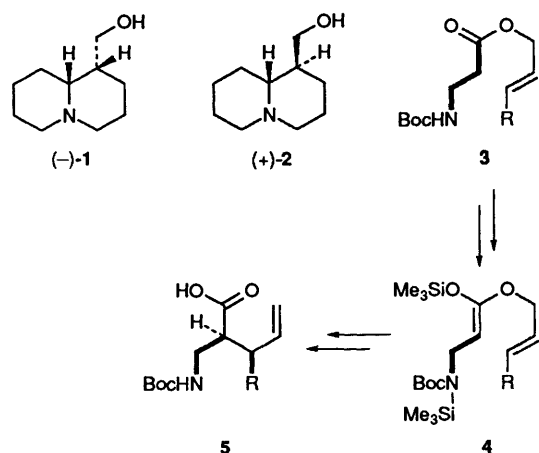


## Complementary Enantioselective Approaches to the Quinolizidine Alkaloids Lupinine and Epilupinine by Enolate Claisen Rearrangements or Direct Alkylation of Piperidin-2-ylacetic Acid Derivatives

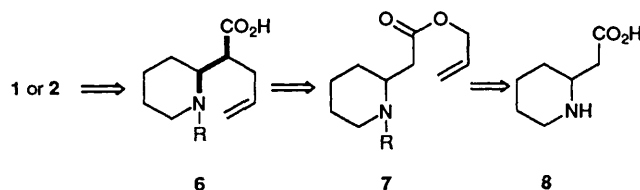
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Enolate Claisen rearrangement of the piperidinylacetic acid allyl ester **11** leads mainly to the diastereoisomer **12**, whereas direct alkylation of the lithio enolate of the corresponding methyl ester **14** gives a preponderance of the alternative diastereoisomer **13**. Hydroboration and cyclisation of the latter isomer has been used to obtain (+)-lupinine **17**; in principle, this approach is adaptable to the synthesis of either enantiomer of both lupinine and epilupinine, given the correct choice of C-alkylation method.

(-)-Lupinine **1** is one of the parent members of the quinolizidine group of alkaloids whose presence in significant quantities in the yellow lupin seeds (*Lupinus luteus*) was first reported over a hundred years ago.<sup>1</sup> The compound is also present in other *Lupinus* species,<sup>2</sup> while the (*E*)-4-hydroxycinnamate derivative has been found in seedlings of *L. luteus* but, perhaps significantly, not in either the seeds or during later growth.<sup>3</sup> Somewhat unusually, other *Lupinus* species including *L. pilosus* and *L. varius* contain the epimeric and thermodynamically more stable (+)-epilupinine **2** as a major metabolite together with the corresponding *N*-oxide but not accompanied by any lupinine **1**.<sup>4</sup> Early synthetic approaches

