An alkylation route to carbo- and heteroaromatic amino acids

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Abstract
Amino acids carrying aromatic carbo- and heterocycles in the side chain, such as naphthyl-, biphenyl- and pyridylalanines, have been prepared by alkylation of a glycine enolate with a haloalkyl carbocycle or heterocycle, with enantiomeric excess up to 87% using the ephedrine amide protocol.

Keywords: Amino acid, non-proteinogenic, ephedrine glycinamide, glycine enolate, pyridylalanine

Introduction
We have a programme to prepare unusual α-amino acids including those carrying carbocyclic and heterocyclic moieties not covered by the proteinogenic set: phenylalanine, tyrosine, histidine and tryptophan. 1, 2 With this in mind we have investigated the disconnection of Scheme 1, involving a glycine enolate equivalent and a side-chain electrophile. The glycine enolate had to be optically active to induce asymmetry during the alkylation process, and we elected to explore the enolate derived from the ephedrine-based glycinamide 1. 3 We detail herein our findings on the synthetic methodology, and the synthesis of naphthylalanine, biphenylalanine, the regioisomers of pyridylalanine, and an isoxazole derivative. Although some of these compounds have been reported, 4 we are not aware of the application of the alkylation of glycine enolates to their construction. 5

‡ Ray Jones was Secretary and Treasurer of the RSC Heterocyclic Group during the period 1992-1996 and Chairman during the period 2001-2003
Scheme 1. Disconnection to form amino acids.

Results and Discussion

From the possible glycine enolate sources, we selected the ephedrine-based glycinamide 1 developed by Myers, based on the low cost and availability (of both enantiomers) of the precursors, the tendency of pseudoephedrine amides to be crystalline, and the reported high diastereoselectivity of the alkylation reaction and facile removal of the chiral auxiliary. Furthermore, the manipulations are performed without the need for protection on the glycine amino group, so that in principle unnatural amino acids are prepared in three steps in good yields and enantiomeric excess.

The first task was to prepare the glycine pseudoephedrine amide 1. This was performed using (1R,2R)-pseudoephedrine and glycine methyl ester under the basic conditions of Myers. We found that treatment of glycine methyl ester hydrochloride in dry diethyl ether with dry ammonia for 3-4 h, followed by filtration of the ammonium chloride and careful concentration of the ethereal solution afforded a sufficiently pure solution of the glycine methyl ester and avoided the need for distillation, whereas the use of triethylamine (1 equiv.) in dry ether to neutralize the ester salt resulted in the formation of unwanted side-products in the later alkylation. The coupling protocol involved deprotonation of the hydroxyl group with n-butyllithium (0.8 equiv.) in THF in the presence of anhydrous lithium chloride at 0 ºC and addition of the ethereal glycine methyl ester solution (1.2 equiv.). High yields (up to 80%) were only obtained when rigorously dried LiCl was used and the glycine ester solution was added slowly over 1.5 h. The glycinamide 1 was obtained as a hydrate without chromatography, and it was essential to dehydrate this using anhydrous potassium carbonate and subsequent recrystallisation from toluene. This material could be satisfactorily stored in vacuo over P2O5.

There are three sites for deprotonation of 1, the secondary hydroxyl group, the amino group and the desired α-carbon. It has been shown that 2 equiv. of base gives the N,O-dianion A as kinetic product at −78 ºC, but that after warming to 0 ºC the thermodynamic C,O-dianion B is formed, a glycine enolate that can undergo C-alkylation. Since decomposition has been found to result from use of excess base (>2 equiv.), the reported protocol for enolate formation is to add LDA (1.95 equiv.) in THF dropwise to a slurry of the amide 1 (1 equiv.) and anhydrous LiCl (6
equiv.) in dry THF; we have performed this at 0 °C, rather than at –78 °C, then warming to 0 °C. In our hands, when >2 equiv. of LDA was present, free pseudoephedrine was liberated and the reaction mixture developed an orange coloration in contrast to the normal yellow colour. We used this as a titration for the amount of LDA, stopping base addition when the solution was still just yellow, even if this meant using less than the calculated 1.95 equiv. of base. We adopted this protocol, using a slurry of anhydrous pseudoephedrine glycinamide and flame-dried LiCl in THF at 0 °C under argon, adding freshly prepared LDA solution over 30 min until just before the colour change, and then after stirring for 30 min at 0 °C, adding a solution of a haloalkane (1.1-1.2 equiv.) in THF. After a further period of 2 h at 0 °C, the mixture was worked up to provide the C-alkylation product. The use of commercial LDA solutions was found to give less satisfactory results. It also proved necessary to dry the LiCl under vacuum for 12 h, then to flame-dry it prior to use and cool it under argon.8

Scheme 2

Using this protocol, we first validated the method using benzyl bromide as electrophile. The alkylation product 2a was obtained in 62% yield. As expected, it displayed rotational isomerism in the 1H and 13C NMR spectra, for example two NCH3 signals, δH 2.60 & 2.90, δC 27.1 & 30.4. VT-NMR studies up to 100 °C did not show peak coalescence. Attempts to determine diastereoisomer ratios by HPLC or chiral column GC were unsuccessful. We therefore proceeded directly to hydrolytic removal of the chiral auxiliary.

