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

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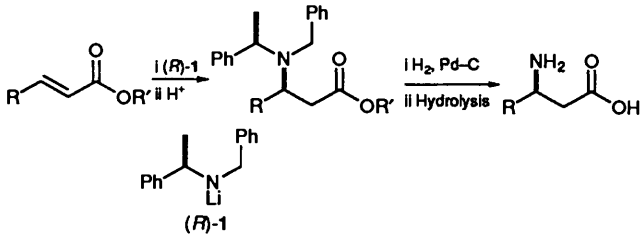
An investigation into the asymmetric induction accompanying alkylations of enolates derived from the highly diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide (*R*)-**1** to crotonate and cinnamate esters has been performed. The access to different enolate geometries afforded by the conjugate addition process and subsequent enolate regeneration by deprotonation of the β-amino ester conjugate adducts enabled two disparate sets of selectivity data to be compiled. Although both approaches furnished predominantly *anti*-α-alkyl-β-amino esters, the two-step procedure proved to be considerably more selective. Several factors which play a major role in determining the alkylation selectivity are identified, including the cooperative influence of the α-methylbenzylamino stereocentre. Since debenzylation and hydrolysis of the alkylated products was straightforward, this methodology provides a direct route to *anti*-α-alkyl-β-amino acids in homochiral form.

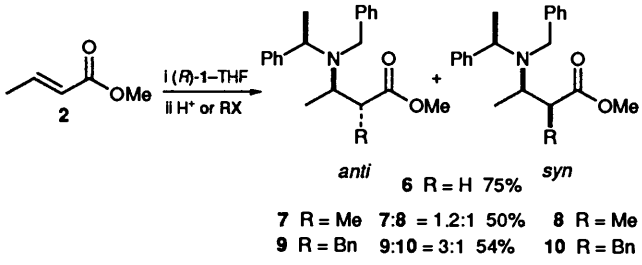
The conjugate addition of a nucleophile to a polarized π-system is an invaluable synthetic tool, particularly when followed by the tandem capture of the conjugate adduct intermediates with electrophiles. We have previously demonstrated that lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide (*R*)-**1** shows a very high degree of diastereoselection in its conjugate addition to α,β-unsaturated esters where the intermediate enolates are simply protonated.[1] Since the conjugate addition products are easily hydrolysed and debenzylated, this constitutes a general route for the synthesis of homochiral β-amino acids which contain only a β-stereogenic centre (Scheme 1).



Scheme 1

With the aim of extending this methodology to include α-alkyl-β-amino acids, we have surveyed the alkylation selectivities elicited by quenching with alkyl halides the β-amino enolates generated by the conjugate addition of (*R*)-**1** to crotonate and cinnamate esters, and describe herein this approach to the asymmetric synthesis of *anti*-α-alkyl-β-amino acids. Part of this work has been previously communicated.[2]

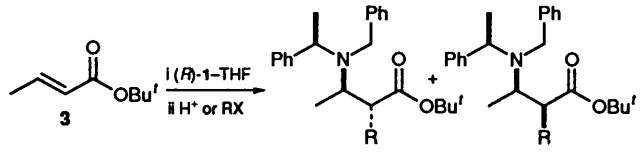
In addition to their incorporation into β-lactam antibiotics such as thienamycin[3] and (+)-(PS)-5,[4] α-alkyl-β-amino acids can be found as components of several biologically interesting natural products,[5] and may also exhibit significant bacteriological and fungicidal properties in themselves.[6] However, few general approaches to their enantioselective synthesis have been reported, with the most successful strategies based on diastereoselective enolate-imine condensations[7] or alkylations of cyclic β-amino acid synthetic equivalents.[8]



6 R = H 75%

7 R = Me **7:8** = 1.2:1 50% **8** R = Me
9 R = Bn **9:10** = 3:1 54% **10** R = Bn

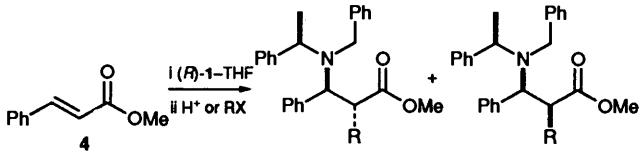
Scheme 2



11 R = H 75%

12 R = Me **12:13** = 1.36:1 60% **13** R = Me
14 R = Bn **14:15** = 1:1 42% **15** R = Bn

Scheme 3



16 R = H 77%

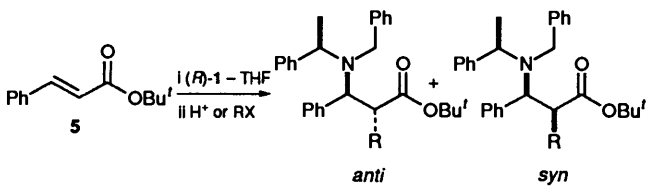
17 R = Me **17:18** ≥ 13:1 61% **18** R = Me
19 R = Bn **19:20** = 3:1 55% **20** R = Bn
21 R = Allyl **21:22** = 3:1 79% **22** R = Allyl

Scheme 4

Results and Discussion

The first set of alkylation selectivity data was obtained from the tandem addition–alkylation of (*R*)-**1** with the methyl and *tert*-butyl esters of crotonic and cinnamic acids (Schemes 2–5). The conjugate additions were performed in THF at −78 °C, generating the intermediate β-amino enolates in ≥95% d.e. as reported previously.[1,2] The alkylations were allowed to warm gradually from −78 °C to ambient temperature overnight, and all diastereoselectivities determined by ^{1}H NMR spectroscopy.

With the exception of the tandem methylation of methyl cinnamate **4**, these results indicate a disappointingly small preference for the *anti* product diastereoisomer in these tandem

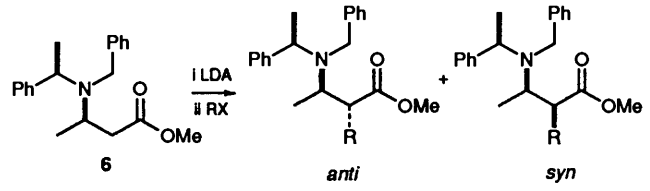


23 R = H 87%

24 R = Me 24:25 = 1.36:1 78% 25 R = Me
26 R = Bn 26:27 = 2.5:1 46% 27 R = Bn

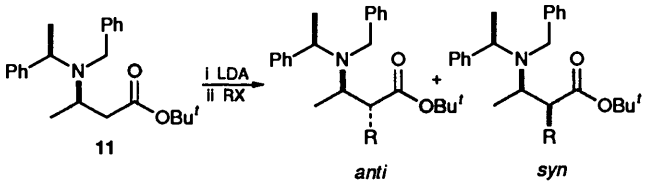
Scheme 5

alkylations. The low magnitude of the stereocontrol deterred further investigation into this type of system. Instead, a stepwise approach was next adopted, in which the proton-quenched conjugate adducts **6**, **11**, **16** and **23** were first isolated before subsequent re-deprotonation with lithium diisopropylamide (LDA) or potassium hexamethyldisilazide (KHMDS), followed by alkylation as before (Schemes 6–9).



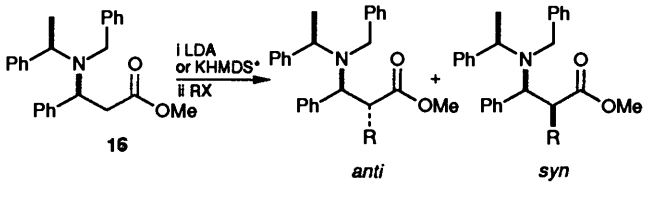
7 R = Me 7:8 = 5:1 89% 8 R = Me
9 R = Bn 9:10 = 1.35:1 52% 10 R = Bn

Scheme 6



12 R = Me 12:13 = 9:1 69% 13 R = Me
14 R = Bn 14:15 = 1:1 83% 15 R = Bn

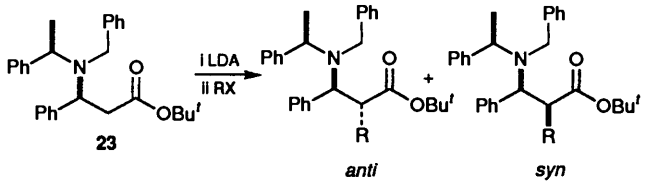
Scheme 7



17 R = Me 17:18 ≥ 20:1 76% 18 R = Me
19 R = Bn 19:20 = 5:1* 80% 20 R = Bn
21 R = Allyl 21:22 = 8:1 70% 22 R = Allyl
21:22 = 8:1* 76% (X = Br)
21:22 = 8:1* 70% (X = I)

Scheme 8

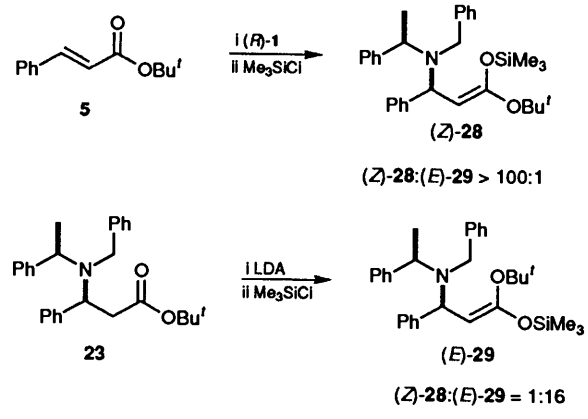
As with the tandem alkylations, the stepwise reactions show a preference for the *anti* diastereoisomer. This is particularly the case for the methylations, whose stereoselectivities are of sufficient magnitude for the alkylations to be synthetically useful. The alkylations of the methyl cinnamate adduct **16** show that variation in halide leaving group or enolate counterion has little effect on the stepwise alkylation selectivity. One of the most distinctive features of the results presented above is the tendency for the stepwise alkylation selectivities to exceed those of



24 R = Me 24:25 = 30:1 70% 25 R = Me
26 R = Bn 26:27 = 1.25:1 41% 27 R = Bn

Scheme 9

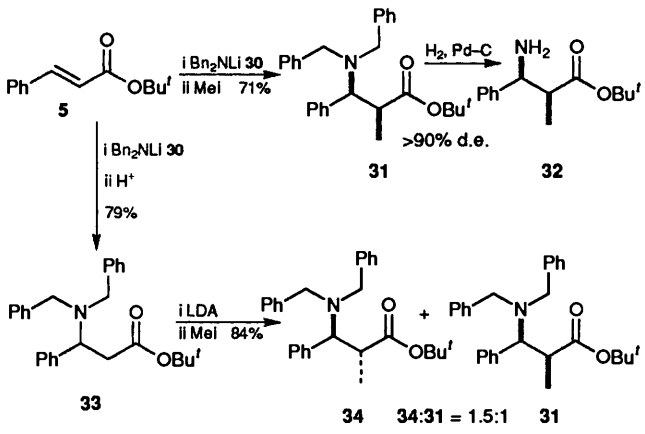
the tandem reactions. This trend is highlighted by the methylations of *tert*-butyl cinnamate **5**: whereas the tandem reaction is virtually non-selective, the stepwise reaction affords almost exclusively the *anti* diastereoisomer **24**. This is, presumably, a consequence of the different enolate geometries involved in the two modes of alkylation. Evidence for the intermediacy of different enolates came from quenching the β-amino ester enolates derived from *tert*-butyl cinnamate with trimethylsilyl chloride. Conjugate addition of (*R*)-**1** to compound **5** afforded a single silyl ketene acetal **28**, whereas deprotonation of the adduct **23** gave predominantly the alternative isomer **29** although a small amount of **28** was detectable (Scheme 10). Unfortunately, all attempts to assign the double bond geometry of these two silyl ketene acetals by ^{1}H NMR NOE difference experiments were rewarded with inconclusive results. However, the related experiments[9] of Yamamoto and coworkers performed with lithium benzyltrimethylsilylamide and methyl crotonate provide strong literature precedent for the stereochemical assignments made in Scheme 10.



