Efficient tin hydride-mediated radical cyclisation of secondary amides leading to substituted pyrrolidinones. Part 2. Application to the synthesis of aromatic kainic acid analogues

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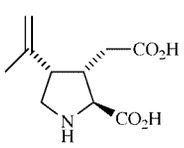
An enantioselective synthesis of phenyl allokainoid, starting from D-serine, is reported. Tin-mediated cyclisation of a secondary amide was used in the key step to produce a trisubstituted pyrrolidinone in excellent yield (*ca.* 80%). The predominant formation of the all-*trans* diastereoisomer is consistent with a reversible cyclisation to give the thermodynamically more stable product.

Introduction

Substituted pyrrolidines and pyrrolidinones are attractive synthetic targets because of their widespread occurrence and diverse range of important biological activities. One important family of naturally occurring pyrrolidines are the kainoid amino acids which possess anthelmintic, insecticidal and most importantly, neuroexcitatory properties.[1] This is attributed to their action as conformationally restricted analogues of the neurotransmitter L-glutamic acid. Numerous syntheses of the parent member, kainic acid **1**, and the C-4 epimer, allokainic



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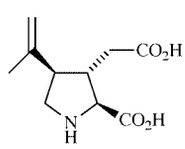

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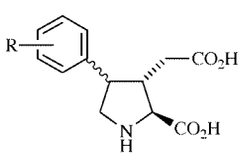
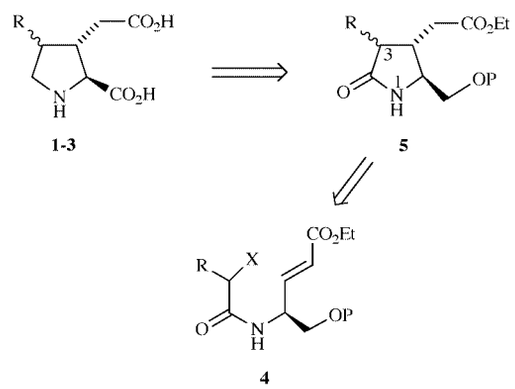


3

acid **2**, have been reported[1] and interest has now turned towards the preparation of (C-4) aromatic analogues **3**.[2] These aromatic amino acids have been shown to exhibit the most potent neuroexcitatory activity of this family of compounds.

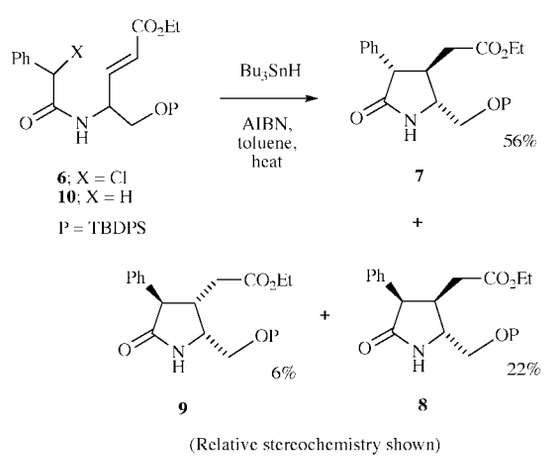
Our earlier work had shown that trisubstituted pyrrolidinones could be isolated in good yield from radical cyclisation of secondary haloamides.[3] We envisaged that this type of cyclisation could be employed to construct the 5-membered ring present in the kainoid amino acids. As shown in the retrosynthetic analysis (Scheme 1), reaction of a halide precursor of type **4** with tributyltin hydride could allow the preparation of pyrrolidinone **5**. Steric interactions were expected to give predominantly the *trans*-C-4–C-5 isomer. Elaboration to the amino acid would then include oxidation of the primary alcohol and reduction of the lactam carbonyl. An aromatic substituent (R = Ph) at the site of radical generation was of particular interest as this is required for the preparation of biologically important aromatic analogues **3**. The chiral cyclisation



Scheme 1

precursor **4**, required for an enantioselective synthesis of **3**, could be prepared from the amino acid D-serine.

To test the feasibility of this approach, the preparation of benzylic chloride **6**, containing a silyl protected alcohol, was then carried out starting from DL-serine (Scheme 2). Reaction

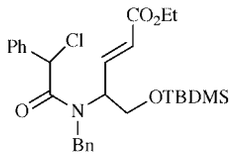


Scheme 2

of the TBDPS derivative **6** with tin hydride in boiling toluene yielded three separable pyrrolidinones **7–9** in a combined yield of 84% after column chromatography. Simple reduction, to give

ethanamide **10**, was only observed in low yield (8%). A similar result was obtained using the corresponding TBDMS-protected alcohol to give the related pyrrolidinones (as an 8.6:4.5:1 mixture of isomers) in a combined 85% yield.

The formation of three pyrrolidinone diastereomers, **7–9**, in the ratio 8.9:3.5:1 can be compared to the cyclisation of a similar *N*-benzyl precursor **11** which gave a 1:1:1 mixture of



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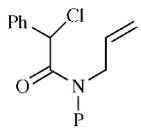
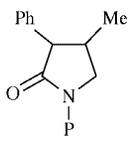
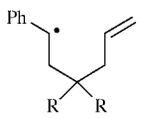


12a; P = H
12b; P = Me
12c; P = Bn



13a; P = H (d.r., 8.5:1)
13b; P = Me (d.r., 5.5:1)
13c; P = Bn (d.r., 4.1:1)

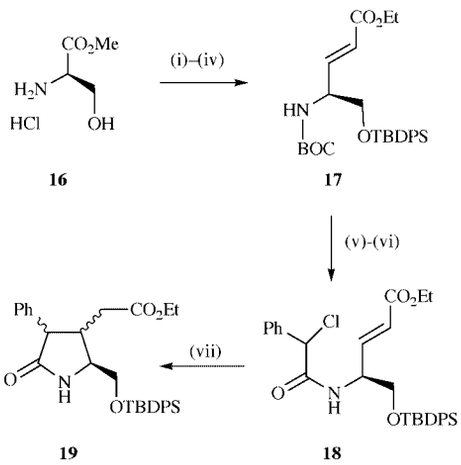


14; R = H
15; R = CO_2Et

pyrrolidinone isomers.[4] This marked change in diastereoselectivity can be explained by steric effects—the size of the nitrogen protecting group could influence the reversibility of the radical cyclisation process. A bulky benzyl substituent on nitrogen could lower the rate of ring opening of the pyrrolidinone radical leading to less of the *trans*-pyrrolidinone isomer. In order to investigate this, the *N*-methyl and *N*-benzyl precursors, **12b** and **12c** were prepared by acylation of the corresponding secondary amines. These were reacted with Bu_3SnH and the ratio of diastereomers for pyrrolidinones **13b** and **13c** was compared to that obtained from cyclisation of the corresponding secondary amide **12a**.[3] The presence of an *N*-Me substituent was shown to lower the diastereoselectivity from 8.5:1 (for **13a**) to 5.5:1 for **13b** and this was lowered further (to 4.1:1) using the *N*-benzyl precursor **13c**. These results clearly show that the size of the *N*-protecting group influences the diastereoselectivity of the cyclisation; the smaller the group the greater the proportion of the *trans*-isomer. This is consistent with a faster rate of ring opening for a pyrrolidinone methyl radical with no nitrogen protecting group. Reaction of the *N*–Me precursor **12b** with tin hydride added in one portion (rather than over 1 h) was shown, as expected, to lead to more simple reduction. However, pyrrolidinone **13b** was formed and analysis of the crude ^1H NMR spectrum showed the diastereomer ratio was 3:1, rather than 5.5:1, observed when the tin hydride was added over 1 h. This is further evidence for a reversible cyclisation reaction; in the presence of a high concentration of tin hydride the rate of trapping of the pyrrolidinone methyl radical will be increased leading to less ring opening and consequently more of the *cis*-isomer of **13b**.