The hydrolysis of glycinamide alkylation products was originally reported by heating under reflux in a slightly alkaline solution.3 However, we noted that the products of alkylation
displayed some water solubility to produce alkaline solutions, presumably due to the presence of the free amino group. We therefore found that simply heating a solution of the alkylation product in water-dioxane for 12 h led to quantitative hydrolysis to afford the free amino acid plus pseudoephedrine. The latter was removed by extraction with DCM. Evaporation of the aqueous layers and subsequent trituration of the crude amino acid in ethanol served to remove any residual traces of pseudoephedrine. An advantage of this simple hydrolysis is that the amino acid product does not require a desalting procedure such as ion exchange chromatography.

Using the above procedure, phenylalanine \textbf{3a} was isolated from \textbf{2a} in 76% yield, and pure pseudoephedrine was recovered in 70% yield. To assess the enantiomeric purity of the acid obtained, the NMR method of Mosher was employed. Thus, the amino acid was esterified using HCl solution in ethanol, and treating the ester with (\(R\))-2-methoxy-2-phenyl-3,3,3-trifluoropropanoyl chloride [(\(R\))-MTPA-Cl]. \(^{19}\)F NMR spectroscopy of the ‘Mosher amide’ \textbf{4a} produced in this way from the above sample of phenylalanine displayed two singlets at \(\delta_F = 69.087\) (major) and \(-69.141\) (minor), and the ratio indicated an e.e of 87%. To check the chiral integrity during the sequence, commercial (\(S\))-phenylalanine ethyl ester hydrochloride was coupled to (\(1R,2R\))-pseudoephedrine using the same conditions as the coupling with glycine, the amide hydrolysed and the amino acid converted in the same way into the Mosher amide. The \(^{19}\)F NMR spectrum showed one peak only, corresponding to the major diastereoisomer of \textbf{4a}. This sequence was repeated starting with commercial (\(R\))-phenylalanine and (\(1S,2S\))-pseudoephedrine, and the Mosher amide displayed just one peak in the \(^{19}\)F NMR spectrum, now corresponding to the minor diastereoisomer of \textbf{4a}. These results confirmed that (i) the e.e of 87% was due to the diastereoselectivity in the pseudoephedrine glycinamide alkylation step, and (ii) that the alkylation of (\(R,R\))-pseudoephedrine glycinamides produces predominantly the (\(S\))-amino acids. This latter is in line with the reported predictive mnemonic of 1,4-\textit{syn} products when the (\(Z\))-enolate is drawn in a planar extended conformation (Figure 1).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1}
\caption{Mnemonic for prediction of stereochemistry of alkylation products \textbf{2}.}
\end{figure}

With the synthetic protocols and analytical methodology in place and validated, we were in a position to extend the sequence to other haloalkyl hetero- and carboaromatics that would afford non-proteinogenic amino acids. Therefore, we reacted the glycinamide \textbf{1} according to the procedures detailed above with the following commercially available halides: 1-chloromethylnaphthalene, 1-(2-bromoethyl)naphthalene, 2-phenylbenzyl chloride, 2-
chloromethylpyridine, 3-chloromethylpyridine, 4-chloromethylpyridine and 4-chloromethyl-3,5-dimethylisoxazole. This afforded the alkylation products 2b-h in yields of 33-97% (see Table 1) as sticky oils that could not be crystallized; in the pyridyl cases, the chlorides proved unstable after liberation from the purchased hydrochloride salts, and the alkylation products 2e-g could not be fully purified for spectroscopic analysis. We thus decided to subject these alkylation products to hydrolysis directly.

Table 1. Alkylation of 1 to form amides 2, hydrolysis to amino acids 3, and determination of ee by conversion into Mosher amides 4

<table>
<thead>
<tr>
<th>Entry</th>
<th>R Alkylated amide 2 (% yield)</th>
<th>Amino acid 3 (% yield)</th>
<th>ee of 3 (from Mosher amide 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Ph 2a (62)</td>
<td>3a (76)</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>CH₂(1-naphthyl) 2b (61)</td>
<td>3b (76)</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>CH₂CH₂(1-naphthyl) 2c (33)</td>
<td>3c (74)</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>CH₂(2-PhC₆H₄) 2d (68)</td>
<td>3d (48)</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td>CH₂(2-pyridyl) 2e (62*)</td>
<td>3e (59)</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>CH₂(3-pyridyl) 2f (55*)</td>
<td>3f (49)</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>CH₂(4-pyridyl) 2g (36*)</td>
<td>3g (40)</td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td>CH₂(3,5-dimethylisoxazo-l-4-yl) 2h (97)</td>
<td>3h (59)</td>
<td>74</td>
</tr>
</tbody>
</table>

* crude yields (see text)

The amides 2b-h, in a minimum amount of dioxan to ensure solution, were hydrolysed in water at reflux as outlined above to afford, after DCM extraction to remove pseudoephedrine, evaporation of the aqueous layer to dryness and trituration of the residue with ethanol, the non-proteinogenic amino acids 3b-h. The progress of hydrolysis was monitored by HPLC and found to be complete after 12 h. In our hands this procedure afforded the amino acids 3b-h in yields of 40-76% (Table 1) with good purity. This procedure assisted in the purification of the pyridyl derivatives 3e-g, although the amino acids were somewhat soluble in ethanol, which may account for the reduced isolated yields.