Scheme 10

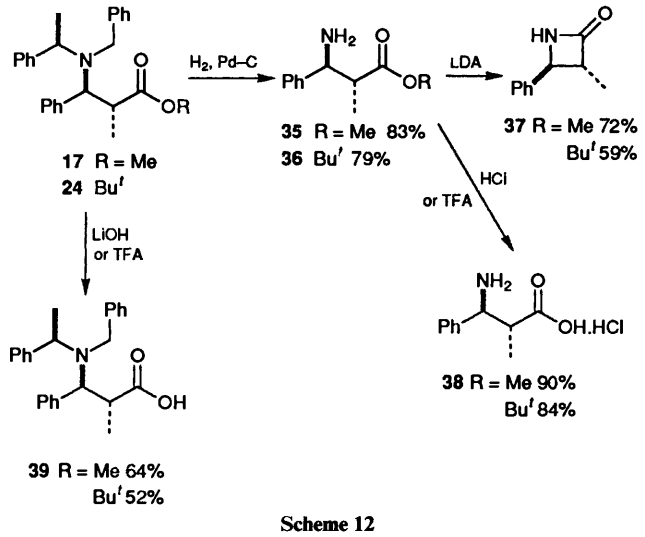
Surprisingly, the 3-C configuration of these enolates was found to be by no means the sole determinant of the *anti* selectivity of these alkylation reactions. The tandem and stepwise methylations of *tert*-butyl cinnamate **5** with achiral lithium dibenzylamide **30** were performed with the expectation that they would give rise to similar selectivities as the corresponding reactions of (*R*)-**1**. However, in marked contrast, the tandem methylation was found to favour the *syn* adduct **31** (shown by subsequent debenzylation to give compound **32**), whereas the stepwise reaction was essentially non-selective (Scheme 11). These results implicate the configuration of the distant α-methylbenzylamino stereocentre as a significant influence on the tandem and stepwise alkylation selectivities of the lithium amide **1**.

The 2-C–3-C relative stereochemistry of the alkylated conjugate adducts was assigned on the basis of several deprotection reactions. Debenzylation of the methylated methyl or *tert*-butyl cinnamate adducts **17** and **24** proved straightforward, and the resultant primary β-amino esters **35** and **36** could



Scheme 11

be either hydrolysed to the same β-amino acid **38** or cyclized to the known β-lactam **37** (Scheme 12). Identification of this latter

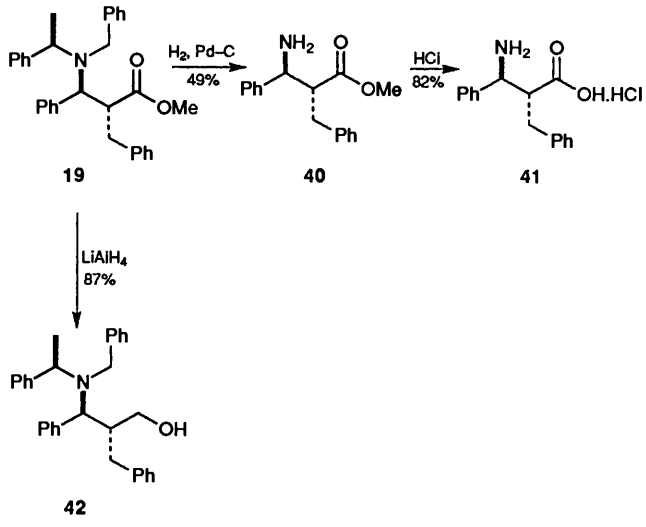


Scheme 12

compound established the *anti* stereochemistry of **17** and **24**, and also the *syn* stereochemistry of **31** since **36** and **32** were different.

Unlike the methylated adducts **17** and **24**, the bulkier α-benzylated adduct **19** was resistant to hydrolysis conditions, though reduction with lithium aluminium hydride to the alcohol **42** proceeded smoothly. However, the debenzylated amino ester **40** was susceptible to acidic hydrolysis, yielding the same amino acid hydrochloride **41** as produced from the analogous addition–benzylation of *N*,*N*-dimethyl cinnamide,[10] thus establishing the *anti*-relative stereochemistry of **41**, **40** and **19** (Scheme 13).

The alkylations of homochiral β-amino enolates described above indicate that a variety of factors are responsible for determining the extent of diastereofacial discrimination shown by an incoming electrophile. Not surprisingly, the size of the 3-C substituents, enolate geometry and nature of the electrophile are all important, but so too may be the presence of an additional, more distant stereogenic centre. Since the products of these alkylations are easily deprotected, the more selective of these, such as the stepwise methylations, provide a synthetically useful route to *anti*-α-alkyl-β-amino acids.



Scheme 13

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 (J) 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. Flash column chromatography was performed on silica gel (Kieselgel 60). Tetrahydrofuran (THF) 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**, **11**, **16**, **23** and **32** will be reported elsewhere.[11,12]

Procedure for Conjugate Additions to Ester Acceptors.—(*a*) A solution of (*R*)-(+)-*N*-benzyl-*N*-α-methylbenzylamine[13] (3.2 mmol) in THF (10 cm^3) was cooled to −78 °C prior to the slow addition of butyllithium (1.6 mol dm^{-3}; 3.0 mmol). The resultant pink solution of the lithium amide (*R*)-**1** (3.0 mmol) was stirred for 30 min, after which a THF (2 cm^3) solution of the requisite conjugate acceptor (2.0 mmol) was added dropwise to it by syringe. Stirring was continued for 2 h at −78 °C and then the reaction quenched by the addition of sat. aq. NH_4Cl to the reaction mixture. This was allowed to warm to room temp. over 30 min after which it was evaporated under reduced pressure. The residue was partitioned between brine and diethyl ether–dichloromethane (1:1) and the organic phase subsequently dried ($MgSO_4$), filtered and then concentrated to furnish the crude conjugate adduct.

Procedure for Tandem Conjugate Additions–Alkylations of Ester Acceptors.—(*b*) The conjugate addition of (*R*)-**1** (3.2 mmol) to the requisite conjugate acceptor (2.0 mmol) was performed as described in procedure (*a*). However, in this case

the reaction was quenched by the addition of neat alkyl halide (9.0 mmol) and then allowed to warm gradually to room temp. over 15 h, unless otherwise stated. Work-up, as described in procedure (*a*), furnished the crude alkylated conjugate adducts.

Procedure for Stepwise Alkylations of Ester Conjugate Adducts.—(*c*) A solution of the requisite conjugate adduct (2.0 mmol) in THF (2 cm^3) was added dropwise to a solution of lithium diisopropylamide (LDA) (3.0 mmol) in THF (10 cm^3) at −78 °C. The reaction mixture was stirred for 1 h at −78 °C and then neat alkyl halide (9.0 mmol) injected into it by syringe. The reaction mixture was allowed to warm gradually to room temp. over 15 h. Work-up, as described in procedure (*a*), then furnished the crude alkylated conjugate adducts.

Procedure for Pd–C Catalysed Debenzylations.—(*d*) The requisite conjugate adduct (1.0 mmol) and Pd–C (30% by mass) were placed in a Fischer–Porter bottle which was flushed with argon prior to charging with acetic acid (5 cm^3). The reaction mixture was placed under a hydrogen atmosphere (4 bar) and stirred vigorously at 50 °C overnight. The reaction mixture was then filtered through a plug of Celite, washing through with methanol, and the filtrate concentrated to give a white solid. This residue was dissolved in sat. aq. $NaHCO_3$ which was subsequently extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to afford the debenzylated product.

Conjugate Addition to Methyl Crotonate **2**.—The conjugate addition of (*R*)-**1** (13.8 mmol) to methyl crotonate **2** (1.26 g, 12.5 mmol) was performed according to procedure (*a*). Purification of the crude product by flash column chromatography on silica gel with a petroleum–diethyl ether (4:1) eluent afforded the conjugate adduct **6** as a colourless oil (2.92 g, 75%).

Tandem Addition–Methylation of Methyl Crotonate **2**.—The conjugate addition of (*R*)-**1** (3.00 mmol) to methyl crotonate **2** (200 mg, 2.00 mmol) followed by alkylation with methyl iodide (1.0 cm^3, 16 mmol) was carried out according to procedure (*b*). Purification of the crude product, which contained the product diastereoisomers **7** and **8** in the ratio of 1.2:1, was achieved by flash column chromatography on silica gel with a dichloromethane eluent. First eluted was compound **8** with a d.e. of 95% (152 mg, 23%), followed by a mixed fraction and finally compound **7** with a d.e. of 87% (132 mg, 20%), all as colourless oils; the combined product yield was 50%.

Methyl (2S,3R,αR)-3-(N-*benzyl*-N-α-*methylbenzylamino*)-2-*methylbutyrate* (2S,3R,αR)-**8**. $[\alpha]_D^{25}$ −12.4 (*c* 2.50 in $CHCl_3$) (Found: C, 77.4; H, 8.5; N, 4.0. $C_{21}H_{27}NO_2$ requires C, 77.50; H, 8.36; N, 4.30%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1725 (C=O); δ_H(300 MHz; $CDCl_3$) 7.40–7.28 (10 H, m, Ph), 3.97 (1 H, q, *J* 6.9, PhC*H*N), 3.80 and 3.70 (2 H, AB system, J_{AB} 14.0, PhCH_2N), 3.60 (3 H, s, OMe), 2.97 (1 H, dq, *J* 6.7 and 9.4, MeC*H*N), 2.41 (1 H, dq, *J* 6.9 and 9.4, $CHCO_2$), 1.42 (3 H, d, *J* 6.9, *Me*CH), 1.12 (3 H, d, *J* 6.7, *Me*CH) and 0.89 (3 H, d, *J* 6.9, *Me*CH); δ_C(50 MHz; $CDCl_3$) 177.1 (CO_2), 144.3 and 141.3 (PhC_{ipso}), 129.1, 128.3 and 128.0 (Ph), 127.0 and 126.8 (PhC_{para}), 56.8 and 54.2 (CHN), 51.3 (OMe), 50.2 (CH_2N), 45.2 (*C*HCO), 15.7, 15.2 and 14.4 (*Me*CH); *m*/*z* 326 (MH^+, 100%), 238 (80, MH^+ − $MeCH_2CO_2Me$), 236 (35, MH^+ − PhCH), 134 (40, MeCH=NH^+CH_2Ph) and 105 (35, $PhCHCH_3^+$).

Methyl (2R,3R,αR)-3-(N-*benzyl*-N-α-*methylbenzylamino*)-2-*methylbutyrate* (2R,3R,αR)-**7**. (Found: C, 77.3; H, 8.6; N, 4.1. $C_{21}H_{27}NO_2$ requires C, 77.50; H, 8.36; N, 4.30%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730 (C=O); δ_H(300 MHz; $CDCl_3$) 7.40–7.17 (10 H, m, Ph), 3.97 (1 H, q, *J* 6.9, PhC*H*N), 3.81 and 3.65 (2 H, AB system, J_{AB} 14.1, PhCH_2N), 3.44 (3 H, s, OMe), 3.21 (1 H, dq, *J* 6.7 and 9.7, MeC*H*N), 2.55 (1 H, dq, *J* 7.0 and 9.7, $CHCO_2$), 1.39 (3 H, d, *J* 6.9, *Me*CH), 1.10 (3 H, d, *J* 6.7, *Me*CH) and 0.99 (3 H, d, *J* 7.0, *Me*CH); δ_C(50 MHz; $CDCl_3$) 176.4 (CO_2), 144.4 and 141.3 (PhC_{ipso}), 129.2, 128.2 and 127.9 (Ph), 126.8 and 126.6 (PhC_{para}), 57.2 and 55.1 (CHN), 51.1 (OMe), 49.9 (CH_2N), 45.6 (*C*HCO), 15.4, 14.9 and 14.0 (MeCH); *m*/*z* 326 (MH^+, 100%), 238 (80, MH^+ − $MeCH_2CO_2Me$), 236 (45, MH^+ − PhCH), 134 (45, MeCH=NH^+CH_2Ph) and 105 (40, $PhCHMe^+$).