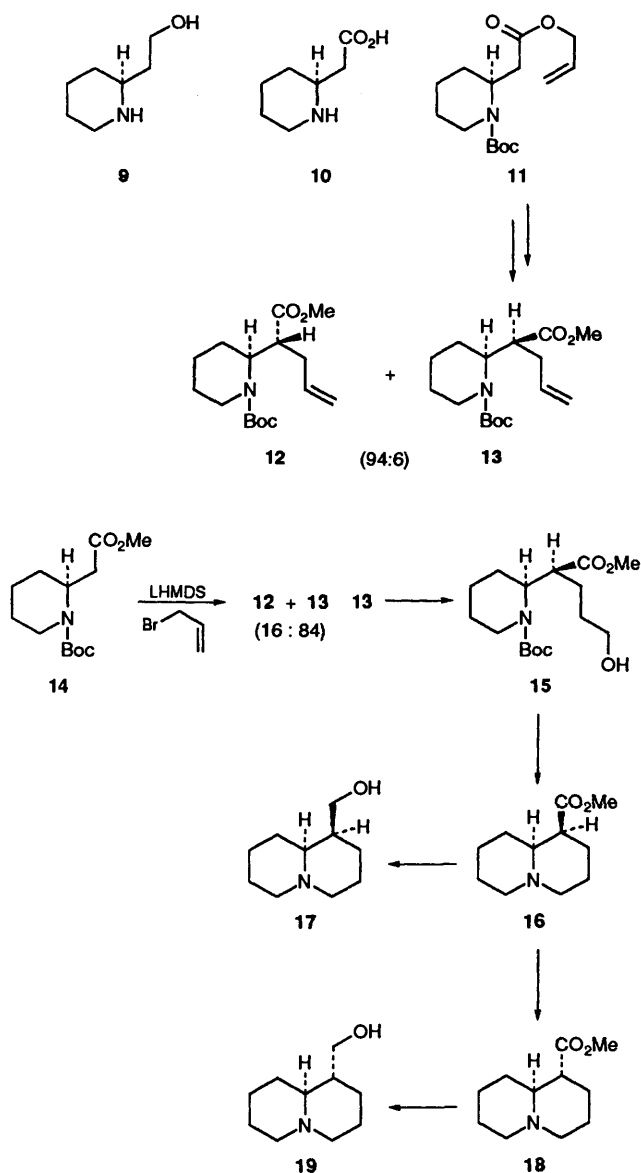


to these structures featured construction of the right-hand ring starting from piperidin-2-ylacetic acid ethyl ester by sequential C-alkylation, reduction and intramolecular *N*-alkylation,<sup>5</sup> a biomimetic route based on an intramolecular Mannich cyclisation<sup>6</sup> and intramolecular cyclisations of ketone-based nucleophiles onto tetrahydropyridinium<sup>7</sup> or pyridinium species.<sup>8</sup> More recently, intermolecular additions of various functionalised organometallic reagents to *N*-acylpyridinium species have been used in elegant approaches to both (±)-lupinine and (±)-epilupinine.<sup>9</sup> Enamine carboxylation using a chloroformate has been used to introduce the one-carbon side-chain;<sup>10</sup> by using a menthyl chloroformate, the first asymmetric synthesis of lupinine, albeit in only ~10% enantiomeric enrichment, was achieved.<sup>11</sup> The bicyclic ring system has also been established by various intramolecular cyclisations involving β-enamino ester functions,<sup>12</sup> by a Nazarov cyclisation<sup>13</sup> and by intramolecular Michael addition of an amino function to an enoate<sup>14</sup> or a dienolate.<sup>15</sup> A very brief synthesis of (±)-



epilupinine features an intramolecular Michael addition of an alkyl radical to an enoate<sup>16</sup> while a more recent development in this area reaches the same target but by intramolecular cyclisation of an α-amino radical onto an allylic chloride group, effectively by an S<sub>N</sub>2 process.<sup>17</sup> The presence of six-membered rings in the target molecules suggests that the Diels–Alder reaction should be useful in their preparation; this has so far been exemplified by the use of imino<sup>18</sup> and iminium dienophiles<sup>19</sup> as well as azadienes.<sup>20</sup> Usually, only epilupinine can be prepared by this methodology (but see ref. 19) although the first two, closely related, routes should be amenable to an asymmetric approach to this compound. Both diastereoisomers [(±)-**1** and (±)-**2**] have also been prepared using 1,3-dipolar cycloadditions as the key step.<sup>21</sup> Perhaps the most popular approach to this ring system however, features the use of an acyliminium species as the key intermediate in combination with an intramolecular nucleophilic trapping function, examples of which include a malonate residue,<sup>22</sup> a ketene dithioacetal group,<sup>23</sup> an allylsilane<sup>24</sup> and a bromoalkyne function.<sup>25</sup> While some of the foregoing approaches could, in principle, be adapted to the elaboration of enantiomers of lupinine and/or epilupinine, it was not until 1988 that the first asymmetric synthesis giving rise to homochiral material was reported.<sup>26</sup> Again, an acyliminium species was a key component; the nucleophile was a tin(II) enolate derived from a homochiral dihydrothiazolethione, the structure of which is reminiscent of the corresponding Evans-type oxazolidinones. Both (+)- and (-)-epilupinine were prepared by this brief and efficient route. More recently, both (-)-lupinine and (+)-epilupinine have been prepared by a rather different route in which alkylation of a homochiral α-sulfinyl ketimine is a key step.<sup>27</sup>

The relatively few asymmetric approaches to these structures prompted us to attempt to extend our recently developed approach to α-allyl-β-amino acid derivatives **5** by enolate Claisen rearrangements of allyl esters of *N*<sup>α</sup>-Boc-β-amino acids **3**<sup>28</sup> to syntheses of these natural products. Thus, we anticipated that by starting with a homochiral piperidin-2-ylacetic acid **8**, the esters **7** should be available by sequential *N*-protection and esterification. A successful enolate Claisen rearrangement



should then deliver the  $\alpha$ -allyl derivative **6** in a stereocontrolled fashion; subsequent manipulation of the alkene function and cyclisation would then complete the synthesis. One potential problem associated with this approach was the possibility that enolisation of esters **7**, in which 'R' was anticipated to be an alkoxy carbonyl function, could result in  $\beta$ -elimination of the nitrogen group. At the worst, this could result in complete failure or, at best, recyclisation by a Michael addition resulting in loss of chirality. In our original version of this type of rearrangement (**3**→**4**→**5**), such an elimination process was unlikely to occur as the carbamate function contained a secondary amide group which would also undergo deprotonation.

We therefore began by resolving commercially available ( $\pm$ )-piperidin-2-ylethanol by fractional crystallisation of the (+)-10-camphorsulfonic acid ester of the racemic material.<sup>29</sup> As the less soluble diastereoisomer is formed from the (*S*)-(+)-enantiomer **9**, we chose to use this as our starting material purely for convenience and therefore anticipated that we would eventually synthesize the enantiomers of the natural targets **1** and **2**. The alcohol **9**  $\{[\alpha]_D +9.9$  (*c* 3,  $\text{CHCl}_3$ ); lit.,<sup>29</sup>  $[\alpha]_D +11$  (*c* 3,  $\text{CHCl}_3$ ) $\}$  was conveniently oxidised to the corresponding (*S*)-(+)-acid **10** {m.p. 234–235 °C,  $[\alpha]_D +33.5$  (*c* 0.6,  $\text{H}_2\text{O}$ ); lit.,<sup>30</sup> m.p. 218–221 °C,  $[\alpha]_D +22.1$  (*c* 0.6,  $\text{H}_2\text{O}$ )}

