnCl}_4$ ,  $\text{Sc}(\text{OTf})_3$  and  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ .  $\text{Me}_2\text{AlCl}$  gave product ratios similar to  $\text{MeAlCl}_2$ , but the reactions were not as clean.  $\text{AlCl}_3$ ,  $\text{TiCl}_4$  and  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  gave rather less of the three piperidines **24–26** and led to the formation of significant amounts of dimerisation products **30–32** (Scheme 13), analogous to those isolated in our earlier work, which were identified by mass spectrometry.

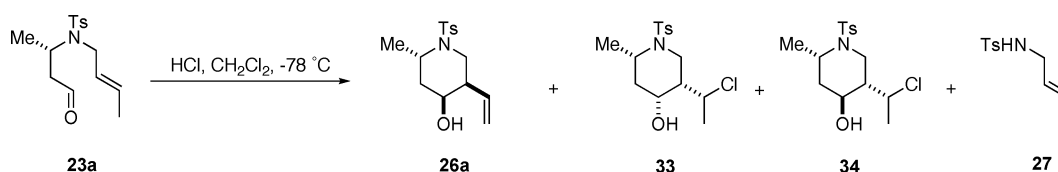
The attempted cyclisation of **23a** in dichloromethane saturated with hydrogen chloride gas (Scheme 14) gave chiefly the  $\beta$ -elimination product **27**, along with small amounts of three piperidines: **26a** and two chlorine-containing compounds, identified as **33** and **34**, both as mixtures of epimers at the carbon bearing the chlorine.

### Removal of the *p*-toluenesulfonyl protecting group

Removal of the *p*-toluenesulfonyl protecting group was carried out on a representative range of examples by stirring the *N*-tosylpiperidines with sodium naphthalenide in THF at  $-78^\circ\text{C}$



Scheme 13 Proposed route to dimerisation products.

Scheme 14 Cyclisation of **23a** in  $\text{CH}_2\text{Cl}_2$  saturated with HCl.

(Scheme 15). The yields were good to excellent in most cases, with some loss of material noted for the alanine derivatives **35a** and **36a** due to their significant polarity and water solubility.

## Conclusion

In summary, we have discovered a diastereoselective synthesis of *cis*, *cis* and *trans*, *trans* 2,4,5-trisubstituted piperidines from simple acyclic precursors. Cyclisation catalysed by HCl at low temperature affords predominantly the kinetic *cis*, *cis* product resulting from the preferred axial disposition of the 2- and 4-substituents. The 2-substituent adopts an axial orientation to minimise pseudo  $\text{A}^{1,3}$  strain with the *N*-tosyl group, while the axial 4-hydroxyl group is able to provide a stabilising interaction with the carbocationic centre attached to the 5-position. The diastereoselectivity of the reaction is good for small and medium sized 2-substituents, although an unfavourable 1,3-diaxial interaction with the 4-hydroxyl results in a loss of stereoselectivity for larger 2-substituents. Cyclisation catalysed by  $\text{MeAlCl}_2$  at 20–60 °C affords the thermodynamically more stable *trans*, *trans* isomer with good to excellent diastereoselectivity. The method should find application in the synthesis of more complex molecules.

## Experimental section

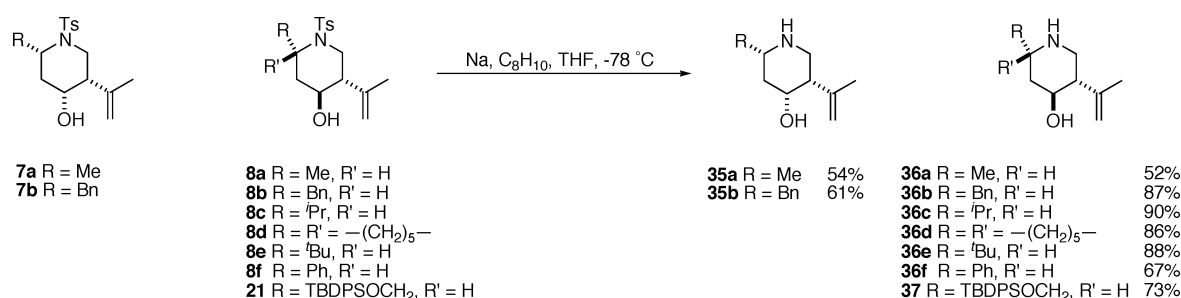
### Typical procedure for tosylation: (2*S*)-*O*-(*p*-toluenesulfonyl)-*N*-(*p*-toluenesulfonyl)phenylalaninol

To a solution of *p*-toluenesulfonyl chloride (19.43 g, 101.99 mmol) and pyridine (26.2 mL, 324.50 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 mL) at 0 °C was added a solution of (*S*)-phenylalaninol (7.00 g, 46.36 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 mL). The resulting solution was warmed to ambient temperature and stirred until the reaction was judged to be complete by TLC analysis (*ca.* 24 h). The reaction mixture was poured into a separating funnel containing cold aqueous HCl (1 M, 60 mL) and  $\text{CH}_2\text{Cl}_2$ . The organic phase was separated

