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Synthesis of protected γ-carboxyglutamates and γ-acylglutamates by rearrangement of *N*,*N*-diacylglutamates†

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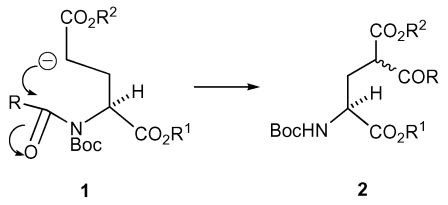
A new method for γ-acylation of protected glutamic acids, involving intramolecular rearrangement of an acyl urethane, has been devised to prepare the protected γ-carboxyglutamates **7**, **9** and **11** and the protected 4-acylglutamates **15** and **22** from *N*,*N*-bisurethanes or *N*-acyl-*N*-urethanes of general structure **1**. When the formyl-urethane **17** was used in the reaction, then the intermediate **18** in the intramolecular rearrangement was obtained.

Introduction

Methods for direct γ-alkylation of protected glutamates have been remarkably stereoselective.[1] γ-Acylglutamates have been accessed by a variety of indirect methods involving the reaction of a malonate or acylacetate anion on an alanyl-β-carbocation equivalent[2] and it has been shown that use of a 9-(9-phenylfluorenyl)-protecting group will allow protected glutamic acids to be directly γ-acylated in good yields, using a variety of acyl halides.[3] The ready reaction of pyroglutamate urethane esters with nucleophiles at the amide carbonyl group has prompted us to consider the possibility of the preparation of γ-acylglutamates by intramolecular nucleophilic attack by a γ-glutamate anion **1** on an *N*-acylurethane group which should be expected to behave similarly to a mixed anhydride as in Scheme 1.



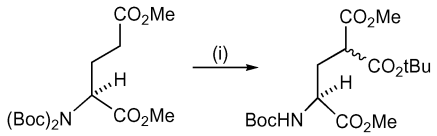
1 **2**

Scheme 1

Results and discussion

Because of our interest[4] in γ-carboxyglutamic acid, formed in the proteins of the blood clotting cascade, we elected to test the method by first synthesising a series of orthogonally protected derivatives of γ-carboxyglutamate from symmetrical *N*,*N*-bisurethanes. For our first substrate, we prepared the acid **4** by hydrolysis of the protected pyroglutamate **3**[5] using 1 N aqueous LiOH in THF, as shown in Scheme 2. The acid **4** was converted into the γ-benzyl ester **5** in 67% yield using benzyl chloride and triethylamine in acetone and thence into the *N*,*N*-bisurethane **6** in 80% yield using di-*tert*-butyl dicarbonate and DMAP in acetonitrile. The specific rotation of this compound was in accord with that of a sample prepared by an alternative route.[6] We now reacted the bisurethane **6** with NaHMDS in THF at −40 °C to obtain a mixture of diastereoisomers **7** in 53% yield. The product was isomeric with the starting compound **6** but it clearly showed an exchangeable NH proton at 4.92 ppm in the ^{1}H NMR spectrum, and the two proton multiplet at 2.27 ppm for H-4 in the ^{1}H NMR spectrum of the bisurethane **6** had been replaced by a one proton multiplet at 3.35 ppm in the ^{1}H NMR spectrum of the product **7**. The characteristic bisurethane absorption at 1793 cm^{-1} was no longer present in the infra-red spectrum. It was evident that rearrangement had occurred to yield the protected γ-carboxyglutamate **7**.

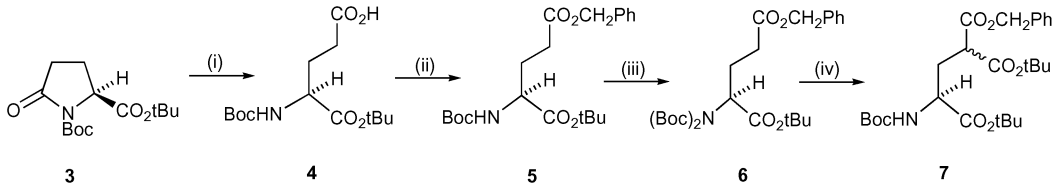
The bisurethane dimethyl ester **8** was now prepared by the method of Kokotos *et al.*[7] and reacted with NaHMDS in DMF at −40 °C, as shown in Scheme 3, to give the rearranged product **9** as a mixture of diastereoisomers in 39% yield. The ^{1}H NMR spectrum of the product exhibited a one proton exchangeable NH doublet at 4.97 ppm and, instead of the two proton multiplet for H-4 at 2.40 ppm in the spectrum of the starting bisurethane **6**, exhibited a one proton multiplet at 3.32 ppm. Further, the bisurethane absorption at 1800 cm^{-1} in the infra-red spectrum of **8** was no longer present in the infra-red spectrum of **9**. A final orthogonally protected γ-carboxyglutamate derivative was prepared when the bisurethane **10**[8] was reacted with NaHMDS in DMF at −40 °C to give the product **11** in 58% yield (Scheme 4). The ^{1}H NMR spectrum of this compound again showed an exchangeable NH doublet (4.9 ppm) and a one proton multiplet for H-4 (3.29 ppm) (compared with a two proton



8 **9**

Scheme 3 *Reagents and conditions:* (i) NaHMDS, DMF, THF, −40 °C, 5 h (39%).

† Electronic supplementary information (ESI) available: all ^{1}H, ^{13}C and COSY NMR spectra for compound **18**. See http://www.rsc.org/suppdata/ob/b5/b503900b/



3 **4** **5** **6** **7**

Scheme 2 *Reagents and conditions:* (i) 1N aq LiOH, THF, 30 min, 0 °C (96%); (ii) $PhCH_2Cl$, Et_3N, acetone, reflux, 4 days (67%); (iii) Boc_2O, DMAP, CH_3CN, rt, 72 h (80%); (iv) NaHMDS, THF, −40 °C, 2 h (53%).

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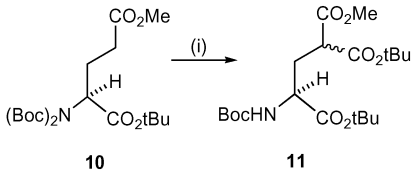


Scheme 4 *Reagents and conditions:* (i) NaHMDS, DMF, THF, −40 °C, 6 h (58%).

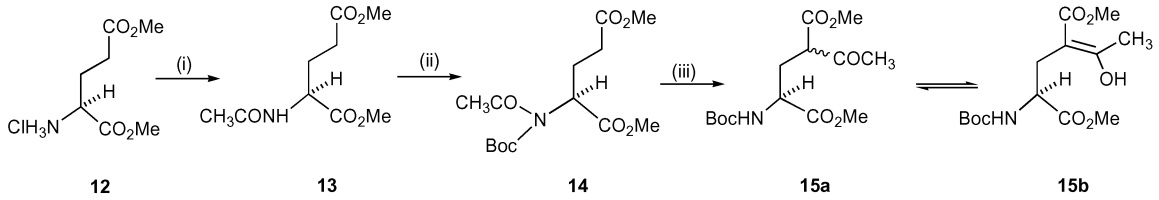
multiplet for H-4 at 2.34 ppm in **10**). The bisurethane absorption in the infra-red spectrum was no longer present.