In order to determine the enantiomeric purity of the acids 3b-h, they were subjected to the sequence developed above for preparation of the Mosher’s amides 4b-h, via synthesis of their ethyl ester hydrochlorides (EtOH, HCl, reflux) and reaction with (R)-MTPA-Cl. The diastereomer mixtures were examined by 19F NMR spectroscopy; in each case the presence of two singlets revealed the presence of two diastereoisomers. The δe values, calculated from the integrals and which can be equated to ee values for the amino acids 3b-h, were in the range 61-87% (Table 1), with the exception of the 2-pyridyl case 3e (10%). We assume, based on precedent, that the major isomers have the (S)-configuration. The ee values were not as high as has been reported, and not always reproduced, most likely due to difficulties in determination of
the end-point for BuLi addition to 1 to form its enolate, and to variability in the physical state of the LiCl, both critical factors in the alkylation protocol, *vide supra*.

Nevertheless, we have successfully prepared several interesting non-proteinogenic amino acids carrying aromatic side chains *via* a flexible glycine enolate approach that could be easily extended to a range of carbo- and heteroaromatic moieties. We also report several technical issues in the experimental protocols. The naphthyl and biphenyl amino acids 3b-d are potential nucleic acid intercalators, the pyridylalanines 3e-g have been used as histidine replacements and have diverse pharmacological effects, and the isoxazolyl amino acid 3h is an analogue of 2-amino3-(3-hydroxy-5-methylisazol-4-yl)propionic acid (AMPA), an excitatory amino acid.

**Experimental Section**

**General Procedures.** Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 1710 FT-IR spectrometer. NMR spectra were obtained at 376 MHz on a JEOL JNM-EX400 spectrometer, and 1H and 13C NMR spectra recorded at 300 MHz or at 75 MHz, respectively, on a JEOL JNM-LA300 spectrometer, in deuteriochloroform unless otherwise stated. Low-resolution mass spectra were recorded on a VG Micromass VG20-250 spectrometer, or by the EPSRC National Mass Spectrometry Service Centre (University of Wales Swansea) who also performed the accurate mass measurements. All reagents were purified by distillation or recrystallisation where appropriate, or according to standard procedures. Column chromatography was carried out using Fluka Silica Gel 60 (220-440 mesh). TLC analysis was performed using Macherey-Nagel Polygram SIL G/UV254 plates and visualized by UV light or aqueous KMnO4 spray (KMnO4:K2CO3:water 6:1:100 w/v/v). Organic extracts were dried over anhydrous MgSO4.

**General method for alkylation of pseudoephedrine glycinamide (1).** A freshly prepared solution of LDA (2M, 1.95 equiv.) in hexanes was added over 0.25-0.5 h to a stirred slurry of anhydrous pseudoephedrine glycinamide 1 (1.0 equiv.) and flame-dried LiCl (6 equiv.) in THF under a positive argon atmosphere at 0 °C. After stirring at 0 °C for 0.5-1 h, the haloalkane (1.1 equiv.) was added dropwise. After 12 h, hydrochloric acid (1M) was added, followed by ethyl acetate. The organic layer was extracted with a second portion of hydrochloric acid (1M). The aqueous extracts were combined and the resulting solution was cooled in an ice-bath and carefully basified to pH 14 by addition of aqueous sodium hydroxide solution (50%). The basic aqueous solution was extracted with DCM. The combined organic extracts were combined and dried over potassium carbonate, filtered and concentrated under reduced pressure to provide the alkylated products 2.

**(1R,2R,2'S)-2'Amino-3'-phenylpropanoylpseudoephedrine (2a).** Prepared as above using LDA (2M, 17.56 mL, 0.035 mol), (1R,2R)-pseudoephedrine glycinamide 1 (4.00 g, 18 mmol) and lithium chloride (4.58 g, 108 mmol) in THF (100 mL), with benzyl bromide (3.39 g, 20 mmol) in THF (10 mL). After 2 h, hydrochloric acid (1M, 100 mL) was added followed by ethyl
acetate (200 mL). The organic layer was extracted with a second portion of hydrochloric acid (1M, 100 mL). The aqueous extracts were combined, cooled, basified and extracted with DCM (3 x 80 mL). Removal of the solvent provided a hygroscopic solid residue (3.45 g, 62%), \( R_F = 0.53 \) (DCM:MeOH:Et\(_3\)N 90:5:5 v/v/v); Found: MH\(^+\) (ES\(^+\)) 313.1908. C\(_{15}\)H\(_{24}\)N\(_2\)O\(_2\) requires: MH\(^+\) 313.1916.

\[ \nu_{\text{max}}/\text{cm}^{-1} \text{ (KBr)} \]

- 3300, 3250, 1625, 1500, 1450, 1400, 1300, 1100;
- \( \delta_H \) (4:1 rotamer ratio, the asterisk denotes the minor isomer)
  - 0.88 and 0.99* (3H, d, \( J \) 6.2, CHCH\(_3\)), 2.60 and 2.90* (3H, s, NCH\(_3\)), 2.70-2.82 (2H, 2 x dd, \( J \) 13.2 and 7.2, CHCH\(_2\)), 3.70 (1H, t, \( J \) 7.1, CHCH\(_3\)), 4.30 and 4.45* (1H, d, \( J \) 6.6, CHOH), 4.60 and 4.70* (1H, m, CHCH\(_3\)), 7.00-7.30 (10H, m, ArH);
- \( \delta_C \)
  - 14.4 and 15.5* (CHCH\(_3\)), 27.1* and 30.4 (NCH\(_3\)), 41.9* and 30.4 (CH\(_2\)) 53.2 (CHHCH\(_2\)), 56.5 and 57.9* (CHCH\(_3\)), 75.0* and 75.6 (CHOH), 126.5, 126.6, 126.7, 126.8, 127.7, 128.2, 128.3, 128.4, 128.5, 128.6, 129.2, 129.4 (6 x ArCH and 6 x ArCH*), 137.5 and 138.4*, 141.7* and 142.0 (2 x ArC), 175.2* and 176.2 (C=O); 
- \( m/z \) (CI) 313 (MH\(^+\), 100%), 295 (40), 277 (25), 267 (15), 255 (60), 231 (30).

