Stereoselective Michael addition of benzylamines to homochiral methylenebutanedioates

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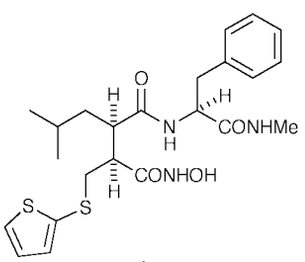
The Michael addition of benzylamine to the homochiral methylenebutanedioate **10** gave an adduct **11** in good yield with high stereoselectivity. By performing the reaction in methanol the (2*R*,3*R*) diastereoisomer **11** was obtained in 88% de, which was increased to 98% de after recrystallisation of the primary amine derivative **13**. The ratio of diastereoisomers was reversed by performing the reaction in aprotic solvents, with the (2*R*,3*S*) diastereoisomer **12** being obtained in 40% de in tetrahydrofuran. The Michael adduct **11** is formed under kinetic control. The primary amine **15** is a key intermediate in the synthesis of novel matrix metalloproteinase inhibitors.

Introduction

Matrix metalloproteinases (MMPs)[1] are a family of enzymes which are responsible for the degradation of all the major components of extracellular matrix. Over-activation of MMP's has been linked with a range of diseases such as arthritis and cancer; thus inhibition of these proteinases could serve as effective treatments for such disease states.[2] For example, other workers at British Biotech Pharmaceuticals (BBP), have recently described the substrate-based inhibitors, batimastat **1**[3] and marimastat **2**.[4]



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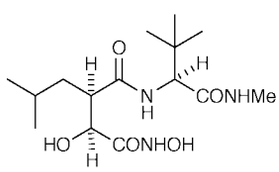

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Clearly these inhibitors possess very similar structural features; in particular they possess an hydroxamic acid zinc binding group and structure–activity relationship (SAR) studies have been carried out involving substitution α to this group. As an extension to that work we were interested in gaining access to aminomethyl substituents α to the hydroxamic acid, such as in **3** (Fig. 1). Given our interest in asymmetric β-amino acid synthesis *via* Michael addition of nitrogen nucleophiles,[5] a retro-synthetic analysis (Fig. 1) suggested that such molecules could be constructed by a Michael addition of an amine to an appropriately functionalised acrylate ester **5**. This in turn could be obtained from the acid **6**,[3,6] a readily available bulk intermediate used by BBP for the synthesis of batimastat.

Our goal was thus twofold: (i) to synthesise an amino diester such as **4** (Fig. 1) in which the ester groups are differentiated, to allow selective manipulation, and (ii) to prepare the amino diester **4** as a single stereoisomer with the (2*R*,3*R*) absolute configuration, required for optimum enzyme inhibitory activity.

The Michael additions of amines to acrylate esters[7] and β-substituted α,β-unsaturated esters are well documented.[5a,7a,8] However, a survey of the literature revealed that although attention has been focused on the addition of amines to methylenebutanedioates[9] there are no references to homochiral 3-substituted methylenebutanedioates. Other workers have shown that amines can be added to an α-substituted acrylate bearing a stereogenic centre to furnish a β-aminoester with high (20 : 1) stereochemical control.[10] Thus we were encouraged to examine the Michael addition of benzylamine to the acrylate ester **10**, both as a synthetic goal and also to gain more insight into the mechanistic aspects of the reaction.

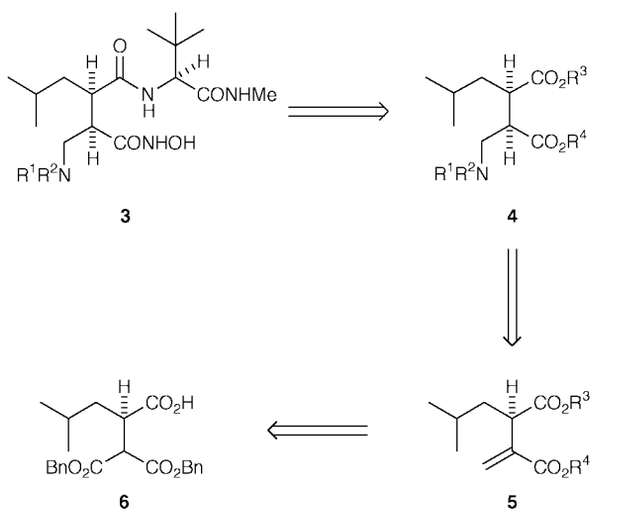
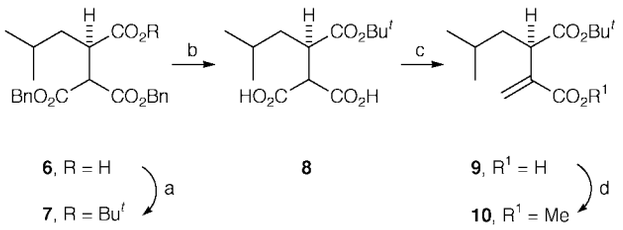


Fig. 1 Retrosynthetic analysis for α-aminomethyl substituted MMPs (Bn = $PhCH_2$).