Having shown the method to be viable for preparing γ-carboxyglutamates from *N*,*N*-bisurethanes, we now turned to investigating the use of *N*-acylurethanes as substrates for the reaction. Dimethyl *N*-acetylglutamate **13** was first prepared from the dimethyl ester **12**[9] and converted into the urethane **14** in 74% yield using di-*tert*-butyl dicarbonate and DMAP in acetonitrile, as shown in Scheme 5. When this was reacted with NaHMDS in DMF at −40 °C, the product **15** was obtained in 20% yield. The ^{1}H and ^{13}C NMR spectra in C^2HCl_3 were compatible with the keto structure **15a** and there was no chromophore in neutral methanol. However when ^2H_2O was added to the C^2HCl_3 solution to exchange the NH group, the spectrum underwent wholesale change, eventually giving a clean spectrum which could be interpreted as being due to the enol form **15b**. The spectrum assigned to **15a** had a one proton multiplet at 5.18 ppm for H-4 which was not present in the spectrum assigned to **15b**. Most convincingly, there was long range coupling between the acetate methyl and both protons H-3 in the spectrum assigned to **15b**. This suggested an intervening double bond, and the ^{13}C spectrum of **15b** was in accord with this, exhibiting a signal at 106.2, typical of a quaternary olefinic carbon. A chromophore became evident (λ_{max} 282 nm) when sodium hydroxide was added to a methanolic solution of the product.

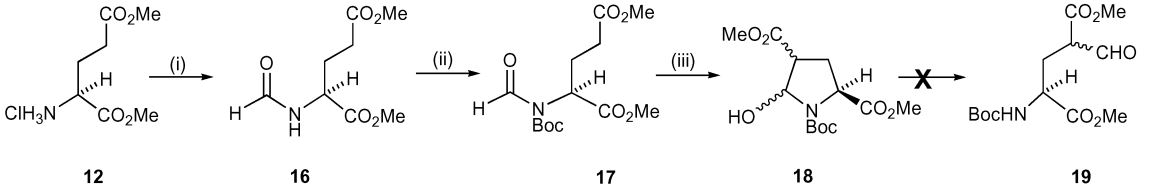
For the precursor, **17**, of the *N*-formyl compound **19**, we used the route outlined in Scheme 6. Formylation of dimethyl glutamate **12**[9] using formic acetic anhydride as solvent and reagent gave the amide **16** in 47% yield and this was treated with Boc_2O and DMAP in acetonitrile to give **17** in 57% yield. When the precursor **17** was treated with NaHMDS in DMF at −40 °C, we could see no evidence for the presence of the expected product **19**, there being no formyl CH signal in the ^{1}H NMR spectrum. The ^{1}H NMR spectrum in C^2HCl_3 (spectrum 1 in the ESI†) was complex but integration suggested that it was an isomer of the starting material **17** and of the desired product. When the signal due to water in C^2HCl_3 was irradiated in a spin saturation transfer experiment, six signals at 4.08, 3.80, 3.44, 3.40, 3.30 and 3.12 ppm were affected and so were evidently due to OH or NH protons. Further, an NOE was observed for five signals integrating as one proton between 5.93 and 5.62 ppm in this experiment. Use of saturation transfer experiments, irradiating the signals between 5.93 and 5.62 ppm in turn, suggested that these signals were due to three pairs of rotamers. There were six OMe signals at *ca.* 3.7 ppm integrating for six protons. The data so far were compatible with structure **18** which might exist as four diastereoisomers, each having the possibility of existing as two rotamers, a well known[10] property of proline-type urethanes. Three of these are apparent in the ^{1}H NMR spectrum, each having a rotational isomer (labelled 1, 1′, 2, 2′ and 3, 3′ in spectrum 1 in the ESI†). An $[(M - H_2O) + H]^+$ ion in the mass spectrum was in keeping with the mass spectrum of a carbinolamine of this type which we had prepared by reduction of a pyroglutamic acid derivative.[11] When $C^2H_3O^2H$ was added to the C^2HCl_3 solution, the ^{1}H NMR spectrum simplified (spectrum 2 in ESI†) and 2D COSY double quantum filtered spectra were run at 253 K (ESI, spectra 4–7†). These clearly showed that the carbinolamine signals for proton H-5 were coupled to the signals assigned to H-4 (spectrum 5), that the signals for H-4 were coupled to the signals assigned to H-3A and H-3B (spectrum 6), and that the signals assigned to H-2 were coupled to H-3A and H-3B (spectrum 7). As expected for a compound with such possibilities for rotational- and diastereoisomerism, the ^{13}C NMR spectrum (ESI, spectrum 3†) was very complex but the data, supported by DEPT experiments, were in accord with the structure **18**. All of the data were in accord with the product of attempted formyl migration being the compound **18**, which is the structure for the intermediate in the intramolecular acylation reaction. This would imply that the intermediate is more stable when *N*-formylurethane is the electrophile for the 4-anion and may be due to steric considerations.

Benzoylation of the diester **12**[9] with benzoyl chloride and triethylamine in acetonitrile gave the amide **20** in 51% yield, as shown in Scheme 7. Urethanylation as before gave the compound **21** in 91% yield. This was now subjected to a reaction with NaHMDS in DMF at −40 °C to give a product in 32% yield. This had the spectral characteristics expected of the product **22** and had λ_{max} (MeOH) 247 and 320 nm.

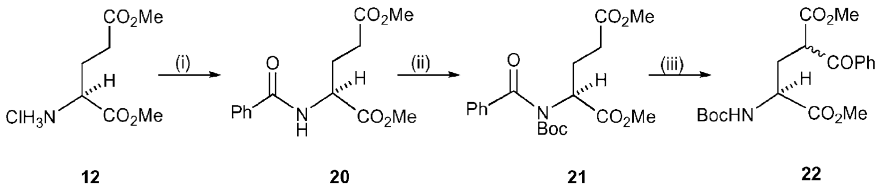
We have shown that the intramolecular route outlined in Scheme 1 for the preparation of γ-carboxyglutamates and 4-acylglutamates is viable, although when the migrating group is formyl, the intermediate **18** in the rearrangement is isolated. Ready enolisation of the products has been shown by spectroscopic experiments. The method presents a new route to



Scheme 5 *Reagents and conditions:* (i) (a) Et_3N, CH_3CN, rt, (b) CH_3COCl, CH_3CN, rt, overnight (44%); (ii) Boc_2O, DMAP, CH_3CN, rt, 3 days (74%); (iii) NaHMDS, DMF, THF, −40 °C, 3 h (20%).



