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Asymmetric synthesis of homochiral differentially protected bis-β-amino acid scaffolds

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Abstract—A strategy for the asymmetric synthesis of homochiral [(*R*,*R*)- or (*S*,*S*)-], or *meso*-(*R*,*S*) bis-β-amino acid scaffolds, formally resulting from the stepwise conjugate addition of two differentially protected homochiral lithium amides to two α,β-unsaturated esters attached to a central arene, is demonstrated. Further manipulation enables the efficient synthesis of orthogonally protected pseudo-*meso* or pseudo-C_2 symmetric scaffolds via selective *N*-benzyl or *N*-allyl deprotection, enabling regio-, stereo- and chemoselective functionalisation.

1. Introduction

Chiral lithium amides have been extensively used and studied[1] within organic synthesis as effective reagents for a range of transformations including enantioselective reduction,[2] alkylation,[3] deprotonation,[4] desymmetrisation[5] and kinetic resolution.[6] While these procedures typically use the powerful basic properties of lithium amides, their propensity to take part in nucleophilic reactions, particularly conjugate addition, has also been widely investigated. This reaction manifold was first recognised by Schlessinger, who reported that LDA added in a conjugate fashion to ethyl crotonate.[7] Yamamoto later introduced lithium *N*-benzyl-*N*-trimethylsilyl amide (LSA) for conjugate addition,[8] and showed the versatility of this process for a range of transformations.[9] The preparation of a homochiral ammonia equivalent for the asymmetric synthesis of β-amino acid derivatives was first demonstrated by Hawkins et al. with the diastereoselective addition of homochiral lithium amide 3,5-dihydro-4*H*-dinaphth[2,1-*c*:1′,1′-*e*]azepine **1** to methyl crotonate,[10] and Bovy[11] and Sewald[12] investigated the use of lithium *N*-trimethylsilyl-*N*-α-methylbenzylamide **2** toward the same aim. While powerful, these methodologies show limited versatility, either due to the extreme conditions required for *N*-deprotection or limited substrate applicability. Concurrently within this area, we have developed a range of homochiral lithium amides **3**–**5**[13] derived from α-methylbenzylamines which undergo highly diastereoselective conjugate addition to a wide range of α,β-unsaturated esters and amides (Fig. 1).

N,*N*-protected β-amino esters arising from conjugate addition of lithium amides **3**–**5** offer the facility for selective mono- or bis-*N*-deprotection, enabling the asymmetric synthesis of a variety of homochiral β-amino acid derivatives as demonstrated in Scheme 1.[14]

The high and predictable levels of diastereoselectivity observed using this conjugate addition protocol[15] has been widely applied to a variety of synthetic targets,[16] including the total syntheses of negamycin,[17] sperabillin C[18] and andrimid.[19] While β-amino acids are an integral part of many biologically active species, much recent interest in this structural motif has been due to the propensity of pseudopeptide sequences containing this functionality to generate novel secondary and tertiary structures.[20] Similarly, advances in the understanding of the factors which promote peptide folding have led to the use of topological templates[21] that constrain the conformational freedom of attached peptides and help to nucleate structural

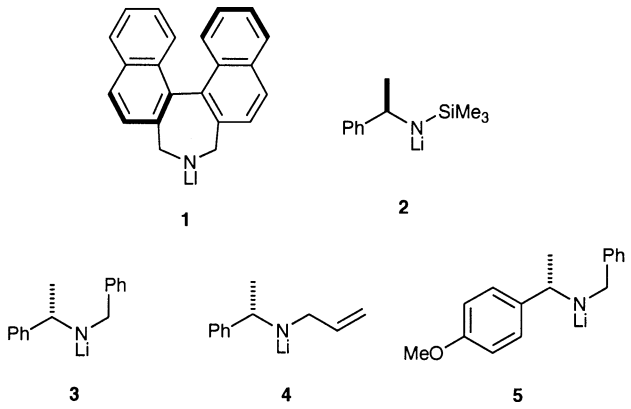

Figure 1. Homochiral ammonia equivalents for conjugate addition.

Keywords: conjugate addition; lithium amides; asymmetric synthesis; differential deprotection.

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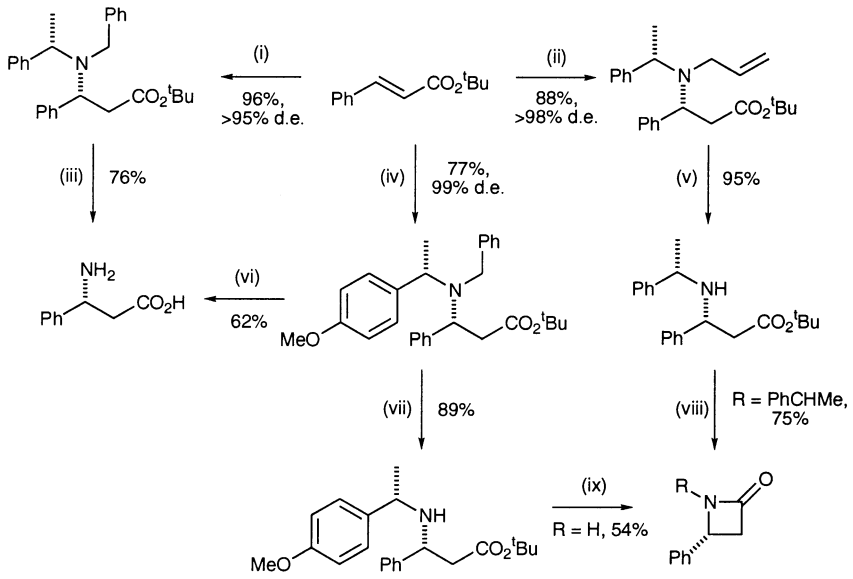
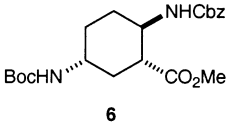


Scheme 1. *Reagents and conditions*: (i) (*S*)-**3** (1.6 equiv.), THF, −78°C; (ii) (*S*)-**4** (1.6 equiv.), THF, −78°C; (iii) $Pd(OH)_2$ on C, MeOH, AcOH, H_2 (5 atm) then TFA/DCM (1:1) and ion exchange; (iv) (*S*)-**5** (1.6 equiv.), THF, −78°C and recrystallisation; (v) $Rh(PPh_3)_3Cl$, $MeCN/H_2O$ (8.5:1.5), Δ; (vi) CAN (6 equiv.), $MeCN/H_2O$ (5:1), rt then HCl (1 $M)_{aq}$, rt and ion exchange; (vii) CAN (2.1 equiv.), $MeCN/H_2O$ (5:1), rt; (viii) MeOH, HCl then MeMgBr, Et_2O, 0°C; (ix) TFA/DCM (1:1) then $(PyS)_2$–PPh_3, MeCN then CAN (3.0 equiv.), $MeCN/H_2O$ (5:1).

interactions, enabling progress in the area of synthetic protein design.[22] The potential combination of these two concepts has led to the proposed use of β-amino based scaffolds for specific sidechain attachments in an attempt to understand the factors that control peptide folding. For instance, Gellman et al. have prepared (*R*,*R*,*R*)-2,5-diaminocyclohexanecarboxylic acid derivative **6** and proposed its use as a template to direct functional groups in specific arrangements,[23] while we have recently reported the synthesis of a range of C_2-symmetric bis-β-amino acid templates for probing the secondary structure of attached α- and β-pseudopeptidic fragments.[24] For example, (*R*,*R*)-bis-β-amino ester **9** can be efficiently prepared in 95% de and >99% ee using the double conjugate addition of homochiral lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **3** to bis-functionalised α,β-unsaturated acceptor **7** to furnish *N*-protected diamine (3*R*,α*S*,3′*R*,α′*S*)-**8**, followed by hydrogenolytic debenzylation (Scheme 2).

The potential utility of these bis-β-amino acid derivatives could be extended if a flexible approach could be developed that would allow for the preparation of not only the C_2 symmetric (*R*,*R*)- or (*S*,*S*)- diastereoisomers,[25] as previously demonstrated by Frejd et al. for poly-α-amino acid derivatives,[26] but also a suitably protected variant of either the (*R*,*S*)-*meso*, (*R*,*R*)- or (*S*,*S*)- diastereoisomers. Our synthetic strategy toward this aim relied upon the supposition that the dominant stereocontrol offered by homochiral lithium amides would allow the construction of either the C_2 or *meso* bis-β-amino acid diastereoisomers **11** and **12**, respectively from an α,β-unsaturated ester **10**. α,β-Unsaturated ester **10** may in turn be constructed using Horner–Wadsworth–Emmons methodology from aldehyde **13**, or via palladium mediated Heck methodology from halide **14** (Fig. 2).

While the generation of C_2 symmetric or *meso* bis-β-amino



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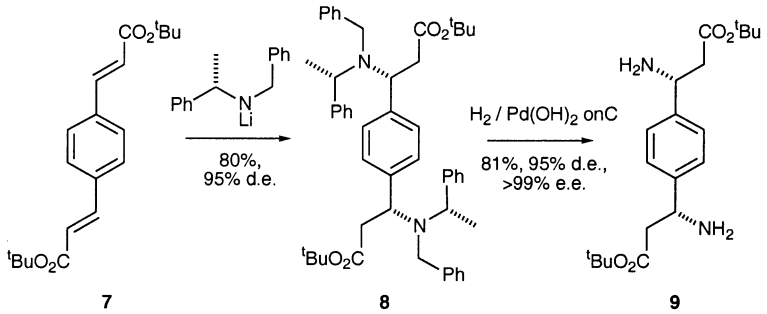


7 **8** **9**

Scheme 2.

