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Asymmetric synthesis of *anti*-α-alkyl-β-amino carboxamides

Stephen G. Davies *, Alison J. Edwards and Iain A.S. Walters

The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, UK
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Abstract. The alkylation reactions of enolates derived from the highly diastereoselective conjugate additions of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide (*R*)-**1** to *N*,*N*-dimethyl crotonamide **2** and *N*,*N*-dimethyl cinnamide **3** have been investigated. The alkylations of enolates derived from **3** are shown to afford *anti*-α-alkyl-β-amino carboxamides with excellent stereocontrol: the stereochemistry is assigned with the aid of a single crystal X-ray structure of (2*R*,3*S*,α*R*)-*N*,*N*-dimethyl 2-benzyl-3-phenyl-3-(*N*-benzyl-*N*-α-methylbenzylamino)propanamide (2*R*,3*S*,α*R*)-**10**. As a result of the difficulty encountered in hydrolysing these hindered β-amino amides such as **10**, an alternative procedure is developed involving conjugate addition-alkylations with α,β-unsaturated *N*-acyloxazolidin-2-ones as substrates, giving selectively alkylated products which are susceptible to reductive cleavage.

Introduction

As part of our investigations into the conjugate addition chemistry[1] of the homochiral lithium amide, lithium *N*-benzyl-*N*-(α-methylbenzyl)amide ($PhCH_2$)(PhCHMe)NLi (**1**), we have examined the alkylation behaviour of several types of β-amino metal enolates with the aim of developing a general approach for the asymmetric synthesis of α-alkyl-β-amino acids. We have previously reported[2] the result of trimethylsilyl chloride trapping experiments which show that the tandem [a] quench of the conjugate addition of (*R*)-**1** to an α,β-unsaturated ester gives rise to a different enolate geometry than the corresponding stepwise deprotonation of the conjugate addition product. We also observed that the tandem and stepwise alkylation reactions of these β-amino ester enolates both generated *anti* α-alkyl-β-amino esters, but with different degrees of stereoselectivity (Scheme 1).

Herein we would like to report the alkylation stereoselectivity patterns of the corresponding β-amino amide enolates. It was of interest to us to discover whether the different steric and electronic properties of the carboxamide functionality would give rise to a disparate set of selectivity data, particularly in the light of the dependence of β-amino ester enolate alkylation on enolate geometry. Consequently, the tandem and stepwise conjugate addition–alkylation properties of (*R*)-**1** with crotonamide [b] and cinnamamide [b] systems were determined.

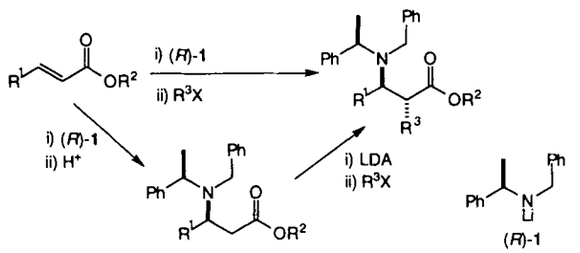
Results and discussion

The first requirement of this work was confirmation that the hitherto excellent β-stereocontrol of the lithium amide (*R*)-**1** over its conjugate additions to ester substrates[1,2] was maintained in additions to α,β-unsaturated amides. Accordingly, *N*,*N*-dimethyl crotonamide **2** and cinnamamide **3** were subjected to the previously established lithium amide conjugate addition conditions. In both cases a conjugate addition stereoselectivities of > 94% d.e. [c] could be confidently asserted from ^{1}H nmr spectroscopic analysis of the crude conjugate adducts **4** and **5**, which were both isolated in good yield (Scheme 2).

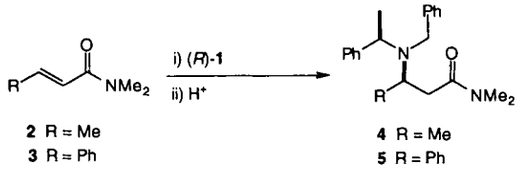
With the stereoselective formation of the C-3 stereocentre thus assured, the tandem and stepwise alkylation reactions of (*R*)-**1** with **2** (Scheme 3) and **3** (Scheme 4) were performed in a similar manner to that described previously for the corresponding ester reactions[1,2].

It was found that both the tandem and stepwise crotonamide methylation reactions were essentially non-selective, in common with the reactions of the corresponding β-amino ester enolates.[2] However, in contrast to the variably selective ester reactions, the tandem and stepwise cinnamamide alkylations were marked by a high selectivity in favour of the *anti* product. Also noteworthy is the uniform selectivity of the two modes of alkylation, a feature which is suggestive of a common (*Z*) enolate geometry in these amide alkylations, which is to be expected given the known preferences for *Z*-enolate formation shown by lithium amide conjugate additions[3] and carboxamide deprotonations.[4] The *anti* C-2/C-3 relative stereochemistry of the cinnamamide adducts **8**, **9** and **11** were assigned by analogy with **10**, the structure of which was determined by single crystal X-ray structure analysis (Figure 1). Fractional atomic coordinates are listed in Table I and selected torsion angles are listed in Table II. The reason for the high *anti* selectivity of the cinnamamide alkylations is not entirely clear, given that the tandem benzylation of **3** with lithium *N*,*N*-dibenzylamide

[a] Tandem means: one pot sequential amide/electrophile quench
[b] Crotonamide = (*E*)-but-2-enamide; cinnamamide (*E*)-3-phenylprop-2-enamide.
[c] d.e. = diastereoisomeric excess.



Scheme 1.



Scheme 2.

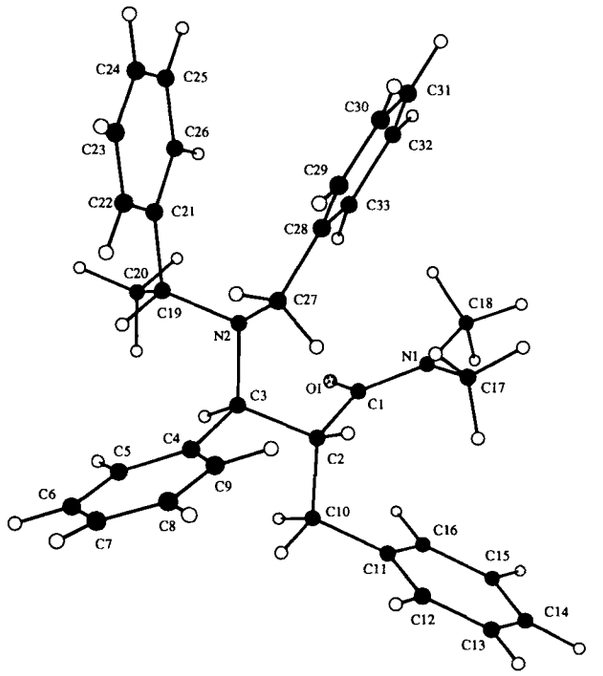


Figure 1. Crystal structure of amide (2R,3S,αR)-10.

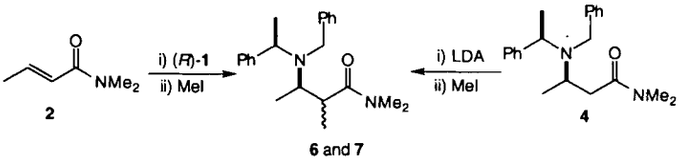
Table I Fractional atomic coordinates for (2R,3S,αR)-N,N-dimethyl-2-benzyl-3-phenyl-3-(N-[benzyl-N-(α-methylbenzyl)amino]propanamide [(2R,3S,αR)-10].

Atom	x / a	y / b	z / c	U(eq)
O(1)	−0.1445(2)	−0.22076(8)	−0.72435(7)	0.0618
N(1)	0.0900(3)	−0.30758(8)	−0.73234(8)	0.0581
N(2)	0.2363(2)	−0.12912(7)	−0.77423(6)	0.0423
C(1)	0.0309(3)	−0.24284(9)	−0.71440(8)	0.0490
C(2)	0.1815(3)	−0.19738(8)	−0.67895(7)	0.0436
C(3)	0.1944(3)	−0.12408(8)	−0.70885(7)	0.0416
C(4)	0.3398(3)	−0.07394(8)	−0.67557(7)	0.0435
C(5)	0.2696(4)	−0.00645(9)	−0.66146(8)	0.0519
C(6)	0.3984(4)	0.0428(1)	−0.6351(1)	0.0584
C(7)	0.6002(4)	0.0255(1)	−0.6216(1)	0.0600
C(8)	0.6714(4)	−0.0414(1)	−0.63401(9)	0.0582
C(9)	0.5437(3)	−0.0905(1)	−0.66119(8)	0.0507
C(10)	0.0956(4)	−0.1904(1)	−0.61458(8)	0.0534
C(11)	0.0678(4)	−0.2599(1)	−0.58268(8)	0.0527
C(12)	0.2226(4)	−0.2866(1)	−0.54650(9)	0.0644
C(13)	0.1959(6)	−0.3497(1)	−0.5162(1)	0.0793
C(14)	0.0147(6)	−0.3866(1)	−0.5219(1)	0.0774
C(15)	−0.1387(5)	−0.3620(1)	−0.5580(1)	0.0769
C(16)	−0.1142(4)	−0.2979(1)	−0.5883(1)	0.0680
C(17)	0.2876(5)	−0.3407(1)	−0.7197(1)	0.0766
C(18)	−0.0638(5)	−0.3506(1)	−0.7639(1)	0.0835
C(19)	0.2009(3)	−0.05972(9)	−0.80388(8)	0.0468
C(20)	−0.0295(4)	−0.0418(1)	−0.8043(1)	0.0662
C(21)	0.2908(3)	−0.05499(9)	−0.86655(8)	0.0490
C(22)	0.4794(4)	−0.0222(1)	−0.8749(1)	0.0666
C(23)	0.5651(5)	−0.0159(2)	−0.9320(2)	0.0896
C(24)	0.4574(7)	−0.0414(2)	−0.9805(2)	0.0969
C(25)	0.2699(7)	−0.0731(2)	−0.9733(1)	0.0875
C(26)	0.1865(4)	−0.0802(1)	−0.91697(9)	0.0639
C(27)	0.4333(3)	−0.16245(9)	−0.78967(8)	0.0469
C(28)	0.4190(3)	−0.20865(9)	−0.84542(8)	0.0473
C(29)	0.5955(4)	−0.2226(1)	−0.8783(1)	0.0616
C(30)	0.5856(5)	−0.2665(1)	−0.9289(1)	0.0699
C(31)	0.4014(5)	−0.2959(1)	−0.9460(1)	0.0700
C(32)	0.2257(5)	−0.2828(1)	−0.9132(1)	0.0669
C(33)	0.2344(4)	−0.2394(1)	−0.86278(9)	0.0564

Table II Selected torsion angles for (2R,3S,αR)-10.