Results and discussion

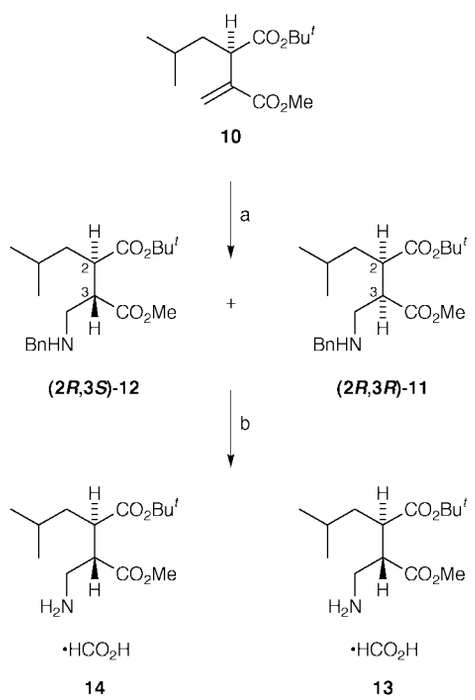
Synthesis of the required methylenebutanedioate **10** from the available acid **6** was achieved readily (Scheme 1). The acid **6**[6] was protected as its *tert*-butyl ester **7**, then the benzyl groups were removed by hydrogenolysis. The resulting substituted malonic acid **8** was subjected, without purification, to a Mannich type reaction using formaldehyde and piperidine to



Scheme 1 *Reagents*: a, isobutene, H_2SO_4, CH_2Cl_2, 97%; b, H_2, 10% Pd–C, EtOH; c, HCHO, piperidine, 86% from **7**; d, K_2CO_3, MeI, Me_2CO, 96%.

furnish the acrylic acid **9** in 84% yield from **6**. The potassium salt of **9** was then methylated in 96% yield using iodomethane, providing the required acrylate **10**.

Addition of a methanolic solution of benzylamine to **10** gave a 90 : 10 mixture of the Michael adducts **11** and **12** after 18 h at ambient temperature (Scheme 2). Isolation of the individual



Scheme 2 *Reagents*: a, $BnNH_2$, MeOH, 70%; b, HCO_2H, MeOH, 10% Pd–C, 100%.

diastereoisomers was not possible, although chromatography did provide enriched mixtures of each diastereomer. However, hydrogenolysis of the mixture of benzylamines **11** and **12** gave the formate salts **13** and **14**, from which the major diastereomer **13** was obtained in greater than 98% de after a single recrystallisation from ethyl acetate.

The absolute configuration of the amine **15**, derived from salt **13**, and by inference the precursor Michael adduct **11,** was established from X-ray crystallographic analysis of the (1*S*)-10-camphorsulfonic acid salt **16** (Scheme 3), by comparison with the known absolute configuration of (1*S*)-10-camphorsulfonic acid (Fig. 2).

In order to explain the origin of the surprisingly high stereoselectivity found in the formation of **11**, the mechanism of the Michael addition of amines to acrylate esters was considered. Although studies have been performed on the addition of amines to acrylate esters,[11] the nature of the mechanism is still not fully understood, and in particular whether the Michael adducts are formed under kinetic or thermodynamic control.[12]

Before the origins of the observed diastereoselectivity could be investigated, the question of kinetic *vs.* thermodynamic

Table 1 Variation of the diastereomeric ratio **11** : **12** with reaction temperature

T/°C	Ratio (NMR) [isolated yield, %] **11** : **12**
−20	94 : 6[a]
Ambient	90 : 10 [70]
65	72 : 28[b]

[a] Incomplete reaction after 168 h. [b] Products not isolated.

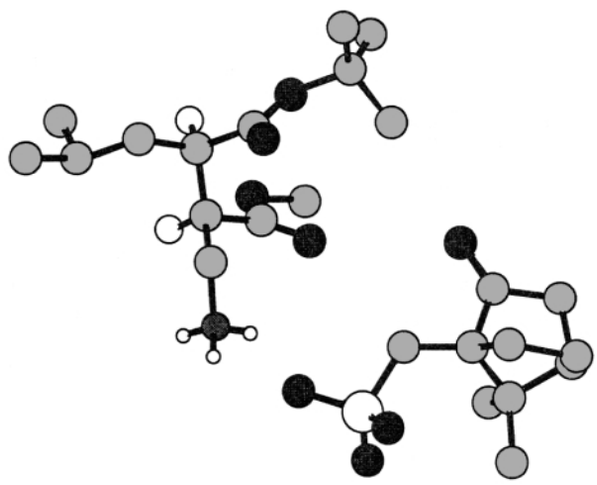
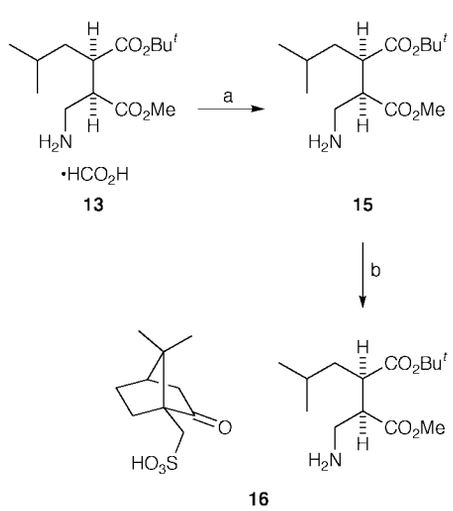


Fig. 2 X-Ray crystal structure of 1-(*tert*-butyl) 4-methyl (2*R*,3*R*)-3-(aminomethyl)-2-isobutylbutanedioate, (1*S*)-10-camphorsulfonic acid salt **16**.