Tandem Addition–Benzylation of Methyl Crotonate **2**.—The conjugate addition of (*R*)-**1** (4.49 mmol) to methyl crotonate **2** (300 mg, 3.00 mmol) followed by alkylation with benzyl bromide (0.89 cm^3, 7.5 mmol) was carried out according to procedure (*b*). Purification of the crude oil by flash column chromatography on silica gel with a petroleum–diethyl ether (10:1) eluent gave the benzylated products as a 3:1 mixture of diastereoisomers (644 mg, 54%). Separation of these products was achieved by flash column chromatography on silica gel with a petroleum–dichloromethane (2:1) eluent. First eluted was the major product **9** (382 mg, 32%), subsequently recrystallized from methanol, followed by a mixed fraction and finally the minor product **10** (78 mg, 6%) as a colourless oil.

Major diastereoisomer: methyl (2R,3R,αR)-2-*benzyl*-3-(N-*benzyl*-N-α-*methylbenzylamino*)*butyrate* (2R,3R,αR)-**9**. $[\alpha]_D^{25}$ +36.9 (*c* 1.03 in $CHCl_3$); m.p. 65 °C (Found: C, 80.5; H, 7.7; 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; $CDCl_3$) 7.46–6.87 (15 H, m, Ph), 4.02 (1 H, q, *J* 6.9, PhCHN), 3.88 and 3.76 (2 H, AB system, J_{AB} 14.0, PhCH_2N), 3.43 (3 H, s, OMe), 3.10 (1 H, dq, *J* 6.7 and 9.4, MeC*H*N), 3.04 and 2.09 (2 H, AB of ABX system, J_{AB} 13.7, J_{AX} 3.8 and J_{BX} 11.7, PhCH_2CH), 2.59 (1 H, ddd, *J* 3.8, 9.4 and 11.7, $PhCH_2CH$), 1.44 (3 H, d, *J* 6.9, *Me*CH) and 1.14 (3 H, d, *J* 6.7, *Me*CH); δ_C(50 MHz; $CDCl_3$) 175.8 (CO_2), 144.4, 141.3 and 140.5 (PhC_{ipso}), 129.3, 128.8, 128.7, 128.5 and 128.3 (Ph), 127.3, 127.1 and 126.2 (PhC_{para}), 57.3 and 53.9 (CHN), 53.9 (*C*HCO), 51.1 (OMe), 50.3 (CH_2N), 36.7 (CH_2CH), 15.0 and 14.8 (*Me*CH); *m*/*z* 402 (MH^+, 75%), 238 (100, MH^+ − $PhCH_2CH_2CO_2Me$) and 134 (20, MeCH=NH^+CH_2Ph).

Minor diastereoisomer: methyl (2S,3R,αR)-2-*benzyl*-3-(N-*benzyl*-N-α-*methylbenzylamino*)*butyrate* (2S,3R,αR)-**10**. $[\alpha]_D^{25}$ +64.8 (*c* 1.02 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%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730 (C=O); δ_H(300 MHz; $CDCl_3$) 7.41–7.02 (15 H, m, Ph), 3.99 (1 H, q, *J* 7.0, PhC*H*N), 3.88 and 3.68 (2 H, AB system, J_{AB} 13.9, PhCH_2N), 3.32 (1 H, dq, *J* 6.7 and 9.5, MeC*H*N), 3.24 (3 H, s, O*Me*), 2.81 (1 H, ddd, *J* 4.2, 9.5 and 11.6, $PhCH_2CH$), 2.70 and 2.61 (2 H, AB of ABX system, J_{AB} 13.1, J_{AX} 4.2 and J_{BX} 11.6, PhCH_2CH), 1.40 (3, H, d, *J* 7.0, *Me*CH) and 1.25 (3 H, d, *J* 6.7, *Me*CH); δ_C(50 MHz; $CDCl_3$) 174.6 (CO_2), 144.3, 141.1 and 139.7 (PhC_{ipso}), 129.5, 129.0, 128.5, 128.4 and 128.1 (Ph), 127.1, 126.8 and 126.5 (PhC_{para}), 56.7 and 54.5 (CHN), 54.4 (*C*HCO), 50.9 (OMe), 50.2 (CH_2N), 36.2 (CH_2CH), 15.1 and 15.0 (MeCH); *m*/*z* 402 (MH^+, 70%), 238 (100, MH^+ − $PhCH_2CH_2CO_2Me$) and 134 (15, MeCH=NH^+CH_2Ph).

Conjugate Addition to tert-*Butyl Crotonate* **3**.—The conjugate addition of (*R*)-**1** (10.6 mmol) to *tert*-butyl crotonate **3** (1.00 g, 7.04 mmol) was performed according to procedure (*a*). Purification of the crude product by flash column chromatography on silica gel with a petroleum–diethyl ether (10:1) eluent afforded the conjugate adduct **11** as a colourless oil (1.25 g, 50%).

Tandem Addition–Methylation of tert-*Butyl Crotonate* **3**.—The conjugate addition of (*R*)-**1** (1.06 mmol) to *tert*-butyl crotonate **3** (100 mg, 0.70 mmol) followed by alkylation with methyl iodide (0.22 cm^3, 3.5 mmol) was carried out according to procedure (*b*). Purification of the crude oil, which contained

compounds **12** and **13** in the ratio of 1.36:1, by flash column chromatography on silica gel with a dichloromethane eluent gave first the *syn* methylated adduct **13** (90 mg, 35%) followed by the *anti* adduct **12** (64 mg, 25%), both as colourless oils.

tert-*Butyl* (2S,3R,αR)-3-(N-*benzyl*-N-α-*methylbenzylamino*)-2-*methylbutyrate* (2S,3R,αR)-**13**. $[\alpha]_D^{25}$ −8.4 (*c* 1.10 in $CHCl_3$) (Found: C 78.6; H, 9.0; N, 4.05. $C_{24}H_{33}NO_2$ requires C, 78.43; H, 9.05; N, 3.81%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1710 (C=O); δ_H(300 MHz; $CDCl_3$) 7.39–7.18 (10 H, m, Ph), 3.96 (1 H, q, *J* 6.8, PhC*H*N), 3.80 and 3.69 (2 H, AB system, J_{AB} 14.0, PhCH_2N), 2.91 (1 H, dq, *J* 6.6 and 9.7, MeC*H*N), 2.28 (1 H, dq, *J* 6.9 and 9.7, $CHCO_2$), 1.41 (9 H, s, CMe_3), 1.41 (3 H, d, *J* 6.8, *Me*CH), 1.14 (3 H, d, *J* 6.6, *Me*CH) and 0.83 (3 H, d, *J* 6.9 *Me*CH); δ_C(50 MHz; $CDCl_3$) 176.3 (CO_2), 144.5 and 141.5 (PhC_{ipso}), 129.2, 128.4 and 128.0 (Ph), 127.0 and 126.8 (PhC_{para}), 79.9 (*C*Me_3), 56.6 and 54.2 (CHN), 50.2 (CH_2N), 46.3 (*C*HCO), 27.9 (C*Me*$_3$), 16.1, 15.4 and 14.5 (*Me*CH); *m/z* 368 (MH^+, 80%), 238 (100, $MH^+ - MeCH_2CO_2Bu^t$), 134 (45, MeCH=NH^+CH_2Ph), 105 (40, $PhCHMe^+$) and 91 (30, $PhCH_2^+$).

tert-*Butyl* (2R,3R,αR)-3-(N-*benzyl*-N-α-*methylbenzylamino*)-2-*methylbutyrate* (2R,3R,αR)-**12**. $[\alpha]_D^{25}$ −22.2 (*c* 1.00 in $CHCl_3$) (Found: C, 78.4; H, 8.8; N, 4.1. $C_{24}H_{33}NO_2$ requires C, 78.43; H, 9.05; N, 3.81%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1715 (C=O); δ_H(300 MHz; $CDCl_3$) 7.39–7.17 (10 H, m, Ph), 4.01 (1 H, q, *J* 6.9, PhC*H*N), 3.71 and 3.67 (2 H, AB system, J_{AB} 14.5, PhCH_2N), 3.31 (1 H, dq, *J* 6.9 and 9.0, MeC*H*N), 2.34 (1 H, dq, *J* 7.0 and 9.0, $CHCO_2$), 1.45 (9 H, s, CMe_3), 1.36 (3 H, d, *J* 6.9, *Me*CH), 0.96 (3 H, d, *J* 6.9, *Me*CH) and 0.95 (3 H, d, *J* 7.0, *Me*CH); δ_C(50 MHz; $CDCl_3$) 175.9 (CO_2), 144.4 and 142.2 (PhC_{ipso}), 128.6, 128.4 and 128.0 (Ph), 126.7 and 126.6 (PhC_{para}), 79.5 (*C*Me_3), 59.7 and 56.2 (CHN), 49.8 (CH_2N), 46.2 (*C*HCO), 28.0 (C*Me*$_3$), 17.7, 14.6 and 13.1 (MeCH); *m/z* 368 (MH^+, 100%), 238 (60, $MH^+ - MeCH_2CO_2Bu^t$), 134 (15, MeCH=NH^+CH_2Ph), 105 (10, $PhCHMe^+$) and 91 (10, $PhCH_2^+$).

Tandem Addition–Benzylation of tert-*Butyl Crotonate* **3**.—The conjugate addition of (*R*)-**1** (3.17 mmol) to *tert*-butyl crotonate **3** (300 mg, 2.11 mmol) followed by alkylation with benzyl bromide (0.63 cm^3, 5.28 mmol) was carried out according to procedure (*b*). Purification of the crude oil by flash column chromatography on silica gel with a petroleum–diethyl ether (25:1) eluent gave the benzylated products as a 1:1 mixture of diastereoisomers (396 mg, 42%). Separation of these products was achieved by flash column chromatography on silica gel with a petroleum–dichloromethane (2:1) eluent. First eluted was compound **14** (138 mg, 15%), subsequently recrystallized from methanol, followed by a mixed fraction and finally compound **15** (68 mg, 7%) as a colourless oil.

Less polar diastereoisomer: tert-*butyl* (2R,3R,αR)-2-*benzyl*-3-(N-*benzyl*-N-α-*methylbenzylamino*)*butyrate* (2R,3R,αR)-**14**. $[\alpha]_D^{25}$ +33.0 (*c* 1.06 in $CHCl_3$); m.p. 70–72 °C (Found: C, 81.1; H, 8.5; N, 3.0. $C_{30}H_{37}NO_2$ requires C, 81.22; H, 8.41; N, 3.16%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1715 (C=O); δ_H(300 MHz; $CDCl_3$) 7.46–6.94 (15 H, m, Ph), 4.02 (1 H, q, *J* 6.9, PhC*H*N), 3.91 and 3.76 (2 H, AB system, J_{AB} 14.0, PhCH_2N), 3.10–3.00 (2 H, m, PhCH_2CHC*H*N), 2.51 (1 H, m, $PhCH_2CH$), 1.94 (1 H, dd, *J* 13.8 and 12.0, PhCH_2CH), 1.44 (3 H, d, *J* 6.9, *Me*CH), 1.18 (3 H, d, *J* 6.5, *Me*CH) and 1.17 (9 H, s, CMe_3); δ_C(50 MHz; $CDCl_3$) 174.7 (CO_2), 144.4, 141.4 and 140.6 (PhC_{ipso}), 129.3, 129.2, 129.0, 128.6, 128.5 and 128.2 (Ph), 127.2, 127.0 and 126.0 (PhC_{para}), 80.1 (*C*Me_3), 57.0 and 54.2 (CHN), 53.8 (*C*HCO), 50.4 (CH_2N), 37.0 (CH_2CH), 27.7 (C*Me*$_3$), 15.2 and 14.6 (*Me*CH); *m/z* 444 (MH^+, 100%), 238 (90, $MH^+ - PhCH_2CH_2CO_2Bu^t$) and 134 (60, MeCH=$NH^+CH_2Ph$).