and the aqueous phase re-extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were washed with aqueous  $\text{CuSO}_4$ , brine, dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to give the crude product as a solid. Purification by flash column chromatography (silica; eluent 1 : 2 EtOAc–petroleum ether,  $R_f$  = 0.36) afforded the *title compound* as a white powder (15.93 g, 75%); mp 96–98 °C (from EtOAc–petroleum ether);  $[\alpha]_D^{23}$  –42.7 (*c* 1.0 in  $\text{CHCl}_3$ ); (Found: C, 60.19; H, 5.49; N, 2.99.  $\text{C}_{23}\text{H}_{25}\text{NO}_5\text{S}_2$  requires C, 60.11; H, 5.48; N, 3.05%);  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  3290 (NH), 3067 (CH aromatic), 2953 ( $\nu_{\text{as}}$   $\text{CH}_2$ ), 2892 ( $\nu_{\text{s}}$   $\text{CH}_2$ ), 1598 (C=C aromatic), 1495 (C=C aromatic), 1456 (C=C aromatic), 1160 ( $\nu_{\text{s}}$   $\text{SO}_2$ );  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 2.40 (3H, s, Ph- $\text{CH}_3$ ), 2.46 (3H, s, Ph- $\text{CH}_3$ ), 2.65 (1H, dd, *J* 13.9 and 7.2, Ph-CHH), 2.80 (1H, dd, *J* 13.9 and 7.4, Ph-CHH), 3.52–3.60 (1H, m, CH), 3.84 (1H, dd, *J* 10.1 and 5.3, CHH-OPh), 3.97 (1H, dd, *J* 10.1 and 3.5, CHH-OPh), 4.71 (1H, d, *J* 7.7, NH), 6.86 (2H, d, *J* 7.2, Ar CH), 7.11–7.18 (5H, m, Ar CH), 7.35 (2H, d, *J* 8.5, Ar CH), 7.51 (2H, d, *J* 8.1, Ar CH), 7.75 (2H, d, *J* 8.1, Ar CH);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 21.6 (Ph- $\text{CH}_3$ ), 21.8 (Ph- $\text{CH}_3$ ), 37.7 (Ph- $\text{CH}_2$ ), 53.7 (CH), 70.3 ( $\text{CH}_2$ -OPh), 127.0 (Ar CH), 128.1 (Ar CH), 128.8 (Ar CH), 129.2 (Ar CH), 129.8 (Ar CH), 130.1 (Ar CH), 132.4 ( $\text{C}_q$ ), 135.8 ( $\text{C}_q$ ), 136.9 ( $\text{C}_q$ ), 143.6 ( $\text{C}_q$ ), 145.3 ( $\text{C}_q$ ); *m/z* ( $\text{ES}^+$ ) 482.1 (100%,  $[\text{M} + \text{Na}]^+$ ), 310.1 (85) [HRMS Found: ( $\text{M} + \text{Na})^+$  482.1060.  $\text{C}_{23}\text{H}_{25}\text{NNaO}_5\text{S}_2$  requires *M*, 482.1072].

### Typical procedure for preparation of nitriles: (3*S*)-(*p*-toluenesulfonyl)amino-4-phenylbutyronitrile (**3b**)

To a suspension of NaCN (2.24 g, 45.70 mmol) in DMF (90 mL) was added a solution of (2*S*)-*O*-(*p*-toluenesulfonyl)-*N*-(*p*-toluenesulfonyl)phenylalaninol (7.00 g, 15.25 mmol) in DMF (60 mL), and stirring was continued until the reaction was judged to be complete by TLC analysis (24 h). The reaction mixture was diluted with water and extracted with  $\text{Et}_2\text{O}$ . The combined organic phases were washed with water, brine, dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to give nitrile **3b** as colourless crystals (4.32 g, 90%), which were used without further purification:

Scheme 15 Removal of the *p*-toluenesulfonyl protecting group.

$R_f = 0.38$  (silica; eluent 2 : 1 toluene–diethyl ether); mp 82–84 °C (from toluene–diethyl ether) (lit.<sup>16</sup> oil);  $[a]_D^{23} -65.5$  ( $c$  1.0 in  $\text{CHCl}_3$ ) (lit.<sup>16</sup>  $[a]_D -58.6$  ( $c$  4.0 in  $\text{CHCl}_3$ )); (Found: C, 64.79; H, 5.84; N, 8.81.  $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$  requires C, 64.94; H, 5.77; N, 8.91%);  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  3350 (NH), 2920 ( $\nu_{\text{as}} \text{CH}_2$ ), 2850 ( $\nu_{\text{s}} \text{CH}_2$ ), 2246 (CN), 1597 (C=C aromatic), 1380 ( $\nu_{\text{as}} \text{SO}_2$ ), 1160 ( $\nu_{\text{s}} \text{SO}_2$ );  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 2.42 (3H, s, Ph- $\text{CH}_3$ ), 2.56 (1H, dd,  $J$  16.8 and 3.9, CHH-CN), 2.67 (1H, dd,  $J$  16.8 and 6.3, CHH-CN), 2.77 (1H, dd,  $J$  14.0 and 7.7, Ph-CHH), 2.90 (1H, dd,  $J$  14.0 and 7.0, Ph-CHH), 3.58–3.69 (1H, m, CH), 4.85 (1H, d,  $J$  7.0, NH), 6.99 (2H, m, Ar CH), 7.20–7.22 (5H, m, Ar CH), 7.55 (2H, d,  $J$  8.1, Ar CH);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 21.6 (Ph- $\text{CH}_3$ ), 24.3 ( $\text{CH}_2$ -CN), 39.9 (Ph- $\text{CH}_2$ ), 51.5 (CH), 116.9 (CN), 127.0 (2  $\times$  Ar CH), 127.4 (Ar CH), 129.0 (2  $\times$  Ar CH), 129.1 (2  $\times$  Ar CH), 129.9 (2  $\times$  Ar CH), 135.3 ( $\text{C}_q$ ), 136.6 ( $\text{C}_q$ ), 143.8 ( $\text{C}_q$ );  $m/z$  ( $\text{ES}^+$ ) 337.1 (100%,  $[\text{M} + \text{Na}]^+$ ) [HRMS Found:  $(\text{M} + \text{Na})^+$  337.0993.  $\text{C}_{17}\text{H}_{18}\text{N}_2\text{NaO}_2\text{S}$  requires  $M$ , 337.0987].