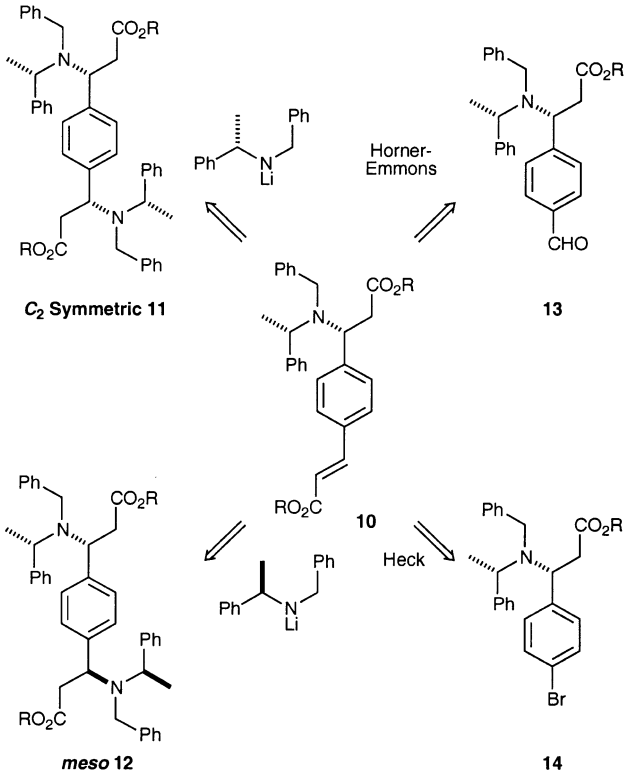
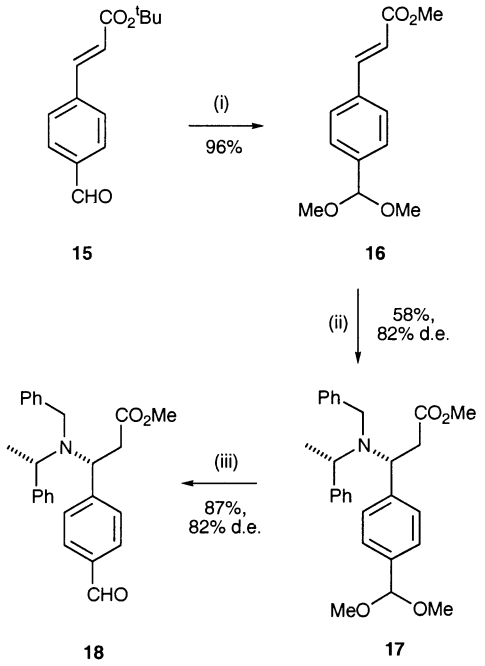


Figure 2.

esters **10** and **11** is of interest, it would not be possible to elaborate selectively peptide chains onto either of the nitrogen or carboxylate fragments due to the equivalent protecting groups employed in their synthesis. However, it was envisaged that differentially protected bis-β-amino acid esters could be regio-, stereo- and chemoselectively elaborated at either of the nitrogen or carboxylate functionality, and would therefore be the most appropriate targets. We now report herein our progress in this area, part of which have been communicated previously.[27]

2. Results and discussion

Initial investigations were directed towards the preparation of non-racemic chiral aldehyde **18** (Scheme 3). α,β-Unsaturated acetal **16** was therefore prepared in two steps via palladium mediated Heck coupling of 4-bromobenzaldehyde with *tert*-butyl acrylate to give α,β-unsaturated acceptor **15** in 91% yield,[28] with subsequent protection of the aldehyde functionality through treatment with trimethylorthoformate in a saturated solution of HCl in MeOH in 96% yield. Conjugate addition of lithium amide (*S*)-**3** gave a crude reaction mixture containing the required acetal protected β-amino ester **17** in 82% de,[29] which gave **17** in 58% yield and 82% de after purification. While deprotection of acetal **17** with amberlyst **15** in acetone[30] furnished the required aldehyde **18** in 87% isolated yield (82% de), neither acetal **17** nor aldehyde **18** could be purified to homogeneity. An alternative protection strategy was therefore sought for the synthesis of the required aldehyde in high diastereoisomeric purity.

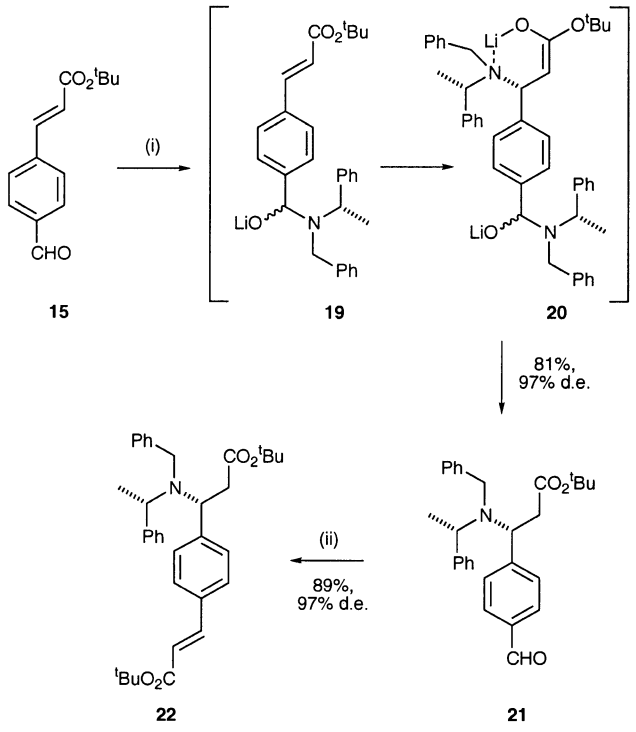


Scheme 3. *Reagents and conditions*: (i) $CH(OMe)_3$, MeOH, HCl, Δ; (ii) (*S*)-**3** (1.6 equiv.), THF, −78°C; (iii) Amberlyst 15, Me_2CO/H_2O (10:1), rt.

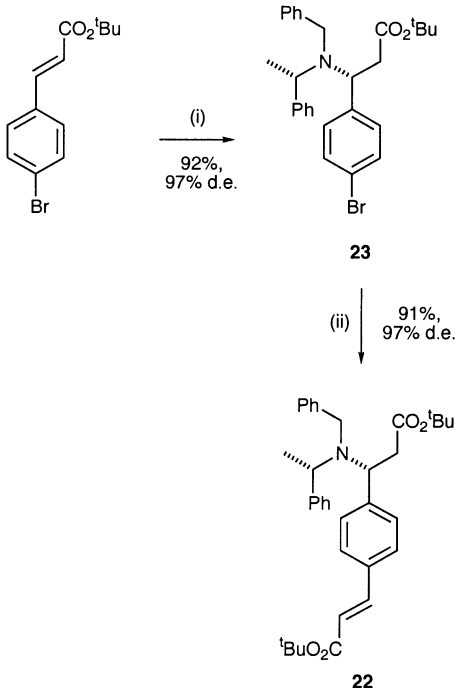
The propensity of lithium amide (*S*)-**3** to act as an in situ protecting group for the aldehyde functionality, whilst undergoing conjugate addition, was next investigated.[31] Thus, conjugate addition of an excess of lithium amide (*S*)-**3** to *tert*-butyl 3-(4-formylphenyl)prop-2-enoate **15** gave the required β-amino aldehyde **21** in 97% de and in 81% isolated yield, presumably via the intermediate α-amino alkoxides **19** and **20**. Subsequent Horner–Wadsworth–Emmons reaction of aldehyde **21** with the lithium anion of *tert*-butyl diethylphosphonoacetate gave α,β-unsaturated acceptor **22** in 89% yield and 97% de after chromatographic purification (Scheme 4). The difference in diastereoselectivity observed upon conjugate addition of (*S*)-**3** to **16** (82% de) and **15** (97% de) is presumably due to the chelating ability of the acetal functionality of **16** which may serve to disrupt the normal chelation controlled lithium amide transition state.[15]

An alternative synthesis of acceptor **22** involving Heck coupling was also evaluated. Thus, conjugate addition of lithium amide (*S*)-**3** to (*E*)-*tert*-butyl 3-(4-bromophenyl)-prop-2-enoate[32] gave (3*R*,α*S*)-**23** in 92% yield and 97% de after purification. Further treatment of (3*R*,α*S*)-**23** under Heck coupling conditions with *tert*-butyl acrylate gave α,β-unsaturated acceptor **22** in 91% yield and 97% de (Scheme 5).