using Jones reagent.<sup>31</sup> The allyl ester **11** required for the enolate Claisen rearrangement, was then obtained in good yield by sequential *N*-protection [ $(\text{Boc})_2\text{O}$ , NaOH,  $\text{Bu}^t\text{OH}$ ,  $\text{H}_2\text{O}$ ] and esterification using allyl alcohol and the 1,3-dicyclohexylcarbodiimide–4-dimethylaminopyridine (DCC–DMAP) coupling method.<sup>32</sup> The  $^1\text{H}$  NMR spectra of these compounds showed some common features which were present in all of the piperidines synthesized during this work. Line broadening due to rotation of the carbamate function was evident in spectra run at ambient temperature, especially in the resonances of protons attached to the 2- and 6-positions adjacent to the nitrogen atom. Similar broadening of the 2- and 6-carbons also occurred in the ambient temperature  $^{13}\text{C}$  NMR spectra. It was deduced some time ago<sup>33</sup> that a 2-substituent in *N*-acylpiperidines will adopt an axial position in preference to the expected equatorial placement in order to avoid steric interactions with the acyl function; coupling constant data in the  $^1\text{H}$  NMR spectra showed this was the case in the present examples of 2-substituted piperidines. In these conformations, the 2- and 6-equatorial protons are shifted downfield ( $\delta_{\text{H}} \leq 4.0$ ) with respect to the 6-axial proton ( $\delta_{\text{H}} \sim 2.8$ ).

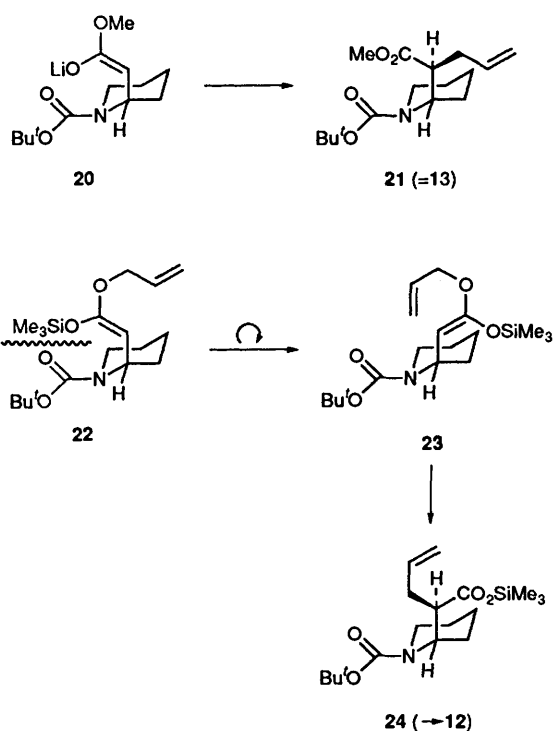
The central enolate Claisen rearrangement<sup>28</sup> of the allyl ester **11** was effected by treatment with lithium hexamethyldisilazide (LHMDS) in tetrahydrofuran at  $-78$  °C; in order to minimize the possibility of  $\beta$ -elimination, the trapping agent, trimethylsilyl chloride (TMSCl) was added just before the ester.<sup>34</sup> The solution was slowly warmed to ambient temperature and then refluxed for 6 h. A simple work-up, methanolysis of the intermediate silyl ester and finally methylation of the acidic product using diazomethane gave an encouraging 76% return of the hoped for  $\alpha$ -allyl esters **12** and **13** as a 94:6 ratio of diastereoisomers, according to integration of the two methyl ester resonances in the  $^1\text{H}$  NMR spectrum. The excellent level of diastereoselection was confirmed by  $^{13}\text{C}$  NMR data; the assignment of structure **12** to the major diastereoisomer was made mainly on the grounds of mechanistic considerations and only confirmed upon completion of the synthesis. The use of less than 2 equiv. of base gave inferior yields, an observation made during our previous studies.<sup>28</sup> The success of this transformation led us to attempt direct allylation of the intermediate lithium enolate derived from the corresponding piperidine methyl ester **14**. We were pleased to find that this led directly to the desired  $\alpha$ -allyl esters **12** and **13** but in a ratio of 14:86, according to  $^1\text{H}$  NMR data. Careful chromatography resulted in the separation of the major diastereoisomer **13**, in 71% yield, which was clearly distinguishable from the major product **12** of the Claisen sequence. As the product **13** showed optical activity, intervention of the retro-Michael–Michael reclosure process was only happening to a limited extent, if at all.

Completion of the sequence, using the product **13** of direct allylation, proceeded uneventfully. Hydroboration led to an excellent yield of the alcohol **15** which upon mesylation, *N*-deprotection using trifluoroacetic acid and cyclisation by basification of the resulting salt was smoothly converted into the quinolizidinecarboxylate **16** in good yield. A final reduction using lithium aluminium hydride then provided a sample of (+)-lupinine **17** which, after crystallisation from hexane, proved to be identical according to spectroscopic<sup>2,35–37</sup> and analytical data with natural (–)-lupinine **1**, except for the sign of rotation.<sup>2c,8</sup> Therefore, the foregoing, speculative stereochemical assignments were correct; the high optical purity of the final product indicates that retro-Michael reactions were not occurring during the central enolate chemistry.

