Asymmetric Synthesis of *syn*-α-Alkyl-β-amino Acids

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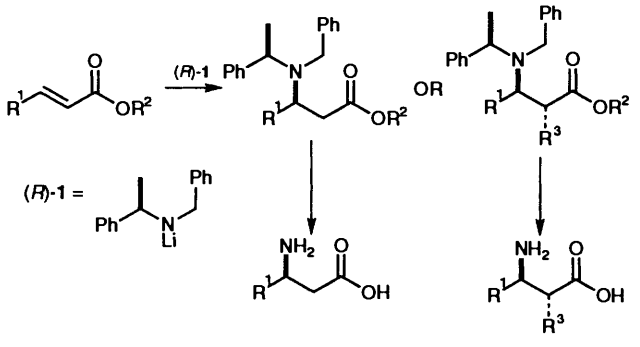
An investigation into the reactivity of the highly stereoselective conjugate nucleophile lithium *N*-benzyl-*N*-α-methylbenzylamide **1** with α-alkyl-α,β-unsaturated esters has led to the development of a versatile asymmetric synthesis of *syn*-α-alkyl-β-amino acids. By performing the conjugate additions in toluene and diluting the reaction mixtures with THF prior to quenching of the reactions with the hindered acid, 2,6-di-*tert*-butylphenol **13**, the product *syn*-α-alkyl-β-amino esters may be generated in good yield and with excellent stereocontrol. Several examples illustrate the ease with which these products may be debenzylated and hydrolysed to afford homochiral *syn*-α-alkyl-β-amino acids.

The generation of stereogenic centres α to a carbonyl group by diastereoselective conjugate additions–protonations has been investigated by several groups. For example, the conjugate addition of a bulky silyl cuprate reagent to a variety of α-alkyl-α,β-unsaturated esters has been shown to proceed with high levels of *syn* selectivity.[1] Excellent diastereocontrol has also been proclaimed for the protonation of lithium enolates generated by the conjugate addition of dithioacetal based lithium carbanions.[2] Chiral conjugate acceptors such as an α-substituted alkenoyl sultam[3] have also been employed to prepare homochiral products by this approach. A C_2-symmetric bis(α-methylbenzyl)amino group has been used to control the formation of an α-alkyl-β-amino ester by the conjugate addition of an enolate to an α-substituted acrylate ester.[4] We have previously reported highly stereoselective syntheses of β-amino acids[5] and *anti*-α-alkyl-β-amino acids[6] *via* the conjugate addition of the homochiral lithium amide, lithium *N*-benzyl-*N*-α-methylbenzylamide **1**, to simple α,β-unsaturated esters (Scheme 1).

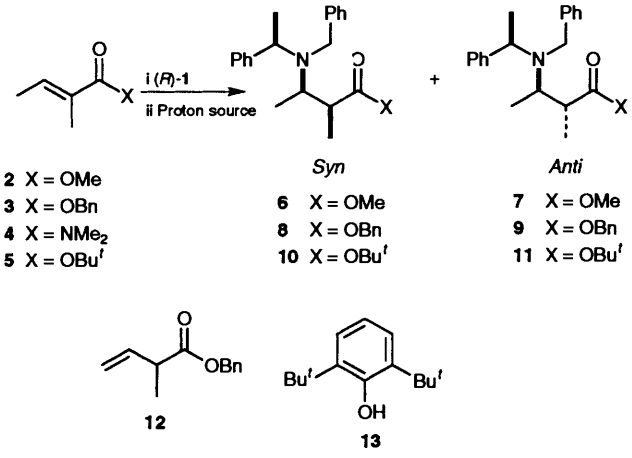


Scheme 1

In this report, we describe a highly selective preparation of homochiral *syn*-α-alkyl-β-amino acids *via* the conjugate addition of the homochiral lithium amide **1**, to α-alkyl-α,β-unsaturated esters. Part of this work has been previously communicated.[7]

Results and Discussion

Our preliminary investigations involved the conjugate addition of (*R*)-**1** to methyl (*E*)-2-methylbut-2-enoate **2** (Scheme 2, Table 1, runs 1–5). THF was initially selected as the reaction solvent since it had previously given satisfactory results for analogous conjugate additions to crotonate[5] and cinnamate[7] esters. However, the presence of an α-methyl substituent on the conjugate acceptor was observed to exert a deleterious effect on the reaction yield for additions to the (*E*)-2-methylbut-2-enoate



Scheme 2

acceptor, with the conjugate adducts **6** and **7** isolated in only 20–40%. The products **6** and **7** were identified as C-2 epimers since the same two diastereoisomers were generated by tandem and stepwise conjugate additions–methylations with methyl crotonate.[6] These early results showed a promising protonation selectivity in favour of the *syn*-α-alkyl diastereoisomer, indicating that protonation shares the same diastereofacial preference as the corresponding alkylations described elsewhere.[6] No C-3 epimeric products derived from lithium amide attack at the disfavoured face of the conjugate acceptor were seen in any of the additions described in this article. In the case of additions to compound **2**, no side products were in evidence upon reaction work-up, giving no clue as to the cause of the poor yields. That no improvement in yield was engendered by the use of 20 equiv. of the lithium amide (*R*)-**1** implied that acceptor polymerization was not the problem; this view was supported when an excess of acceptor **2** was recovered from the run involving a deficiency of (*R*)-**1**. Other typical side reactions known to sometimes compromise lithium amide conjugate addition yields include γ-deprotonation and 1,2-attack.[8] With these possibilities in mind, several alternative conjugate acceptors were investigated in an effort to optimize both addition yield and protonation selectivity.

It was hoped that the reduced volatility of methyl (*E*)-2-methylcinnamate **17** would render any side products more conspicuous. In addition, the absence of γ-protons ruled out any chance of γ-deprotonation. When compound **17** was submitted to the standard conjugate addition procedure (Scheme 4, Table 3, runs 1 and 2), the adduct diastereoisomers **21** and **22** were obtained in slightly augmented yield. The use of the hindered

Table 1 Conjugate additions of (*R*)-**1** to (*E*)-2-methylbut-2-enoate acceptors

Run	Acceptor	Solvent	Proton source	*anti*:*syn* Selectivity	Yield (%)
1	**2**	THF	AcOH	**6**:**7** = 6:1	21
2	**2**	THF	pH 7 Buffer	**6**:**7** = 10:1	23
3[a]	**2**	THF	pH 7 Buffer	**6**:**7** = 10:1	23
4[b]	**2**	THF	pH 7 Buffer	**6**:**7** = 10:1	20[c]
5	**2**	THF	**13**	**6**:**7** = 10:1	40
6	**3**	THF	pH 7 Buffer	**8**:**9** > 10:1	11[d]
7	**4**	THF	pH 7 Buffer	—	0
8	**5**	THF	pH 7 Buffer	**10**:**11** = 15:1	43
9	**5**	Toluene	Bu^{t}OH	**10**:**11** = 1.5:1	78
10	**5**	Toluene	pH 7 Buffer	**10**:**11** = 4:1	70
11	**5**	Toluene–THF	pH 7 Buffer	**10**:**11** = 18:1	75
12	**5**	Toluene–THF	**13**	**10**:**11** > 99:1	72

[a] 20 Eq. (*R*)-**1**. [b] 0.5 Eq. (*R*)-**1**. [c] Based on (*R*)-**1**, excess **2** detected in crude product. [d] Side products **12** and benzyl alcohol also formed.