\((1R,2R,2'S)-2'-\text{Amino}-3'-(1-naphthyl)propanoylpseudoephedrine (2b).\) Prepared by the general method, using (1R,2R)-pseudoephedrine glycinamide \(1 \) (2 g, 9 mmol), LDA (8.78 mL, 18 mmol), lithium chloride (2.29 g, 54 mmol) and 1-chloromethylnaphthalene (1.67 g, 9.5 mmol). After the usual extraction, the yellow gum was purified by column chromatography (DCM:MeOH:Et\(_3\)N 90:5:5 v/v/v) to yield the title compound as a yellow hygroscopic gum (1.98 g, 61%).

\[ \nu_{\text{max}}/\text{cm}^{-1} \text{ (film)} \]

- 3400, 3200, 2850, 1650, 1300, 950;
- \( \delta_H \) (4:1 rotamer ratio, the asterisk denotes the minor isomer)
  - 0.90 and 1.00* (3H, d, \( J \) 4.9, CHCH\(_3\)), 2.60 (3H, s, NCH\(_3\)), 3.10 and 3.20 (2H, 2 x dd, \( J \) 5.4 and 9.9, CHCH\(_2\)), 3.80 and 3.90* (1H, t, \( J \) 5.4, CHCH\(_2\)), 4.15* and 4.40 (IH, m, CHCH\(_3\)), 4.10 and 4.20* (1H, d, \( J \) 6.7, CHOH), 6.90-7.90 (12H, m, ArH);
- \( \delta_C \)
  - 15.2 and 15.6* (CHCH\(_3\)), 29.8* and 30.8 (NCH\(_3\)), 39.4 and 39.5* (CH\(_2\)), 52.2 and 56.9* (CHCH\(_2\)), 53.7 and 68.9* (CHCH\(_3\)), 75.6 and 75.5* (CHOH), 123.3, 123.4, 125.3, 125.4, 125.6, 126.1, 126.2, 126.3, 126.7, 126.8, 127.4, 127.5, 127.7, 128.1, 128.3, 128.4, 128.8, 128.9, 131.9 and 132.0 (10 x ArCH and 10 x ArCH*), 132.2 and 133.6*, 133.8 and 134.2*, 135.1 and 135.3*, 141.9 and 142.0* (4 x ArC), 176.3* and 176.4 (C=O); 
- \( m/z \) (CI) 363 (MH\(^+\), 100%), 293 (40), 277 (25), 267 (15), 255 (60), 231 (30).

\((1R,2R,2'S)-2'-\text{Amino}-4'-(1-naphthyl)butanoylpseudoephedrine (2c).\) Prepared by the general method, using (1R,2R)-pseudoephedrine glycinamide \(1 \) (1.51 g, 6.77 mmol), LDA (6.60 mL, 13.21 mmol), lithium chloride (1.73 g, 40.64 mmol) and 1-(2-bromoethyl)naphthalene (1.75 g, 7.45 mmol). After the usual extraction, the yellow gum was purified by column chromatography (DCM:MeOH:Et\(_3\)N 90:5:5 v/v/v) to yield the title compound as a yellow gum (0.85 g, 33%).

\[ \nu_{\text{max}}/\text{cm}^{-1} \text{ (film)} \]

- 3400, 3200, 2850, 1650, 1300, 950;
- \( \delta_H \) (4:1 rotamer ratio, the asterisk denotes the minor isomer)
  - 0.65* and 0.80 (3H, d, \( J \) 4.9, CHCH\(_3\)), 2.60 (3H, s, NCH\(_3\)), 3.10 and 3.20 (2H, 2 x dd, \( J \) 5.4 and 9.9, CHCH\(_2\)), 3.80 and 3.90* (1H, t, \( J \) 5.4, CHCH\(_2\)), 4.15* and 4.40 (IH, m, CHCH\(_3\)), 4.10 and 4.20* (1H, d, \( J \) 6.7, CHOH), 6.90-7.90 (12H, m, ArH);
- \( \delta_C \)
  - 14.0 and 15.5* (CHCH\(_3\)), 29.8* and 30.8 (NCH\(_3\)), 39.4 and 39.5* (CH\(_2\)), 52.2 and 56.9* (CHCH\(_2\)), 53.7 and 68.9* (CHCH\(_3\)), 75.6 and 75.5* (CHOH), 123.3, 123.4, 125.3, 125.4, 125.6, 126.1, 126.2, 126.3, 126.7, 126.8, 127.4, 127.5, 127.7, 128.1, 128.3, 128.4, 128.8, 128.9, 131.9 and 132.0 (10 x ArCH and 10 x ArCH*), 132.2 and 133.6*, 133.8 and 134.2*, 135.1 and 135.3*, 141.9 and 142.0* (4 x ArC), 176.3* and 176.4 (C=O); 
- \( m/z \) (CI) 363 (MH\(^+\), 100%), 230 (20) and 166 (100).
126.7, 127.0, 127.5, 127.6, 127.8, 127.9, 128.1, 128.3, 128.5 and 128.6 (10 x ArCH and 10 x ArCH*), 131.6 and 131.8*, 133.7, 137.4 and 138.0*, 141.7* and 142.1 (4 x ArC), 175.9* and 176.8 (C=O); m/z (CI) 377 (MH, 70%), 355 (60) and 337 (80).