The foregoing approaches are thus complementary in that either enantiomer of lupinine or epilupinine could be prepared by starting with a single enantiomer of the piperidine acid **10** and using either the Claisen or direct allylation method to add

the extra carbon atoms required. It was established some time ago<sup>10</sup> that base-catalysed epimerisation of the carboxylate precursor **16** of the lupinine diastereoisomer to the thermodynamically more stable 'epilupinine' structure **18** was possible<sup>9,21</sup> by exposure to sodium ethoxide in hot ethanol. In an attempt to render the direct allylation approach more flexible, we treated a sample of our synthetic (+)-lupinine precursor **16** with sodium methoxide in refluxing methanol for 16 h.<sup>10</sup> While the product was clearly the related epilupinine diastereoisomer according to spectroscopic data, subsequent reduction (LiAlH<sub>4</sub>) gave samples of epilupinine (*cf.* **2**) with much reduced or even no optical activity {lit.,<sup>4,26</sup> [ $\alpha$ ]<sub>D</sub> +32 (*c* 1.49, EtOH)}. This suggests that under these conditions, the retro-Michael-Michael reclosure process does occur and that the foregoing approaches must diverge at the central C-allylation steps rather than at a later epimerisation step.

A rationale which accounts for the observed stereoselectivities in the key steps is based on the assumption that the acetate side chains in the enolates derived from esters **11** and **14** are positioned axially, as discussed above.<sup>33</sup> In line with the conclusions of our previous studies,<sup>28</sup> the (*E*)-lithio enolate would be expected to predominate, due to complexation with the *N*-Boc function. The likely conformation **20** of the (*E*)-



enolate derived from the methyl ester **14** would then be expected to react preferentially with allyl bromide from the more exposed *si* face, to give mainly the diastereoisomer **21** (= **13**). In similar fashion, the corresponding allyl ester **11** should give the related (*E*)-lithio enolate upon deprotonation, and thence the (*Z*)-silyl enolate **22**. The steric crowding indicated could then result in rotation to the alternative conformation **23**, prior to rearrangement to give the diastereoisomer **24** as the major product, in which the *si* face (= *re* face of lithio enolate) is now the more exposed.

## Experimental

For general experimental details, see ref. 28. [ $\alpha$ ]<sub>D</sub> Values are given in units of 10<sup>-1</sup> deg cm<sup>2</sup> g<sup>-1</sup>.

(*S*)-*N*-*tert*-Butoxycarbonylpiperidin-2-ylacetic Acid.—To a stirred solution of sodium hydroxide (0.236 g, 5.9 mmol) in water (7 cm<sup>3</sup>) was added (*S*)-(+)-piperidin-2-ylacetic acid **10** (0.849 g, 5.9 mmol) and *tert*-butyl alcohol (5 cm<sup>3</sup>). The resulting solution was treated dropwise with di-*tert*-butyl dicarbonate [(Boc)<sub>2</sub>O] (1.37 g, 5.9 mmol) and then stirred at ambient temperature for 16 h. The now turbid mixture (pH ~8) was washed with pentane (2 × 25 cm<sup>3</sup>) and the combined washings were back extracted with saturated aqueous sodium hydrogen carbonate (3 × 25 cm<sup>3</sup>). The aqueous portion of the reaction mixture and the washings extracts were combined, cooled in ice-water and carefully acidified to pH 1–1.5 by the slow addition of a solution of potassium hydrogen sulfate (4.68 g) in water (25 cm<sup>3</sup>). The resulting mixture was extracted using diethyl ether (5 × 25 cm<sup>3</sup>) and the combined extracts were washed with water (2 × 25 cm<sup>3</sup>) and then dried, filtered and evaporated to give the desired product (1.24 g, 86%) as a colourless solid, which was pure enough for use in the next step. An analytical sample was obtained by crystallisation from ethyl acetate–light petroleum which gave colourless crystals, m.p. 93–95 °C (Found: C, 59.1; H, 8.8; N, 5.7. C<sub>12</sub>H<sub>21</sub>NO<sub>4</sub> requires C, 59.2; H, 8.7; N, 5.8%); [ $\alpha$ ]<sub>D</sub> ~0 (*c* 0.5, CHCl<sub>3</sub>);  $\nu_{\max}$ (Nujol)/cm<sup>-1</sup> 3150–2870, 1728 and 1622;  $\delta_{\text{H}}$ (400 MHz) 1.33–1.58 (2 H, m), 1.44 (9 H, s, Bu<sup>t</sup>), 1.59–1.73 (4 H, m), 2.56 (1 H, dd, *J* 14.5 and 7.9, CH<sub>A</sub>H<sub>B</sub>CO), 2.62 (1 H, dd, *J* 14.5 and 7.1, CH<sub>A</sub>CH<sub>B</sub>CO), 2.77 (1 H, app. br t, *J* ~12.8, 6-H<sub>ax</sub>), 4.00 (1 H, app. br d, *J* ~12.8, 6-H<sub>eq</sub>), 4.70 (1 H, app. br s, 2-H<sub>eq</sub>) and 9.10–9.55 (1 H, br, OH);  $\delta_{\text{C}}$ (100 MHz) 18.85 (CH<sub>2</sub>), 25.24 (CH<sub>2</sub>), 28.37 (Bu<sup>t</sup>), [28.37 (CH<sub>2</sub>)-not resolved] 35.26 (CH<sub>2</sub>), 39.26 (CH<sub>2</sub>-6), 47.64 (CH-2), 79.92 [C(CH<sub>3</sub>)<sub>3</sub>], 154.97 [C(O)N] and 176.85 [C(O)O]; *m/z* 187 (7%), 142 (12), 128 (57), 84 (100) and 57 (86).