Table 2 Tandem addition–alkylation of (*R*)-**1** with *tert*-butyl (*E*)-2-methylbut-2-enoate **5**

RX	Solvent	*anti*:*syn* Selectivity	Yield (%)
MeI	Toluene–THF	—	50
BnBr	Toluene–THF	**15**:**16** > 10:1	56
EtI	Toluene–THF	—	0

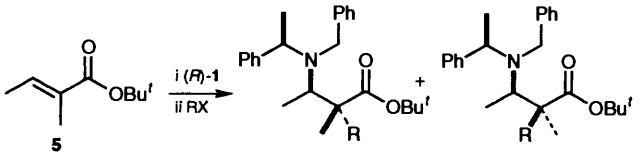
acid 2,6-di-*tert*-butylphenol **13** as the proton source in this case resulted in an excellent diastereoselection for the *syn* C-2 epimer **21**.

More conclusive proof for the rival operation of γ-deprotonation of the (*E*)-2-methylbut-2-enoate acceptors was forthcoming when benzyl ester **3** was employed as the conjugate acceptor (Scheme 2, Table 1, run 6). As well as a low yield of the *syn* adduct **8**, also identified among the products of this reaction were benzyl alcohol, recovered ester **3** and the deconjugated ester **12**. The formation of compound **12** validated the conjecture that γ-deprotonation was partly responsible for the low conjugate addition yields recorded with these (*E*)-2-methylbut-2-enoate acceptors. The observation of benzyl alcohol was suggestive that either 1,2-attack at the carbonyl group had occurred, or that an enolate intermediate had decomposed to a ketene.

Conjugate addition to the *N*,*N*-dimethyl amide **4** was attempted next in the belief that 1,2-attack would be less likely with this acceptor (Scheme 2, Table 1, run 7). However, no trace of any addition products was witnessed in this experiment. The unreactivity of the amide **4** may be tentatively attributed to the severe allylic strain between the C-2 methyl group and the *N*-methyl group *anti* to the carbonyl which would arise in the s-*cis* conformation believed necessary for conjugate addition to occur.[9]

A second option for reducing any 1,2-attack entailed the reaction of *tert*-butyl ester substrates. Conjugate addition to the *tert*-butyl ester **5** was immediately rewarded with both yield and selectivity enhancements (Scheme 2, Table 1, run 8) in comparison with the corresponding methyl ester reactions. Moreover, further improvements were achieved by a judicious choice of solvent and quenching agent. The altered aggregation properties of lithium amides in hydrocarbon solvents[10] may be of some relevance to the dramatic increase in reaction yield observed when the addition was performed in toluene (Scheme 2, Table 1, runs 9 and 10). Unfortunately, this change was mirrored by an equally striking deterioration in the protonation selectivity. However, it was possible to capitalize on the individual assets of the two solvent systems by performing the conjugate addition in toluene, and then diluting the reaction medium with a greater volume of THF before quenching with pH 7 buffer solution (Scheme 2, Table 1, run 11). This afforded the *syn* adduct **10** in good yield with full restoration of the stereocontrol observed in the neat THF reaction. The concluding optimization step involved quenching the addition with the hindered phenol **13**, which elevated the protonation selectivity to the limits of ^{1}H NMR detection.

It was of interest to quench these additions with alkyl halides, since this would generate quaternary stereogenic centres. Consequently, conjugate additions of (*R*)-**1** to the *tert*-butyl ester **5** were quenched with methyl iodide and benzyl bromide (Scheme 3, Table 2). The former reaction produced the C-2



14 R = Me

15 R = Bn **16** R = Bn

Scheme 3

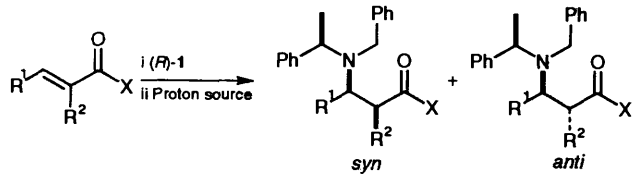
gem-dimethyl adduct **14**, whilst the latter furnished a 10:1 mixture of C-2 epimers **15** and **16**. This revealed the contribution of the conjugate acceptor's α-alkyl substituent to the protonation selectivity, since the corresponding tandem benzylation of *tert*-butyl crotonate was essentially non-selective.[6] The (*E*)-2-methylbut-2-enoate derived enolate proved to be too unreactive to permit alkylation with ethyl iodide.

Three other α,β-unsaturated *tert*-butyl esters were submitted to the optimized reaction conditions of the conjugate addition (Scheme 4, Table 3, runs 3–5). In each case, the *syn* conjugate adduct was generated with excellent stereocontrol and in moderate to good yield.

Conversion of some of the conjugate addition products to the corresponding free amino acids was judged to be a useful exercise, both to underline the value of this stereocontrolled protonation protocol and as a means to establish its sense of asymmetric induction (Scheme 5). A procedure for the selective debenzylation of C-3 aryl conjugate adducts had previously been developed.[5] Consequently, deprotection of the adduct **23** was straightforward and the resultant primary amino ester **29** was hydrolysed to the β-amino acid hydrochloride **31**. Although base-induced cyclization of compound **29** to the *cis* β-lactam **34** was unsuccessful, in contrast to the reaction of its C-2 epimer,[7] the amino acid **31** was dehydrated to form the lactam **34**. This was identified by comparison with literature NMR data;[11] in particular, the 3-H–4-H ^{1}H NMR coupling constant of 5.5 Hz was fully consonant with the assigned *cis* stereochemistry of **34**,

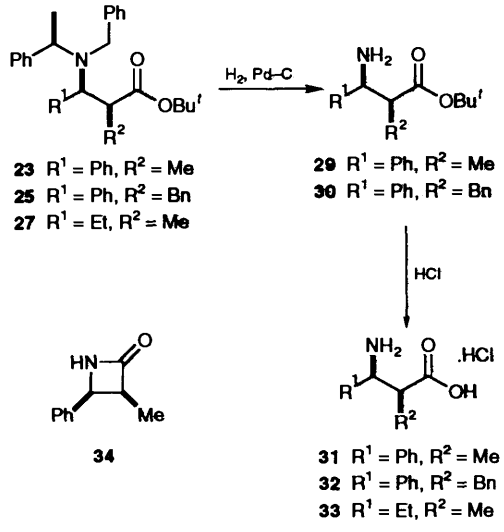
Table 3 Conjugate additions of (*R*)-**1** to various acceptors

