Syntheses of (2S,3R)- and (2S,3S)-3-Methylglutamic Acid

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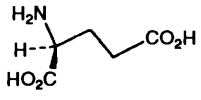
Arndt–Eistert homologation of suitably protected (2S,3S)-3-methylaspartic acid occurs with retention of configuration at C-3 to give, ultimately, (2S,3R)-3-methylglutamic acid. (2S,3R)-3-Methylglutamic acid was also prepared in good yield *via* the conjugate addition of the lithiated anion of the bis-lactim ether of *cyclo*-(R-Val-Gly) to methyl (*E*)-butenoate. The analogous reaction performed using isopentyl (*Z*)-butenoate ultimately gave (2S,3S)-3-methylglutamic acid. Both conjugate additions occurred with high diastereoselectivity.

In addition to its presence in peptides and proteins, (2*S*)-glutamic acid **1** plays a pivotal role in metabolism. For example, glutamic acid provides an amino group for a vast array of pyridoxal 5'-phosphate-dependent transaminations in which aldehydes or α-keto acids are converted into amines or amino acids.[1] Glutamic acid also serves as a 'carbon' precursor in the biosynthesis of other amino acids, including γ-aminobutyric acid (GABA), glutamine, proline and arginine, and for a myriad of natural products. While both C-3 and C-4-halogenated derivatives of glutamic acid have been prepared,[2] in particular, to probe the mechanism of glutamate-utilising enzymes, the C-3 alkyl derivatives have received very litle synthetic attention. In order to both facilitate mechanistic studies on enzymes which process glutamic acid and to provide material for the preparation and conformational analysis of constrained peptides, we set out to devise efficient syntheses of (2*S*,3*R*)-3-methylglutamic acid **2** and (2*S*,3*S*)-3-methylglutamic acid **3**.



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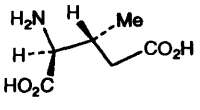

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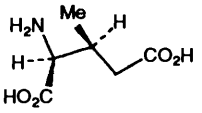

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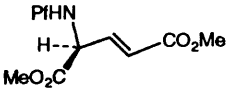

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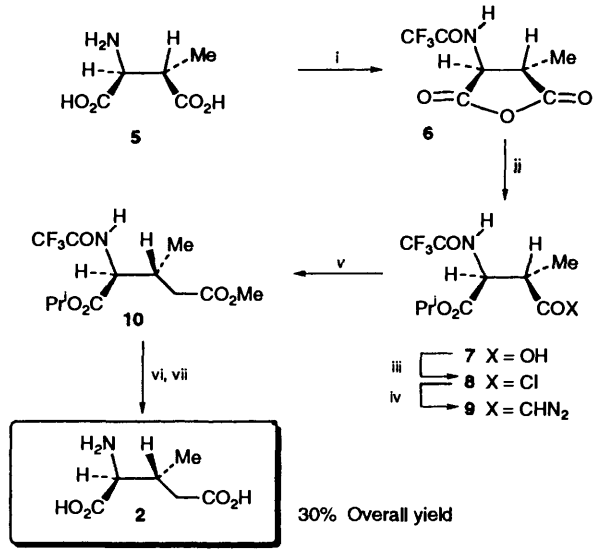
Reported methods for preparing C-3 substituted amino acids indicated that several different strategies might be employed to construct the carbon skeleton of 3-alkylglutamic acids, for example, the nucleophilic attack of carbanions on β-lactones, as developed by Vederas,[3] Evan's chiral auxiliary methodology,[4] and other methods.[5] Nevertheless, it was apparent that neither of these syntheses would allow for the stereospecific (or highly stereoselective) introduction of defined chirality at the C-3 centre, and that it would be necessary to use laborious separation techniques to obtain the pure individual (2*S*)-diastereoisomers.[6] A very recent report by Paz and Sardina[7] had described a synthesis of 3-methylglutamate esters starting from the (2*S*)-antipode of N-blocked 3,4-dehydroglutamate dimethyl ester **4**. Here, the configuration at C-2 was expected to influence the facial selectivity for nucleophilic attack at C-3 in conjugate additions. However, in the event, the conjugate addition of Me_2CuLi occurred non-stereoselectively to afford each the diastereoisomeric 3-methylglutamate diesters. Given that these methods were unsuitable for syntheses of each pure (2*S*,3*S*)- and (2*S*,3*R*)-diastereoisomer **2** and **3**, new methods were investigated.

Synthesis of (2S,3R)-3-*Methylglutamic Acid* **2**.—On the basis of earlier reports by Young and co-workers on the conversion of (2*S*)-aspartic acid into (2*S*)-glutamic acid **1**,[8] the Arndt–Eistert homologation of suitably protected (2*S*,3*S*)-3-methylaspartic acid **5** was expected to proceed with retention of configuration at the migrating C-atom to give a (2*S*,3*R*)-3-methylglutamic acid derivative.

Accordingly, (2*S*,3*S*)-3-methylaspartic acid **5** was prepared *via* the enzymic amination of mesaconic acid[9] and was treated with an excess of trifluoroacetic acid in THF to give the cyclic anhydride **6** (Scheme 1). Treatment with dry methanol at 0 °C gave a 3:1 mixture of α-ester:β-ester as judged by examination of the methyl ester signals in the ^1H NMR spectrum of the mixture. However, alcoholysis of the cyclic anhydride with propan-2-ol at 30 °C gave exclusively the α-ester β-acid **7**.

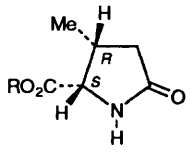
The β-carboxylic acid was converted into the β-acid chloride **8** through treatment with thionyl chloride and the acid chloride was converted into the diazo ketone **9** in the presence of an excess of dry ethereal diazomethane. The diazo ketone **9** was obtained in 96% yield from the free acid **7** as large bright yellow crystals (m.p. 22–24 °C). Upon either irradiation under



Scheme 1 *Reagents and conditions:* i, $(CF_3CO)_2O$, THF, 100%; ii, Pr^iOH, 24 h, 30 °C, 85%; iii, $SOCl_2$ 4 equiv., CH_2Cl_2, reflux 1 h, 83%; iv, CH_2N_2, ether, 1 h, 25 °C, 96%; v, MeOH, Ag_2O, 30 min, 50 °C, 53%; vi, 6 mol dm^{-3} HCl, 2 h; vii, propylene oxide in EtOH, reflux 30 min, 58% (over steps vi and vii)

a medium-pressure mercury lamp, or, heating with silver oxide in the presence of methanol, the diazo ketone **9** gave the desired *N*-trifluoroacetyl-3-methylglutamate diester **10** in ~ 50% yield, regardless of how the ketene was generated, after flash chromatography on silica. Deprotection under acidic conditions gave the 3-methylglutamic acid·HCl salt which was converted into the free base **2** through treatment with propylene oxide in 58% overall yield, m.p. 166–168 °C; $[\alpha]_D$ +22.6 (6 mol dm^{-3} HCl).