(*S*)-(-)-Allyl *N*-*tert*-Butoxycarbonylpiperidin-2-ylacetate **11**.—The foregoing acid (0.333 g, 1.38 mmol), allyl alcohol (0.08 g, 1.38 mmol) and DMAP (~10 mg) were dissolved in dry diethyl ether (50 cm<sup>3</sup>) and the resulting solution treated dropwise with a solution of DCC (0.29 g, 1.39 mmol) in dry diethyl ether (5 cm<sup>3</sup>). The mixture was stirred overnight at ambient temperature and then filtered. The solid residue was washed with dry diethyl ether and the combined filtrates were evaporated. SG chromatography (20:1, CH<sub>2</sub>Cl<sub>2</sub>–EtOAc) of the residue gave the ester **11** (0.314 g, 81%) as a colourless oil (Found: C, 63.4; H, 9.1; N, 4.7. C<sub>15</sub>H<sub>25</sub>NO<sub>4</sub> requires C, 63.6; H, 8.9; N, 4.9%); [ $\alpha$ ]<sub>D</sub> -6.3 (*c* 4, CHCl<sub>3</sub>);  $\nu_{\max}$ (film)/cm<sup>-1</sup> 1742 and 1698;  $\delta_{\text{H}}$ (400 MHz) 1.30–1.52 (2 H, m), 1.45 (9 H, s, Bu<sup>t</sup>), 1.54–1.76 (4 H, m), 2.56 (1 H, dd, *J* 14.2 and 7.9, CH<sub>A</sub>H<sub>B</sub>CO), 2.62 (1 H, dd, *J* 14.2 and 7.3, CH<sub>A</sub>CH<sub>B</sub>CO), 2.78 (1 H, app. br dd, *J* ~13.8 and ~12.2, 6-H<sub>ax</sub>), 3.99 (1 H, app. br d, *J* ~12.2, 6-H<sub>eq</sub>), 4.56 [2H, ddd, *J* 5.7, 1.5 and 1.3, C(O)OCH<sub>2</sub>], 4.67–4.78 (1 H, m, 2-H<sub>eq</sub>), 5.24 (1 H, ddt, *J* 10.4, 1.5 and 1.3, CH=CH<sub>2</sub>H<sub>1</sub>), 5.33 (1 H, ddt, *J* 17.2, 1.5 and 1.5, CH=CH<sub>2</sub>H<sub>2</sub>) and 5.91 (1 H, ddt, *J* 17.2, 10.4 and 5.7, CH=CH<sub>2</sub>);  $\delta_{\text{C}}$ (100 MHz) 18.91 (CH<sub>2</sub>), 25.32 (CH<sub>2</sub>), 28.25 (CH<sub>2</sub>), 28.44 (Bu<sup>t</sup>), 35.27 (CH<sub>2</sub>), 39.24 (CH<sub>2</sub>-6), 47.95 (CH-2), 65.23 (CH<sub>2</sub>O), 79.57 [C(CH<sub>3</sub>)<sub>3</sub>], 118.27 (=CH<sub>2</sub>), 132.21 (=CH), 154.74 [C(O)N] and 171.06 [C(O)O]; *m/z* 283 (M<sup>+</sup>, 2%), 227 (6), 182 (41), 168 (15), 142 (17), 128 (77), 84 (100) and 57 (94).

(*S*)-(-)-Methyl *N*-*tert*-Butoxycarbonylpiperidin-2-ylacetate **14**.—The foregoing esterification procedure but with methanol in place of allyl alcohol, on a 2.5 mmol scale, gave the methyl ester **14** (~80%) as a colourless oil (Found: C, 60.7; H, 9.4; N, 5.4. C<sub>13</sub>H<sub>23</sub>NO<sub>4</sub> requires C, 60.7; H, 9.0; N, 5.4%); [ $\alpha$ ]<sub>D</sub> -8.3 (*c* 4.54, CHCl<sub>3</sub>);  $\nu_{\max}$ (film)/cm<sup>-1</sup> 1742 and 1692;  $\delta_{\text{H}}$ (400 MHz) 1.32–1.53 (2 H, m), 1.45 (9 H, s, Bu<sup>t</sup>), 1.54–1.72 (4 H, m), 2.52 (1 H, dd, *J* 14.1 and 7.8, CH<sub>A</sub>H<sub>B</sub>CO), 2.60 (1 H, dd, *J* 14.1 and 7.4, CH<sub>A</sub>CH<sub>B</sub>CO), 2.78 (1 H, app. br t, *J* ~12.7, 6-H<sub>ax</sub>), 3.66

