Synthesis of α-amino acids by reaction of aziridine-2-carboxylic acids with carbon nucleophiles†

Kenneth J. M. Beresford, Nicola J. Church and Douglas W. Young*

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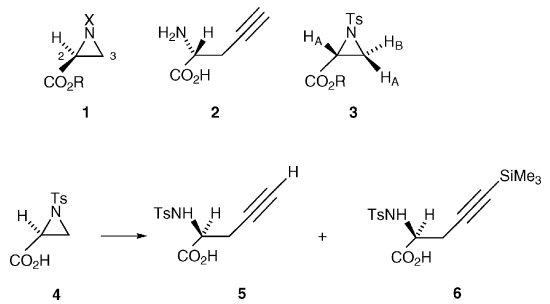
A variety of homochiral α-amino acids have been prepared in good yield *via* regioselective reaction of higher order cuprates with (2*S*)-*N*-*para*-toluenesulfonylaziridine-2-carboxylic acid **4**. The reaction was much less regioselective and low yielding when higher order cuprates were reacted with the more hindered aziridine carboxylic acid **30**, the principal products being protected β-amino acids. Reaction of lithium trimethylsilylacetylide with the aziridine acid **30**, however, gave a protected α-amino acid which was converted to the protected isoleucine ester **37**.

Introduction

The biological importance of α-amino acids has led to the development of a large variety of methods for their synthesis.[2] One such method is the reaction of protected optically pure aziridine-2-carboxylic esters **1** with a variety of sulfur nucleophiles,[3,4] oxygen nucleophiles,[4,5] nitrogen nucleophiles,[6] or halides.[4,7] These heteronucleophiles invariably reacted solely at the β-carbon atom. To be truly general the method should be extended to carbon nucleophiles, but, apart from the use of indoles as nucleophiles,[8] only Baldwin *et al.*[9] have used aziridine-2-carboxylates relevant to the synthesis of optically pure amino acids to address this question. They found that carbonyl stabilised Wittig reagents reacted with suitably N-activated aziridines *via* C-3–N-1 cleavage to provide optically pure ylides, suitable for modification to the (2*S*)-4-alkylideneglutamic acid family of natural products.[9a] When organometallic reagents such as organolithium or Grignard reagents were used as nucleophiles, the ester group of *N*-*para*-toluenesulfonylaziridine-2-carboxylate esters was attacked.[9c] With higher order organocuprates or Grignard reagents in the presence of $CuBr{\cdot}Me_2S$, nucleophilic attack occurred at the aziridine carbon rather than the carbonyl group but it occurred at *both* C-2 *and* C-3.[9b,c]

In the course of our studies of the mechanism of action of enzyme inhibitors, we required samples of D-propargylglycine **2** which were labelled stereospecifically at C-3 with deuterium. We had already developed a synthesis of the labelled aziridine esters (**3**, R = Me, H_A or $H_B = {}^2H$)[4] and so an attractive synthetic route to our target would be to react these with a protected acetylene anion. This should occur with inversion of stereochemistry at the labelled atom C-3. When we used the *N*-*para*-toluenesulfonylaziridine esters (**3**, R = Me) and (**3**, R = ^{t}Bu), we found,[10] like Baldwin,[9c] that the ester group reacted in preference to the aziridine functionality. Arguing that, by using a carboxylic acid in the reaction, the carboxylate anion would discourage attack at the carbonyl group and might also encourage regiospecific attack at C-3 of the aziridine, we reacted the aziridine free acid **4**[10] with an excess of lithium trimethylsilylacetylide and obtained a mixture of the free acetylene **5** (30%) and the trimethylsilyl derivative **6** (49%) as shown in Scheme 1.[10] Although we found it necessary to change the activating group on the aziridine nitrogen to the 2,2,5,7,8-pentamethylchroman-6-sulfonyl (Pmc) group[10] so that the product could be deprotected successfully to the acetylenic amino acid, it was evident that we had achieved our objective of regiospecific ring opening at C-3. This suggested that we might have overcome the problem of regiospecificity in the synthesis of homochiral α-amino acids by reaction of N-activated aziridine-2-carboxylates with carbon nucleophiles by the simple expedient of using the carboxylic acid in the reaction. We therefore resolved to examine the generality of the method.



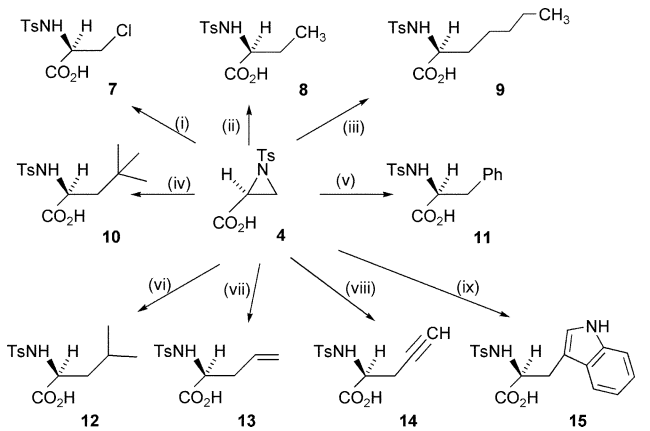
Scheme 1

Results and discussion

When the aziridine-2-carboxylic acid **4** was reacted with methyl magnesium chloride in THF at −70 °C, the protected chloroalanine **7** was obtained in 53% yield as shown in Scheme 2. The Grignard reagent had therefore acted as a source of chloride ion. The higher order cuprate $Me_2CuCNLi_2$ however, gave the desired product **8** in 94% yield with evidence in the ^{1}H NMR spectrum of only a small amount of the product expected from α-attack on the aziridine. Reaction of the aziridine **4** separately with *n*-$Bu_2CuCNLi_2$ and *t*-$Bu_2CuCNLi_2$ gave the protected amino acids **9** and **10** as the only products in 56% and 69% yields respectively. This regioselectivity contrasted with the reactions

Department of Chemistry, University of Sussex, Falmer, Brighton, UK BN1 9QJ

† Part of this work has been reported as a preliminary communication in ref. 1.

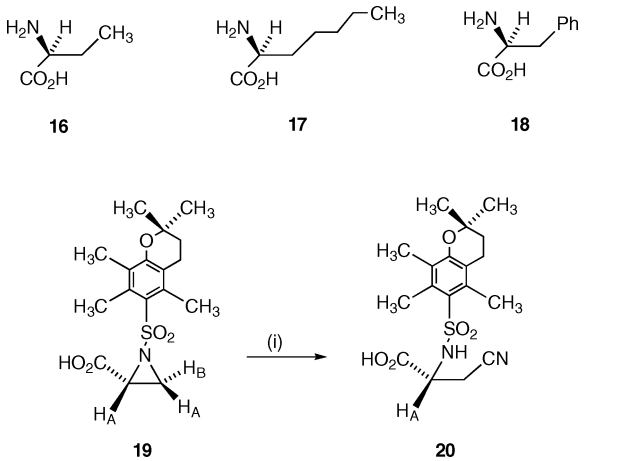


Scheme 2 *Reagents and conditions*: (i) MeMgCl, THF, −78 °C, 10 min, then rt, 3 h (53%); (ii) $Me_2CuCNLi_2$, THF, −78 °C, 3 h, then rt, 18 h (94%); (iii) $^nBu_2CuCNLi_2$, THF, −78 °C, 5 h (56%); (iv) $^tBu_2CuCNLi_2$, THF, −78 °C, 4 h (69%); (v) $Ph_2CuCNLi_2$, THF, −78 °C, 3 h, then rt, 18 h (57%); (vi) $^iPr_2CuCNLi_2$, THF, −78 °C, 3 h, then rt, overnight (48%); (vii) $(H_2C{=}CH)_2CuCNLi_2$, THF, −78 °C, 30 min, then warm to rt (54%); (viii) $(Me_3SiC{=}C)_2CuLi_2$, −78 °C, 30 min, then rt, 18 h (18%); (ix) indolyl-Li, Et_2O, rt, 4 h (20%).

on the corresponding ester[9c] where reaction with $Me_2CuCNLi_2$ occurred at both α and β-carbon atoms equally. Use of the free acid had thus overcome the regiospecificity problem.

When the acid **4** was reacted with $Ph_2CuCNLi_2$, $((CH_3)_2CH)_2CuCNLi_2$, $(H_2C{=}CH)_2CuCNLi_2$ and $(Me_3SiC{=}C)_2$-$CuCNLi_2$ the single products **11**, **12**, **13** and **14** were obtained in 57%, 48%, 54% and 18% yields respectively. The method was, therefore, a useful and general route to α-amino acids. Reaction with the lithium salt of indole gave the protected tryptophan **15** in 20% yield. Deprotection of the products **8**, **9** and **11** was achieved by treatment with 30% HBr in acetic acid and the free amino acids L-2-aminobutyric acid **16**, L-2-aminoheptanoic acid **17** and L-phenylalanine **18** were obtained. Comparison of data with those of authentic samples showed that the reactions had proceeded both regiospecifically and without loss of stereochemistry.

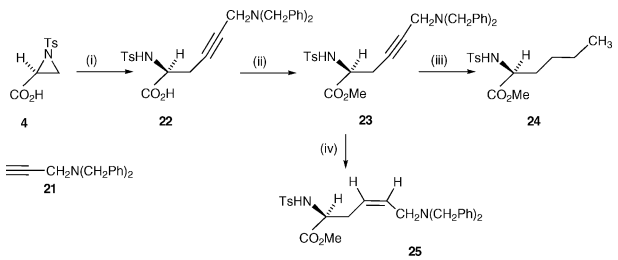
When the Pmc protected aziridine **19** was treated with KCN, the protected β-cyanoalanine **20** was obtained in 56% yield (Scheme 3). On using the stereospecifically labelled aziridines, (**19**, $H_A = {}^2H$) and (**19**, $H_B = {}^2H$) in this reaction, however, the



Scheme 3 *Reagents and conditions*: (i) KCN, MeOH, 40 °C, 18 h (56%).