Run	Acceptor	Solvent	Proton source	*anti*:*syn* Selectivity	Yield (%)
1	**17**	THF	pH 7 Buffer	**21**:**22** = 15:1	38
2	**17**	THF	**13**	**21**:**22** = 26:1	37
3	**18**	Toluene–THF	**13**	**23**:**24** > 99:1	61
4	**19**	Toluene–THF	**13**	**25**:**26** > 50:1	45
5	**20**	Toluene–THF	**13**	**27**:**28** > 99:1	65



17 R^1 = Ph, R^2 = Me, X = OMe **21** **22**
18 R^1 = Ph, R^2 = Me, X = OBu^t **23** **24**
19 R^1 = Ph, R^2 = Bn, X = OBu^t **25** **26**
20 R^1 = Et, R^2 = Me, X = OBu^t **27** **28**

Scheme 4



23 R^1 = Ph, R^2 = Me
25 R^1 = Ph, R^2 = Bn
27 R^1 = Et, R^2 = Me

29 R^1 = Ph, R^2 = Me
30 R^1 = Ph, R^2 = Bn

34

31 R^1 = Ph, R^2 = Me
32 R^1 = Ph, R^2 = Bn
33 R^1 = Et, R^2 = Me

Scheme 5

and the *syn* stereochemistry attributed to compounds **31**, **29** and **23**.

The α-benzyl adduct **25** was also deprotected, in similar fashion, to generate the free ester **30** and the acid hydrochloride **32**. Characterization of the salt **32** revealed it to be epimeric with the corresponding *anti* amino acid, prepared *via* the highly selective conjugate addition–benzylation of *N*,*N*-dimethyl cinnamide, in which the *anti* C-2–C-3 relative stereochemistry was assigned with the aid of a single crystal X-ray structure determination.[12]

Deprotection of the adduct **27** was performed since the free amino acid (2*S*,3*R*)-2-methyl-3-aminopentanoic acid is a component of several biologically interesting natural products.[13] Debenzylation and hydrolysis furnished the β-amino acid hydrochloride **33**. Comparison of the ^{1}H NMR spectroscopic data for the salt **33** with the literature data [13a,d] established its *syn* relative stereochemistry, while the sign of its specific rotation established its absolute configuration as (2*S*,3*R*). The relative stereochemistry of the (*E*)-2-methylbut-2-enoate conjugate adducts was assigned by analogy with these three deprotected conjugate adducts.

In summary, the results presented above constitute the development of a highly diastereoselective preparation of *syn*-α-alkyl-β-amino acids *via* the conjugate addition–protonation of a simple homochiral lithium amide with α,β-unsaturated esters. The successful application of this methodology to several conjugate acceptor systems clearly demonstrated its generality, and the deprotection of the conjugate adducts, including cyclization to a β-lactam in one case, unambiguously defined the sense of asymmetric induction of the protonation step. The asymmetric synthesis of the natural product (2*S*,3*R*)-3-amino-2-methylpentanoic acid (as its HCl salt) confirmed the *syn* selectivity of the protonation and also revealed the expected sense of asymmetric induction to be operating in the conjugate addition reaction.

Experimental

Specific rotations were determined using a Perkin-Elmer 241 polarimeter with a thermally jacketted 10 cm cell and are given in units of 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed by the Dyson Perrins analytical department. Melting points were recorded on a Gallenkamp hot stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer either as chloroform solutions in 1.0 mm NaCl cells or as Nujol mulls. Unless otherwise stated, all NMR spectra were recorded using samples dissolved in deuteriochloroform and referenced with respect to residual protio solvent as an internal standard. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ 0.00 ppm) and coupling constants are measured in Hz. Three instruments were used to obtain ^{1}H NMR spectra, a Varian Gemini 200 and Bruker AM500 and WH300 spectrometers, with the former two also providing ^{13}C NMR spectra with DEPT editing. Mass spectra were recorded on a VG MASSLAB VG 20-250 instrument. Column chromatography was performed on silica gel (Kieselgel 60) or Dowex 50X8-200 resin. Tetrahydrofuran and toluene were distilled from sodium benzophenone ketyl under an atmosphere of dry nitrogen. Petroleum refers to light petroleum (b.p. 40–60 °C), redistilled before use. Reactions involving lithium amides were performed under an atmosphere of dry nitrogen. In every case, reaction diastereoselectivities were determined by peak integration of the crude reaction products' ^{1}H NMR spectra. All new compounds were fully characterized; data for compounds **6**, **7**, **10**, **11**, **21**, **22–25** and **26** have been reported elsewhere.[6]

The conjugate acceptors **2–5**, **17** and **18** were prepared by standard methods from commercially available (*E*)-2-methylbut-2-enoic acid and (*E*)-2-methylcinnamic acid. The novel compounds **19** and **20** were prepared as follows.

tert-Butyl (E)-2-*Benzylcinnamate* **19**.—A mixture of benzaldehyde (51.0 g, 481 mmol), acetic anhydride (59.0 g, 578 mmol) and sodium hydrocinnamate (3-phenylpropionate) (49.0 g, 284 mmol) was heated at 120 °C for 48 h according to the literature procedure.[14] After concentration, the residue was triturated with boiling water and toluene. The organic phase was separated and allowed to cool slowly to room temp.,

causing crystallization of a brown solid. This solid was filtered off and washed with petroleum and then partitioned between hot chloroform and aq. HCl. The organic phase was separated, dried ($MgSO_4$), filtered and concentrated to give a white solid, which was recrystallized from ethanol to give (*E*)-2-benzylcinnamic acid as a white crystalline solid (9.65 g, 14%). Some of this material (5 g, 21.0 mmol) was converted into the title compound by stirring a solution of it with 2-methylpropene (10 cm^3) and conc. H_2SO_4 in dichloromethane (20 cm^3) for 24 h. The reaction mixture was then partitioned between sat. aq. $NaHCO_3$ and diethyl ether and the organic phase separated, dried ($MgSO_4$), filtered and concentrated to give a crude product which was purified by flash column chromatography on silica gel with petroleum–diethyl ether (40:1) as eluent to give the title compound as a colourless oil (4.58 g, 74%) (Found: C, 81.4; H, 7.8. $C_{20}H_{22}O_2$ requires C, 81.60; H, 7.53%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1700 (C=O) and 1635 (C=C); δ_H(300 MHz; $CDCl_3$) 7.85 (1 H, s, PhC*H*), 7.37–7.18 (10 H, m, Ph), 3.91 (2 H, s, PhCH_2) and 1.40 (9 H, s, CMe_3); δ_C(50 MHz; $CDCl_3$) 167.7 (CO_2), 140.2, 136.0 and 133.0 (PhC_{ipso}, $PhCH_2C$), 140.0 (Ph*C*H), 129.3, 128.7, 128.6, 128.2 and 126.2 (Ph), 80.8 (*C*Me_3), 33.3 (Ph*C*H_2) and 27.9 (*C*Me_3); *m/z* 295 (MH^+, 10%) and 256 (100).