Scheme 6 *Reagents and conditions:* (i) (a) Et_3N, CH_2Cl_2, (b) HCO_2Ac, 0 °C, 15 min then rt, 2 h (47%); (ii) Boc_2O, DMAP, CH_3CN, rt, overnight (57%); (iii) NaHMDS, DMF, −40 °C, 5 h (40%).



Scheme 7 *Reagents and conditions:* (i) (a) Et_3N, CH_3CN, 0 °C, 15 min, (b) PhCOCl, 1 h, 0 °C then rt, 1 h (51%); (ii) Boc_2O, DMAP, CH_3CN, rt, overnight (91%); (ii) NaHMDS, DMF, THF, −40 °C, 5 h (32%).

such compounds although yields are, so far, less synthetically useful than the route[3] involving direct acylation of 9-(9-phenylfluorenyl)-protected glutamates.

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 PE241 polarimeter using a 1 dm path length cell. IR spectra were recorded on a Perkin Elmer Spectrum 1710 FT-IR spectrometer and UV spectra on a ATI Unicam UV2-00 Fourier transform scanning spectrophotometer. ^{1}H NMR spectra were recorded on Bruker DPX300 (300 MHz) and AMX500 (500 MHz) Fourier transform instruments. *J* values are given in Hertz. ^{13}C NMR spectra (^{1}H decoupled) were recorded on Bruker DPX300 (75.5 MHz) and AMX500 (125.8 MHz) Fourier transform instruments. DEPT experiments were used to help assign ^{13}C resonances where necessary. Low resolution mass spectra were recorded by Dr A. Al Sada on Kratos MS-80RF and MS25 double focusing spectrometers. High resolution mass measurements were performed by the EPSRC Central Mass Spectrometry Service at Swansea. Column chromatography was performed using Fluka silica gel 60 (230–400 mesh). Petroleum ether refers to that fraction of hexanes of bp 60–80 °C.

1-*tert*-Butyl (2*S*)-2-*tert*-butoxycarbonylaminopentanedioate (4)

A solution of 1,2-di-*tert*-butyl (2*S*)-5-oxopyrrolidinedicarboxylate **3**[5] (6.77 g, 23.74 mmol) in THF (130 ml) was cooled to 0 °C and 1 N aqueous lithium hydroxide (27.1 ml) was added dropwise with vigorous stirring over 15 min. The reaction was stirred for a further 15 min at 0 °C. Ethyl acetate (160 ml) and saturated aqueous sodium hydrogen carbonate (160 ml) were added. The organic layer was separated and extracted with further saturated aqueous sodium hydrogen carbonate (40 ml). The aqueous layers were combined and acidified at 0 °C to pH 4–4.5 using 10% aqueous citric acid. The aqueous layer was extracted with ethyl acetate (5 × 100 ml). The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo* to give 1-*tert*-butyl (2*S*)-*tert*-butoxycarbonylaminopentanedioate **4** as a white solid (7.53 g, 96%); mp 103.3–105.5 °C, (lit[12] 102–105 °C); *m*/*z* [+ve FAB (3-NBA)] 327 ([M + Na]$^+$) and 304 ([M + H]$^+$); ν_{max} (nujol)/cm $^{-1}$ 3380 (NH), 1744 (ester) and 1701 (acid); δ_H (300 MHz, C^2HCl_3) 10.40 (1H, br s, OH), 6.29, 5.25 (1H, d, $J_{NH,2}$ 8.0, NH), 4.15 (1H, dd, $J_{2,NH}$ 8.0, $J_{2,3}$ 13.0, H-2), 2.45–2.27 (2H, m, H-4), 2.09 (1H, m, H-3A), 1.84 (1H, m, H-3B), 1.39 (9H, s, $OC(CH_3)_3$) and 1.36 (9H, s, $OC(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 179.8, 172.4 (acid and ester), 156.2 (urethane), 82.8 and 81.2 (2 × $OC(CH_3)_3$), 53.6 (C-2), 30.5 (C-4 and C-3), 28.6 and 28.3 (2 × $C(CH_3)_3$).

1-*tert*-Butyl 5-benzyl (2*S*)-2-*tert*-butoxycarbonylaminopentanedioate (5)

Triethylamine (3.38 ml, 24.29 mmol) was added to a solution of 1-*tert*-butyl (2*S*)-2-*tert*-butoxycarbonylaminopentanedioate **4** (6.7 g, 22.1 mmol) in acetone (45 ml) at room temperature under nitrogen. The solution was stirred for 1 h. Benzyl chloride (2.8 ml, 24.3 mmol) was added slowly and the solution was heated at reflux for 4 days. The mixture was allowed to cool and the white deposit was removed by filtration to give a yellow solution. The solvent was removed *in vacuo* to give a brown oil which was dissolved in ethyl acetate (200 ml) and extracted with saturated aqueous sodium hydrogen carbonate (3 × 50 ml). The aqueous layer was extracted with ethyl acetate (50 ml). The combined organic layers were dried (Na_2SO_4) and the solvents were removed *in vacuo* to give a yellow clear oil which was purified by flash column chromatography on silica gel using diethyl ether–petroleum ether (1 : 4) as eluent to give 1-*tert*-butyl 5-benzyl (2*S*)-2-*tert*-butoxycarbonylaminopentanedioate **5** as a clear colourless oil (5.79 g, 67%); $[\alpha]_D^{29}$ [5] +10.03 (*c* 1, $CHCl_3$), (lit[13] $[\alpha]_D^{25}$ +9 (*c* 1, $CHCl_3$)); *m*/*z* [+ve FAB (3-NBA)] 394 ([M + H]$^+$); ν_{max} (nujol)/cm^{-1} 3386 (NH), 1744 (ester) and 1720 (urethane); δ_H (300 MHz, C^2HCl_3) 7.27 (5H, s, ArH), 5.01 (3H, br s, OCH_2Ar and NH), 4.14 (1H, dd, $J_{2,NH}$ 7.9, $J_{2,3}$ 12.9, H-2), 2.37 (2H, m, H-4), 2.11 (1H, m, H-3A), 1.85 (1H, m, H-3B), 1.38 (9H, s, $C(CH_3)_3$) and 1.31 (9H, s, $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 173.1, 171.1 (ester), 156.9 (urethane), 136.2, 128.9, 128.6 and 128.6 (Ar), 82.6 and 80.2 (2 × $OC(CH_3)_3$), 66.8 (OCH_2Ar), 53.7 (C-2), 30.7 (C-4), 28.7 ($C(CH_3)_3$), 28.4 ($C(CH_3)_3$) and 28.3 (C-3).