At low pH the ^1H NMR spectrum of 3-methylglutamic acid **2** showed that the C-3 and C-4 and protons possessed very similar chemical shifts (2.4–2.6 ppm). Even at high pH these signals were very difficult to distinguish. Fortunately, 3-methylglutamic acid **2** could be induced to cyclise under basic or neutral conditions[10] to give the 4-methylpyrroglutamate **11**. Treatment with diazomethane furnished the 2-oxo-4-methyltetrahydropyrrole-5-carboxylate methyl ester **12** which displayed well

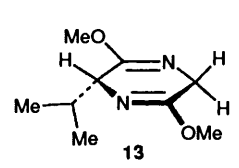


11 R = H
12 R = Me

separated signals and the two C-4 methylene protons (which occurred as characteristic AMX quartets) could be reliably assigned in the ^1H NMR spectrum.

Synthesis of (2S,3S)-3-*Methylglutamic Acid* **3**.—Although, in principle, the (2*S*,3*S*)-diastereoisomer of 3-methylglutamic acid could be prepared from (2*S*,3*R*)-3-methylaspartic acid using parallel methods to those described above, this precursor is not readily available and is difficult to prepare as a single stereoisomer.[11] Schollkopf's bis-lactim ether methodology[12] had been used successfully in our laboratory to prepare a wide variety of α-amino acid analogues.[11,13] Therefore, its utility in the construction of the two stereocentres of (2*S*,3*S*)-3-methylglutamic acid **3** was assessed.

The anion **14**, generated through treatment of the bis-lactim ether of *cyclo*-(R-Val-Gly) **13** with BuLi, can attack various electrophiles including alkyl halides and alkenoates to give alkylated dihydropyrazines. The reaction takes place almost exclusively from the least hindered face (away from the bulky Pr^i group) and gives high diastereoisomeric excesses with respect to the new stereogenic centre in the dihydropyrazine ring.[12,13] Schollkopf and co-workers treated the anion **14** with various alkenoates to obtain a number of C-3′ substituted



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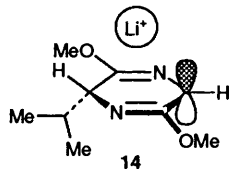

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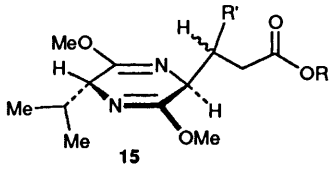

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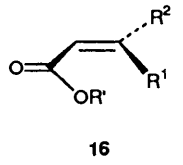


16

(*E*)- R^1 = H, R^2 = Me
(*Z*)- R^1 = Me, R^2 = H

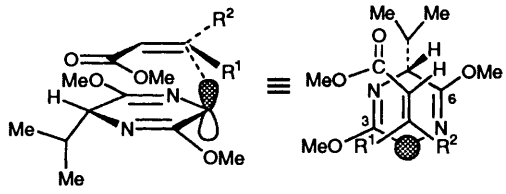
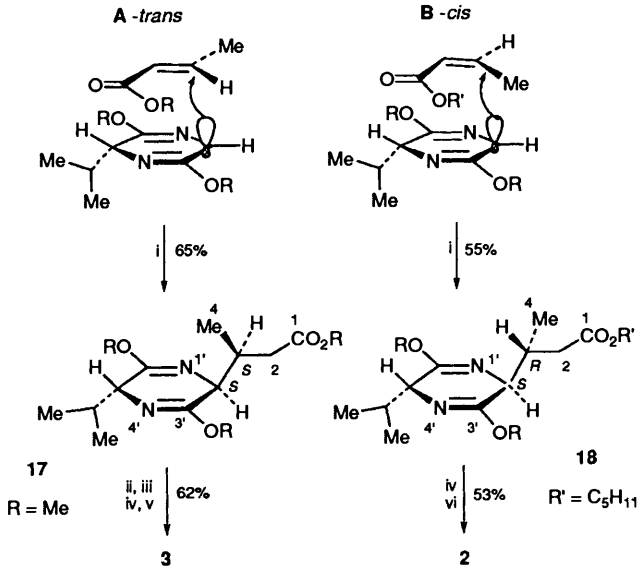


Fig. 1 Geometry of the transition state for asymmetric conjugate addition

dihydropyrazin-2-ylpropanoic acid methyl esters **15**.[14] The stereochemistry and chiral integrity at C-3′ of compound **15** (R = Me, R′ = Ph) was determined by comparison to known structures while, for the remainder of the dihydropyrazines synthesised, the stereochemistry and chiral integrity at C-3′ were deduced from ^1H NMR spectroscopic and/or chromatographic data. Importantly, with regard to our own interests only a moderate diastereoisomeric excess of 3 : 1 was reported for the 3-methylglutamic acid precursor **15** (R = R′ = Me).

The proposed rationalisation for the stereoselectivity[14] invoked a transition state in which the π-systems derived from the diazapentadienyl anion **14** and the alk-2-enoate, **16** form a π-complex which is stabilised by HOMO-LUMO interactions, Fig. 1. According to this proposal, there is only one orientation that minimises the electrostatic interactions (in particular, repulsions between the O-atoms) and that occurs when the carboxy group of the but-2-enoate ester **16** is positioned over *N*-4 of the dihydropyrazine ring. A plan view of the transition state suggests that (*E*)-alkenoates **16** will accommodate themselves over the cyclic anion more favourably than the corresponding *Z*-compounds. Nevertheless, it does appear as though the stereochemical outcome of the reaction with respect to C-3′ should be defined by the nature of the alkenoate and that the reaction of the anion **14** with the (*E*)-crotonate should provide the (2*S*,3*S*)-3-methylglutamate **3** carbon skeleton.

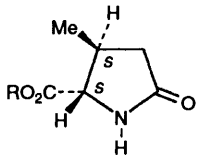
In our hands, as expected, the alkylation of anion of dihydropyrazine **13** using methyl (*E*)-crotonate **16** (R^1 = R′ = H, R^2 = Me) as the Michael acceptor afforded methyl (3′*S*,2*S*,5*R*)-3′-(5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)butanoate **17** as the major product (Scheme 2). The



Scheme 2 *Reagents and conditions:* i, BuLi to generate anion, then alkyl crotonate −78 °C; ii, 0.25 mol dm^{-3} HCl, 25 °C, 2 days; iii, flash chromatography on silica; iv, 6 mol dm^{-3} HCl, reflux; v, propylene oxide in ethanol; vi, NH_3 to pH 1.5, then recrystallisation from aqueous ethanol

dihydropyrazine **17** was carefully purified by flash chromatography twice on silica gel (1:20 ethyl acetate–hexane) and was obtained pure in moderate yield (60%). Each of the impurities present in the reaction mixture were also isolated and were subjected to careful analysis by NMR spectroscopy. None of the side products showed spectral properties consistent with those expected for the other 3'-diastereoisomer **18** (R' = Me) and, therefore, the diastereoselectivity of the conjugate addition must exceed ~ 10:1, much better than the ratio of 3:1 that was originally reported.[14]