tert-*Butyl* (E)-2-*Methylpent*-2-*enoate* **20**.—To a solution of lithium diisopropylamine (LDA) (127 mmol) in THF (150 cm^3) at −78 °C was added dropwise by cannula a solution of *tert*-butyl propionate (15.0 g, 115 mmol) in THF (15 cm^3). After 1 h, a solution of propionaldehyde (10.8 cm^3, 150 mmol) in THF (10 cm^3) was also added dropwise by cannula to the solution. The reaction was quenched after 2 h at −78 °C with sat. aq. NH_4Cl and partitioned between brine and diethyl ether. The organic phase was separated, dried ($MgSO_4$), filtered and cautiously evaporated to give a colourless oil (26.2 g). This material (23.6 g, 90%), was dissolved in dichloromethane–triethylamine (1:1) (200 cm^3) and the solution cooled to 0 °C. A solution of methanesulfonyl chloride (14.2 g, 124 mmol) in dichloromethane (20 cm^3) was then added dropwise to the reaction mixture which was stirred at room temp. for 2 h. Evaporation of solvent under reduced pressure gave a residue which was filtered through a plug of Celite, washing with diethyl ether. Evaporation of the filtrate gave an orange oil (27.2 g), a portion of which (25 g, 92%) was dissolved in THF (100 cm^3) at 0 °C. A solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (15.2 g, 100 mmol) in THF (20 cm^3) was added slowly by cannula to the solution which was then stirred at room temp. for 16 h. The solvent was evaporated and the residue filtered through a plug of silica, washing with petroleum–diethyl ether (2:1). The crude product was purified by flash column chromatography on silica gel with petroleum–diethyl ether (40:1) to give the title compound as a colourless oil (7.61 g, 47% overall) (Found: C, 70.7; H, 11.0. $C_{10}H_{18}O_2$ requires C, 70.55; H, 10.66%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1695 (C=O) and 1650 (C=C); δ_H(300 MHz; $CDCl_3$) 6.65 (1 H, td, *J* 7.4 and 1.4, CH_2CH), 2.17 (2 H, dq, *J* 7.4 and 7.6, CH_2CH), 1.79 (3 H, s, $MeCCO_2$), 1.50 (9 H, s, CMe_3) and 1.05 (3 H, t, *J* 7.6, *Me*CH_2); δ_C(50 MHz; $CDCl_3$) 167.9 (CO_2), 142.8 (CH_2CH), 128.7 ($MeCCO_2$), 79.8 (*C*Me_3), 28.0 (*C*Me_3), 21.8 ($MeCH_2$), 12.9 and 12.0 (*Me*CH_2 and *Me*CCO_2); *m/z* 171 (MH^+, 100%).

Optimized Procedure for Conjugate Additions–Protonations.—(*a*) A solution of (*R*)-(+)-*N*-benzyl-*N*-α-methylbenzylamine[15] (3.2 mmol) in toluene (4 cm^3) was cooled to 0 °C prior to the slow addition of butyllithium (1.6 mol dm^{-3}, 3.0 mmol). The resultant pink solution of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide (*R*)-**1** (3.0 mmol) was stirred for 15 min and then cooled to −78 °C. A toluene (2 cm^3) solution of the requisite conjugate acceptor (2.0 mmol) was then added dropwise to it by syringe. The reaction mixture was stirred for 1 h at −78 °C and then maintained at −30 °C for 2 h, before being recooled to −78 °C. Precooled THF (−78 °C, 20 cm^3) was added swiftly by cannula to the reaction mixture which was then stirred for a further 30 min at −78 °C. Finally, a solution of 2,6-di-*tert*-butylphenol **13** (6.0 mmol) in THF (2 cm^3) was added by syringe to the reaction mixture which was then allowed to warm to room temp. over 30 min. Evaporation of the mixture under reduced pressure left a residue which was partitioned between brine and diethyl ether and the combined organic layers were subsequently dried ($MgSO_4$), filtered and concentrated to furnish the crude conjugate adduct.

Debenzylation Procedure.—(*b*) This procedure was described as (*d*) in the preceding paper.

Hydrolysis Procedure.—(*c*) A solution of the requisite amino ester (0.2 mmol) in trifluoroacetic acid (2 cm^3) was stirred at room temp. for 24 h. Removal of the solvent left a residue which was dissolved in methanol (2 cm^3) and sat. HCl in diethyl ether (2 cm^3). Concentration of this solution afforded the β-amino acid hydrochloride salt as a white solid.

The unoptimized conjugate additions to compounds **2**, **4**, **5** and **17** were performed at −78 °C in the standard manner described previously.[6] The addition of the lithium amide (*R*)-**1** to compound **3** was carried out as follows.

Conjugate Addition of (R)-**1** *to Benzyl* (E)-2-*Methylbut*-2-*enoate* **3**.—A solution of (*R*)-(+)-*N*-benzyl-*N*-α-methylbenzylamine[15] (889 mg, 4.21 mmol) in THF (10 cm^3) at −78 °C was treated with butyllithium (1.6 mol dm^{-3} in hexanes; 3.95 mmol) to give a pink solution of the lithium amide (*R*)-**1**. After 30 min, a solution of compound **3** (500 mg, 2.63 mmol) in THF (2 cm^3) was added to the reaction mixture which was then stirred for 2 h at −78 °C and for 1 h at −30 °C, before being quenched with pH 7 aqueous phosphate buffer. Work-up as described in procedure (*a*) gave a crude product which was partially purified by flash column chromatography on silica gel. First eluted with petroleum–dichloromethane (1:1) as eluent was a fraction (202 mg) shown by ^1H NMR spectroscopy to comprise of the *syn* adduct (2*S*,3*R*,α*R*)-**8** (11%), recovered starting material **3** (8%) and benzyl 2-methylbut-3-enoate[16] **12** (8%). A second fraction (185 mg) was eluted with dichloromethane, but ^1H NMR spectroscopy revealed it to consist of a complex mixture of components. A final fraction (812 mg) was eluted with diethyl ether and shown to contain recovered secondary amine and benzyl alcohol (17%) by ^1H NMR spectroscopy.