#### Typical procedure for nitrile hydrolysis: (3S)-(p-toluenesulfonyl)-amino-4-phenylbutyric acid (4b)

A mixture of nitrile **3b** (1.01 g, 3.2 mmol), glacial acetic acid (3.2 mL), water (3.2 mL) and concentrated sulfuric acid (3.2 mL) was stirred at 110 °C overnight under a reflux condenser. After cooling, the reaction mixture was diluted with water and the aqueous phase extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were washed with brine, dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to afford the crude acid. Purification by flash column chromatography (silica; eluent 1 : 1 petroleum ether–ethyl acetate,  $R_f = 0.33$ ) afforded acid **4b** as a grey powder (0.87 g, 81%); mp 63–65 °C (from petroleum ether–EtOAc) (lit.<sup>17</sup> 85 °C (from petroleum ether–EtOAc));  $[a]_D^{20} -21.2$  ( $c$  1.0 in  $\text{CHCl}_3$ ) (lit.<sup>18</sup>  $[a]_D^{23} -14.6$  ( $c$  0.9 in  $\text{CH}_2\text{Cl}_2$ )); (Found: C, 61.16; H, 5.84; N, 4.01.  $\text{C}_{17}\text{H}_{19}\text{NO}_4\text{S}$  requires C, 61.24; H, 5.74; N, 4.20%);  $\nu_{\text{max}}$  (KBr)/ $\text{cm}^{-1}$  3500 (OH), 3280 (NH), 2926 ( $\nu_{\text{as}} \text{CH}_2$ ), 2875 ( $\nu_{\text{s}} \text{CH}_2$ ), 1712 (C=O), 1599 (C=C aromatic), 1496 (C=C aromatic), 1454 (C=C aromatic), 1325 ( $\nu_{\text{as}} \text{SO}_2$ ), 1157 ( $\nu_{\text{s}} \text{SO}_2$ );  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 2.40 (3H, s, Ph- $\text{CH}_3$ ), 2.54 (2H, d,  $J$  5.2,  $\text{CH}_2$ -COOH), 2.78 (1H, dd,  $J$  13.6 and 7.0, Ph-CHH), 2.87 (1H, dd,  $J$  13.6 and 7.7, Ph-CHH), 3.70–3.81 (1H, m, CH), 5.59 (1H, br d,  $J$  5.9, NH), 7.01–7.03 (2H, m, Ar CH), 7.19–7.23 (5H, m, Ar CH), 7.62 (2H, d,  $J$  8.6, Ar CH);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 21.7 (Ph- $\text{CH}_3$ ), 37.8 ( $\text{CH}_2$ -COOH), 40.7 (Ph- $\text{CH}_2$ ), 51.8 (CH), 127.0 (Ar CH), 127.1 (2  $\times$  Ar CH), 128.9 (2  $\times$  Ar CH), 129.4 (2  $\times$  Ar CH), 129.8 (2  $\times$  Ar CH), 136.8 ( $\text{C}_q$ ), 137.4 ( $\text{C}_q$ ), 143.6 ( $\text{C}_q$ ), 175.9 (COOH);  $m/z$  ( $\text{EI}^+$ ) 334 (9%,  $[\text{M} + \text{H}]^+$ ), 242 (52), 155 (38), 91 (100) [HRMS Found:  $(\text{M} + \text{H})^+$  334.1110.  $\text{C}_{17}\text{H}_{20}\text{NO}_4\text{S}$  requires  $M$ , 334.1113].

#### Typical procedure for alkylation of the acid: 3-methylbut-2-enyl (3S)-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonyl)amino]-4-phenylbutanoate

Caesium carbonate (1.70 g, 5.2 mmol) was added to a solution of acid **4b** (0.87 g, 2.6 mmol) in acetonitrile (110 mL). The reaction mixture was stirred at ambient temperature for 30 min before 1-bromo-3-methylbut-2-ene (0.60 mL, 5.2 mmol) was added and stirring was continued until the reaction was judged to be complete

by TLC analysis (12 h). The solvent was removed *in vacuo* to give a white solid, which was partitioned between water and  $\text{Et}_2\text{O}$  (4  $\times$  100 mL). The combined organic phases were washed with water and brine, dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography (silica; eluent 5 : 1 hexane–EtOAc,  $R_f = 0.3$ ) afforded the *title compound* as a colourless oil (1.02 g, 83%);  $[a]_D^{21} -6.7$  ( $c$  1.0 in  $\text{CHCl}_3$ ); (Found: C, 69.00; H, 7.44; N, 2.92.  $\text{C}_{27}\text{H}_{35}\text{NO}_4\text{S}$  requires C, 69.05; H, 7.51; N, 2.98%);  $\nu_{\text{max}}$  (film)/ $\text{cm}^{-1}$  3028 (=CH), 2971 ( $\nu_{\text{as}} \text{CH}_3$ ), 2929 ( $\nu_{\text{as}} \text{CH}_2$ ), 1731 (C=O), 1675 (C=C aliphatic), 1600 (C=C aromatic), 1496 (C=C aromatic), 1453 (C=C aromatic), 1338 ( $\nu_{\text{as}} \text{SO}_2$ ), 1155 ( $\nu_{\text{s}} \text{SO}_2$ );  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 1.64 (9H, s, 3  $\times$  C=C( $\text{CH}_3$ )<sub>2</sub>), 1.72 (3H, s, C=C( $\text{CH}_3$ )<sub>2</sub>), 2.38 (3H, s, Ph- $\text{CH}_3$ ), 2.52 (1H, dd,  $J$  15.8 and 6.6, CHH-COO), 2.71 (1H, dd,  $J$  15.8 and 7.7, CHH-COO), 2.87 (1H, dd,  $J$  13.6 and 8.1, Ph-CHH), 2.97 (1H, dd,  $J$  13.6 and 6.6, Ph-CHH), 3.81 (2H, d,  $J$  6.8, N- $\text{CH}_2$ ), 4.35–4.38 (1H, m, N-CH), 4.41 (2H, d,  $J$  7.3, O- $\text{CH}_2$ ), 5.08 (1H, t,  $J$  6.8, N- $\text{CH}_2$ -CH), 5.24 (1H, t,  $J$  7.3, O- $\text{CH}_2$ -CH), 7.12–7.27 (7H, m, Ar CH), 7.59 (2H, d,  $J$  8.1, Ar CH);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 17.9 (C=C( $\text{CH}_3$ )<sub>2</sub>), 18.1 (C=C( $\text{CH}_3$ )<sub>2</sub>), 21.6 (Ph- $\text{CH}_3$ ), 25.8 (C=C( $\text{CH}_3$ )<sub>2</sub>), 25.9 (C=C( $\text{CH}_3$ )<sub>2</sub>), 38.4 ( $\text{CH}_2$ -COO), 40.8 (Ph- $\text{CH}_2$ ), 44.0 (N- $\text{CH}_2$ ), 57.5 (Ph- $\text{CH}_2$ -CH), 61.7 ( $\text{CH}_2$ -O-CO), 118.6 (O- $\text{CH}_2$ -CH), 121.5 (N- $\text{CH}_2$ -CH), 126.7 (Ar CH), 127.5 (2  $\times$  Ar CH), 128.6 (2  $\times$  Ar CH), 129.41 (2  $\times$  Ar CH), 129.45 (2  $\times$  Ar CH), 135.4 ( $\text{C}_q$ ), 138.2 ( $\text{C}_q$ ), 138.5 ( $\text{C}_q$ ), 139.1 ( $\text{C}_q$ ), 142.9 ( $\text{C}_q$ ), 171.2 (C=O);  $m/z$  ( $\text{ES}^+$ ) 492.3 (100%,  $[\text{M} + \text{Na}]^+$ ) [HRMS Found:  $(\text{M} + \text{Na})^+$  492.2169.  $\text{C}_{27}\text{H}_{35}\text{NNaO}_4\text{S}$  requires 492.2185].