(3 H, s, OMe), 3.99 (1 H, app. br d,  $J \sim 10$ , 6- $H_{eq}$ ) and 4.61–4.72 (1 H, m, 2- $H_{eq}$ );  $\delta_c$ (100 MHz) 18.92 ( $CH_2$ ), 25.33 ( $CH_2$ ), 28.43 (Bu<sup>t</sup>), 28.43 ( $CH_2$ ) (visible in DEPT spectrum), 35.16 ( $CH_2$ ), 39.19 ( $CH_2$ -6), 47.96 (CH-2), 51.64 ( $CH_3$ O), 79.55 [ $C(CH_3)_3$ ], 154.76 [ $C(O)N$ ] and 171.88 [ $C(O)O$ ];  $m/z$  257 ( $M^+$ , 3%), 201 (9), 184 (8), 170 (8), 156 (34), 142 (32), 128 (83), 84 (100) and 57 (98).

(2R,2'S)-Methyl 2-(N-tert-Butoxycarbonylpiperidin-2'-yl)-pent-4-enoate **12** (Claisen Rearrangement).—To a solution of hexamethyldisilazane (0.84 cm<sup>3</sup>, 6 mmol) in dry THF (10 cm<sup>3</sup>) stirred at  $-20^\circ C$  was added butyllithium (1.6 mol dm<sup>-3</sup> solution in hexanes; 2.5 cm<sup>3</sup>, 4 mmol). After 20 min, the solution was cooled to  $-78^\circ C$  and treated sequentially with trimethylsilyl chloride (0.56 cm<sup>3</sup>, 4.4 mmol) and the ester **11** (0.566 g, 2 mmol) in THF (2 cm<sup>3</sup>). After 0.5 h, the resulting mixture was warmed to ambient temperature during 1 h and then refluxed for 6 h. The cooled mixture was then concentrated by rotary evaporation and the residue treated with wet methanol (5 cm<sup>3</sup>). The solution was stirred for 0.5 h and then evaporated. The residue was acidified using aqueous citric acid to pH < 4 and then extracted with diethyl ether (4  $\times$  25 cm<sup>3</sup>). The combined extracts were dried and evaporated and the residue treated with a slight excess of ethereal diazomethane for 1 h. Evaporation left a residue which was subjected to SG chromatography (20:1,  $CH_2Cl_2$ -EtOAc) to give the (2R,2'S)-isomer **12** (0.452 g, 76%) as a colourless oil (Found: C, 64.2; H, 9.6; N, 4.7.  $C_{16}H_{27}NO_4$  requires C, 64.6; H, 9.2; N, 4.7%);  $\nu_{max}$ (film)/cm<sup>-1</sup> 1742 and 1698;  $\delta_H$ (400 MHz) 1.38–1.51 (2 H, m), 1.47 (9 H, s, Bu<sup>t</sup>), 1.55–1.73 (4 H, m), 2.11–2.21 (1 H, m,  $CH_AH_BCH=$ ), 2.23–2.40 (1 H, m,  $CH_ACH_BCH=$ ), 2.55–2.73 (1 H, app. br t,  $J \sim 12$ , 6'- $H_{ax}$ ), 3.01 (1 H, td,  $J$  11.1 and 4.0, CHCO), 3.67 (3 H, s, OMe), 4.13 (1 H, app. br d,  $J \sim 12$ , 6'- $H_{eq}$ ), 4.32–4.43 (1 H, m, 2'- $H_{eq}$ ), 5.00 (1 H, br d,  $J$  10.4,  $CH=CH_cH_i$ ), 5.05 (1 H, br d,  $J$  17.2,  $CH=CH_cCH_i$ ) and 5.91 (1 H, ddt,  $J$  17.2, 10.4 and 6.8,  $CH=CH_2$ );  $\delta_c$ (100 MHz) 18.95 ( $CH_2$ ), 25.08 ( $CH_2$ ), 27.37 (br,  $CH_2$ ), 28.23 (Bu<sup>t</sup>), 33.53 (br,  $CH_2$ ), 38.8 (v br,  $CH_2$ -6), 45.51 (CH), 51.30 (OMe), 52.20 (br, CH-2'), 79.52 [ $C(CH_3)_3$ ], 116.51 (=CH<sub>2</sub>), 135.01 (=CH), 154.80 [ $C(O)N$ ] and 174.13 [ $C(O)O$ ];  $m/z$  224 (2%), 210 (4), 196 (5), 184 (20), 142 (22), 128 (83), 84 (100) and 57 (77).

The product was contaminated by ca. 4% of the (2S,2'S)-isomer **13**.