Pure samples of (2*S*,3*R*,α*R*)-**8** and (2*R*,3*R*,α*R*)-**9** were prepared by the tandem additions–methylations of (*R*)-**1** (4.26 mmol) with benzyl crotonate (300 mg, 1.70 mmol) following standard procedures reported elsewhere.[6] Purification of the crude product, which contained the *syn* and *anti* methylated conjugate adducts (2*S*,3*R*,α*R*)-**8** and (2*R*,3*R*,α*R*)-**9** in the ratio of 1:1.3, was accomplished by flash column chromatography on silica gel with a dichloromethane–petroleum (3:2) eluent. First eluted was the *syn* adduct (2*S*,3*R*,α*R*)-**8** (97 mg, 14%), followed by the *anti* diastereoisomer (2*R*,3*R*,α*R*)-**9** (115 mg, 17%), both as colourless oils.

Benzyl (2S,3R,αR)-2-*methyl*-3-(N-*benzyl*-N-α-*methylbenzylamino*)*butanoate* (2S,3R,αR)-**8**. $[\alpha]_D^{20}$ −10.1 (*c* 0.87 in $CHCl_3$) (Found: C, 80.8; H, 8.1; N, 3.2. $C_{27}H_{31}NO_2$ requires C, 80.76; H, 7.78; N, 3.49%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 (C=O); δ_H(300 MHz; $CDCl_3$) 7.38–7.20 (15 H, m, Ph), 5.04 (2 H, s, PhCH_2O), 3.96 (1 H, q, *J* 6.9, PhC*H*N), 3.79 and 3.68 (2 H, AB system, J_{AB} 14.0, PhCH_2N), 2.99 (1 H, dq, *J* 6.7 and 9.5, MeC*H*N), 2.45 (1 H, dq, *J* 6.9 and 9.5, CHCO), 1.39 (3 H, d, *J* 6.9, *Me*CH), 1.10 (3 H, d, *J* 6.7, *Me*CH) and 0.90 (3 H, d, *J* 6.9, *Me*CH); δ_C(50 MHz; $CDCl_3$) 176.6 (CO_2), 144.4, 141.3 and 136.4 (PhC_{ipso}),

129.2, 128.8, 128.5, 128.4, 128.1, 127.1 and 126.9 (Ph), 66.0 (CH_2O), 56.8 and 54.2 (CHN), 50.2 (CH_2N), 45.4 (*C*HCO), 15.9, 15.5 and 14.4 (*Me*CH); *m/z* 402 (MH^+, 100%), 238 (95, $MH^+ - MeCH_2CO_2CH_2Ph$), 134 (75, $MeCH{=}NH^+CH_2Ph$), 105 (45, $PhCHMe^+$) and 91 (70, $PhCH_2^+$).

Benzyl (2R,3R,αR)-3-(N-*benzyl*-N-α-*methylbenzylamino*)-2-*methylbutyrate* (2R,3R,αR)-**9**. $[\alpha]_D^{20}$ +0.7 (*c* 1.36 in $CHCl_3$) (Found: C, 81.0; H, 8.1; N, 3.4. $C_{27}H_{31}NO_2$ requires C, 80.76; H, 7.78; N, 3.49%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1725 (C=O); δ_H(300 MHz; $CDCl_3$) 7.41–7.16 (15 H, m, Ph), 5.02 and 4.83 (2 H, AB system, J_{AB} 12.5, $PhCH_2O$), 3.98 (1 H, q, *J* 6.9, PhC*H*N), 3.78 and 3.66 (2 H, AB system, J_{AB} 14.2, $PhCH_2N$), 3.30 (1 H, dq, *J* 6.8 and 9.5, MeC*H*N), 2.57 (1 H, dq, *J* 7.0 and 9.5, CHCO), 1.37 (3 H, d, *J* 7.0, *Me*CH), 1.07 (3 H, d, *J* 6.8, *Me*CH) and 1.01 (3 H, d, *J* 6.9, *Me*CH); δ_C(50 MHz; $CDCl_3$) 176.0 (CO_2), 144.4, 141.5 and 136.6 (PhC_{ipso}), 129.2, 128.7, 128.3, 128.2, 128.0, 126.9 and 126.8 (Ph), 65.9 (CH_2O), 57.8 and 55.4 (CHN), 49.9 (CH_2N), 45.6 (*C*HCO), 15.8, 14.8 and 13.9 (*Me*CH); *m/z* 402 (MH^+, 90%), 238 (100, $MH^+ - MeCH_2CO_2CH_2Ph$), 134 (65, $MeCH{=}NH^+CH_2Ph$), 105 (45, $PhCHMe^+$) and 91 (60, $PhCH_2^+$).

Optimized Conjugate Addition of (R)-**1** *to* tert-*Butyl* (E)-2-*methylbut-2-enoate*.—The conjugate addition of the lithium amide (*R*)-**1** (0.96 mmol) to *tert*-butyl (*E*)-2-*methylbut-2-enoate* **5** (100 mg, 0.64 mmol) was carried out according to procedure (*a*) Purification of the crude product, which contained (2*S*,3*R*,α*R*)-**10** in >98% d.e., by flash column chromatography on silica gel with petrol–diethyl ether (10:1) as eluent allowed the isolation of (2*S*,3*R*,α*R*)-**10** as a colourless oil (169 mg, 72%), after elution of excess of phenol **13**.

Tandem Addition–Methylation of Compound **5**.—The conjugate addition of (*R*)-**1** (0.96 mmol) to compound **5** (100 mg, 0.64 mmol) was carried out according to procedure (*a*) except that the reaction was quenched by the addition of methyl iodide (0.20 cm^3, 3.2 mmol) to the reaction mixture before it was allowed to warm to room temp. overnight. Work-up followed by flash column chromatography of the crude product on silica gel with petroleum–diethyl ether (20:1) as eluent allowed isolation of a mixture of the adducts (3*R*,α*R*)-**14** and (2*S*,3*R*,α*R*)-**10** (137 mg, 8:1, 50% yield of compound **14**). Crystallization of this oil on storage for several months followed by washing with heptane afforded pure (3R,α*R*)-**14** as a white crystalline solid.

tert-*Butyl* (3R,αR)-3-(N-*benzyl*-N-α-*methylbenzylamino*)-2,2-*dimethylbutyrate* (3R,αR)-**14**. $[\alpha]_D^{25}$ −20.9 (*c* 1.09 in $CHCl_3$); m.p. 86–87 °C (Found: C, 78.7; H, 9.35; N, 3.6. $C_{25}H_{35}NO_2$ requires C, 78.70; H, 9.25; N, 3.67%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1710 (C=O); δ_H(300 MHz; $CDCl_3$) 7.55–7.19 (10 H, m, Ph), 3.92 (1 H, q, *J* 7.0, PhC*H*N), 3.91 and 3.71 (2 H, AB system, J_{AB} 14.6, $PhCH_2N$), 3.28 (1 H, q, *J* 6.9, MeC*H*N), 1.41 (9 H, s, CMe_3), 1.34 (3 H, d, *J* 7.0, *Me*CH), 1.11 (3 H, d, *J* 6.9, *Me*CH), 0.95 (3 H, s, $MeCCO_2$) and 0.59 (3 H, s, $MeCCO_2$); δ_C(50 MHz; $CDCl_3$) 177.7 (CO_2), 143.8 and 142.1 (PhC_{ipso}), 129.1, 128.9, 128.5, 127.9 and 127.0 (Ph), 79.6 (*C*Me$_3$), 58.3 and 55.6 (CHN), 52.1 (CH_2N), 49.0 (CHCCO), 27.9 (C*Me*$_3$), 24.3, 19.5, 13.0 and 12.0 (Me); *m/z* 382 (MH^+, 100%), 238 (75, $MH^+ - Me_2CHCO_2Bu^t$), 134 (50, $MeCH{=}NH^+CH_2Ph$), 105 (25, $PhCHMe^+$) and 91 (20, $PhCH_2^+$).