More polar diastereoisomer: tert-*butyl* (2S,3R,αR)-2-*benzyl*-3-(N-*benzyl*-N-α-*methylbenzylamino*)*butyrate* (2S,3R,αR)-**15**. $[\alpha]_D^{25}$ +42.3 (*c* 1.06 in $CHCl_3$) (Found: C, 81.0; H, 8.25; N, 3.4. $C_{30}H_{37}NO_2$ requires C, 81.22; H, 8.41; N, 3.16%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 (C=O); δ_H(300 MHz; $CDCl_3$) 7.41–7.06 (15 H, m, Ph), 4.05 (1 H, q, *J* 7.0, PhC*H*N), 3.82 and 3.70 (2 H, AB system, J_{AB} 14.5, PhCH_2N), 3.40 (1 H, dq, *J* 8.5 and 6.9, MeC*H*N), 2.75–2.50 (3 H, m, $PhCH_2CH$), 1.37 (3 H, d, *J* 7.0, *Me*CH), 1.15 (9 H, s, CMe_3) and 1.11 (3 H, d, *J* 6.9, *Me*CH); δ_C(50 MHz; $CDCl_3$) 174.3 (CO_2), 144.3, 142.0 and 139.7 (PhC_{ipso}), 129.5, 129.2, 128.5, 128.2 and 128.1 (Ph), 126.9, 126.8 and 126.2 (PhC_{para}), 79.9 (*C*Me_3), 59.4 and 56.2 (CHN), 53.5 (*C*HCO), 50.1 (CH_2N), 36.2 (CH_2CH), 27.8 (C*Me*$_3$), 17.5 and 14.2 (*Me*CH); *m/z* 444 (MH^+, 100%), 238 (80, $MH^+ - PhCH_2CH_2CO_2Bu^t$) and 134 (60, MeCH=$NH^+CH_2Ph$).

Conjugate Addition to Methyl Cinnamate **4**.—The conjugate addition of (*R*)-**1** (25.0 mmol) to methyl cinnamate **4** (2.85 g, 17.6 mmol) was performed according to procedure (*a*). Purification of the crude product by flash column chromatography on silica gel with a dichloromethane eluent afforded the conjugate adduct **16** as a colourless oil (5.07 g, 77%).

Tandem Addition–Methylation of Methyl Cinnamate **4**.—The conjugate addition of (*R*)-**1** (15.7 mmol) to methyl cinnamate **4** (1.70 g, 10.5 mmol) followed by alkylation with methyl iodide (5.00 cm^3, 80.3 mmol) was carried out according to procedure (*b*). Purification of the crude oil, which contained compound **17** in ⩾ 86% d.e., was accomplished by crystallization from ethanol (20 cm^3) which yielded white crystals of compound **17** (1.90 g). Hexane (20 cm^3) was added to the mother liquor and the solution maintained at −30 °C for 20 h to give a further 0.58 g of compound **17** (total yield 61%). A sample of the *syn* diastereoisomer **18** (93% d.e.) was prepared by the tandem addition–protonation of (*R*)-**1** with methyl (*E*)-2-methylcinnamate.[12]

Methyl (2R,3S,αR)-3-(N-*benzyl*-N-α-*methylbenzylamino*)-2-*methyl*-3-*phenylpropionate* (2R,3S,αR)-**17**. $[\alpha]_D^{25}$ −46.9 (*c* 1.00 in $CHCl_3$); m.p. 110–112 °C (Found: C, 80.8; H, 7.7; N, 3.6. $C_{26}H_{29}NO_2$ requires C, 80.59; H, 7.54; N, 3.62%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730 (C=O); δ_H(300 MHz; $CDCl_3$) 7.41–7.20 (15 H, m, Ph), 4.17 and 3.63 (2 H, AB system, J_{AB} 13.6, PhCH_2N), 4.16 (1 H, q, *J* 6.9, MeC*H*N), 3.97 (1 H, d, *J* 11.3, PhC*H*CH), 3.57 (3 H, s, OMe), 3.28 (1 H, dq, *J* 11.3 and 6.8, CHCO), 0.94 (3 H, d, *J* 6.9, *Me*CH) and 0.76 (3 H, d, *J* 6.8, *Me*CH); δ_C(50 MHz; $CDCl_3$) 176.0 (CO_2), 144.0, 140.3 and 139.1 (PhC_{ipso}), 129.4, 129.3, 128.6, 128.4, 128.3 and 128.0 (Ph), 127.6, 127.1 and 126.7 (PhC_{para}), 64.5 and 55.5 (CHN), 51.4 (OMe), 50.7 (CH_2N), 43.0 (*C*HCO), 15.8 and 13.9 (*Me*CH); *m/z* 388 (MH^+, 70%), 300 (95, $MH^+ - MeCH_2CO_2Me$), 196 (100, PhCH=NH^+CH_2Ph), 105 (75, $PhCHMe^+$) and 91 (90, $PhCH_2^+$).

Methyl (2S,3S,αR)-3-(N-*benzyl*-N-α-*methylbenzylamino*)-2-*methyl*-3-*phenylpropionate* (2S,3S,αR)-**18**. $[\alpha]_D^{25}$ −75.4 (*c* 0.90 in $CHCl_3$; 93% d.e.) (Found: C, 80.4; H, 7.3; N, 3.5. $C_{26}H_{29}NO_2$ requires C, 80.59; H, 7.54; N, 3.62%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730 (C=O); δ_H(300 MHz; $CDCl_3$) 7.43–7.27 (15 H, m, Ph), 4.16 (1 H, q, *J* 6.7, MeC*H*N), 3.95 and 3.63 (2 H, AB system, J_{AB} 13.9, PhCH_2N), 3.86 (1 H, d, *J* 11.2, PhC*H*CH), 3.26 (3 H, s, OMe), 3.21 (1 H, dq, *J* 11.2 and 6.9, CHCO), 1.23 (3 H, d, *J* 6.7, *Me*CH) and 0.92 (3 H, d, *J* 6.9, *Me*CH); δ_C(50 MHz; $CDCl_3$) 176.1 (CO_2), 144.8, 140.3 and 139.7 (PhC_{ipso}), 129.3, 129.0, 128.5, 128.2 and 128.0 (Ph), 127.4, 127.1 and 126.8 (PhC_{para}), 63.3 and 55.4 (CHN), 51.1 (OMe), 50.5 (CH_2N), 42.9 (*C*HCO), 16.4 and 14.5 (*Me*CH); *m/z* 388 (MH^+, 100%), 300 (40, $MH^+ - MeCH_2CO_2Me$), 196 (65, PhCH=NH^+CH_2Ph), 105 (30, $PhCHMe^+$) and 91 (40, $PhCH_2^+$).

Tandem Addition–Benzylation of Methyl Cinnamate **4**.—The conjugate addition of (*R*)-**1** (1.00 mmol) to methyl cinnamate **4** (108 mg, 0.67 mmol) followed by alkylation with benzyl bromide (0.24 cm^3, 2.0 mmol) was carried out according to

procedure (*b*). Purification of the crude product by flash column chromatography on silica gel with a petroleum–diethyl ether (4:1) eluent gave a colourless oil containing the benzylated products **19** and **20** as a 3:1 mixture of diastereoisomers (170 mg, 55%). A diastereomerically pure sample of compound **19** was prepared from the corresponding stepwise benzylation described below, and compound **20** was generated as a single diastereoisomer *via* the tandem addition–protonation of (*R*)-**1** with *tert*-butyl (*E*)-2-benzylcinnamate[12] after trifluoroacetic acid hydrolysis and methyl ester formation with diazomethane.

Methyl (2R,3S,αR)-2-*benzyl*-3-(N-*benzyl*-N-α-*methylbenzylamino*)-3-*phenylpropionate* (2R,3S,αR)-**19**. $[\alpha]_D^{25}$ +14.8 (*c* 1.10 in $CHCl_3$); m.p. 94–96 °C (Found: C, 82.6; H, 7.5; N, 3.2. $C_{32}H_{33}NO_2$ requires C, 82.90; H, 7.17; N, 3.02%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730 (C=O); δ_H(300 MHz; $CDCl_3$) 7.50–6.90 (20 H, m, Ph), 4.23 (1 H, d, *J* 10.8, PhC*H*CH), 4.23 (1 H, q, *J* 6.9, MeC*H*N), 4.11 and 3.67 (2 H, AB system, J_{AB} 12.6, PhCH_2N), 3.52 (1 H, ddd, *J* 11.6, 10.8 and 3.3, CHCO), 3.38 (3 H, s, OMe), 2.50 and 2.28 (2 H, AB of ABX system, J_{AB} 13.5, J_{AX} 11.6 and J_{BX} 3.3, PhCH_2CH) and 0.93 (3 H, d, *J* 6.9, *Me*CH); δ_C(50 MHz; $CDCl_3$) 174.4 (CO_2), 144.5, 140.0, 139.7 and 139.2 (PhC_{ipso}), 129.5, 129.4, 128.9, 128.8, 128.6, 128.3, 128.1 and 128.0 (Ph), 127.8, 127.3, 126.8 and 126.5 (PhC_{para}), 63.7 and 55.2 (CHN), 52.1 (*C*HCO), 51.2 (OMe), 50.9 (CH_2N), 36.9 (CH_2CH) and 14.1 (*Me*CH); *m*/*z* 464 (MH^+, 15%), 300 (100, $MH^+ - PhCH_2CH_2CO_2Me$), 196 (50, PhCH=N$^+$$CH_2$Ph), 105 (40, $PhCHMe^+$) and 91 (65, $PhCH_2^+$).

Methyl (2S,3S,αR)-2-*benzyl*-3-(N-*benzyl*-N-α-*methylbenzylamino*)-3-*phenylpropionate* (2S,3S,αR)-**20**. $[\alpha]_D^{25}$ −43.7 (*c* 0.99 in $CHCl_3$) (Found: C, 82.8; H, 7.4; N, 2.7. $C_{32}H_{33}NO_2$ requires C, 82.90; H, 7.17; N, 3.02%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1725 (C=O); δ_H(300 MHz; $CDCl_3$) 7.51–6.97 (20 H, m, Ph), 4.25 (1 H, q, *J* 6.9, MeC*H*N), 4.08 and 3.71 (2 H, AB system, J_{AB} 13.8, PhCH_2N), 4.03 (1 H, d, *J* 11.1, PhC*H*CH), 3.57 and 2.38 (2 H, AB of ABX system, J_{AB} 13.5, J_{AX} 3.5 and J_{BX} 11.9, PhCH_2CH), 3.34 (1 H, ddd, *J* 11.9, 11.1 and 3.5, CHCO), 3.04 (3 H, s, OMe) and 1.00 (3 H, d, *J* 6.9, *Me*CH); δ_C(50 MHz; $CDCl_3$) 174.6 (CO_2), 145.0, 140.4, 140.2 and 138.9 (PhC_{ipso}), 129.5, 129.4, 128.9, 128.8, 128.6, 128.3 and 128.1 (Ph), 127.7, 127.4, 127.1 and 126.4 (PhC_{para}), 63.2 and 56.1 (CHN), 52.0 (*C*HCO), 50.9 (OMe), 50.9 (CH_2N), 37.4 (CH_2CH) and 15.1 (*Me*CH); *m*/*z* 464 (MH^+, 65%), 300 (60, $MH^+ - PhCH_2CH_2CO_2Me$), 196 (95, PhCH=NHCH_2Ph), 105 (55, $PhCHMe^+$) and 91 (100, $PhCH_2^+$).

Tandem Addition–Allylation of Methyl Cinnamate **4**.—The conjugate addition of (*R*)-**1** (3.00 mmol) to methyl cinnamate **4** (324 mg, 2.00 mmol) followed by alkylation with allyl bromide (0.85 cm^3, 9.8 mmol) was carried out according to procedure (*b*). Purification of the crude product by flash column chromatography on silica gel with a dichloromethane eluent gave a pale yellow oil containing the allylated products **21** and **22** as a 3:1 mixture of diastereoisomers (650 mg, 79%) which could not be separated. Compound **22** was characterized as this mixture and compound **21** as that prepared *via* the more selective stepwise allylation described below.