(2S,2'S)-Methyl 2-(N-tert-Butoxycarbonylpiperidin-2'-yl)-pent-4-enoate **13** (Direct Allylation).—A solution of lithium hexamethyldisilazide (LHMDS) (4.4 mmol) in THF (5 cm<sup>3</sup>) was prepared as described in the foregoing reaction and cooled to  $-78^\circ C$  and then treated with a solution of the ester **14** (1.028 g, 4 mmol) in THF (4 cm<sup>3</sup>). After 0.5 h, allyl bromide (0.49 g, 4 mmol) in THF (2.5 cm<sup>3</sup>) was added and the resulting solution stirred for 0.5 h then allowed to warm to ambient temperature and quenched with water (5 cm<sup>3</sup>). The organic products were extracted into diethyl ether (3  $\times$  25 cm<sup>3</sup>) and the combined extracts were dried and evaporated. Careful SG chromatography (20:1,  $CH_2Cl_2$ -EtOAc) separated the (2S,2'S)-isomer **13** (0.842 g, 71%) as a colourless oil (Found: C, 64.5; H, 9.5; N, 4.6%);  $[\alpha]_D -7.5$  ( $c$  2.84,  $CHCl_3$ );  $\nu_{max}$ (film)/cm<sup>-1</sup> 1736 and 1688;  $\delta_H$ (400 MHz) 1.36–1.52 (2 H, m), 1.43 (9 H, s, Bu<sup>t</sup>), 1.55–1.70 (4 H, m), 2.16–2.24 (1 H, m,  $CH_AH_BCH=$ ), 2.29–2.41 (1 H, m,  $CH_ACH_BCH=$ ), 2.93 (1 H, app. br dd,  $J \sim 13.8$  and  $\sim 12.7$ , 6'- $H_{ax}$ ), 3.01 (1 H, td,  $J$  10.9 and 3.9, CHCO), 3.61 (3 H, s, OMe), 3.99 (1 H, m, 6'- $H_{eq}$ ), 4.40 (1 H, m, 2'- $H_{eq}$ ), 5.03 (1 H, br d,  $J$  10.4,  $CH=CH_cH_i$ ), 5.08 (1 H, br d,  $J$  17.2,  $CH=CH_cCH_i$ ) and 5.75 (1 H, ddt,  $J$  17.2, 10.4 and 6.7,  $CH=CH_2$ );  $\delta_c$ (100 MHz) 19.00 ( $CH_2$ ), 25.30 ( $CH_2$ ), 25.84 (sl. br,  $CH_2$ ), 28.35 (Bu<sup>t</sup>), 33.93 ( $CH_2$ ), 39.30 (br,  $CH_2$ -6'), 45.21 (CH), 51.48 (OMe), 52.51 (br, CH-2'), 79.42 [ $C(CH_3)_3$ ], 116.99 (=CH<sub>2</sub>), 134.98 (=CH), 154.39 [ $C(O)N$ ] and 173.66 [ $C(O)O$ ];

$m/z$  224 (2%), 210 (4), 196 (3), 184 (11), 142 (10), 128 (100), 84 (88) and 57 (45).

A sample (0.14 g, 12%) of the (2R,2'S)-isomer **12** was also isolated.

(2S,2'S)-Methyl 2-(N-tert-Butoxycarbonylpiperidin-2'-yl)-5-hydroxypentanoate **15**.—Borane–methyl sulfide (30 mm<sup>3</sup>, 0.33 mmol) was added dropwise to a stirred, ice-cold solution of the ester **13** (0.297 g, 1 mmol) in dry hexane (6 cm<sup>3</sup>). After 0.5 h, the cooling bath was removed and stirring was continued for 3 h. Ethanol (2 cm<sup>3</sup>) was added to the mixture followed by aqueous sodium hydroxide (1% solution; 1.6 cm<sup>3</sup>) and hydrogen peroxide (30% solution; 0.2 cm<sup>3</sup>). The resulting solution was heated at reflux for 1 h, then cooled, diluted with water (5 cm<sup>3</sup>) and extracted with diethyl ether (4  $\times$  25 cm<sup>3</sup>). The combined extracts were washed with brine (20 cm<sup>3</sup>) then dried, filtered through a pad of silica and the filtrate was evaporated to leave the hydroxy ester **15** (0.299 g, 95%), which was pure according to TLC and <sup>1</sup>H NMR, as a colourless semi-solid (Found: C, 61.2; H, 9.6; N, 4.2.  $C_{16}H_{29}NO_5$  requires C, 60.9; H, 9.3; N, 4.4%);  $[\alpha]_D -4.7$  ( $c$  2.34,  $CHCl_3$ );  $\nu_{max}$ (film)/cm<sup>-1</sup> 3400, 1738 and 1676;  $\delta_H$ (400 MHz) 1.43 (9 H, s, Bu<sup>t</sup>), 1.47–1.90 (8 H, m), 2.65 (1 H, app. br t,  $J \sim 12$ , CHCO), 2.95 (1 H, app. br dd,  $J \sim 13$  and  $\sim 12$ , 6'- $H_{ax}$ ), 3.66 (3 H, s, OMe), 3.90–4.12 (3 H, m,  $CH_2O$  and 6'- $H_{eq}$ ) and 4.35–4.44 (1 H, m, 2'- $H_{eq}$ );  $m/z$  214 (2%), 184 (15), 128 (100), 84 (97) and 57 (41).