The introduction of substituents in a carbocyclic chain has also been shown to increase the rate of 5-*exo* radical cyclisation onto a double bond. Substrates bearing geminal dimethyl or diester substituents, for example, have been shown to cyclise very rapidly.[5,6] For the (reversible) cyclisation of benzylic radicals, these substituents have also been shown to influence the cyclopentane diastereoselectivity; whereas the 1-phenylhex-5-enylradical **14** gave only the *trans*-cyclopentane,[7] the related diester precursor **15** (in which the benzylic radical was generated by a 1,5-hydrogen atom transfer) afforded the cyclopentane as a 47:53 mixture of *cis*:*trans* isomers.[6] As for the pyrrolidinone system, it appears that the rate of ring opening is influenced by substitution within the chain — the introduction of large substituents slows the radical ring opening reaction leading to more of the *cis*-isomer.†

The successful formation of trisubstituted pyrrolidinones, bearing a protected alcohol side chain, suggested that this cyclisation method could be applied to the synthesis of kainoid amino acids. This was investigated using D-serine methyl ester hydrochloride **16** which was initially *N*-protected and converted to the α,β-unsaturated ester **17** *via* Wittig reaction of the intermediate α-amino aldehyde (Scheme 3). The ^1H NMR spectrum



16 **17** **19** **18**

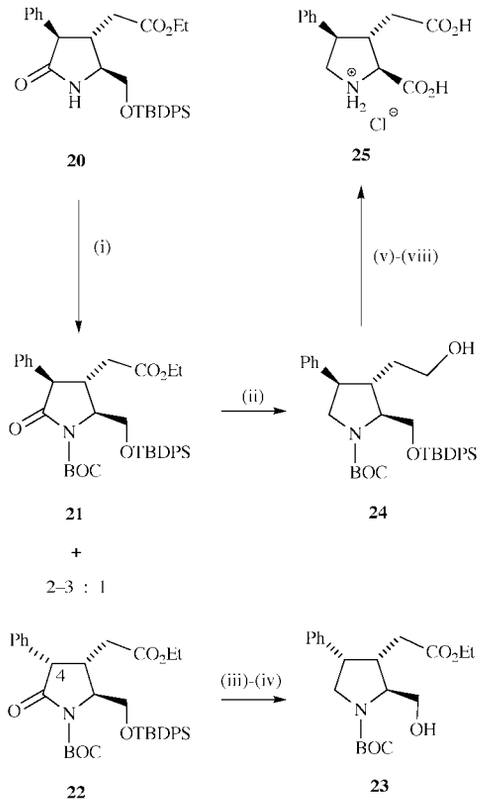
Scheme 3 *Reagents and conditions*: (i) $(Boc)_2O$, Et_3N, CH_2Cl_2 (85%); (ii) TBDPSCl, DMAP (cat.), Et_3N, CH_2Cl_2 (87%); (iii) DIBAL-H, toluene, −78 °C; (iv) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2 (74% over two steps); (v) TFA, CH_2Cl_2, 0 °C to room temp.; (vi) PhCH(Cl)COCl, Et_3N, Et_2O, 0 °C to room temp. (81% over two steps); (vii) Bu_3SnH, AIBN, toluene, heat (79%; dr 8.9:3.5:1).

showed the exclusive formation of the *trans*-double bond isomer (J = 16 Hz). In order to investigate if any racemisation of the α-centre had taken place during these reactions, the silyl ether **18** was deprotected using TBAF and the resultant alcohol reacted with either (+)- or (±)-MTPA [α-methoxy-α-(trifluoromethyl)phenyl] chloride at 0 °C in the presence of DMAP. Analysis of the ^1H and ^{19}F NMR spectra of the crude esters indicated an ee of ≥95%. For example, two peaks (of approximately the same ratio) were observed in the ^{19}F NMR spectrum at −69.50 and −70.75 ppm for the ester derived from (±)-MTPA chloride while only one of these (at −70.75 ppm) was present in the spectrum of the ester prepared from (+)-MTPA chloride.‡ *N*-Deprotection of **17** using TFA followed by acylation of the crude primary amine afforded chloroamide **18** in excellent yield. Treatment of **18** with tin hydride, added over 1 h, gave the trisubstituted pyrrolidinone **19** in similar yield and diastereoselectivity to that observed earlier (in the racemic studies). The cyclisation reaction was carried out a number of times using 0.2–1.8 mmol of **18** and in some cases the product of simple reduction was observed but only in ≤8% yield. The stereochemistry of the three pyrrolidinone diastereomers was deduced from comparison of the ^1H and ^{13}C NMR spectra with that of related compounds[4] and confirmed by base-induced epimerisation experiments. For example, the *cis*-C-3–C-4 isomer [of type **8**] could be isomerised (in 75% yield) to the more stable all *trans*-diastereomer **20** (Scheme 4) on heating with DBU in toluene.

The *trans*-pyrrolidinone **20** was then converted to the *N*-Boc derivative so as to facilitate lactam reduction. Under the basic conditions used for the *N*-protection, epimerisation occurred to

† This is well documented for ring opening of cyclobutylmethyl radicals. The cyclobutylmethyl radical ring opens 1.6 times faster than the 3,3-dimethylcyclobutylmethyl radical at 60 °C.[8]

‡ The ^{19}F NMR spectra were referenced to residual (±)-MTPA chloride at −70.45 ppm.