Methyl (2R,3S,αR)-2-*allyl*-3-(N-*benzyl*-N-α-*methylbenzylamino*)-3-*phenylpropionate* (2R,3S,αR)-**21**. (Found: C, 81.1; H, 7.9; N, 3.3. $C_{28}H_{31}NO_2$ requires C, 81.32; H, 7.56; N, 3.39%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730 (C=O); δ_H(300 MHz; $CDCl_3$) 7.45–7.21 (15 H, m, Ph), 5.57–5.46 (1 H, m, C*H*=CH_2), 4.87–4.81 (2 H, m, CH=CH_2), 4.22 and 3.65 (2 H, AB system, J_{AB} 13.6, PhCH_2N), 4.19 (1 H, q, *J* 7.0, MeC*H*N), 4.02 (1 H, d, *J* 11.3, PhC*H*CH), 3.54 (3 H, s, OMe), 3.31 (1 H, ddd, *J* 3.6, 11.3 and 11.3, CHCO), 1.99–1.88 and 1.75–1.68 (2 H, m, CH_2CHCO) and 0.92 (3 H, d, *J* 7.0, *Me*CH); δ_C(50 MHz; $CDCl_3$) 174.4 (CO_2), 144.3, 140.1 and 139.1 (PhC_{ipso}), 135.4 (*C*H=CH_2), 129.4, 128.7, 128.5, 128.3 and 128.1 (Ph), 127.8, 127.2 and 126.8 (PhC_{para}), 116.8 (CH=*C*H_2), 63.5 and 55.3 (CHN), 51.2 (OMe), 50.8 (CH_2N), 49.4 (*C*HCO), 34.9 (*C*H_2CHCO) and 13.8 (*Me*CH); *m*/*z* 414 (MH^+, 100%), 300 (45, $MH^+ - CH_2$=$CHCH_2CH_2CO_2Me$), 196 (35, PhCH=N$^+$$CH_2$Ph), 105 (25, $PhCHMe^+$) and 91 (40, $PhCH_2^+$).

Methyl (2S,3S,αR)-2-*allyl*-3-(N-*benzyl*-N-α-*methylbenzylamino*)-3-*phenylpropionate* (2S,3S,αR)-**22**. (Found: C, 81.1; H, 7.7; N, 3.3. $C_{28}H_{31}NO_2$ requires C, 81.32; H, 7.56; N, 3.39%); $\nu_{max}(CHCl_3/cm^{-1}$ 1725 (C=O); δ_H(300 MHz; $CDCl_3$) 7.43–7.22 (15 H, m, Ph), 5.68–5.60 (1 H, m, C*H*=CH_2), 4.98–4.94 (2 H, m, CH=CH_2), 4.17 (1 H, q, *J* 6.8, MeC*H*N), 3.95 and 3.63 (2 H, AB system, J_{AB} 13.8, PhCH_2N), 3.92 (1 H, d, *J* 11.2, PhC*H*CH), 3.22 (3 H, s, OMe), 3.17 (1 H, ddd, *J* 3.4, 11.2 and 11.2, CHCO), 2.94–2.90 and 1.99–1.91 (2 H, m, CH_2CHCO) and 0.97 (3 H, d, *J* 6.8, *Me*CH); δ_C(125 MHz; $CDCl_3$) 174.0 (CO_2), 144.5, 140.0 and 138.9 (PhC_{ipso}), 135.9 (C*H*=CH_2), 129.1, 129.0, 128.4, 128.0 and 127.8 (Ph), 127.0, 126.7 and 126.4 (PhC_{para}), 116.2 (CH=*C*H_2), 62.6 and 56.0 (CHN), 50.7 (OMe), 50.6 (CH_2N), 49.3 (*C*HCO), 35.3 (*C*H_2CHCO) and 15.0 (MeCH); *m*/*z* 414 (MH^+, 35%), 300 (100, $MH^+ - CH_2$=$CHCH_2CH_2CO_2Me$), 196 (75, PhCH=N$^+$$CH_2$Ph), 105 (50, $PhCHCH_3^+$) and 91 (55, $PhCH_2^+$).

Conjugate Addition to tert-*Butyl Cinnamate* **5**.—The conjugate addition of (*R*)-**1** (14.7 mmol) to *tert*-butyl cinnamate **5** (2.00 g, 9.80 mmol) was performed according to procedure (*a*). Purification of the crude product by flash column chromatography on silica gel with a petroleum–diethyl ether (10:1) eluent afforded the conjugate adduct **23** as a colourless oil (3.52 g, 87%).

Tandem Addition–Methylation of tert-*Butyl Cinnamate* **5**.—The conjugate addition of (*R*)-**1** (2.21 mmol) to *tert*-butyl cinnamate **5** (300 mg, 1.47 mmol) followed by alkylation with methyl iodide (0.45 cm^3, 7.3 mmol) was carried out according to procedure (*b*), except that the reaction was warmed to −30 °C for 20 min before the addition of methyl iodide at −78 °C. Purification of the crude product by flash column chromatography on silica gel with a petroleum–diethyl ether (20:1) eluent gave a colourless oil containing the methylated adducts **24** and **25** as a 1.36:1 mixture of diastereoisomers (489 mg, 78%) which could not be separated. However, samples of **24** and **25** were prepared by stepwise methylation and tandem addition–protonation of *tert*-butyl (*E*)-2-methylcinnamate[12] respectively, each with a diastereoisomeric purity of at least 94%.

tert-*Butyl* (2R,3S,αR)-3-(N-*benzyl*-N-α-*methylbenzylamino*)-2-*methyl*-3-*phenylpropionate* (2R,3S,αR)-**24**. $[\alpha]_D^{25}$ −36.8 (*c* 0.60 in $CHCl_3$) (Found: C, 81.2; H, 8.4; N, 3.25. $C_{29}H_{35}NO_2$ requires C, 81.08; H, 8.21; N, 3.26%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 (C=O); δ_H(300 MHz; $CDCl_3$) 7.44–7.16 (15 H, m, Ph), 4.16 (1 H, q, *J* 6.9, MeC*H*N), 4.08 (1 H, d, *J* 11.1, PhC*H*CH), 3.99 and 3.57 (2 H, AB system, J_{AB} 14.2, PhCH_2N), 3.11 (1 H, dq, *J* 6.9 and 11.1, CHCO), 1.50 (9 H, s, CMe_3), 1.04 (3 H, d, *J* 6.9, *Me*CH) and 0.74 (3 H, d, *J* 6.9, *Me*CH); δ_C(50 MHz; $CDCl_3$) 175.3 (CO_2), 144.8, 140.9 and 138.9 (PhC_{ipso}), 129.7, 129.3, 128.5, 128.4, 128.1 and 128.0 (Ph), 127.4, 126.8 and 126.7 (PhC_{para}), 80.0 (*C*Me_3), 65.0 and 57.0 (CHN), 50.8 (CH_2N), 43.7 (*C*HCO), 28.0 (C*Me*$_3$), 16.2 and 15.5 (*Me*CH); *m*/*z* 430 (MH^+, 85%), 300 (60, $MH^+ - MeCH_2CO_2Bu^t$), 196 (100, PhCH=N$^+$$CH_2$Ph), 105 (50, $PhCHMe^+$) and 91 (60, $PhCH_2^+$).

tert-*Butyl* (2S,3S,αR)-3-(N-*benzyl*-N-α-*methylbenzylamino*)-2-*methyl*-3-*phenylpropionate* (2S,3S,αR)-**25**. $[\alpha]_D^{25}$ −68.1 (*c* 1.00 in $CHCl_3$) (Found: C, 80.7; H, 8.5; N, 3.0. $C_{29}H_{35}NO_2$ requires C, 81.08; H, 8.21; N, 3.26%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 (C=O); δ_H(300 MHz; $CDCl_3$) 7.47–7.22 (15 H, m, Ph), 4.18 (1 H, q, *J* 6.8, MeC*H*N), 3.96 and 3.60 (2 H, AB system, J_{AB} 13.7,

PhCH_2N), 3.76 (1 H, d, *J* 11.2, PhC*H*CH), 3.07 (1 H, dq, *J* 6.7 and 11.2, CHCO), 1.18 (3 H, d, *J* 6.7, *Me*CH), 1.00 (9 H, s, CMe_3) and 0.93 (3 H, d, *J* 6.8, *Me*CH); δ_C(50 MHz; $CDCl_3$) 175.0 (CO_2), 144.9, 140.4 and 140.0 (PhC_{ipso}), 129.6, 129.4, 128.5, 128.3 and 128.1 (Ph), 127.3, 127.1 and 126.8 (PhC_{para}), 79.9 (*C*Me_3), 63.5 and 55.3 (CHN), 50.5 (CH_2N), 43.9 (*C*HCO), 27.3 (CMe_3), 16.4 and 14.4 (*Me*CH); *m/z* 430 (MH^+, 80%), 300 (60, $MH^+ - MeCH_2CO_2Bu^t$), 196 (100, $PhCH{=}NH^+CH_2Ph$), 105 (35, $PhCHMe^+$) and 91 (60, $PhCH_2^+$).

Tandem Addition–Benzylation of tert-*Butyl Cinnamate* **5**.—The conjugate addition of (*R*)-**1** (2.21 mmol) to *tert*-butyl cinnamate **5** (300 mg, 1.47 mmol) followed by alkylation with benzyl bromide (0.52 cm^3, 4.41 mmol) was carried out according to procedure (*b*), except that the reaction mixture was warmed to −30 °C for 1 h before the addition of benzyl bromide at −78 °C. Partial purification of the crude oil, which contained both product diastereoisomers **26** and **27** in the ratio of 2.5:1, was achieved by flash column chromatography on silica gel with a petroleum–diethyl ether (30:1) eluent. First compound **26** was eluted with a d.e. of 71% (161 mg, 22%), then a mixed fraction (180 mg, 24%) was collected, both isolated as colourless oils. Compound **27**, however, was prepared in diastereomerically pure form by the tandem addition–protonation of (*R*)-**1** with (*E*)-*tert*-butyl 2-benzylcinnamate.[12]

tert-*Butyl* (2R,3S,αR) 2-*benzyl*-3-(N-*benzyl*-N-α-*methylbenzylamino*)-3-*phenylpropionate* (2R,3S,αR)-**26**. (Found: C, 83.3; H, 7.95; N, 2.7. $C_{35}H_{39}NO_2$ requires C, 83.13; H, 7.77; N, 2.77%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 (C=O); δ_H(300 MHz; $CDCl_3$) 7.55–7.00 (20 H, m, Ph), 4.24 (1 H, q, *J* 6.7, MeC*H*N), 4.17 and 3.66 (2 H, AB system, J_{AB} 14.1, PhCH_2N), 4.16 (1 H, d, *J* 10.8, PhC*H*CH), 3.48 (1 H, td, *J* 4.6 and 10.8, $PhCH_2CH$), 2.41–2.28 (2 H, m, PhCH_2CH), 1.17 (9 H, s, CMe_3), 0.99 (3 H, *J* 6.7, *Me*CH); δ_C(50 MHz; $CDCl_3$) 173.8 (CO_2), 144.5, 140.5, 139.4 and 139.0 (PhC_{ipso}), 130.0, 129.7, 129.3, 128.6, 128.5, 128.2 and 128.0 (Ph), 127.7, 127.0, 126.8 and 126.3 (PhC_{para}), 80.5 (*C*Me_3), 64.5 and 56.5 (CHN), 51.0 (*C*HCO), 51.0 (CH_2N), 37.4 (CH_2CH), 27.8 (CMe_3) and 15.4 (*Me*CH); *m/z* 506 (MH^+, 100%), 300 (90, $MH^+ - PhCH_2CH_2CO_2Bu^t$), 196 (75, $PhCH{=}NH^+CH_2Ph$).

tert-*Butyl* (2S,3S,αR)-2-*benzyl*-3-(N-*benzyl*-N-α-*methylbenzylamino*)-3-*phenylpropionate* (2S,3S,αR)-**27**. $[\alpha]_D^{25}$ −32.7 (*c* 1.06 in $CHCl_3$) (Found: C, 83.2; H, 7.7; N, 2.5. $C_{35}H_{39}NO_2$ requires C, 83.13; H, 7.77; N, 2.77%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 (C=O); δ_H(300 MHz; $CDCl_3$) 7.53–7.03 (20 H, m, Ph), 4.28 (1 H, q, *J* 6.9, MeC*H*N), 4.13 and 3.70 (2 H, AB system, J_{AB} 13.7, PhCH_2N), 3.95 (1 H, d, *J* 11.2, PhC*H*CH), 3.54 and 2.33 (2 H, AB of ABX system, J_{AB} 13.6, J_{AX} 3.5 and J_{BX} 11.9, PhCH_2CH), 3.23 (1 H, ddd, *J* 3.5, 11.2 and 11.9, $PhCH_2CH$), 1.01 (3 H, d, *J* 6.9, *Me*CH) and 0.80 (9 H, s, CMe_3); δ_C(50 MHz; $CDCl_3$) 173.3 (CO_2), 144.9, 140.4 and 139.2 (PhC_{ipso}), 130.0, 129.5, 129.4, 129.1, 128.7, 128.5, 128.3, 128.2 and 128.1 (Ph), 127.6, 127.4, 127.1 and 126.2 (PhC_{para}), 79.9 (*C*Me_3), 63.3 and 55.8 (CHN), 52.1 (*C*HCO), 50.9 (CH_2N), 37.4 (CH_2CH), 27.2 (CMe_3) and 14.7 (*Me*CH); *m/z* 506 (MH^+, 20%), 300 (100, $MH^+ - PhCH_2CH_2CO_2Bu^t$) and 196 (80, $PhCH{=}NH^+CH_2Ph$).