Tandem Addition–Benzylation of Compound **5**.—The conjugate addition of (*R*)-**1** (0.96 mmol) to compound **5** (100 mg, 0.64 mmol) was carried out according to procedure (*a*) except that the reaction was quenched by the addition of benzyl bromide (0.23 cm^3, 1.9 mmol) to the reaction mixture which was then allowed to warm to room temp. overnight before work-up. Flash column chromatography of the crude product, which contained (2*R*,3*R*,α*R*)-**15** in 82% d.e., on silica gel with petroleum–diethyl ether (25:1) as eluent allowed isolation of (2*R*,3*R*,α*R*)-**15** in diastereoisomerically pure form as a colourless oil (164 mg, 56%).

tert-*Butyl*(2R,3R,αR)-2-*benzyl*-3-(N-*benzyl*-N-α-*methylbenzylamino*)-2-*methylbutyrate* (2R,3R,αR)-**15**. $[\alpha]_D^{25}$ +26.6 (*c* 1.00 in $CHCl_3$) (Found: C, 81.5; H, 8.3; N, 3.3. $C_{31}H_{39}NO_2$ requires C, 81.36; H, 8.59; N, 3.06%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1710 (C=O); δ_H(300 MHz; $CDCl_3$) 7.62–7.09 (15 H, m, Ph), 3.99 and 3.78 (2 H, AB system, J_{AB} 14.4, $PhCH_2N$), 3.96 (1 H, q, *J* 6.8, PhC*H*N), 3.39 (1 H, q, *J* 6.9, MeC*H*N), 2.61 and 1.79 (2 H, AB system, J_{AB} 13.6, $PhCH_2C$), 1.42 (3 H, d, *J* 6.8, *Me*CH), 1.36 (9 H, s, CMe_3), 1.22 (3 H, d, *J* 6.9, *Me*CH) and 0.89 (3 H, s, $MeCCO_2$); δ_C(50 MHz; $CDCl_3$) 176.2 (CO_2), 143.7, 141.8 and 139.4 (PhC_{ipso}), 130.5, 129.2, 128.9, 128.7, 128.1, 127.8, 127.2 and 126.1 (Ph), 80.2 (*C*Me$_3$), 57.7 and 55.8 (CHN), 54.0 (CHCCO), 52.6 (CH_2N), 43.2 (CH_2C), 27.8 (C*Me*$_3$), 15.1, 13.3 and 11.2 (Me); *m/z* 458 (MH^+, 70%), 238 (100, $MH^+ - PhCHMeCO_2Bu^t$), 134 (45, $MeCH{=}NH^+CH_2Ph$), 105 (20, $PhCHMe^+$) and 91 (25, $PhCH_2^+$).

Conjugate Addition of (R)-**1** *to* tert-*Butyl* (E)-2-*Methylcinnamate* **18**.—The conjugate addition of (*R*)-**1** (3.30 mmol) to *tert*-butyl (*E*)-2-methylcinnamate **18** (300 mg, 1.38 mmol) was carried out according to procedure (*a*), except that the reaction was allowed 4 h at −30 °C. Purification of the crude product, which contained (2*S*,3*S*,α*R*)-**23** in >98% d.e., by flash column chromatography on silica gel with petroleum–diethyl ether (10:1) allowed isolation of (2*S*,3*S*,α*R*)-**23** as a colourless oil (361 mg, 61%), after elution of excess of phenol **13**.

Conjugate Addition of (R)-**1** *to* tert-*Butyl* (E)-2-*Benzylcinnamate* **19**.—The conjugate addition of (*R*)-**1** (12.8 mmol) to *tert*-butyl (*E*)-2-*benzylcinnamate* **19** (2.50 g, 8.50 mmol) was carried out according to procedure (*a*). Purification of the crude product, which contained (2*S*,3*S*,α*R*)-**25** in ≥96% d.e., by flash column chromatography on silica gel with petroleum–diethyl ether (25:1) as eluent allowed isolation of (2*S*,3*S*,α*R*)-**25** as a colourless oil (1.93 g, 45%), after elution of the excess of phenol **13**.

Conjugate Addition of (R)-**1** *to* tert-*Butyl* (E)-2-*Methylpent-2-enoate* **20**.—The conjugate addition of (*R*)-**1** (17.6 mmol) to *tert*-butyl (*E*)-2-methylpent-2-enoate **20** (1.50 g, 8.80 mmol) was carried out according to procedure (*a*). Purification of the crude product, which contained (2*S*,3*R*,α*R*)-**27** in >98% d.e., by flash column chromatography on silica gel with petroleum–diethyl ether (20:1) as eluent allowed isolation of (2*S*,3*R*,α*R*)-**27** as a colourless oil (2.18 g, 65%), after elution of the excess phenol **13**.

tert-*Butyl* (2S,3R,αR)-3-(N-*benzyl*-N-α-*methylbenzylamino*)-2-*methylpentanoate* (2S,3R,αR)-**27**. $[\alpha]_D^{20}$ +46.1 (*c* 1.41 in $CHCl_3$) (Found: C, 78.6; H, 9.2; N, 3.9. $C_{25}H_{35}NO_2$ requires C, 78.70; H, 9.25; N, 3.67%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1715 (C=O); δ_H(500 MHz; $CDCl_3$) 7.41–7.20 (10 H, m, Ph), 4.02 (1 H, q, *J* 6.9, PhC*H*N), 3.93 and 3.82 (2 H, AB system, J_{AB} 15.0, $PhCH_2N$), 2.73 (1 H, td, *J* 4.7 and 7.2, CH_2CHN), 2.39 (1 H, dq, *J* 7.1 and 7.2, $CHCO_2$), 1.63–1.45 (2 H, m, $MeCH_2$), 1.41 (9 H, s, CMe_3), 1.32 (3 H, d, *J* 6.9, *Me*CH), 0.96 (3 H, t, *J* 7.4, *Me*CH_2) and 0.90 (3 H, d, *J* 7.1, *Me*CH); δ_C(50 MHz; $CDCl_3$) 176.2 (CO_2), 145.0 and 142.7 (PhC_{ipso}), 128.5, 128.3 and 128.2 (Ph), 127.0 and 126.6 (PhC_{para}), 79.9 (*C*Me$_3$), 62.4 and 59.2 (CHN), 51.0 (CH_2N), 44.1 (*C*HCO), 27.9 (C*Me*$_3$), 23.4 (CH_2CHN), 19.2, 16.8 and 12.8 (Me); *m/z* 382 (MH^+, 55%), 252 (100, $MH^+ - MeCH_2CO_2Bu^t$) and 105 (30, $PhCHMe^+$).