Scheme 4 *Reagents and conditions*: (i) $(Boc)_2O$, Et_3N (2 equiv.), DMAP, CH_2Cl_2, (75%); (ii) BH_3·DMS (6 equiv.), THF, heat (75%); (iii) BH_3·DMS (2 equiv.), THF, heat (49%); (iv) TBAF, THF (50%); (v) TBAF, THF (90%); (vi) $RuCl_3$·H_2O, $NaIO_4$, MeCN, H_2O, CCl_4; (vii) CH_2N_2, Et_2O (44% over two steps); (viii) HCl_2, H_2O, 70 °C (93%).

give a mixture of the C-4 epimers **21** and **22**. It is of interest to note that whereas isomerisation of the *cis*-C-3–C-4 NH isomer [of type **8**] to **20** occurred readily on heating with DBU, the corresponding *N*-Boc compound **22** was more resistant and a mixture of **21** and **22** (in the ratio 1 : 1) was isolated under the same conditions. Presumably epimerisation of **21** occurs after *N*-protection and this phenomenon has previously been observed for alkylated *N*-Boc pyroglutamates.[9] Reduction of lactam **22** using two equivalents of borane–dimethyl sulfide complex gave the pyrrolidine in moderate yield and subsequent desilylation to alcohol **23** was achieved in a similar yield. The deprotection of related compounds, with alternative protecting groups, has previously been reported as a route to phenylkainic acid.[1,2] A much cleaner transformation was observed when **21** was reacted with six equivalents of borane–dimethyl sulfide complex to promote both lactam and ester reduction. The product alcohol **24** was then desilylated and oxidised to the dicarboxylic acid. For ease of characterisation, this was reacted with diazomethane and the dimethyl ester was isolated in reasonable yield. This could be efficiently deprotected using hot aqueous HCl to afford the amino acid salt **25** in 13 steps (4.5% overall yield) from serine methyl ester **16**. The spectroscopic data for **25** was consistent with that reported previously for related compounds.[2b]

This work has shown that secondary haloamides bearing a protected alcohol side chain can produce trisubstituted pyrrolidinones in excellent yield. Elaboration of the cyclised product has demonstrated a novel approach to an aromatic allokainoid amino acid.

Experimental

For general experimental and a procedure for radical cyclisation see the preceding paper.[3]

Radical cyclisation of alkene 6

Following the general radical cyclisation procedure, the alkene **6** (155 mg, 0.21 mmol) (prepared in the same manner as the enantiomerically pure alkene **18**) in degassed toluene (9 cm^3) was treated with tributyltin hydride (67 mg, 0.23 mmol) and azobisisobutyronitrile (7 mg, 0.04 mmol) in toluene (17 cm^3) over a 1 h addition period, and the reaction mixture stirred at reflux for a further 18 h. Column chromatography (dichloromethane–ethyl acetate, 4 : 1) afforded the 3-phenyl-4-(ethoxycarbonylmethyl)-5-(*tert*-butyldiphenylsilyloxymethyl)pyrrolidin-2-ones **7**, **8** and **9** (90 mg, 84%) as colourless oils in a ratio of 8.9 : 3.5 : 1, together with reduced product **10** (4 mg, 4%) as a colourless oil.

(3*R**,4*S**,5*S**) *Major diastereoisomer* **7**: R_f 0.3 (dichloromethane–ethyl acetate, 4 : 1); ν_{max}/cm^{-1} ($CHCl_3$) 3429 (w), 3008 (w), 2931 (w), 2862 (w), 1705 (s), 1427 (w), 1111 (w), 706 (w); δ_H (270 MHz, $CDCl_3$) 7.60–7.51 (4H, m, aromatics), 7.39–7.08 (11H, m, aromatics), 6.21 (1H, br s, N*H*), 3.85–3.66 (3H, m, CO_2CH_2, NHC*H*), 3.59–3.50 (2H, m, CH_2OSi), 3.39 (1H, d, $J = 10$, PhC*H*), 2.45 (1H, m, $CHCH_2CO_2$), 2.37 (2H, d, $J = 7$, CH_2CO_2), 1.00 (9H, s, $SiC(CH_3)_3$), 0.98 (3H, t, $J = 7$, $CO_2CH_2CH_3$); δ_C (67.5 MHz, $CDCl_3$) 177.4, 171.4 (*C*ONH, *C*O_2Et), 138.0 (*C*=CH), 136.0 (*C*H=C), 133.2 (*C*=CH), 130.4, 129.9, 128.9, 128.3, 127.9 (*C*H=C), 66.4 (CH_2OSi), 61.1 (CO_2CH_2), 59.8 (PhCH), 54.8 (NHCH), 43.1 ($CHCH_2CO_2$), 37.3 (CH_2CO_2), 27.3 ($SiC(CH_3)_3$), 19.6 ($SiCMe_3$), 14.4 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 516 (M + H^+, 100%), 458 (28) (Found: M + H^+, 516.2563. $C_{31}H_{37}NO_4Si$ requires for M + H^+, 516.2570).

(3*R**,4*R**,5*R**) *Minor diastereoisomer* **8**: R_f 0.4 (dichloromethane–ethyl acetate, 4 : 1); ν_{max}/cm^{-1} ($CHCl_3$) 3429 (w), 2958 (w), 2862 (w), 1705 (s), 1600 (w), 1427 (w), 1111 (w), 779 (w); δ_H (270 MHz, $CDCl_3$) 7.60–7.55 (4H, m, aromatics), 7.39–7.16 (9H, m, aromatics), 7.05–7.02 (2H, m, aromatics), 6.11 (1H, br s, N*H*), 3.91–3.83 (3H, m, CO_2CH_2, PhC*H*), 3.70 (1H, dd, $J = 10$, 5, CH_AH_BOSi), 3.59 (1H, m, CH_AH_BOSi), 3.46 (1H, m, NHC*H*), 2.85 (1H, m, $CHCH_2CO_2$), 2.01 (1H, dd, $J = 16.5$, 7.5, $CH_AH_BCO_2$), 1.81 (1H, dd, $J = 17$, 8, $CH_AH_BCO_2$), 1.04 (3H, t, $J = 7$, $CO_2CH_2CH_3$), 0.95 (9H, s, $SiC(CH_3)_3$); δ_C (67.5 MHz, $CDCl_3$) 177.0, 171.6 (*C*ONH, *C*O_2Et), 135.5 (*C*H=C), 135.1, 132.7 (*C*=CH), 130.2, 129.3, 128.8, 127.9, 127.5 (*C*H=C), 66.4 (CH_2OSi), 60.5 (CO_2CH_2), 59.5 (PhCH), 51.1 (NHCH), 37.9 ($CHCH_2CO_2$), 34.6 (CH_2CO_2), 26.8 ($SiC(CH_3)_3$), 19.2 ($SiCMe_3$), 14.0 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 516 (M + H^+, 100%), 458 (11) (Found: M + H^+, 516.2560. $C_{31}H_{37}NO_4Si$ requires for M + H^+, 516.2570).

(3*R**,4*S**,5*R**) *Minor diastereoisomer* **9**: the presence of this was indicated by NMR spectroscopy; δ_H (270 MHz, $CDCl_3$) 7.61–7.50 (4H, m, aromatics), 7.39–7.21 (11H, m, aromatics), 3.97–3.79 (4H, m, CO_2CH_2, NHC*H*, CH_AH_BOSi), 3.66 (1H, app. d, $J = 5$, CH_AH_BOSi), 3.63 (1H, d, $J = 10$, PhC*H*), 2.93 (1H, m, $CHCH_2CO_2$), 2.67 (1H, dd, $J = 17$, 10.5, $CH_AH_BCO_2$), 2.48 (1H, dd, $J = 17$, 5, $CH_AH_BCO_2$), 1.06 (3H, t, $J = 7$, $CO_2CH_2CH_3$), 1.00 (9H, s, $SiC(CH_3)_3$).