(1S,9aS)-Methyl Octahydro-1H-quinolizine-1-carboxylate **16**.—Methanesulfonyl chloride (0.097 g, 0.84 mmol) was added dropwise to an ice-cold, stirred solution of the foregoing hydroxy ester **15** (0.2203 g, 0.699 mmol) and dry triethylamine (0.0848 g, 0.84 mmol) in dry dichloromethane (5 cm<sup>3</sup>). The reaction was monitored by TLC and adjudged to be complete after 1.75 h. After a further 0.25 h, the mixture was diluted with dichloromethane (15 cm<sup>3</sup>) and washed with water (2  $\times$  5 cm<sup>3</sup>) then dried and filtered. The filtrate was concentrated to  $\sim 5$  cm<sup>3</sup> and to this was added trifluoroacetic acid (1 cm<sup>3</sup>). The resulting solution was stirred at ambient temperature for 1.5 h and then evaporated and the residue finally dried under high vacuum. The dry residue was then treated with ice-cold, aqueous sodium hydroxide (2 mol dm<sup>-3</sup>; 2 cm<sup>3</sup>) and dichloromethane (5 cm<sup>3</sup>). After mixing, the layers were separated and the aqueous layer was extracted with dichloromethane (4  $\times$  5 cm<sup>3</sup>). The combined organic extracts were dried and then evaporated. SG chromatography of the residue (20:1:0.1  $CHCl_3$ -MeOH-Pr<sup>i</sup>NH<sub>2</sub>) gave the ester **16** (0.087 g, 63%) as a pale yellow oil,  $[\alpha]_D +10.2$  ( $c$  1.5,  $CHCl_3$ );  $\nu_{max}$ (film)/cm<sup>-1</sup> 1735;  $\delta_H$ (250 MHz) 1.17–2.18 (11 H, m), 2.48–3.00 (5 H, m) and 3.68 (3 H, s, OMe);  $\delta_c$ (100 MHz) 24.04, 24.25, 25.41, 29.54, 30.65, 51.19, 51.60, 56.56, 57.26, 66.14 and 173.60;  $m/z$  197 ( $M^+$ , 28%), 196 (21), 182 (21), 166 (20), 138 (29), 124 (15), 123 (13), 111 (45), 110 (40), 97 (58), 96 (21), 84 (96), 83 (100), 82 (26) and 55 (31) (Found:  $M^+$ , 197.1419.  $C_{11}H_{19}NO_2$  requires  $M$ , 197.1416).

The <sup>13</sup>C NMR data suggested that the sample was contaminated with ca. 5% of the (1R,9aS) diastereoisomer.

(1S,9aS)-(Octahydro-1H-quinolizin-1-yl)methanol [(+)-Lupinine] **17**.—A solution of the foregoing ester **16** (0.094 g, 0.52 mmol) in dry diethyl ether (3 cm<sup>3</sup>) containing THF (1 cm<sup>3</sup>) was added dropwise to a suspension of lithium aluminium hydride (0.025 g) in diethyl ether (6 cm<sup>3</sup>). The resulting mixture was refluxed for 4 h, then cooled and quenched with water (0.1 cm<sup>3</sup>) followed by aqueous sodium hydroxide (15% solution; 0.1 cm<sup>3</sup>) and then more water (0.3 cm<sup>3</sup>). The organic layer was decanted and the aqueous residue was extracted with diethyl ether (3  $\times$  5 cm<sup>3</sup>). The combined organic solutions were dried and evaporated to leave essentially pure (+)-lupinine **17** (0.074 g, 91%). Crystallisation from hexane provided an analytical

sample (> 80% yield) as colourless crystals which showed m.p. 67–68 °C (lit.,<sup>2c</sup> m.p. 68–69 °C) (Found: C, 71.2; H, 11.4; N, 8.3. Calc. for C<sub>10</sub>H<sub>19</sub>NO: C, 71.0; H, 11.3; N, 8.3%); [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 19.5 (c 1, EtOH) {lit.,<sup>2c</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup> – 20.91 (c 9.5, EtOH); lit.,<sup>35</sup> – 21 (c 1, EtOH) for (–)-lupinine **1**};  $\nu_{\max}$ (CHCl<sub>3</sub>)/cm<sup>-1</sup> 3450;  $\delta_{\text{H}}$ (400 MHz) 1.20–2.21 (15 H, m), 2.72–2.95 (2 H, m), 3.67 (1 H, d, *J* 10.8) and 4.11 (1 H, ddd, *J* 10.8, 4.4 and 1.5);<sup>9b,21b</sup>  $\delta_{\text{C}}$ (100 MHz) 22.92, 24.66, 25.61, 29.71, 31.34 (all CH<sub>2</sub>), 38.21 (CH), 57.08 (2 × CH<sub>2</sub>N), 65.11 (CH) and 65.86 (CH<sub>2</sub>OH);<sup>9,35,36</sup> *m/z* 169 (M<sup>+</sup>, 21%), 168 (19), 152 (44), 138 (43), 124 (14), 111 (24), 110 (33), 98 (40), 97 (38), 96 (36), 84 (100), 83 (68), 82 (38) and 55 (38).<sup>37</sup>

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