#### Typical procedure for reduction of the ester: (3S)-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonyl)amino]-4-phenylbutanol (6b)

To a solution of 3-methylbut-2-enyl (3S)-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonyl)amino]-4-phenylbutanoate (0.34 g, 0.72 mmol) in THF (1.6 mL) at 0 °C was added  $\text{LiAlH}_4$  (1.0 M in  $\text{Et}_2\text{O}$ , 0.59 mL, 0.59 mmol) dropwise. The ice bath was removed and stirring continued for 3 h. After cooling to 0 °C, the reaction mixture was carefully acidified with 2 M aqueous HCl and the aqueous phase extracted with EtOAc. The combined organic phases were washed with brine, dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to afford the crude alcohol. Purification by flash column chromatography (silica; eluent 2 : 1 petroleum ether–EtOAc,  $R_f = 0.32$ ) afforded alcohol **6b** as a colourless oil (0.22 g, 78%);  $[a]_D^{23} -43$  ( $c$  1.0 in  $\text{CHCl}_3$ ); (Found: C, 68.19; H, 7.31; N, 3.62.  $\text{C}_{22}\text{H}_{29}\text{NO}_3\text{S}$  requires C, 68.18; H, 7.54; N, 3.61%);  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3436 (OH), 2928 ( $\nu_{\text{as}} \text{CH}_2$ ), 1651 (C=C aliphatic), 1599 (C=C aromatic), 1495 (C=C aromatic), 1454 (C=C aromatic), 1331 ( $\nu_{\text{as}} \text{SO}_2$ ), 1153 ( $\nu_{\text{s}} \text{SO}_2$ ), 1050 (C–O);  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 1.57 (1H, tt,  $J$  12.9 and 3.3, CHH- $\text{CH}_2$ -OH), 1.65–1.72 (7H, stack, C=C( $\text{CH}_3$ )<sub>2</sub> and CHH- $\text{CH}_2$ -OH), 2.41 (3H, s, Ph- $\text{CH}_3$ ), 2.50–2.63 (2H, m, Ph- $\text{CH}_2$ ), 3.55 (1H, ddd,  $J$  11.7, 4.8 and 3.3, CHH-OH), 3.78 (1H, td,  $J$  11.7 and 3.3, CHH-OH), 3.83 (1H, dd,  $J$  16.2 and 5.5, N-CHH), 3.94 (1H, dd,  $J$  16.2 and 8.1, N-CHH), 4.14–4.24 (1H, m, N-CH), 5.17 (1H, t,  $J$  6.5, CH=C), 6.95–7.0 (2H, m, Ar CH), 7.18–7.23 (5H, m, Ar CH), 7.61 (2H, d,  $J$  8.1, Ar CH);  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 17.9 (=C- $\text{CH}_3$ ), 21.5 (Ph- $\text{CH}_3$ ), 25.7 (=C- $\text{CH}_3$ ), 34.6 ( $\text{CH}_2$ - $\text{CH}_2$ -OH), 40.1 (Ph- $\text{CH}_2$ ), 41.6 (N- $\text{CH}_2$ ), 56.4 (N-CH), 58.4 ( $\text{CH}_2$ -OH), 121.6 (CH=C), 126.5 (Ar CH), 127.1 (2  $\times$  Ar CH), 128.6 (2  $\times$  Ar CH), 129.1 (2  $\times$  Ar CH), 129.6 (2  $\times$  Ar CH),

134.9 ( $\text{CH}=\text{C}(\text{CH}_3)_2$ ), 137.9 ( $C_q$ ), 138.1 ( $C_q$ ), 143.2 ( $C_q$ );  $m/z$  ( $\text{ES}^+$ ) 410 (100%,  $[\text{M} + \text{Na}]^+$ ) [HRMS Found:  $(\text{M} + \text{Na})^+$  410.1761.  $\text{C}_{22}\text{H}_{29}\text{NNaO}_3\text{S}$  requires  $M$ , 410.1766].

**Typical procedure for alkylation of the nitrile: (3S)-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonyl)amino]-4-phenylbutyronitrile**