With two viable synthetic routes toward acceptor **22** in hand, conjugate addition of both enantiomers of lithium amide **3** was examined. Addition of lithium amide (*S*)-**3** to α,β-unsaturated acceptor **22** proceeded in 96% de,[29] furnishing the known C_2 symmetric bis-β-amino ester (3*R*,α*S*,3′*R*,α′*S*)-**8** in 82% yield and in 96% de after purification, with spectroscopic properties consistent with those previously reported.[24] Conjugate addition of lithium amide (*R*)-**3** to acceptor **22** proceeded in 97% de,[29] furnishing

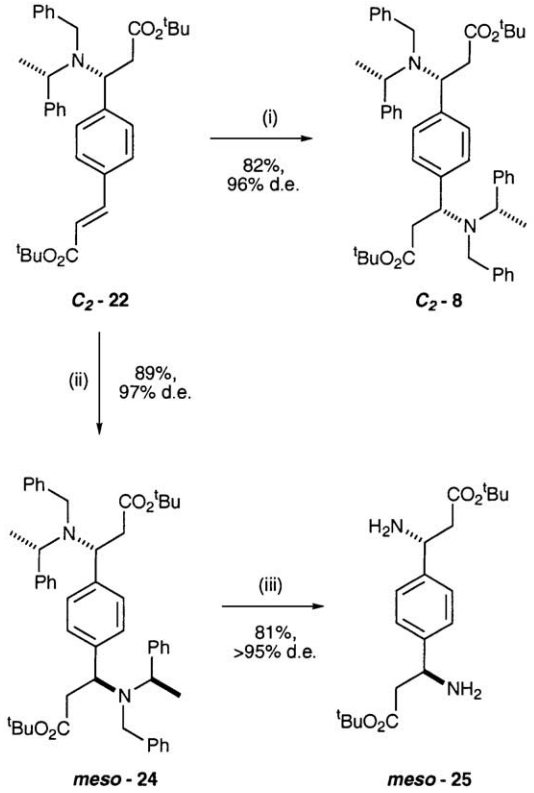


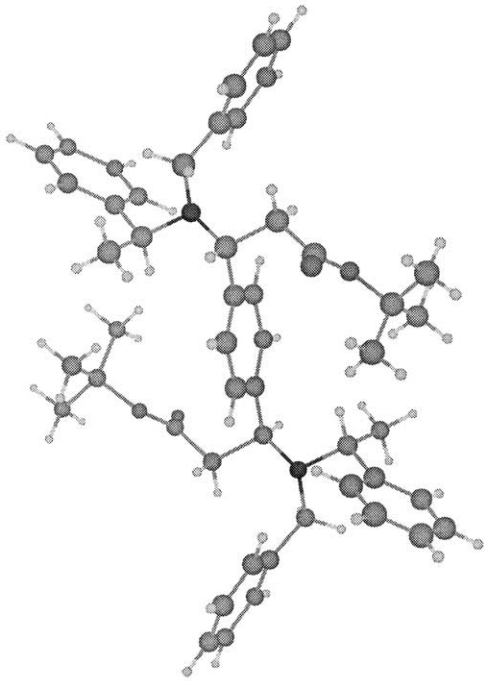
Scheme 4. *Reagents and conditions*: (i) (*S*)-**3** (3 equiv.), THF, −78°C; (ii) *tert*-butyl diethylphosphonoacetate (1.15 equiv.), *n*-BuLi (1.1 equiv.), THF, −78°C to rt.



Scheme 5. *Reagents and conditions*: (i) (*S*)-**3** (1.6 equiv.), THF, −78°C; (ii) $Pd(OAc)_2$ (5 mol%), NEt_3, *tert*-butyl acrylate (1.5 equiv.), tri-(*o*-tolyl)-phosphine (20 mol%).

meso-bis-β-amino ester (3*R*,α*S*,3′*S*,α′*R*)-**24** in 89% yield and in 97% de. The (3*R*,α*S*,3′*S*,α′*R*)-*meso* stereochemistry of **24** was unambiguously proven by X-ray crystallographic analysis, consistent with the model developed previously to explain the observed stereoselectivity during addition of





X-ray crystal structure of *meso*-(3*R*,α*S*,3'*S*,α'*R*)-**23**

Scheme 6. *Reagents and conditions*: (i) (*S*)-**3** (3 equiv.), THF, −78°C; (ii) (*R*)-**3** (3 equiv.), THF, −78°C; (iii) $Pd(OH)_2$, MeOH, AcOH, H_2 (5 atm).

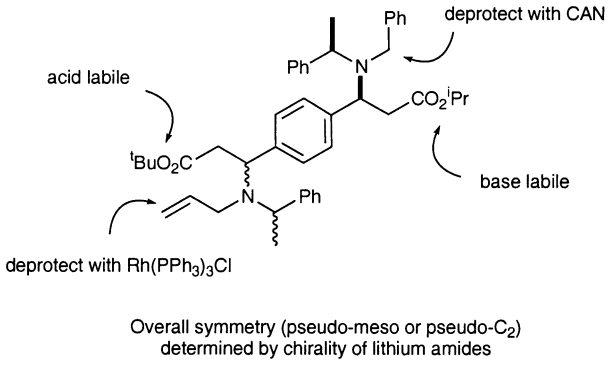
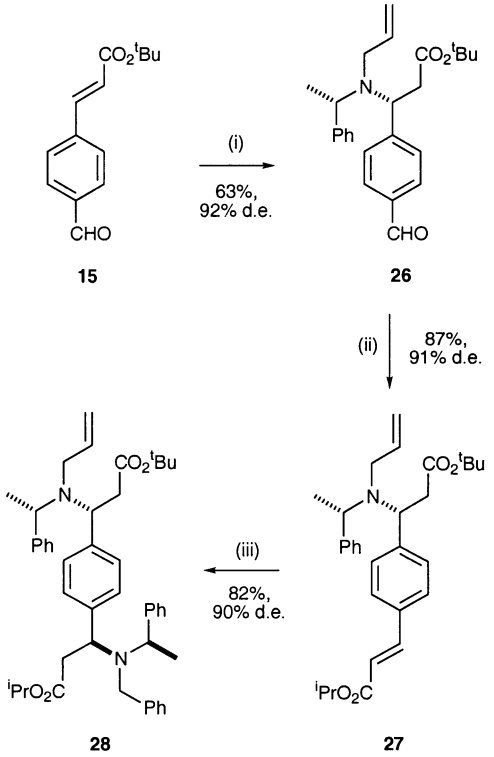


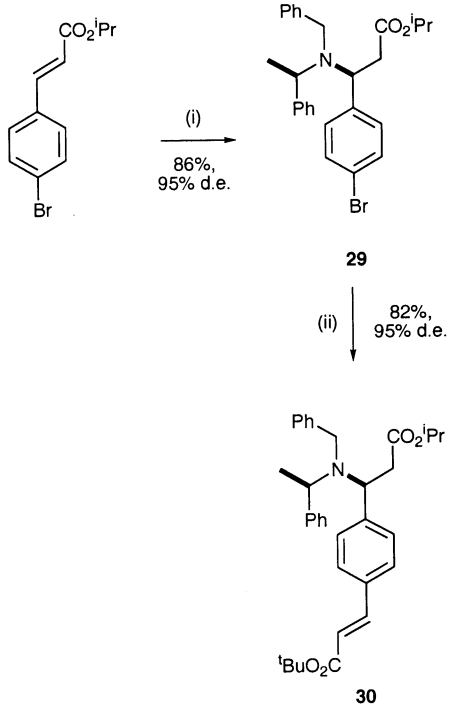
Figure 3. Possible differentially protected bis-β-amino acids.

lithium amide (*R*)-**3** to α,β-unsaturated acceptors.[15] Subsequent *N*-benzyl deprotection via hydrogenolysis, a process known to proceed without loss of stereochemical integrity,[24] furnished *meso*-diamine (3*R*,3′*S*)-**25** in 81% yield (Scheme 6).

With synthetic routes established for the preparation of either C_2 symmetric [(*R*,*R*)- or (*S*,*S*)-] diastereoisomers or *meso*-(*R*,*S*) diastereoisomers of bis-β-amino acids, investigations were directed towards the preparation of second generation templates incorporating differentially protected amino and carboxylate functionality. This concept has previously been applied by Mutter et al. for protein de novo design, with regioselectively addressable functionalised templates (RAFTs) proposed for the preparation of complex protein architectures.[22] For this purpose, the synthesis of model differentially protected bis-β-diamino



Scheme 7. *Reagents and conditions*: (i) (*S*)-**4** (3 equiv.), THF, −78°C; (ii) *iso*-propyl diethylphosphonoacetate (1.15 equiv.), *n*BuLi (1.1 equiv.), THF, −78°C to rt; (iii) (*R*)-**3** (3 equiv.), THF, −78°C.

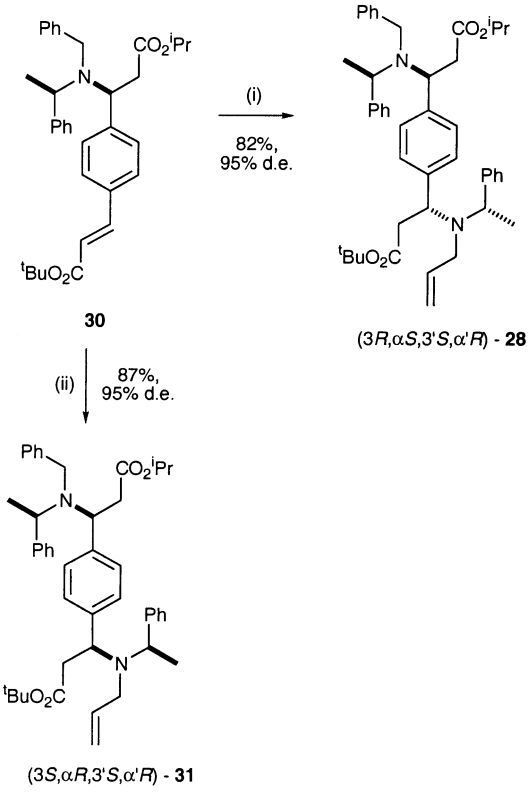


Scheme 8. *Reagents and conditions*: (i) (*R*)-**3** (1.6 equiv.), THF, −78°C; (ii) $Pd(OAc)_2$ (5 mol%), NEt_3, *tert*-butyl acrylate (1.5 equiv.), tri(*o*-tolyl)-phosphine (20 mol%).

esters, in which either the pseudo-C_2 or pseudo-*meso* symmetry of the molecule is determined by the chirality of the lithium amide, was investigated (Fig. 3).