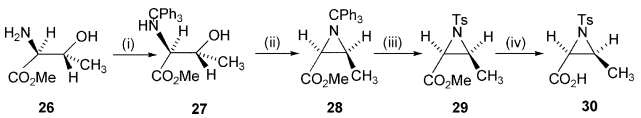
deuterium label was "washed out" due to the enhanced acidity of the β-hydrogens in the product. Thus, although the method was synthetically successful, it was not appropriate for preparation of stereospecifically labelled samples of the enzyme inhibitor β-cyanoalanine.

Since entry to a variety of further amino acids and stereospecifically labelled amino acids might be obtained by use of substituted acetylenes, the acid **4** was reacted with the lithium salt of *N*,*N*-dibenzylpropargylamine **21** to yield the product **22** (Scheme 4). In an attempt to investigate the possibility of using this as a synthon for L-lysine and, by extension, stereospecifically labelled samples of L-lysine, we first converted the acid **22** to the methyl ester **23** using diazomethane. Hydrogenation for 4 days in ethyl acetate using 10% palladium–carbon gave the protected fully-reduced amino acid **24** in which hydrogenolysis of the terminal amino group had occurred, presumably at the stage of the intermediate allylic amine. Shorter reduction times resulted in mixtures containing the compound **24**. Hydrogenation for 8 hours using Lindlar's catalyst gave the *Z*-olefin **25** in 65% yield.



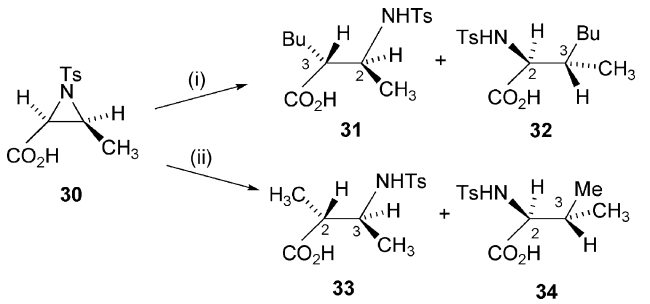
Scheme 4 *Reagents and conditions*: (i) *n*BuLi + **21**, THF, 0 °C, 3.5 h (61%); (ii) CH_2N_2, Et_2O, THF, 0 °C (75%); (iii) H_2, 10% Pd–C, EtOAc, rtp (room temperature and pressure), 4 days (65%); (iv) H_2, Lindlar's catalyst, EtOAc, rtp, 8 h (65%).

Having developed a successful general synthesis of optically pure α-amino acids with one chiral centre, it was of interest to see if the method could be extended to the preparation of α-amino acids with two chiral centres. We therefore prepared the tritylaziridine **28** from L-threonine by adaptation of the method of Wakamiya *et al.*[3b] as shown in Scheme 5 and described in the experimental section. Deprotection using trifluoroacetic acid in $CHCl_3$–MeOH at 0 °C and reaction with *para*-toluenesulfonyl chloride under Schotten Baumann conditions for 20 hours at room temperature gave the tosyl ester **29** in 72% yield. This was converted into the free acid **30** in quantitative yield by hydrolysis with 1 N aqueous sodium hydroxide in THF at room temperature for 3 hours.



Scheme 5 *Reagents and conditions*: (i) Ph_3CCl, $CHCl_3$, Et_3N, 0 °C, 20 h (quantitative); (ii) (a) TsCl, pyridine, 0 °C, 20 h, (b) THF, Et_3N, reflux 20 h (75%); (iii) (a) CF_3CO_2H, $CHCl_3$, MeOH, 0 °C, 5 h, (b) TsCl, EtOAc, aq. $NaHCO_3$, rt, 20 h (72%); (iv) 1 N NaOH, THF, rt, 3 h (quantitative).

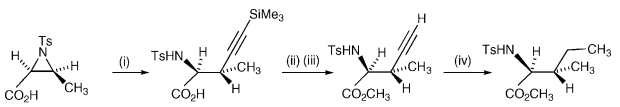
Reaction of higher order cuprates with the aziridine **30** was less regiospecific than had been the case with the reaction using the aziridine **4**. Thus reaction with *n*-$Bu_2CuCNLi_2$ gave a 34% yield of a 3 : 1 mixture of regioisomers with the β-amino acid **31** as



Scheme 6 *Reagents and conditions*: (i) $^{n}Bu_2CuCNLi_2$, THF, −78 °C, 30 min, then rt, 18 h (34%); (ii) $Me_2CuCNLi_2$, THF −78 °C, 30 min, then rt, 18 h (36%).

the major isomer and the α-amino acid **32** as the minor isomer (Scheme 6). Assignment of the ^{1}H NMR spectrum was aided by decoupling experiments. Irradiation of the one proton multiplet at δ 3.4 ppm caused the three-proton doublet at δ 0.8 ppm to become a singlet, assigning these to H-2 and the methyl group at C-2 in compound **31**. Decoupling was also observed between the one proton multiplet at δ 2.2 ppm and the multiplet for CH_2 at 1.1–1.5 ppm confirming the former peak as H-3 in compound **31**. Reaction with $Me_2CuCNLi_2$ gave a 36% yield of a 3.5 : 1 mixture of regioisomers. The major isomer was the protected β-amino acid **33**, assignment of the ^{1}H NMR spectrum again being aided by a double irradiation experiment. Irradiation of one methyl doublet at δ 0.9 ppm caused decoupling of the multiplet at δ 3.5 ppm due to C*H*N, whereas irradiation of the other methyl doublet at δ 1.1 ppm caused decoupling of the multiplet at δ 2.4 ppm due to C*H*CO_2H. The α-amino acid **34** was the minor product.

When lithium trimethylsilylacetylide was reacted with the aziridine acid **30**, the adduct **35** was obtained in 70% yield (Scheme 7). Regiospecific attack at C-3 was evident from the fact that the doublet of doublets at δ 3.9 ppm for H-2 in the ^{1}H NMR spectrum was reduced to a doublet on exchange of the NH proton in ^2H_2O. The synthesis was therefore valid for preparation of α-amino acids with two chiral centres when this nucleophile was used. The product **35** was deprotected in 94% yield using 1 N NaOH and then converted into the ester **36** in 37% yield by heating with methanol containing $BF_3{\cdot}Et_2O$. Hydrogenation using Lindlar's catalyst gave not the expected partially reduced product but the fully reduced methyl *N*-*para*-toluenesulfonylisoleucine **37** in 79% yield.



Scheme 7 *Reagents and conditions*: (i) $Me_3SiC{\equiv}CLi$, 0 °C, 30 min, then rt, 2 h (70%); (ii) 1 N NaOH, EtOAc, 50 °C, 18 h (94%); (iii) EtOAc, $BF_3{\cdot}Et_2O$, reflux, 20 h (37%); (iv) H_2, EtOAc, Lindlar's catalyst, rtp, 20 h (79%).

Conclusions

A high yielding and general synthesis of optically pure α-amino acids has been developed using regiospecific attack of carbon nucleophiles at C-3 of the protected aziridine carboxylic acid **4**. The synthesis could be extrapolated to the aziridine **30** containing two chiral centres when the sterically undemanding nucleophile lithium trimethylsilylacetylide was used. However when higher order cuprates were used, yields were low and the principal products were the β-amino acids.

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations (given in units of 10^{-1} deg cm^2 g^{-1}) were measured on a Perkin Elmer 241 polarimeter using a 1 dm path length micro cell. IR spectra were recorded on a Perkin Elmer 1720 Fourier transform instrument. ^{1}H NMR spectra were recorded using a Bruker WM360 (360 MHz) instrument. ^{13}C NMR spectra were recorded using a Bruker AMX 500 (125.8 MHz) instrument. *J*-values are given in Hz. The residual solvent peak was used as the reference for all NMR spectra. Low resolution mass spectra were recorded by Mr A. Greenway and Dr A. Abdul Sada using Kratos MS80RF and Fisons VG autospec instruments and by Dr S. Chotai and D. Dell at the Wellcome Research Laboratories, Beckenham using Kratos Concept 1S and MS50 instruments. High resolution mass measurements were performed by Dr S. Chotai at the Wellcome Research Laboratories, Beckenham using a Kratos Concept 1S instrument and by the EPSRC Central Mass Spectrometry Service as Swansea. Microanalyses were performed by Miss M. Patel at Sussex University, and by Carol Lawless and Wai Chi Man at the Wellcome Research Laboratories, Beckenham. Column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh-Art 9385). Ion exchange resins were purchased in the required form from Aldrich. Copper(I) cyanide was vacuum desiccated over phosphorus pentoxide before use. Petroleum ether refers to that fraction of hexanes bp 60–80 °C.

(2*R*)-*N*-*para*-Toluenesulfonyl-3-chloroalanine (7)

Methylmagnesium chloride (3 M in THF, 0.3 ml, 0.9 mmol) was added to a solution of (2*S*)-*N*-*para*-toluenesulfonylaziridine-2-carboxylate **4**[10] (70 mg, 0.3 mmol) in tetrahydrofuran (3 ml) under argon at −78 °C. The reaction was stirred at −78 °C for 10 min, warmed to room temperature and stirred for a further 3 h. Water (20 ml) was added. The organic layer was extracted with water (3 × 10 ml) and the combined aqueous layers were cooled on ice and acidified to pH 4 using 10% aqueous citric acid. The acidified aqueous layer was extracted with ethyl acetate (3 × 20 ml) and the combined organic layers were dried (Na_2SO_4). The solvent was removed *in vacuo*. Column chromatography on silica gel using (chloroform–methanol–water–acetic acid 7 : 3 : 0.6 : 0.3)–ethyl acetate (1 : 2) as eluant gave (2*R*)-*N*-*para*-toluenesulfonyl-3-chloroalanine **7** as a white solid which was recrystallised from methanol (44 mg, 53%); mp 144–148 °C; $[\alpha]_D^{30}$ +24.1 (*c* 0.2, MeOH); *m*/*z* (EI) found 277.02014; $C_{10}H_{12}O_4S^{35}Cl$ requires 277.01756; *m*/*z* [+ve FAB (3-nba)] 278 and 280 (3 : 1) ($[M+H]^+$); ν_{max} (KBr)/cm^{-1} 1636 (acid); δ_H (360 MHz, $C^2H_3O^2H$) 2.4 (3H, s, $ArCH_3$), 3.7 (1H, dd, $J_{3A,2}$ 4.1, $J_{3A,3B}$ 11.2, H-3A), 3.8 (1H, dd, $J_{3B,2}$ 4.1, $J_{3B,3A}$ 11.2, H-3B), 4.1 (1H, t, $J_{2,3B} = J_{2,3A}$ 4.1, H-2), 7.3 (2H, d, *J* 8.0, ArH) and 7.7 (2H, d, *J* 8.3, ArH); δ_C (125.8 MHz, $C^2H_3O^2H$) 22.0 ($ArCH_3$), 47.3 (C-3), 59.0 (C-2), 128.7, 131.1, 139.6 and 145.3 (Ar) and 172.1 (acid).