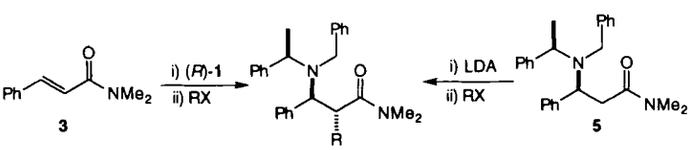
N(2)–C(3)–C(2)–C(1)	−51.17
C(20)–C(19)–N(2)–C(3)	−69.49
C(4)–C(3)–C(2)–C(10)	61.33
C(26)–C(21)–C(19)–C(20)	−41.68
N(2)–C(27)–C(28)–C(29)	156.41

12 was weakly *syn* selective (Scheme 5). The *syn* selectivity became apparent when debenzylation of the major product **13** afforded a primary amino amide **15** epimeric



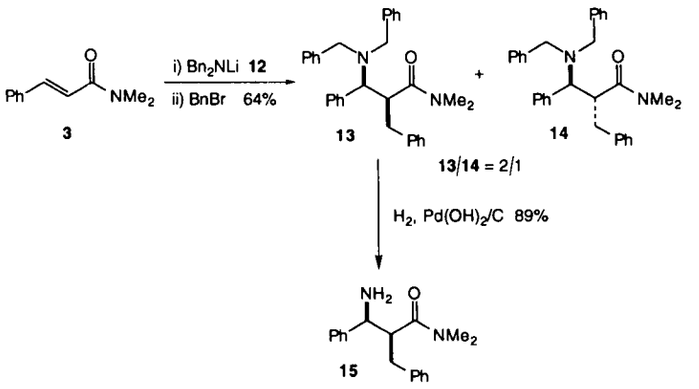
Tandem: 6 / 7 = 1.5 / 1; 20% d.e.; 29% yield *Stepwise: 6 / 7 = 1 / 1; 0% d.e.; 46% yield*
Tandem: 6 / 7 = 2.5 / 1; 43% d.e.; 54% yield (with 3 eq. TMEDA)

Scheme 3.

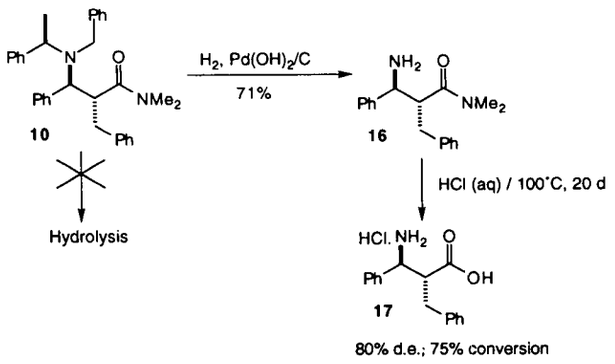


Tandem: 8 > 94% d.e.; 70% yield *8 R = Me* *Stepwise: 8 > 94% d.e.; 80% yield*
Tandem: 9 > 94% d.e.; 71% yield *9 R = Allyl* *Stepwise: 9 > 94% d.e.; 75% yield*
Tandem: 10 > 94% d.e.; 89% yield *10 R = Bn (benzyl)* *Stepwise: 10 > 94% d.e.; 72% yield*
Tandem: 11 82% d.e.; 80% yield *11 R = Et*

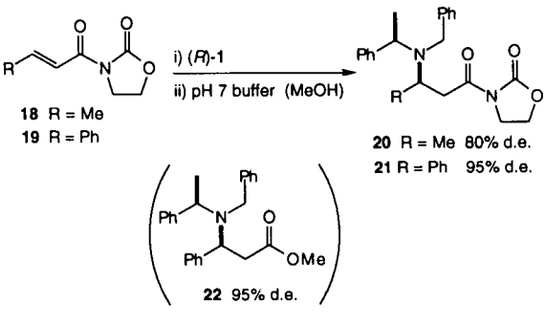
Scheme 4.



Scheme 5.



Scheme 6.

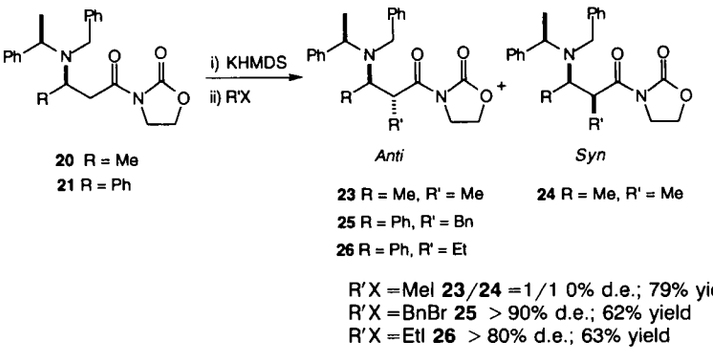


Scheme 7.

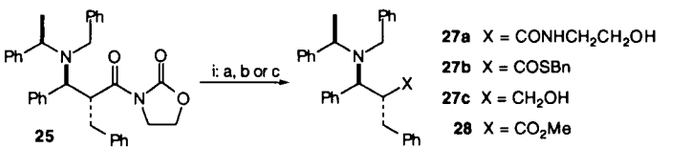
with that derived from **10** (see Schemes 5 and 6). These results are consistent with chelation-controlled addition of the lithium amide (*R*)-**1** to one face of *N*,*N*-dimethyl cinnamamide **3**, with subsequent steric shielding of that face in the thus formed chelated *Z*-enolate; the (α-methylbenzyl)amino stereocentre is evidently essential for this enolate diastereofacial discrimination.

Debenzylation of the corresponding major (α-methylbenzyl)amino adduct **10** also proved straightforward, but all attempts to hydrolyse the carboxamide group met with failure. Furthermore, although acidic hydrolysis of the debenzylated amide **16** was possible, the harsh conditions required resulted in partial loss of stereochemical integrity (Scheme 6).

The reluctance of **10** to undergo hydrolysis is presumably caused by excessive steric hindrance to nucleophilic attack as a result of the bulky C-2 centre since similar problems were encountered in attempts to hydrolyse the corresponding methyl ester[2]. This difficulty limits the practical usefulness of these amide alkylations, and so a surrogate conjugate acceptor was sought which could emulate the selective alkylations of **3** but products of which would be more amenable to hydrolysis. The most promising candidate was found to be the *N*-acyloxazolidin-2-one **19**. Con-



Scheme 8.



Scheme 9. Reagents: a, LiOOH; b, LiSBn; c, $LiAlH_4$

jugate addition to **19** followed by methanol quench generated the methyl ester adduct **22** in 95% d.e. and 80% yield. Use of a pH 7 buffer solution in place of methanol allowed isolation of the oxazolidin-2-one adduct **21** with comparable reaction stereocontrol. However, addition to the crotonoyl acceptor **18** was found to proceed with diminished stereoselectivity giving **20** in 80% d.e. (Scheme 7).

The lithium enolates derived from the conjugate addition to these acceptors were insufficiently reactive to permit satisfactory alkylation. Since the alkylation reactions of enolates bound to the Evans' oxazolidin-2-one chiral auxiliaries were known to proceed at a lower temperature with sodium in place of lithium as a counter-ion[5], it was decided to investigate the reactivity of a more electropositive metal enolate with our system. Adoption of a stepwise approach employing potassium enolates proved successful (Scheme 8), generating similar alkylation stereoselectivities to those described for the carboxamide reactions. Thus, methylation of **20** was non-selective, but benzylation and ethylation of **21** appeared to be highly selective. Consequently, the hydrolysis of **25** became a worthwhile objective. Unfortunately, the hydrolytic lability of the straight conjugate adduct **21** was not matched by the more hindered **25**. Oxygen nucleophiles, even hydroperoxide, selectively attacked the endocyclic carbonyl; only lithium benzyl thiolate and lithium aluminium hydride afforded the desired exocyclic cleavage (Scheme 9).

Reductive cleavage with lithium aluminium hydride represents a potential solution to the amide hydrolysis problem, since it may be possible to oxidise the alcohol **27c** to an amino acid by known methods[6]. The preparation of **27c** allows the assignment of *anti* C-2/C-3 relative stereochemistry to **25**, since **27c** has also been prepared from the *anti* methyl ester **28**[2].

The results presented in this paper demonstrate the improvement in diastereofacial selectivity in the alkylation of a β-amino enolate brought about by replacing the ester functionality with a tertiary amide. The high *anti* asymmetric induction of cinnamamide alkylations evidently relies on the cooperative influence of the (α-methylbenzyl)amino stereocentre, since tandem conjugate addition–benzylation with the achiral lithium *N*,*N*-dibenzylamide was weakly *syn* selective. Although further investigation into amide conjugate acceptors was forestalled by the hydrolytic intransigence of the amide group, use of an oxazolidin-2-one group in place of the amide furnished a system with comparable selectivity results but which was susceptible to reductive cleavage.

Experimental

Optical rotations were determined using a Perkin–Elmer 241 polarimeter with a thermally jacketed 10-cm cell. 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 Hertz. 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 and toluene were distilled from sodium benzophenone ketyl under an atmosphere of dry nitrogen. Petrol refers to 40/60 petroleum ether, 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.

Procedure for conjugate additions to amide acceptors

(*a*) A solution of (*R*)-(+)-*N*-benzyl-*N*(α-methylbenzyl)amine[7] (3.2 mmol) in THF (10 cm^3) was cooled to −78°C prior to the slow addition of butyllithium (1.6 M, 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 ml) solution of the requisite conjugate acceptor (2.0 mmol) was added dropwise by syringe. Stirring was continued for 2 h at −78°C and then the reaction quenched by the addition of satd. aq. NH_4Cl. The reaction mixture was allowed to warm to room temperature over 30 min and then the solvent was removed *in vacuo*. The residue was partitioned between brine and 1/1 diethyl ether/dichloromethane, and the organic phase subsequently dried over $MgSO_4$, filtered and concentrated to furnish the crude conjugate adduct.

Procedure for tandem conjugate addition–alkylation reactions of amide 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 temperature over 15 h, unless otherwise stated. Work-up as described in procedure (*a*) then furnished the crude alkylated conjugate adducts.

Procedure for stepwise alkylation reactions of amide 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) was injected by syringe. The reaction mixture was allowed to warm gradually to room temperature over 15 h, unless otherwise stated. Work-up as described in procedure (*a*) then furnished the crude alkylated conjugate adducts.

Procedure for stepwise alkylation reactions of oxazolidin-2-one conjugate adducts

(*d*) Potassium bis(trimethylsilyl)amide (2.0 mmol) was added to a THF (20 ml) solution of the requisite conjugate adduct (1.0 mmol) at −78°C. After stirring at this temperature for 1 h, neat alkyl halide (5.0 mmol) was added to the reaction mixture, which was then allowed to warm slowly to room temperature overnight. Work-up as described in procedure (*a*) then furnished the crude alkylated conjugate adducts.