The ready availability of lithium *N*-benzyl-*N*-α-methylbenzylamide **3** and lithium *N*-allyl-*N*-α-methylbenzylamide **4** in either homochiral form seemed ideally suited for differentiation of the *N*-protecting groups. It was envisaged that the ability to deprotect the *N*-allyl functionality using Wilkinson's catalyst,[33] coupled with the ability of *N*-benzyl tertiary amines to be chemoselectively debenzylated upon treatment with CAN,[34] would allow selective deprotection and subsequent elaboration at nitrogen. The relative acid and base lability of *tert*-butyl and *iso*-propyl esters would allow selective access to the carboxylate functionality.[35] Thus, following the aldehyde self protection protocol developed previously, inverse addition of lithium (*S*)-*N*-allyl-*N*-α-methylbenzylamide **4** to aldehyde **15** gave (3*R*,α*S*)-**26** in 92% de,[29] and in 63% yield and in 92% de after purification. Wadsworth–Emmons extension using *iso*-propyl diethylphosphonoacetate furnished the required α,β-unsaturated ester **27** in 91% de,[29] and in 87% yield and 91% de after purification. Conjugate addition of lithium amide (*R*)-**3** to acceptor **27** furnished the required pseudo-*meso* scaffold **28** in 82% yield and 90% de after purification (Scheme 7).

While this route provides an efficient synthesis of template **28**, attempts to increase the levels of diastereoselectivity of **28** from 90% by further purification proved impossible, so an alternative synthesis of **28** was developed, using a Heck coupling approach. Thus, conjugate addition of lithium amide (*R*)-**3** to (*E*)-*iso*-propyl 3-(4-bromophenyl)prop-2-enoate gave β-amino ester (3*S*,α*R*)-**29** in 95% de,[29] and in



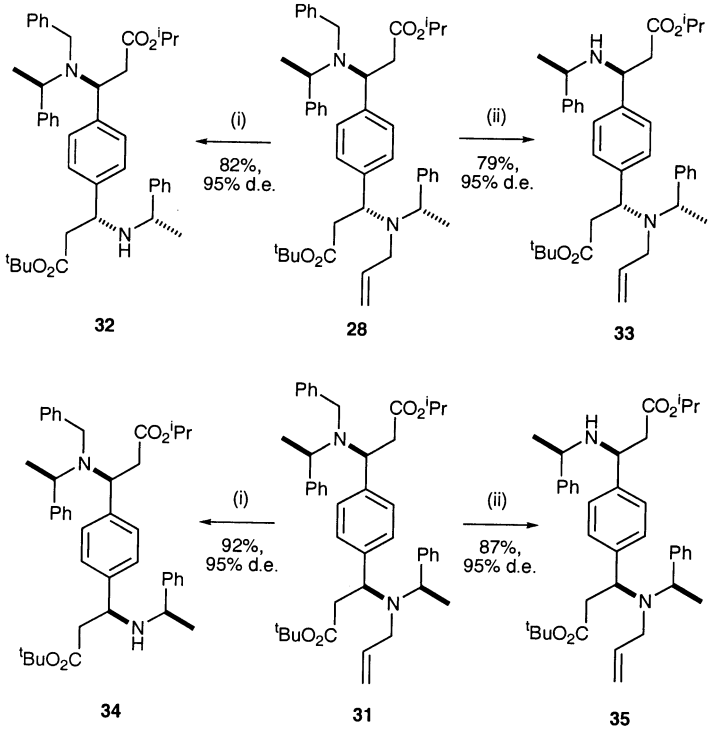
Scheme 9. *Reagents and conditions*: (i) (*S*)-**4** (3 equiv.), THF, −78°C; (ii) (*R*)-**4** (3 equiv.), THF, −78°C.

86% yield and 95% de after purification. Subsequent palladium mediated Heck reaction of (3*S*,α*R*)-bromide **29** with *tert*-butyl acrylate furnished α,β-unsaturated ester (3*S*,α*R*)-**30** in 82% yield and in 95% de (Scheme 8).

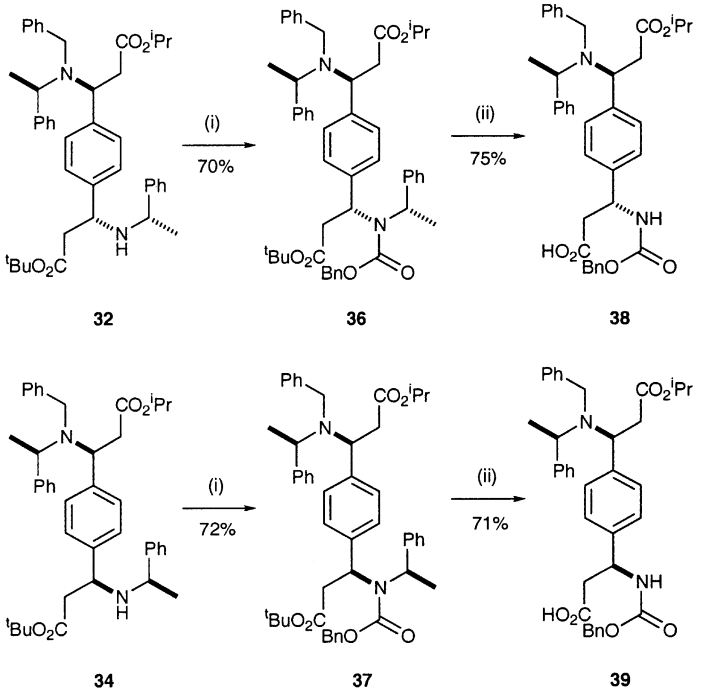
Conjugate addition of lithium (*S*)-*N*-allyl-*N*-α-methylbenzylamide **4** gave pseudo-*meso* scaffold **28** in 95% de and in 82% yield, while conjugate addition of lithium (*R*)-*N*-allyl-*N*-α-methylbenzylamide **4** furnished the pseudo-C_2 symmetric scaffold **31** in 87% yield and in 95% de after purification (Scheme 9).

With the required diamino esters **28** and **31** in hand, differentiation between the *N*-protecting groups was next investigated to allow for the selective functionalisation of either (*R*)- or (*S*)-β-amino acid containing fragment in either template. Thus, treatment of either pseudo-*meso* diamino or pseudo-C_2 diamino esters **28** and **31** with Wilkinson's catalyst in refluxing aqueous acetonitrile gave selective deallylation, furnishing diamines **32** and **34** in 82 and 92% yield respectively, and in 95% de. Alternatively, treatment of pseudo-*meso* **28** or pseudo-C_2 **31** with CAN gave selective mono *N*-debenzylation, furnishing diamines **33** and **35** in 79 yield and 87% yield respectively, and in 95% de (Scheme 10).

Having demonstrated that either (*R*)- or (*S*)-β-amino acid containing fragments can be selectively accessed, this methodology was used as a model for selective peptide elaboration. Thus, simulation of the formation of a peptide bond with the secondary amine functionality of diamines **32** and **34** through protection as their *Z*-carbamates gave amides **36** and **37** in 70 and 72% yields respectively. Subsequent treatment of amides **36** and **37** with formic acid under reflux[36] gave acids **38** and **39** in 75 and 71% yield respectively, in which differential deprotection of both the ester and *N*-protecting fragments of the pseudo-*meso* and pseudo-C_2 templates **27** and **31** has been achieved (Scheme 11).



Scheme 10. *Reagents and conditions*: (i) $Rh(PPh_3)_3Cl$ (0.1 equiv.), $MeCN/H_2O$ (8.5:1.5), Δ; (ii) CAN (2.1 equiv.), $MeCN/H_2O$ (5:1), rt.



Scheme 11. *Reagents and conditions*: (i) dibenzyl dicarbonate, vacuum, rt; (ii) HCO_2H, 60°C.

3. Conclusion

In conclusion, the unambiguous preparation of either C_2 symmetric [(*R*,*R*)- or (*S*,*S*)-] or *meso*-(*R*,*S*)-diastereoisomers of bis-β-amino acid templates has been achieved. Extension of this methodology allows for the synthesis and selective deprotection of both pseudo-*meso* and pseudo-C_2 symmetric bis-β-amino acid templates using a matrix of protecting groups. This strategy shows potential for the attachment of α- and β-pseudopeptidic fragments for secondary structural investigations. Further investigations within this area are currently underway.