(1R,2R,2'S)-2'-Amino-3'-(2-phenylphenyl)propanoylpseudoephedrine (2d). Prepared following the general method using (1R,2R)-pseudoephedrine glycaminide 1 (2.50 g, 11.3 mmol), lithium chloride (2.86 g, 67.5 mmol), LDA (10.9 mL, 21.8 mmol) and 2-phenylbenzyl chloride (3.06 g, 12.4 mmol) to yield the title compound as a white hygroscopic powder (2.97 g, 68%). Found: MH+ (ES+) 389.2234. C25H28N2O2 requires: MH 389.2229.

ν max/cm–1 (film) 3100, 3000, 1256, 750, 700; δ H (4:1 rotamer ratio, the asterisk denotes the minor isomer) 0.60* and 0.90 (3H, d, J 4.9, CHC H3), 2.00 (3H, s, NCH3), 2.40 and 2.80 (2H, 2 x dd, J 8.7 and 11.7, CH2), 3.30 and 3.40* (1H, m, C HCH2), 3.20 (1H, m, CHCH3), 4.40 (1 H, d, J 6.3, CHOH), 7.10-7.40 (14H, m, ArH); δ C 14. 1 and 14.2 (CH C H3), 31.0 (NCH3), 39.2* and 39.5 (CHC H2), 50.6* and 51.8 (CHC H2), 74.8* and 75.0 (CHOH), 75.4 (CHCH3), 126.0, 126.1, 126.3, 126.8, 126.9, 127.2, 127.4, 127.5, 127.6, 128.2, 128.4, 128.6, 128.8, 129.1, 129.3, 130.2, 130.4, 130.5, 130.6, 131.0 (10 x ArCH and 10 x ArCH*), 132.0 and 132.3*, 133.0 and 133.2*, 141.0 and 141.2*, 141.9* and 142.2 (4 x ArC), 175.0* and 176.1 (C=O); m/z (CI) 389 (MH+, 40%), 166 (100) and 58 (15).

(1R,2R,2'S)-2'-Amino-3'-(2-pyridyl)propanoylpseudoephedrine (2e). 2-Chloromethylpyridine hydrochloride (5 g, 30.5 mmol) and triethylamine (3.1 g, 30.5 mmol) were stirred for 3 h at room temperature in dry THF (100 mL) under an atmosphere of nitrogen. The triethylamine hydrochloride salt was filtered off and the solution reduced to 20 mL under reduced pressure and used immediately in the alkylation. The alkylated compound was prepared following the general method, using (1R,2R)-pseudoephedrine glycaminide 1 (5.64 g, 25.4 mmol), lithium chloride (6.46 g, 152.4 mmol), LDA (24.4 mL, 48.8 mmol) and 2-chloromethylpyridine (3.89 g, 30 mmol). The crude brown gum (6.2 g) that was obtained was subjected several times to column chromatography (DCM:MeOH:Et3N 90:5:5 v/v/v) to yield the title compound (4.95 g, 62%) which was used directly in the next step.

(1R,2R,2'S)-2'-Amino-3'-(3-pyridyl)propanoylpseudoephedrine (2f). 3-Chloromethylpyridine hydrochloride (3 g, 18.3 mmol) and triethylamine (3.1 g, 30.5 mmol) were stirred for 3 h at room temperature in dry THF (100 mL) under an atmosphere of nitrogen. The triethylamine hydrochloride salt was filtered off and the solution reduced to 20 mL under reduced pressure and used immediately in the alkylation. The alkylated compound was prepared following the general method, using (1R,2R)-pseudoephedrine glycaminide 1 (5.64 g, 25.4 mmol), lithium chloride (6.46 g, 152.4 mmol), LDA (24.4 mL, 48.8 mmol) and 2-chloromethylpyridine (3.89 g, 30 mmol). The crude brown gum (6.2 g) that was obtained was subjected several times to column chromatography (DCM:MeOH:Et3N 90:5:5 v/v/v) to yield the title compound (4.95 g, 62%) which was used directly in the next step.

(1R,2R,2'S)-2'-Amino-3'-(4-pyridyl)propanoylpseudoephedrine (2g). 4-Chloromethylpyridine hydrochloride (3 g, 18.3 mmol) and triethylamine (1.85 g, 18.3 mmol) were stirred for 3 h at room temperature in dry THF (100 mL) under an atmosphere of nitrogen. The triethylamine hydrochloride salt was filtered off and the solution reduced to 20 mL under reduced pressure and used immediately in the alkylation. The alkylated compound was prepared following the general method, using (1R,2R)-pseudoephedrine glycaminide 1 (3.4 g, 15.3 mmol), lithium chloride (3.89 g, 91.8 mmol), LDA (14.9 mL, 29.8 mmol) and 3-chloromethylpyridine (2.33 g, 18.3 mmol). The brown gum that was obtained was subjected several times to column chromatography (DCM:MeOH:Et3N 90:5:5 v/v/v) to yield the title compound (2.65 g, 55%) which was used directly in the next step.
used immediately for the alkylation. The alkylated compound was prepared following the general method, using (1R,2R)-pseudoephedrine glycineamide 1 (2.96 g, 13.3 mmol), lithium chloride (3.4 g, 80.2 mmol), LDA (13 mL, 26.0 mmol) and 4-chloromethylpyridine (2.04 g, 16.0 mmol). The black gum that was obtained was subjected several times to column chromatography (DCM:MeOH:Et3N 90:5:5 v/v/v) to yield the title compound as a brown hydroscopic solid (1.5 g, 36%) which was used directly in the next step.