Stepwise Methylation of the Methyl Crotonate Adduct **6**.—Deprotonation of compound **6** (300 mg, 0.96 mmol) with LDA (1.25 mmol) followed by alkylation with methyl iodide (0.30 cm^3, 4.8 mmol) was carried out according to procedure (*c*). Purification of the crude product by filtration through a plug of silica, washing with diethyl ether, afforded a colourless oil made up of the *anti* and *syn* methylated diastereoisomers **7** and **8** in the ratio of 5:1 (280 mg, 89%).

Stepwise Benzylation of Methyl Crotonate Adduct **6**.—Deprotonation of compound **6** (800 mg, 2.57 mmol) with LDA (3.34 mmol) followed by alkylation with benzyl bromide (0.61 cm^3, 5.1 mmol) was carried out according to procedure (*c*). Purification of the crude oil by flash column chromatography on silica gel with a petroleum–dichloromethane (2:1) eluent afforded first compound **9** (225 mg, 22%), followed by a mixed fraction, and then compound **10** (219 mg, 21%); the combined product yield was 52%.

Stepwise Methylation of tert-*Butyl Crotonate Adduct* **11**.—Deprotonation of compound **11** (500 mg, 1.42 mmol) with LDA (2.12 mmol) followed by alkylation with methyl iodide (0.44 cm^3, 7.1 mmol) was carried out according to procedure (*c*). Purification of the crude oil, which contained the product diastereoisomers **12** and **13** in the ratio of 9:1, was accomplished by flash column chromatography on silica gel with a petroleum–dichloromethane (1:1) eluent. After elution of a mixed fraction, pure compound **12** was obtained as a colourless oil (289 mg, 56%); the combined product yield was 69%.

Stepwise Benzylation of tert-*Butyl Crotonate Adduct* **11**.—Deprotonation of compound **11** (300 mg, 0.85 mmol) with LDA (1.10 mmol) followed by alkylation with benzyl bromide (0.20 cm^3, 1.7 mmol) was carried out according to procedure (*c*). Purification of the crude product by flash column chromatography on silica gel with a petroleum–dichloromethane (2:1) eluent gave first compound **14** (177 mg, 47%), followed by compound **15** (136 mg, 36%).

Stepwise Methylation of Methyl Cinnamate Adduct **16**.—Deprotonation of compound **16** (300 mg, 0.80 mmol) with LDA (0.88 mmol) followed by alkylation with methyl iodide (0.30 cm^3, 4.8 mmol) was carried out according to procedure (*c*). Purification of the crude oil by flash column chromatography on silica gel with diethyl ether as eluent furnished the *anti* methylated diastereoisomer **17** in ⩾90% d.e. (236 mg, 76%), subsequently recrystallized from ethanol.

Stepwise Allylation of Methyl Cinnamate Adduct **16**.—Deprotonation of compound **16** (100 mg, 0.27 mmol) with LDA (0.40 mmol) followed by alkylation with allyl bromide (0.20 cm^3, 2.3 mmol) was carried out according to procedure (*c*). Purification of the crude oil by flash column chromatography on silica gel with a petroleum–diethyl ether (4:1) eluent gave the products **21** and **22** as an 8:1 mixture of diastereoisomers (389 mg, 70%).

In a second experiment, potassium bis(trimethylsilyl)amide (0.5 mol dm^{-3} solution in toluene; 4.00 cm^3, 2.00 mmol) was added to a THF (10 cm^3) solution of compound **16** (500 mg, 1.34 mmol) at −98 °C. After the reaction mixture had been stirred at this temp. for 1 h, allyl bromide (1.0 cm^3, 12 mmol was added to it; it was subsequently stirred at −98 °C for 2 h and then at −78 °C for 2 h. Work-up and chromatography, as described above, gave the products **21** and **22** in the ratio of 8:1 (422 mg, 76%).

In a third run, deprotonation of compound **16** (100 mg, 0.27 mmol) was carried out with potassium bis(trimethylsilyl)amide (0.80 cm^3, 0.40 mmol) at −78 °C as described above, and followed by alkylation with allyl iodide (0.20 cm^3, 2.2 mmol, freshly distilled). Work-up and chromatography as described above gave the products **21** and **22** in the ratio of 8:1 (388 mg, 70%).

Stepwise Benzylation of Methyl Cinnamate Adduct **16**.—Potassium bis(trimethylsilyl)amide (27.1 cm^3, 13.6 mmol) was added to a THF (100 cm^3) solution of compound **16** (3.37 g, 9.03 mmol) at −78 °C. After the reaction mixture had been stirred at this temp. for 1 h, benzyl bromide (3.20 cm^3, 27.0 mmol) was added to it. It was then warmed gradually to room temp. overnight, and worked up as described in procedure (*c*). Purification of the crude product was accomplished by flash

column chromatography on silica gel with petroleum–diethyl ether (10:1) as eluent. First eluted was the *anti* benzylated diastereoisomer **19** (2.14 g, 51%), subsequently recrystallized from ethanol, followed by a mixed fraction containing both compound **19** and **20** (1.20 g, 29%).

Stepwise Methylation of tert-*Butyl Cinnamate Adduct* **23**.—Deprotonation of compound **23** (292 mg, 0.70 mmol) with LDA (1.80 mmol) followed by alkylation with methyl iodide (0.22 cm^3, 3.5 mmol) was carried out according to procedure (*c*). Purification of the crude product by flash column chromatography on silica gel with petroleum–diethyl ether (20:1) as eluent furnished the *anti* methylated diastereoisomer **24** in 94% d.e. as a colourless oil (210 mg, 70%).

Stepwise Benzylation of tert-*Butyl Cinnamate Adduct* **23**.—Deprotonation of compound **23** (103 mg, 0.25 mmol) with LDA (0.62 mmol) followed by alkylation with benzyl bromide (0.15 cm^3, 1.2 mmol) was carried out according to procedure (*c*). Purification of the crude product was achieved by flash column chromatography on silica gel with petroleum–diethyl ether (20:1) as eluent, which gave the benzylated products **26** and **27** as a 1.25:1 mixture (51 mg, 41%).

Tandem Enolate Capture with Trimethylsilyl Chloride.—To a solution of (*R*)-**1** (2.36 mmol) in THF (10 cm^3) at −78 °C was added a THF (2 cm^3) solution of *tert*-butyl cinnamate **5** (482 mg, 2.36 mmol). After the mixture had been stirred for 1 h at −78 °C, neat trimethylsilyl chloride (0.30 cm^3, 2.36 mmol, freshly distilled from calcium hydride) was added to it by syringe. The reaction mixture was then warmed to room temp. over 30 min and solvent removed to give a brown oil. ^1H NMR spectroscopic analysis of this crude oil revealed it to consist of approximately 15% starting materials in addition to an 85% yield of the silyl ketene acetal (*Z*)-**28**, free from any trace of its geometrical isomer (*E*)-**29**.

(Z,3S,αR)-3-(N-*Benzyl*-N-α-*methylbenzylamino*)-1-tert-*butoxy*-3-*phenyl*-1-*trimethylsiloxypropene* (Z,3S,αR)-**28**. δ_H(300 MHz; $CDCl_3$) 7.57–7.11 (15 H, m, Ph), 4.57 and 4.21 (2 H, 2 d, *J* 10.1, $CHCO_2$ and CHN), 3.94 (1 H, q, *J* 6.8, MeC*H*N), 3.86 and 3.52 (2 H, AB system, J_{AB} 14.9, PhCH_2N), 1.36 (9 H, s, CMe_3), 1.11 (3 H, d, *J* 6.8, *Me*CH) −0.08 (9 H, s, $SiMe_3$); δ_C(50 MHz; $CDCl_3$) 153.8 (CO_2), 147.1, 145.2 and 143.4 (PhC_{ipso}), 128.3, 128.1, 127.9 and 127.1 (Ph), 126.7, 126.4 and 126.2 (PhC_{para}), 87.6 (*C*HCO_2), 78.3 (*C*Me_3), 60.9 and 59.7 (CHN), 52.2 (CH_2N), 28.7 (C*Me*$_3$), 22.3 (*Me*CH) and 0.1 ($SiMe_3$).

Stepwise Enolate Capture with Trimethylsilyl Chloride.—To a solution of LDA (2.36 mmol) in THF (15 cm^3) at −78 °C was added a THF (2 cm^3) solution of compound **23** (979 mg, 2.36 mmol). After the mixture had been stirred for 1 h at −78 °C, neat trimethylsilyl chloride (0.30 cm^3, 2.36 mmol, freshly distilled from calcium hydride) was added to it by syringe. The reaction mixture was warmed to room temp. over 30 min and then evaporated to give a white oil. ^1H NMR spectroscopic analysis of this crude oil revealed it to consist of approximately 25% starting material **23** in addition to a 75% yield of the two isomeric silyl ketene acetals (*Z*)-**28** and (*E*)-**29** in the ratio of 1:16.

(E,3S,αR)-3-(N-*Benzyl*-N-α-*methylbenzylamino*)-1-tert-*butoxy*-1-*trimethylsiloxy*-3-*phenylpropene* (E,3S,αR)-**29**. δ_H(300 MHz; $CDCl_3$) 7.59–7.12 (15 H, m, Ph), 4.62 and 4.13 (2 H, 2 d, *J* 10.0, $CHCO_2$ and CHN), 3.92 (1 H, q, *J* 6.9, MeC*H*N), 3.79 and 3.52 (2 H, AB system, J_{AB} 15.0, PhCH_2*N*), 1.10 (9 H, s, CMe_3), 1.10 (3 H, d, *J* 6.9, MeCH) and 0.26 (9 H, s, $SiMe_3$); δ_C(50 MHz; $CDCl_3$) 154.5 (CO_2), 147.1, 145.6 and 143.5 (PhC_{ipso}), 128.2 and 128.0 (Ph), 126.5, 126.3 and 126.1 (PhC_{para}), 87.5 (*C*HCO_2), 78.9 (*C*Me_3), 60.7 and 60.1 (CHN), 52.0 (CH_2N), 29.0 (C*Me*$_3$), 21.5 (*Me*CH) and −0.1 ($SiMe_3$).