4. Experimental

4.1. General

All reactions involving organometallic or other moisture sensitive reagents were performed under an atmosphere of nitrogen via standard vacuum line techniques. All glassware was flame-dried and allowed to cool under vacuum. In all cases, the reaction diastereoselectivity was assessed by peak integration of the ^{1}H NMR spectrum of the crude reaction mixture. Tetrahydrofuran was distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl. All other solvents were used as supplied (Analytical or HPLC grade), without prior purification. Thin layer chromatography (TLC) was performed on aluminium or plastic sheets coated with 60 F_{254} silica. Sheets were visualised using iodine, UV light or 1% aqueous $KMnO_4$ solution. Flash chromatography was performed on Kieselgel 60 silica. Melting points were recorded on a Gallenkamp hot stage apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC 200 (^{1}H: 200 MHz and ^{13}C: 50.3 MHz) or Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) or Bruker AMX 500 (^{1}H: 500 MHz and ^{13}C: 125 MHz) spectrometer in the deuterated solvent stated. All chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Coupling constants are quoted twice, each being recorded as observed in the spectrum without averaging. Residual signals from the solvents were used as an internal reference. ^{13}C multiplicities were assigned using a DEPT sequence. Infrared spectra were recorded on a Perkin–Elmer 1750 IR Fourier Transform spectrophotometer using either thin films on NaCl plates (film) or KBr discs (KBr) as stated. Only the characteristic peaks are quoted in cm^{-1}. Low resolution mass spectra (m/z) were recorded on VG MassLab 20–250 or Micromass Platform 1 spectrometers and high resolution mass spectra (HRMS) on a Micromass Autospec 500 OAT spectrometer or on a Waters 2790 Micromass LCT Exact Mass Electrospray Ionisation Mass Spectrometer. Techniques used were chemical ionisation (CI, NH_3), atmospheric pressure chemical ionisation (APCI) or electrospray ionisation (ESI) using partial purification by HPLC with methanol/acetonitrile/water (40:40:20) as eluent. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. Concentrations are quoted in g/100 mL. Elemental analyses were performed by the microanalysis service of the Inorganic Chemistry Laboratory, Oxford.

4.2. Representative procedure 1a and 1b for lithium amide addition

n-BuLi (1.55 equiv.) was added dropwise to a stirred solution of amine (1.6 equiv.) in anhydrous THF at −78°C and stirred for 30 min under nitrogen. A solution of the α,β-unsaturated ester (1.0 equiv.) in anhydrous THF was added dropwise via cannula and stirred at −78°C for (a) 2 h and (b) 12 h before the addition of saturated aqueous ammonium chloride. The resultant solution was partitioned

between brine and 1:1 DCM/Et_2O, and the combined organic extracts dried ($MgSO_4$), filtered and concentrated in vacuo before being partitioned between 10% aqueous citric acid and DCM, dried and concentrated in vacuo before purification by column chromatography.

4.3. Representative procedure 2 for lithium amide inverse addition

n-BuLi (1.55 equiv.) was added dropwise to a stirred solution of amine (1.6 equiv.) in anhydrous THF at −78°C and stirred for 30 min under nitrogen before being added dropwise via cannula to a solution of the α,β-unsaturated ester (1.0 equiv.) in anhydrous THF and stirred for 12 h before the addition of saturated aqueous ammonium chloride. The resultant solution was partitioned between brine and 1:1 DCM/Et_2O, and the combined organic extracts dried ($MgSO_4$), filtered and concentrated in vacuo before being partitioned between 10% aqueous citric acid and DCM, dried and concentrated in vacuo before purification by column chromatography.

4.4. Representative procedure 3 for Horner–Wadsworth–Emmons olefination

n-BuLi (1.1 equiv.) was added dropwise to a stirred solution of phosphonate (1.15 equiv.) in anhydrous THF at −78°C and stirred for 30 min under nitrogen before the dropwise addition of aldehyde (1.0 equiv.) in THF via cannula. After 30 min, the solution was warmed to rt and stirred for a further 12 h before cooling to −78°C and addition of saturated aqueous ammonium chloride. The resultant solution was partitioned between brine and DCM, and the combined organic extracts dried ($MgSO_4$), filtered and concentrated in vacuo before purification by column chromatography.

4.4.1. (*E*)-*tert*-Butyl 3-(4-formyl-phenyl)prop-2-enoate[28] 15. A mixture of 4-bromobenzaldehyde (10.0 g, 54.0 mmol), *tert*-butyl acrylate (11 g, 86.4 mmol), tri-*o*-tolyl phosphine (0.64 g, 2.10 mmol) and $Pd(OAc)_2$ (120 mg, 0.54 mmol) in NEt_3 (25 mL) was refluxed overnight. The resultant mixture was filtered through celite (eluent Et_2O), washed with water (50 mL), extracted with DCM (3×100 mL), dried and concentrated in vacuo. Recrystallization (DCM/pentane) gave **15** (11.4 g, 91%) as a pale yellow solid; δ_H (200 MHz, $CDCl_3$) 1.54 (9H, s, $CO_2C(Me)_3$), 6.48 (1H, d, J=16.1 Hz, C═C*H*$CO_2C(Me)_3$), 7.60 (1H, d, J=16.1 Hz, *H*C═C$HCO_2C(Me)_3$), 7.62–7.91 (4H, m, *Ph*), 10.0 (1H, s, C*H*O); data consistent with that of the literature.[28]

4.4.2. (*E*)-Methyl-3-(4-dimethoxymethyl-phenyl)prop-2-enoate 16. Trimethylorthoformate (0.80 g, 7.5 mmol) was added to a stirred solution of MeOH (20 mL) saturated with HCl prior to the portionwise addition of **15** (1.65 g, 7.1 mmol) and refluxed for 1 h. After concentration in vacuo, the pH was adjusted to pH7 with saturated sodium bicarbonate solution and partitioned between DCM (3×100 mL) and brine. The residue was purified by column chromatography on silica gel (hexane/Et_2O 5:1) to give **16** (1.6 g, 96%) as a colourless oil; $C_{13}H_{16}O_4$ requires C 66.1, H, 6.8%; found C 65.7, H 6.9%; δ_H (200 MHz, $CDCl_3$) 3.33 (6H, s, $CH(OMe)_2$), 3.82 (3H, s, CO_2Me), 5.41 (1H, s, C*H*$(OMe)_2$), 6.45 (1H, d, J=16.0 Hz, ArCH═C*H*), 7.45–7.56 (4H, m, *Ph*), 7.70 (1H, d, J=16.0 Hz, ArC*H*═CH); δ_C (50 MHz, $CDCl_3$) 51.4, 52.2, 102.2, 118.0, 127.3, 127.9, 134.5, 140.4, 144.4, 167.3; *m/z* ($APCI^+$) 237.0 (MH^+, 30%), 205.0 (MH^+−MeOH, 100%); ν_{max} (film) 2950, 2830 (C–H), 1721 (C═O), 1637 (C═C).

4.4.3. (3*R*,α*S*)-Methyl 3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-(4-dimethoxymethyl-phenyl)propanoate 17. Following representative procedure 1a, *n*-BuLi (2.5 M, 1.0 mL, 2.55 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (614 mg, 2.6 mmol, 1.6 equiv.) in THF (5 mL) and **16** (236 mg, 1.0 mmol, 1.0 equiv.) in THF (5 mL) gave, after purification by column chromatography on silica gel (hexane/Et_2O 2:1), **17** (260 mg, 58%) as a colourless oil in 82% de; δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, J=6.8 Hz, C(α)*Me*), 2.57 (1H, dd, $J_{2A,2B}$=14.9 Hz, $J_{2A,3}$=9.3 Hz, C(2)H_A), 2.69 (1H, dd, $J_{2B,2A}$=14.9 Hz, $J_{2B,3}$=5.7 Hz, C(2)H_B), 3.33 (6H, s, $CH(OMe)_2$), 3.48 (3H, s, CO_2Me), 3.66 (1H, AB, J=14.6 Hz, NCH_A), 3.74 (1H, AB, J=14.6 Hz, NCH_B), 4.00 (1H, q, J=6.8 Hz, C(α)*H*), 4.46 (1H, dd, $J_{3,2A}$=9.3 Hz, $J_{3,2B}$=5.7 Hz, C(3)*H*), 7.18–7.45 (14H, m, *Ph*); selected peaks for minor diastereoisomer 2.95 (1H, dd, $J_{2B,2A}$=14.5 Hz, $J_{2B,3}$=6.0 Hz, C(2)H_B), 3.90 (1H, q, J=6.9 Hz, C(α)*H*); δ_C (50 MHz, $CDCl_3$) 15.9, 37.2, 50.7, 51.5, 52.7, 56.7, 58.9, 103.0, 126.9, 127.1, 127.5, 127.6, 128.8, 128.4, 137.2, 141.5, 142.3, 144.1, 172.4; *m/z* ($APCI^+$) 448.6 (MH^+, 100%), 470.0 (MNa^+, 10%), 344.1 ($MH^+-C_4H_8$, 20%); HRMS (CI^+) $C_{28}H_{34}NO_4$ requires 448.2488; found 448.2492; ν_{max} (film) 2948, 2830 (C–H), 1738 (C═O).

4.4.4. (3*R*,α*S*)-Methyl 3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-(4-formylphenyl)-propanoate 18. Amberlyst-**15** (wet) (200 mg) was added to a stirred solution of acetal **17** (100 mg, 0.22 mmol) at rt in acetone/H_2O (10:1, 5.5 mL). After 30 min, TLC analysis indicated that the reaction had gone to completion and the resin was removed by filtration and the filtrate evaporated. Purification by column chromatography on silica gel (petrol (30/40)/Et_2O 6:1) gave **18** as a pale yellow oil (78 mg, 87%) in 82% de; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, J=6.7 Hz, C(α)*Me*), 2.59–2.72 (2H, m, C(2)H_2), 3.51 (3H, s, CO_2Me), 3.69 (1H, AB, J=14.6 Hz, NCH_A), 3.74 (1H, AB, J=14.6 Hz, NCH_B), 3.99 (1H, q, J=6.8 Hz, C(α)*H*), 4.55 (1H, dd, $J_{3,2A}$=8.9 Hz, $J_{3,2B}$=5.5 Hz, C(3)*H*), 7.21–7.44 (10H, m, *Ph*), 7.59–7.61 (2H, m, *Ph*), 7.83–7.86 (2H, m, *Ph*), 10.0 (1H, s, C*H*O); selected peaks for minor diastereoisomer 2.85 (1H, dd, $J_{2A,2B}$=14.5 Hz, $J_{2A,3}$=9.0 Hz, C(2)H_A), 2.95 (1H, dd, $J_{2A,2B}$=14.5 Hz, $J_{2A,3}$=6.0 Hz, C(2)H_B); δ_C (100 MHz, $CDCl_3$) 16.6, 36.4, 50.9, 51.6, 57.2, 58.9, 126.9, 127.2, 127.8, 128.1, 128.3, 128.6, 129.8, 135.5, 140.8, 143.5, 149.2, 171.8, 191.9; *m/z* ($APCI^+$) 402.2 (MH^+, 70%), 298.1 ($MH^+-C_8H_9$, 100%); HRMS (CI^+) $C_{26}H_{27}NO_3$ requires 402.2074; found 402.2069; ν_{max} (film) 3027, 2974 (C–H), 1737 (C═O), 1700 (C═O).