Hydrolysis of the dihydropyrazine **17** in 6 mol dm^{-3} hydrochloric acid gave a mixture of 3-methylglutamic acid **2** and valine. However, whereas (2*S*)-glutamic acid and valine can be easily separated using anion exchange chromatography, under the separation conditions (~pH 7.0), (2*S*,3*S*)-3-methylglutamic acid **3** cyclised to give the pyrrolidone **19**, which



19 R = H
20 R = Me

was difficult to separate from valine. Therefore, the dihydropyrazine **17** was stirred in 0.25 mol dm^{-3} hydrochloric acid for 2 days to give the amino acid esters, and the solution was adjusted to pH 9.0 with 0.2 mol dm^{-3} aqueous NaOH to give the tetrahydropyrrolidone ester **20** and valine methyl ester which were easily separated by chromatography on silica gel.

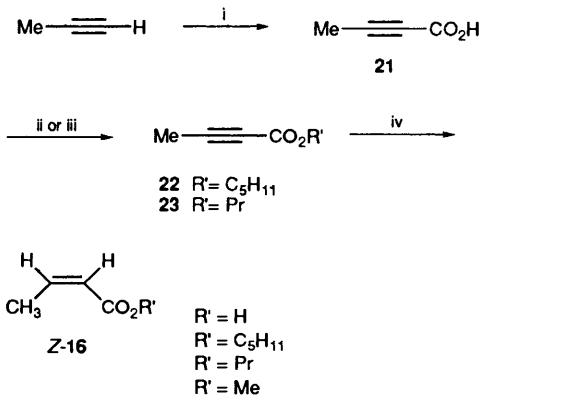
A comparison of the ^1H NMR spectrum of the (4*S*,5*S*)-tetrahydropyrrolidone ester **20** to that for (4*R*,5*S*)-diastereoisomer **12**, *vide supra*, verified the existence of large differences in the chemical shifts for the α- and β-protons.

Hydrolysis of the (4*S*,5*S*)-pyrrolidone ester **20** in 6 mol dm^{-3} hydrochloric acid and crystallisation in ethanol using propylene oxide furnished (2*S*,3*S*)-3-methylglutamic acid **3** in moderate overall yield; 42% from the dihydropyrazine **13**, m.p. 169–171 °C $[\alpha]_D$ +36.8 (6 mol dm^{-3} HCl).

Although we had achieved our initial objectives, the syntheses of each diastereoisomer of (2*S*)-3-methylglutamic acid, the high diastereoselectivity observed for the conjugate addition of anion **14** to methyl (*E*)-butenoate prompted an examination of the stereoselectivity of the analogous reaction with (*Z*)-butenoate ester.

The first reliable method for the synthesis of (*Z*)-crotonic acid **16** (R^1 = Me, R^2 = R' = H) was reported in 1956. A 1:5 mixture of (*E*)- and (*Z*)-but-2-enoic acid was obtained after hydrogenation of but-2-ynoic acid **21** over Lindlar's catalyst.[15] Separation of the two isomers was easily achieved. Accordingly, the but-2-ynoic acid **21** was prepared in multigram quantities through the addition of lithium methylacetylide to carbon dioxide at −50 °C. The crude acid **21** was distilled and recrystallised twice. Hydrogenation of the but-2-ynoic acid over Lindlar's catalyst in MeOH for 1 h afforded (*Z*)-crotonic acid **16** (R^1 = Me, R^2 = R' = H) and 10% of the (*E*)-isomer **16** (R^1 = R' = H, R^2 = Me). The regioselectivity of the hydrogenation improved markedly, as judged by NMR spectroscopy, when ethyl acetate–pyridine (9:1)[16] was used as the solvent. No (*E*)-isomer could be detected but reaction times increased to 2–3 days. The time required for complete reaction to give the (*Z*)-isomer was reduced to 3 h when freshly prepared Pd on $BaSO_4$ was employed as the catalyst.[17]

Since (*Z*)-butenoic acid **16** (R^1 = Me, R^2 = R' = H) isomerised under acidic conditions the methyl ester was obtained by treatment with ethereal diazomethane. Its low b.p. hampered the isolation of the pure material and, therefore, the



Scheme 3 *Reagents and conditions:* i, BuLi, CO_2, THF, −50 °C, 75%; ii, Me_2CHOH, $SOCl_2$ (4 equiv.), reflux, 30 min., 63%; iii, $Me_2CHCH_2CH_2OH$, $SOCl_2$ (4 equiv.), reflux, 30 min. 63%; iv, Pd on $BaSO_4$, H_2, EtOAc–Pyr (10:1), 2–4 h, 94%

isopentyl and isopropyl esters of but-2-ynoic acid were prepared and then reduced to the corresponding but-2-enoates **16** (R^1 = Me, R^2 = H, R' = Pentyl^i and Pr^i) (Scheme 3). Both esters were purified on silica gel but the higher boiling isopentyl(*Z*)-crotonate (b.p. 135 °) was much easier to handle.

Treatment of the isopentyl (*Z*)-crotonate **16** (R^1 = Me, R^2 = H, R' = Pentyl^i) with the diazapentadienyl anion **14** gave the pure dihydropyrazine **18** which was isolated in slightly lower yield (45%) than the diastereoisomer **17**, as expected, *vide supra*. The remaining material was unchanged starting material **13** and there was no evidence for the formation of significant amounts of the diastereoisomer **17** (R = Pentyl^i). Similarly, in a reaction performed using isopropyl (*Z*)-crotonate **16** (R^1 = Me, R^2 = H, R' = Pr^i), none of the diastereoisomer **17** (R = Pr^i) could be detected by NMR spectroscopy.

The (2*S*,3*R*)-3-methylglutamic acid **2** could not be isolated in an analogous manner to the (2*S*,3*S*)-isomer **3**, because the (4*R*,5*S*)-tetrahydropyrrolidone isopentyl ester did not form during mild acidic hydrolysis of the dihydropyrazine **18**. Therefore, the dihydropyrazine **18** was subjected to hydrolysis with 6 mol dm^{-3} aqueous hydrochloric acid and the pure 3-methylglutamic acid **2** was obtained by crystallisation from an aqueous ethanolic solution of the hydrolysate at pH 1.5. Recrystallisation gave an analytically pure sample in 42% yield, m.p. 167–169 °C; $[\alpha]_D$ + 23.7 (6 mol dm^{-3} HCl). This optical rotation value compares well with that obtained for the compound prepared *via* the Arndt–Eistert homologation, $[\alpha]_D$ +22.6 (6 mol dm^{-3} HCl).