1-*tert*-Butyl 5-benzyl (2*S*)-2-(*N*,*N*-bis-*tert*-butoxycarbonyl)-aminopentanedioate (6)

A solution of 1-*tert*-butyl 5-benzyl (2*S*)-2-*tert*-butoxycarbonylaminopentanedioate **5** (159 mg, 0.404 mmol) in acetonitrile (2 ml) was stirred at room temperature under nitrogen and cooled to 0 °C. 4-Dimethylaminopyridine (14 mg, 0.115 mmol) was added followed by a solution of di-*tert*-butyl dicarbonate (115 mg, 0.525 mmol) in acetonitrile (1.8 ml). The mixture was warmed to room temperature and stirred for 72 h. The solvent was removed to give a dark brown oil which was purified by flash column chromatography on silica gel, using diethyl ether–petroleum ether (1 : 4) as eluent to give 1-*tert*-butyl 5-benzyl (2*S*)-2-(*N*,*N*-bis-*tert*-butoxycarbonyl)-aminopentanedioate **6** as a clear colourless oil (160 mg, 80%); $[\alpha]_D^{22}$ −27.3 (*c* 1, $CHCl_3$), (lit[6] $[\alpha]_D^{25}$ −23.0 (*c* 1.3, EtOH)); *m*/*z* [+ve FAB (3-NBA)] 516 ([M + Na]$^+$) and 494 ([M + H]$^+$); ν_{max} (film)/cm^{-1} 1793 (w, bisurethane), 1739 (ester) and 1702 (urethane); δ_H (300 MHz, C^2HCl_3) 7.26 (5H, s, ArH), 5.03 (2H, s, OCH_2Ar), 4.72 (1H, dd, $J_{2,3A}$ 9.3, $J_{2,3B}$ 3.6, H-2), 2.37 (3H, m, H-4 and H-3A), 2.09 (1H, m, H-3B), 1.43 (18H, s, 2 × $C(CH_3)_3$) and 1.36 (9H, s, $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 173.0 and 169.6 (ester), 152.7 (urethane), 136.3, 128.9 and 128.5 (Ar), 83.3 (2 × $OC(CH_3)_3$), 81.7 ($OC(CH_3)_3$), 66.6 (OCH_2Ar), 58.5 (C-2), 31.4 (C-4), 28.3 (2 × $C(CH_3)_3$), 28.3 ($C(CH_3)_3$) and 24.9 (C-3).

1-Benzyl 5-*tert*-butyl (2*S*,4*RS*)-4-*tert*-butoxycarbonyl-2-*tert*-butoxycarbonylaminopentanedioate (7)

A solution of 1-*tert*-butyl 5-benzyl (2*S*)-2-(*N*,*N*-bis-*tert*-butoxycarbonyl)-aminopentanedioate **6** (147 mg, 0.298 mmol) in THF (1 ml) was stirred at −30 °C under nitrogen. Sodium hexamethyldisilazide (1 M in THF, 0.596 ml, 0.596 mmol) was added slowly over 30 min and the mixture was stirred at −30 °C for a further 2 h. Ethyl acetate (3 ml) and 5% aqueous sodium dihydrogen phosphate (5 ml) were added and the reaction was allowed to warm to room temperature. The

aqueous layer was extracted with ethyl acetate (3 × 5 ml). The organic layers were combined and dried (Na_2SO_4), and the solvent was removed *in vacuo* to give a clear oil. Purification by flash chromatography on silica gel using diethyl ether–petroleum ether (1 : 4) as eluent gave 1-benzyl 5-*tert*-butyl (2*S*,4*RS*)-4-*tert*-butoxycarbonyl-2-*tert*-butoxycarbonylaminopentanedioate **7** as a clear oil (77 mg, 53%); *m/z* [CI] (found 494.2759; $[C_{26}H_{39}NO_8 + H]^+$ requires 494.2754); *m/z* [+ve FAB (3-NBA)] 517 ($[M + Na]^+$) and 494 ($[M + H]^+$); ν_{max} (film)/cm^{-1} 3392 (NH) and 1727 (ester); δ_H (300 MHz, C^2HCl_3, mixture of diastereoisomers) 7.29 (5H, br, ArH), 5.10 (2H, 2 × overlapping AB, J_{AB} 12, OCH_2Ar), 4.92 (1H, d, $J_{NH,2}$ 8.5, NH), 4.05 (1H, ddd, $J_{2,NH}$ 8.5, $J_{2,3A}$ 6.3, $J_{2,3B}$ 1.7, H-2), 3.35 (1H, m, H-4), 2.37 (1H, ddd, $J_{3A,3B}$ 13.9, $J_{3A,2}$ 6.3, $J_{3A,4}$ 2.9, H-3A), 2.04 (1H, m, H-3B) and 1.39–1.29 (27H, 5 × s, $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3, mixture of diastereoisomers) 170.0, 168.3, 167.9, 166.9, 166.4 (ester), 154.7 and 154.2 (urethane), 134.4 and 134.3, 127.5, 127.4, 127.3 (Ar), 82.7, 81.2 and 78.7 (3 × $OC(CH_3)_3$), 66.1 (OCH_2Ar), 51.6 and 51.3 (C-2), 48.8, 48.5 and 48.3 (C-4), 30.5 and 30.2 (C-3), 27.2, 26.9 and 26.7 (3 × $C(CH_3)_3$).

1,5-Dimethyl (2*S*,4*RS*)-4-*tert*-butoxycarbonyl-2-*tert*-butoxycarbonylaminopentanedioate (9)

A solution of 1,5-dimethyl (2*S*)-2-(*N*,*N*-bis-*tert*-butoxycarbonyl)-aminopentanedioate **8**[7] (33 mg, 0.087 mmol) in dry dimethylformamide (1 ml) was stirred at −40 °C under nitrogen. Sodium hexamethyldisilazide (1 M in THF, 87 µl, 0.087 mmol) was added slowly and the yellow solution was left stirring at −40 °C for 5 h. Ethyl acetate (1 ml) and 5% aqueous sodium dihydrogen phosphate (1 ml) were added and the reaction was allowed to warm to room temperature. The aqueous layer was extracted with ethyl acetate (3 × 2 ml). The organic layers were combined and dried (Na_2SO_4), and the solvent was removed *in vacuo* to give a clear yellow oil. Purification by flash column chromatography on silica gel using diethyl ether–petroleum ether (1 : 4) as eluent gave 1,5-dimethyl (2*S*,4*RS*)-4-*tert*-butoxycarbonyl 2-*tert*-butoxycarbonylaminopentanedioate **9** as a clear colourless oil (13 mg, 39%); *m/z* [CI] (found 376.1972; $[C_{17}H_{29}NO_8 + H]^+$ requires 376.1971); *m/z* [+ve FAB (3-NBA)] 398 ($[M + Na]^+$) and 376 ($[M + H]^+$); ν_{max} (film)/cm^{-1} 3374 (NH) and 1730 (br, ester); δ_H (300 MHz, C^2HCl_3, mixture of diastereoisomers) 4.97 (1H, d, $J_{NH,2}$ 6.7, NH), 4.30 (1H, m, H-2), 3.68 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 3.32 (1H, dd, $J_{4,3A}$ 7.1, $J_{4,3B}$ 5.8, H-4), 2.37 (1H, m, H-3A), 2.15 (1H, m, H-3B), 1.39, 1.38 and 1.37 (18H, 3 × s, $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3, mixture of diastereoisomers) 172.8, 169.9 and 167.9 (ester), 155.7 (urethane), 82.9 and 80.4 (2 × $OC(CH_3)_3$), 53.0, 52.9, 52.4 and 52.2 (C-2 and C-4), and 31.8 (C-3) and 28.2 (2 × $C(CH_3)_3$).