Tandem Addition–Methylation of tert-*Butyl Cinnamate* **5** *with the Lithium* N,N-*Dibenzylamide* **30**.—The conjugate addition of compound **30** (1.10 mmol) to *tert*-butyl cinnamate **5** (150 mg, 0.74 mmol) followed by alkylation with methyl iodide (0.23 cm^3, 3.7 mmol) was carried out according to procedure (*b*), starting with dibenzylamine. Purification of the crude oil by flash column chromatography on silica gel with petroleum–diethyl ether (20:1) as eluent furnished the *syn* methylated adduct **31** as a colourless oil in ⩾90% d.e. (218 mg, 71%). Recrystallization from methanol–diethyl ether afforded compound **31** in diastereoisomerically pure form.

tert-*Butyl* (2SR,3SR)-3-(N,N-*dibenzylamino*)-2-*methyl*-3-*phenylpropionate* (2SR,3SR)-**31**. M.p. 59–61 °C (Found: C, 80.7; H, 8.1; N, 3.4. $C_{28}H_{33}NO_2$ requires C, 80.93; H, 8.00; N, 3.37%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 (C=O); δ_H(300 MHz; $CDCl_3$) 7.47–7.19 (15 H, m, Ph), 3.87 and 3.02 [4 H, AB system, J_{AB} 13.7, $(PhCH_2)_2N$], 3.75 (1 H, d, *J* 11.5, PhC*H*N), 3.19 (1 H, dq, *J* 6.7 and 11.5, CHCO), 1.45 (3 H, d, *J* 6.7, *Me*CH) and 1.01 (9 H, s, CMe_3); δ_C(50 MHz; $CDCl_3$) 174.9 (CO_2), 140.0 and 135.8 (PhC_{ipso}), 130.1, 129.1, 128.6, 127.9, 127.6 and 127.2 (Ph), 79.9 (*C*Me_3), 64.6 (CHN), 53.7 [$(PhCH_2)_2N$], 42.7 (*C*HCO), 27.3 (C*Me*$_3$) and 16.0 (*Me*CH); *m*/*z* 416 (MH^+, 65%), 286 [90, $PhCH{=}N^+(CH_2Ph)_2$] and 91 (100, $PhCH_2^+$).

Debenzylation of Compound **31**.—Debenzylation of compound **31** (50 mg, 0.12 mmol) was carried out according to procedure (*d*). ^1H NMR spectroscopic analysis of the crude colourless oil (37 mg) served to identify the product as the *syn* methylated diastereoisomer **32**.

Conjugate Addition of Lithium N,N-*Dibenzylamide* **30** *to* tert-*Butyl Cinnamate* **5**.—The conjugate addition of compound **30** (5.15 mmol) to *tert*-butyl cinnamate **5** (700 mg, 3.43 mmol) was performed according to procedure (*a*), starting from dibenzylamine. Purification of the crude oil by flash column chromatography on silica gel with petroleum–diethyl ether (10:1) as eluent afforded the conjugate adduct **33** as a white foam (1.08 g, 79%).

tert-*Butyl* (RS)-3-(N,N-*dibenzylamino*)-3-*phenylpropionate* (RS)-**33**. M.p. 64–66 °C (Found: C, 80.45; H, 7.8; N, 3.5. $C_{27}H_{31}NO_2$ requires C, 80.76; H, 7.78; N, 3.49%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 (C=O); δ_H(300 MHz; $CDCl_3$) 7.39–7.20 (15 H, m, Ph), 4.28 (1 H, m, PhC*H*N), 3.72 and 3.29 [4 H, AB system, J_{AB} 13.7, $(PhCH_2)_2N$], 3.00 and 2.73 (2 H, AB of ABX system, J_{AB} 14.4, J_{AX} 7.0 and J_{BX} 8.6, CH_2CO) and 1.34 (9 H, s, CMe_3); δ_C(50 MHz; $CDCl_3$) 171.4 (CO_2), 140.1 and 138.6 (PhC_{ipso}), 129.1, 128.9, 128.4 and 128.2 (Ph), 127.5 and 127.1 (PhC_{para}), 80.5 (*C*Me_3), 59.2 (CHN), 53.9 (CH_2N), 37.2 (*C*H_2CO) and 27.9 (C*Me*$_3$); *m*/*z* 402 (MH^+, 80%), 286 [40, $PhCH{=}N^+(CH_2Ph)_2$], 196 (55, $PhCH{=}NH^+CH_2Ph$) and 91 (100, $PhCH_2^+$).

Stepwise Methylation of tert-*Butyl Cinnamate Adduct* **33**.—Deprotonation of compound **33** (500 mg, 1.25 mmol) with LDA (2.00 mmol) followed by alkylation with methyl iodide (0.39 cm^3, 6.2 mmol) was carried out according to procedure (*c*). Purification of the crude oil by flash column chromatography on silica gel with petroleum–diethyl ether (20:1) as eluent afforded a white solid made up of the *anti* and *syn* methylated diastereoisomers **34** and **31** in the ratio of 1.5:1 (434 mg, 84%). Although separation of these products by chromatography was not possible, a single recrystallization of the mixture from methanol furnished the *anti* methylated diastereoisomer **34** in 96% d.e. (192 mg, 37%).

tert-*Butyl* (2RS,3SR)-3-(N,N-*dibenzylamino*)-2-*methyl*-3-*phenylpropionate* (2RS,3SR)-**34**. M.p. 103–106 °C (Found: C, 81.0; H, 8.2; N, 3.3. $C_{28}H_{33}NO_2$ requires C, 80.93; H, 8.00; N, 3.37%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 (C=O); δ_H(300 MHz; $CDCl_3$)

7.62–7.06 (15 H, m, Ph), 3.97 and 2.96 [4 H, AB system, J_{AB} 13.5, $(PhCH_2)_2N$], 3.90 (1 H, d, *J* 11.6, PhC*H*N), 3.26 (1 H, dq, *J* 6.7 and 11.6, CHCO), 1.57 (9 H, s, CMe_3) and 0.81 (3 H, d, *J* 6.7, *Me*CH); δ_C(50 MHz; $CDCl_3$) 175.1 (CO_2), 139.8 and 134.9 (PhC_{ipso}), 129.9, 129.4, 128.3, 127.7 and 127.1 (Ph), 80.2 (*C*Me_3), 65.6 (CHN), 54.1 [(Ph*C*H_2)N], 43.1 (*C*HCO), 28.2 (C*Me*$_3$), 16.2 (*Me*CH); *m*/*z* 416 (MH^+, 50%), 286 [50, $PhCH{=}N^+(CH_2Ph)_2$] and 91 (100, $PhCH_2^+$).

Debenzylation of Compound **17**.—To a solution of compound **17** (531 mg, 1.37 mmol) in methanol–water–acetic acid (20:2:1, 10 cm^3) was added $Pd(OH)_2$–C (Pearlman's catalyst, 250 mg) and the resultant black suspension stirred under a hydrogen balloon overnight. The reaction mixture was then filtered through a plug of Celite, washing with methanol and the filtrate concentrated to give a white solid. This residue was dissolved in sat. aq. $NaHCO_3$ which was subsequently extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to afford the free amino ester **35** as a colourless crystalline solid (219 mg, 83%).

Methyl (2R,3S)-3-*amino*-2-*methyl*-3-*phenylpropionate* (2R,-3S)-**35**. $[\alpha]_D^{25}$ −29.2 (*c* 1.00 in $CHCl_3$); m.p. 28–29 °C (Found: C, 68.6; H, 8.1; N, 7.0. $C_{11}H_{15}NO_2$ requires C, 68.37; H, 7.82; N, 7.25%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 br (NH) and 1725 (C=O); δ_H (300 MHz; $CDCl_3$) 7.38–7.25 (5 H, m, Ph), 4.03 (1 H, d, *J* 9.5, PhC*H*CH), 3.74 (3 H, s, OMe), 2.71 (1 H, dq, *J* 9.5 and 7.1, MeC*H*), 1.69 (2 H, br s, NH_2) and 0.96 (3 H, d, *J* 7.1, *Me*CH); δ_C(50 MHz; $CDCl_3$) 176.5 (CO_2), 143.7 (PhC_{ipso}), 128.6 (Ph), 127.6 (PhC_{para}), 127.1 (Ph), 59.0 ($CHNH_2$), 51.5 (OMe), 47.9 (*C*HCO) and 15.1 (*Me*CH); *m*/*z* 194 (MH^+, 75%), 177 (35, $MH^+ - NH_3$) and 106 (100, $PhCH{=}NH_2^+$).

Hydrolysis of the Methyl Ester **35**.—A sample of compound **35** (6 mg, 30 μmol) was dissolved in 20% aq. hydrochloric acid (5 cm^3) and the solution stirred for 16 h at 100 °C. Removal of solvent by evaporation afforded the β-amino acid hydrochloride salt **38** as a white solid (6 mg, 90%).

(2R,3S)-2-*Methyl*-3-*phenyl*-3-*aminopropionoic acid hydrochloride* (2R,3S)-**38**. $[\alpha]_D^{25}$ +10.2 (*c* 1.94 in MeOH); m.p. 235–240 °C (dec.) (Found: C, 55.4; H, 6.55; N, 6.5. $C_{10}H_{14}NO_2Cl$ requires C, 55.69; H, 6.54; N, 6.49%); ν_{max}(Nujol mull)/cm^{-1} 1720, 1595, 1200 and 725; δ_H(300 MHz; CD_3OD) 7.52–7.43 (5 H, m, Ph), 4.42 (1 H, d, *J* 10.0, PhC*H*N), 3.06 (1 H, dq, *J* 7.2 and 10.0, CHCO) and 1.06 (3 H, d, *J* 7.2, *Me*CH); δ_C(50 MHz; D_2O) 177.4 (CO_2), 134.2 (PhC_{ipso}), 129.6 (PhC_{para}) 129.4, 127.4 (Ph), 56.6 (CHN), 42.5 (*C*HCO) and 13.8 (*Me*CH); *m*/*z* 180 (MH^+, 100%) and 106 (55, $PhCH{=}NH_2^+$).

Hydrolysis of Compound **17**.—A solution of compound **17** (800 mg, 2.07 mmol) and lithium hydroxide monohydrate (5.00 g, 120 mmol) in methanol–water–THF (6:3:1, 50 cm^3) was heated at reflux for 4 h. After evaporation of solvent under reduced pressure, the residue was partitioned between diethyl ether and water. The organic phase was dried ($MgSO_4$), filtered and evaporated to give a colourless oil which was purified by flash column chromatography on silica gel. The first fraction, eluted with dichloromethane, consisted of recovered starting material **17** (130 mg, 16%); however, the second, eluted with diethyl ether, contained the desired amino acid product **39** (500 mg, 64%), obtained as a white foam after evaporation of the solvent.

(2R,3S,αR)-3-(N-*Benzyl*-N-α-*methylbenzylamino*)-2-*methyl*-3-*phenylpropionic acid* (2R,3S,αR)-**39**. $[\alpha]_D^{25}$ −27.0 (*c* 1.00 in $CHCl_3$); m.p. 102–104 °C (Found: C, 80.2; H, 7.5; N, 3.45. $C_{25}H_{27}NO_2$ requires C, 80.40; H, 7.29; N, 3.75%); ν_{max}-$(CHCl_3)/cm^{-1}$ 1700 br s (C=O); δ_H(300 MHz; $CDCl_3$) 7.52–7.07 (15 H, m, Ph), 4.27 and 3.71 (2 H, AB system, J_{AB} 13.3, PhCH_2N), 4.18 (1 H, q, *J* 7.0, MeC*H*N), 4.11 (1 H, d, *J* 11.8, PhC*H*CH), 3.02 (1 H, dq, *J* 11.8 and 7.0, CHCO), 1.18 (3 H, d, *J* 7.0, *Me*CH) and 0.88 (3 H, d, *J* 7.0, *Me*CH); δ_C(50 MHz; $CDCl_3$) 177.2 (CO_2), 140.4, 136.5 and 136.3 (PhC_{ipso}), 129.8, 129.6, 128.9, 128.8, 128.7, 128.3, 128.1 and 128.0 (Ph), 64.2 and 57.6 (CHN), 50.7 (CH_2N), 39.3 (*C*HCO), 14.8 and 14.0 (*Me*CH); *m*/*z* (FAB^+) 374 (M^+, 30%), 196 (30, $PhCH{=}NH^+CH_2Ph$), 105 (100, $PhCHMe^+$) and 91 (30, $PhCH_2^+$).