Phenylethanamide **10**: R_f 0.7 (dichloromethane–ethyl acetate, 4 : 1); δ_H (270 MHz, $CDCl_3$) 7.43–7.21 (15H, m, aromatics), 6.75 (1H, dd, $J = 16$, 16, 5, C*H*=$CHCO_2$), 5.90 (1H, d, $J = 8$, N*H*), 5.73 (1H, dd, $J = 16$, 2, CH=C*H*CO_2), 4.60 (1H, m, NHC*H*), 4.13 (2H, q, $J = 7$, CO_2CH_2), 3.64–3.54 (2H, m, CH_2OSi), 3.63 (2H, s, $PhCH_2$), 1.21 (3H, t, $J = 7$, $CO_2CH_2CH_3$), 1.03 (9H, s, $SiC(CH_3)_3$).

1,4-Dimethyl-3-phenylpyrrolidin-2-one 13b. (3*R**,4*S**) *Major diastereoisomer*: Oil; 39%; R_f 0.3 (ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$) 3003 (m), 2929 (m), 2873 (m), 1689 (s), 1496 (s), 1454 (s), 1405 (s), 1267 (s), 1240 (m), 1151 (w), 698 (m); δ_H (270 MHz, $CDCl_3$) 7.36–7.15 (5H, m, aromatics), 3.51 (1H, dd, $J = 10$, 8, NCH_AH_B), 3.16 (1H, d, $J = 10$, PhC*H*), 3.04 (1H, app. t, $J = 9.5$, NCH_AH_B), 2.92 (3H, s, NCH_3), 2.38 (1H, m,

C*H*CH_3), 1.15 (3H, d, J = 7, CHC*H*$_3$); δ_C (67.5 MHz, $CDCl_3$) 174.7 (N*C*O), 138.7 (*C*=CH), 128.5, 128.3, 126.9 (*C*H=C), 56.6 (Ph*C*H), 54.8 (N*C*H_2), 37.2 (*C*HCH_3), 29.9 (N*C*H_3), 17.4 (CH*C*H_3); *m*/*z* (CI, NH_3) 190 (M + H^+, 100%) (Found: M + H^+, 190.1228. $C_{12}H_{15}NO$ requires for M + H^+, 190.1232).

(3*R**,4*R**) *Minor diastereoisomer*: the presence of this was indicated by NMR spectroscopy; δ_H (270 MHz, $CDCl_3$) 3.75 (1H, d, J = 8.5, PhC*H*), 2.97 (3H, s, NCH_3), 2.74 (1H, m, C*H*CH_3), 0.68 (3H, d, J = 7.5, CHCH_3); δ_C (67.5 MHz, $CDCl_3$) 175.0 (N*C*O), 136.1 (*C*=CH), 129.1, 128.3, 126.7 (*C*H=C), 55.1 (N*C*H_2), 52.7 (Ph*C*H), 31.8 (*C*HCH_3), 29.7 (N*C*H_3), 15.2 (CH*C*H_3).

1-Benzyl-4-methyl-3-phenylpyrrolidin-2-one 13c. (3*R**,4*S**) *Major diastereoisomer*: Oil; 57%; R_f 0.4 (petroleum ether–ethyl acetate, 1:1); ν_{max}/cm^{-1} ($CHCl_3$) 3064 (m), 3001 (s), 2873 (m), 1675 (s), 1492 (s), 1442 (s), 1358 (w), 1259 (s), 908 (m), 771 (m), 754 (s), 721 (s), 700 (s); δ_H (270 MHz, $CDCl_3$) 7.39–7.18 (10H, m, aromatics), 4.60 (1H, d, J = 14.5, NC*H*$_A$H$_B$Ph), 4.11 (1H, d, J = 14.5, NCH$_A$*H*$_B$Ph), 3.39 (1H, dd, J = 10, 8, NC*H*$_A$H$_B$CH), 3.22 (1H, d, J = 9.5, PhC*H*), 2.90 (1H, dd, J = 9.5, 8.5, NCH$_A$*H*$_B$CH), 2.36 (1H, septet of t, J = 8, 1.5, C*H*CH_3), 1.09 (3H, d, J = 7, CHCH_3); δ_C (67.5 MHz, $CDCl_3$) 174.5 (N*C*O), 138.6, 136.5 (*C*=CH), 128.6, 128.4, 128.1, 127.5, 127.0, 126.8 (*C*H=C), 56.8 (Ph*C*H), 51.9, 46.8 (N*C*H_2Ph, N*C*H_2CH), 37.1 (*C*HCH$_3$), 17.4 (CH*C*H$_3$); *m*/*z* (CI, NH_3) 266 (M + H^+, 100%), 91 (10) (Found: M + H^+, 266.1542. $C_{18}H_{19}NO$ requires for M + H^+, 266.1545).

(3*R**,4*R**) *Minor diastereoisomer*: Oil; R_f 0.3 (petroleum ether–ethyl acetate, 1:1); ν_{max}/cm^{-1} ($CHCl_3$) 3016 (m), 2873 (w), 1676 (s), 1602 (w), 1494 (w), 1433 (w), 1263 (w); δ_H (270 MHz, $CDCl_3$) 7.37–7.03 (10H, m, aromatics), 4.65 (1H, d, J = 14.5, NC*H*$_A$H$_B$Ph), 4.50 (1H, d, J = 14.5, NCH$_A$*H*$_B$Ph), 3.80 (1H, d, J = 9, PhC*H*), 3.40 (1H, dd, J = 10, 8.5, NC*H*$_A$H$_B$CH), 2.93 (1H, dd, J = 9, 6, NCH$_A$*H*$_B$CH), 2.70 (1H, m, C*H*CH_3), 0.64 (3H, d, J = 7, CHCH_3); δ_C (67.5 MHz, $CDCl_3$) 174.7 (N*C*O), 136.6, 136.3 (*C*=CH), 129.2, 128.7, 128.2, 127.7, 127.5, 127.0 (*C*H=C), 53.0 (Ph*C*H), 52.3, 46.8 (N*C*H_2Ph, N*C*H_2CH), 32.0 (*C*HCH$_3$), 15.2 (CH*C*H$_3$); *m*/*z* (CI, NH_3) 266 (M + H^+, 100%), 176 (5), 91 (11) (Found: M + H^+, 266.1541. $C_{18}H_{19}NO$ requires for M + H^+, 266.1545).