1-*tert*-Butyl 5-methyl (2*S*)-2-(*N*,*N*-bis-*tert*-butoxycarbonyl)-aminopentanedioate (10)

This was prepared by the method of Adamczyk[8] as a clear oil (94%), $[\alpha]_D^{22}$ −21.0 (*c* 1, $CHCl_3$), (lit[8] $[\alpha]_D^{22}$ −24.5 (*c* 1.46, MeOH)); *m/z* [CI] (found 418.2446; $[C_{20}H_{35}NO_8 + H]^+$ requires 418.2441); *m/z* [+ve FAB (3-NBA)] 440 ($[M + Na]^+$) and 418 ($[M + H]^+$); ν_{max} (film)/cm^{-1} 1793 (w, bisurethane), 1741 (ester) and 1702 (urethane); δ_H (300 MHz, C^2HCl_3) 4.72 (1H, m, H-2), 3.60 (3H, s, OCH_3), 2.34 (3H, m, H-4 and H-3A), 2.11 (1H, m, H-3B), 1.43 (18H, s, 2 × $C(CH_3)_3$) and 1.37 (9H, s, $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 174.9 and 170.9 (2 × ester), 153.9 (urethane), 84.5 and 83.0 (2 × $OC(CH_3)_3$), 59.7 (C-2), 53.2 (OCH_3), 32.4 (C-4), 29.6 and 29.5 (2 × $C(CH_3)_3$) and 26.2 (C-3).

1-Methyl 5-*tert*-butyl (2*S*,4*RS*)-4-*tert*-butoxycarbonyl-2-*tert*-butoxycarbonylaminopentanedioate (11)

A solution of 1-*tert*-butyl 5-methyl (2*S*)-2-(*N*,*N*-bis-*tert*-butoxycarbonyl)-aminopentanedioate **10** (60 mg, 0.144 mmol) in dry dimethylformamide (1 ml) was stirred under nitrogen at −40 °C. Sodium hexamethyldisilazide (1 M in THF, 0.144 ml, 0.144 mmol) was slowly added and stirring was continued at −40 °C for 6 h. Ethyl acetate (1 ml) and 5% aqueous sodium dihydrogen phosphate (2 ml) were added and the reaction was allowed to warm to room temperature. The aqueous layer was extracted with ethyl acetate (3 × 2 ml) and the combined organic layers were dried (Na_2SO_4), and the solvent was removed *in vacuo* to give an orange oil. This was purified by flash chromatography on silica gel using ethyl acetate–petroleum ether (15 : 85) as eluent to give 1-methyl 5-*tert*-butyl (2*S*,4*RS*)-4-*tert*-butoxycarbonyl-2-*tert*-butoxycarbonylaminopentanedioate **11** as a clear colourless oil (35 mg, 58%); *m/z* [CI] (found 418.2447; $[C_{20}H_{35}NO_8 + H]^+$ requires 418.2441); *m/z* [+ve FAB (3-NBA)] 440 ($[M + Na]^+$) and 418 ($[M + H]^+$); ν_{max} (film)/cm^{-1} 3379 (NH), 1728 (br, ester) and 1708 (br, urethane); δ_H (300 MHz, C^2HCl_3, mixture of diastereoisomers) 4.90 (1H, d, $J_{NH,2}$ 8.3, NH), 4.0 (1H, m, H-2), 3.66 and 3.65 (3H, 2 × s, OCH_3), 3.29 (1H, dd, $J_{4,3A}$ 7.5, $J_{4,3B}$ 1.0, H-4), 2.35 (1H, m, H-3A), 2.03 (1H, m, H-3B), 1.38 (9H, s, $C(CH_3)_3$), 1.37 (9H, s, $C(CH_3)_3$) and 1.34 (9H, s, $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3, mixture of diastereoisomers) 171.4, 170.5, 170.0, 168.5 and 168.0 (esters), 155.7 (urethane), 82.6 and 80.1 (2 × $OC(CH_3)_3$), 52.9 and 52.7 (C-4), 50.1 and 49.9 (C-2), 32.0 and 31.6 (C-3), 28.6, 28.3 and 28.2 (3 × $OC(CH_3)_3$).

Dimethyl (2*S*)-2-acetylaminopentanedioate (13)

A solution of dimethyl (2*S*)-2-aminopentanedioate hydrochloride **12**[9] (200 mg, 0.944 mmol) in acetonitrile (1 ml) was stirred at room temperature under nitrogen. Triethylamine (0.39 ml, 2.8 mmol) was added and the solution was cooled to 0 °C. Acetyl chloride (0.06 ml, 0.85 mmol) in acetonitrile (1 ml) was added slowly and the solution was allowed to warm to room temperature and stirred for 2 h. A further equivalent of acetyl chloride (0.06 ml, 0.85 mmol) in acetonitrile (1 ml) was added and the mixture was stirred overnight. The white precipitate was removed by filtration and the solvent was removed *in vacuo* to give a brown oil. The oil was dissolved in water (15 ml) and extracted with ethyl acetate (3 × 5 ml). The aqueous layer was acidified to pH 3 with 1 N aqueous hydrochloric acid and extracted with ethyl acetate (3 × 5 ml). The combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo* giving dimethyl (2*S*)-2-acetylaminopentanedioate **13** as a colourless oil (91 mg, 44%), $[\alpha]_D^{23}$ +25.89 (*c* 1.4, $CHCl_3$); *m/z* [ApcI+] (found 218.1029; $[C_9H_{15}NO_5 + H]^+$ requires 218.1028); *m/z* [+ve FAB (3-NBA)] 218 ($[M + H]^+$); ν_{max} (film)/cm^{-1} 3287 (NH), 1740 (ester) and 1658 (amide); δ_H (300 MHz, C^2HCl_3) 6.22 (1H, d, $J_{NH,2}$ 7.0, NH), 4.56 (1H, ddd, $J_{2,3A}$ 12.9, $J_{2,NH}$ 7.0, $J_{2,3B}$ 5.1, H-2), 3.68 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 2.30 (2H, m, H-4), 2.09 (1H, m, H-3A) and 1.96–1.86 (4H, s + m, CH_3CON and H-3B); δ_C (75.5 MHz, C^2HCl_3) 171.8 and 170.9 (ester) 168.8 (urethane), 51.0 (OCH_3), 50.3 (OCH_3), 50.1 (C-2), 28.5 (C-4), 25.8 (C-3), and 21.6 (CH_3CON).