(2*S*)-2-(*para*-Toluenesulfonylamino)-butyric acid (8)

Methyl lithium (1.6 M in Et_2O, 2.0 ml, 3.2 mmol) was added to copper(I) cyanide (139 mg, 1.5 mmol) in tetrahydrofuran (2 ml) at −78 °C under argon and the reaction was left for 10 min at this temperature and then allowed to warm to room temperature. The mixture was cooled to −78 °C and a solution of (2*S*)-*N*-*para*-toluenesulfonylaziridine-2-carboxylate **4**[10] (150 mg, 0.62 mmol) in tetrahydrofuran (2 ml) was added. The mixture was stirred at −78 °C for 3 h, slowly warmed to room temperature and left for 18 h. Water (10 ml) was added and the mixture was filtered. The filtrate was cooled on ice and acidified to pH 4 using 10% aqueous citric acid. The aqueous mixture was extracted with ethyl acetate (3 × 20 ml), the combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. Column chromatography on silica gel using (chloroform–methanol–water–acetic acid 7 : 3 : 0.6 : 0.3)–ethyl acetate (1 : 2) as eluant gave (2*S*)-2-(*para*-toluenesulfonylamino)-butyric acid **8** as a white solid which was recrystallised from dichloromethane and petroleum ether (150 mg, 94%); mp 95–100 °C; $[\alpha]_D^{31}$ −3.5 (*c* 0.3, $CHCl_3$); *m*/*z* (EI) found 257.07124; $C_{11}H_{15}O_4NS$ requires 257.07218; *m*/*z* [+ve FAB (3-nba)] 258 ($[M + H]^+$); ν_{max} (KBr)/cm^{-1} 1717 (acid); δ_H (360 MHz, C^2HCl_3) 0.9 (3H, t, *J* 7.4, CH_3), 1.7 (1H, m, H-3A), 1.8 (1H, m, H-3B), 2.4 (3H, s, $ArCH_3$), 3.9 (1H, br dd, H-2), 5.2 (1H, exch. d, $J_{NH,2}$ 8.7, NH), 7.3 (2H, d, *J* 8.3, ArH) and 7.7 (2H, d, *J* 8.3, ArH), a small peak δ_H 1.2 (d, *J* 7.2, CH_3) suggested the presence of <10% of the regioisomer); δ_C (125.8 MHz, C^2HCl_3) 9.3 (CH_3), 21.5 ($ArCH_3$), 26.2 (C-3), 56.7 (C-2), 127.2, 129.7, 136.7 and 143.8 (Ar) and 176.3 (acid).

(2*S*)-2-(*para*-Toluenesulfonylamino)-heptanoic acid (9)

n-Butyl lithium (1.6 M in hexanes, 2.7 ml, 4.3 mmol) was added to a suspension of copper(I) cyanide (186 mg, 2.1 mmol) in tetrahydrofuran (2 ml) at −78 °C under argon. The mixture was left at −78 °C for 30 min and allowed slowly to warm to room temperature. The mixture was cooled to −78 °C and a solution of (2*S*)-*N*-*para*-toluenesulfonylaziridine-2-carboxylate **4**[10] (200 mg, 0.8 mmol) in tetrahydrofuran (2 ml) was added. The reaction was stirred for 5 h at −78 °C under argon. Water (8 ml) was added and the mixture was filtered through a plug of Celite. The filtrate was cooled on ice and acidified to pH 4 using 10% aqueous citric acid. The aqueous phase was extracted with ethyl acetate (3 × 15 ml) and the combined organic layers were dried (Na_2SO_4). Removal of the solvent *in vacuo* yielded a colourless oil. Column chromatography on silica gel using (chloroform–methanol–water–acetic acid 7 : 3 : 0.6 : 0.3)–ethyl acetate (1 : 2) as eluant gave (2*S*)-2-(*para*-toluenesulfonylamino)-heptanoic acid **9** as a white solid which was recrystallised from dichloromethane and petroleum ether (137 mg, 56%); mp 74–78 °C; $[\alpha]_D^{34}$ +7.9 (*c* 0.5, $CHCl_3$); (found C, 55.7; H, 7.0; N, 4.6. $C_{14}H_{21}O_4NS$ requires C, 56.2; H, 7.1; N, 4.7%); *m*/*z* [+ve FAB (3-nba)] 300 ($[M + H]^+$) and 254 ($[M–CO_2H]^+$); ν_{max} (KBr)/cm^{-1} 1718 (acid); δ_H (360 MHz, C^2HCl_3) 0.8 (3H, t, *J* 7.0, CH_3), 1.1–1.3 (6H, m, CH_2), 1.6 (1H, m, H-3A), 1.7 (1H, m, H-3B), 2.4 (3H, s, $ArCH_3$), 3.9 (1H, m, H-2), 5.7 (1H, exch. d, $J_{NH,2}$ 8.7, NH), 7.3 (2H, d, *J* 8.3, ArH), 7.7 (2H, d, *J* 8.3, ArH) and 9.6 (1H, br exch. s, OH); δ_C (125.8 MHz, C^2HCl_3) 13.9 (CH_3), 21.5 ($ArCH_3$), 22.3 (C-3), 24.5, 31.0 and 33.0 (3 × CH_2), 55.4 (C-2), 127.3, 129.7, 136.7 and 143.9 (Ar) and 176.4 (acid).

(2*S*)-*N*-*para*-Toluenesulfonyl-*tert*-leucine (10)

tert-Butyl lithium (1.7 M in pentanes, 1.2 ml, 2.1 mmol) was added to a suspension of copper(I) cyanide (93 mg, 1.0 mmol) in tetrahydrofuran (2 ml) at −78 °C and the mixture was stirred at −78 °C for 20 min under argon. The solution was allowed to warm to room temperature slowly, and cooled to −78 °C. A solution of (2*S*)-*N*-*para*-toluenesulfonylaziridine-2-carboxylate **4**[10] (100 mg, 0.4 mmol) in tetrahydrofuran (2 ml) was added. The reaction was stirred at −78 °C for 4 h under argon. Water (10 ml) was added and the mixture was filtered through Celite. The filtrate was cooled on ice and acidified to pH 4 using 10% aqueous citric acid. The aqueous mixture was extracted with ethyl acetate (3 × 20 ml) and the combined organic layers were dried (Na_2SO_4). The solvent was removed *in vacuo*. Column chromatography on silica gel using (chloroform–methanol–water–acetic acid 7 : 3 : 0.6 : 0.3)–ethyl acetate (1 : 2) as eluant gave (2*S*)-*N*-*para*-toluenesulfonyl-*tert*-leucine **10** as a white solid which was recrystallised from dichloromethane and petroleum ether (85 mg, 69%); mp 172–173 °C; $[\alpha]_D^{27}$ +9.9 (*c* 0.7, $CHCl_3$); (found C, 56.1; H, 7.1; N, 4.8. $C_{14}H_{21}O_4NS$ requires C, 56.2; H, 7.1; N, 4.7%); *m*/*z* [+ve FAB (3-nba)] 322 ($[M + Na]^+$) and 300 ($[M + H]^+$); ν_{max} (KBr)/cm^{-1} 3277 (NH) and 1713 (acid); δ_H (360 MHz, $C^2H_3O^2H$) 0.9 (9H, s, $C(CH_3)_3$), 1.5 (1H, dd, $J_{3A,2}$ 8.3, $J_{3A,3B}$ 14.3, H-3A), 1.6 (1H, dd, $J_{3B,2}$ 4.1, $J_{3B,3A}$ 14.3, H-3B), 2.4 (3H, s, $ArCH_3$), 3.9 (1H, dd, $J_{2,3B}$ 4.1, $J_{2,3A}$ 8.3, H-2), 7.3 (2H, d, *J* 8.2, ArH) and 7.7 (2H, d, *J* 8.2, ArH); δ_C (125.8 MHz, $C^2H_3O^2H$) 22.0 ($ArCH_3$), 30.5 ($C(CH_3)_3$), 32.0 ($C(CH_3)_3$), 47.8 (C-3), 55.6 (C-2), 128.8, 131.0, 139.7 and 145.0 (Ar) and 176.6 (acid).

(2*S*)-*N*-*para*-Toluenesulfonylphenylalanine (11)

Phenyl lithium (1.8 M in Bu_2O, 2.3 ml, 4.2 mmol) was added to a suspension of copper(I) cyanide (150 mg, 1.7 mmol) in tetrahydrofuran (3 ml) under argon at −78 °C. The mixture was stirred for 10 min and then allowed to warm to room temperature. After 30 min the cuprate was cooled to −78 °C and a solution of (2*S*)-*N*-*para*-toluenesulfonylaziridine-2-carboxylate **4**[10] (200 mg, 0.8 mmol) in tetrahydrofuran (2 ml) was added. The reaction was left for 3 h at −78 °C, allowed to warm to room temperature and stirred for 18 h under argon. Water was added and the aqueous mixture was extracted with ethyl acetate (3 × 20 ml). The combined organic fractions were dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield an oil. Column chromatography on silica gel using (chloroform–methanol–water–acetic acid 7 : 3 : 0.6 : 0.3)–ethyl acetate (1 : 2) as eluant gave (2*S*)-*N*-*para*-toluenesulfonylphenylalanine **11** as a white solid which was recrystallised from dichloromethane and petroleum ether (150 mg, 57%); mp 139–142 °C; $[\alpha]_D^{34}$ −5.5 (*c* 0.3, $CHCl_3$); *m*/*z* (EI) found 319.08619; $C_{16}H_{17}O_4NS$ requires 319.08783; *m*/*z* [+ve FAB (3-nba)] 320 ($[M + H]^+$); ν_{max} (KBr)/cm^{-1} 1713 (acid); δ_H (360 MHz, $C^2H_3O^2H$) 2.4 (3H, s, $ArCH_3$), 2.8 (1H, dd, $J_{3A,2}$ 8.2, $J_{3A,3B}$ 13.7, H-3A), 3.0 (1H, dd, $J_{3B,2}$ 5.6, $J_{3B,3A}$ 13.7, H-3B), 4.0 (1H, dd, $J_{2,3B}$ 5.6, $J_{2,3A}$ 8.2, H-2) and 7.1–7.5 (9H, m, ArH); δ_C (125.8 MHz, $C^2H_3O^2H$) 21.9 ($ArCH_3$), 40.4 (C-3), 59.5 (C-2), 128.2, 128.5, 130.0, 131.0, 138.4, 139.6 and 144.9 (Ar) and 175.4 (acid).