(4*S*)-Ethyl (*E*)-4-(*tert*-butoxycarbonylamino)-5-(*tert*-butyldiphenylsilyloxy)pent-2-enoate 17

A solution of (3*S*)-methyl 2-(*tert*-butoxycarbonylamino)-3-(*tert*-butyldiphenylsilyloxy)propanoate[10] (265 mg, 0.58 mmol) in toluene (5 cm^3) at −78 °C was treated with diisobutylaluminium hydride (1.45 cm^3, 1.45 mmol, 1 M in toluene), *via* a syringe pump over 1 h. After stirring for 1 h, 10% aqueous citric acid (25 cm^3) and ethyl acetate (25 cm^3) were added and the mixture stirred for 1 h. The organic layer was separated and washed with brine, dried (magnesium sulfate) and concentrated *in vacuo* to afford the crude aldehyde (195 mg) as an oil; R_f 0.55 (petroleum ether–ethyl acetate, 2:1); δ_H (270 MHz, $CDCl_3$) 9.59 (1H, s, C*H*O), 7.64–7.50 (4H, m, aromatics), 7.42–7.27 (6H, m, aromatics), 5.35 (1H, br s, N*H*), 4.22 (1H, m, NHC*H*), 4.05 (1H, dd, J = 10, 3, C*H*$_A$H$_B$OSi), 3.92 (1H, dd, J = 10, 3, CH$_A$*H*$_B$OSi), 1.39 (9H, s, NHCO$_2$C(CH_3)$_3$), 0.96 (9H, s, SiC(CH_3)$_3$).

The aldehyde was then treated with ethoxycarbonylmethylenetriphenylphosphorane (300 mg, 0.87 mmol) in dichloromethane (5 cm^3). The organic layer was separated and washed with brine, dried (magnesium sulfate) and concentrated *in vacuo*. Column chromatography (petroleum ether–ethyl acetate, 5:1) afforded the alkene **17** (214 mg, 74% over two steps) as a colourless oil; R_f 0.35 (petroleum ether–ethyl acetate, 5:1); $[\alpha]_D^{20}$ −14.8 (*c* 0.52, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3381 (w), 2940 (w), 1705 (s), 1512 (m), 733 (w); δ_H (270 MHz, $CDCl_3$) 7.68–7.57 (4H, m, aromatics), 7.48–7.32 (6H, m, aromatics), 6.91 (1H, dd, J = 16, 6, C*H*=CHCO$_2$), 5.96 (1H, dd, J = 16, 2, CH=C*H*CO$_2$), 4.89 (1H, br s, N*H*), 4.41 (1H, m, NHC*H*), 4.20 (2H, q, J = 7, CO$_2$C*H*$_2$), 3.78 (1H, dd, J = 10, 4.5, C*H*$_A$H$_B$OSi), 3.69 (1H, dd, J = 10, 4.5, CH$_A$*H*$_B$OSi), 1.45 (9H, s, NHCO$_2$C(CH_3)$_3$), 1.29 (3H, t, J = 7, CO$_2$CH$_2$CH_3), 1.05 (9H, s, SiC(CH_3)$_3$); δ_C (67.5 MHz, $CDCl_3$) 166.0 (*C*O$_2$Et), 155.1 (NH*C*O), 146.2 (*C*H=CHCO$_2$), 135.5 (*C*H=C), 132.9, 137.7 (*C*=CH), 129.9, 127.7 (*C*H=C), 122.0 (CH=*C*HCO$_2$), 79.8 (NHCO$_2$*C*Me$_3$), 65.4 (*C*H$_2$OSi), 60.4 (CO$_2$*C*H$_2$), 53.1 (NH*C*H), 28.3 (NHCO$_2$C(*C*H$_3$)$_3$), 26.8, 26.5 (SiC(*C*H$_3$)$_3$), 19.2 (Si*C*Me$_3$), 14.2 (CO$_2$CH$_2$*C*H$_3$); *m*/*z* (CI, NH_3) 498 (M + H^+, 12%), 442 (32), 398 (76), 381 (90), 364 (50), 320 (50), 274 (20), 216 (62), 196 (100), 142 (16), 79 (24) (Found: M + H^+, 498.2675. $C_{28}H_{39}NO_5Si$ requires for M + H^+, 498.2676).

(4*S*)-Ethyl (*E*)-4-(2-chloro-2-phenylethanamido)-5-(*tert*-butyldiphenylsilyloxy)pent-2-enoate 18

To a stirred solution of the protected amine **17** (224 mg, 0.45 mmol) in dichloromethane (5 cm^3) at 0 °C was added trifluoroacetic acid (0.41 cm^3, 5.40 mmol) and the solution was stirred for 0.5 h, before warming to room temp. and stirring for a further 16 h. The solvent was removed *in vacuo* and the remaining acid removed *via* its azeotrope with chloroform to afford the crude amine salt as a brown oil (210 mg); δ_H (400 MHz, $CDCl_3$) 7.66–7.58 (4H, m, aromatics), 7.46–7.37 (6H, m, aromatics), 6.80 (1H, dd, J = 16, 6.5, C*H*=CHCO$_2$), 6.06 (1H, d, J = 16, CH=C*H*CO$_2$), 4.14 (2H, q, J = 7, CO$_2$C*H*$_2$), 4.05 (1H, m, NHC*H*), 3.86–3.78 (2H, m, C*H*$_2$OSi), 1.22 (3H, t, J = 7, CO$_2$CH$_2$CH_3), 1.06 (9H, s, SiC(CH_3)$_3$). The crude amine was treated with 2-chloro-2-phenylacetyl chloride (0.08 cm^3, 0.50 mmol) and triethylamine (0.14 cm^3, 0.99 mmol) in diethyl ether (7 cm^3). Column chromatography (petroleum ether–diethyl ether, 1:1) afforded the alkene **18** (200 mg, 81% over two steps) as a colourless oil; R_f 0.3 (petroleum ether–diethyl ether, 1:1); $[\alpha]_D^{20}$ −13.6 (*c* 0.5, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3413 (m), 3008 (s), 2958 (s), 2862 (s), 1712 (s), 1678 (s), 1512 (s), 1469 (m), 1307 (m), 1277 (m), 1184 (m), 1111 (s), 983 (m), 702 (s); δ_H (270 MHz, $CDCl_3$) 7.76–7.70 (4H, m, aromatics), 7.60–7.44 (11H, m, aromatics), 6.83 (1H, m, C*H*=CHCO$_2$), 6.03 and 5.98 (1H, 2 × d, J = 16, CH=C*H*CO$_2$), 5.55 and 5.53 (1H, 2 × s, PhC*H*), 4.60 (1H, m, NHC*H*), 4.17–4.07 (2H, m, CO$_2$C*H*$_2$), 3.77–3.04 (2H, m, C*H*$_2$OSi), 1.24–1.09 (3H, m, CO$_2$CH$_2$CH_3), 0.97 (9H, s, SiC(CH_3)$_3$); δ_C (67.5 MHz, $CDCl_3$) 167.2, 165.3 (*C*ONH, *C*O$_2$Et), 144.2 (*C*H=CHCO$_2$), 136.7 (*C*=CH), 135.5 (*C*H=C), 132.3 (*C*=CH), 130.0, 129.1, 128.9, 128.7, 127.7 (*C*H=C), 122.7 (CH=*C*HCO$_2$), 64.7 (*C*H$_2$OSi), 61.7 (Ph*C*H), 60.5 (CO$_2$*C*H$_2$), 52.0 (NH*C*H), 26.7 (SiC(*C*H$_3$)$_3$), 19.2 (Si*C*Me$_3$), 14.2 (CO$_2$CH$_2$*C*H$_3$); *m*/*z* (CI, NH_3) 552 (^{37}M + H^+, 20%), 550 (^{35}M + H^+, 46), 516 (100), 492 (27), 472 (60), 458 (23), 438 (10), 391 (26), 352 (7), 323 (7), 274 (12), 260 (23) (Found: ^{35}M + H^+, 550.2181. $C_{31}H_{36}ClNO_4Si$ requires for ^{35}M + H^+, 550.2180).