4.4.5. (3*R*,α*S*)-*tert*-Butyl 3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-(4-formyl-phenyl)-propanoate 21. Following representative procedure 2, *n*-BuLi (1.6 M, 8.0 mL, 12.7 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (2.7 g, 12.9 mmol) in THF (20 mL) and **15** (1.0 g, 4.3 mmol) in

THF (20 mL) gave, after purification by column chromatography on silica gel (hexane/Et_2O 6:1), **21** (1.5 g, 81%) as a pale yellow oil in 97% de; δ_H (400 MHz, $CDCl_3$) 1.24 (9H, s, $CO_2C(Me)_3$), 1.29 (3H, d, J=6.9 Hz, C(α)*Me*), 2.54 (2H, m, C(2)H_2), 3.68 (2H, app s, NCH_2), 3.96 (1H, q, J=6.9 Hz, C(α)*H*), 4.49 (1H, app t, J=7.5 Hz, C(3)*H*), 7.18–7.42 (10H, m, *Ph*), 7.59–7.61 (2H, m, *Ph*), 7.86–7.88 (2H, m, *Ph*), 10.00 (1H, s, C*H*O); δ_C (50 MHz, $CDCl_3$) 17.2, 27.8, 37.4, 51.0, 57.6, 59.1, 80.6, 126.8, 127.1, 127.7, 127.9, 128.3, 128.8, 129.6, 130.1, 135.3, 141.1, 143.5, 149.5, 170.8, 192.0; *m/z* ($APCI^+$) 444.5 (MH^+, 100%), 388.1 ($MH^+-C_4H_8$, 20%); HRMS (CI^+) $C_{29}H_{34}NO_3$ requires 444.2539; found 444.2547; ν_{max} (film) 2973 (C–H), 1724 (C=O), 1704 (C=O), 1153 (C–O); $[\alpha]_D^{23}$=+18.0 (*c* 1.0, $CHCl_3$).

4.4.6. Horner–Wadsworth–Emmons preparation of (3*R*,α*S*,*E*)-*tert*-butyl 3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-[4-*tert*-butoxy-3-oxoprop-1-enyl)phenyl]propanoate 22. Following representative procedure 3, *tert*-butyl diethylphosphonoacetate (1.0 g, 3.9 mmol), *n*-BuLi (2.5 M, 1.5 mL, 3.7 mmol) in THF (15 mL) and aldehyde **21** (1.5 g, 3.4 mmol) gave, after purification by column chromatography on silica gel (pentane/Et_2O 20:1), **22** (1.63 g, 89%) as a white foam in 97% de; δ_H (400 MHz, $CDCl_3$) 1.23 (9H, s, $CO_2C(Me)_3$), 1.28 (3H, d, J=6.9 Hz, C(α)*Me*), 1.54 (9H, s, $CO_2C(Me)_3$), 2.46–2.54 (2H, m, C(2)H_2), 3.68 (2H, app s, NCH_2), 3.98 (1H, q, J=6.9 Hz, C(α)*H*), 4.41 (1H, dd, $J_{3,2A}$=9.3 Hz, $J_{3,2B}$=5.8 Hz, C(3)*H*), 6.35 (1H, d, J=16.0 Hz, ArCH=C*H*), 7.17–7.50 (14H, m, *Ph*), 7.58 (1H, d, J=16.0 Hz, ArC*H*=CH); δ_C (100 MHz, $CDCl_3$) 16.7, 27.8, 28.2, 37.8, 50.9, 57.3, 59.2, 80.3, 80.4, 119.7, 126.6, 126.9, 127.8, 127.9, 128.1, 128.2, 128.6, 133.4, 141.4, 143.3, 143.8, 144.2, 166.4, 170.9; *m/z* ($APCI^+$) 542.9 (MH^+, 100%), 486.3 ($MH^+-C_4H_8$, 20%); HRMS (EI^+) $C_{35}H_{44}NO_4$ requires 542.3270; found 542.3272; ν_{max} (KBr) 2976, 2931 (C–H), 1726, 1707 (C=O), 1635 (C=C), 1150 (C–O); $[\alpha]_D^{23}$ = +13.2 (*c* 1.1, $CHCl_3$).

4.4.7. (3*R*,α*S*)-*tert*-Butyl 3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-(4-bromophenyl)propanoate 23. Following representative procedure 1a, *n*-BuLi (2.5 M, 6.6 mL, 16.4 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (3.6 g, 17.0 mmol) in THF (35 mL) and (*E*)-*tert*-butyl 3-(4-bromophenyl)propanoate (3.0 g, 10.6 mmol) in THF (35 mL) gave, after purification by column chromatography on silica gel (pentane/Et_2O 20:1), **23** (4.8 g, 91%) as a colourless oil in 97% de; δ_H (400 MHz, $CDCl_3$) 1.25 (9H, s, $CO_2C(Me)_3$), 1.28 (3H, d, J=6.8 Hz, C(α)*Me*), 2.42–2.54 (2H, m, C(2)H_2), 3.66 (2H, app s, NCH_2), 3.95 (1H, q, J=6.8 Hz, C(α)*H*), 4.37 (1H, dd, $J_{3,2A}$=10.1 Hz, $J_{3,2B}$=5.1 Hz, C(3)*H*), 7.17–7.48 (14H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.9, 27.8, 37.8, 50.8, 57.3, 58.8, 80.4, 120.9, 126.6, 127.0, 127.7, 127.9, 128.1, 128.2, 129.9, 131.2, 141.1, 141.3, 143.7, 170.9; *m/z* ($APCI^+$) 496.2 (MH^+, 100%), 438.2 ($MH^+-C_4H_8$, 20%); HRMS (EI^+) $C_{28}H_{33}NO_2Br$ requires 494.1695; found 494.1684; ν_{max} (film) 2975, 2932 (C–H), 1726 (C=O), 1153 (C–O); $[\alpha]_D^{23}$=+3.6 (*c* 1.8, $CHCl_3$).

4.5. Heck preparation of (3*R*,α*S*,*E*)-*tert*-butyl 3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-[4-*tert*-butoxy-3-oxoprop-1-enyl)phenyl]propanoate 22

$Pd(OAc)_2$ (23 mg, 0.1 mmol) was added to a stirred solution of bromide **23** (1.0 g, 2.0 mmol), tri-*o*-tolylphosphine (123 mg, 0.4 mmol) and *tert*-butyl acrylate (0.6 mL, 4.05 mmol) in NEt_3 (10 mL) and heated at reflux for 12 h. After cooling, the residue was filtered though celite, partitioned between H_2O (20 mL) and DCM (3×100 mL), and concentrated in vacuo. Purification by column chromatography (pentane/Et_2O 20:1) gave **22** (1.02 g, 93%) as a white foam with consistent spectroscopic properties to those previously described.

4.5.1. (3*R*,α*S*,3′*R*,α′*S*)-Di-*tert*-butyl benzene-1,4-bis[3-(*N*-benzyl-*N*-α-methylbenzylamino)propanoate][24] 8. Following representative procedure 1b, *n*-BuLi (2.5 M, 2.2 mL, 5.45 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (1.2 g, 5.5 mmol) in THF (15 mL) and **22** (1.0 g, 1.85 mmol) in THF (15 mL) gave, after purification by column chromatography on silica gel (pentane/Et_2O 12:1), **8** (1.14 g, 82%) as a hygroscopic white foam in 96% de; $[\alpha]_D^{24}$=+11.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.17 (18H, s, $CO_2C(Me)_3$), 1.21 (6H, d, J=6.8 Hz, C(α)*Me*), 2.49–2.57 (4H, m, C(2)H_2), 3.66 (4H, app s, NCH_2), 3.97 (2H, q, J=6.8 Hz, C(α)*H*), 4.39 (2H, dd, $J_{3,2A}$=9.0 Hz, $J_{3,2B}$=6.1 Hz, C(3)*H*), 7.14–7.42 (24H, m, *Ph*); data consistent with that contained in the literature.[24]

4.5.2. (3*R*,α*S*,3′*S*,α′*R*)-Di-*tert*-butyl benzene-1,4-bis[3-(*N*-benzyl-*N*-α-methylbenzylamino)propanoate] 24. Following representative procedure 1b, *n*-BuLi (2.5 M, 2.2 mL, 5.45 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (1.2 g, 5.5 mmol) in THF (15 mL) and 22 (1.0 g, 1.85 mmol) in THF (15 mL) gave, after washing with pentane, **24** (1.24 g, 89%) as a white solid in 97% de; mp 158–160°C; δ_H (400 MHz, $CDCl_3$) 1.20 (18H, s, $CO_2C(Me)_3$), 1.22 (6H, d, J=7.1 Hz, C(α)*Me*), 2.50–2.58 (4H, m, C(2)H_2), 3.67 (4H, app s, NCH_2), 3.97 (2H, q, J=7.1 Hz, C(α)*H*), 4.41 (2H, dd, $J_{3,2A}$=9.2 Hz, $J_{3,2B}$=6.0 Hz, C(3)*H*), 7.16–7.42 (24H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.1, 28.2, 38.6, 51.2, 57.5, 59.5, 80.5, 126.9, 127.2, 128.2, 128.4, 128.4, 128.5, 141.0, 142.0, 144.6, 171.5; ν_{max} (KBr) 2971, 2930 (C–H), 1716 (C=O), 1151 (C–O); *m/z* ($APCI^+$) 753.5 (MH^+, 100%); HRMS (EI^+) $C_{50}H_{61}N_2O_4$ requires 753.4631; found 753.4656.