N,N-dimethyl crotonamamide **2**

A solution of crotonoyl chloride (10.0 ml, 104 mmol) and dimethylamine hydrochloride (9.36 g, 115 mmol) in dry dichloromethane (150 ml) was cooled to 0°C prior to the addition of pyridine (18.6 ml, 230 mmol). The reaction was stirred at room temperature for 1 h, after which solvent was evaporated *in vacuo* to give a solid residue. This was partitioned between brine and 1/1 diethyl ether/dichloromethane, and the organic phase dried (Na_2SO_4), filtered and concentrated to give **2** as a pale yellow oil (8.55 g, 73%). δ_H (lit.[8] 300 MHz; $CDCl_3$) 6.88 (1H, dq, *J* 15.0 and 6.9, CH_3CH), 6.27 (1H, dq, *J* 15.0 and 1.7, CHCO), 3.07 (3H, s, NCH_3), 3.00 (3H, s, NCH_3), 1.88 (3H, dd, *J* 6.9 and 1.7 CH_3CH).

(*3*R,αR)-N,N-*Dimethyl*-3-[N-*benzyl*-N-(α-*methylbenzyl*)*amino*]*butanamide* [(*3*R,αR)-**4**]. The conjugate addition of (*R*)-**1** (12.8 mmol) to *N*,*N*-dimethyl crotonamide **2** (950 mg, 8.41 mmol) was carried out according to procedure (a). Purification of the crude oil, which contained the conjugate adduct (*3R*,a*R*)-**4** in ≥ 95% d.e. was accomplished by flash column chromatography on silica gel with a diethyl ether eluent. After elution of excess secondary amine, the product (*3R*,a*R*)-**4** was collected as a colourless oil (1.81 g, 66%); $[\alpha]_D^{25}$ −6.3 (*c* 1.00 in $CHCl_3$); Anal. found: C 77.47; H 8.92; N 8.62; $C_{21}H_{28}N_2O$ requires C 77.74; H 8.70; N 8.63%. IR $\nu_{max}(CHCl_3)/cm^{-1}$: 1630 (C=O). ^{13}C-NMR δ_H (300 MHz; $CDCl_3$): 7.46–7.17 (10H, m, Ph), 3.92 (1H, q, *J* 6.9, PhC*H*N), 3.80; 3.74 (2H, AB system, J_{AB} 14.7, PhCH_2N), 3.50–3.39 (1H, m, CH_3CHN), 2.82 (3H, s, NCH_3), 2.52

(3H, s, NCH_3), 2.33; 2.16 (2H, ABX system, J_{AB} 14.2, J_{AX} 4.8 and J_{BX} 9.2, CH_2CO), 1.37 (3H, d, J 6.9, CH_3CH), 1.16 (3H, d, J 6.6, CH_3CH). ^{13}C-NMR δ_C (50 MHz; $CDCl_3$): 171.9 (CON), 144.9; 142.2 (PhC_{ipso}), 128.5; 128.3; 128.2; 128.0 (Ph), 126.7 (PhC_{para}), 57.6 (CHN), 49.7 (CH_2N), 49.2 (CHN), 39.4 (CH_2CO), 36.8; 35.1 (NCH_3), 18.1; 17.3 (CH_3CH). MS *m/z*: 325 (MH^+, 100%), 219 (50, MH^+,–$PhCH_2CH_3$), 212 (100, $PhCH_2NH_2^+$ CHMePh).

Tandem addition–methylation of N,N-dimethyl crotonamide **2**. The conjugate addition of (*R*)-**1** (1.28 mmol) to *N,N*-dimethyl crotonamide **2** (100 mg, 0.88 mmol) followed by alkylation with methyl iodide (0.40 cm^3, 6.4 mmol) was carried out according to procedure (*b*), except that the reaction was quenched after 4 h at −78°C instead of warming to room temperature. Purification of the crude oil was accomplished by flash column chromatography on silica gel with diethyl ether as eluent. Following elution of excess secondary amine, a mixture of both product diastereoisomers (3*R*,a*R*)-**6** and (3*R*,a*R*)-**7** in the ratio of 1.5:1 was collected as a colourless oil (87 mg, 29%).

The reaction was repeated on the same scale in the presence of *N,N,N′,N′*-tetramethylethane-1,2-diamine (328 mg, 2.83 mmol), added to the reaction before the butyllithium. After injection of the methyl iodide, the reaction was stirred at −78°C for 3 h, then maintained at −30°C for 16 h, and finally quenched as before. Work-up and chromatography as described above gave a mixture of both product diastereoisomers (3*R*,a*R*)-**6** and (3*R*,a*R*)-**7** in the ratio of 2.5:1 (164 mg, 54%).

Stepwise methylation of N,N-*dimethyl crotonamide adduct* **4**. Deprotonation of **4** (470 mg, 1.45 mmol) with LDA (2.90 mmol) followed by alkylation with methyl iodide (1.0 ml, 16 mmol) was carried out according to procedure (*c*), except that the reaction was quenched after 3 h at −78°C instead of warming to room temperature. Purification of the crude oil was accomplished by flash column chromatography on silica gel with a 4:1 dichloromethane/diethyl ether eluent. First eluted was (3*R*,α*R*)-**7** (75 mg, 15%), followed by a mixed fraction, and finally (3*R*,α*R*)-**6** (67 mg, 14%), all as colourless oils; the combined product yield was 46%.

(3R,αR)-N,N-*Dimethyl-2-methyl-3-*[N-*benzyl*-N-(α-*methylbenzyl-amino)butanamide* [(3R,αR)-**6**] (more polar diastereoisomer) $[\alpha]_D^{25}$ −21.2 (*c* 1.00 in $CHCl_3$). Anal. found: C, 77.78, H 9.23, N 7.98; $C_{22}H_{30}N_2O$ requires: C 78.06, H 8.93, N 8.28%). IR $\nu_{max}(CHCl_3)/cm^{-1}$: 1630 (C=O). ^{1}H-NMR δ_H (300 MHz; $CDCl_3$): 7.39–7.17 (10H, m, Ph), 4.02 (1H, q, J 6.9, PhC*H*N), 3.76 (2H, s, $PhCH_2N$), 3.44 (1H, dq, J 7.0 and 7.6, CH_3CHN), 2.86 (3H, s, NCH_3), 2.56 (1H, dq, J 7.0 and 7.6, CHCO), 2.34 (3H, s, NCH_3), 1.41 (3H, d, J 6.9, CH_3CH), 1.00 (3H, d, J 7.0, CH_3CH), 0.98 (3H, d, J 7.0, CH_3CH). ^{13}C-NMR δ_C (50 MHz; $CDCl_3$) 175.8 (CON), 145.0; 142.4 (PhC_{ipso}), 128.4; 128.2; 128.0 (Ph), 126.6 (PhC_{para}), 59.7; 55.2 (CHN), 49.7 (CH_2N), 41.6 (*C*HCO), 36.3; 35.4 (NCH_3), 17.3; 13.8; 12.6 (CH_3CH). MS *m/z*: 339 (MH^+, 100%), 238 (40, MH^+,–$CH_3CH_2CONMe_2$), 233 (40, MH^+,–$PhCH_2CH_3$), 134 (25, $CH_3CH{=}NH^+CH_2Ph$), 91 (25, $PhCH_2^+$).

(3R,αR)-N,N-*Dimethyl-2-methyl-3-*[N-*benzyl*-N-(α-*methylbenzyl)-amino]butanamide* [3R,αR)-**7**] (less polar diastereoisomer) $[\alpha]_D^{25}$ +27.3 (*c* 1.00 in $CHCl_3$). Anal. found: C 77.75, H 9.21, N 7.99; $C_{22}H_{30}N_2O$ requires: C 78.06, H 8.93, N 8.28%. IR $\nu_{max}(CHCl_3)/cm^{-1}$: 1625 (C=O). ^{1}H-NMR δ_H (300 MHz; $CDCl_3$): 7.43–7.20 (10H, m, Ph), 3.95 (1H, q, J 6.9, PhC*H*N), 3.76; 3.72 (2H, AB system, J_{AB} 14.0, $PhCH_2N$), 3.16 (1H, dq, J 6.6 and 9.9, CH_3CHN), 2.87 (3H, s, NCH_3), 2.82 (3H, s, NCH_3), 2.44 (1H, dq, J 6.7 and 9.9, CHCO), 1.45 (3H, d, J 6.9, CH_3CH), 1.02 (3H, d, J 6.6, CH_3CH), 0.86 (3H, d, J 6.7, CH_3CH). ^{13}C-NMR δ_C (50 MHz; $CDCl_3$): 176.8 (CON), 144.6; 141.7 (PhC_{ipso}), 129.1; 128.5; 128.3, 128.1 (Ph), 126.9, 126.8 (PhC_{para}), 58.9; 55.6 (CHN), 50.5 (CH_2N), 40.4 (*C*HCO), 37.2; 35.3 (NCH_3), 16.0; 15.7; 14.7 (CH_3CH). MS *m/z*: 339 (MH^+, 100%), 238 (50, MH^+,–$CH_3CH_2CONMe_2$), 233 (40, MH^+,–$PhCH_2CH_3$), 212 (45, $PhCH_2NH_2^+$ CHMePh), 91 (35, $PhCH_2^+$).

N,N-*Dimethyl cinnamamide* (**3**)

A solution of cinnamoyl chloride (23.0 g, 138 mmol) in THF (200 ml) was cooled to 0°C prior to the slow addition of dimethylamine (70 ml, 390 mmol, 33% w/w solution in methanol). The reaction was stirred at room temperature for 15 h, then acidified with 5% aq. HCl (300 ml) and extracted with dichloromethane. The organic phase was dried ($MgSO_4$), filtered and evaporated to give a brown solid which was recrystallized from diethyl ether to give **3** as a white solid (19.6 g, 81%). ^{1}H-NMR δ_H (lit.[9]; 200 MHz; $CDCl_3$) 7.69 (1H, d, J 15.6, PhC*H*), 7.56–7.34 (5H, m, Ph), 6.89 (1H, d, J 15.6, CHCO), 3.12 [6H, s, $N(CH_3)_2$].