(3*R*,4*S*,5*S*)-1-(*tert*-Butoxycarbonyl)-3-phenyl-4-(ethoxycarbonylmethyl)-5-(*tert*-butyldiphenylsilyloxymethyl)pyrrolidin-2-one 21

To a stirred solution of the lactam **20** (220 mg, 0.43 mmol) in dry dichloromethane (5 cm^3) under an atmosphere of nitrogen was added triethylamine (0.06 cm^3, 0.43 mmol), di-*tert*-butyl dicarbonate (186 mg, 0.85 mmol) and 4-dimethylaminopyridine (52 mg, 0.43 mmol) and the solution was stirred at room temp. for 24 h. Concentration *in vacuo* and column chromatography (dichloromethane–ethyl acetate, 49:1) afforded **21** (131 mg, 50%) and the 3*S* isomer **22** (67 mg, 25%) as pale yellow oils.

21; R_f 0.2 (dichloromethane–ethyl acetate, 49:1); $[\alpha]_D^{20}$ −22.7 (*c* 0.38, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3012 (w), 2931 (w), 1782 (s), 1728 (s), 1473 (w), 1369 (w), 1307 (w), 1153 (m), 1114 (m), 706 (m); δ_H (270 MHz, $CDCl_3$) 7.73–7.65 and 7.55–7.32 (15H, 2 × m, aromatics), 4.16 (1H, dd, J = 10, 5.5, C*H*$_A$H$_B$OSi), 4.09–3.94 (3H, m, CO$_2$C*H*$_2$, NC*H*), 3.87 (1H, dd, J = 10.5, 2, C*H*$_A$H$_B$-

OSi), 3.74 (1H, d, $J = 9$, PhC*H*), 3.15 (1H, m, C*H*CH_2CO_2), 2.67 (1H, dd, $J = 15$, 5, C$H_AH_BCO_2$), 2.56 (1H, dd, $J = 15$, 7.5, $CH_AH_BCO_2$), 1.55 (9H, s, $NCO_2C(CH_3)_3$), 1.20 (3H, t, $J = 7$, $CO_2CH_2CH_3$), 1.16 (9H, s, $SiC(CH_3)_3$); δ_C (67.5 MHz, $CDCl_3$) 173.3, 170.9 (N*C*O, *C*O_2Et), 150.0 (N*C*O_2^{t}Bu), 137.4 (*C*=CH), 135.5 (*C*H=C), 132.9 (*C*=CH), 132.7, 129.8, 128.7, 127.8, 127.4 (*C*H=C), 83.2 (NCO_2CMe_3), 61.9 (*C*H_2OSi), 61.5 (Ph*C*H), 60.7 (CO_2CH_2), 54.6 (N*C*H), 37.6 (*C*HCH_2CO_2), 37.2 (CH_2CO_2), 27.9, 26.8 ($NHCO_2C(CH_3)_3$, $SiC(CH_3)_3$), 19.3 (Si*C*Me_3), 13.9 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 616 (M + H^+, 18%), 558 (45), 533 (7), 516 (100), 458 (17) (Found: M + H^+, 616.3094. $C_{36}H_{45}NO_6Si$ requires for M + H^+, 616.3094).

22; R_f 0.35 (dichloromethane–ethyl acetate, 49 : 1); $[a]_D^{20}$ −66.0 (*c* 0.30, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3012 (w), 2962 (w), 1781 (s), 1728 (s), 1369 (m), 1307 (s), 1111 (s), 705 (m); δ_H (270 MHz, $CDCl_3$) 7.77–7.64 and 7.52–7.21 (total 15H, 2 × m, aromatics), 4.74 (1H, d, $J = 10$, PhC*H*), 4.19–3.95 (5H, m, CO_2CH_2, NC*H*, CH_2OSi), 3.20 (1H, m, C*H*CH_2CO_2), 2.23 (1H, dd, $J = 17$, 11, C$H_AH_BCO_2$), 2.03 (1H, dd, $J = 17$, 4.5, $CH_AH_BCO_2$), 1.52 (9H, s, $NCO_2C(CH_3)_3$), 1.20 (3H, t, $J = 7$, $CO_2CH_2CH_3$), 1.15 (9H, s, $SiC(CH_3)_3$); δ_C (67.5 MHz, $CDCl_3$) 174.5, 172.3 (N*C*O, *C*O_2Et), 150.6 (N*C*O_2^{t}Bu), 136.0 (CH=*C*), 134.9 (*C*H=C), 133.0 (CH=*C*), 130.4, 129.0, 128.4, 127.9 (*C*H=C), 83.6 (NCO_2CMe_3), 65.3 (*C*H_2OSi), 62.8 (Ph*C*H), 61.1 (CO_2CH_2), 52.7 (N*C*H), 37.2 (*C*HCH_2CO_2), 36.1 (CH_2CO_2), 28.5, 27.3 ($NCO_2C(CH_3)_3$, $SiC(CH_3)_3$), 19.7 (Si*C*Me_3), 14.5 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 616 (M + H^+, 12%), 558 (50), 533 (16), 516 (100), 458 (9), 136 (5), 94 (5) (Found: M + H^+, 616.3102. $C_{36}H_{45}NO_6Si$ requires for M + H^+, 616.3094).

(2*S*,3*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-2-(hydroxymethyl)-3-(ethoxycarbonylmethyl)-4-phenylpyrrolidine 23