Although our own assessments of the diastereoselectivities for the conjugate additions of the anion of the dihydropyrazine **14** to (*E*)-and (*Z*)-butenoate esters are based solely upon ^1H and ^{13}C NMR spectroscopic data, it appears that additions occur with high diastereoselectivity (≥90%).

The availability of each of the diastereoisomers of the L-antipode of 3-methylglutamic acid will facilitate many mechanistic and structural studies of biological systems that contain, require, biosynthesize or process (2*S*)-glutamic acid. The methodology described here can be extended to provide different 3-alkylglutamic acids and a whole range of stereospecifically labelled analogues.

Experimental

Elemental microanalyses were performed in the departmental microanalytical laboratory. NMR spectra were recorded on a Bruker AM-300 (300 MHz; f.t. ^1H NMR, and 74.76 MHz; ^{13}C NMR), or a Varian Gemini 200 (200 MHz; f.t. ^1H NMR and 50.31 MHz; ^{13}C NMR) spectrometers. ^1H NMR spectra were referenced internally on ^2HOH (4.68 ppm), $CHCl_3$ (7.27 ppm)

or DMSO (2.47 ppm). ^{13}C NMR spectra were referenced on CH_3OH (49.9 ppm), C^2HCl_3 (77.5 ppm), or DMSO (39.70 ppm). *J* Values are recorded in Hz. IR spectra were recorded on a Perkin-Elmer 1710 f.t. IR spectrometer. The samples were prepared as Nujol mulls, solutions in chloroform or thin films between sodium chloride discs. Mass spectra and accurate mass measurements were recorded on a VG 70-250 SE, a Kratos MS-50 or by the SERC service at Swansea using a VG AZB-E. Fast atom bombardment spectra were recorded using glycerol as a matrix. Major peaks are given as percentages of the base peak intensity (100%). UV spectra were recorded on Pye-Unicam SP8-500 or SP8-100 spectrophotometers. Melting points were taken on an Electrothermal melting point apparatus and are uncorrected. Optical rotations were measured at 23 °C on a Optical Activity AA-100 polarimeter using 10 or 20 cm path-length cells. Flash chromatography was performed according to the method of Still *et al.*[18] using Sorbsil C 60 (40–60 μm mesh) silica gel. Analytical thin layer chromatography was carried out on 0.25 mm precoated silica gel plates (Macherey-Nagel SIL g/UV254) and compounds were visualised using UV fluorescence, iodine vapour, ethanolic phosphomolybdic acid, or ninhydrin. Ether refers to diethyl ether and LP to light petroleum.

All chemicals were of analytical grade or were recrystallised or redistilled before use.

1-*Isopropyl* (2S,3S)-3-*Methyl* N-*trifluoroacetylaspartate* **7**.—Trifluoroacetic anhydride (50 g, 0.24 mol) was added to a stirred suspension of 3-methylaspartic acid **2** (4 g, 27 mmol) in dry tetrahydrofuran (50 cm^3) at 0 °C over 10 min under nitrogen. The reaction mixture was then allowed to warm to room temperature and stirred until dissolution was complete (*ca.* 1.5 h). After this, the mixture was evaporated under reduced pressure and the residue dried for 3–4 h under high vacuum. Dry Pr^iOH (40 cm^3) was then added to the residue and the solution left at 30 °C overnight. Pr^iOH was removed under reduced pressure to give the title ester **7** which crystallised from ether–LP as a white solid (6.6 g, 85%), m.p. 113–115 °C (Found: C, 42.0; H, 4.8; N, 4.8. Calc. for $C_{10}H_{14}F_3NO_5$: C, 42.1; H, 4.95; N, 4.9%); $[\alpha]_D$ +11.8 (*c* 0.53 in CH_2Cl_2); $\nu_{max}(CHCl_3)/cm^{-1}$ 3410 (NH), 2987–3155 (CO_2H) and 1705, 1732 (2 × CO); δ_H(200 MHz; C^2HCl_3) 1.26, 1.30 [6 H, 2 d, *J* 2, $(CH_3)_2CH$], 1.36 (3 H, d, *J* 3.6, CH_3), 3.08 (1 H, dq, $J_{3',3}$ 3.6 and $J_{2,3}$ 2, 3-H), 4.79 (1 H, dd, $J_{3,2}$ 2 and $J_{NH,2}$ 4, 2-H), 5.11 [1 H, sep, *J* 3, $(CH_3)_2CH$], 7.23 (1 H, d, NH) and 8.3 (1 H, s, CO_2H); δ_C(50 MHz; C^2HCl_3) 13.71 (CH_3), 21.99, 22.06 [$(CH_3)_2CH$], 42.01 (C-3), 54.68 (C-2), 71.44 [$(CH_3)_2CH$], 118.75 (CF_3), 159.10 (CONH), 168.75 (CO_2CH) and 177.80 (CO_2H); *m/z* (EI) 240 (5.5%), 226 (31), 198 (74), 102 (68), 153 (76), 69 (41) and 43 (100). No 4-isopropyl 3-methylaspartate could not be detected in the crude product by ^1H NMR spectroscopy at 200 MHz.

1-*Isopropyl* (2S,3S)-3-*Methyl* N-*trifluoroacetylaspartoyl Chloride* **8**.—The acid **7** (5.5 g, 19 mmol) was dissolved in dry CH_2Cl_2 (30 cm^3) and the solution was cooled in an ice-bath. $SOCl_2$ (9.0 g, 5.65 cm^3, 4 eq.) was added dropwise over 5 min to the solution which was then heated to reflux for 1 h. Removal of the volatile material under reduced pressure gave the title acid chloride **8** as an off-white solid, which crystallised from dry ether–LP (1.76 g, 83%), m.p. 67–69 °C; *m/z* (Found: M^+, 304.0562. $C_{10}H_{13}ClF_3NO_4$ requires 304.0563); $\nu_{max}(CHCl_3)/cm^{-1}$ 3326 (NH), 2987, 1780 (COCl) and 1727 (CO); δ_H(200 MHz; C^2HCl_3) 1.30 [6 H, 2d, $(CH_3)_2CH$], 1.43 (3 H, d, CH_3), 3.48 (1 H, dq, 3-H), 4.88 (1 H, dd, 2-H), 5.14 [1 H, sep., $(CH_3)_2CH$] and 7.12 (1 H, d, NH); δ_C(50 MHz; C^2HCl_3) 14.33 (CH_3), 22.01, 22.07 [$(CH_3)_2CH$], 53.58 (C-3), 54.49 (C-2), 68.47 [$(CH_3)_2CH$], 113.04 (CF_3), 157.27 (CONH), 168.05 (CO_2CH) and 175.08 (COCl); *m/z* (Cl) 303 (M^+, 92%) and 240 (10, $[M - COCl]^+$).