Scheme 3 *Reagents*: a, aqueous $NaHCO_3$, 90%; b, (1*S*)-10-camphorsulfonic acid, EtOAc.

control in our system required addressing. Several experiments were devised to this end and the following results are consistent with the Michael addition of benzylamine to the acrylate **10** proceeding under *kinetic control*: (i) a variable temperature study (Table 1) showed that the diastereomeric ratio of **11** : **12** was temperature dependent; (ii) samples taken from a reaction at ambient temperature after 0.5, 1, 2, 4, 8 and 168 h showed no change in the 90 : 10 diastereomeric ratio **11** : **12**, indicating that there is no equilibration between **11** and **12**; (iii) no change in the diastereomeric ratio was observed by re-subjecting a 30 : 70 mixture of **11** : **12** (from reaction in tetrahydrofuran, see Table 2) to the reaction conditions that had previously produced a ratio of 90 : 10 (methanol).

The Michael addition of benzylamine to a methylenebutanedioate such as **10** is believed to give the enolate **17**[11] which is

Table 2 Variation of diastereomeric ratio **11**:**12** with solvent

Solvent[a]	Ratio (NMR) **11**:**12**
No solvent[b]	30:70
MeOH[b]	90:10
$CHCl_3$[c]	50:50
MeCN[c]	40:60
THF[c]	30:70

[a] All reactions performed at ambient temperature. [b] Complete reaction after 18 h. [c] Incomplete reaction after 168 h.

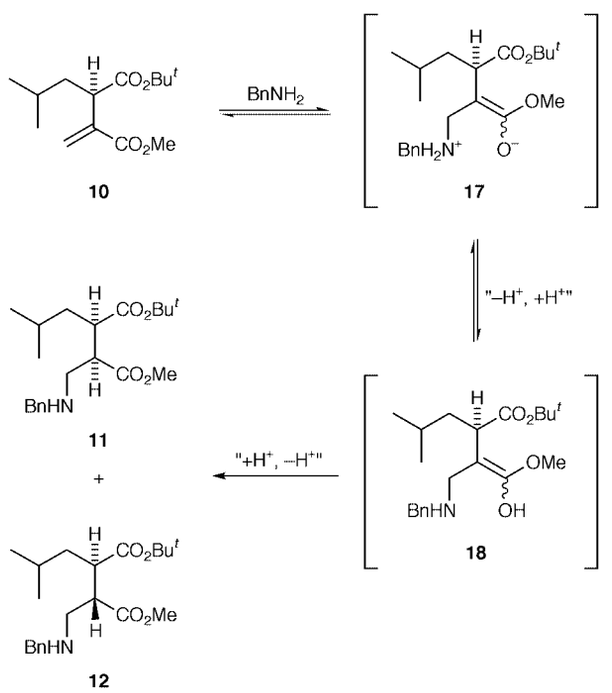
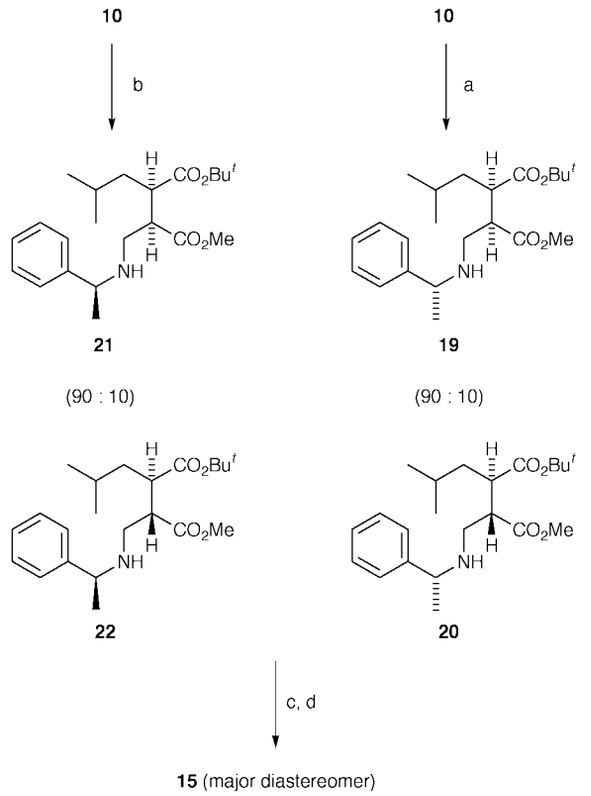


Fig. 3 Proposed mechanism for the formation of **11** and **12** under kinetic control.

rapidly, or simultaneously, depending on the solvent, protonated to furnish the enol **18**. The new stereocentre in **11** is created as a result of the tautomerisation of the enol **18**, and it is the facial selectivity of this protonation step which gives rise to the diastereoselectivity of the reaction. The factors which may be responsible for the origin of the diastereoselectivity during the tautomerisation of **18** to **11** include: (i) the geometry of the enol **18** and (ii) the nature of the enol **18** in terms of intramolecular hydrogen-bonded species *vs.* solvated open-chain species.[11] Additionally we were interested to see what effect changing the solvent would have on the ratio **11**:**12**, as this might provide more information on the nature of protonation of the enol **18**. For the reaction in solvents other than methanol, the diastereoselectivity was zero, in a relatively low polarity solvent (chloroform), whereas a significant reversal of stereoselectivity was observed in an ether solvent (tetrahydrofuran) (Table 2).

In order to show that the products obtained by performing the Michael addition in aprotic solvents were derived from kinetic control, a 90:10 mixture of diastereomers (Table 2) was subjected to the Michael addition conditions in chloroform. If the reaction is thermodynamically controlled in aprotic solvent then the ratio of **11**:**12** would be expected to change to 50:50. However, no change in the diastereomeric ratio was observed, confirming kinetic control. Despite the above observations, the origin of the stereocontrol of the protonation of enol **18** is still unclear and requires further studies.