Caesium carbonate (0.23 g, 0.70 mmol) was added to a solution of nitrile **3b** (0.20 g, 0.64 mmol) in  $\text{CH}_3\text{CN}$  (15 mL). The reaction mixture was stirred at ambient temperature for 30 min before 1-bromo-3-methylbut-2-ene (74  $\mu\text{L}$ , 0.64 mmol) was added. The resulting mixture was stirred until the reaction was judged to be complete by TLC analysis (12 h), before the solvent was removed *in vacuo*. The resulting solid was partitioned between water and  $\text{Et}_2\text{O}$ . The combined organic phases were washed with water ( $2 \times 50$  mL), brine (50 mL), dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to afford the crude alkylated product. Purification by flash column chromatography (silica; eluent 5 : 1 hexane– $\text{EtOAc}$ ,  $R_f$  = 0.24) afforded the *title compound* as a yellow powder (0.20 g, 82%): mp 65–67 °C (from hexane– $\text{EtOAc}$ );  $[\alpha]_D^{25}$  –24.6 ( $c$  0.5 in  $\text{CHCl}_3$ ); (Found: C, 68.91; H, 6.80; N, 7.27.  $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_2\text{S}$  requires C, 69.08; H, 6.85; N, 7.32%);  $\nu_{\text{max}}$  (film)/ $\text{cm}^{-1}$  3029 ( $=\text{CH}$  aliphatic), 2927 ( $\nu_{\text{as}} \text{CH}_2$ ), 2249 (CN), 1599 ( $\text{C}=\text{C}$  aromatic), 1496 ( $\text{C}=\text{C}$  aromatic), 1454 ( $\text{C}=\text{C}$  aromatic), 1379 ( $\delta_s \text{CH}_3$ ), 1340 ( $\nu_{\text{as}} \text{SO}_2$ ), 1157 ( $\nu_s \text{SO}_2$ ), 1092 (C–N);  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 1.67 (3H, s,  $=\text{C}-\text{CH}_3$ ), 1.70 (3H, s,  $=\text{C}-\text{CH}_3$ ), 2.41 (3H, s,  $\text{Ph}-\text{CH}_3$ ), 2.52 (1H, dd,  $J$  16.9 and 5.5,  $\text{CHH}-\text{CN}$ ), 2.83 (1H, dd,  $J$  16.9 and 8.5,  $\text{CHH}-\text{CN}$ ), 2.94–3.08 (2H, m,  $\text{Ph}-\text{CH}_2$ ), 3.85 (2H, br d,  $J$  6.8,  $\text{N}-\text{CH}_2$ ), 4.10–4.20 (1H, m,  $\text{N}-\text{CH}$ ), 5.10 (1H, br t,  $J$  6.8,  $=\text{CH}$ ), 7.10–7.14 (2H, m,  $\text{Ar CH}$ ), 7.23–7.30 (7H, m,  $\text{Ar CH}$ ), 7.66 (2H, d,  $J$  8.1,  $\text{Ar CH}$ );  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 18.0 ( $=\text{C}-\text{CH}_3$ ), 21.6 ( $\text{Ph}-\text{CH}_3$ ), 22.2 ( $\text{CH}_2-\text{CN}$ ), 25.9 ( $=\text{C}-\text{CH}_3$ ), 39.6 ( $\text{Ph}-\text{CH}_2$ ), 43.8 ( $\text{N}-\text{CH}_2$ ), 56.9 ( $\text{N}-\text{CH}$ ), 117.8 (CN), 120.6 ( $=\text{CH}$ ), 127.3 ( $\text{Ar CH}$ ), 127.5 ( $2 \times \text{Ar CH}$ ), 129.0 ( $2 \times \text{Ar CH}$ ), 129.1 ( $2 \times \text{Ar CH}$ ), 129.8 ( $2 \times \text{Ar CH}$ ), 136.6 ( $C_q$ ), 136.9 ( $C_q$ ), 137.5 ( $C_q$ ), 143.7 ( $C_q$ );  $m/z$  ( $\text{ES}^+$ ) 405.4 (100%,  $[\text{M} + \text{Na}]^+$ ) [HRMS Found:  $(\text{M} + \text{Na})^+$  405.1611.  $\text{C}_{22}\text{H}_{26}\text{N}_2\text{NaO}_2\text{S}$  requires  $M$ , 405.1613].

**Typical procedure for oxidation of the alcohol: (3S)-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonyl)amino]-4-phenylbutanal (1b)**

Distilled DMSO (88  $\mu\text{L}$ , 1.24 mmol) was added dropwise at a rapid rate to a solution of oxalyl chloride (54  $\mu\text{L}$ , 0.62 mmol) in  $\text{CH}_2\text{Cl}_2$  (8 mL) at –60 °C. After 5 min a solution of alcohol **6b** (0.20 g, 0.52 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) was added dropwise. The mixture was stirred for another 20 min before dry  $\text{Et}_3\text{N}$  (362  $\mu\text{L}$ , 2.59 mmol) was added dropwise and then the solution was stirred for a further 3 h at –60 °C. The mixture was allowed to warm to room temperature before addition of water (25 mL). The aqueous phase was separated and extracted with  $\text{CH}_2\text{Cl}_2$  ( $4 \times 25$  mL). The combined organic phases were washed with aqueous HCl (1 M, 50 mL), water (50 mL), brine (50 mL), dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to afford aldehyde **1b** as a colourless oil (0.20 g, 100%), which was used without further purification:  $[\alpha]_D^{20}$  –20 ( $c$  0.5 in  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3028 ( $=\text{CH}$  aliphatic), 2965 ( $\nu_{\text{as}} \text{CH}_3$ ), 2925 ( $\nu_{\text{as}} \text{CH}_2$ ), 2863 ( $\nu_s \text{CH}_3$ ), 1724 (CHO), 1599 ( $\text{C}=\text{C}$  aromatic), 1495 ( $\text{C}=\text{C}$  aromatic), 1454 ( $\text{C}=\text{C}$  aromatic), 1337 ( $\nu_{\text{as}} \text{SO}_2$ ), 1156 ( $\nu_s \text{SO}_2$ );  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 1.69 (6H, s,  $\text{C}(\text{CH}_3)_2$ ),

2.40 (3H, s,  $\text{Ph}-\text{CH}_3$ ), 2.52 (1H, dd,  $J$  17.1 and 5.7,  $\text{CHH}-\text{CHO}$ ), 2.71–2.80 (2H, stack,  $\text{Ph}-\text{CHH}$  and  $\text{CHH}-\text{CHO}$ ), 2.89 (1H, dd,  $J$  13.6 and 5.9,  $\text{Ph}-\text{CHH}$ ), 3.84 (2H, d,  $J$  6.6,  $\text{N}-\text{CH}_2$ ), 4.43–4.53 (1H, m,  $\text{N}-\text{CH}$ ), 5.08 (1H, t,  $J$  6.6,  $=\text{CH}$ ), 7.08–7.11 (2H, m,  $\text{Ar CH}$ ), 7.12–7.29 (5H, m,  $\text{Ar CH}$ ), 7.62 (2H, d,  $J$  8.5,  $\text{Ar CH}$ ), 9.44 (1H, s, CHO);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 18.0 ( $=\text{C}-\text{CH}_3$ ), 21.6 ( $\text{Ph}-\text{CH}_3$ ), 25.8 ( $=\text{C}-\text{CH}_3$ ), 40.6 ( $\text{Ph}-\text{CH}_2$ ), 43.5 ( $\text{N}-\text{CH}_2$ ), 46.7 ( $\text{CH}_2-\text{CHO}$ ), 55.3 ( $\text{N}-\text{CH}$ ), 121.2 ( $\text{CH}=\text{C}$ ), 126.9 ( $\text{Ar CH}$ ), 127.3 ( $2 \times \text{Ar CH}$ ), 128.8 ( $2 \times \text{Ar CH}$ ), 129.3 ( $2 \times \text{Ar CH}$ ), 129.7 ( $2 \times \text{Ar CH}$ ), 135.8 ( $C_q$ ), 137.7 ( $C_q$ ), 138.1 ( $C_q$ ), 143.3 ( $C_q$ ), 200.2 (CHO);  $m/z$  ( $\text{ES}^+$ ) 408.0 (100%,  $[\text{M} + \text{Na}]^+$ ), 274.0 (17) [HRMS Found:  $(\text{M} + \text{Na})^+$  408.1622.  $\text{C}_{22}\text{H}_{27}\text{NNaO}_3\text{S}$  requires  $M$ , 408.1609].