(3S,αR)-N,N-*Dimethyl-3-phenyl-3-*[N-*benzyl*-N-(α-*methylbenzyl-amino)propanamide* [(3S,αR)-**5**. The conjugate addition of (*R*)-**1** (2.50 mmol) to *N,N*-dimethyl cinnamamide **3** (300 mg, 1.71 mmol) was performed according to procedure (*a*). Purification of the crude oil, which contained the conjugate adduct **5** in ≥95% d.e., was accomplished by flash column chromatography on silica gel with diethyl as ether eluent. After elution of excess secondary amine, the product (3*S*,α*R*)-**5** was collected as a colourless oil (599 mg, 91%), $[\alpha]_D^{25}$ −10.6 (*c* 0.90 in CH_2Cl_2). Anal. found: C 80.8, H 7.7, N 7.1. $C_{26}H_{30}N_2O$ requires C 80.8, H 7.8, N 7.2%). IR $\nu_{max}(CHCl_3)/cm^{-1}$ 1633 (C=O). ^{1}H-NMR δ_H (300 MHz; $CDCl_3$) 7.51–7.14 (15H, m, Ph), 4.59 (1H, dd, J 7.3 and 6.4, $PhCHCH_2$), 4.00 (1H, q, J 6.7, CH_3CHN), 3.80; 3.69 (2H, AB system, J_{AB} 15.1, $PhCH_2N$), 2.76 (3H, s, NCH_3), 2.49–2.46 (2H, m, CH_2CO), 2.41 (3H, s, NCH_3), 1.33 (3H, d, J 6.7, CH_3CH); ^{13}C-NMR δ_C (50 MHz; $CDCl_3$) 171.2 (CON), 144.4; 143.7; 142.6 (PhC_{ipso}), 128.5; 128.1; 127.2; 126.8; 126.6 (Ph), 60.3; 56.5 (CHN), 50.6 (CH_2N), 37.8 (CH_2CO), 36.7; 35.2 (NCH_3), 13.5 (CH_3CH). MS *m/z*: 387 (MH^+).

Tandem addition–methylation of N,N-*dimethyl cinnamamide* (**3**). The conjugate addition of (*R*)-**1** (2.56 mmol) to *N,N*-dimethyl cinnamamide **3** (300 mg, 1.71 mmol) followed by alkylation with methyl iodide (0.80 m^3, 13 mmol) was carried out according to procedure (*b*). Purification of the crude product, which contained (2*R*,3*S*,α*R*)-**8** in >95% d.e., was accomplished by flash column chromatography on silica gel with a 10:1 dichloromethane/diethyl-ether eluent. The product (2*R*,3*S*,α*R*)-**8** was collected as a white solid (480 mg, 70%), and subsequently recrystallized from hexane.

(2R,3S,αR)-N,N-*Dimethyl-2-methyl-3-phenyl-3-*[N-*benzyl*-N-(α-*methylbenzyl)amino]propanamide* [(2R,3S,αR)-**8**]: $[\alpha]_D^{25}$ −3.2 (*c* 1.00 in $CHCl_3$); m.p. 80–82°C. Anal. found: C 81.03, H 8.09, N 6.92; $C_{27}H_{32}N_2O$ requires: C 80.96, H, 8.05, N 6.99%. The $\nu_{max}(CHCl_3)/cm^{-1}$: 1635 (C=O). ^{1}H-NMR δ_H (300 MHz; $CDCl_3$) 7.39–7.11 (15H, m, Ph), 4.42 (1H, d, J 10.5, PhC*H*CH), 4.15 (1H, q, J 6.8, CH_3CHN), 3.80; 3.63 (2H, AB system, J_{AB} 15.5, $PhCH_2N$), 3.24 (1H, dq, J 6.8 and 10.5, CHCO), 2.93 (3H, s, NCH_3), 2.54 (3H, s, NCH_3), 1.24 (3H, d, J 6.8, CH_3CH), 0.68 (3H, d, J 6.8, CH_3CH). ^{13}C-NMR δ_C (50 MHz; $CDCl_3$) 175.3 (CON), 145.1; 141.8; 139.8 (PhC_{ipso}), 129.6; 128.4; 128.2; 128.0 (Ph), 127.3; 126.6 (PhC_{para}), 65.9; 57.6 (CHN), 50.2 (CH_2N), 37.8 (*C*HCO), 36.7; 35.6 (NCH_3), 16.6 (2 CH_3CH). MS *m/z*: 401 (MH^+, 40%), 295 (40, MH^+,–$PhCH_2CH_3$), 196 (100, $PhCH{=}NH^+CH_2Ph$), 105 (45, $PhCHCH_3^+$), 91 (85, $PhCH_2^+$).

Tandem addition–allylation of N,N-*dimethyl cinnamamide* **3**. The conjugate addition of (*R*)-**1** (2.40 mmol) to *N,N*-dimethyl cinnamamide **3** (300 mg, 1.71 mmol) followed by alkylation with allyl bromide (1.0 ml, 12 mmol) was carried out according to procedure (*b*). Purification of the crude product, which contained (2*R*,3*S*,α*R*)-**9** in >95% d.e., was accomplished by flash column chromatography on silica gel with a 10/1 dichloromethane/diethyl-ether eluent. The product (2*R*,3*S*,α*R*)-**9** was isolated as a colourless oil (518 mg, 71%).

(2R,3S,αR)-N,N-*Dimethyl-2-allyl-3-phenyl-3-*[N-*benzyl*-N-(α-*methylbenzyl)amino]propanamide* [(2R,3S,αR)-**9**]; $[\alpha]_D^{25}$ −4.4 (*c* 1.00 in $CHCl_3$). Anal found: C 81.55, H 8.07, N, 6.58, $C_{29}H_{34}N_2O$ requires: C 81.65, H 8.03, N 6.57%. IR $\nu_{max}(CHCl_3)/cm^{-1}$; 1635 (C=O). ^{1}H-NMR δ_H (300 MHz; $CDCl_3$): 7.48–7.17 (15H, m, Ph), 5.70–5.45 (1H, m, $CH{=}CH_2$), 4.90–4.82 (2H, m, $CH{=}CH_2$), 4.30 (1H, d, J 11.0, PhC*H*CH), 4.29 (1H, q, J 6.8, CH_3CHN), 3.95; 3.64 (2H, AB system, J_{AB} 15.1, $PhCH_2N$), 3.56 (1H, ddd, J 10.7, 10.7 and 3.6, CHCO), 2.95 (3H, s, NCH_3), 2.71 (3H, s, NCH_3), 2.15–2.00; 1.85–1.70 (2H, m, CH_2CHCO), 1.08 (3H, d, J 6.8, CH_3CH); ^{13}C-NMR δ_C (50 MHz; $CDCl_3$) 173.5 (CON), 144.8; 140.3; 139.1 (PhC_{ipso}), 135.6 ($CH{=}CH_2$), 129.4; 128.8; 128.6; 128.4; 128.0; 127.8 (Ph), 127.6; 127.0; 126.6 (PhC_{para}), 116.9 ($CH{=}CH_2$), 64.7; 55.9 (CHN), 50.9 (CH_2N), 43.1 (*C*HCO), 37.1 (NCH_3), 36.0 (CH_2CHCO), 35.5 (NCH_3), 16.6 (CH_3CH). MS *m/z*: 427 (MH^+, 50%), 321 (60, MH^+,–$PhCH_2CH_3$), 210 (100, $PhCH_2NCHMePh^+$), 105 (75, $PhCHCH_3^+$), 91 (80, $PhCH_2^+$), 72 (65, Me_2NCO^+).

Tandem addition–benzylation of N,N-*dimethyl cinnamide* (**3**). The conjugate addition of (*R*)-**1** (12.8 mmol) to *N,N*-dimethylcinnamide **3** (1.40 g, 8.00 mmol) followed by alkylation with benzyl bromide (3.0 cm^3, 25 mmol) was carried out according to procedure (*b*). Purification of the crude product, which contained (2*R*,3*S*,α*R*)-**10** in >95% d.e., was accomplished by flash column chromatography on silica gel with a 10/1 dichloromethane/diethyl-ether eluent. The product (2*R*,3*S*,α*R*)-**10** was collected as a white solid (3.39 g, 89%) and subsequently recrystallized from ethanol.

(2R,3S,αR)-N,N-*Dimethyl-2-benzyl-3-phenyl-3-*[N-*benzyl*-N-(α-*methylbenzyl)amino]propanamide* [(2R,3S,αR)-**10**]; $[\alpha]_D^{25}$ +18.2 (*c* 1.00 in

$CHCl_3$); m.p. 125–126°C. Anal found: C 83.06, H 7.84, N 5.85; $C_{33}H_{36}N_2O$ requires: C 83.15, H 7.61, N 5.88%). IR $\nu_{max}(CHCl_3)/cm^{-1}$: 1635 (C=O). ^{1}H-NMR δ_H (300 MHz; $CDCl_3$); 7.38–6.96 (20H, m, Ph), 4.34 (1H, d, *J* 11.0, PhC*H*CH), 4.26 (1H, q, *J* 6.8, CH_3CHN), 3.92; 3.62 (2H, AB system, J_{AB} 14.7, PhCH_2N), 3.66 (1H, ddd, *J* 11.0, 11.0 and 3.0, CHCO), 2.73 (3H, s, NCH_3), 2.56; 2.29 (2H, AB of ABX system, J_{AB} 12.7, J_{AX} 3.0 and J_{BX} 11.0, PhCH_2CH), 2.00 (3H, s, NCH_3), 1.03 (3H, d, *J* 6.8, CH_3CH); δ_C (50 MHz; $CDCl_3$) 173.4 (CON), 144.6; 140.2; 139.3 (PhC_{ipso}), 129.4; 129.0; 128.9; 128.7; 128.3; 127.9; 127.7 (Ph), 127.0; 126.5; 126.4 (PhC_{para}), 64.4; 55.5 (CHN), 50.9 (CH_2N), 46.3 (*C*HCO), 37.8 (*C*H_2CH), 36.3; 35.3 (NCH_3), 16.4 (*C*H_3CH); *m/z*: 477 (MH^+, 10%), 196 (95, PhCH=NH^+CH_2Ph), 178 (100, $PhCH_2CH_2CONMe_2H^+$), 105 (30, $PhCHCH_3^+$), 91 (90, $PhCH_2^+$).

Crystal data. $C_{33}H_{35}N_2O$, M = 475.65, orthorhombic, $a = 6.4535(5)$, $b = 19.009(2)$, $c = 22.278(2)$ Å, $U = 2732.9$ Å^3, space group $P2_12_12_1$ (No. 19), $Z = 4$, $D_x = 1.156$ g/cm^3, $T = 295$K, final $R = 0.032$, $R_w = 0.042$.

Data collection and reduction. Data were collected on a CAD4-F diffractometer using CuKα radiation in the range $0 < 2\sigma \leq 75°$ ($-1 \leq h \leq 8$, $-1 \leq k \leq 23$, $-27 \leq l \leq 27$), 7415 reflections measured. Data were corrected for Lorentz, polarisation and absorption (minimum and maximum corrections 1.16 and 1.26)[10]. 3214 unique reflections $R_{int} = 0.025$ of which 2583 observed, $I \geq 2\sigma I$.