(1R,2R,2'S)-2'-Amino-3'-(3,5-dimethylisoxazol-4-yl)propanoylpseudoephedrine (2h).

Prepared following the general method using (1R,2R)-pseudoephedrine glycineamide 1 (5.88 g, 26.5 mmol), lithium chloride (6.73 g, 159 mmol), LDA (25.8 mL, 51.6 mmol) and 4-chloromethyl-3,5-dimethylisoxazole (4.24 g, 29.1 mmol) to yield the title compound as a white hygroscopic powder (8.46 g, 97%). Found: MH+ (ES+) 332.1976. C18H25N3O3 requires: MH 332.1974. νmax/cm–1 (film) 3390, 2950, 2900, 1650, 1450, 1400, 1250, 1200, 1050, 750, 700; δH (4:1 rotamer ratio, the asterisk denotes the minor isomer) 0.66* and 0.77 (3H, d, J 4.8, CHCH3), 2.05* and 2.10 (3H, s, isoxazole CH3), 2.15* and 2.25 (3H, s, isoxazole CH3), 2.35 and 2.45 (2H, 2 x dd appears as multiplets, CHCH2), 2.65 (3H, s, NCH3), 3.60 and 3.80* (1H, m, CHCH2), 4.30* and 4.40 (1H, d, J 6.6, CHO), 4.64 (1H, m, CHCH3), 7.19-7.27 (5H, m, ArH); δC 10.0 and 10.5* (isoxazole CH3), 11.0 and 11.5* (isoxazole CH3), 14.0 and 14.5* (CHCH3), 28.0 and 28.5* (CHCH2), 31.0 (NCH3), 51.0 and 51.5* (CHCH3), 55.8 (CHCH3), 75.0 and 75.5* (CHOH), 109.5 and 110.0* (ArC), 126.3, 126.5, 126.6, 126.7, 126.9, 127.6, 135.9 (ArC), 174.74 (C=O); m/z (Cl) 332 (MH+, 100%), 166 (65), 112 (18), and 58 (20).

General method for the hydrolysis of alkylated pseudoephedrine glyciamides

The alkylated pseudoephedrine glycineamide 2 was dissolved in the minimum volume of dioxane and water was added. The solution was then heated at reflux for 12 h, cooled to 20 ºC and diluted with water. This solution was extracted with DCM (2 x 25 mL). The combined organic extracts were extracted with water. The aqueous layers were combined and concentrated under reduced pressure to afford a white solid. The solid was triturated in ethanol to remove residual pseudoephedrine, filtered and dried in vacuo to give the free amino acid. The combined organic extracts were dried over potassium carbonate, filtered, and concentrated to afford pseudoephedrine.

Phenylalanine (3a). Prepared following the general method, using amide 2a (2g, 6.4 mmol) in dioxane (5 mL) and water (25 mL). Work-up afforded pseudoephedrine (1.0g, 70%) and the title compound (0.81 g, 76%); data in accord with genuine sample, e.g. δH (D2O) 2.95 and 3.15 (2H, 2 x dd, J 8.0, 14.5 and 5.2, CH2), 3.83 (1H, dd, J 8.0 and 5.2, CHCH2), 7.16-7.26 (5H, m, ArH); δC (D2O) 37.2 (CH2), 56.8 (CH), 128.5, 129.9 and 130.2 (3 x ArCH and 3 x ArCH*), 141.0 and 141.5*, 159.0 and 159.5*, 166.0 and 166.5* (3 x ArC), 175.0* and 176.0 (C=O); m/z (Cl) 332 (MH+, 100%), 166 (65), 112 (18), and 58 (20).

2-Amino-3-(1-naphthyl)propanoic acid (3b). Prepared following the general method, using amide 2b (0.36g, 4.1 mmol) in dioxane (2 mL) and water (10 mL). Work-up afforded pseudoephedrine (0.11g, 50%) and the title compound (0.16 g, 76%). M.p. 185-186 ºC (lit. 14179 ºC); Found: MH+ (ES+) 216.1022. C13H13NO2 requires: MH 216.1024; νmax/cm–1 (KBr) 3100, 2600, 2300, 1675, 1600, 1500, 1400, 1350, 1150, 800, 750; δH (D2O) 3.17 and 3.78 (2H, 2 x dd,
$J$ 5.3, 8.5 and 14.5, CH$_2$), 3.95 (1H, dd, $J$ 5.3 and 8.5, CH), 7.33-7.89 (7H, m, ArH); m/z (CI) 216 (MH$^+$, 20%), 170 (100) and 145 (40).

2-Amino-4-(1-naphthyl)butanoic acid (3c). Prepared following the general method, using amide 2c (0.75 g, 4.2 mmol) in dioxane (5 mL) and water (20 mL). Work-up afforded pseudoephedrine (0.19 g, 58%) and the title compound (0.34 g, 74%) as a hygroscopic solid. Found: MH$^+$ (ES$^+$) 230.1181. C$_{14}$H$_{15}$NO$_2$ requires: MH 230.1181; $\nu_{\text{max}}$/cm$^{-1}$ (KBr) 3150, 2600, 2350, 1670, 1620, 1500, 1350, 1150, 850; $\delta$ (D$_2$O) 2.15 (2H, m, CH$_2$), 3.20 (2H, m, CH$_2$), 3.80 (1H, t, $J$ 7.2, CHCH$_2$), 7.30-7.80 (7H, m, ArH); m/z (El) 229 (M$^+$, 12%), 167 (50), 141 (100) and 115 (50).