A sample of the *anti* diastereoisomer (2*R*,3*R*,α*R*)-**28** was prepared by the tandem addition–methylation of (*R*)-**1** (2.88 mmol) with *tert*-butyl pent-2-enoate[17] (300 mg, 1.92 mmol) following standard procedures reported elsewhere.[6] Partial

purification of the crude product by flash column chromatography on silica gel with petroleum–diethyl ether (20:1) furnished the *anti* and *syn* methylated adducts (2*R*,3*R*,α*R*)-**28** and (2*S*,3*R*,α*R*)-**27** in the ratio of 3:1 as a colourless oil (473 mg, 65%); the *anti* adduct (2*R*,3*R*,α*R*)-**28** was characterized as this mixture.

tert-*Butyl* (2R,3R,αR)-2-*methyl*-3-(N-*benzyl*-N-α-*methylbenzylamino*)*pentanoate* (2R,3R,αR)-**28**. (Found: C, 78.7; H, 9.5; N, 3.6. $C_{25}H_{35}NO_2$ requires C, 78.70; H, 9.25; N, 3.67%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1715 (C=O); δ_H(500 MHz; $CDCl_3$) 7.44–7.18 (10 H, m, Ph), 3.96 (1 H, q, *J* 6.9, PhC*H*N), 3.88 and 3.74 (2 H, AB system, J_{AB} 14.7, PhCH_2N), 3.11 (1 H, dt, *J* 5.6 and 7.0, CH_2CHN), 2.39 (1 H, m, $CHCO_2$), 1.62–1.43 (2 H, m, MeCH_2), 1.42 (9 H, s, CMe_3), 1.32 (3 H, d, *J* 6.9, *Me*CH), 0.97 (3 H, t, *J* 7.4, *Me*CH_2) and 0.95 (3 H, d, *J* 7.1, *Me*CH); δ_C(50 MHz; $CDCl_3$) 175.9 (CO_2), 144.6 and 142.6 (PhC_{ipso}), 128.7, 128.6, 128.4, 128.3 and 128.1 (Ph), 126.9 and 126.7 (PhC_{para}), 79.7 (*C*Me_3), 60.6 and 59.1 (CHN), 51.0 (CH_2N), 42.9 (*C*HCO), 28.0 (C*Me*$_3$), 22.0 (CH_2CHN), 18.4, 14.0 and 12.7 (Me); *m*/*z* 382 (MH^+, 65%) and 252 (100, $MH^+ - MeCH_2CO_2Bu^t$).

tert-*Butyl* (2S,3S)-3-*amino*-2-*methyl*-3-*phenylpropanoate* (2S,3S)-**29**.—Debenzylation of compound (2*S*,3*S*,α*R*)-**23** (740 mg, 1.72 mmol) was carried out according to procedure (*b*). Purification of the crude product by flash column chromatography on silica gel with a diethyl ether–methanol (30:1) eluent afforded the free amino ester (2*S*,3*S*)-**29** as a colourless oil (330 mg, 81%); $[\alpha]_D^{25}$ +19.3 (*c* 2.37 in $CHCl_3$) (Found: C, 62.1; H, 8.3; N, 5.1. $C_{14}H_{21}NO_2$·HCl requires C, 61.87; H, 8.16; N, 5.15%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1715 (C=O); δ_H(300 MHz; $CDCl_3$) 7.33–7.22 (5 H, m, Ph), 4.16 (1 H, d, *J* 6.9, PhC*H*N), 2.65 (1 H, dq, *J* 6.9 and 7.0, CHCO), 1.77 (2 H, br s, NH_2), 1.29 (9 H, s, CMe_3) and 1.18 (3 H, d, *J* 7.0, *Me*CH); δ_C(50 MHz; $CDCl_3$) 174.7 (CO_2), 144.2 (PhC_{ipso}), 128.4 (Ph), 127.3 (PhC_{para}), 127.1 (Ph), 80.2 (*C*Me_3), 57.9 (CHN), 48.2 (*C*HCO), 27.7 (C*Me*$_3$) and 12.6 (*Me*CH); *m*/*z* 236 (MH^+, 90%), 180 (100, $MH^+ - Me_2C{=}CH_2$) and 106 (85, $PhCH{=}NH_2^+$).

(2S,3S)-2-*Methyl*-3-*phenyl*-3-*aminopropionic Acid Hydrochloride* (2S,3S)-**31**.—Hydrolysis of (2*S*,3*S*)-**29** (725 mg, 3.09 mmol) was carried out according to procedure (*c*). Recrystallization of the crude product from ethanol afforded the title compound as a white crystalline solid (564 mg, 85%); $[\alpha]_D^{25}$ +1.7 (*c* 1.06 in H_2O); m.p. 220–225 °C (decomp.) (Found: C, 55.9; H, 6.8; N, 6.8. $C_{10}H_{14}NO_2Cl$ requires C, 55.69; H, 6.54; N, 6.49%); ν_{max}(Nujol mull)/cm^{-1} 2040, 1720, 1655, 1525 and 700; δ_H(300 MHz; CD_3OD) 7.45–7.36 (5 H, m, Ph), 4.43 (1 H, d, *J* 5.6, PhC*H*N), 2.78 (1 H, dq, *J* 5.6 and 7.2, CHCO), 1.12 (3 H, d, *J* 7.2, *Me*CH); δ_C(50 MHz; D_2O) 176.6 (CO_2), 134.3 (PhC_{ipso}), 129.7 (PhC_{para}), 129.3 and 127.3 (Ph), 56.6 (CHN), 43.3 (*C*HCO) and 13.0 (*Me*CH); *m*/*z* 180 (MH^+, 100%) and 106 (40, $PhCH{=}NH_2^+$).