4.5.3. (3*R*,3′*S*)-Di-*tert*-butyl benzene-1,4-bis[3-aminopropanoate] 25. $Pd(OH)_2$ on C (150 mg) was added to a solution of **24** (200 mg, 0.27 mmol) in a mixture of degassed MeOH/acetic acid (5:1, 6 mL) and the resultant black suspension stirred under a hydrogen atmosphere (5 atm) for 16 h. The reaction mixture was filtered through a plug of celite (eluent MeOH) and concentrated in vacuo before purification by column chromatography on silica gel ($CHCl_3$/MeOH 20:1) to give **25** (78 mg, 81%) as a colourless oil in >95% de which solidified upon standing; ν_{max} (film) 3491 (N–H), 2973, 2931 (C–H), 1721 (C=O); δ_H (500 MHz, $CDCl_3$) 1.41 (18H, s, $CO_2C(Me)_3$), 1.79 (4H, br s, N*H*), 2.55–2.57 (4H, m, C(2)H_2), 4.34–4.37 (2H, br m, C(3)*H*), 7.32 (4H, s, *Ph*); δ_C (125 MHz, $CDCl_3$) 28.0, 45.1, 52.3, 80.6, 126.4, 143.7, 171.2; *m/z* ($APCI^+$) 365 (MH^+, 20%); HRMS (EI^+) $C_{20}H_{33}N_2O_4$ requires 365.2440; found 365.2434.

4.5.4. (3*R*,α*S*)-*tert*-Butyl 3-(*N*-allyl-*N*-α-methylbenzylamino)-3-(4-formyl-phenyl)propanoate 26. Following representative procedure 2, *n*-BuLi (1.6 M, 8.0 mL,

12.7 mmol), (*S*)-*N*-allyl-*N*-α-methylbenzylamine (2.7 g, 12.9 mmol) in THF (20 mL) and **15** (1.0 g, 4.3 mmol) in THF (20 mL) gave, after purification by column chromatography on silica gel (hexane/Et_2O 6:1), **26** (1.07 g, 63%) as a pale yellow oil in 92% de; δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, J=6.8 Hz, C(α)*Me*), 1.30 (9H, s, $CO_2C(Me)_3$), 2.61 (1H, dd, $J_{2A,2B}$=15.0 Hz, $J_{2A,3}$=9.4 Hz, C(2)H_A), 2.73 (1H, dd, $J_{2B,2A}$=15.0 Hz, $J_{2B,3}$=5.5 Hz, C(2)H_B), 3.15 (2H, m, $NCH_2CH{=}CH_2$), 4.00 (1H, q, J=6.8 Hz, C(α)*H*), 4.51 (1H, dd, $J_{3,2A}$=9.4 Hz, $J_{3,2B}$=5.5 Hz, C(3)*H*), 5.05–5.08 (2H, m, $NCH_2CH{=}CH_2$), 5.74–5.84 (1H, m, $NCH_2CH{=}CH_2$), 7.22–7.41 (5H, m, *Ph*), 7.56–7.58 (2H, m, *Ph*), 7.85–7.88 (2H, m, *Ph*), 10.01 (1H, s, C*H*O); δ_C (100 MHz, $CDCl_3$) 17.2, 27.9, 38.1, 49.9, 56.8, 58.8, 80.6, 116.1, 126.8, 127.4, 128.2, 128.7, 129.6, 135.3, 138.4, 144.2, 149.4, 170.8, 192.0; *m*/*z* ($APCI^+$) 394.1 (MH^+, 100%), 338.1 ($MH^+-C_4H_8$, 20%); HRMS (CI^+) $C_{25}H_{32}NO_3$ requires 394.2382; found 394.2381; ν_{max} (film) 2972 (C–H), 1724 (C=O), 1704 (C=O), 1605 (C=C), 1153 (C–O); $[\alpha]_D^{23}$=+18.7 (*c* 1.0, $CHCl_3$).

4.5.5. (3*R*,α*S*,*E*)-*tert*-Butyl 3-(*N*-allyl-*N*-α-methylbenzylamino)-3-[4-*iso*-propoxy-3-oxoprop-1-enyl)phenyl]propanoate 27. Following representative procedure 3, *iso*-propyl diethylphosphonoacetate (1.13 g, 4.75 mmol, 1.5 equiv.), *n*-BuLi (2.5 M, 4.58 mmol, 1.8 mL) in THF (10 mL) and **26** (1.2 g, 3.16 mmol) gave, after purification by column chromatography on silica gel (hexane/Et_2O 20:1), **27** (1.3 g, 87%) as a white foam in 91% de; δ_H (400 MHz, $CDCl_3$) 1.20 (3H, d, J=6.8 Hz, C(α)*Me*), 1.30 (9H, s, $CO_2C(Me)_3$), 1.32 (6H, d, J=6.3 Hz, $OCH(Me)_2$), 2.59 (1H, dd, $J_{2',2'B}$=14.8 Hz, $J_{2'A,3'}$=9.3 Hz, C(2′)H_A), 2.73 (1H, dd, $J_{2'B,2'A}$=14.8 Hz, $J_{2'B,3'}$=5.7 Hz, C(2′)H_B), 3.15 (2H, app d, $NCH_2CH{=}CH_2$), 4.01 (1H, q, J=6.8 Hz, C(α′)*H*), 4.45 (1H, dd, $J_{3',2'A}$=9.3 Hz, $J_{3',2'B}$=5.7 Hz, C(3′)*H*), 5.04–5.17 (3H, m, $OCH(CH_3)_2$ and $NCH_2CH{=}CH_2$), 5.75–5.84 (1H, m, $NCH_2CH{=}CH_2$), 6.41 (1H, d, J=16.0 Hz, PhCH=C*H*), 7.21–7.50 (9H, m, *Ph*), 7.67 (1H, d, J=16.0 Hz, PhC*H*=CH); δ_C (125 MHz, $CDCl_3$) 16.8, 22.0, 27.8, 38.6, 49.7, 56.5, 58.7, 67.7, 80.3, 115.8, 118.3, 126.6, 127.4, 127.8, 128.0, 128.5, 133.3, 144.3, 144.5, 138.6, 144.0, 166.6, 171.0; ν_{max} (film) 2968 (C–H), 1726 (C=O), 1637 (C=C), 1171 (C–O); *m*/*z* ($APCI^+$) 478.0 (MH^+, 100%), 500.1 (MNa^+, 5%), 422.2 ($MH^+-C_4H_8$, 20%); HRMS (CI^+) $C_{30}H_{40}NO_4$ requires 478.2957; found 478.2975; $[\alpha]_D^{23}$=+9.1 (*c* 1.0, $CHCl_3$).

4.5.6. (3*S*,α*R*)-*iso*-Propyl 3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-(4-bromophenyl)propanoate 29. Following representative procedure 1a, *n*-BuLi (2.5 M, 6.9 mL, 17.4 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (3.8 g, 17.9 mmol) in THF (40 mL) and (*E*)-*iso*-propyl 3-(4-bromophenyl)propanoate (3.0 g, 11.2 mmol) in THF (40 mL) gave, after purification by column chromatography on silica gel (pentane/Et_2O 20:1), **29** (4.8 g, 89%) as a colourless oil in 95% de; δ_H (400 MHz, $CDCl_3$) 1.03, 1.08 (2×3H, d, J=6.2 Hz, $CH(Me)_2$), 1.30 (3H, d, J=6.8 Hz, C(α)*Me*), 2.48–2.60 (2H, m, C(2)H_2), 3.69 (2H, app s, NCH_2), 3.98 (1H, q, J=6.8 Hz, C(α)*H*), 4.43 (1H, dd, $J_{3,2A}$=9.8 Hz, $J_{3,2B}$=5.0 Hz, C(3)*H*), 4.83 (1H, sept, J=6.2 Hz, C*H*$(Me)_2$), 7.20–7.49 (14H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.6, 16.7, 21.6, 37.2, 50.8, 57.2, 58.9, 67.7, 121.0, 126.7, 127.0, 127.8, 127.9, 128.2, 129.8, 131.1, 131.3, 141.0, 141.3, 143.7, 171.1; *m*/*z* ($APCI^+$) 480.1 (MH^+, 30%); HRMS (EI^+) $C_{27}H_{31}NO_2Br$ requires 480.1538; found 480.1527; ν_{max} (film) 2978, 2933 (C–H), 1728 (C=O); $[\alpha]_D^{23}$=+5.1 (*c* 1.0, $CHCl_3$).