**Typical procedure for reduction of the nitrile: (3S)-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonyl)amino]-4-phenylbutanal (1b)**

To a solution of (3S)-[N-(3-methylbut-2-enyl)-N-(p-toluenesulfonyl)amino]-4-phenylbutyronitrile (0.31 g, 0.80 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) at –78 °C was added dropwise a solution of DIBAL-H (1.0 M in toluene, 960  $\mu\text{L}$ , 0.96 mmol). The mixture was stirred for 3 h, after which it was quenched by addition of MeOH (1 mL). The reaction mixture was allowed to warm to room temperature and then poured into ice-cold aqueous sulfuric acid (1 M, 2.5 mL) and stirred vigorously. The aqueous phase was separated and extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were washed with brine, dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to afford aldehyde **1b** (0.31 g, 100%) as a colourless oil, which was used without further purification. Data as above.

**Typical procedure for Lewis acid-catalysed cyclisation: (2S,4S,5S)-2-benzyl-4-hydroxy-5-isopropenyl-1-(p-toluenesulfonyl)piperidine (8b)**

To a solution of aldehyde **1b** (100 mg, 0.26 mmol) in  $\text{CHCl}_3$  (10 mL) was added methylaluminium dichloride (1.0 M in hexane, 260  $\mu\text{L}$ , 0.26 mmol). The solution was stirred overnight at reflux, after which it was quenched by addition of water and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were washed with brine, dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to afford the crude piperidine. Purification by flash column chromatography (silica; eluent 1 : 2  $\text{EtOAc}$ –hexane,  $R_f$  = 0.19) afforded piperidine **8b** as a colourless oil (73 mg, 73%);  $[\alpha]_D^{27}$  –16.1 ( $c$  0.18 in  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film)/ $\text{cm}^{-1}$  3498 (OH), 3058 ( $\nu_{\text{as}} =\text{CH}_2$ ), 2925 ( $\nu_{\text{as}} \text{CH}_2$ ), 2855 ( $\nu_s \text{CH}_2$ ), 1644 ( $\text{C}=\text{C}$  aliphatic), 1599 ( $\text{C}=\text{C}$  aromatic), 1495 ( $\text{C}=\text{C}$  aromatic), 1454 ( $\text{C}=\text{C}$  aromatic), 1378 ( $\delta_s \text{CH}_3$ ), 1337 ( $\nu_{\text{as}} \text{SO}_2$ ), 1155 ( $\nu_s \text{SO}_2$ ), 1087 (C–O);  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 1.30–1.40 (1H, m,  $\text{N}-\text{CH}-\text{CHH}$ ), 1.77 (3H, s,  $=\text{C}-\text{CH}_3$ ), 1.88–2.02 (2H, stack,  $\text{N}-\text{CH}-\text{CHH}$  and  $\text{N}-\text{CH}_2-\text{CH}$ ), 2.08 (1H, br s, OH), 2.40 (3H, s,  $\text{Ph}-\text{CH}_3$ ), 2.80–2.83 (2H, m,  $\text{Ph}-\text{CH}_2$ ), 2.99 (1H, dd,  $J$  14.3 and 11.7,  $\text{N}-\text{CHH}$ ), 3.82 (1H, dd,  $J$  14.3 and 4.1,  $\text{N}-\text{CHH}$ ), 3.95 (1H, td,  $J$  10.8 and 4.4,  $\text{CH}-\text{OH}$ ), 4.40–4.47 (1H, m,  $\text{N}-\text{CH}$ ), 4.90 (1H, s,  $=\text{CHH}$ ), 5.03 (1H, s,  $=\text{CHH}$ ), 7.14–7.31 (7H, m,  $\text{Ar CH}$ ), 7.56 (2H, d,  $J$  8.5,  $\text{Ar CH}$ );  $\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 20.3 ( $=\text{C}-\text{CH}_3$ ), 21.3 ( $\text{Ph}-\text{CH}_3$ ), 34.1 ( $\text{N}-\text{CH}-\text{CH}_2-\text{CH}$ ), 37.9 ( $\text{Ph}-\text{CH}_2$ ), 44.2 ( $\text{N}-\text{CH}_2$ ), 51.9 ( $\text{N}-\text{CH}_2-\text{CH}$ ), 55.2 ( $\text{N}-\text{CH}$ ), 65.8 ( $\text{CH}-\text{OH}$ ), 114.9 ( $=\text{CH}_2$ ), 127.1 ( $\text{Ar CH}$ ), 127.4 ( $2 \times \text{Ar CH}$ ), 129.2 ( $2 \times \text{Ar CH}$ ), 129.6 ( $2 \times \text{Ar CH}$ ), 130.2 ( $2 \times \text{Ar CH}$ ), 138.4 ( $C_q$ ), 143.0 ( $C_q$ ), 143.8 ( $C_q$ );  $m/z$  ( $\text{ES}^+$ ) 408.1 (40%,  $[\text{M} + \text{Na}]^+$ ),

386.1 (100, [M + H]<sup>+</sup>), 376.1 (26), 368.1 (11), 270.1 (64), 226.1 (42) [HRMS Found: (M + Na)<sup>+</sup> 408.1601. C<sub>22</sub>H<sub>27</sub>NNaO<sub>3</sub>S *M*, requires 408.1609].