Cyclization of Compound **35** *to* (3R,4S)-3-*Methyl*-4-*phenylazetidinone* **37**.—To a solution of LDA (2.19 mmol) in THF (10 cm^3) at −78 °C was added a THF (2 cm^3) solution of the methyl ester **35**, causing a pale purple coloration to appear. Stirring was continued at −78 °C for 2 h after which the reaction was quenched by the addition of pH 7 aqueous phosphate buffer to the mixture. The residue obtained by evaporation of solvent under reduced pressure was partitioned between diethyl ether and water and the organic phase dried ($MgSO_4$), filtered and evaporated to give a yellow solid. This crude product was filtered through a plug of silica, washing with diethyl ether, to afford the β-lactam **37** as a pale yellow solid (85 mg, 72%), subsequently recrystallized from diethyl ether–ethyl acetate.

(3R,4S)-3-*Methyl*-4-*phenylazetidinone* (3R,4S)-**37**. $[\alpha]_D^{25}$ −39.0 (*c* 1.00 in $CHCl_3$); m.p. (lit.,[14]) 118–120 °C (Found: C, 74.6; H, 7.0; N, 8.8. $C_{10}H_{11}NO$ 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.,[14,15]; 300 MHz; $CDCl_3$) 7.47–7.30 (5 H, m, Ph), 6.13 (1 H, br s, NH), 4.32 (1 H, d, *J* 2.3, PhC*H*N), 3.08 (1 H, dq, *J* 7.5 and 2.3, CHCO) and 1.44 (3 H, d, *J* 7.5, *Me*CH); δ_C(lit.,[15]; 50 MHz; $CDCl_3$) 172.2 (CON), 140.2 (PhC_{ipso}), 129.0 (Ph), 128.3 (PhC_{para}), 125.7 (Ph), 59.2 (CHN), 56.4 (*C*HCO) and 12.9 (*Me*CH); *m*/*z* 162 (MH^+, 100%) and 106 (20, $PhCH{=}NH_2^+$).

Debenzylation of Compound **24**.—Debenzylation of compound **24** (1.08 g, 2.52 mmol, 94% d.e.) was carried out according to procedure (*d*). Purification of the crude oil (466 mg, 79%, 94% d.e.) thus obtained by flash column chromatography on silica gel with diethyl ether–petroleum (2:1) as eluent furnished the free amino ester **36** in diastereoisomerically pure form as a colourless oil (347 mg, 59%).

tert-*Butyl* (2R,3S)-3-*amino*-2-*methyl*-3-*phenylpropionate* (2R,3S)-**36**. $[\alpha]_D^{25}$ −37.7 (*c* 1.06 in $CHCl_3$) (Found: C, 71.65; H, 9.2; N, 5.8. $C_{14}H_{21}NO_2$ requires C, 71.46; H, 9.00; N, 5.95%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1715 (C=O); δ_H(300 MHz; $CDCl_3$) 7.34–7.24 (5 H, m, Ph), 4.00 (1 H, d, *J* 9.3, PhC*H*N), 2.59 (1 H, dq, *J* 7.1 and 9.3, CHCO), 1.66 (2 H, br s, NH_2), 1.48 (9 H, s, CMe_3) and 0.92 (3 H, d, *J* 7.1, *Me*CH); δ_C(50 MHz; $CDCl_3$) 175.7 (CO_2), 143.7 (PhC_{iiso}), 128.7 and 127.4 (Ph), 127.6 (PhC_{para}), 80.6 (*C*Me_3), 59.0 (CHN), 48.8 *C*HCO), 28.0 (C*Me*$_3$) and 15.4 (*Me*CH); *m*/*z* 236 (MH^+, 100%), 180 (80, $MH^+ - Me_2C{=}CH_2$) and 106 (70, $PhCH{=}NH_2^+$).

Hydrolysis of the tert-*Butyl Ester* **36**.—A solution of compound **36** (31 mg, 0.13 mmol) in trifluoroacetic acid (2 cm^3) was stirred at room temp. for 2 h. Evaporation of solvent under reduced pressure gave a colourless oil which was dissolved in methanol (5 cm^3). Gaseous hydrogen chloride was bubbled through the solution for 10 s after which it was evaporated to afford the β-amino acid hydrochloride **38** as a white solid (24 mg, 84%).

Hydrolysis of the tert-*Butyl Ester* **24**.—A solution of compound **24** (110 mg, 0.26 mmol, 94% d.e.) in trifluoroacetic acid (TFA) (5 cm^3) was refluxed for 2 h. Evaporation of the solvent under reduced pressure gave a colourless oil which was purified by flash column chromatography on silica gel with petroleum–diethyl ether (1:1) as eluent. The purified TFA salt

was then dissolved in diethyl ether and the solution was washed with aqueous 1 mol dm^{-3} lithium hydroxide. The organic phase was dried ($MgSO_4$), filtered and evaporated to give the amino acid product **39** as a colourless oil (50 mg, 52%, 94% d.e.).

Methanolysis of the tert-*Butyl Ester* **36**.—Gaseous hydrogen chloride was bubbled through a solution of compound **36** (33 mg, 0.14 mmol) in methanol (5 cm^3) for 1 min after which the reaction mixture was stirred at room temp. overnight. After evaporation of solvent, the residue was partitioned between dichloromethane and sat. aq. $NaHCO_3$. The organic phase was dried ($MgSO_4$), filtered and evaporated to give the free amino ester **35** as a colourless solid (22 mg, 81%).

Cyclization of the tert-*Butyl Ester* **36** *to* (3R,4S)-3-*Methyl*-4-*phenylazetidinone* **37**.—In an analogous fashion to that described for the methyl ester **35** above, a sample of compound **36** (50 mg, 0.21 mmol) was cyclized to the β-lactam **37** with LDA (0.63 mmol). The crude product was purified by flash column chromatography on silica gel with a diethyl ether–petroleum (2:1) eluent to give the pure β-lactam **37** as a white solid (20 mg, 59%).

Debenzylation of Compound **19**.—Debenzylation of compound **19** (350 mg, 0.76 mmol) was carried out according to procedure (*d*). Purification of the crude product by flash column chromatography on silica gel with diethyl ether as eluent afforded the free amino ester **40** as a white solid (99 mg, 49%), subsequently recrystallized from heptane–diethyl ether.

Methyl (2R,3S)-3-*amino*-2-*benzyl*-3-*phenylpropionate* (2R,3S)-**40**. $[\alpha]_D^{25}$ +3.3 (*c* 0.48 in $CHCl_3$); m.p. 51–52 °C (Found: C, 75.8; H, 7.1; N, 5.2. $C_{17}H_{19}NO_2$ requires C, 75.92; H, 7.21; N, 5.00%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730 (C=O); δ_H(300 MHz; $CDCl_3$) 7.41–7.02 (10 H, m, Ph), 4.11 (1 H, d, *J* 9.0, PhC*H*CH), 3.55 (3 H, s, OMe), 2.97 (1 H, ddd, *J* 10.7, 9.0 and 4.4, CHCO), 2.79 and 2.57 (2 H, AB of ABX system, J_{AB} 13.4, J_{AX} 10.7 and J_{BX} 4.4, PhCH_2CH) and 1.64 (2 H, br s, NH_2); δ_C(50 MHz; $CDCl_3$) 175.3 (CO_2), 144.1 and 139.1 (PhC_{ipso}), 129.0, 128.8 and 128.6 (Ph), 127.9 (PhC_{para}), 127.0 (Ph), 126.6 (PhC_{para}), 58.4 (CHN), 56.3 (*C*HCO), 51.4 (OMe) and 36.5 (CH_2CH); *m*/*z* 270 (MH^+, 85%) and 106 (100, $PhCH{=}NH_2^+$).

Hydrolysis of the Methyl Ester **40**.—A sample of compound **40** (35 mg, 0.13 mmol) was dissolved in 20% aq. hydrochloric acid and stirred for 16 h at 100 °C. Evaporation of solvent under reduced pressure afforded the β-amino acid hydrochloride salt **41** as a white solid (31 mg, 82%) which was subsequently recrystallized from ethanol.

(2R,3S)-3-*Amino*-2-*benzyl*-3-*phenylpropionic acid hydrochloride* (2R,3S)-**40**. $[\alpha]_D^{25}$ +31.3 (*c* 0.90 in MeOH); m.p. 205–210 °C (dec.) (Found: C, 65.9; H, 6.2; N, 4.8. $C_{16}H_{18}NO_2Cl$ requires C, 65.94; H, 6.16; N, 4.75%); ν_{max}(Nujol mull)/cm^{-1} 1710, 1610, 720 and 700; δ_H(300 MHz; D_2O) 7.38–6.92 (10 H, m, Ph), 4.37 (1 H, d, *J* 9.5, PhC*H*CH), 3.17 (1 H, m, CHCO), 2.67 and 2.58 (2 H, AB of ABX system, J_{AB} 13.9, J_{AX} 4.5 and J_{BX} 9.2, PhCH_2CH); δ_C(50 MHz; $CDCl_3$) 176.5 (CO_2), 138.0 and 134.8 (PhC_{ipso}), 130.6, 130.3, 129.6, 129.4 and 128.4 (Ph), 127.8 (PhC_{para}), 56.8 (CHN), 51.6 (*C*HCO) and 35.9 (CH_2CH); *m*/*z* 256 (MH^+, 25%) and 106 (100, $PhCH{=}NH_2^+$).

Reduction of Compound **19**.—A solution of compound **19** (1.00 g, 2.16 mmol) and lithium aluminium hydride (123 mg, 3.24 mmol) in THF (50 cm^3) was heated at reflux under an atmosphere of nitrogen for 3 h. The cooled reaction was quenched by the cautious addition of water followed by sufficient 10% aq. hydrochloric acid to render the reaction mixture acidic. After evaporation of solvent under reduced pressure, the residue was partitioned between diethyl ether and sat. aq. $NaHCO_3$. The organic phase was dried ($MgSO_4$), filtered and evaporated to give a colourless oil which was filtered through a plug of silica, washing with diethyl ether. Final evaporation of that solvent yielded the product alcohol **42** as a white foam (814 mg, 87%), subsequently recrystallized from hexane.

(2R,3S,αR)-2-*Benzyl*-3-(N-*benzyl*-N-α-*methylbenzylamino*)-3-*phenylpropan*-1-*ol* (2R,3S,αR)-**42**. $[\alpha]_D^{25}$ −54.6 (*c* 1.00 in $CHCl_3$); m.p. 106–108 °C (Found: C, 85.6; H, 7.7; N, 3.4. $C_{31}H_{33}NO$ requires C, 85.48; H, 7.64; N, 3.22%); ν_{max}-($CHCl_3$)/cm^{-1} 3570 (OH); δ_H(300 MHz; $CDCl_3$) 7.48–6.92 (20 H, m, Ph), 4.26 and 3.67 (2 H, AB system, J_{AB} 13.2, PhCH_2N), 4.19 (1 H, q, *J* 7.0, PhC*H*N), 3.79 (1 H, m, CH_2OH), 3.76 (1 H, d, *J* 11.0, PhC*H*CH), 3.14–3.05 (2 H, m, C*H*CH_2 and O*H*), 2.47 (1 H, m, CH_2OH), 2.15 and 1.96 (2 H, AB of ABX system, J_{AB} 13.6, J_{AX} 2.6 and J_{BX} 11.0, PhCH_2CH) and 0.94 (3 H, d, *J* 7.0, *Me*CH); δ_C(50 MHz; $CDCl_3$) 143.9, 141.0, 139.6 and 139.5 (PhC_{ipso}), 130.0, 129.5, 129.1, 129.0, 128.7, 128.3, 127.6, 127.4 and 125.9 (Ph), 64.2 (CHN), 62.7 (CH_2N), 55.8 (CHN), 51.4 (CH_2OH), 43.7 (*C*HCH_2), 34.5 (PhCH_2CH) and 13.0 (*Me*CH); *m*/*z* 436 (MH^+, 85%), 300 (100, MH^+ − Ph-$[CH_2]_3OH$), 196 (70, $PhCH{=}NH^+CH_2Ph$), 105 (65, $PhCHMe^+$) and 91 (100, $PhCH_2^+$).

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