Structure solution and refinement. The structure was solved by direct methods[11] which revealed the positions of all non-hydrogen atoms, which were refined in a full matrix least-squares procedure[12]. Difference electron-density maps revealed the position of most hydrogen atoms. Prior to merging Friedel pairs, refinement of a Flack enantiopole[13] was undertaken. This was an inconclusive test of absolute configuration as the structure does not give rise to any significant calculated anomalous differences. Final refinement cycles included positional and anisotropic thermal parameters for all non-hydrogen atoms, isotropic thermal parameters for hydrogen atoms (in calculated positions) and an extinction parameter. A Chebychev polynomial weighting scheme was employed, and refinement of 354 parameters converged at $R = 0.032$, $R_w = 0.042$.

Tandem addition–ethylation of N,N-*dimethylcinnamamide* (**3**). The conjugate addition of (*R*)-**1** (2.24 mmol) to *N,N*-dimethylcinnamamide **3** (200 mg, 1.14 mmol) followed by alkylation with ethyl iodide (0.80 cm^3, 10 mmol) was carried out according to procedure (*b*). Purification of the crude oil by flash column chromatography on silica gel with a 10/1 dichloromethane/diethyl ether eluent gave the ethylated product (2*R*,3*S*,α*R*)-**11** as a colourless oil with a d.e. of 82% (377 mg, 82%). Recrystallization from hexane afforded diastereomerically pure (2*R*,3*S*,α*R*)-**11** (264 mg, 56%).

(2R,3*S*,αR)-N,N-*Dimethyl-2-ethyl-3-phenyl-3-*[N-*benzyl*-N-(α-*methylbenzyl*)*amino*]*propanamide* (2R,3S,αR)-**11**; $[\alpha]_D^{25}$ −15.2 (*c* 1.00 in $CHCl_3$); m.p. 112–114°C. Anal found: C 81.10, H 7.97, N 6.61; $C_{28}H_{34}N_2O$ requires: C 81.12, H 8.27, N 6.76%. IR $\nu_{max}(CHCl_3)/cm^{-1}$: 1635 (C=O); ^{1}H-NMR δ_H (300 MHz; $CDCl_3$): 7.44–7.15 (15H, m, Ph), 4.25 (1H, q, *J* 6.8, CH_3CHN), 4.23 (1H, d, *J* 10.7, PhC*H*CH), 3.93; 3.60 (2H, AB system, J_{AB} 14.9, PhCH_2N), 3.43 (1H, ddd, *J* 10.5, 10.5 and 3.6, CHCO), 2.94 (3H, s, NCH_3), 2.75 (3H, s, NCH_3), 1.40–1.24; 1.10–1.00 (2H, m, CH_2CH$_3$), 1.04 (3H, d, *J* 6.8, CH_3CH), 0.67 (3H, t, *J* 7.4, CH_2CH_3). ^{13}C-NMR δ_C (50 MHz; $CDCl_3$): 174.1 (CON), 144.7; 140.4; 139.5 (PhC_{ipso}), 129.3; 128.7; 128.3; 128.2; 127.8 (Ph), 127.3; 126.8; 126.4 (PhC_{para}), 64.8; 55.8 (CHN), 50.8 (CH_2N), 44.1 (*C*HCO), 37.1; 35.5 (NCH_3), 24.6 (*C*H_2CH$_3$), 16.4 (CH_3CH), 11.3 ($CH_{2C}H_3$). MS *m/z*: 415 (MH^+, 100%), 309 (25, MH^+,−PhCH_2CH$_3$), 300 (20, MH^+,−$CH_3CH_2CH_2CONMe_2$), 210 (30, $PhCH_2NCHMePh^+$), 196 (95, PhCH=NH^+CH_2Ph).

Stepwise methylation of N,N-*dimethyl cinnamamide adduct* (3*S*,αR)-**5**. Deprotonation of (3*S*,α*R*)-**5** (300 mg, 0.78 mmol) with LDA (1.55 mmol) followed by alkylation with methyl iodide (0.24 cm^3, 3.9 mmol) was carried out according to procedure (*c*). The crude oil was purified by filtration through a plug of silica, washing with diethyl ether, to afford the methylated product (2R,3S,αR)-**8** as a pale yellow solid in ≥ 95% d.e. (257mg, 80%).

Stepwise benzylation of N,N-*dimethylcinnamamide adduct* (3S,αR)-**5**. Deprotonation of (3*S*,α*R*)-**5** (200 mg, 0.52 mmol) with LDA (0.78 mmol) followed by alkylation with benzyl bromide (0.20 ml, 1.7 mmol) was carried out according to procedure (*c*). Examination of the crude material by ^{1}H-NMR spectroscopy revealed only the presence of the benzylated product (2*R*,3*S*,α*R*)-**10** in ≥ 95% d.e.

Stepwise allylation of N,N-*dimethyl cinnamide adduct* (3S,αR)-**5**. Deprotonation of (3*S*,α*R*)-**5** (300 mg, 0.78 mmol) with LDA (1.17 mmol) followed by alkylation with allyl bromide (0.50 ml, 5.8 mmol) was carried out according to procedure (*c*). The crude oil was filtered through a plug of silica, washing with diethyl ether, to afford the allylated product (2*R*,3*S*,α*R*)-**9** as a pale yellow oil in ≥ 95% d.e. (238 mg, 72%).

Tandem addition–benzylation of N,N-*dimethylcinnamamide* (**3**) *with lithium dibenzylamide* **12**. The conjugate addition of **12** (15.9 mmol) to *N,N*-dimethylcinnamamide **3** (2.32 g, 13.3 mmol) followed by alkylation with benzyl bromide (3.77 ml, 55.0 mmol) was carried out according to procedure (*b*). Purification of the crude product, which contained (2*SR*,3*SR*)-**13** and (2*RS*,3*SR*)-**14** in the ratio of 2/1, was accomplished by flash column chromatography on silica gel with dichloromethane as eluent to give the two product diastereoisomers together as a white solid (3.90 g, 64%). These were separated by recrystallization from ethanol/dichloromethane and flash column chromatography of the mother liquors on silica gel with a 1:1 hexane/diethyl-ether eluent.

(2SR,3SR)-N,N-*Dimethyl-2-benzyl-3-phenyl-3-*(*dibenzylamino*)*propanamide* [(2SR,3SR)-**13**]; m.p. 177–179°C. Anal found: C 82.92, H 7.48, N 6.19; $C_{32}H_{34}N_2O$ requires C 83.08, H 7.41, N 6.06%. IR $\nu_{max}(CHCl_3)/cm^{-1}$ 1630 (C=O). ^{1}H-NMR δ_H (300 MHz; $CDCl_3$): 7.52–7.14 (20H, m, Ph), 4.19 (1H, d, *J* 11.0, PhC*H*CH), 3.97; 3.15 (4H, AB system, J_{AB} 13.7, $(PhCH_2)_2N$), 3.90; 2.79 (2H, AB of ABX system, J_{AB} 12.8, J_{AX} 3.0 and J_{BX} 11.9, PhCH_2CH), 3.69 (1H, ddd, *J* 11.0, 11.9 and 3.0, CHCO), 2.41 (3H, s, NCH_3), 2.21 (3H, s, NCH_3). ^{13}-NMR δ_C (50 MHz; $CDCl_3$) 173.4 (CON), 140.6; 139.9; 135.9 (PhC_{ipso}), 129.4; 129.3; 129.0; 128.7; 128.4; 128.0 (Ph), 127.4; 127.3; 126.4 (PhC_{para}), 64.7 (CHN), 54.4 (CH_2N), 45.7 (*C*HCO), 37.7 (*C*H_2CH), 36.5; 35.0 (NCH_3). MS *m/z*: 463 (MH^+, 100%), 371 (15, MH^+,−$PhCH_3$), 286 (40, MH^+,−$PhCH_2CH_2CONMe_2$), 196 (75, PhCH=NH^+CH_2Ph), 91 (50, $PhCH_2^+$).

(2RS,3SR)-N,N-*Dimethyl-2-benzyl-3-phenyl-3-*(*dibenzylamino*)*propanamide* [(2RS,3SR)-**14**]; m.p. 149–151°C. Anal found: C 82.85, H 7.66, N, 5.90; $C_{32}H_{34}N_2O$ requires: C 83.08, H 7.41, N 6.06%. IR $\nu_{max}(CHCl_3)/cm^{-1}$: 1640 (C=O). ^{1}H-NMR δ_H (300 MHz; $CDCl_3$) 7.52–7.02 (20H, m, Ph), 4.29 (1H, d, *J* 11.1, PhC*H*CH), 3.88; 3.05 (4H, AB system, J_{AB} 14.2, [$(PhCH_2)_2N$], 3.78 (1H, ddd, *J* 11.1, 11.6 and 2.9, CHCO), 2.96 (3H, s, NCH_3), 2.66; 2.32 (2H, AB of ABX system, J_{AB} 12.5, J_{AX} 11.6 and J_{BX} 2.9, PhCH_2CH), 2.32 (3H, s, NCH_3). ^{13}C-NMR δ_C (50 MHz; $CDCl_3$): 173.4 (CON), 140.2; 139.5; 135.6 (PhC_{ipso}), 129.7; 129.0; 128.6; 128.3; 127.7 (Ph), 127.0; 126.4 (PhC_{para}), 65.0 (CHN); 54.6 (CH_2N), 45.8 (*C*HCO), 37.5 (*C*H_2CH), 36.6; 35.6 (NCH_3). MS *m/z*: 463 (MH^+, 100%), 371 (15, MH^+,−$PhCH_3$), 286 (35, MH^+,−$PhCH_2CH_2CONMe_2$), 196 (55, PhCH=NH^+CH_2Ph), 91 (35, $PhCH_2^+$).

(2SR,3SR)-N,N-*Dimethyl 2-benzyl-3-phenyl-3-aminopropanamide* (2SR,3SR)-**15**]

To a solution of (2*SR*,3*SR*)-**13** (500 mg, 1.08 mmol) in methanol/ethyl acetate/10% aq.-HCl (20/5/2, 10 ml) was added $Pd(OH)_2$/C (Pearlman's catalyst, 250 mg) and the resultant black suspension stirred under an atmosphere of hydrogen overnight. The reaction mixture was then filtered through a plug of celite, washed with methanol, and the filtrate condensed to give a white solid. This residue was partitioned between satd. aq. $NaHCO_3$ and dichloromethane, and the organic phase dried ($MgSO_4$), filtered and condensed to give (2*SR*,3*SR*)-**15** as a white crystalline solid (271 mg, 89%); m.p. 75–77°C. Anal found: C 76.40, H 7.86, N 9.89; $C_{18}H_{22}N_2O$ requires: C 76.56, H 7.85, N 9.92%). IR $\nu_{max}(CHCl_3)/cm^{-1}$: 3390br (NH), 1630 (C=O). ^{1}H-NMR δ_H (300 MHz; $CDCl_3$) 7.42–7.13 (10H, m, Ph), 4.30 (1H, d, *J* 6.8, PhC*H*CH), 3.17–3.06 (3H, m, PhCH_2CH), 2.57 (3H, s, NCH_3), 2.20 (3H, s, NCH_3), 1.76 (2H, br s, NH_2). ^{13}C-NMR δ_C (50 MHz; $CDCl_3$) 173.7 (CON), 144.3; 140.1 (PhC_{ipso}), 129.1; 128.3 (Ph), 127.4 (PhC_{para}), 126.8 (Ph), 126.3 (PhC_{para}), 57.7 (CHN), 52.5 (*C*HCO), 36.6 (NCH_3), 35.2 (CH_2), 35.0 (NCH_3). MS *m/z*: 283 (MH^+, 100%), 178 (50, $PhCH_2CH_2CONMe_2H^+$), 106 (50, $PhCH{=}NH_2^+$).