(2*S*)-*N*-*para*-Toluenesulfonylleucine (12)

Isopropyl lithium[11] (0.8 M in pentane, 2.6 ml, 2.07 mmol) was added to a stirred suspension of copper(I) cyanide (75 mg,

083 mmol) in tetrahydrofuran (3 ml) at −78 °C. The mixture was warmed to 0 °C and stirred until all the solid material had dissolved. The mixture was cooled to −78 °C and (2*S*)-*N*-*para*-toluenesulfonylaziridine-2-carboxylate **4**[10] (90 mg, 0.373 mmol) was added dropwise as a solution in tetrahydrofuran (1 ml). The mixture was stirred at −78 °C for 3 h before being allowed to warm to room temperature and stirred overnight. Water (10 ml) was added and the solvent was concentrated *in vacuo*. The resulting aqueous mixture was acidified to pH 4 with aqueous 10% citric acid and extracted with ethyl acetate (4 × 10 ml). The organic extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo*. Flash chromatography on silica gel, eluting with dichloromethane, then 10% ethyl acetate–dichloromethane, then 20% ethyl acetate–dichloromethane and finally 30% ethyl acetate–dichloromethane afforded (2*S*)-*N*-*para*-toluenesulfonylleucine **12** (51 mg, 48%) which was recrystallised from dichloromethane–petroleum ether as a white solid, mp 112–115 °C; $[\alpha]_D^{25}$ +11.6 (*c* 0.7, EtOH); *m*/*z* (FAB) found 286.1115, $[C_{13}H_{19}NO_4S + H]^+$ requires 286.1113; *m*/*z* [+ ve FAB (3-nba)] 308 ($[M + Na]^+$) and 286 ($[M + H]^+$); ν_{max} (KBr)/cm^{-1} 3279 (NH), 2925 (OH) and 1708 (acid); δ_H (360 MHz, C^2HCl_3) 0.79 (3H, d, $J_{Me,4}$ 6.5, CH_3), 0.87 (3H, d, $J_{Me,4}$ 6.5, CH_3), 1.48 (2H, m, H-3), 1.73 (1H, m, H-4), 2.39 (3H, s, CH_3Ar), 3.89 (1H, ddd, $J_{2,3A}$ 6.2, $J_{2,NH}$ 9.7, $J_{2,3B}$ 8.5, H-2), 5.08 (1H, br s, OH), 5.12 (1H, d, $J_{NH,2}$ 9.7, NH), 7.25 (2H, d, *J* 8.5, ArH) and 7.7 (2H, d, *J* 8.5, ArH); δ_C (125.8 MHz, C^2HCl_3, −60 °C) 20.4 (CH_3), 21.6 (CH_3), 22.9 (CH_3Ar), 29.7 (C-4), 41.0 (C-3), 53.5 (C-2), 127.0, 129.5, 135.4 and 143.7 (Ar) and 178.4 (acid).

(2*S*)-*N*-*para*-Toluenesulfonylvinylglycine (13)

n-Butyl lithium (1.6 M in hexanes, 1.3 ml, 2.1 mmol) was added to tetravinyl tin (0.95 ml, 5.2 mmol) and the mixture was stirred for 3 h at room temperature under argon. The solvent was removed *in vacuo* and the resultant solid was washed with portions of diethyl ether (3 × 10 ml). The solvent was removed *in vacuo* to yield a solid which was dissolved in tetrahydrofuran (4 ml) and cooled to −78 °C. Copper(I) cyanide (93 mg, 1.0 mmol) was added and the mixture was stirred at −78 °C for 20 min under argon. The mixture was warmed to room temperature and stirred for a further 30 min. The cuprate was cooled to −78 °C, a solution of (2*S*)-*N*-*para*-toluenesulfonylaziridine-2-carboxylate **4**[10] (100 mg, 0.4 mmol) in tetrahydrofuran (2 ml) was added, and the mixture was stirred for 30 min, and warmed very slowly to room temperature. Water was added and the mixture was filtered through Celite. The filtrate was cooled on ice, acidified to pH 4 using 10% aqueous citric acid and extracted with ethyl acetate (3 × 20 ml). The combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield an oil. Column chromatography on silica gel using (chloroform–methanol–water–acetic acid 7 : 3 : 0.6 : 0.3)–ethyl acetate (1 : 2) as eluant gave (2*S*)-*N*-*para*-toluenesulfonylvinylglycine **13** as a colourless oil, (60 mg, 54%); $[\alpha]_D^{21}$ +10.6 (*c* 0.8, $CHCl_3$); *m*/*z* (EI) found 269.07054; $C_{12}H_{15}O_4NS$ requires 269.07218; ν_{max} (film)/cm^{-1} 1728 (acid); δ_H (360 MHz, C^2HCl_3) 0.8 and 1.2 (2H, 2m, H-3), 2.4 (>3H, $ArCH_3$), 4.0 (1H, t, $J_{2,3A} = J_{2,3B}$ 6.0, H-2), 4.9 and 5.0 (2H, m, H-5), 5.5 (2H, m, NH and H-4), 7.3 (2H, d, *J* 8.1, ArH) and 7.7 (2H, d, *J* 8.3, ArH); δ_C (125.8 MHz, C^2HCl_3) 21.5 ($ArCH_3$), 37.0 (C-3), 55.2 (C-2), 119.8 (=CH_2), 127.2 and 129.7 (Ar), 131.4 (CH=), 136.8 and 143.8 (Ar) and 175.4 (acid).

(2*S*)-*N*-*para*-Toluenesulfonylpropynylglycine (14)

A solution of trimethylsilylacetylene (0.3 ml, 2.1 mmol) and *n*-butyl lithium (1.6 M in hexanes, 1.4 ml, 2.2 mmol) at 0 °C was added *via* cannula transfer to a suspension of copper(I) cyanide (93 mg, 1.0 mmol) in tetrahydrofuran (2 ml) at −78 °C under argon. The mixture was warmed to room temperature after 10 min and cooled to −78 °C. (2*S*)-*N*-*para*-Toluenesulfonylaziridine-2-carboxylate **4**[10] (100 mg, 0.4 mmol) in tetrahydrofuran (2 ml) was added. The reaction was stirred for 30 min at −78 °C and for 18 h at room temperature under argon. The reaction was quenched by addition of water (10 ml) and filtered through Celite. The filtrate was cooled on ice and acidified to pH 4 using 10% aqueous citric acid and the acidified aqueous phase was extracted with ethyl acetate (3 × 20 ml). The solvent was removed *in vacuo* to yield an oil. Column chromatography on silica gel using (chloroform–methanol–water–acetic acid 7 : 3 : 0.6 : 0.3)–ethyl acetate (1 : 2) as eluant gave (2*S*)-*N*-*para*-toluenesulfonylpropynylglycine **14** as a pale yellow oil (20 mg, 18%) with identical spectra to the sample prepared previously.[10]

(2*S*)-*N*-*para*-Toluenesulfonyltryptophan (15)

n-Butyl lithium (1.6 M in hexanes, 0.4 ml, 0.6 mmol) was added to an ice-cooled solution of indole (59 mg, 0.5 mmol) in diethyl ether (0.5 ml) under nitrogen. (2*S*)-*N*-*para*-Toluenesulfonylaziridine-2-carboxylate **4**[10] (50 mg, 0.2 mmol) in diethyl ether (1 ml) was added and the reaction was stirred at room temperature under nitrogen for 4 h. Water (10 ml) was added and the mixture was extracted with diethyl ether (3 × 15 ml). The aqueous layer was cooled on ice, acidified to pH 4 using 10% aqueous citric acid and extracted with ethyl acetate (3 × 10 ml). The combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield an oil. Column chromatography on silica gel using (chloroform–methanol–water–acetic acid 7 : 3 : 0.6 : 0.3)–ethyl acetate (1 : 2) as eluant gave (2*S*)-*N*-*para*-toluenesulfonyltryptophan **15** as a brown solid (15 mg, 20%); mp 125–130 °C; *m*/*z* (EI) found 358.09642; $C_{18}H_{18}O_4N_2S$ requires 358.09873; δ_H (360 MHz, C^2HCl_3) 2.4 (3H, s, $ArCH_3$), 3.4 (1H, dd, $J_{3A,2}$ 6.7, $J_{3A,3B}$ 13.8, H-3A), 3.7 (1H, dd, $J_{3B,2}$ 7.5, $J_{3B,3A}$ 13.8, H-3B), 5.2 (1H, dd, $J_{2,3A}$ 6.7, $J_{2,3B}$ 7.5, H-2), 5.5 (1H, exch. br d, NH), 6.5–7.8 (9H, m, ArH) and 8.0 (1H, exch. s, NH).