The Michael additions of both (*R*)- and (*S*)-1-phenylethylamines with **10** were also investigated, in order to see whether we could enhance further the diastereomeric excess of the



Scheme 4 *Reagents*: a, (*R*)-1-phenylethylamine, MeOH, 91%; b, (*S*)-1-phenylethylamine, MeOH, 93%; c, 1 M HCO_2H–MeOH, 10% Pd–C, 100%; d, aqueous $NaHCO_3$.

Michael adduct and/or change the configuration of the stereogenic centre *via* double asymmetric induction[13] (Scheme 4). We were aware that the Michael addition of (*S*)-1-phenylethylamine to methyl crotonate furnishes adducts with poor diastereomeric excesses (up to 20%),[5a,8a] so were therefore not surprised that there were no differences observed in the configuration of the major diastereomers **19** and **21** and that of **11**, and that the diastereomeric ratios **19**:**20** and **21**:**22**, were identical with the ratio **11**:**12**. Hydrogenolysis of pure **19** gave the primary amine **15** after basification, thus establishing its absolute configuration. The 90:10 mixture of **21**:**22** was reacted similarly, giving **15** as the major diastereomer.

Conclusion

We have shown that high levels of stereochemical control (90:10) are obtained from the addition of benzylamine to the substituted methylenebutanedioate **10** in *methanolic* solution, and that this ratio of diastereomers can be reversed (30:70) by change of solvent to *tetrahydrofuran*. The configuration of the newly formed stereogenic centre is controlled entirely from the existing stereogenic centre in **10,** as both (*R*)- and (*S*)-1-phenylethylamines furnish the Michael adducts **19** and **21** as the major diastereomers with an identical absolute configuration of *the newly formed stereogenic centre* and the same ratio of diastereomers.

The Michael adduct **11** is formed under kinetic control. The origin of the stereoselectivity requires further investigation, and these studies are in progress. Amines **4** have been further elaborated to MMP inhibitors, details of which will appear in future publications.

Experimental

Melting points (mps) were recorded on a Gallenkamp capillary melting point apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 341 polarimeter and $[\alpha]_D$

values are given in units of 10^{-1} deg cm^2 g^{-1}. Microanalyses were performed by Medac Ltd, Brunel University. IR spectra were recorded on a Perkin-Elmer 1600 Series FTIR spectrometer as neat liquids or solids. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX 250 spectrometer (250 MHz and 62.6 MHz) or a Bruker AMX 500 spectrometer (500 MHz and 125.7 MHz), with tetramethylsilane as internal standard. *J* values are given in Hz. High resolution mass spectra (HRMS) were obtained by the University of Manchester Spectroscopic Services Department.

1,1-Dibenzyl 2-*tert*-butyl (2*R*)-4-methylpentane-1,1,2-tricarboxylate 7

Concentrated sulfuric acid (5 ml) was added to a stirred solution of (2*R*)-2-[2-(benzyloxy)-1-(benzyloxycarbonyl)-2-oxoethyl]-4-methylpentanoic acid **6** (50 g, 126 mmol) in dichloromethane (100 ml) at −70 °C, in a screw-cap pressure bottle. 2-Methylpropene was then condensed into the reaction until the volume had approximately doubled, when the bottle was sealed and allowed to warm to ambient temperature. After 23 h the reaction was cooled to −70 °C, the contents poured slowly into well-stirred 1 M aqueous sodium carbonate (250 ml) and the mixture stirred for a further 3 h. The mixture was saturated with sodium chloride to facilitate separation, separated and the organic phase was washed with saturated aqueous sodium chloride (100 ml) then dried ($MgSO_4$), filtered and evaporated to give the triester **7** (54.35 g, 97.6%) as a thick oil, which slowly crystallised, mp 36–37 °C; $[\alpha]_D^{20}$ +5.3 (*c* 0.024 in MeOH) (Found: C, 71.25; H, 7.75; $C_{27}H_{34}O_6$ requires C, 71.3; H, 7.5%); ν_{max} (neat)/cm^{-1} 1750, 1719; δ_H ($CDCl_3$) 7.35–7.26 (10H, m, ArH), 5.22–5.07 (4H, m, 2 × ArCH_2), 3.77 (1H, d, *J* 10.2, 1-H), 3.08 (1H, ddd, *J* 10.2, 10.2, 4.3, 2–H), 1.66–1.44 (2H, m, 3-H and 4-H), 1.41 (9H, s, CO_2Bu^t), 1.15–1.04 (1H, m, 3-H), 0.865 (3H, d, *J* 6.4, CH*Me*), 0.835 (3H, d, *J* 6.4, CH*Me*); δ_C ($CDCl_3$) 172.6 (*C*O_2Bu^t), 167.6 (2 × *C*O_2Bn), 135.1 and 135.0 (2 × quaternary Ar), 128.4–128.0 (10 × Ar), 81.1 (*C*Me$_3$), 67.1 and 67.0 (2 × Ar*C*H$_2$), 54.6 (C-2), 43.4 (C-3), 39.3 (CH*C*H$_2$), 27.7 (C*Me*$_3$), 25.6 (*C*HMe$_2$), 23.4 and 21.0 (CH*Me*$_2$).