(2R,3S)-N,N-*Dimethyl-2-benzyl-3-phenyl-3-aminopropanamide* [(2R,3S)-**16**]. To a solution of (2*R*,3*S*,α*R*)-**10** (500 mg, 1.05 mmol) in methanol/water/acetic-acid (20/2/1, 10 ml) was added $Pd(OH)_2$/C (wet Degussa type Pearlman's catalyst, 250 mg) and the resultant black suspension stirred under an atmosphere of hydrogen overnight. Work-up as for the reaction described above followed by recrystallization of the crude product from hexane gave (2*R*,3*S*)-**16** as a white crystalline solid (211 mg, 71%), $[\alpha]_D^{25}$ −21.5 (*c* 1.00 in $CHCl_3$); m.p. 95–97°C. Anal found: C 76.62, H 8.12, N 9.66; $C_{18}H_{22}N_2O$ requires: C 76.56, H 7.85, N 9.92%. IR $\nu_{max}(CHCl_3)/cm^{-1}$: 3380br (NH), 1625 (C=O). ^{1}H-NMR δ_H (300 MHz; $CDCl_3$): 7.45–7.02 (10H, m, Ph), 4.26 (1H, d, *J* 8.2, PhC*H*CH), 3.19 (1H, ddd, *J* 3.9, 8.2 and 12.1, CHCO), 2.87; 2.52 (2H, AB of ABX system, J_{AB} 12.9, J_{AX} 12.1 and J_{BX} 3.9, PhCH_2CH), 2.80 (3H, s, NCH_3), 2.35 (3H, s, NCH_3), 1.83

(2H, br s, NH_2). ^{13}C-NMR δ_C (50 MHz; $CDCl_3$): 174.3 (CON), 144.3; 139.7 (PhC_{ipso}), 128.9; 128.7; 128.3; 127.7 (Ph), 127.3; 126.4 (PhC_{para}), 59.0 (CHN), 51.8 (*C*HCO), 37.3 (CH_2), 36.9; 35.3 (NCH_3). MS *m/z*: 283 (MH^+, 100%), 178 (20, $PhCH_2CH_2CONMe_2H^+$), 106 (30, $PhCH{=}NH_2^+$).

Hydrolysis of (2R,3S)-**16**. A suspension of (2*R*,3*S*)-**16** (50 mg, 0.18 mmol) in 20% aq. HCl (5 ml) was heated at 100°C for 20 d. ^{1}H-NMR spectroscopic analysis of the residue obtained after evaporation of solvent revealed a 75% conversion to the amino acid (2*R*,3*S*)-**17** (80% d.e.)[2].

N-*Cinnamoyloxazolidin-2-one* (**19**)

A suspension of oxazolidin-2-one (5.73 g, 65.9 mmol) in THF (50 ml) was added slowly to a suspension of sodium hydride (2.63 g, 65.9 mmol) in THF (100 ml). The mixture was stirred at room temperature for 1 h, and then a solution of cinnamoyl chloride (10.0 g, 59.9 mmol) in THF (50 ml) was added slowly. After heating the mixture at reflux for 2 h under an atmosphere of nitrogen, it was cooled and quenched with water. Removal of solvent *in vacuo* yielded a residue which was partitioned between dichloromethane and water. The organic phase was dried ($MgSO_4$), filtered and concentrated to give a yellow solid, recrystallization of which from ethyl acetate/dichloromethane at -30°C afforded **19** as a white crystalline solid (8.90 g, 69%). ^{1}H-NMR δ_H (lit.[14] 300 MHz; $CDCl_3$) 7.93; 7.86 (2H, AB system, J_{AB} 15.7, CH=CH), 7.65–7.27 (5H, m, Ph), 4.47 (2H, t, *J* 8.0, CH_2O), 4.15 (2H, t, *J* 8.0, CH_2N).

Conjugate additions to N-*cinnamoyloxazolidin-2-one* (**19**). The conjugate addition of (*R*)-**1** (1.68 mmol) to *N*-cinnamoyloxazolidin-2-one **19** (148 mg, 0.69 mmol) was carried out according to procedure (*a*), except that the reaction was quenched with methanol. Purification of the crude oil, which contained the methyl cinnamate adduct (3*S*,α*R*)-**22** in 95% d.e., was accomplished by flash column chromatography on silica gel with a dichloromethane eluent to afford (3*S*,α*R*)-**22** as a colourless oil in 95% d.e. (206 mg, 80%)[2].
The conjugate addition of (*R*)-**1** (41.5 mmol) to *N*-cinnamoyloxazolidin-2-one **19** (6.00 g, 27.6 mmol) was carried out according to procedure (*a*), except that the reaction was quenched with pH 7 phosphate buffer solution. Purification of the crude oil was accomplished by flash column chromatography on silica gel with a 1/2 petrol/diethyl ether eluent to give (3*S*,α*R*)-**21** as a white foam (9.24 g, 80%).
(3S,αR)-N-[3-*phenyl*-3-[N-*benzyl*-N-(α-*methylbenzyl*)*amino*]*propanoyl*]*oxazolidin*-2-*one* (3S,αR)-**21**; $[\alpha]_D^{25}$ −13.7 (*c* 1.00 in $CHCl_3$); m.p. 46–49°C. Anal found: C 75.82, H 6.56, N 6.38; $C_{27}H_{28}N_2O_3$ requires: C 75.68, H 6.59, N 6.54%. IR $\nu_{max}(CHCl_3)/cm^{-1}$: 1780 ($CH_2C$=O), 1700 (OC=O). ^{1}H-NMR δ_H (300 MHz; $CDCl_3$) 7.58–7.19 (15H, m, Ph), 4.59 (1H, t, *J* 7.3, $PhCHCH_2$), 4.22 (2H, m, CH_2O), 4.07 (1H, q, *J* 6.9, CH_3CHN), 3.90; 3.71 (2H, AB system, J_{AB} 14.3, $PhCH_2N$), 3.85–3.74 (2H, m, CH_2NCO), 3.42; 3.18 (2H, AB of ABX system, J_{AB} 15.7, J_{AX} 7.9 and J_{BX} 6.8, CH_2CO), 1.18 (3H, d, *J* 6.9, CH_3CH). ^{13}C-NMR δ_C (50 MHz; $CDCl_3$) 171.5 (CH_2CON), 153.4 (NCO_2), 144.4; 141.9; 141.4 (PhC_{ipso}), 128.5; 128.3; 128.2; 128.0 (Ph), 127.4; 126.9 (PhC_{para}), 61.7 (CH_2O), 58.3; 56.3 (CHN), 50.7 ($PhCH_2N$), 42.3 (CH_2NCO), 37.9 (CH_2CO), 15.3 (CH_3CH). MS *m/z*: 429 (MH^+, 100%), 300 (60, MH^+,−$CH_3CONCH_2CH_2OCO$), 218 (40, MH^+,−$PhCH_2NHCHMePh$), 212 (60, $PhCH_2NH_2^+CHMePh$), 196 (65, $PhCH{=}NH^+CH_2Ph$).

Stepwise benzylation of N-*cinnamoyloxazolidin-2-one adduct* (3S,α*R*)-**21**. Deprotonation of (3*S*,α*R*)-**21** (6.00 g, 14.0 mmol) with potassium bis(trimethylsilyl)amide (56.0 ml, 28.0 mmol) followed by alkylation with benzyl bromide (5.0 ml, 42 mmol) was carried out according to procedure (*d*). Purification of the crude oil, which contained the benzylated product (2*R*,3*S*,α*R*)-**25** in ≥ 90% d.e., was accomplished by flash column chromatography on silica gel with a 1/1 petrol:diethyl ether eluent followed by recrystallization from hexane/dichloromethane, affording (2*R*,3*S*,α*R*)-**25** in diastereomerically pure form as a white crystalline solid (4.47 g, 62%).
(2R,3S,αR)-N-[2-*benzyl*-3-*phenyl*-3-[N-*benzyl*-N-(α-*methylbenzyl*)*amino*]*propanoyl*]*oxazolidin*-2-*one* [(2*R*,3*S*,a*R*)-**25**]; $[\alpha]_D^{25}$ +39.8 (*c* 1.00 in $CHCl_3$); m.p. 132–134°C. Anal found: C 78.51, H 6.64, N 5.35; $C_{34}H_{34}N_2O_3$ requires: C 78.74, H 6.61, N 5.40%. IR $\nu_{max}(CHCl_3)/cm^{-1}$: 1770 (CHC=O), 1690 (OC=O). ^{1}H-NMR δ_H (300 MHz; $CDCl_3$): 7.59–7.01 (20H, m, Ph), 5.53 (1H, ddd, *J* 11.1, 11.1 and 4.0, CHCO), 4.76 (1H, q, *J* 6.8, CH_3CHN), 4.21 (1H, d, *J* 11.1, PhCHCH), 4.07; 3.61 (2H, AB system, J_{AB} 15.0, $PhCH_2N$), 3.73; 3.27 (2H, AB of ABX_2 system, J_{AB} 8.4, J_{AX} 7.2 and J_{BX} 8.4, CH_2NCO), 3.53–3.46 (2H, m, CH_2O), 2.57; 2.46 (2H, AB of ABX system, J_{AB} 13.1, J_{AX} 11.2 and J_{BX} 4.0, $PhCH_2CH$), 0.92 (3H, d, *J* 6.8, CH_3CH). ^{13}C-NMR δ_C (50 MHz; $CDCl_3$) 174.7 (CHCON), 153.0 (NCO_2), 146.4; 139.4; 138.7; 137.6 (PhC_{ipso}), 129.6; 129.3; 129.0; 128.8; 128.7; 128.2; 128.1; 128.0 (Ph), 127.2; 126.5; 126.4; 126.1 (PhC_{para}), 65.1 (CHN), 60.8 (CH_2O), 53.6 (CHN), 51.2 ($PhCH_2N$), 45.5 (*C*HCO), 42.3 (CH_2NCO), 38.1 (CH_2CH), 17.5 (CH_3CH). MS *m/z*: 519 (MH^+, 100%), 300 (95, MH^+,−$PhCH_2CH_2CONCH_2CH_2OCO$), 196 (70, $PhCH{=}NH^+CH_2Ph$), 105 (20, $PhCHCH_3^+$), 91 (25, $PhCH_2^+$).