1-*Isopropyl* (2S,3S)-5-*Diazo*-4-*oxo*-N-*trifluoroacetylisoleucinate* **9**.—The crude acid chloride **8** (5.8 g, 18.5 mmol) was dissolved in dry THF (10 cm^3). The resulting cloudy solution was added dropwise over 10 min to an ethereal solution of dry diazomethane (2.66 g, 150 cm^3, 63 mmol) cooled in an ice–water bath. After 1 h at room temperature the solution was purged with nitrogen to remove the excess of diazomethane and filtered. The volatile material was removed under reduced pressure to afford the diazo ketone **9** as a bright yellow solid (5.75 g, 96% from **7**), m.p. 23–25 °C (Found: C, 42.45; H, 4.9; N, 13.4. Calc. for $C_{11}H_{14}F_3N_3O_4$: C, 42.7; H, 4.6 N, 13.6%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3326 (NH) and 2113 (CHN_2); δ_H(200 MHz; C^2HCl_3) 1.19 [6 H, d, $(CH_3)_2CH$], 1.26 (3 H, d, CH_3), 3.01 (1 H, m, 3-H), 4.52 (1 H, m, 2-H), 5.05 [1 H, sep., $(CH_3)_2CH$], 5.37 (1 H, s, CHN_2) and 7.24 (1 H, d, NH); δ_C(50 MHz; C^2HCl_3) 14.65 (CH_3), 22.03, 22.08 [$(CH_3)_2CH$], 46.30 (C-3), 55.14 (C-2), 67.54 (CHN_2), 70.92 [$(CH_3)_2CHO$], 113 (CF_3), 169.9 (CO_2Pr^i), 179 ($COCHN_2$) and 183 (CF_3CO); *m/z* (EI) 308 (M^+, 1%), 239 (13), 166 (26), 154 (36), 126 (71), 69 (100) and 43 (92).

1-*Isopropyl* 5-*Methyl* (2S,3R)-3-*Methyl*-N-*trifluoroacetylglutamate* **10**.—The diazo ketone **9** (5.5 g, 18.6 mmol) was dissolved in dry MeOH (50 cm^3) and the solution was flushed with nitrogen. Silver oxide (0.5 g) was added to the solution which was then heated at 50 °C for 30 min. The suspension was filtered through a Celite pad and the filtrate evaporated under reduced pressure. The resulting dark oil was subjected to flash chromatography (10% ethyl acetate in LP) to give the title diester **10** as a clear oil (3.1 g, 53%), b.p. 115 °C/15 mmHg (Found: C, 46.1; H, 6.2; N, 4.8. Calc. for $C_{12}H_{18}F_3NO_4$: C, 46.0; H, 5.8; N, 4.5%); *m/z* (Found: M^+, 313.1137. $C_{12}H_{18}F_3N_5O$ requires 313.1137); $[\alpha]_D$ +32.1 (*c* 1.15 in CH_2Cl_2); δ_H(200 MHz; C^2HCl_3) 0.96 (3 H, d, *J* 3.4, CH_3), 1.29 [6 H, d, $(CH_3)_2CH$], 2.11–2.52 (2 H, ABX q, $J_{3,4}$ 3.4, 4-H_2), 2.66 (1 H, m, $J_{3',3}$ 3.4 and $J_{2,3}$ 1.4, 3-H), 3.69 (3 H, s, OCH_3), 4.7 (1 H, dd, 2-H), 5.10 [1 H, sep., $(CH_3)_2CH$] and 7.38 (1 H, d, *J* 4, NH); δ_C(50 MHz; C^2HCl_3) 15.73 (CH_3), 22.14 [$(CH_3)_2$], 33.23 (C-4), 37.94 (C-3), 52.38 (OCH_3), 56.42 (C-2), 70.86 [$(CH_3)_2CH$], 112.86 (CF_3), 169.91 (CO_2pr^i) and 173.02 (CO_2CH_3), 179.7 (CF_3C); *m/z* (EI) 313 (M^+, 2%), 271 (5, $[M - C_3H_7]^+$), 226 (67, $[M - C_4H_7O_2]^+$), 194 (69, $[M - C_7H_{10}O_3]^+$), 166 (85, $[M - C_3H_7]^+$) and 43 (100); R_F 0.35 (20% ethyl acetate in LP).

(2S,3R)-3-*Methylglutamic Acid* **2**.—The diester **10** (0.4 g, 1.27 mmol) was refluxed in 6 mol dm^{-3} HCl (20 cm^3) for 2 h after which the mixture was evaporated under reduced pressure and the residue dissolved in water. The solvent was again evaporated under reduced pressure and this was repeated to remove the excess of acid. The residue was dried under high vacuum and then dissolved in dry ethanol (10 cm^3). Propylene oxide (4 cm^3) was added to the solution which was then refluxed for 30 min and finally cooled to room temperature. The precipitated crystalline title acid **2** was collected by centrifugation and dried for 2 days *in vacuo* (120 mg, 58%), m.p. 166–168 °C (Found: C, 44.45; H, 6.7; N, 8.7. Calc. for $C_6H_{11}NO_4$: C, 44.7; H, 6.9; N, 8.7%); *m/z* (Found: $[M + H]^+$, 162.0766. $C_6H_{12}NO_4$ requires 162.0766); $[\alpha]_D$ +22.6 (*c* 1.03 in 6 mol dm^{-3} HCl); δ_H(200 MHz; ^2H_2O) 0.93 (3 H, d, CH_3), 2.26 (1 H, m, 3-H), 2.38–2.43 (2 H, m, 4-CH_2) and 3.66 (1 H, s, 2-H); δ_C(50 MHz; ^2H_2O) 17.11 (CH_3), 34.00 (C-3), 41.86 (C-4), 61.56 (C-2) and 177.8, 179.9 (2 × CO_2H); *m/z* (FAB) 162 ($[M + H]^+$, 23%), 144 (32, $[M - H_2O + H]^+$ and 98 (40 $[M - CH_4O_2N]^+$).

Methyl (4R,5S)-4-*Methyl*-2-*oxotetrahydropyrrole*-5-*carboxylate* **12**.—The acid **2** (20 mg, 0.1 mmol) was refluxed in water for 12 h after which the solvent was removed under reduced pressure. The residue was treated with diazomethane after which the mixture was evaporated under reduced pressure and the residual oil purified by flash chromatography on silica gel (3:1, hexane–ethyl acetate) to give the title ester **12** (17 mg, 90%); *m/z* (Found: $[M + H]^+$, 157.0739. $C_7H_{11}NO_3$ requires 157.0739); δ_H(200 MHz; C^2HCl_3) 1.04 (3 H, d, CH_3), 2.08 (1 H, q, 3-H_b), 2.48 (1 H, q, 3-H_a), 2.83 (1 H, m, 4-H_a), 3.76 (3 H, s, CH_3O), 4.26 (1 H, d, 5-H) and 6.3 (1 H, br, NH); δ_C(50 MHz; C^2HCl_3) 15.71 (CH_3), 32.61 (C-3), 37.50 (C-4), 52.12 (C-5), 59.93 (CH_3O) and 171.3 (CO_2), 177.7 (CO); *m/z* (EI) 158 ($[M + H]^+$, 30%), 157 (28, M^+), 115 (14), 99 (41), 98 (84), 88 (19), 83 (23), 70 (44), 55 (96) and 42 (100).