(2*S*)-2-Aminobutyric Acid (16)

A solution of hydrogen bromide in acetic acid (1 ml, 30% w/v) was added dropwise to a mixture of (2*S*)-2-(*para*-toluenesulfonylamino)-butyric acid **8** (20 mg, 0.08 mmol) and phenol (15 mg, 0.2 mmol), and the reaction was stirred at room temperature under argon for 4.5 h. The solvent was removed *in vacuo*, and the resultant brown gum was dissolved in water (2 ml) and washed with ethyl acetate (3 × 15 ml). The aqueous phase was applied to a Dowex 50 × 8–100 (H^+) ion exchange column, and inorganic contaminants were eluted with water (100 ml). (2*S*)-2-Aminobutyric acid **16** was recovered using 1 M aqueous ammonium hydroxide as an off-white solid (4 mg, 50%); mp 297 °C (dec.) (lit[12] mp 270–280 °C); $[\alpha]_D^{27}$ +21.7 (*c* 0.4, 6 N HCl) (lit[12] $[\alpha]_D$ +21.2 (5 N HCl)); *m*/*z* (EI) found 58.06521; $[C_4H_9NO_2 - CO_2H]^+$ requires 58.06567; ν_{max} (KBr)/cm^{-1} 1636 (br, acid); δ_H (360 MHz,

$C^2H_3O^2H$) 1.1 (1H, t, *J* 7.5, CH_3), 1.9 (2H, m, H-3) and 3.5 (1H, t, $J_{2,3}$ 6.0, H-2).

(2*S*)-2-Aminoheptanoic acid (17)

A solution of hydrogen bromide in acetic acid (1 ml, 30% w/v) was added dropwise to a mixture of (2*S*)-2-(*para*-toluenesulfonylamino)-heptanoic acid **9** (20 mg, 0.07 mmol) and phenol (13 mg, 0.1 mmol), and the reaction was stirred at room temperature under argon for 4.5 h. The solvent was removed *in vacuo*, and the resultant brown gum was dissolved in water (2 ml) and washed with ethyl acetate (3 × 15 ml). The aqueous phase was applied to a Dowex 50 × 8–100 (H^+) ion exchange column. Inorganic contaminants were eluted with water (100 ml) and (2*S*)-2-aminoheptanoic acid **17** was recovered using 1 M aqueous ammonium hydroxide as an off-white solid, (5 mg, 50%); mp 269–271 °C (lit[13a] mp 274 °C); $[\alpha]_D^{26}$ +27.3 (*c* 0.3, 6 N HCl) (lit[13a] $[\alpha]_D$ +23.9 (6 N HCl)); *m/z* (EI) found 145.11031; $C_7H_{15}O_2N$ requires 145.11028; *m/z* [+ve FAB (3-nba)] 146 ($[M + H]^+$); ν_{max} (KBr)/cm^{-1} 1615 (br, acid); δ_H (360 MHz, $C^2H_3O^2H$) 0.9 (3H, t, *J* 6.8, CH_3), 1.4 (6H, m, CH_2), 1.8 (2H, m, H-3) and 3.5 (1H, dd, $J_{2,3A}$ 6.9, $J_{2,3B}$ 7.0, H-2).

(2*S*)-Phenylalanine (18)

A solution of hydrogen bromide in acetic acid (1 ml, 30% w/v) was added dropwise to a mixture of (2*S*)-*N*-*para*-toluenesulfonylphenylalanine **11** (65 mg, 0.2 mmol) and phenol (38 mg, 0.4 mmol), and the reaction was stirred at room temperature under argon for 4.5 h. The solvent was removed *in vacuo*, and the resultant brown gum was dissolved in water (2 ml) and washed with ethyl acetate (3 × 15 ml). The aqueous phase was applied to a Dowex 50 × 8–100 (H^+) ion exchange column. Inorganic contaminants were eluted with water (100 ml) and (2*S*)-phenylalanine **18** was recovered using 1 M aqueous ammonium chloride as an off-white solid (14 mg, 42%); mp 272–275 °C (lit[13b] mp 283–284 °C); $[\alpha]_D^{25}$ −30.1 (*c* 0.4, H_2O) (lit[13b] $[\alpha]_D$ −34.5 (H_2O)); *m/z* (EI) found 165.07797; $C_9H_{11}O_2N$ requires 165.07898; *m/z* [+ve FAB (3-nba)] 166 ($[M + H]^+$); ν_{max} (KBr)/cm^{-1} 1618 (br, acid); δ_H (360 MHz, $C^2H_3O^2H$) 3.0 (1H, dd, $J_{3A,2}$ 9.0, $J_{3A,3B}$ 14.5, H-3A), 3.3 (1H, partially masked by solvent, $J_{3B,2}$ 4.3, H-3B), 3.8 (1H, dd, $J_{2,3B}$ 4.3, $J_{2,3A}$ 9.0, H-2) and 7.6 (5H, m, ArH).

(2*R*)-*N*-2,2,5,7,8-Pentamethylchroman-6-sulfonyl-3-cyanoalanine (20)

Potassium cyanide (70 mg, 1.1 mmol) was added to a solution of (2*R*)-*N*-2,2,5,7,8-pentamethylchroman-6-sulfonylaziridine-2-carboxylate **19**[10] (100 mg, 0.3 mmol) in methanol (2 ml). The mixture was warmed to 40 °C under nitrogen for 18 h. The mixture was cooled and the solvent was removed *in vacuo*. The resultant solid was dissolved in water (2 ml), cooled on ice and carefully acidified to pH 4 using 10% aqueous citric acid under a stream of nitrogen. The aqueous layer was extracted with ethyl acetate (3 × 10 ml), the combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield an amber oil. Column chromatography on silica gel using (chloroform–methanol–water–acetic acid 7 : 3 : 0.6 : 0.3)–ethyl acetate (1 : 2) as eluant gave (2*R*)-*N*-2,2,5,7,8-pentamethylchroman-6-sulfonyl-3-cyanoalanine **20** as a white solid, (60 mg, 56%); mp 240 °C (dec.); $[\alpha]_D^{29}$ −5.8 (*c* 0.9, MeOH); *m/z* (EI) found 380.14072; $C_{18}H_{24}O_5N_2S$ requires 380.14059; *m/z* [+ve FAB (3-nba)] 403 ($[M + Na]^+$); ν_{max} (KBr)/cm^{-1} 2255 (C≡N) and 1619 (acid); δ_H (360 MHz, $C^2H_3O^2H$) 1.3 (2 × 3H, 2 × s, 2 × CH_3), 1.8 (2H, t, *J* 6.7, CH_2), 2.1 (3H, s, CH_3), 2.5 (2 × 3H, 2 × s, $C(CH_3)_2$), 2.7 (2H, t, *J* 6.7, CH_2), 2.8 (1H, dd, $J_{3S,2}$ 5.0, $J_{3S,3R}$ 16.7, H-3*S*), 2.9 (1H, dd, $J_{3R,2}$ 4.9, $J_{3R,3S}$ 16.7, H-3*R*) and 3.7 (1H, dd, $J_{2,3R}$ 4.9, $J_{2,3S}$ 5.0, H-2); δ_C (125.8 MHz, $C^2H_3O^2H$) 12.8 (CH_3), 18.1 and 19.1 (2 × CH_3), 22.9 (CH_2), 24.1 (CH_2), 27.3 (CH_3), 34.1 (CH_2), 54.9 (C-2), 75.8 ($C(CH_3)_2$), 119.1 (C≡N), 120.6, 126.2, 129.9, 138.2, 138.4 and 156.4 (Ar) and 174.5 (acid).

N,*N*-Dibenzylpropargylamine (21)

A vigorously stirred mixture of benzyl bromide (6.9 ml, 58.0 mmol), propargylamine (2 ml, 29.16 mmol), aqueous sodium carbonate (12.32 g in 25 ml of water, 116.24 mmol) and dichloromethane (70 ml) was heated to reflux for 4 h. The aqueous layer was extracted with dichloromethane (3 × 15 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo.* Kugelrohr distillation afforded *N*,*N*-dibenzylpropargylamine **21** as a colourless liquid which solidified on cooling (4.84 g, 71%), mp 39–41 °C (lit[14] mp 42–43.5 °C); *m/z* [+ve FAB (3-nba)] 236 ($[M + H]^+$); δ_H (360 MHz, C^2HCl_3) 2.29 (1H, t, $J_{1,3}$ 2.1, H-1), 3.27 (2H, d, $J_{3,1}$ 2.1, H-3), 3.70 (4H, s, NCH_2Ph) and 7.24–7.42 (10H, m, ArH); δ_C (75.5 MHz, C^2HCl_3) 41.1 (C-3), 57.4 (CH_2Ph), 72.1 (C-2), 78.5 (C-1) and 127.2–138.8 (Ar).

(2*S*)-6-(*N*,*N*-Dibenzylamino)-2-(*para*-toluenesulfonylamino)-hex-4-ynoic acid (22)

n-Butyl lithium (1.6M in hexane, 4.3 ml, 6.88 mmol) was added dropwise to a solution of *N*,*N*-dibenzylpropargylamine **21** (1.56 g, 6.638 mmol) in tetrahydrofuran (19 ml) at 0 °C and the mixture was stirred for 30 min at 0 °C. A solution of (2*S*)-*N*-*para*-toluenesulfonylaziridine-2-carboxylate **4** (640 mg, 2.656 mmol) in tetrahydrofuran (5 ml) was added dropwise. The reaction was stirred at 0 °C for 3.5 h and the solvent was removed *in vacuo.* Flash chromatography on silica gel, eluting with (chloroform–methanol–water–acetic acid 7 : 3 : 0.6 : 0.3)–ethyl acetate (3 : 7) yielded (2*S*)-6-(*N*,*N*-dibenzylamino)-2-(*para*-toluenesulfonylamino)-hex-4-ynoic acid **22** (771 mg, 61%) as a tan solid, mp 141–145 °C; $[\alpha]_D^{32}$ +30.4 (*c* 1, THF); *m/z* (FAB, PEGH/NOBA) found 477.1827; $[C_{27}H_{28}N_2O_4S + H]^+$ requires 477.1848; ν_{max} (KBr)/cm^{-1} 3260 (NH), 2923 (OH) and 1719 (acid); δ_H (360 MHz, $C_5^2H_5N$) 2.05 (3H, s, CH_3Ar), 3.19 (2H, m, H-6), 3.23 (2H, m, H-3), 4.80 (1H, br m, H-2), 5.70 (4H, s, NCH_2Ar) and 7.11–7.56 (15H, m, NH and ArH); δ_C (125.8 MHz, $C_5^2H_5N$) 21.7 (CH_3Ar), 30.6 (C-2), 42.3 (C-6), 58.2 (2 × CH_2Ar), 78.2 (C-4 and C-5) and 129.3–143.5 (Ar).