Dimethyl (2*S*) 2-(*N*-acetyl-*N*-*tert*-butoxycarbonyl)-aminopentanedioate (14)

A solution of 1,5-dimethyl (2*S*)-2-acetylaminopentanedioate **13** (1.64 g, 7.57 mmol) in acetonitrile (50 ml) was stirred under nitrogen at room temperature and di-*tert*-butyl dicarbonate (4.95 g, 22.72 mmol) in acetonitrile (50 ml), and 4-dimethylaminopyridine (460 mg, 3.78 mmol) were added. The mixture was stirred at room temperature for 3 days. The solvent was removed *in vacuo* and the product was purified by flash column chromatography on silica gel, using ethyl acetate–petroleum ether (1 : 4) as eluent to give dimethyl (2*S*) 2-(*N*-acetyl-*N*-*tert*-butoxycarbonyl)-aminopentanedioate **14** as a clear oil (1.78 g, 74%); $[\alpha]_D^{23}$ −30.72 (*c* 1.1, $CHCl_3$); *m/z* [CI] (found 318.1554; $[C_{14}H_{23}NO_7 + H]^+$ requires 318.1553); *m/z* [+ve FAB (3-NBA)] 340 ($[M + Na]^+$) and 318 ($[M + H]^+$); ν_{max}

(film)/cm^{-1} 1741 (br, ester and urethane) and 1701 (br, amide); δ_H (300 MHz, C^{2}HCl$_3$) 5.23 (1H, dd, $J_{2,3A}$ 9.0, $J_{2,3B}$ 4.8, H-2), 3.63 (3H, s, OCH$_3$), 3.59 (3H, s, OCH$_3$), 2.44 (3H, s, NCOCH$_3$), 2.41–2.02 (4H, 3 × m, H-3 and H-4) and 1.42 (9H, s, C(CH$_3$)$_3$); δ_C (75.5 MHz, C^{2}HCl$_3$) 172.0 and 171.8 (ester), 169.6 (amide), 150.9 (urethane), 83.2 (O*C*(CH$_3$)$_3$), 53.7 (C-2), 51.2 (OCH$_3$), 50.6 (OCH$_3$), 29.7 (C-4), 26.8 (C(*C*H$_3$)$_3$), 25.4 (*C*H$_3$CON) and 23.9 (C-3).

Dimethyl (2*S*,4*RS*)-4-acetyl-2-*tert*-butoxycarbonyl-aminopentanedioate (15)

A solution of dimethyl (2*S*)-2-(*N*-acetyl-*N*-*tert*-butoxycarbonyl)-aminopentanedioate **14** (52 mg, 0.163 mmol) in dry dimethylformamide (4 ml) was stirred at −40 °C under nitrogen. Sodium hexamethyldisilazide (1 M in THF, 0.163 ml, 0.163 mmol) was added dropwise and stirring was continued at −40 °C for 3 h. Ethyl acetate (4 ml) and 1 M aqueous sodium dihydrogen orthophosphate (4 ml) were added to the mixture which was allowed to warm to room temperature. The aqueous layers were extracted with ethyl acetate (3 × 10 ml). The combined organic layers were dried (Na_2SO_4) and the solvent was removed to give an orange oil. Purification by flash column chromatography on silica gel using ethyl acetate–petroleum ether (3 : 7) as eluent gave dimethyl (2*S*,4*RS*)-4-acetyl-2-*tert*-butoxycarbonylaminopentanedioate **15** as a clear oil (35 mg, 20%); *m*/*z* [CI] (found 318.1553; [$C_{14}H_{23}NO_7$ + H]$^+$ requires 318.1553); ν_{max} (film)/cm^{-1} 3372 (NH), 1741 (ester) and 1720 (ketone/urethane); λ_{max} (MeOH–NaOH)/nm 282 (3,182); *keto-form* **15a**, δ_H (300 MHz, C^{2}HCl$_3$, mixture of diastereoisomers) 5.18 (1H, dd, $J_{4,3A}$ 9.0, $J_{4,3B}$ 4.8, H-4), 5.02 (1H, d, $J_{NH,2}$ 7.9, NH), 4.21 (1H, br m, H-2), 3.62, 3.58, 3.55 and 3.54 (6H, 4 × s, 2 × OCH$_3$), 2.39 (3H, s, CH$_3$CO), 2.37–2.11 (2H, m, H-3), 1.36 and 1.31 (9H, 2 × s, C(CH$_3$)$_3$); δ_C (75.5 MHz, C^{2}HCl$_3$ mixture of diastereoisomers) 174.5, 174.4, 174.2 and 172.0 (ester and acetyl), 153.3 (urethane), 85.6 (O*C*(CH$_3$)$_3$), 56.1, 54.1, 53.7, 53.5, 53.1 and 53.0 (2 × OCH$_3$, C-2 and C-4), 31.3 (C-3), 29.6 and 29.2 (C(*C*H$_3$)$_3$) and 27.8 (CH$_3$CO); *enol-form* **15b**, δ_H (500 MHz, C^{2}HCl$_3$ and ^{2}H$_2$O) 4.66 (1H, dd, $J_{2,3A}$ 12.4, $J_{2,3B}$ 5.0, H-2), 3.75 (3H, s, OCH$_3$), 3.69 (3H, s, OCH$_3$), 3.06 (1H, ddq, with overlap, $J_{3A,2}$ 12.4, $J_{3A,3B}$ 16.0, $J_{3A,Me}$ 2, H-3A), 2.69 (1H, ddq, with overlap, $J_{3B,3A}$ 16.0, $J_{3B,2}$ 5.0, $J_{3B,Me}$ 1.2, H-3B), 2.62 (3H, s, C*H*$_3$) and 1.45 (9H, s, C(CH$_3$)$_3$)–decoupling at 2.62 ppm caused the signal at 3.6 ppm to become an ABX system, *J* 16 and 12.3, and the signal at 2.69 ppm to become an ABX system, *J* 16 and 5; δ_C (125.8 MHz C^{2}HCl$_3$ and ^{2}H$_2$O) 172.0 and 166.0 (ester), 151.2 (urethane), 106.2 (C-4), 82.3 (O*C*(CH$_3$)$_3$), 59.5 (C-2), 52.3 (OCH$_3$), 50.9 (OCH$_3$), 31.9 (C-3), 20.0 (C(*C*H$_3$)$_3$) and 14.4 (C*C*H$_3$).