Methyl (3S,2'S,5'R)-3-[5'-*Isopropyl*-3',6'-*dimethoxy*-2',5'-*dihydropyrazin*-2'-*yl*]*butanoate* **17**.—BuLi (1.6 mol dm^{-3}; 1.86 cm^3, 2.9 mmol, 1.1 equiv.) in hexane was added (under nitrogen *via* a syringe) to a solution of the bis-lactim ether **13** (0.5 g, 2.7 mmol) in dry THF (10 cm^3) cooled at −78 °C. After 15 min a solution of methyl (*E*)-crotonate (0.4 g, 4 mmol, 1.5 equiv.) in THF (5 cm^3) was added to the solution and after 3 h, this was followed by a solution of acetic acid (0.16 g, 2.7 mmol, 1 equiv.) in THF (2 cm^3). The mixture was allowed to warm to room temperature when it was evaporated under reduced pressure and the residue partitioned between ethyl acetate/water (50% v/v, 20 cm^3). The aqueous phase was extracted with ethyl acetate (2 × 20 cm^3) and the combined extracts were dried ($MgSO_4$) and concentrated to give the crude alkylated product. This was purified by column chromatagraphy on silica by eluting with a mixture of 4% ethyl acetate in hexane, to give dihydropyrazine **17** as a viscous oil (0.47 g, 62%); *m/z* (Found: $[M + H]^+$, 285.1814. $C_{14}H_{24}N_2O_4$ requires 285.1814); $[\alpha]_D$ +18.3 (*c* 0.61 in EtOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3154, 2960, 1702 (ester), 1644 (C=N) and 1485; δ_H(300 MHz; C^2HCl_3) 0.65 [3 H, d, $CH_3CH(CH_3)$], 1.01 [3 H, d, $CH_3CH(CH_3)$], 1.05 (3 H, d, CH_3), 1.98–2.19 (2 H, m, $CH_2CO_2CH_3$), 2.20–2.25 (1 H, m, 3'-CH), 3.62 (3 H, s, $CH_2CO_2CH_3$), 3.65, 3.66 (6 H, s, 2 × OCH_3) and 3.9 (2 H, m, 2 and 5-H); δ_C(75 MHz; C^2HCl_3) 16.38 [$CH(CH_3)_2$], 18.85 (CH_3), 31.53 [$CH(CH_3)_2$], 33.76 (C-3'), 36.56 (C-4'), 51.25 (CO_2CH_3), 52.18, 52.22 (2 × OCH_3), 59.46 (C-5), 60.46 (C-2), 162.49 (C-6), 163.81 (C-3) and 173.27 (CO_2); *m/z* (EI) 285 ($[M + H]^+$, 50%), 241 (84, $[M - C_3H_7]^+$), 209 (100, $[M - C_4H_{10}O]^+$), 184 (63, $[M - C_5H_9O_2]^+$), 167 (96) and 141 (92); R_f 0.32 (10% ethyl acetate in hexane).

Methyl (4S,5S)4-*Methyl*-2-*oxotetrahydropyrrole*-5-*carboxylate* **20**.—A suspension of the 3-methylpyrazine **17** (300 mg, 1.05 mmol) was stirred in 0.25 mol dm^{-3} HCl (8 cm^3, 2 equiv.) for 2 days after which it was extracted with ether (2 × 10 cm^3) and the organic phases were discarded. The mixture was adjusted to pH 9.5 with concentrated aqueous ammonia after which it was stirred overnight and then evaporated under reduced pressure. The resulting tetrahydropyrrole-5-carboxylic acid and valine were esterified with an excess of diazomethane in ether after which the solvents were removed under reduced pressure and the methyl valinate was removed under high vacuum. The title ester **20** was chromatographed on silica gel eluting with hexane–ethyl acetate (3:1) to give pure material (120 mg, 72%); *m/z* (Found: M^+, 157.0739. $C_7H_{11}NO_3$ requires 157.0739); δ_H(200 MHz; C^2HCl_3) 1.28 (3 H, d, CH_3), 2.01 (1 H, q, 3-H_b), 2.51 (1 H, q, 3-H_a), 2.58 (1 H, m, 4-H_a), 3.77 (3 H, s, CH_3O), 3.83 (1 H, d, 5-H) and 6.5 (1 H, b, NH); δ_C(50 MHz; C^2HCl_3) 20.10 (CH_3), 33.97 (C-3), 37.88 (C-4), 52.43 (C-2), 62.13 (CH_3O) and 172.15 (CO_2) and 177.27 (CO); *m/z* (FAB) 157 (M^+, 6%), 99 (9), 98 (100), 55 (66) and 42 (10).

(2S,3S)-3-*Methylglutamic Acid* **3**.—A suspension of the ester **20** (300 mg, 1.05 mmol) was refluxed in 6 mol dm^{-3} HCl for 2 h. The solvent was removed under reduced pressure and the residue was dried thoroughly. Ethanol (5 cm^3) and propylene oxide (2 cm^3) were added to the mixture and the resulting solution was refluxed for 30 min. The white crystalline precipitate was collected by centrifugation and crystals of the title compound **3** were dried for 2 days *in vacuo* at 50 °C (87 mg, 51%), m.p. 169–171 °C (Found: C, 41.5; H, 6.6; N, 7.8. Calc. for $C_6H_{12}O_4N{\cdot}0.75\ H_2O$: C, 41.25; H, 6.9; N, 8.0%); *m/z* (Found: $[M + H]^+$, 162.0766. $C_6H_{12}NO_4$ requires 162.0766); $[\alpha]_D$ +36.8 (*c* 1.02 in 6 mol dm^{-3} HCl); δ_H(300 MHz; ^2H_2O) 0.93 (3 H, d, CH_3), 2.26 (1 H, m, 3-H), 2.38–2.43 (2 H, m, 4-CH_2) and 3.66 (1 H, s, 2-H); δ_C(75 MHz; ^2H_2O) 16.76 (CH_3), 33.29 (C-3), 40.16 (C-4), 60.54 (C-2) and 175.07, 179.11 (2 × CO_2); *m/z* (FAB) 162 ($[M + H]^+$, 23%), 144 ($[M - H_2O + H]^+$, 32) and 98 ($[M - CH_4O_2N]^+$, 40).