#### Typical procedure for Brønsted acid-catalysed cyclisation:

##### (2*S*,4*R*,5*S*)-2-benzyl-4-hydroxy-5-isopropenyl-1-(*p*-toluenesulfonyl)piperidine (**7b**)

Concentrated hydrochloric acid (37%, 130  $\mu$ L, 1.54 mmol) was added to a solution of aldehyde **1b** (197 mg, 0.51 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) at  $-78^{\circ}\text{C}$ . The solution was stirred at  $-78^{\circ}\text{C}$  overnight, after which water was added and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were washed with brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo* to afford the crude piperidine. Purification by flash column chromatography (silica; eluent 1 : 2 EtOAc–hexane, *R*<sub>f</sub> = 0.36) afforded piperidine **7b** as a colourless thick oil (160 mg, 81%); [ $\alpha$ ]<sub>D</sub><sup>27</sup>  $-16.1$  (*c* 0.18 in CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3530 (OH), 3027 (=CH), 2923 ( $\nu_{\text{as}}$  CH<sub>2</sub>), 1644 (C=C aliphatic), 1599 (C=C aromatic), 1495 (C=C aromatic), 1453 (C=C aromatic), 1340 ( $\nu_{\text{as}}$  SO<sub>2</sub>), 1157 ( $\nu_{\text{s}}$  SO<sub>2</sub>), 1105 (C–O);  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 1.55–1.68 (2H, stack, N-CH-CHH and OH), 1.76 (3H, s, =C-CH<sub>3</sub>), 1.93 (1H, dd, *J* 14.3 and 2.0, N-CH-CHH), 2.23 (1H, br d, *J* 11.8, N-CH<sub>2</sub>-CH), 2.39 (3H, s, Ph-CH<sub>3</sub>), 2.87 (1H, dd, *J* 13.0 and 6.6, Ph-CHH), 3.19 (1H, dd, *J* 13.0 and 9.6, Ph-CHH), 3.43 (1H, dd, *J* 13.6 and 12.1, N-CHH), 3.64 (1H, dd, *J* 13.6 and 3.9, N-CHH), 4.04 (1H, app d, *J* 2.0, CH-OH), 4.20–4.30 (1H, m, N-CH), 4.74 (1H, s, =CHH), 5.05 (1H, s, =CHH), 7.17–7.29 (7H, m, Ar CH), 7.53 (2H, d, *J* 8.1, Ar CH);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 21.6 (Ph-CH<sub>3</sub>), 22.9 (=C-CH<sub>3</sub>), 31.5 (N-CH-CH<sub>2</sub>), 38.3 (CH<sub>2</sub>), 38.9 (CH<sub>2</sub>), 46.2 (N-CH<sub>2</sub>-CH), 53.3 (N-CH), 64.8 (CH-OH), 112.5 (=CH<sub>2</sub>), 126.3 (Ar CH), 127.2 (2  $\times$  Ar CH), 128.5 (2  $\times$  Ar CH), 129.7 (2  $\times$  Ar CH), 129.8 (2  $\times$  Ar CH), 138.2 (C<sub>q</sub>), 139.4 (C<sub>q</sub>), 143.1 (C<sub>q</sub>), 144.2 (C<sub>q</sub>); *m/z* (ES<sup>+</sup>) 408.1 (90%, [M + Na]<sup>+</sup>), 386.1 (26, [M + H]<sup>+</sup>), 368.1 (9), 286.0 (27), 274.0 (100) [HRMS Found: (M + Na)<sup>+</sup> 408.1598. C<sub>22</sub>H<sub>27</sub>NNaO<sub>3</sub>S *M*, requires 408.1609].

##### Typical detosylation procedure: (2*S*,4*S*,5*S*)-2-benzyl-4-hydroxy-5-isoproprenyl piperidine (**36b**)

To a solution of piperidine **8b** (99 mg, 0.26 mmol) in THF (1.5 mL) at  $-78^{\circ}\text{C}$  was added a freshly prepared solution of sodium naphthalenide (1.0 M in THF, 1.18 mL, 1.18 mmol). After 5 min the reaction was quenched with MeOH (0.3 mL), warmed up to room temperature, diluted with water and acidified to pH 1 with aqueous HCl. The aqueous phase was washed with Et<sub>2</sub>O, basified to pH 9 with aqueous NaOH (2 M) and extracted with EtOAc. The combined organic phases were washed with brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo* to afford piperidine **36b** as a white powder (52 mg, 87%); [ $\alpha$ ]<sub>D</sub><sup>23</sup>  $-49$  (*c* 0.98 in CHCl<sub>3</sub>); mp 119–121  $^{\circ}\text{C}$  (from CH<sub>2</sub>Cl<sub>2</sub>–hexane); (Found: C, 77.80; H, 9.22; N, 6.19. C<sub>15</sub>H<sub>21</sub>NO requires C, 77.88; H, 9.15; N, 6.05%);  $\nu_{\text{max}}$  (film)/cm<sup>-1</sup> 3306 (OH, NH), 2917 ( $\nu_{\text{as}}$  CH<sub>2</sub>), 1641 (C=C aliphatic), 1602 (C=C aromatic), 1493 (C=C aromatic), 1455 (C=C aromatic), 1090 (C–O);  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 1.63 (1H, ddd, *J* 12.9, 9.9 and 5.1, N-CH-CHH), 1.79 (3H, s, CH<sub>3</sub>), 1.91 (1H, br s, OH and NH), 1.97 (1H, dt, *J* 12.9 and 3.7, N-CH-CHH), 2.07–2.15 (1H, m, N-CH<sub>2</sub>-CH), 2.72 (1H, dd, *J* 13.4 and 6.4, N-CHH), 2.86–2.94 (3H, stack, N-CHH and Ph-CH<sub>2</sub>), 3.32–3.41 (1H, m, N-CH), 3.99

(1H, td, *J* 9.4 and 4.1, CH-OH), 4.94 (1H, s, =CHH), 4.98 (1H, s, =CHH), 7.16–7.33 (5H, m, Ar CH);  $\delta_{\text{C}}$  (75 MHz, CDCl<sub>3</sub>) 21.2 (CH<sub>3</sub>), 37.0 (N-CH-CH<sub>2</sub>-CH), 38.8 (Ph-CH<sub>2</sub>), 43.7 (N-CH<sub>2</sub>), 53.4 (N-CH<sub>2</sub>-CH), 54.4 (N-CH), 66.4 (CH-OH), 113.3 (=CH<sub>2</sub>), 126.4 (Ar CH), 128.7 (2  $\times$  Ar CH), 129.1 (2  $\times$  Ar CH), 139.6 (C<sub>q</sub>), 144.4 (C<sub>q</sub>); *m/z* (ES<sup>+</sup>) 232.1 (65%, [M + H]<sup>+</sup>), 214.1 (100) [HRMS Found: (M + H)<sup>+</sup> 232.1700. C<sub>15</sub>H<sub>22</sub>NO requires *M*, 232.1701].

## Acknowledgements

We thank the Engineering and Physical Sciences Research Council for a studentship to C. A. M. C., the University of Birmingham for financial support and Dr J. T. Williams for some preliminary experiments.