Dimethyl (2*S*)-2-formylaminopentanedioate (16)

Triethylamine (1.22 ml, 8.7 mmol) was added to a solution of dimethyl (2*S*)-2-aminopentanedioate hydrochloride **12**[9] (1.69 g, 8.0 mmol) in dichloromethane (10 ml) and the solution was stirred under nitrogen for 1 h. The white solid was filtered off and the pale yellow filtrate was washed with water. The organic layer was dried (Na_2SO_4) and the organic solvent was removed *in vacuo* to give a yellow oil which was cooled to 0 °C, dissolved in a large excess of formic acetic anhydride and stirred for 15 min. The reaction was allowed to warm to room temperature and stirred for a further 2 h. The solvents were removed *in vacuo* and the resulting oil was partitioned between water and dichloromethane (20 ml). The aqueous layer was extracted with dichloromethane (3 × 10 ml). The organic layers were combined and dried (Na_2SO_4), and the solvent was removed *in vacuo* to give dimethyl (2*S*)-2-formylaminopentanedioate **16** as a pale yellow oil (750 mg, 47%); $[\alpha]_D^{30}$ +69.7 (*c* 1.4, CHCl$_3$); *m*/*z* [+ve FAB (3-NBA)] 407 ([2M + H]$^+$) and 204 ([M + H]$^+$); ν_{max} (film)/cm^{-1} 3353 (NH), 1740 (ester) and 1677 (amide); δ_H (300 MHz, C^{2}HCl$_3$ 2 rotamers, ratio 82 : 18 at 26 °C) 7.95 (1H, s, NCHO), 6.69 (1H, br s, NH *major*), 6.45 (1H, br s, NH *minor*), 4.43 (1H, m, H-2 *major*), 4.33 (1H, m, H-2 *minor*), 3.49 (3H, s, OCH$_3$), 3.40 (3H, s, OCH$_3$), 2.17 (2H, m, H-4), 2.00 (1H, m, H-3A) and 1.80 (1H, m, H-3B); δ_C (75.5 MHz, C^{2}HCl$_3$) 172.9 and 171.6 (ester), 161.0 (amide), 52.5 (OCH$_3$), 51.6 (OCH$_3$), 49.9 (C-2), 29.7 (C-4) and 26.9 (C-3).

Dimethyl (2*S*)-2-(*N*-*tert*-butoxycarbonyl-*N*-formyl)-aminopentanedioate (17)

A solution of dimethyl (2*S*)-2-formylaminopentanedioate **16** (200 mg, 0.98 mmol) in acetonitrile (3 ml) was stirred at room temperature under nitrogen. Di-*tert*-butyl dicarbonate (644 mg, 2.95 mmol) in acetonitrile (3 ml) and 4-dimethylaminopyridine (60 mg, 0.492 mmol) were added. The reaction was stirred overnight. The solvents were removed *in vacuo* and the resulting oil was purified by flash column chromatography on silica gel, using ethyl acetate and petroleum ether (1 : 4) as eluent. Dimethyl (2*S*)-2-(*N*-*tert*-butoxycarbonyl-*N*-formyl)-aminopentanedioate **17** was isolated as a clear oil (171 mg, 57%); $[\alpha]_D^{23}$ +206.0 (*c* 1, CHCl$_3$); *m*/*z* [CI] (found 304.1401, [$C_{13}H_{21}NO_7$ + H]$^+$ requires 304.1396); *m*/*z* [+ve FAB (3-NBA)] 304 ([M + H]$^+$); ν_{max} (film)/cm^{-1} 1741 (br, ester and urethane) and 1697 (br, amide); δ_H (300 MHz, C^{2}HCl$_3$, 2 rotamers, ratio 89 : 11 at 26 °C) 9.12 (1H, s, NCHO), 5.23 (1H, dd, $J_{2,3A}$ 9.0, $J_{2,3B}$ 4.7, H-2 *minor*), 4.95 (1H, dd, $J_{2,3A}$ 9.6, $J_{2,3B}$ 5.1, H-2 *major*), 3.65 (3H, s, OCH$_3$), 3.59 (3H, s, OCH$_3$), 2.43 (1H, m, H-3A), 2.28 (2H, m, H-4), 2.10 (1H, m, H-3B), 1.45 (9H, s, C(CH$_3$)$_3$ *major*) and 1.42 (9H, s, C(CH$_3$)$_3$ *minor*); δ_C (75.5 MHz, C^{2}HCl$_3$) 171.9 and 168.8 (ester), 161.6 (amide), 150.6 (urethane), 84.2 (O*C*(CH$_3$)$_3$), 51.5 (OCH$_3$), 51.1 (C-2), 50.8 (OCH$_3$), 29.5 (C-4), 26.9 (C(*C*H$_3$)$_3$) and 23.4 (C-3).

Methyl (2*S*,4*RS*,5*RS*)-*N*-*tert*-butoxycarbonyl-4-methoxycarbonyl-5-hydroxypyrrolidine-2-carboxylate (18)

Sodium hexamethyldisilazide (1 M in THF, 0.564 ml, 0.564 mmol) was added dropwise to a solution of dimethyl (2*S*)-2-(*N*-*tert*-butoxycarbonyl-*N*-formyl)-aminopentanedioate **17** (171 mg, 0.564 mmol) in dry dimethylformamide (2 ml) with stirring at −40 °C under nitrogen. The solution was allowed to stir for a further 2 h at −40 °C. Ethyl acetate (4 ml) and 1 M aqueous sodium dihydrogen orthophosphate (4 ml) were added to the mixture which was allowed to warm to room temperature. The aqueous layer was extracted with ethyl acetate (3 × 4 ml). The organic layers were combined and dried (Na_2SO_4), and the solvent was removed *in vacuo* to give an orange oil. Purification by flash column chromatography on silica gel using ethyl acetate–petroleum ether (3 : 7) as eluent gave methyl (2*S*,4*RS*,5*RS*)-*N*-*tert*-butoxycarbonyl-4-methoxycarbonyl-5-hydroxypyrrolidine-2-carboxylate **18** as a clear colourless oil (69 mg, 40%); *m*/*z* (EI) 286 ([M − OH]$^+$); the spectra of this compound are shown as seven documents in the ESI† and are discussed in the results and discussion section.