Methyl (2*S*)-6-(*N*,*N*-dibenzylamino)-2-(*para*-toluenesulfonylamino)-hex-4-ynoate (23)

Diazomethane[15] (*ca.* 16.6 mmol of diazomethane in diethyl ether) was added with stirring to a solution of (2*S*)-6-(*N*,*N*-dibenzylamino)-2-(*para*-toluenesulfonylamino)-hex-4-ynoic acid **22** (240 mg, 0.504 mmol) in diethyl ether (5 ml) and tetrahydrofuran (5 ml) at 0 °C. Nitrogen was bubbled through the solution

to remove excess diazomethane and the solvent was removed *in vacuo*. Flash chromatography on silica gel, eluting with ethyl acetate–petroleum ether (3 : 7) afforded methyl (2*S*)-6-(*N*,*N*-dibenzylamino)-2-(*para*-toluenesulfonylamino)-hex-4-ynoate **23** (186 mg, 75%) as a white solid, mp 91–92 °C; $[\alpha]_D^{31}$ +9.3 (*c* 1, $CHCl_3$); *m*/*z* (FAB, PEGH, 3-nba) found 490.1937; $C_{28}H_{30}N_2O_4S$ requires 490.1926; *m*/*z* [+ ve FAB (3-nba)] 491 ($[M + H]^+$); ν_{max} (KBr)/cm^{-1} 3287 (NH) and 1746 (ester); δ_H (360 MHz, C^2HCl_3) 2.35 (3H, s, CH_3Ar), 2.75 (2H, m, H-3), 3.14 (2H, s, H-6), 3.56 (3H, s, OCH_3), 3.57 (4H, s, CH_2Ar), 4.11 (1H, ddd, $J_{2,NH}$ 8.5, $J_{2,3A}$ 4.8, $J_{2,3B}$ 4.6, H-2), 5.40 (1H, d, $J_{NH,2}$ 8.5, NH) and 7.18–7.72 (14H, m, ArH); δ_C (125.8 MHz, C^2HCl_3) 21.5 (CH_3Ar), 24.4 (C-6), 41.2 (C-3), 52.9 (OCH_3), 54.3 (C-2), 57.4 (NCH_2Ar), 78.5 (C-4), 78.6 (C-5), 127.1, 128.3, 128.9, 129.7, 136.8, 138.7 and 143.8 (Ar) and 170.3 (ester).

Methyl (2*S*)-2-(*para*-toluenesulfonylamino)-hexanoate (24)

A solution of methyl (2*S*)-6-(*N*,*N*-dibenzylamino)-2-(*para*-toluenesulfonylamino)-hex-4-ynoate **23** (179 mg, 0.365 mmol) in ethyl acetate (20 ml) was stirred with 10% palladium on carbon (15 mg) under an atmosphere of hydrogen for 4 days. The mixture was filtered through Celite, washing with ethyl acetate (10 ml). The solvent was removed *in vacuo*. Flash chromatography on silica gel, eluting with ethyl acetate–petroleum ether (3 : 7) afforded methyl (2*S*)-2-(*para*-toluenesulfonylamino)-hexanoate **24** (71 mg, 65%) as a white solid, mp 43–45 °C; $[\alpha]_D^{30}$ +21.6 (*c* 1, $CHCl_3$); *m*/*z* (FAB, PEGH, 3-nba) found 300.1281; $[C_{14}H_{21}NO_4S + H]^+$ requires 300.1270; ν_{max} (KBr)/cm^{-1} 3269 (NH) and 1743 (ester); δ_H (360 MHz, C^2HCl_3) 0.86 (3H, t, *J* 6.8, H-6), 1.27–1.73 (6H, m, H-3, H-4 and H-5), 2.42 (3H, s, CH_3Ar), 3.49 (3H, s, OCH_3), 3.90 (1H, ddd, $J_{2,NH}$ 9.3, $J_{2,3A}$ 5.5, $J_{2,3B}$ 5.7, H-2), 5.16 (1H, d, $J_{NH,2}$ 9.3, NH), 7.28 (2H, d, *J* 8, ArH) and 7.66 (2H, d, *J* 8, ArH); δ_C (125.8 MHz, C^2HCl_3) 13.7 (C-6), 21.4 (CH_3Ar), 22.0 (C-5), 26.9 (C-4), 33.0 (C-3), 52.3 (OCH_3), 55.6 (C-2), 127.2, 129.6 and 136.7 (Ar) and 172.3 (ester).

Methyl (2*S*,4*Z*)-6-(*N*,*N*-dibenzylamino)-2-(*para*-toluenesulfonylamino)-hex-4-enoate (25)

A solution of methyl (2*S*)-6-(*N*,*N*-dibenzylamino)-2-(*para*-toluenesulfonylamino)-hex-4-ynoate **23** (140 mg, 0.286 mmol) in ethyl acetate (80 ml) was stirred with quinoline (6 mg) and Lindlar's catalyst (28 mg) under an atmosphere of hydrogen for 8 h. The reaction was filtered through Celite, washing with ethyl acetate (20 ml). The solvent was removed *in vacuo*. Flash chromatography on silica gel, eluting with ethyl acetate–petroleum ether (3 : 7) afforded methyl (2*S*,4*Z*)-6-(*N*,*N*-dibenzylamino)-2-(*para*-toluenesulfonylamino)-hex-4-enoate **25** (91 mg, 65%) as a colourless oil, $[\alpha]_D^{25}$ +17.0 (*c* 1, $CHCl_3$); *m*/*z* (FAB, PEGH, 3-nba) found 493.2149; $[C_{28}H_{32}N_2O_4S + H]^+$ requires 493.2161; ν_{max} (film)/cm^{-1} 3274 (NH) and 1742 (ester); δ_H (360 MHz, C^2HCl_3) 2.35 (2H, m, H-3), 2.38 (3H, s, CH_3Ar), 2.91 (2H, d, $J_{6,5}$ 6.3, H-6), 3.44 (3H, s, OCH_3), 3.53 (4H, AB, J_{AB} 13.6, CH_2Ar), 3.94 (1H, ddd, $J_{2,NH}$ 7.2, $J_{2,3A}$ 4, $J_{2,3B}$ 4, H-2), 5.36–5.43 (1H, m, H-4), 5.60 (1H, d, $J_{NH,2}$ 7.2, NH), 5.70–5.76 (1H, m, H-5) and 7.23–7.69 (14H, m, ArH); δ_C (125.8 MHz, C^2HCl_3) 21.5 (CH_3Ar), 31.2 (C-3), 49.2 (C-6), 52.4 (OCH_3), 55.2 (C-2), 57.9 (CH_2Ar), 125.7 (C-5), 126.9–129.5 (Ar), 131.7 (C-4), 136.8–143.5 (Ar) and 171.5 (ester).

Methyl (2*S*,3*R*)-threoninate hydrochloride (26)

(2*S*,3*R*)-Threonine (5 g, 42.0 mmol) was added with constant stirring and under a slow stream of nitrogen to a solution of methanol (50 ml) and thionyl chloride (8.3 ml, 0.113 mol) at 0 °C. When all of the starting material had dissolved, the mixture was allowed to warm to room temperature and stirred for 20 h at 0 °C under nitrogen. The solvent was removed *in vacuo* and the resultant solid was azeotroped with carbon tetrachloride (3 × 100 ml) to remove last traces of thionyl chloride. Methyl (2*S*,3*R*)-threoninate hydrochloride **26** was obtained as a colourless oil (7 g, 97%); $[\alpha]_D^{29}$ −14.9 (*c* 2.1, H_2O); (found C, 32.8; H, 7.5; N, 7.7. $C_5H_{12}O_3NCl$. 0.75 H_2O requires C, 32.8; H, 7.4; N, 7.7%); *m*/*z* [+ve FAB (3-nba)] 134 ([free base + H]$^+$); ν_{max} (film)/cm^{-1} 1747 (ester); δ_H (360 MHz, $C^2H_3O^2H$) 1.3 (3H, d, $J_{Me,3}$ 6.5, CH_3), 3.8 (3H, s, OCH_3), 3.9 (1H, d, $J_{2,3}$ 3.7, H-2) and 4.3 (1H, m, H-3); δ_C (125.8 MHz, $C^2H_3O^2H$) 21.0 (CH_3), 54.2 (OCH_3), 60.3 (C-3), 66.8 (C-2) and 170.1 (ester).

Methyl (2*S*,3*R*)-*N*-triphenylmethylthreoninate (27)

A solution of methyl (2*S*,3*R*)-threoninate hydrochloride **26** (7 g, 41.3 mmol) in chloroform (40 ml) and triethylamine (13 ml, 93.4 mmol) was cooled to 0 °C and a solution of triphenylmethyl chloride (11.5 g, 41.3 mmol) in chloroform (25 ml) was added over a period of 30 min. The mixture was stirred at 0 °C under argon for 20 h. The solution was washed with 10% aqueous citric acid (3 × 50 ml) and water (3 × 50 ml) and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave methyl (2*S*,3*R*)-*N*-triphenylmethylthreoninate **27** as a yellow oil (16.4 g, quant.); $[\alpha]_D^{25}$ +6.6 (*c* 2.1, $CHCl_3$) (lit[3b] enantiomer $[\alpha]_D^{17}$ −6.4 (*c* 1.1, $CHCl_3$)); (found C, 77.3; H, 6.6; N, 3.1. $C_{24}H_{25}O_3N$ requires C, 76.8; H, 6.7; N, 3.7%); *m*/*z* [+ve FAB (3-nba)] 376 ($[M + H]^+$); ν_{max} (film)/cm^{-1} 1732 (ester); δ_H (360 MHz, C^2HCl_3) 1.2 (3H, d, $J_{Me,3}$ 7.4, CH_3), 3.2 (3H, s, OCH_3), 3.4 (1H, d, $J_{2,3}$ 7.5, H-2), 3.8 (1H, m, H-3) and 7.2–7.5 (15H, m, ArH); δ_H (125.8 MHz, C^2HCl_3) 18.9 (CH_3), 51.7 (OCH_3), 62.5 (C-3), 69.7 (C-2), 70.7 ($NCPh_3$), 126.6, 127.9, 128.9 and 145.4 (Ar) and 173.6 (ester).