To a solution of lactam **22** (90 mg, 0.15 mmol) in dry THF (3 cm^3) at reflux under an atmosphere of nitrogen was added borane–dimethyl sulfide complex (0.22 cm^3, 0.44 mmol, 2 M in THF) and the reaction mixture stirred at reflux for 18 h. Diethyl ether (10 cm^3) and saturated ammonium chloride (10 cm^3) were added and the organic layer was separated, before further extraction of the aqueous layer with diethyl ether (20 cm^3). The combined organic extracts were washed with 5% HCl, 5% aqueous sodium bicarbonate and brine, dried (magnesium sulfate) to give crude material. Purification by column chromatography (petroleum ether–ethyl acetate, 9 : 1) afforded the protected pyrrolidine (44 mg, 49%) as a colourless oil; R_f 0.3 (petroleum ether–ethyl acetate, 9 : 1); ν_{max}/cm^{-1} ($CHCl_3$) 3012 (w), 2931 (w), 1728 (s), 1685 (s), 1403 (s), 758 (m), 733 (m), 706 (m); δ_H (270 MHz, toluene-d_8) 7.78–7.65 (4H, m, aromatics), 7.22–6.92 (11H, m, aromatics), 4.22 (1H, dd, $J = 10$, 3, CH_AH_BOSi), 3.91 (2H, q, $J = 7$, CO_2CH_2), 3.99–3.62 (5H, m, NCH_2, PhC*H*, NC*H*, CH_AH_BOSi), 3.16 (1H, m, C*H*CH_2CO_2), 2.18 (1H, dd, $J = 16$, 7, C$H_AH_BCO_2$), 1.94 (1H, dd, $J = 16$, 5, $CH_AH_BCO_2$), 1.34 (9H, s, $NCO_2C(CH_3)_3$), 1.20 (3H, t, $J = 7$, $CO_2CH_2CH_3$), 1.10 (9H, s, $SiC(CH_3)_3$); δ_C (67.5 MHz, $CDCl_3$) 172.5 (*C*O_2Et), 154.5 (N*C*O_2^{t}Bu), 139.5 (*C*H=C), 138.8 (*C*=CH), 134.8 (*C*H=C), 133.5 (*C*=CH), 129.7, 128.8, 128.6, 128.2, 127.9, 127.7, 127.2, 126.8 (*C*H=C), 79.4 (NCO_2CMe_3), 66.4 (*C*H_2OSi), 63.3 (Ph*C*H), 60.4 (CO_2CH_2), 50.7, 49.2 (NCH_2), 44.8, 43.7 (N*C*H), 42.4, 41.2 (*C*HCH_2CO_2), 34.2 (CH_2CO_2), 28.5, 26.9 ($NCO_2C(CH_3)_3$, $SiC(CH_3)_3$), 19.2 (Si*C*Me_3), 14.1 ($CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 602 (M + H^+, 100%), 572 (10), 546 (42), 502 (89) (Found: M + H^+, 602.3296. $C_{36}H_{47}NO_5Si$ requires for M + H^+, 602.3302).

A stirred solution of the pyrrolidine (17 mg, 0.028 mmol) in THF (2 cm^3) at room temp. was treated dropwise with tetrabutylammonium fluoride (0.04 cm^3, 0.042 mmol, 1 M in THF) and stirred for 18 h. The mixture was then poured into saturated aqueous ammonium chloride and extracted three times with dichloromethane. The combined organic extracts were dried (magnesium sulfate) and concentrated *in vacuo* to afford crude product, which was purified by column chromatography (petroleum ether–ethyl acetate, 3 : 2) to give the alcohol **23** (10 mg, 50%) as a colourless oil; R_f 0.3 (petroleum ether–ethyl acetate, 3 : 2); δ_H (500 MHz, $CDCl_3$) 7.41–7.22 (5H, m, aromatics), 4.09 (2H, app. t, $J = 7$, CO_2CH_2), 3.82–3.72 and 3.62–3.58 (6H, 2 × m, NCH_2, NC*H*, CH_2OH, PhC*H*), 2.62 (1H, m, C*H*CH_2CO_2), 2.20 (1H, dd, $J = 16.5$, 6.5, C$H_AH_BCO_2$), 1.94 (1H, dd, $J = 16.5$, 7.5 $CH_AH_BCO_2$), 1.51 (9H, s, $NCO_2C(CH_3)_3$), 1.22 (3H, t, $J = 7$, $CO_2CH_2CH_3$); *m*/*z* (CI, NH_3) 391 (11%), 364 (M + H^+, 13), 308 (100), 290 (17), 264 (65), 246 (21), 232 (90), 218 (27) (Found: M + H^+, 364.2130. $C_{20}H_{29}NO_5$ requires for M + H^+, 364.2124).

(2*S*,3*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-2-(*tert*-butyldiphenylsilyloxymethyl)-3-(2-hydroxyethyl)-4-phenylpyrrolidine 24

To a stirred solution of lactam **21** (167 mg, 0.27 mmol) in dry THF (3 cm^3) at reflux (under an atmosphere of nitrogen) was added borane–dimethyl sulfide complex (0.82 cm^3, 1.62 mmol, 2 M in THF) and the reaction mixture stirred at reflux for 24 h. Diethyl ether (10 cm^3) and saturated ammonium chloride (10 cm^3) were added and the organic layer separated, before further extraction of the aqueous layer with diethyl ether (20 cm^3). The combined organic extracts were washed with 5% aqueous HCl, 5% aqueous $NaHCO_3$ and brine, dried (magnesium sulfate) and concentrated *in vacuo* to give crude product, which was purified by column chromatography (petroleum ether–ethyl acetate, 9 : 1) to give the pyrrolidine **24** (103 mg, 75%) as a colourless oil; R_f 0.45 (petroleum ether–ethyl acetate, 1 : 1); $[a]_D^{20}$ −18.5 (*c* 0.29, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3614 (w), 2931 (w), 1681 (s), 1411 (m), 1169 (w), 760 (s), 709 (m); δ_H (270 MHz, toluene-d_8) 7.72–7.63 (4H, m, aromatics), 7.20–6.78 (11H, m, aromatics), 4.33 (1H, m, NC*H*), 4.00 (1H, m, PhC*H*), 3.76 (1H, app. d, $J = 8$, CH_AH_BOH), 3.60 (1H, m, C*H*CH_2CH_2), 3.30 (1H, app. t, $J = 8$, CH_AH_BOH), 3.10 (2H, app. td, $J = 5$, 1, CH_2OSi), 2.80 (1H, m, NH_AH_B), 2.60 (1H, m, NCH_AH_B), 1.44–1.35 (11H, m, $NCO_2C(CH_3)_3$, CH_2CH_2OH), 1.09 (9H, s, $SiC(CH_3)_3$); δ_C (67.5 MHz, $CDCl_3$) (mixture of conformers) 153.8 (N*C*O_2^{t}Bu), 140.4 (*C*=CH), 135.6 (*C*H=C), 133.2 (*C*=CH), 129.8, 129.6, 129.4, 128.7, 128.5, 128.4, 127.8, 127.0 (*C*H=C), 79.5, 79.2 (NCO_2CMe_3), 64.0 (Ph*C*H), 64.2, 62.6 (*C*H_2OH), 61.2, 61.0 (*C*H_2OSi), 55.2, 54.0 (NCH_2), 51.0, 50.8 (N*C*H), 45.1, 43.3 (*C*HCH_2-CH_2OH), 36.5, 36.0 (*C*H_2CH_2OH), 28.5, 28.4, 26.9, 26.8 ($NCO_2C(CH_3)_3$, $SiC(CH_3)_3$), 19.4, 19.3 (Si*C*Me_3); *m*/*z* (CI, NH_3) 560 (M + H^+, 32%), 504 (19), 460 (100), 446 (23), 391 (17), 190 (37) (Found: M + H^+, 560.3193. $C_{34}H_{45}NO_4Si$ requires for M + H^+, 560.3196).