2-[(1*R*)-1-(*tert*-Butoxycarbonyl)-3-methylbutyl]acrylic acid 9

A slurry of 10% Pd–C (9.1 g) in ethyl acetate (~50 ml) was added to a solution of the triester **7** (90.8 g, 0.2 mol) in ethanol (900 ml), under an atmosphere of argon. Hydrogen gas was bubbled through the well stirred mixture for 2 h then the reaction stirred under an hydrogen atmosphere for 16 h. The catalyst was removed by filtration through Celite, the filtrate transferred to a round-bottomed flask and cooled to <10 °C. Piperidine (25 ml) was added in several portions, the reaction stirred for a further 10 min then an aqueous solution of formaldehyde (37% wt; 80 ml) added dropwise over 10 min. The cooling bath was removed and the reaction stirred for 16 h then the solvents were evaporated to leave a thick oil, which was dissolved in ethyl acetate (500 ml) and washed with hydrochloric acid (1 M; 250 ml), then saturated aqueous sodium chloride (100 ml). The solution was dried ($MgSO_4$) and evaporated to leave a gum which was subjected to column chromatography (SiO_2, eluting with 2:3 ethyl acetate–hexane) to give the acid **9** (41.69 g, 86%) as a gum; $[\alpha]_D^{20}$ +2.1 (*c* 0.012 in MeOH) (Found: C, 64.4; H, 9.3. $C_{13}H_{22}O_4$ requires C, 64.4; H, 9.15%); ν_{max} (film)/cm^{-1} 3506–2613 (br.), 1731, 1696, 1625; δ_H ($CDCl_3$; 500 MHz) 6.45 (1H, s, *Z*-C*H*=C), 5.82 (1H, s, *E*-C*H*=C), 3.49 (1H, t, *J* 7.5, C*H*CO_2Bu^t), 1.77–1.71 (1H, m, CH$_2$), 1.57 (1H, m, C*H*Me$_2$), 1.52–1.44 (1H, m, CH$_2$), 1.42 (9H, s, Bu^t), 0.93 (3H, d, *J* 6.5, CH*Me*), 0.90 (3H, d, *J* 6.5, CH*Me*); δ_C ($CDCl_3$) 172.6 and 171.9 (2 × CO), 138.7 (CH$_2$=*C*), 128.2 (*C*H$_2$=C), 80.8 (*C*Me$_3$), 45.2 (*C*CO_2Bu^t), 40.4 (*C*H$_2$), 27.8 (C*Me*$_3$), 25.9 and 22.3 (CH*Me*$_2$) [Found (CI): $(M+NH_4)^+$ *m/z* 260.1860, $C_{13}H_{22}O_4$ requires $(M+NH_4)$ 260.1862].

1-*tert*-Butyl 4-methyl (2*R*)-2-isobutyl-3-methylenebutanedioate 10

Potassium carbonate (43 g, 311 mmol) was added to a stirred solution of the acid **9** (15 g, 61 mmol) in acetone (500 ml). Stirring was continued for 0.5 h then iodomethane (7.6 ml, 122 mmol) was added and the mixture stirred for 24 h, then filtered, the solid washed with diethyl ether (100 ml) and the filtrate evaporated. The residue was taken up in diethyl ether, filtered through a pad of SiO_2 and evaporated to give the methyl ester **10** (15.22 g, 96%) as a pale yellow oil, $[\alpha]_D^{20}$ +1.1 (*c* 0.046 in MeOH) (Found: C, 65.25; H, 9.3. $C_{14}H_{24}O_4$ requires C, 65.6; H, 9.27%); ν_{max} (film)/cm^{-1} 1739, 1719, 1629; δ_H ($CDCl_3$; 500 MHz) 6.29 (1H, s, *Z*-C*H*=C), 5.69 (1H, s, *E*-C*H*=C), 3.74 (3H, s, CO_2*Me*), 3.48 (1H, t, *J* 7.5, C*H*CO_2Bu^t), 1.74–1.69 and 1.48–1.42 (each 1H, m, CH$_2$), 1.60–1.52 (1H, m, C*H*Me$_2$), 1.40 (9H, s, Bu^t), 0.91 and 0.88 (each 3H, d, *J* 6.5, CH*Me*$_2$); δ_C ($CDCl_3$) 172.6 and 166.9 (2 × CO), 139.1 (CH$_2$=*C*), 125.8 (*C*H$_2$=C), 80.5 (*C*Me$_3$), 51.9 (CO_2*Me*), 45.5 (*C*CO_2Bu^t), 40.3 (CH$_2$), 27.9 (C*Me*$_3$), 25.9 (*C*HMe$_2$), 22.4 and 22.3 (CH*Me*$_2$); [Found (CI): $(M + H)^+$ *m/z* 257.1760, $C_{14}H_{24}O_4$ requires $(M + H)^+$ 257.1753].

(2*R*,3*R*)- and (2*R*,3*S*)-1-*tert*-Butyl 4-methyl 3-(benzylaminomethyl)-2-isobutylbutanedioate 11/12