Methyl (2*S*,3*S*)-*N*-triphenylmethyl-3-methylaziridine-2-carboxylate (28)

This was prepared in 75% yield from methyl (2*S*,3*R*)-*N*-triphenylmethylthreoninate **27** using the method[3b] described for preparation of the (2*R*,3*R*)-isomer. It was obtained as a white solid by recrystallisation from methanol, mp 102–104 °C; $[\alpha]_D^{25}$ −98.5 (*c* 1.7, $CHCl_3$) (lit[3b] enantiomer $[\alpha]_D^{23}$ +98 (*c* 1, $CHCl_3$)); (found C, 81.0; H, 6.7; N, 3.9. $C_{24}H_{23}O_2N$ requires C, 80.6; H, 6.5; N, 3.9%); *m*/*z* [+ve FAB (3-nba)] 358 ($[M + H]^+$); ν_{max} (KBr)/cm^{-1} 1744 (ester); δ_H (360 MHz, C^2HCl_3) 1.4 (3H, d, $J_{Me,3}$ 5.4, CH_3), 1.7 (1H, m, H-3), 1.9 (1H, d, $J_{2,3}$ 6.5, H-2), 3.8 (3H, s, OCH_3) and 7.2–7.5 (15H, m, ArH); δ_C (125.8 MHz, C^2HCl_3) 13.3 (CH_3), 34.7 (C-3), 35.9 (C-2), 51.7 (OCH_3), 75.0 ($NCPh_3$), 126.8, 127.6, 129.4 and 143.9 (Ar) and 170.7 (ester).

Methyl (2*S*,3*S*)-*N*-*para*-toluenesulfonyl-3-methylaziridine-2-carboxylate (29)

Methyl (2*S*,3*S*)-*N*-triphenylmethyl-3-methylaziridine-2-carboxylate **28** (1.1 g, 3.1 mmol) was dissolved in a mixture of chloroform

(5 ml) and methanol (5 ml) and the solution was cooled to 0 °C in an ice bath. Trifluoroacetic acid (6 ml, 77.9 mmol) was added dropwise over a period of 10 min and the mixture was stirred under argon at 0 °C for 5 h. The solvents were removed *in vacuo* at 0 °C, and the resultant solid was azeotroped with diethyl ether (3 × 30 ml) to remove the last traces of trifluoroacetic acid, and partitioned between diethyl ether (20 ml) and water (20 ml). The ether layer was extracted with water (3 × 30 ml) and neutralised with solid sodium bicarbonate (250 mg). Ethyl acetate (50 ml) was added to the aqueous portion and the mixture was cooled to 0 °C. *para*-Toluenesulfonyl chloride (600 mg, 3.1 mmol) was added and the reaction mixture was stirred vigorously under argon at room temperature for 20 h. The aqueous layer was extracted with ethyl acetate (3 × 50 ml). The combined organic fractions were washed with brine (3 × 50 ml) and dried (Na_2SO_4). Removal of the solvent *in vacuo* yielded a colourless oil. Column chromatography on silica gel using chloroform–petroleum ether (1 : 5) as eluant gave methyl (2*S*,3*S*)-*N*-*para*-toluenesulfonyl-3-methylaziridine-2-carboxylate **29** as a white solid which was recrystallised from methanol (600 mg, 72%); mp 57–59 °C; $[\alpha]_D^{26}$ −37.4 (*c* 2.4, $CHCl_3$); (found C, 53.4; H, 5.7; N, 5.1. $C_{12}H_{15}O_4NS$ requires C, 53.5; H, 5.6; N, 5.2%); *m*/*z* [+ve FAB (3-nba)] 270 ($[M + H]^+$); ν_{max} (KBr)/cm^{-1} 1753 (ester); δ_H (360 MHz, C^2HCl_3) 1.3 (3H, d, $J_{Me,3}$ 5.8, CH_3), 2.4 (3H, s, $ArCH_3$), 3.1 (1H, m, H-3), 3.4 (1H, d, $J_{2,3}$ 7.5, H-2), 3.7 (3H, s, OCH_3), 7.3 (2H, d, *J* 8.1, ArH) and 7.8 (2H, d, *J* 8.1, ArH); δ_C (125.8 MHz, C^2HCl_3) 12.1 (CH_3), 21.6 ($ArCH_3$), 40.0 (C-3), 41.1 (C-2), 52.6 (OCH_3), 127.9, 129.8, 143.9 and 145.0 (Ar) and 166.2 (ester).

(2*S*,3*S*)-*N*-*para*-Toluenesulfonyl-3-methylaziridine-2-carboxylate (30)

A solution of methyl (2*S*,3*S*)-*N*-*para*-toluenesulfonyl-3-methylaziridine-2-carboxylate **29** (100 mg, 0.37 mmol) in tetrahydrofuran (2 ml) was cooled to 0 °C. 1 N NaOH (0.6 ml, 0.6 mmol) was added and the reaction was stirred at room temperature for 3 h. The solvent was removed *in vacuo* and the resultant gum was partitioned between ethyl acetate (10 ml) and saturated aqueous sodium bicarbonate (10 ml). The aqueous fraction was cooled on ice and acidified to pH 4 with 10% aqueous citric acid. The acidified aqueous layer was extracted with ethyl acetate (3 × 20 ml), the combined organic fractions were dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield (2*S*,3*S*)-*N*-*para*-toluenesulfonyl-3-methylaziridine-2-carboxylate **30** as a white solid which was recrystallised from dichloromethane and petroleum ether (95 mg, quant.); mp 107–108 °C; $[\alpha]_D^{33}$ −43.6 (*c* 2.0, $CHCl_3$); (found C, 51.5; H, 5.1; N, 5.4. $C_{11}H_{13}O_4NS$ requires C, 51.8; H, 5.1; N, 5.5%); *m*/*z* [+ve FAB (3-nba)] 256 ($[M + H]^+$); ν_{max} (KBr)/cm^{-1} 1718 (acid); δ_H (360 MHz, C^2HCl_3) 1.3 (3H, d, $J_{Me,3}$ 5.6, CH_3), 2.4 (3H, s, $ArCH_3$), 3.1 (1H, m, H-3), 3.4 (1H, d, $J_{2,3}$ 7.6, H-2), 7.4 (2H, d, *J* 8, ArH), 7.8 (2H, d, *J* 8, ArH) and 8.9 (1H, exch. br s, OH); δ_C (125.8 MHz, C^2HCl_3) 12.1 (CH_3), 21.6 ($ArCH_3$), 40.3 (C-3), 40.9 (C-2), 128.0, 129.9, 133.9 and 145.2 (Ar) and 170.9 (acid).

(2*S*,3*R*)-3-Carboxy-2-(*para*-toluenesulfonylamino)-heptane (31) and (2*S*,3*S*)-2-(*para*-toluenesulfonylamino)-3-methylheptanoic acid (32)

n-Butyl lithium (1.6 M in hexanes, 2.5 ml, 4.0 mmol) was added to a suspension of copper(I) cyanide (176 mg, 2.0 mmol) in tetrahydrofuran (2 ml) at −78 °C under argon. The mixture was left at −78 °C for 30 min and allowed to warm slowly to room temperature. The cuprate was cooled to −78 °C and a solution of (2*S*,3*S*)-*N*-*para*-toluenesulfonyl-3-methylaziridine-2-carboxylate **30** (200 mg, 0.8 mmol) in tetrahydrofuran (2 ml) was added. The mixture was allowed to warm to room temperature and stirred for 18 h under argon. Water (8 ml) was added and the mixture was filtered through a plug of Celite to remove any solid residue. The filtrate was cooled on ice and acidified to pH 4 using 10% aqueous citric acid. The aqueous phase was extracted with ethyl acetate (3 × 15 ml) and the combined organic layers were dried (Na_2SO_4). The solvent was removed *in vacuo* to yield a colourless oil. Column chromatography on silica gel using (chloroform–methanol–water–acetic acid 7 : 3 : 0.6 : 0.3)–ethyl acetate (1 : 2) as eluant gave a 3 : 1 mixture containing (2*S*,3*R*)-3-carboxy-2-(*para*-toluenesulfonylamino)-heptane **31** as the major product and (2*S*,3*S*)-2-(*para*-toluenesulfonylamino)-3-methylheptanoic acid **32** as the minor product. This was a colourless oil (83 mg, 34%); *m*/*z* (EI) found 313.13417; $C_{15}H_{23}O_4NS$ requires 313.13478; *m*/*z* [+ve FAB (3-nba)] 314 ($[M + H]^+$); ν_{max} (film)/cm^{-1} 1693 (acid); δ_H (360 MHz, $C^2H_3O^2H$) β-tosylamino acid **31** in mixture 0.8 (3H, t, *J* 6.7, CH_3), 0.9 (3H, d, $J_{Me,2}$ 6.6, CH_3), 1.1–1.5 (6H, m, CH_2), 2.2 (1H, m, H-3), 2.4 (3H, s, $ArCH_3$), 3.4 (1H, m, H-2), 7.3 (2H, d, *J* 8.3, ArH) and 7.8 (2H, d, *J* 8.3, ArH) and δ_H (360 MHz, C^2HCl_3) for α-tosylamino acid **32** in mixture 1.6 (1H, m, H-3) and 3.6 (1H, d, $J_{2,3}$ 7.5, H-2); δ_C (125.8 MHz, C^2HCl_3) 14.7 (CH_3), 20.3 (CH_3), 21.9 ($ArCH_3$), 24.0, 30.9 and 31.0 (3 × CH_2), 52.9 (C-2), 54.3 (C-3), 127.6, 131.0, 140.8 and 144.6 (Ar) and 178.3 (acid).