(3S,4S)-3-*Methyl*-4-*phenylazetidinone* (3S,4S)-**34**.—Ion exchange chromatography of (2*S*,3*S*)-**31** (253 mg, 1.18 mmol) on a Dowex 50X8-200 column, eluting with 1 mol dm^{-3} aq. ammonium hydroxide, afforded a white solid (200 mg,), which was dissolved in dry acetonitrile (10 cm^3). After addition of triphenylphosphine (352 mg, 1.34 mmol) and 2,2-dipyridyl disulfide (295 mg, 1.34 mmol) to the acetonitrile solution it was heated at reflux under a nitrogen atmosphere for 30 h.[18] Evaporation of solvent under reduced pressure left a residue which was partitioned between brine and dichloromethane–diethyl ether (1:1). The organic phase was separated, dried ($MgSO_4$), filtered and evaporated to give a yellow oil which was purified by flash column chromatography on silica gel with dichloromethane–diethyl ether (2:1) as eluent to give the pure β-lactam (3*S*,4*S*)-**34** as a white solid (87 mg, 45%), subsequently recrystallized from diethyl ether–dichloromethane, $[\alpha]_D^{25}$ −206.7 (*c* 1.04 in $CHCl_3$); m.p. 138–140 °C (Found: C, 74.7; H, 7.0; N, 8.4. $C_{10}H_{11}NO$ requires C, 74.51; H, 6.88; N, 8.69%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3420 (NH) and 1755 br s (C=O); δ_H (lit.;[11] 300 MHz; $CDCl_3$) 7.43–7.28 (5 H, m, Ph), 6.08 (1 H, br s, NH), 4.90 (1 H, d, *J* 5.5, PhC*H*N), 3.60 (1 H, ddq, J 2.1, 5.5 and 7.6, CHCO) and 0.83 (3 H, d, *J* 7.6, *Me*CH); δ_C(lit.;[11] 50 MHz; $CDCl_3$) 172.8 (CON), 137.6 (PhC_{ipso}), 128.7 (Ph), 128.0 (PhC_{para}), 126.7 (Ph), 55.0 (CHN), 50.6 (*C*HCO) and 10.0 (*Me*CH); *m*/*z* 162 (MH^+, 100%) and 106 (25, $PhCH{=}NH_2^+$).

(2S,3S)-tert-*Butyl* 3-*Amino*-2-*benzyl*-3-*phenylpropionate* (2S,3S)-**30**.—Debenzylation of (2*S*,3*S*,α*R*)-**25** (500 mg, 0.99 mmol) was carried out according to procedure (*b*). Purification of the crude product by recrystallization from heptane–dichloromethane afforded the free amino ester (2*S*,3*S*)-**30** as a white crystalline solid (177 mg, 57%); $[\alpha]_D^{25}$ −28.5 (*c* 1.12 in $CHCl_3$); m.p. 83–84 °C (Found: C, 77.1; H, 8.0; N, 4.3. $C_{20}H_{25}NO_2$ requires C, 77.14; H, 8.09; N, 4.50%); $\nu_{max}(CHCl_3)$/cm^{-1} 1715 (C=O); δ_H(300 MHz; $CDCl_3$) 7.39–7.14 (10 H, m, Ph), 4.16 (1 H, d, *J* 7.3, PhC*H*N), 3.10 and 2.95 (2 H, AB of ABX system, J_{AB} 12.5, J_{AX} 3.3 and J_{BX} 11.0, PhCH_2CH), 2.90–2.82 (1 H, m, $PhCH_2CH$), 1.69 (2 H, br s, NH_2) and 1.02 (9 H, s, CMe_3); δ_C(50 MHz; $CDCl_3$) 173.1 (CO_2), 144.0 and 139.7 (PhC_{ipso}), 129.3, 128.5, 128.4 and 127.3 (Ph), 127.6 and 126.3 (PhC_{para}), 80.3 (*C*Me_3), 58.2 (CHN), 56.7 (*C*HCO), 35.1 (CH_2CH) and 27.5 (C*Me*$_3$); *m*/*z* 312 (MH^+, 75%), 256 (45, $MH^+ - Me_2C{=}CH_2$) and 106 (100, $PhCH{=}NH_2^+$).

(2S,3S)-3-*Amino*-2-*benzyl*-3-*phenylpropionic Acid Hydrochloride* (2S,3S)-**32**.—Hydrolysis of compound (2*S*,3*S*)-**30** (50 mg, 0.16 mmol) was carried out according to procedure (*c*) to give the title compound as a white solid (46 mg, 98%), subsequently recrystallized from ethanol, $[\alpha]_D^{25}$ −16.4 (*c* 0.28 in MeOH); m.p. 210–215 °C (decomp.) (Found: C, 65.7; H, 6.5; N, 4.5. $C_{16}H_{18}ClNO_2$ requires C, 65.86; H, 6.22; N, 4.80%); ν_{max}(Nujol mull)/cm^{-1} 1720, 1610, 1520, 1200 and 705; δ_H(300 MHz; D_2O) 7.31–7.08 (10 H, m, Ph), 4.42 (1 H, d, *J* 8.6, PhC*H*N), 3.24 (1 H, ddd, *J* 5.2, 8.6 and 10.7, $PhCH_2CH$), 2.92 and 2.77 (2 H, AB of ABX system, J_{AB} 13.6, J_{AX} 5.2 and J_{BX} 10.7, PhCH_2CH); δ_C(50 MHz; D_2O) 175.2 (CO_2), 137.3 and 134.0 (PhC_{ipso}), 129.9, 129.4, 128.9, 127.3 and 127.2 (Ph), 56.0 (CHN), 52.2 (*C*HCO) and 34.4 (CH_2CH); *m*/*z* 256 (MH^+, 80%) and 106 (100, $PhCH{=}NH_2^+$).

(2S,3R)-3-*Amino*-2-*methylpentanoic Acid Hydrochloride* (2S,3R)-**33**.—Debenzylation of (2*S*,3*R*,α*R*)-**27** (350 mg, 0.93 mmol) was carried out according to procedure (*c*). However, instead of the crude product being isolated, the dried organic phase obtained after the aqueous sodium hydrogen carbonate wash was acidified with sat. HCl in diethyl ether (5 cm^3) and the residue obtained after evaporation of solvent under reduced pressure was dissolved in 1 mol dm^{-3} aq. HCl (3 cm^3) and heated at 80 °C for 16 h. Evaporation of solvent yielded the amino acid hydrochloride (2*S*,3*R*)-**33** as a glassy solid (87 mg, 57%; $[\alpha]_D^{25}$ +5.0 (*c* 2.60 in H_2O) (Found: C, 42.7; H, 8.1; N, 8.4. $C_6H_{14}ClNO_2$ requires C, 42.99; H, 8.42; N, 8.36%); δ_H(lit.,[13a,13d] 300 MHz; 10% DCl in D_2O; referenced to dioxane) 3.55 (1 H, m, C*H*NH_2), 2.98 (1 H, qd, *J* 3.9 and 7.4, CHCO), 1.77–1.64 (2 H, m, MeCH_2), 1.24 (3 H, d, *J* 7.4, *Me*CH) and 0.99 (3 H, t, *J* 7.5, *Me*CH_2); δ_C(50 MHz; D_2O; referenced to dioxane) 178.8 (CO_2), 54.8 (CHN), 40.8 (*C*HCO), 23.3 (CH_2CH) and 11.4; 9.8 (Me); *m*/*z* 132 (MH^+, 100%).

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