Benzylamine (10.5 ml, 97.5 mmol) was added dropwise to a stirred solution of the diester **10** (5.00 g, 19.5 mmol) in methanol (25 ml) at ambient temperature, under an argon atmosphere. After 18 h the solvent was evaporated and a solution of the residue in ethyl acetate (200 ml) was washed with 1 M aqueous citric acid (100 ml; 50 ml) then water (50 ml), saturated aqueous sodium hydrogen carbonate solution (100 ml) and saturated aqueous sodium chloride (100 ml). The organic phase was dried ($MgSO_4$) and evaporated to give a 90:10 mixture of the Michael adducts **11** and **12** (4.95 g, 70%) as a pale yellow oil. Purification was achieved by chromatography (SiO_2, eluting with 4:1 hexane–ethyl acetate), $[\alpha]_D^{20}$ −1.3 (*c* 0.0294 in MeOH) for 80% de (Found: C, 69.4; H, 9.15; N, 3.85. $C_{21}H_{33}NO_4$ requires C, 69.35; H, 9.0; N, 3.9%); ν_{max} (film)/cm^{-1} 3350, 1725; δ_H ($CDCl_3$) 7.33–7.19 (5H, m, ArH), 3.77–3.76 (1H, d, *J* 2, ArCH_2N), 3.70 (3H, s, CO_2*Me*), 2.92–2.63 (4H, m, NCH_2C*H* and C*H*CO_2Bu^t), 1.68–1.41 (3H, m, N*H* and C*H*C*H*Me$_2$), 1.38 (9H, s, Bu^t), 1.05 (1H, ddd, *J* 13.2, 9.4, 3.8, C*H*CHMe$_2$), 0.88 and 0.87 (each 3H, d, *J* 6.3, CH*Me*$_2$); δ_C ($CDCl_3$) 174.2 and 173.2 (2 × CO), 139.9 (quaternary Ar), 128.3, 128.0 and 126.9 (Ar), 80.8 (*C*Me$_3$), 53.4 (Ar*C*H$_2$N), 51.6 and 49.4 (*C*CO_2Bu^t and *C*CO_2Me), 48.5 (NCH_2CH), 45.0 (CO_2*Me*), 39.7 (CHCH_2CH), 27.9 (C*Me*$_3$), 26.1 (*C*HMe$_2$), 23.4 and 21.3 (CH*Me*$_2$) [Found (CI): $(M + H)^+$ *m/z* 364.2487, $C_{21}H_{33}NO_4$ requires $(M + H)^+$ 364.2488].

Minor diastereoisomer (by NMR difference): δ_H ($CDCl_3$) 3.68 (s, CO_2*Me*), 1.41 (s, Bu^t); δ_C 80.5, 53.6, 47.9, 47.7, 44.3, 38.6, 23.5, 21.4.

1-*tert*-Butyl 4-methyl (2*R*,3*R*)-3-(aminomethyl)-2-isobutylbutanedioate, formate salt 13

A mixture of the Michael adducts **11/12** (1.00 g, 2.75 mmol) and 10% Pd–C (0.5 g) in a 1 M solution of formic acid in methanol (60 ml) was stirred for 45 min, filtered and the catalyst washed with methanol. The filtrate was diluted with toluene (50 ml) and evaporated under reduced pressure to leave a gum which was triturated with ethyl acetate to furnish a white solid, 0.90 g (100%), as a 9:1 mixture of diastereomers. Recrystallisation of the solid (0.80 g) from ethyl acetate gave the major diastereomer **13** (0.584 g, 74%; >98% de), mp 116 °C; $[\alpha]_D^{20}$ +7.6 (*c* 0.015 in MeOH) (Found: C, 56.0; H, 9.2; N, 4.3. $C_{15}H_{29}NO_6 \cdot 0.1H_2O$ requires C, 56.1; H, 9.2; N, 4.4%); ν_{max} (neat)/cm^{-1} 1732, 1716, 1557; δ_H (MeOD) 8.50 (1H, br s, *H*CO_2^-), 3.78 (3H, s, CO_2*Me*), 3.27–2.88 (4H, m, NCH_2C*H*

and C*H*CO_2Bu^t), 1.74–1.51 (2H, m, C*H*C*H*Me_2), 1.44 (9H, s, Bu^t), 1.26–1.13 (1H, m, C*H*CHMe_2), 0.94 and 0.925 (each 3H, d, *J* 6.5, CH*Me_2*); δ_C (MeOD) 173.6 and 173.5 (2 × *C*O), 83.0 (*C*Me_3), 53.0 and 46.5 (*C*CO_2Bu^t and *C*CO_2Me), 39.5 and 38.8 (2 × *C*H_2), 28.2 (C*Me_3*), 27.3 (*C*HMe_2), 23.1 and 22.1 (CH*Me_2*) [Found (CI): $(M + H)^+$ *m*/*z* 274.2023, $C_{15}H_{29}NO_6$ requires $(M + H)^+$ 274.2018].

1-*tert*-Butyl 4-methyl (2*R*,3*R*)-3-(aminomethyl)-2-isobutylbutanedioate 15

The formate salt **13** (114 mg, 0.357 mmol) was partitioned between ethyl acetate (10 ml) and saturated aqueous sodium hydrogen carbonate (2 ml). The organic layer was separated, washed with water (1 ml) and dried ($MgSO_4$). Evaporation of the solvent gave the free amine **15** (85 mg, 90%) as an oil, $[\alpha]_D^{20}$ +7.7 (*c* 0.011 in MeOH) (Found: C, 61.2; H, 9.95; N, 5.00. $C_{14}H_{27}NO_4$ requires C, 61.5; H, 9.95; N, 5.15%); ν_{max} (film)/cm^{-1} 3620, 3394, 3330, 1747, 1700; δ_H ($CDCl_3$) 3.75 (3H, s, CO_2*Me*), 3.00–2.60 (4H, m, C*H_2*N, C*H*CO_2Bu^t and C*H*CO_2Me), 1.71–1.49 (2H, m, C*H*Me_2 and C*H*H), 1.45 (9H, s, Bu^t), 1.41 (2H, br s, N*H_2*), 1.05 (1H, ddd, *J* 12.9, 9.5, 3.5, CH*H*), 0.90 and 0.885 (each 3H, d, *J* 6.5, CH*Me_2*); δ_C ($CDCl_3$) 174.0 and 173.3 (2 × CO), 81.0 (*C*Me_3), 51.9 and 51.7 (*C*CO_2Bu^t and *C*CO_2Me), 44.5 (CO_2*Me*), 42.2 (*C*H_2N), 39.8 (*C*H_2CHMe_2), 27.9 (Bu^t), 26.2 (*C*HMe_2), 23.4 and 21.3 (CH*Me_2*) [Found (CI): $(M + H)^+$ *m*/*z* 274.2020, $C_{14}H_{28}NO_4$ requires $(M + H)^+$ 274.2018].