But-2-*ynoic Acid* **21**.—A solution of BuLi (1.55 mol dm^{-3} in hexanes; 0.22 mol, 140 cm^3) was cooled to −50 °C and added *via* a cannula to THF (400 cm^3) at −78 °C under a nitrogen atmosphere. The solution was purged with propyne for 10 min, stirred for 5 min, and then purged with carbon dioxide. Soon the solution became cloudy and a yellow precipitate appeared. As soon as the colour changed to orange, the CO_2 flow was stopped and the solution was stirred for an additional 10 min at room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl (200 cm^3) to the mixture from which the THF was then removed under reduced pressure. The aqueous phase was adjusted to pH 1.5 (conc. HCl) and then extracted with ether (3 × 200 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to afford a brown oil which, after distillation *in vacuo*, solidified with time. Upon recrystallisation from ethyl acetate–hexane it gave the title acid **21** as large white crystals (14.5 g, 80%), m.p. 69–71 °C (lit.,[17] 70–72 °C); b.p. 115–120 °C/0.1 mmHg (Found: C, 57.1; H, 4.9. Calc. for $C_4H_4O_2$: C, 57.1; H, 4.8%); δ_H(200 MHz; C^2HCl_3) 1.95 (3 H, s, CH_3) and 10.0 (1 H, br, CO_2H).

Isopentyl But-2-*ynoate* **22**.—The acid **21** (3 g, 35 mmol) was dissolved in dry isopentyl alcohol (40 cm^3) and $SOCl_2$ (8 cm^3, 0.1 mol, 3 equiv.) was added to the solution at 0 °C over 5 min. The reaction mixture was heated to 50 °C for 30 min. After the mixture had been set aside for 3 h at room temperature isopentyl alcohol was distilled off at 35 °C under reduced pressure (10 mmHg). The desired ester distilled at 60–64 °C. Chromatographic purification of the distillate on silica gel eluting with 5% ethyl acetate in hexane gave the title ester **22** as a clear oil (2.8 g, 64%), b.p. 60–64 °C/10 mmHg; *m/z* (Found: $[M + H]^+$, 155.1071. $C_9H_{14}O_2$ requires 155.1072); δ_H(200 MHz; C^2HCl_3) 0.92 (6 H, d, 2 × CH_3), 1.55 (2 H, m, OCH_2CH_2CH), 1.68 (1 H, m, OCH_2CH_2CH), 1.97 (3 H, s, $(CH_3C{\equiv}C)$ and 4.25 (2 H, t, OCH_2CH_2CH); δ_C(50 MHz; C^2HCl_3) 4.23 ($CH_3C{\equiv}C$), 22.8 [$(CH_3)_2CH$], 25.58 [$(CH_3)_2CH$], 37.5 (OCH_2CH_2CH), 64.9 (OCH_2CH_2CH) 85.7 ($CH_3C{\equiv}C$) 117.3 ($CH_3C{\equiv}C$) and 154.3 (CO_2); *m/z* (Cl) 155 ($[M + H]^+$, 12%), 103 (10) and 58 (3); R_F 0.35 (5% ethyl acetate in hexane). The product contained impurities and was estimated to be ~85% pure.

Isopropyl But-2-*ynoate* **23**.—The acid **21** (3 g, 35 mmol) was dissolved in dry isopropyl alcohol (40 cm^3) and $SOCl_2$ (0.1 mol, 8 cm^3, 3 equiv.) was added to the solution over 5 min at 0 °C. The solution was left at room temperature for 10 min and then refluxed for 30 min. The reaction mixture was concentrated under reduced pressure and the crude product was purified by flash chromatography on silica gel eluting with ethyl acetate–hexane (1:20) to give the ester **23** (2.2 g, 50%), b.p. 64–66 °C/15

mmHg; *m/z* (Found: $[M + H]^+$, 127.0759. $C_7H_{10}O_2$ requires 127.075 89); ν_{max}(Nujol)/cm^{-1} 2985, 2253 (C≡C), 1701 (CO), 1271, 1106 and 1072; δ_H(200 MHz; C^2HCl_3) 1.25 [6 H, d, $(CH_3)_2CH$], 1.97 (3 H, s, $CH_3C{\equiv}C$) and 5.05 [1 H, s, $(CH_3)_2CH$]; δ_C(50 MHz; C^2HCl_3) 4.27 ($CH_3C{\equiv}C$), 22.1 [$(CH_3)_2CH$], 70.13 [$(CH_3)_2CH$], 85.36 ($CH_3C{\equiv}C$), 117.7 ($CH_3C{\equiv}C$) and 153.8 (CO); *m/z* (EI) 127 ($[M + H]^+$, 55%), 67 (7) and 58 (5); R_F 0.3 (5% ethyl acetate in hexane).

Isopentyl (Z)-*But-2-enoate* **16** (R′ = Pentyl^i).—The ester **22** (2 g, 16 mmol) was dissolved in ethyl acetate and dry pyridine (9:1 v:v; 20 cm^3), and 5% palladium-on-barium sulphate (200 mg) was added to the solution; the mixture was then purged with H_2 for 4 h. After the catalyst had been filtered off on a Celite pad, the solution was partitioned between ethyl acetate (30 cm^3) and 1 mol dm^{-3} HCl solution (100 cm^3). The aqueous phase was extracted with ethyl acetate (2 × 20 cm^3) and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford a yellow oil which was chromatographed on silica gel eluting with ethyl acetate–hexane (1:9) to give the pure title compound **16** (R′ = Pentyl^i) as a clear oil (1.9 g, 77%); *m/z* (Found: $[M + H]^+$, 157.1229. $C_9H_{16}O_2$ requires 157.1228); δ_H(200 MHz; C^2HCl_3) 0.92 [6 H, d, $(CH_3)_2CH$)], 1.52 (2 H, m, OCH_2CH_2CH), 1.69 (1 H, m, OCH_2CH_2CH), 2.11 (3 H, s, CH_3CC), 4.13 (2 H, t, OCH_2CH_2CH), 5.79 (1 H, dd, $CH_3CH{=}CH$) and 6.20 (1 H, dq, $CH_3CH{=}CH$); δ_C(50 MHz; C^2HCl_3) 15.8 ($CH_3CH{=}CH$), 22.9 ($(CH_3)_2CH$, 25.58 ($(CH_3)_2CH$, 37.9 (OCH_2CH_2CH), 63.3 (OCH_2CH_2CH) 121.2 ($CH_3CH{=}CH$) 145.3 ($CH_3CH{=}CH$) and 167.2 (CO_2); *m/z* (EI) 157 ($[M + H]^+$, 2%), 121 (18), 103 (57), 70 (100) and 55 (73); R_F 0.55 (10% ethyl acetate in hexane).