Phenylallokainic acid 25

A solution of **24** (95 mg, 0.17 mmol) in THF (3 cm^3) at room temp. was treated dropwise with tetrabutylammonium fluoride (0.51 cm^3, 0.51 mmol, 1 M in THF) and stirred for 18 h. The solvent was removed *in vacuo* and column chromatography (ethyl acetate–petroleum ether, 2 : 1) afforded the diol (49 mg, 90%) as a colourless oil; R_f 0.2 (ethyl acetate–petroleum ether, 2 : 1); $[a]_D^{20}$ −17.0 (*c* 0.08, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3610 (m), 2981 (m), 1666 (m), 1412 (s), 1164 (m), 756 (s); δ_H (270 MHz; $CDCl_3$) (mixture of conformers) 7.28–7.14 (5H, m, aromatics), 5.08 (1H, br s, O*H*), 3.91–3.64 and 3.41–3.13 (8H, 2 × m, PhC*H*, NCH_2, NC*H*, CH_2OH, CHCH_2OH), 2.84 (1H, app. q, $J = 10$, C*H*CH_2CH_2OH), 2.06 (1H, br s, O*H*), 1.66 (2H, app. q, $J = 6$, CH_2CH_2OH), 1.39 (9H, s, $NCO_2C(CH_3)_3$); δ_C (67.5 MHz, $CDCl_3$) 156.2 (N*C*O_2^{t}Bu), 139.5 (*C*=CH), 128.8, 127.7, 127.3 (*C*H=C), 80.5 (NCO_2CMe_3), 66.6 (CH*C*H_2OH), 65.9 (Ph*C*H), 60.3 (*C*H_2CH_2OH), 54.4 (NCH_2), 50.3 (*C*HCH_2CH_2OH), 45.0 (*C*HCH_2OH), 35.0 (*C*H_2CH_2OH), 28.4 ($NCO_2C(CH_3)_3$); *m*/*z* (CI, NH_3) 322 (M + H^+, 100%), 283 (8), 266 (76), 222 (28), 191 (40) (Found: M + H^+, 322.2018. $C_{18}H_{27}NO_4$ requires for M + H^+, 322.2018).

To a solution of the diol (25 mg, 0.08 mmol) in a mixture of

carbon tetrachloride (250 μl), acetonitrile (250 μl) and water (400 μl) was added sodium periodate (100 mg, 0.47 mmol) and ruthenium trichloride monohydrate (catalytic amount) and the reaction stirred for 24 h. The aqueous phase was separated and extracted with dichloromethane (×3), ethyl acetate (×3) and acidified to pH 3 using 3 M aqueous HCl before re-extraction using ethyl acetate. The combined organic extracts were dried (magnesium sulfate) and concentrated *in vacuo* to give the crude acid as an oil; δ_H (270 MHz, $CDCl_3$) 8.00 (2H, br s, 2 × CO_2H), 7.39–7.22 (5H, m, aromatics), 4.05–3.85 (2H, m, C*H*CO_2H, NCH_AH_B), 3.53 (1H, m, NCH_AH_B), 3.10–2.92 (2H, m, PhC*H*, C*H*CH_2CO_2H), 2.54–2.31 (2H, m, CH_2CO_2H), 1.25 (9H, s $NCO_2C(CH_3)_3$).

The crude acid was dissolved in diethyl ether (2 cm^3) at 0 °C and treated with a solution of diazomethane in diethyl ether (generated from Diazald®). After 1 h, glacial ethanoic acid was added to quench the excess diazomethane and concentration gave crude product, purified by column chromatography (dichloromethane–ethyl acetate, 10:1) to give the diester as a colourless oil (13 mg, 44% from the diol); R_f 0.6 (dichloromethane–ethyl acetate, 10:1); $[\alpha]_D^{20}$ −22.6 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 2979 (m), 1739 (s), 1691 (s), 1407 (w), 1367 (w), 1232 (w), 1167 (s), 775 (s), 748 (s); δ_H (270 MHz, $CDCl_3$) (mixture of conformers) 7.39–7.23 (5H, m, aromatics), 4.07 (1H, m, C*H*CO_2), 3.95 (1H, m, NCH_AH_B), 3.78 and 3.76 (3H, 2 × s, CO_2CH_3), 3.52 (1H, app. t, *J* = 12, NCH_AH_B), 3.45 and 3.42 (3H, 2 × s, CO_2CH_3), 3.05 (1H, m, PhC*H*), 2.71 (1H, m, C*H*CH_2CO_2), 2.45 (2H, app. d, *J* = 10, CH_2CO_2), 1.46 and 1.42 (9H, 2 × s, $NCO_2C(CH_3)_3$); δ_C (67.5 MHz, $CDCl_3$) 172.8, 172.6 (2 × *C*O_2CH_3), 153.2 (N*C*O_2^tBu), 137.5, 137.4 (*C*=CH), 128.8, 128.0, 127.7 (*C*H=C), 80.4, 80.3 (NCO_2CMe_3), 64.6, 64.2 (N*C*HCO_2Me), 53.7, 53.0 (N*C*H_2), 52.3, 52.1, 51.6 (2 × CO_2CH_3), 50.1, 49.3, 47.5, 46.8 (Ph*C*H, *C*HCH_2CO_2), 35.6, 35.3 (*C*H_2CO_2), 28.4, 28.3 ($NCO_2C(CH_3)_3$); *m*/*z* (CI, NH_3) 378 (M + H^+, 9%), 322 (25), 278 (100), 218 (20) (Found: M + H^+, 378.1912. $C_{26}H_{27}NO_6$ requires for M + H^+, 378.1917).

A solution of the diester (10 mg, 0.026 mmol) in 6 M HCl (5 cm^3) containing anisole (catalytic amount) was heated at 70 °C for 5 h. Water (5 cm^3) was added and the aqueous solution was washed with ethyl acetate (×3). The aqueous phase was then concentrated and the product was triturated with diethyl ether to give the hydrochloride salt **25** (7 mg, 93%) as an off-white gum; δ_H (270 MHz, $CDCl_3$) 7.44–7.30 (5H, m, aromatics), 4.52 (1H, d, *J* = 10, C*H*CO_2), 3.75 (1H, app. t, *J* = 6, NCH_AH_B), 3.56 (1H, m, NCH_AH_B), 3.47 (1H, app. d, *J* = 10, PhC*H*), 2.83 (1H, m, C*H*CH_2CO_2), 2.66 (1H, dd, *J* = 17, 5, C$H_AH_BCO_2$), 2.57 (1H, dd, *J* = 17, 6, C$H_AH_BCO_2$); δ_C (125 MHz, CD_3OD) 172.9 (*C*O_2), 170.4 (*C*O_2), 137.3 (*C*=CH), 130.3, 129.4, 129.1 (*C*H=C), 64.0 (*C*HCO_2), 52.1, 50.6 (Ph*C*H, N*C*H_2), 47.3 (*C*HCH_2CO_2), 34.9 (*C*H_2CO_2); *m*/*z* (FAB) 284 (M + $2NH_3^+$, 22%), 267 (M + NH_3^+, 100), 253 (6), 221 (67), 158 (20), 140 (22), 118 (15), 104 (12), 91 (20).

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