2-Amino-3-(2-phenylphenyl)propanoic acid (3d). Prepared following the general method, using amide 2d (1.54 g, 3.95 mmol) in dioxane (5 mL) and water (20 mL). Work-up afforded pseudoephedrine (0.69 g, 78%) and the title compound (0.46 g, 48%). M.p. 190-191 ºC; Found: MH$^+$ (ES$^+$) 242.1189. C$_{15}$H$_{15}$NO$_2$ requires: MH 242.1181; $\nu_{\text{max}}$/cm$^{-1}$ (KBr) 3400, 3000, 1600, 1500, 1450, 1400, 1350, 1290, 129.6, 129.7, 130.3, 130.8 and 131.7 (7 x ArCH), 134.7, 142.5 and 144.1 (3 x ArC), 173.8 (C=O); m/z (CI) 242 (MH$^+$, 28%) and 196 (100).

2-Amino-3-(2-pyridyl)propanoic acid (3e). Prepared following the general method, using amide 2e (1.15 g, 3.67 mmol) in dioxane (5 mL) and water (20 mL). Work-up afforded the title compound (0.36 g, 59%). M.p. 206-209 ºC (lit. 210-211 ºC); Found: MH$^+$ (ES$^+$) 167.0820. C$_8$H$_{10}$N$_2$O$_2$ requires: MH 167.0820; $\nu_{\text{max}}$/cm$^{-1}$ (KBr) 3400, 2950, 2850, 2500, 1600, 1450, 1050, 1050; $\delta$ (D$_2$O) 3.30 and 3.45 (2H, 2 x dd overlapped, $J$ 5.0, 7.6, and 14.0, CH$_2$), 4.20 (1H, dd, $J$ 5.0 and 7.6, CHCH$_2$), 7.40 (2H, m, pyridyl H3 and H5), 7.85 (1H, m, pyridyl H4), 8.60 (1H, m, pyridyl H6); m/z (CI) 167 (MH$^+$, 3%), 148 (5), 121 (80), 93 (100) and 78 (15).

2-Amino-3-(3-pyridyl)propanoic acid (3f). Prepared following the general method, using amide 2f (1.0 g, 3.66 mmol) in dioxane (5 mL) and water (20 mL). Work-up afforded the title compound (0.26 g, 49%). M.p. 253-254 ºC (lit. 253-256 ºC); Found: MH$^+$ (ES$^+$) 167.0820. C$_8$H$_{10}$N$_2$O$_2$ requires: MH 167.0820; $\nu_{\text{max}}$/cm$^{-1}$ (KBr) 3400, 2900, 2800, 2500, 1600, 1450, 1050, 1050; $\delta$ (D$_2$O) 3.15 and 3.25 (2H, 2 x dd overlapped, $J$ 14.8, 5.6 and 7.5, CHCH$_2$), 4.05 (1H, dd, $J$ 5.6 and 7.5, CHCH$_2$), 7.38 (1H, m, pyridyl H5), 7.73 (1H, m, pyridyl H4); $\nu_{\text{C}}$/cm$^{-1}$ (D$_2$O) 8.38-8.40 (2H, m, pyridyl H2 and H6); m/z (Cl) 167 (MH$^+$, 30%), 121 (100), 93 (40) and 52 (38).

2-Amino-3-(4-pyridyl)propanoic acid (3g). Prepared following the general method, using amide 2g (1.0 g, 3.66 mmol) in dioxane (5 mL) and water (20 mL). Work-up afforded the title compound (0.21 g, 40%). M.p. 239-241 ºC (lit. 246-248 ºC); Found: MH$^+$ (ES$^+$) 167.0821. C$_8$H$_{10}$N$_2$O$_2$ requires: MH 167.0820; $\nu_{\text{max}}$/cm$^{-1}$ (KBr) 3350, 2900, 2750, 2500, 2200, 1600, 1400, 1300, 1050; $\delta$ (D$_2$O) 3.06 and 3.12 (2H, 2 x dd, $J$ 5.9, 7.5 and 14.5, CHCH$_2$), 4.05 (1H, dd, $J$ 5.9 and 7.5, CHCH$_2$), 7.24-7.40 (4H, m, pyridyl H); $\nu_{\text{C}}$/cm$^{-1}$ (D$_2$O) 38.3 (CH$_2$), 57.6 (CHCH$_2$), 128.4 and 130.4 (2 x ArCH), 137.3 (ArC), 174.0 (C=O); m/z (El) 166 (M$^+$, 100%), 150 (5), 121 (12), 88 (5) and 52 (28).
2-Amino-3-(3,5-dimethylisoxazol-4-yl)propanoic acid (3h). Prepared following the general method, using amide 2h (2.93 g, 8.84 mmol) in dioxane (5 mL) and water (20 mL). Work-up afforded pseudoephedrine (1.21 g, 62%) and the title compound (0.96 g, 59%). M.p. 216-217 °C; Found: MH⁺ (ES⁺) 185.0927. C₇H₁₂N₂O₃ requires: MH 185.0926; νmax/cm⁻¹ (KBr) 3400, 2950, 2600, 2050, 1500, 1450, 1400, 1200; δt (D₂O) 2.09 and 2.20 (2 x 3H, 2 x s, isoxazole CH₃), 2.69-2.88 (2H, 2 x dd overlapped, J 7.0 and 15.4, CH₂), 3.63 (1H, t, J 7.0, CH); δC (D₂O) 10.1 and 11.1 (isoxazole CH₃) 24.5 (CH₂), 55.1 (CH), 109.3, 161.9, and 169.2 (3 x ArC), 174.2 (C=O); m/z (CI) 185 (MH⁺, 20%), 141 (50) and 124 (100).