Isopropyl (Z)-*But-2-enoate* **16** (R′ = Pr^i).—Isopropyl (Z)-but-2-enoic acid was prepared from ester **23** (2 g, 15 mmol) in a manner identical with that described above for the isopentyl ester to give the title compound (1.73 g, 84%), *m/z* (Found: $[M + H]^+$, 129.091. $C_7H_{12}O_2$ requires 129.091); δ_H(200 MHz; C^2HCl_3) 1.22 (6 H, d, $[(CH_3)_2CH]$, 2.13 (3 H, dd, $CH_3CH{=}CH$), 5.02 [1 H, s, $(CH_3)_2CH$] 5.74 (1 H, dd, $CH_3CH{=}CH$) and 6.27 (1 H, dq, $CH_3CH{=}CH$); δ_C(50 MHz; C^2HCl_3) 15.7 ($CH_3CH{=}CH$), 22.4 ($(CH_3)_2CH$, 67.43 ($(CH_3)_2CHO$, 121.6 ($CH_3CH{=}CH$), 144.95 ($CH_3CH{=}CH$ and 166.6 (CO_2); *m/z* (Cl) 155 ($[M + H]^+$, 12%), 103 (10) and 58 (3); R_F 0.6 (10% ethyl acetate in hexane).

Isopentyl (3R,2′S,5′R)-3-[5′-*Isopropyl*-3′,6′-*dimethoxy*-2′,5′-*dihydropyrazin*-2′-*yl*]*butanoate* **18** (R′ = Pentyl^i).—Dihydropyrazine **18** was prepared and purified in a manner identical with that described for the ester **17**, starting from the bis-lactim ether **13** and ester **16** (R′ = Pentyl^i). The product (0.20 g, 44%) showed the following characterisation; *m/z* (Found: $[M + H]^+$, 341.2440. $C_{18}H_{32}N_2O_4$ requires 341.2440); $[\alpha]_D$ +14.3 (*c* 0.78 in EtOH); ν_{max}($CHCl_3$)/cm^{-1} 2961, 2873, 1738 (C=N), 1644 (ester) and 1485; δ_H(300 MHz; C^2HCl_3) 0.68 [3 H, d, $CH_3CH(CH_3)$], 0.92 [6 H, d, ester $(CH_3)_2CHCH_2$], 1.04 [3 H, d, $CH_3CH(CH_3)$], 1.08 (3 H, d, CH_3), 1.51 [2 H, d, $OCH_2CH_2CH(CH_3)_2$], 1.68 [1 H, m, ester $(CH_3)_2CHCH_2$], 1.98–2.15 (2 H, m, CH_2CO_2R), 2.24–2.28 (1 H, m, 3′-CH), 2.64 [1 H, m, ester $(CH_3)_2CHCH_2$], 3.689, 3.696 (6 H, 2s, 2 × OCH_3), 3.93 (2 H, m, 3 and 6-H) and 4.08 (2 H, t, OCH_2); δ_C(75 MHz; C^2HCl_3) 16.40, 16.48 [ring $CH(CH_3)_2$], 19.02 (CH_3), 22.48 [ester $(CH_3)_2CHCH_2$], 25.05 [ester $(CH_3)_2CHCH_2$], 31.69 [ring $CH(CH_3)_2$], 33.94 (C-3′), 36.99 (C-4′), 37.32 [ester $(CH_3)_2CHCH_2$], 52.38, 52.36 (2 × OCH_3), 59.73 (C-5), 60.61 (C-2), 162.49 (C-6), 163.81 (C-3) and 173.27 (CO_2); *m/z* (EI) 285 ($[M + H]^+$, 50%), 241 (84, $[M - C_3H_7]^+$), 209 (100, $[M - C_4H_{10}O]^+$), 184 (63, $[M - C_5H_9O_2]^+$), 167 (96) and 141 (92).

The isopropyl ester **18** (R′ = Pr^i) was prepared and purified in a similar manner. The product (140 mg, 40%) had the following characteristics: (Found: $[M + H]^+$, 313.2127. $C_{16}H_{28}N_2O_4$ requires 313.2127); ν_{max}($CHCl_3$)/cm^{-1} 2961, 2873, 1738 (C=N), 1644 (ester) and 1485; δ_H(300 MHz; C^2HCl_3) 0.68 [3 H, d, ring $CH_3CH(CH_3)$], 1.04 [3 H, d, ring $CH_3CH(CH_3)$], 1.06 (3 H, d, 3′-CH_3), 1.22 [6 H, dd, ester $(CH_3)_2CH$], 1.98–2.15 (2 H, ABX, CH_2CO_2R), 2.24–2.28 [1 H, m, ring $(CH_3)_2CH$], 2.64 (1 H, m, 3′-H), 3.68, 3.69 (6 H, 2 s, 2 × OCH_3), 3.93 (2 H, m, 3 and 6-H) and 5.01 [1 H, s, ester $(CH_3)_2CH$]; δ_C(75 MHz; C^2HCl_3) 16.28, 16.44 [ring $(CH_3)_2CH$], 19.02 (CH_3), 221.71, 21.81 [ester $(CH_3)_2CH$], 31.58 [ring $(CH_3)_2CH$], 33.89 (C-3′), 37.15 (C-4′), 52.31 (2 × OCH_3), 59.72 (C-5), 60.49 (C-2), 67.38 [ester $(CH_3)_2CH$], 162.5 (C-6), 163.8 (C-3) and 172.5 (CO_2); *m/z* (EI) 313 ($[M + H]^+$, 16%), 269 (48), 209 (77), 167 (42), 141 (82), 127 (79) and 43 (100).

(2S,3R)-3-*Methylglutamic Acid* **2**.—The dihydropyrazine **18** (R′ = Pentyl^i) (180 mg, 0.53 mmol) was refluxed in 6 mol dm^{-3} HCl (5 cm^3) for 2 h after which the solvent was removed. The residue was dissolved in water (2 cm^3) and the solution adjusted to pH 1.5 with aqueous ammonia. Ethanol was added (~70 cm^3) to the solution until it became cloudy after which the mixture was kept at 5 °C for 2 days when white crystals formed. These were filtered off and recrystallised from aqueous ethanol to give the pure title compound **2**, identical in all respects with the sample prepared *via* Arndt–Eisert homologation (36 mg, 42%), 166–168 °C (Found: C, 40.05; H, 7.5; N, 7.6. Calc. for $C_6H_{11}O_4N{\cdot}H_2O$: C, 40.2; H, 7.31; N, 7.8%); *m/z* (Found: $[M - H_2O]^+$, 144.0661. $C_6H_{11}NO_4$ requires 144.0661); $[\alpha]_D$ +10.2 (*c* 0.43 in 6 mol dm^{-3} HCl); δ_H(300 MHz; ^2H_2O) 1.04 (3 H, d, CH_3), 2.30–2.65 [3 H, m, $CH(CH_3)CH_2$] and 3.80 (1 H, d, 2-H); δ_C(75 MHz; ^2H_2O) 17.11 (CH_3), 33.63 (C-3), 40.50 (C-4), 60.89 (C-2) and 175.44, 179.49 (2 × CO_2H); *m/z* (EI) 162 ($[M + H]^+$, 8%), 98 (100) and 55 (95).

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