## References

- 1 J. A. Findlay in *The Alkaloids*, ed. A. Brossi, Academic Press, London, 1985, vol. 26, pp. 89–183; A. R. Pinder, *Nat. Prod. Rep.*, 1986, **3**, 171–180; A. R. Pinder, *Nat. Prod. Rep.*, 1987, **4**, 527–537; A. R. Pinder, *Nat. Prod. Rep.*, 1989, **6**, 67–78; A. R. Pinder, *Nat. Prod. Rep.*, 1990, **7**, 447–455; A. R. Pinder, *Nat. Prod. Rep.*, 1992, **9**, 491–504; A. O. Plunkett, *Nat. Prod. Rep.*, 1994, **11**, 581–590; D. O'Hagan, *Nat. Prod. Rep.*, 1997, **14**, 637–651; D. O'Hagan, *Nat. Prod. Rep.*, 2000, **17**, 435–446.
- 2 P. S. Watson, B. Jiang and B. Scott, *Org. Lett.*, 2000, **2**, 3679–3681.
- 3 For reviews see: S. Laschat and T. Dickner, *Synthesis*, 2000, 1781–1813; P. M. Weintraub, J. S. Sabol, J. M. Kane and D. R. Borchering, *Tetrahedron*, 2003, **59**, 2953–2989; M. G. P. Buffat, *Tetrahedron*, 2004, **60**, 1701–1729.
- 4 (a) T. A. Johnson, M. D. Curtis and P. Beak, *J. Am. Chem. Soc.*, 2001, **123**, 1004–1005; A. J. Souers and J. A. Ellman, *J. Org. Chem.*, 2000, **65**, 1222–1224; C. Shu, A. Alcudia, J. Yin and L. S. Liebeskind, *J. Am. Chem. Soc.*, 2001, **123**, 12477–12487; J. M. Harris and A. Padwa, *J. Org. Chem.*, 2003, **68**, 4371–4381; S. J. Hedley, W. J. Moran, D. A. Price and J. P. A. Harrity, *J. Org. Chem.*, 2003, **68**, 4286–4292; B. B. Toure and D. G. Hall, *Angew. Chem., Int. Ed.*, 2004, **43**, 2001–2004; E. Poupon, D. Francois, N. Kunesch and H. P. Husson, *J. Org. Chem.*, 2004, **69**, 3836–3841; J. T. Kuethe and D. L. Comins, *J. Org. Chem.*, 2004, **69**, 2863–2866; C. Y. Legault and A. B. Charette, *J. Am. Chem. Soc.*, 2005, **127**, 8966–8967; R. P. Wurz and G. C. Fu, *J. Am. Chem. Soc.*, 2005, **127**, 12234–12235; G. S. Kauffman, P. S. Watson and W. A. Nugent, *J. Org. Chem.*, 2006, **71**, 8975–8977; G. A. Cortez, R. R. Schrock and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2006, **46**, 4534–4538; M. Terada, K. Machioka and K. Sorimachi, *J. Am. Chem. Soc.*, 2007, **129**, 10336–10337.
- 5 J. T. Williams, P. S. Bahia, B. Kariuki, N. Spencer, D. Philp and J. S. Snaith, *J. Org. Chem.*, 2006, **71**, 2460–2471.
- 6 For a review see: B. B. Snider in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 2, pp. 527–561.
- 7 M. Ishibashi, Y. Ohizumi, T. Sasaki, H. Nakamura, Y. Hirata and J. Kobayashi, *J. Org. Chem.*, 1987, **52**, 450–453; J. Kobayashi, K. Naitoh, Y. Doi, K. Deki and M. Ishibashi, *J. Org. Chem.*, 1995, **60**, 6941–6945. For minor structural revision see: T. Kiguchi, Y. Yuimoto, I. Ninomiya, T. Naito, K. Deki, M. Ishibashi and J. Kobayashi, *Tetrahedron Lett.*, 1992, **33**, 7389–7390; M. Ishibashi, K. Deki and J. Kobayashi, *J. Nat. Prod.*, 1995, **58**, 804–806.
- 8 A. J. Freyer, A. D. Patil, L. Killmer, N. Troupe, M. Mentzer, B. Carte, L. Faucette and R. K. Johnson, *J. Nat. Prod.*, 1997, **60**, 986–990.
- 9 Y. Doi, M. Ishibashi and J. Kobayashi, *Tetrahedron*, 1996, **52**, 4573–4580; D. Ma and H. Sun, *J. Org. Chem.*, 2000, **65**, 6009–6016; N. Langlois, *Org. Lett.*, 2002, **4**, 185–187; B. M. Trost and D. R. Fandrick, *Org. Lett.*, 2005, **7**, 823–826; F. A. Davis, J. Zhang, X. Li, H. Xu and C. DeBrosse, *J. Org. Chem.*, 2005, **70**, 5413–5419; M. Haddad, M. Larcheveque and H. M. Tong, *Tetrahedron Lett.*, 2005, **46**, 6015–6017; K. Tanaka, T. Maesoba and H. Sawanishi, *Heterocycles*, 2006, **68**, 183–192.
- 10 A preliminary account of this work has been published: C. A. M. Cariou and J. S. Snaith, *Org. Biomol. Chem.*, 2006, **4**, 51–53.
- 11 M. McKennon, A. Meyers, K. Drauz and M. Schwarm, *J. Org. Chem.*, 1993, **58**, 3568–3571.

- 12 We are grateful to Dr J. T. Williams for carrying out development work on this synthetic route. J. T. Williams, PhD Thesis, University of Birmingham, 2003.
- 13 (a) F. Johnson, *Chem. Rev.*, 1968, **68**, 375–413; Y. L. Chow, C. J. Colón and J. N. S. Tam, *Can. J. Chem.*, 1968, **46**, 2821–2825.
- 14 For a review of synthetic routes to pipecolic acids see: C. Kadouri-Puchot and S. Comesse, *Amino Acids*, 2005, **29**, 101–130.
- 15 T. Kline, N. H. Andersen, E. A. Harwood, J. Bowman, A. Malanda, S. Endsley, A. L. Erwin, M. Doyle, S. Fong, A. L. Harris, B. Mendelsohn, K. Mdluli, C. R. H. Raetz, C. K. Stover, P. R. Witte, A. Yabannaver and S. G. Zhu, *J. Med. Chem.*, 2002, **45**, 3112–3129.
- 16 B. F. Bonini, M. Comes-Franchini, M. Fochi, J. Gawronski, G. Mazzanti, A. Ricci and G. Varchi, *Eur. J. Org. Chem.*, 1999, 437–445.
- 17 J. Wang and Y. Hou, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1919–1924.
- 18 W. Howson, H. M. I. Osborn and J. Sweeney, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2439–2446.