1-*tert*-Butyl 4-methyl (2*R*,3*R*)-3-(aminomethyl)-2-isobutylbutanedioate, (1*S*)-10-camphorsulfonate salt 16

(1*S*)-10-Camphorsulfonic acid (168 mg, 0.722 mmol) was added to a solution of the free amine **15** (197 mg, 0.722 mmol) in ethyl acetate (6 ml) and the solvent allowed to evaporate slowly over several days, affording white crystals of the (1*S*)-10-camphorsulfonate salt **16**, mp 107–109 °C; $[\alpha]_D^{20}$ +22.7 (*c* 0.0196 in MeOH) (Found: C, 56.9; H, 8.5; N, 2.8. $C_{24}H_{43}NO_8S$ requires C, 57.0; H, 8.6; N, 2.8%); ν_{max} (neat)/cm^{-1} 3107, 1736, 1725, 1208, 1149; δ_H ($CDCl_3$) (ammonium fragment) 7.74 (3H, br s, NH_3^+), 3.78 (3H, s, CO_2*Me*), 3.35–3.11 and 3.02–2.94 (4H, m, NC*H_2*, C*H*CO_2Bu^t and C*H*CO_2Me), 1.77–1.60 (2H, m, C*H*Me_2 and C*H*HCHMe_2), 1.41 (9H, s, Bu^t), 1.36–1.24 (1H, m, CH*H*-CHMe_2), 0.93–0.89 (6H, m, CH*Me_2*); [(1*S*)-10-camphorsulfonate fragment] 3.24 (1H, d, *J* 14.6), 2.77 (1H, d, *J* 14.6), 2.60–2.48 (1H, m), 2.35–2.24 (1H, m), 2.04–1.97 (2H, m), 1.90 (1H, d, *J* 18.2), 1.77–1.60 (1H, m), 1.41 (1H, obscured m), 1.05 (3H, s), 0.82 (3H, s); δ_C ($CDCl_3$) 217.5, 172.8, 172.1, 81.5, 58.3, 52.5, 48.0, 47.3, 44.2, 43.9, 42.8, 42.6, 37.9, 37.5, 27.9, 26.9, 25.9, 24.5, 22.6, 22.0, 19.8, 19.7.

Crystal data for 16

$C_{24}H_{43}NO_8S$, $M = 505.67$, monoclinic, space group $P2_1$, $a = 15.064$ (2), $b = 6.245$ (1), $c = 16.603$ (2) Å, $\beta = 115.99$ (1)°, $V = 1403.9$ D^3 (by the least squares refinement of the setting angles for 24 automatically centered reflections), $Z = 2$, $D_c = 1.20$ g cm^{-3}, $F(000) = 548$, $\mu = 13.5$ cm^{-1}. Crystal dimensions 0.25 × 0.31 × 0.53 mm.

Data collection and processing. Enraf-Nonius CAD4 diffractometer, graphite monochromated Cu-Kα radiation (λ = 1.54180 Å) ω-2θ scan mode with the ω scan width (0.81 + 0.15tanθ)°; 4865 reflections measured (2 > θ > 70°, 0, *h*, ±*k*, l), 2929 unique (merging $R = 0.041$), giving 2819 with $I > 3\sigma(I)$.

Structure analysis and refinement. Direct methods. Full-matrix least-squares refinement with all non-hydrogen atoms in anisotropic approximation (319 variables, observations/variables = 8.8). All hydrogen atoms were located in the difference-Fourier maps and included in the final refinement with fixed positional and thermal parameters (only the atoms attached to the nitrogen were refined isotropically). Chebyshev[14] weighting scheme with parameters 6.39, 2.43 and 2.93 was applied. Corrections for Lorentz and polarisation effects as well as empirical absorption correction based on azimuthal scan data[15] were applied. In the final stage of refinement the data were corrected for the effect of isotropic extinction. Flack test[16] was applied for the absolute configuration determinations (enantiopole parameter was refined to 0.004 using 4529 reflections with the non-averaged Friedel equivalents). Final *R* and *R*′ values are 0.035 and 0.039. Maximum and minimum peaks in the final difference synthesis are 0.18 and −0.30 e Å^{-3}. All crystallographic calculations were carried out using the CRYSTALS[17] program package on a Micro VAX 3800 computer. Neutral atom scattering factors were taken from the usual sources.[18]†

(2*R*,3*R*)- and (2*R*,3*S*)-1-*tert*-Butyl 4-methyl 2-isobutyl-3-({[(1*R*)-1-phenylethyl]amino}methyl)butanedioate 19/20