Stepwise ethylation of N-*cinnamoyloxazolidin-2-one adduct* (3S,α*R*)-**21**. Deprotonation of (3*S*,α*R*)-**21** (500 mg, 1.17 mmol) with potassium bis(trimethylsilyl)amide (3.10 ml, 2.34 mmol) followed by alkylation with ethyl iodide (0.37 ml, 4.7 mmol) was carried out according to procedure (*d*). Purification of the crude oil, which contained the ethylated product (2*R*,3*S*,α*R*)-**26** in ≥ 80% d.e., was accomplished by flash column chromatography on silica gel with a 2/1 dichloromethane/petrol eluent, affording (2*R*,3*S*,α*R*)-**26** in diastereomerically pure form (4.47 g, 62%), subsequently recrystallized from ethanol.
(2*R*,3*S*,α*R*)-N-[2-*ethyl*-3-*phenyl*-3-[N-*benzyl*-N-(α-*methylbenzyl*)-*amino*]*propanoyl*]*oxazolidin*-2-*one* [(2*R*,3*S*,α*R*)-**26**]; $[\alpha]_D^{25}$ −5.4 (*c* 3.40 in $CHCl_3$); m.p. 127–129°C. Anal found: C 76.57, H 7.32, N 6.15; $C_{29}H_{32}N_2O_3$ requires: C 76.29, H 7.06, N 6.14%. IR $\nu_{max}(CHCl_3)/cm^{-1}$: 1775 (CHC=O), 1695 (OC=O). ^{1}H-NMR δ_H (300 MHz; $CDCl_3$): 7.58–7.19 (15H, m, Ph), 5.12 (1H, ddd, *J* 11.4, 10.9 and 3.5, CHCO), 4.75 (1H, q, *J* 6.8, CH_3CHN), 4.07 (1H, d, *J* 11.4, PhCHCH), 4.06–4.00 (1H, m, CH_2O), 4.02; 3.56 (2H, AB system, J_{AB} 15.2, $PhCH_2N$), 3.87 (1H, m, CH_2NCO), 3.65–3.57 (1H, m, CH_2O), 3.32 (1H, m, CH_2NCO), 1.44–1.32; 1.19–1.11 (2H, m, CH_2CH_3), 0.91 (3H, d, *J* 6.8, CH_3CH), 0.71 (3H, t, *J* 7.4, CH_2CH_3). ^{13}C-NMR δ_C (50 MHz; $CDCl_3$) 175.8 (CHCON), 153.8 (NCO_2), 146.9; 139.4; 137.7 (PhC_{ipso}), 129.3; 128.8; 128.6; 128.5; 128.2 (Ph), 127.8; 127.2 (PhC_{para}), 126.5 (Ph), 126.1 (PhC_{para}), 65.2 (CHN), 61.0 (CH_2O), 53.6 (CHN), 51.2 ($PhCH_2N$), 44.7 (*C*HCO), 42.6 (CH_2NCO), 24.9 (CH_2CH_3), 18.0 (CH_3CH), 11.3 ($CH_{2C}H_3$). MS *m/z*: 457 (MH^+, 60%), 300 (100, MH^+,−$CH_3CH_2CH_2CONCH_2CH_2OCO$), 196 (65, $PhCH{=}NH^+CH_2Ph$), 105 (40, $PhCHCH_3^+$), 91 (35, $PhCH_2^+$).

N-Crotonoyloxazolidin-2-one (**18**).

A solution of crotonoyl chloride (10.0 g, 95.7 mmol) in THF (50 ml) was treated in the same manner as described above for the preparation of **19**. Purification of the crude product by flash column chromatography on silica gel with a diethyl ether eluent, followed by recrystallization from diethyl ether/hexane at -30°C, afforded **18** as a white crystalline solid (6.85 g, 46%); m.p. 36–38°C. ^{1}H-NMR δ_H (lit.[14]; 300 MHz; $CDCl_3$): 7.21–7.09 (2H, m, CH=CH), 4.41 (2H, t, *J* 8.0, CH_2O), 4.05 (2H, t, *J* 8.0, CH_2N), 1.95 (3H, d, *J* 5.4, CH_3CH).

Conjugate addition to N-*crotonoyloxazolidin-2-one* (**18**). The conjugate addition of (*R*)-**1** (29.0 mmol) to *N*-crotonoyloxazolidin-2-one **18** (3.00 g, 19.4 mmol) was carried out according to procedure (*a*). Purification of the crude product, which contained the conjugate adduct (3*R*,a*R*)-**20** in 80% d.e., was accomplished by washing with hexane and recrystallization from ethyl acetate/diethyl ether at −30°C, affording the conjugate adduct (3*R*,a*R*)-**20** as a white solid in ≥ 95% d.e. (5.22 g, 74%).
(3*R*,α*R*)-N-[3-[N-*benzyl*-N-(α-*methylbenzyl*)*amino*]*butanoyl*]*oxazolidin*-2-*one* [(3*R*,α*R*)-**20**]; $[\alpha]_D^{25}$ +4.1 (*c* 5.40 in $CHCl_3$); m.p. 104–106°C. Anal found: C 72.24, H 7.14, N 7.56; $C_{22}H_{26}N_2O_3$ requires C 72.11, H 7.15, N 7.64%. IR $\nu_{max}(CHCl_3)/cm^{-1}$ 1780 (CH_2C=O), 1700 (OC=O). ^{1}H-NMR δ_H (300 MHz; $CDCl_3$) 7.53–7.17 (10H, m, Ph), 4.24–4.05 (2H, m, PhCHN and CH_3CHN), 3.89–3.48 (4H, m, NCH_2CH_2O), 3.88; 3.69 (2H, AB system, J_{AB} 13.9, $PhCH_2N$), 2.93; 2.76 (2H, AB of ABX system, J_{AB} 13.8, J_{AX} 8.8 and J_{BX} 5.0, CH_2CO), 1.36 (3H, d, *J* 6.9, CH_3CH), 1.24 (3H, d, *J* 6.6, CH_3CH). ^{13}C-NMR δ_C (50 MHz; $CDCl_3$): 171.6 ($CH_{2C}ON$), 153.4 (NCO_2), 144.9; 141.6 (PhC_{ipso}), 129.3; 128.4; 127.9 (Ph), 127.0; 126.4 (PhC_{para}), 61.5 (CH_2O), 56.2 (CHN), 49.5 ($PhCH_2N$), 48.9 (CHN), 42.2 (CH_2NCO), 41.2 (CH_2CO), 18.7; 14.6 (CH_3CH). MS *m/z*: 367 (MH^+, 95%), 238 (100, MH^+,−$CH_3CONCH_2CH_2OCO$), 134 (50, $CH_3CH{=}NH^+CH_2Ph$), 105 (55, $PhCHCH_3^+$), 91 (60, $PhCH_2^+$).

Stepwise methylation of N-*crotonoyloxazolidin-2-one adduct* (3*R*,α*R*)-**20**. Deprotonation of (3*R*,a*R*)-**20** (1.00 g, 2.73 mmol) with potassium bis(trimethylsilyl)amide (7.30 ml, 5.46 mmol) followed by alkylation with methyl iodide (0.70 ml, 11 mmol) was carried out according to procedure (*d*). Purification of the crude oil, which contained both methylated diastereoisomers (2*R*,3*R*,α*R*)-**23** and (2*S*,3*R*,α*R*)-**24** in equal proportions, was accomplished by flash column chromatography on silica gel. Use of a 2/3 petrol/diethyl ether eluent enabled the less polar product (2*R*,3*R*,α*R*)-**23** to be isolated in pure form as a colourless oil (225 mg, 22%), followed by a

mixed fraction (595 mg, 57%). Rechromatography of this mixture on silica gel with a 5/1 dichloromethane/petrol eluent allowed isolation of the more polar diastereoisomer (2*S*,3*R*,α*R*)-**24** as a colourless oil (155 mg, 15%).

(2R,3R,αR)-N-[2-*methyl*-3-[N-*benzyl*-N-(α-*methylbenzyl*)amino)*butanoyl*]*oxazolidin*-2-*one* [(2R,3R,αR)-**23**]; $[\alpha]_D^{25}$ −0.8 (*c* 5.50 in $CHCl_3$). Anal found: C 72.43, H 7.55, N 7.33; $C_{23}H_{28}N_2O_3$ requires: C 72.60, H 7.42, N 7.36%. IR $\nu_{max}(CHCl_3)/cm^{-1}$: 1775 (CHC=O), 1700 (OC=O). ^{1}H-NMR δ_H (300 MHz; $CDCl_3$) 7.36–7.18 (10H, m, Ph), 4.20–4.13 (2H, m, PhC*H*N and CH_2NCO), 3.97 (1H, dq, *J* 6.8 and 10.3, CH_3CHN), 3.87–3.64 (3H, m, NCH_2CH_2O), 3.86; 3.75 (2H, AB system, J_{AB} 14.7, PhCH_2N), 3.37 (1H, dq, *J* 6.7 and 10.3, CHCO), 1.45 (3H, d, *J* 6.9, CH_3CH), 1.11 (3H, d, *J* 6.7, CH_3CH), 1.01 (3H, d, *J* 6.8, CH_3CH). ^{13}C-NMR δ_C (50 MHz; $CDCl_3$): 176.5 (CHCON), 153.2 (NCO_2), 146.1; 140.9 (PhC$_{ipso}$), 128.7; 128.2; 128.1; 127.4 (Ph), 126.9; 126.4 (PhC$_{para}$), 61.3 (CH_2O), 56.7; 56.5 (CHN), 50.1 (PhCH_2N), 42.6 (CH_2NCO), 41.6 (CHCON), 18.7; 15.7; 12.2 (CH_3CH). MS *m*/*z*: 381 (MH^+, 25%), 238 (100, MH^+,–$CH_3CH_2CONCH_2CH_2OCO$), 134 (10, $CH_3CH{=}NH^+CH_2Ph$), 105 (20, $PhCHCH_3^+$), 91 (15, $PhCH_2^+$).