General method for conversion of an amino acid into its (S)-2-methoxy-2-phenyl-3,3,3-trifluoropropanamide (Mosher amide) derivative.

Acetyl chloride (10 mol equiv.) was added dropwise at 0 °C to a stirred solution of the amino acid (~50 mg) in ethanol (approx. 40 mL). The mixture was then stirred overnight at 25 °C, heated at reflux for 4 h, cooled and the solvent evaporated under reduced pressure to give the ethyl ester hydrochloride salt which was further dried under vacuum overnight. (R)-2-Methoxy-2-phenyl-3,3,3-trifluoropropanoyl chloride (MTPA-Cl) (100 mg) was added dropwise at room temperature to the ester hydrochloride stirred in chloroform (4 mL) and pyridine (4 mL). The mixture was stirred overnight, water (20 mL) was added and the mixture extracted with ethyl acetate (3 x 20 mL). The combined ethyl acetate layers were washed with saturated sodium hydrogen carbonate solution (3 x 10 mL), dried (MgSO₄) and evaporated under reduced pressure to afford the product amide, that was directly analysed by 19F NMR spectroscopy for the determination of diastereomeric purity (and hence enantiomeric purity of the amino acid).

(2'S)-Ethyl 2-(3,3,3-trifluoro-2-methoxy-2-phenylpropanoylamino)-3-phenylpropanoate (4a). Prepared as above using amino acid phenylalanine 3a (~50 mg). δF –69.09 (major diastereoisomer, 93.5%), –69.14 (minor diastereoisomer, 6.5%); ee 87%.

(2'S)-Ethyl 2-(3,3,3-trifluoro-2-methoxy-2-phenylpropanoylamino)-3-(1-naphthyl)propanoate (4b). Prepared as above using amino acid 3b (~50 mg). δF –68.01 (major diastereoisomer, 93.5%), –68.09 (minor diastereoisomer, 6.5%); ee 87%.

(2'S)-Ethyl 2-(3,3,3-trifluoro-2-methoxy-2-phenylpropanoylamino)-4-(1-naphthyl)butanoate (4c). Prepared following the general method using amino acid 3c (~50 mg). δF –68.08 (minor diastereoisomer, 19.5%), –67.96 (major diastereoisomer, 80.5%); ee 61 %.

(2'S)-Ethyl 2-(3,3,3-trifluoro-2-methoxy-2-phenylpropanoylamino)-3-(2-phenylphenyl)propanoate (4d). Prepared following the general method, using amino acid 3d (~50 mg). δF –68.01 (major diastereoisomer, 87%), –68.13 (minor diastereoisomer, 13%); ee 74%.

(2'S)-Ethyl 2-(3,3,3-trifluoro-2-methoxy-2-phenylpropanoylamino)-3-(2-pyridyl)propanoate, (4e). Prepared following the general method using amino acid 3e (~50 mg). δF –69.15 (major diastereoisomer, 55%), –69.52 (minor diastereoisomer, 45%); ee 10%.

(2'S)-Ethyl 2-(3,3,3-trifluoro-2-methoxy-2-phenylpropanoylamino)-3-(3-pyridyl)propanoate, (4f). Prepared following the general method using amino acid 4f (~50 mg). δF –68.85 (minor diastereoisomer, 13%), –69.17 (major diastereoisomer, 87%); ee 74%.
(2'S)-Ethyl 2-(3,3,3-trifluoro-2-methoxy-2-phenylpropanoylamino)-3-(4-pyridyl)-propanoate, (4g). Prepared following the general method using amino acid 4g (~50 mg). $\delta_F$ – 68.95 (minor diastereoisomer, 16%), –69.15 (major diastereoisomer, 84%); ee 68%.

(2'S)-Ethyl 2-(3,3,3-trifluoro-2-methoxy-2-phenylpropanoylamino)-3-(3,5-dimethylisoxazol-4-yl)propanoate (4h). Prepared following the general method, using amino acid 3h (~50 mg). $\delta_F$ – 68.87 (major diastereoisomer, 87%), –69.00 (minor diastereoisomer, 13%); ee 74%.

Acknowledgements

We thank the Open University for financial support (competitive studentship to D. J. C. B.) and the EPSRC National Mass Spectrometry Service Centre (Swansea) for some MS data.

References and Footnotes

4. See refs. 14, 15, vide infra
5. A ring-substituted pyridylalanine has been reported via this approach, ref. 7.
8. Several critical experimental details (quality of LDA quality & quantity, colorations, LiCl quality, amide hydrolysis, etc.) were uncovered by us and later confirmed by the full paper of ref. 7, which appeared after our investigations were underway.
10. Significantly higher e.e.’s were reported by Meyers for amino acid synthesis (ref. 7), but we have been unable to achieve this