(*R*)-1-Phenylethylamine (646 µl, 5 mmol) was added to a stirred solution of the methylenebutanedioate **10** (256 mg, 1 mmol) in methanol (1.3 ml), under an argon atmosphere. After 120 h the solvent was evaporated and a solution of the residue in ethyl acetate (10 ml) was washed with aqueous citric acid (1 M; 5 ml; 2 ml) then water (5 ml), saturated aqueous sodium hydrogen carbonate (5 ml) and saturated aqueous sodium chloride (5 ml). The organic layer was dried ($MgSO_4$) and evaporated to give a 90 : 10 mixture of the Michael adducts **19/20** (344 mg, 91%) as a viscous oil. Chromatography (SiO_2, eluting with 4 : 1 hexane–ethyl acetate) furnished **19** in >99% de, $[\alpha]_D^{20}$ +34.2 (*c* 0.0152 in MeOH) (Found: C, 69.9; H, 9.1; N, 3.7. $C_{22}H_{35}NO_4$ requires C, 70.0; H, 9.3; N, 3.7%); ν_{max} (film)/cm^{-1} 3350, 1732; δ_H ($CDCl_3$) 7.3–7.17 (5H, m, ArH), 3.70 (1H, q, *J* 6.6, PhC*H*Me), 3.70 (3H, s, CO_2*Me*), 2.81–2.45 (4H, m, NC*H_2*, C*H*CO_2Bu^t and C*H*CO_2Me), 1.61–1.40 (3H, m, C*H*Me_2, C*H*HCHMe_2, N*H*), 1.34 (9H, s, Bu^t), 1.30 (3H, d, *J* 6.6, NCH*Me*), 1.08–0.97 (1H, m, CH*H*CHMe_2), 0.85 (6H, d, *J* 6.4, CH*Me_2*); δ_C ($CDCl_3$) 174.3 and 173.3 (2 × CO), 145.6 (quaternary Ar), 128.4, 121.9 and 126.6 (Ar), 80.7 (*C*Me_3), 58.3 and 49.3 (*C*CO_2Bu^t and *C*CO_2Me), 51.6 (Ph*C*N), 47.3 (N*C*H_2), 45.0 (*C*O_2Me), 39.6 (*C*H_2CHMe_2), 27.9 (C*Me_3*), 26.1, 24.4, 23.4 and 21.5 (*C*H*Me_2* and PhCH*Me*); [Found (CI): $(M + H)^+$ *m*/*z* 378.2637, $C_{22}H_{36}NO_4$ requires $(M + H)^+$ 378.2644].

Minor diastereoisomer (by NMR difference): δ_H ($CDCl_3$) 3.695 (CO_2*Me*), 1.43 (Bu^t).

1-*tert*-Butyl 4-methyl (2*R*,3*R*)-3-(aminomethyl)-2-isobutylbutanedioate 15

The Michael adduct **19** was subjected to the hydrogenolysis conditions already described for **11/12**, giving the primary amine **15** (68%) after basification.

(2*R*,3*R*)- and (2*R*,3*S*)-1-*tert*-Butyl 4-methyl 2-isobutyl-3-({[(1*S*)-1-phenylethyl]amino}methyl)butanedioate 21/22

The Michael adducts **21/22** were obtained in an analogous fashion to **19/20** (350 mg, 93%; 88 : 12 mixture of diastereoisomers after chromatography), $[\alpha]_D^{20}$ −37.6 (*c* 0.0205 in MeOH) for an 88 : 12 mixture (Found: C, 69.7; H, 9.3; N, 3.6. $C_{22}H_{35}NO_4$ requires C, 70.0; H, 9.3; N, 3.7%); ν_{max} (film)/cm^{-1} 3350, 1731; δ_H ($CDCl_3$) 7.34–7.17 (5H, m, ArH), 3.73 (1H, q, *J* 6.6, PhC*H*N), 3.71 (3H, s, CO_2*Me*), 2.82–2.48 (4H, m, NC*H_2*C*H* and C*H*CO_2Bu^t), 1.65–1.37 (3H, m, C*H*Me_2, CH*H*-CHMe_2 and N*H*), 1.32 (9H, s, Bu^t), 1.29 (3H, d, *J* 6.6, NCH*Me*), 1.01 (1H, m, C*H*HCHMe_2), 0.85 (6H, d, *J* 6.5, CH*Me_2*); δ_C ($CDCl_3$) 174.2 and 173.2 (2 × CO), 145.3 (quaternary Ar), 128.4, 126.8, 126.4 (Ar), 80.8 (*C*Me_3), 57.7 and 49.1

† CCDC reference 207/375.

(CCO_2Bu^t and CCO_2Me), 51.6 (Ph*C*N), 47.1 (NCH_2), 45.1 (CO_2Me), 39.8 (CH_2CHMe_2), 27.9 (CMe_3), 26.1, 24.7, 23.5 and 21.4 ($CHMe_2$ and PhCH*Me*) [Found (CI): $(M + H)^+$ *m*/*z* 378.2643, $C_{22}H_{36}NO_4$ requires $(M + H)^+$ 378.2644].

Minor diastereoisomer (by NMR difference): δ_H ($CDCl_3$) 3.67 (CO_2Me), 1.37 (Bu^t); δ_C ($CDCl_3$) 80.6, 58.4, 48.2, 46.2, 44.3, 38.4, 26.2, 24.5, 21.5.

1-*tert*-Butyl 4-methyl (2*R*,3*R*)-3-(aminomethyl)-2-isobutylbutanedioate 15

The 88 : 12 mixture of **21** and **22** was subjected to the hydrogenolysis conditions already described for **11/12**, giving an 88 : 12 mixture (93%), with the primary amine **15** as the major diastereoisomer.

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