(2S,3R,αR)-N-[2-*methyl*-3-[N-*benzyl*-N-(α-*methylbenzyl*)amino]*butanoyl*]*oxazolidin*-2-*one* [(2S,3R,αR)-**24**]; $[\alpha]_D^{25}$ +6.8 (*c* 1.30 in $CHCl_3$). Anal found: C 72.58, H 7.79, N 7.32; $C_{23}H_{28}N_2O_3$ requires: C 72.60, H 7.42, N 7.36%). IR $\nu_{max}(CHCl_3)/cm^{-1}$: 1775 (CHC=O), 1690 (OC=O). ^{1}H-NMR δ_H (300 MHz; $CDCl_3$) 7.46–7.17 (10H, m, Ph), 4.34–4.20 (2H, m, PhC*H*N and CH_3CHN), 3.99–3.68 (4H, m, NCH_2CH_2O), 3.94; 3.69 (2H, AB system, J_{AB} 14.0, PhCH_2N), 3.22 (1H, m, CHCO), 1.39 (3H, d, *J* 6.9, CH_3CH), 1.19 (3H, d, *J* 6.6, CH_3CH), 0.97 (3H, d, *J* 6.9, CH_3CH). ^{13}C-NMR δ_C (50 MHz; $CDCl_3$): 176.9 (CHCON), 153.5 (NCO_2), 144.5; 141.3 (PhC$_{ipso}$), 129.3; 128.6; 128.4; 128.0 (Ph), 127.0; 126.6 (PhC$_{para}$), 61.5 (CH_2O), 56.4; 53.3 (CHN), 50.9 (PhCH_2N), 42.5 (CH_2NCO), 42.5 (CHCON), 15.5; 14.7; 13.5 (CH_3CH). MS *m*/*z*: 381 (MH^+, 65%), 238 (100, MH^+,–$CH_3CH_2CONCH_2CH_2OCO$), 134 (40, $CH_3CH{=}NH^+CH_2$ Ph), 105 (40, $PhCHCH_3^+$), 91 (30, $PhCH_2^+$).

(2R,3S,αR)-N-(1-*Hydroxyethyl*)-2-*benzyl*-3-*phenyl*-3-[N-*benzyl*-N-(α-*methyl benzyl*)*amino*]*propanamide* [(2R,3S,αR)-**27a**

To a solution of hydrogen peroxide (30% aqueous solution, 438 mg, 3.86 mmol) and lithium hydroxide monohydrate (65 mg, 1.5 mmol) in water (2 ml) was added a solution of (2*R*,3*S*,α*R*)-**25** (100 mg, 1.5 mmol) in THF (6 ml), and the reaction mixture stirred at room temperature[15]. After 48 h had elapsed, thin layer chromatography still showed the presence of starting material (2*R*,3*S*,α*R*)-**25**, and so the reaction mixture was refluxed for 7 h. Sodium sulfite (535 mg, 4.25 mmol) was added to quench the reaction, which was worked-up by the removal of solvent *in vacuo* and partitioning of the residue thus obtained between dichloromethane and water. The organic layer was dried ($MgSO_4$), filtered and evaporated to yield a white solid (90 mg), which consisted primarily of the alcohol (2*R*,3*S*,α*R*)-**27a**; $[\alpha]_D^{25}$ +7.5 (*c* 1.00 in $CHCl_3$). Anal found: C 80.22, H 7.57, N 5.15; $C_{33}H_{36}N_2O_2$ requires: C 80.45, H 7.37, N 5.69%. $\nu_{max}(CHCl_3)/cm^{-1}$: 3580 (OH), 3460 (NH), 1670 (C=O). ^{1}H-NMR δ_H (300 MHz; $CDCl_3$): 7.48–6.98 (20H, m, Ph), 5.11 (1H, br s, NH), 4.27 (1H, q, *J* 6.9, CH_3CHN), 4.27 (1H, d, *J* 11.0, PhC*H*CH), 3.95; 3.67 (2H, AB system, J_{AB} 14.5, PhCH_2N), 3.37–3.28 (3H, m, CH_2CH_2OH), 2.99 (1H, ddd, *J* 3.7, 10.9 and 11.0, CHCO), 2.81–2.68 (1H, m, CH_2CH$_2$OH), 2.48; 2.38 (2H, AB of ABX system, J_{AB} 13.1, J_{AX} 10.9 and J_{BX} 3.7, PhCH_2CH), 2.22 (1H, br s, OH), 1.06 (3H, d, *J* 6.9, CH_3CH). ^{13}C-NMR δ_C (50 MHz; $CDCl_3$): 174.5 (CON), 145.1; 140.1; 140.1; 138.3 (PhC$_{ipso}$), 129.5; 129.1; 129.0; 128.8; 128.5; 128.3; 127.8 (Ph), 127.3; 126.8; 126.4 (PhC$_{para}$), 63.5 (CHN), 62.2 (CH_2O), 56.1 (CHN), 53.1 (CHCO), 50.7 (PhCH_2N), 42.7 (CH_2NH), 37.0 (CH_2CH), 16.6 (CH_3CH). MS *m*/*z*: 493 (MH^+, 90%), 210 (80, $PhCH_2NCHMePh^+$), 196 (80, $PhCH{=}NH^+CH_2Ph$), 105 (80, $PhCHCH_3^+$), 91 (100, $PhCH_2^+$).

(2R,3S,αR)-S-*Benzyl* 2-*benzyl*-3-*phenyl*-3-[N-*benzyl*-N-(α-*methylbenzyl*)amino]*propanethioate* [(2R,3S,αR)-**27b**]

Butyllithium (0.72 ml, 1.16 mmol) was added to a solution of benzylthiol (144 mg, 1.16 mmol) in THF (10 ml) at −78°C under an atmosphere of nitrogen[16]. After stirring for 10 min, a solution of (2*R*,3*S*,α*R*)-**25** (200 mg, 0.38 mmol) in THF (2 ml) was added by syringe and the reaction allowed to warm gradually to room temperature over 16 h. The reaction was quenched with pH 7 phosphate buffer solution and worked-up as described in procedure (*a*). The crude product was purified by flash column chromatography on silica gel. After elution of benzyl disulfide with 20/1 petrol/diethyl-ether, the product thiol ester (2*R*,3*S*,α*R*)-**27b** was eluted with diethyl ether, and obtained as a colourless oil (145 mg, 68%), $[\alpha]_D^{25}$ +57.5 (*c* 0.50 in $CHCl_3$). Anal found: C 82.19, H 6.80, N 2.27; $C_{38}H_{37}NOS$ requires: C 82.12, H 6.71, N 2.52%. IR $\nu_{max}(CHCl_3)/cm^{-1}$: 1680 (C=O). ^{1}H-NMR δ_H (300 MHz; $CDCl_3$): 7.45–7.07 (23H, m, Ph), 6.85–6.82 (2H, m, Ph), 4.27; 3.73 (2H, AB system, J_{AB} 13.9, PhCH_2N), 4.21 (1H, d, *J* 10.8, PhC*H*CH), 4.11 (1H, q, *J* 7.0, CH_3CHN), 4.07; 3.95 (2H, AB system, J_{AB} 13.8, PhCH_2S), 3.64 (1H, ddd, *J* 10.8, 11.1 and 3.3, CHCO), 2.48; 2.28 (2H, AB of ABX system, J_{AB} 13.5, J_{AX} 11.1 and J_{BX} 3.3, PhCH_2CH), 0.91 (3H, d, *J* 7.0, CH_3CH). ^{13}C-NMR δ_C (50 MHz; $CDCl_3$) 143.8; 140.1; 139.4; 139.0; 137.8 (PhC$_{ipso}$), 129.6; 129.3; 129.2; 128.8; 128.7; 128.6; 128.4; 128.0; 127.9 (Ph), 127.3; 127.2; 127.0; 126.4 (PhC$_{para}$), 64.3; 58.9 (CHN), 55.8 (CHCO), 51.0 (CH_2N), 37.6 (CH_2S), 33.5 (CH_2CH), 13.6 (CH_3CH). MS *m*/*z*: 556 (MH^+, 25%), 300 (60, MH^+,–$PhCH_2CH_2COSCH_2Ph$), 196 (100, $PhCH{=}NH^+CH_2Ph$), 105 (35, $PhCHCH_3^+$), 91 (80, $PhCH_2^+$).

(2R,3S,αaR)-2-*Benzyl*-3-*phenyl*-3-[N-*benzyl*-N-(α-*methylbenzyl*)*amino*]*propan*-1-*ol* [(2*R*,3*S*,α*R*)-**27c**

A solution of (2*R*,3*S*,α*R*)-**25** (300 mg, 0.58 mmol) and lithium aluminium hydride (66 mg, 1.7 mmol) in THF (10 ml) was stirred at 0°C for 2 h. The reaction was quenched with water and the solvent removed *in vacuo*, before the residue was made acidic with dil. aq. HCl and partitioned between satd. aq. Na_2CO_3 and diethyl ether. The crude white solid obtained after drying ($MgSO_4$), filtration and evaporation of the organic phase was purified by flash column chromatography on silica gel. Elution with 3/1 petrol/diethyl ether gave the alcohol product (2*R*,3*S*,α*R*)-**27c** as a white solid, subsequently recrystallized from hexane (221 mg, 88%); $[\alpha]_D^{25}$ −54.6 (*c* 1.00 in $CHCl_3$); m.p. 106–108°C. Anal. found: C 85.60, H 7.69, N, 3.43; $C_{31}H_{33}NO$ requires: C 85.48, H 7.64, N 3.22%. IR $\nu_{max}(CHCl_3)/cm^{-1}$: 3570 (OH). ^{1}H-NMR δ_H (300 MHz; $CDCl_3$): 7.48–6.92 (20H, m, Ph), 4.26; 3.67 (2H, AB system, J_{AB} 13.2, PhCH_2N), 4.19 (1H, q, *J* 7.0, PhC*H*N), 3.79 (1H, m, CH_2OH), 3.76 (1H, d, *J* 11.0, PhC*H*CH), 3.14–3.05 (2H, m, C*H*CH$_2$, O*H*), 2.47 (1H, m, CH_2OH), 2.15; 1.96 (2H, AB of ABX system, J_{AB} 13.6, J_{AX} 2.6 and J_{BX} 11.0, PhCH_2CH), 0.94 (3H, d, *J* 7.0, CH_3CH). ^{13}C-NMR δ_C (50 MHz; $CDCl_3$): 143.9; 141.0; 139.6; 139.5 (PhC$_{ipso}$), 130.0; 129.5; 129.1; 129.0; 128.7; 128.3; 127.6; 127.4; 125.9 (Ph), 64.2 (CHN), 62.7 (CH_2N), 55.8 (CHN), 51.4 (CH_2OH), 43.7 (CHCH$_2$), 34.5 (PhCH$_2$CH), 13.0 (CH_3CH). MS *m*/*z*: 436 (MH^+, 85%), 300 (100, MH^+,–$Ph(CH_2)_3OH$), 196 (70, $PhCH{=}NH^+CH_2Ph$), 105 (65, $PhCHCH_3^+$), 91 (100, $PhCH_2^+$).

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