(2*R*,3*S*)-2-Carboxy-3-(*para*-toluenesulfonylamino)-butane (33) and (2*S*)-*N*-*para*-toluenesulfonylvaline (34)

Methyl lithium (1.6 M in ether, 2.5 ml, 4.0 mmol) was added to a suspension of copper(I) cyanide (176 mg, 2.0 mmol) in tetrahydrofuran (2 ml) at −78 °C under argon. The mixture was left at −78 °C for 30 min and allowed to warm to room temperature very slowly. The cuprate was cooled to −78 °C and a solution of (2*S*,3*S*)-*N*-*para*-toluenesulfonyl-3-methylaziridine-2-carboxylate **30** (200 mg, 0.8 mmol) in tetrahydrofuran (2 ml) was added. The reaction was allowed to warm to room temperature and stirred for 18 h under argon. The reaction was quenched by addition of water (8 ml) and the mixture was filtered through a plug of Celite to remove any solid residue. The filtrate was cooled on ice and acidified to pH 4 using 10% aqueous citric acid. The aqueous phase was extracted with ethyl acetate (3 × 15 ml) and the combined organic layers were dried (Na_2SO_4). The solvent was removed *in vacuo* to yield a colourless oil. Column chromatography on silica gel using (chloroform–methanol–water–acetic acid 7 : 3 : 0.6 : 0.3)–ethyl acetate (1 : 2) as eluant gave a 4 : 1 mixture containing (2*R*,3*S*)-2-carboxy-3-(*para*-toluenesulfonylamino)-butane **33** as the major product and (2*S*)-*N*-*para*-toluenesulfonylvaline **34** as the minor product. This was a colourless oil (80 mg, 36%); *m*/*z* (EI) found 271.08760; $C_{12}H_{17}O_4NS$ requires 271.08783; *m*/*z* [+ve FAB (3-nba)] 272 ($[M + H]^+$); ν_{max} (film)/cm^{-1} 1708 (acid); δ_H (360 MHz, $C^2H_3O^2H$) β-tosylamino acid **33** in mixture 0.9 (3H, d, $J_{Me,3}$ 6.7, CH_3), 1.1 (3H, d, $J_{Me,2}$ 7.1, CH_3), 2.4 (1H, m, H-2), 2.4 (3H, s, $ArCH_3$), 3.5 (1H, m, H-3), 7.4 (2H, d, *J* 8.3, ArH) and 7.8 (2H, d, *J* 8.3, ArH); δ_H (360 MHz, C^2HCl_3) α-tosylamino acid **34** in mixture

1.7 (1H, m, H-3) and 3.6 (1H, d, $J_{2,3}$ 5.5, H-2); δ_C (125.8 MHz, $C^2H_3O^2H$) 13.4 (CH_3), 15.0 (CH_3), 21.5 ($ArCH_3$), 44.6 (C-2), 51.4 (C-3), 127.0, 130.0, 137.9 and 143.4 (Ar) and 178.9 (acid).

(2*S*,3*S*)-2-(*para*-Toluenesulfonylamino)-3-methyl-5-trimethylsilylpent-4-ynoic acid (35)

n-Butyl lithium (1.6 M in hexanes, 2 ml, 3.2 mmol) was added to a solution of trimethylsilylacetylene (0.5 ml, 3.54 mmol) in tetrahydrofuran (2 ml) at 0 °C under argon and the mixture was stirred for 30 min. (2*S*,3*S*)-*N*-*para*-Toluenesulfonyl-3-methylaziridine-2-carboxylate **30** (100 mg, 0.4 mmol) in tetrahydrofuran (2 ml) was added, and the reaction was stirred at 0 °C for 1 h and at room temperature for a further 2 h under argon. Saturated aqueous ammonium chloride was added and the aqueous phase was cooled on ice and acidified to pH 4 with 10% aqueous citric acid. The aqueous phase was extracted with ethyl acetate (3 × 30 ml) and the combined organic layers were dried (Na_2SO_4). Removal of the solvent *in vacuo* yielded an amber oil. Column chromatography on silica gel using (chloroform–methanol–water–acetic acid 7 : 3 : 0.6 : 0.3)–ethyl acetate (1 : 2) as eluant gave (2*S*,3*S*)-2-(*para*-toluenesulfonylamino)-3-methyl-5-trimethylsilylpent-4-ynoic acid **35** as a pale yellow solid which was recrystallised from dichloromethane and petroleum ether (96 mg, 70%); mp 111–114 °C; $[\alpha]_D^{34}$ −25.7 (*c* 2, $CHCl_3$); *m*/*z* (EI) found 353.11109; $C_{16}H_{23}O_4NSSi$ requires 353.11171; *m*/*z* [+ve FAB (3-nba)] 354 ($[M + H]^+$) and 308 ($[M\text{-}CO_2H]^+$); ν_{max} (KBr)/cm^{-1} 2173 (C≡C) and 1720 (acid); δ_H (360 MHz, C^2HCl_3) 0.2 (9H, s, $Si(CH_3)_3$), 1.2 (3H, d, $J_{Me,3}$ 5.1, CH_3), 2.4 (3H, s, $ArCH_3$), 3.1 (1H, m, H-3), 3.9 (1H, dd, $J_{2,3}$ 3.9, $J_{2,NH}$ 9.7, H-2), 5.4 (1H, exch. d, $J_{NH,2}$ 9.7, NH), 7.3 (2H, d, *J* 8.2, ArH) and 7.8 (2H, d, *J* 8.2, ArH); δ_C (125.8 MHz, C^2HCl_3) 0.0 ($Si(CH_3)_3$), 17.9 ($ArCH_3$), 21.5 (CH_3), 30.7 (C-3), 59.3 (C-2), 73.0 (C≡), 104.0 (≡CSi), 127.2, 136.7, 136.7 and 143.8 (Ar) and 174.5 (acid).

Methyl (2*S*,3*S*)-2-(*para*-toluenesulfonylamino)-3-methylpent-4-ynoate (36)

1 N NaOH was added dropwise to a solution of (2*S*,3*S*)-2-(*para*-toluenesulfonylamino)-3-methyl-5-trimethylsilylpent-4-ynoic acid **35** (100 mg, 0.3 mmol) in methanol (3 ml) until the pH reached 8. The mixture was heated at 50 °C for 18 h. The reaction was cooled and acidified to pH 4 using 10% aqueous citric acid. The aqueous mixture was extracted with ethyl acetate (3 × 20 ml) and the combined organic layers were dried (Na_2SO_4). The solvent was removed *in vacuo* to yield an oil. Column chromatography on silica gel using (chloroform–methanol–water–acetic acid 7 : 3 : 0.6 : 0.3)–ethyl acetate (1 : 2) as eluant gave (2*S*,3*S*)-2-(*para*-toluenesulfonylamino)-3-methylpent-4-ynoic acid as a colourless oil (75 mg, 94%); δ_H (360 MHz, $C^2H_3O^2H$) 1.3 (3H, d, $J_{Me,3}$ 5.3, CH_3), 2.4 (3H, s, $ArCH_3$), 3.1 (1H, m, H-3), 3.9 (1H, d, $J_{2,3}$ 4.2, H-2), 7.3 (2H, d, *J* 8.2, ArH) and 7.8 (2H, d, *J* 8.2, ArH). A solution of (2*S*,3*S*)-2-(*para*-toluenesulfonylamino)-3-methylpent-4-ynoic acid (26 mg, 0.09 mmol) in methanol (3 ml) was treated with $BF_3{\cdot}Et_2O$ (0.02 ml, 0.16 mmol) and heated at reflux for 20 h. Water (5 ml) was added and the mixture was extracted with ethyl acetate (3 × 20 ml). The combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. Column chromatography on silica gel using ethyl acetate–petroleum ether (1 : 2) as eluant gave methyl (2*S*,3*S*)-2-(*para*-toluenesulfonylamino)-3-methylpent-4-ynoate **36** as a colourless oil (10 mg, 37%); δ_H (360 MHz, C^2HCl_3) 1.3 (3H, d, $J_{Me,3}$ 6.6, CH_3), 2.1 (1H, d, $J_{5,3}$ 1.6, ≡CH), 2.4 (3H, s, $ArCH_3$), 3.0 (1H, m, H-3), 3.5 (3H, s, OCH_3), 3.9 (1H, dd, $J_{2,3}$ 4.2, $J_{2,NH}$ 10.1, H-2), 5.3 (1H, d, $J_{NH,2}$ 10.1, NH), 7.3 (2H, d, *J* 8.1, ArH) and 7.8 (2H, d, *J* 8.1, ArH).

Methyl (2*S*,3*S*)-*N*-*para*-toluenesulfonylisoleucine (37)

Palladium on calcium carbonate poisoned with lead (Lindlar's catalyst) (6 mg, 20% m/m) and quinoline (1.2 mg, 4% m/m) were added to a solution of methyl (2*S*,3*S*)-2-(*para*-toluenesulfonylamino)-3-methylpent-4-ynoate **36** (10 mg, 0.03 mmol) in ethyl acetate (30 ml). The mixture was flushed three times with argon and a further three times with hydrogen, and stirred under an atmosphere of hydrogen gas at rtp for 20 h. The solvent was removed *in vacuo* to yield an oil. Column chromatography on silica gel using ethyl acetate–petroleum ether (1 : 2) as eluant gave methyl (2*S*,3*S*)-*N*-*para*-toluenesulfonylisoleucine **37** as a white solid which was recrystallised from dichloromethane and petroleum ether (8 mg, 79%); mp 84–86 °C; $[\alpha]_D^{20}$ +12.5 (*c* 0.3, $CHCl_3$); *m*/*z* (EI) found 299.09798; $C_{14}H_{21}O_4NS$ requires 299.11913; *m*/*z* [+ve FAB (3-nba)] 300 ($[M + H]^+$); ν_{max} (KBr)/cm^{-1} 1744 (ester); δ_H (360 MHz, C^2HCl_3) 0.9 (6H, m, 2 × CH_3), 1.2 (1H, m, H-4A), 1.4 (1H, m, H-4B), 1.7 (1H, m, H-3), 2.4 (3H, s, $ArCH_3$), 3.5 (3H, s, OCH_3), 3.7 (1H, dd, $J_{2,3}$ 5.5, $J_{2,NH}$ 10.1, H-2), 5.1 (1H, exch. d, $J_{NH,2}$ 10.1, NH), 7.3 (2H, d, *J* 8.2, ArH) and 7.7 (2H, d, *J* 8.2, ArH).

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