Dimethyl (2*S*)-2-benzoylaminopentanedioate (20)

A solution of dimethyl (2*S*)-2-aminopentanedioate hydrochloride **12**[9] (1.00 g, 4.72 mmol) in acetonitrile (20 ml) was stirred at 0 °C under nitrogen. Triethylamine (1.97 ml, 14.02 mmol) was added and stirring was continued for 15 min. A solution of benzoyl chloride (0.54 ml, 4.65 mmol) in acetonitrile (5 ml) was added at 0 °C, whereupon a white gas evolved. The reaction was stirred for 1 h at 0 °C, allowed to warm to room temperature and stirred for a further 1 h. The white solid was removed by filtration and the solvent was removed *in vacuo* to give an orange oil. The resulting oil was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3 × 10 ml). The organic extracts were combined and dried (Na_2SO_4) and the solvent was removed *in vacuo* to give an orange oil which was recrystallised from diethyl ether to give dimethyl

(2*S*)-2-benzoylaminopentanedioate **20** as a pale yellow solid. (676 mg, 51%); mp 122–124 °C, $[\alpha]_D^{22}$ +18.3 (*c* 1, $CHCl_3$); *m/z* [ES+] 343 ($[M + 2Na]^+$), 302 ($[M + Na]^+$) and 280 ($[M + H]^+$); ν_{max} (film)/cm^{-1} 1745 and 1731 (ester) and 1638 (amide); δ_H (300 MHz, C^2HCl_3) 8.06–7.50 (5H, 2 × m, ArH), 7.30 (1H, d, $J_{NH,2}$ 7.3, NH), 5.06 (1H, ddd, $J_{2,3A}$ 12.6, $J_{2,NH}$ 7.3, $J_{2,3B}$ 5.0, H-2), 4.01 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 2.72 (2H, m, H-4), 2.55 (1H, m, H-3A) and 2.45 (1H, m, H-3B); δ_C (75.5 MHz, C^2HCl_3) 174.1 and 172.8 (2 × ester), 167.5 (amide), 147.3, 133.9, 133.2, 129.0 and 127.5 (Ar), 53.0 (OCH_3), 52.6 (C-2), 52.3 (OCH_3), 30.6 (C-4) and 27.5 (C-3).

Dimethyl (2*S*)-2-(*N*-benzoyl-*N*-*tert*-butoxycarbonyl)-aminopentanedioate (21)

A solution of dimethyl (2*S*)-2-benzoylaminopentanedioate **20** (500 mg, 1.79 mmol) in acetonitrile (15 ml) was stirred at room temperature under nitrogen. Di-*tert*-butyl dicarbonate (780 mg, 3.575 mmol) in acetonitrile (7 ml) was added followed by 4-dimethylaminopyridine (65 mg, 0.533 mmol) and the reaction was stirred overnight. The solvent was removed *in vacuo* and the product was purified by flash column chromatography on silica gel using ethyl acetate–petroleum ether (1 : 4) as eluent. Dimethyl (2*S*)-2-(*N*-benzoyl-*N*-*tert*-butoxycarbonyl)-aminopentanedioate **21** eluted as a clear oil (617 mg, 91%); $[\alpha]_D^{23}$ −37.3 (*c* 1, $CHCl_3$); *m/z* [ES+] (found 402.1536; $[C_{19}H_{25}NO_7 + Na]^+$ requires 402.1529); *m/z* [ES+] 402 ($[M + Na]^+$); ν_{max} (film)/cm^{-1} 1735 (br, ester) and 1676 (urethane/amide); δ_H (300 MHz, C^2HCl_3) 7.55–7.31 (5H, 3 × m, ArH), 5.03 (1H, dd, $J_{2,3A}$ 9.5, $J_{2,3B}$ 4.9, H-2), 3.70 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 2.53 (1H, m, H-3A), 2.37 (2H, m, H-4), 2.24 (1H, m, H-3B) and 1.08 (9H, s, $C(CH_3)_3$); δ_C (75.5 MHz, C^2HCl_3) 172.4 and 172.3 (ester), 170.0 (amide), 152.0 (urethane), 136.5, 130.8, 127.5 and 127.0 (Ar), 83.2 ($OC(CH_3)_3$), 56.4 (C-2), 51.9 (OCH_3), 51.1 (OCH_3), 30.1 (C-4), 26.6 ($C(CH_3)_3$) and 24.0 (C-3).

Dimethyl (2*S*,4*RS*)-4-benzoyl-2-*tert*-butoxycarbonyl-aminopentanedioate (22)

A solution of dimethyl (2*S*)-2-(*N*-benzoyl-*N*-*tert*-butoxycarbonyl)-aminopentanedioate **21** (200 mg, 0.527 mmol) in dry dimethylformamide (2 ml) was stirred at −40 °C under nitrogen. Sodium hexamethyldisilazide (1 M in THF, 0.527 ml, 0.527 mmol) was added slowly to the solution which was left stirring at −40 °C for 1 h. Ethyl acetate (4 ml) and 1 M aqueous sodium dihydrogen orthophosphate (4 ml) were added and the reaction was warmed to room temperature. The aqueous layer was extracted with ethyl acetate (3 × 5 ml). The organic extracts were combined, washed with brine and dried (Na_2SO_4). The solvents were removed *in vacuo* to give a yellow oil which was purified by flash column chromatography on silica gel using ethyl acetate–petroleum ether (1 : 4) as eluent to give dimethyl (2*S*,4*RS*)-4-benzoyl-2-*tert*-butoxycarbonylaminopentanedioate **22** as a clear oil (65 mg, 32%); *m/z* [ES+] (found 402.1521; $[C_{19}H_{25}NO_7 + Na]^+$ requires 402.1529); *m/z* [+ve FAB (3-NBA)] 402 ($[M + Na]^+$) and 380 ($[M + H]^+$), ν_{max} (film)/cm^{-1} 3217 (NH), complex carbonyl region; λ_{max} (MeOH)/nm 247 and 320 (ε 5008 and 1153), λ_{max} (MeOH–NaOH)/nm 249 and 311 (ε 3452 and 4788), λ_{max} (MeOH–HCl)/nm 252 and 299 (ε 3961 and 4112); δ_H (300 MHz, C^2HCl_3, mixture of diastereoisomers A and B, ratio 1 : 1 at 26 °C) 7.97 (2H, m, ArH), 7.59–7.34 (3H, 2 × m, ArH), 5.11 (0.5H, d, $J_{NH,2}$ 8.4, NH *isomer A*), 5.00 (0.5H, d, $J_{NH,2}$ 8.3, NH *isomer B*), 4.65 (1H, m, H-2), 4.50 (0.5H, m, H-4 *isomer A*), 4.28 (0.5H, m, H-4 *isomer B*), 3.68 (6H, m, 2 × OCH_3), 2.63–2.04 (2H, m, H-3) and 1.41 (4.5H, s, $C(CH_3)_3$ *isomer A*) and 1.40 (4.5H, s, $C(CH_3)_3$ *isomer B*); δ_C (75.5 MHz, C^2HCl_3 mixture of diastereoisomers at 26 °C) 194.9, 194.3, 193.8 and 192.7 (benzoyl), 173.4, 172.7, 172.3, 171.8, 171.2, 170.3, 169.9 and 168.8 (ester), 149.5 and 147.2 (urethane), 136.1–127.0 (Ar), 84.6, 84.3, 84.2 and 80.5 ($OC(CH_3)_3$), 58.2, 57.7 and 57.1 (C-4), 53.2, 53.1, 53.0 and 52.9 (OCH_3), 52.6, 52.2 and 51.9 (C-2), 28.6, 28.5, 28.3, 28.2 and 27.1 ($C(CH_3)_3$) and 24.9 and 24.8 (C-3).

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