4.5.7. (3*S*,α*R*,*E*)-*iso*-Propyl 3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-[4-*tert*-butoxy-3-oxoprop-1-enyl)phenyl]propanoate 30. $Pd(OAc)_2$ (70 mg, 0.31 mmol) was added to a stirred solution of bromide **29** (3.0 g, 6.26 mmol), tri-*o*-tolylphosphine (380 mg, 1.25 mmol) and *tert*-butyl acrylate (1.9 mL, 12.5 mmol) in NEt_3 (30 mL) and heated at reflux for 12 h. After cooling, the residue was filtered though celite, partitioned between H_2O (20 mL) and DCM (3×100 mL), and concentrated in vacuo. Purification by column chromatography (pentane/Et_2O 20:1) gave **30** (2.95 g, 89%) as a yellow oil in 95% de; δ_H (400 MHz, $CDCl_3$) 0.99, 1.05 (2×3H, d, J=6.4 Hz, $CH(Me)_2$), 1.28 (3H, d, J=6.8 Hz, C(α)*Me*), 1.54 (9H, s, $CO_2C(Me)_3$), 2.51–2.59 (2H, m, C(2)H_2), 3.69 (2H, app s, NCH_2), 3.98 (1H, q, J=6.8 Hz, C(α)*H*), 4.45 (1H, dd, $J_{3,2A}$=9.0 Hz, $J_{3,2B}$=5.9 Hz, C(3)*H*), 4.80 (1H, sept, J=6.4 Hz, C*H*$(Me)_2$), 6.36 (1H, d, J=15.9 Hz, ArCH=C*H*), 7.17–7.49 (14H, m, *Ph*), 7.57 (1H, d, J=15.9 Hz, ArC*H*=CH); δ_C (100 MHz, $CDCl_3$) 16.5, 21.5, 28.2, 37.2, 50.8, 57.2, 59.2, 67.6, 80.4, 119.8, 126.6, 126.9, 127.8, 127.9, 128.2, 128.6, 133.5, 141.3, 143.2, 143.8, 144.2, 166.4, 171.2; *m*/*z* ($APCI^+$) 528.4 (MH^+, 100%); HRMS (EI^+) $C_{34}H_{42}NO_4$ requires 528.3114; found 528.3116; ν_{max} (KBr) 2976, 2933 (C–H), 1726, 1708 (C=O), 1636 (C=C), 1148 (C–O); $[\alpha]_D^{23}$=−5.9 (*c* 1.55, $CHCl_3$).

4.5.8. (3*R*,α*S*,1′*S*,α′*R*)-*tert*-Butyl 3-(*N*-allyl-*N*-α-methylbenzylamino)-3-[4-*iso*-propoxy-3′-oxo-1′-(*N*-benzyl-*N*-α-methylbenzylamino)propanoate)phenyl]propanoate 28. Following representative procedure 1b, *n*-BuLi (2.5 M, 2.55 mL, 4.1 mmol), (*S*)-(*N*-benzyl-*N*-α-methylbenzylamine (880 mg, 4.15 mmol) in THF (10 mL) and **30** (660 mg, 1.38 mmol, 1 equiv.) in THF (10 mL) gave, after purification by column chromatography on silica gel (hexane/Et_2O 10:1), **28** (780 mg, 82%) as a colourless oil in 95% de; δ_H (400 MHz, $CDCl_3$) 0.98, 1.03 (2×3H, d, J=6.2 Hz, $OCH(Me)_2$), 1.10, 1.25 (2×3H, d, J=6.8 Hz, C(α)*Me* and C(α′)*Me*), 1.28 (9H, s, $CO_2C(Me)_3$), 2.53–2.63 (3H, m, C(2)H_2 and C(2′)H_A), 2.65 (1H, dd, $J_{2'B,2'A}$=14.6 Hz, $J_{2'B,3'}$=6.3 Hz, C(2′)H_B), 3.13 (2H, app d, $NCH_2CH{=}CH_2$), 3.69 (2H, app s, NCH_2Ph), 3.96–4.03 (2H, m, C(α)*H* and C(α′)*H*), 4.43–4.47 (2H, m, C(3)*H* and C(1′)*H*), 4.78 (1H, sept, J=6.2 Hz, $OCH(CH_3)_2$), 5.02–5.17 (2H, m, $NCH_2CH{=}CH_2$), 5.78 (1H, m, $NCH_2CH{=}CH_2$), 7.16–7.44 (19H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.4, 16.7, 21.5, 21.6, 27.9, 37.5, 38.9, 49.7, 50.7, 56.0, 57.0, 58.5, 59.2, 67.5, 80.2, 115.8, 126.5, 126.8, 127.5, 127.8, 127.9, 128.0, 128.1, 138.9, 140.4, 140.5, 141.6, 144.1, 145.0, 171.2, 171.3; ν_{max} (film) 2968 (C–H), 1728 (C=O), 1170 (C–O); *m*/*z* ($APCI^+$) 690 (MH^+, 100%), 712 (MNa^+, 20%); HRMS (CI^+); $C_{45}H_{57}N_2O_4$ requires 689.4318; found 689.4325; $[\alpha]_D^{23}$=+1.4 (*c* 0.85, $CHCl_3$).

4.5.9. (3*S*,α*R*,1′*S*,α′*R*)-*tert*-Butyl 3-(*N*-allyl-*N*-α-methylbenzylamino)-3-[4-*iso*-propoxy-3′-oxo-1′-(*N*-benzyl-*N*-α-methylbenzylamino)propanoate)phenyl]propanoate 31. Following representative procedure 1b, *n*-BuLi (2.5 M,

2.2 mL, 5.6 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (920 mg, 5.7 mmol) in THF (15 mL) and **30** (1.0 g, 1.9 mmol, 1 equiv.) in THF (15 mL) gave, after purification by column chromatography on silica gel (hexane/Et_2O 10:1), **31** (1.13 g, 87%) as a colourless oil in 95% de; δ_H (400 MHz, $CDCl_3$) 1.01, 1.05 (2×3H, d, J=6.2 Hz, OCH(*Me*)$_2$), 1.12, 1.27 (2×3H, d, J=6.7 Hz, C(α)*Me* and C(α′)*Me*), 1.29 (9H, s, $CO_2C(Me)_3$), 2.56–2.66 (3H, m, C(2)H_2 and C(2′)H_A), 2.80 (1H, dd, $J_{2'B,2'A}$=14.9 Hz, $J_{2'B,3'}$=6.5 Hz, C(2′)H_B), 3.15 (2H, app d, $NCH_2CH{=}CH_2$), 3.70 (2H, app s, NCH_2Ph), 3.98–4.07 (2H, m, C(α)*H* and C(α′)*H*), 4.46–4.49 (2H, m, C(3)*H* and C(1′)*H*), 4.81 (1H, sept, J=6.2 Hz, $OCH(CH_3)_2$), 5.04–5.19 (2H, m, $NCH_2CH{=}CH_2$), 5.76–5.86 (1H, m, $NCH_2CH{=}CH_2$), 7.17–7.46 (19H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.2, 17.3, 22.1, 22.2, 28.4, 37.8, 39.6, 50.2, 51.3, 56.6, 57.7, 59.2, 59.7, 68.0, 80.7, 116.3, 127.1, 127.1, 127.3, 127.4, 128.1, 128.2, 128.4, 128.5, 128.6, 128.7, 128.2, 139.5, 140.9, 141.1, 142.2, 144.7, 145.6, 171.8, 171.9; ν_{max} (film) 2976, 2932 (C–H), 1728 (C=O), 1158, 1145 (C–O); *m/z* ($APCI^+$) 689.4 (MH^+, 100%); HRMS (EI) $C_{45}H_{57}N_2O_4$ requires 689.4318; found 689.4332; $[\alpha]_D^{23} = -7.3$ (*c* 1.0, $CHCl_3$).

4.5.10. (3*R*,α*S*,1′*S*,α′*R*)-*tert*-Butyl 3-(*N*-α-methylbenzylamino)-3-[4-*iso*-propoxy-3′-oxo-1′-(*N*-benzyl-*N*-α-methylbenzylamino)propanoate)phenyl]propanoate 32. $Rh(PPh_3)_3Cl$ (93 mg, 0.1 mmol) was added to a stirred solution of **28** (700 mg, 1.0 mmol) in MeCN/H_2O (8.5:1.5) (15 mL) under nitrogen and heated at reflux for 8 h. The volatiles were removed, and the residue passed through a small plug of alumina (eluent Et_2O), before purification by column chromatography on silica gel (pentane/Et_2O 5:1) to give **32** (545 mg, 82%) as a colourless oil in 95% de; δ_H (400 MHz, $CDCl_3$) 0.98, 1.05 (2×3H, d, J=6.3 Hz, OCH(*Me*)$_2$), 1.25 (3H, d, J=6.8 Hz, C(α′)*Me*), 1.34 (3H, d, J=6.5 Hz, C(α)*Me*), 1.35 (9H, s, $CO_2C(Me)_3$), 1.79 (1H, br s, N*H*), 2.49–2.66 (4H, m, C(2)H_2 and C(2′)H_2), 3.60 (1H, q, J=6.5 Hz, C(α)*H*), 3.67 (2H, ABq, J=14.7, NCH_2Ph), 3.98 (1H, q, J=6.8 Hz, C(α′)*H*), 4.14 (1H, dd, $J_{3,2A}$=7.7 Hz, $J_{3,2B}$=6.6 Hz, C(3)*H*), 4.42 (1H, dd, $J_{1',2'A}$ = 9.7 Hz, $J_{1',2'B}$=5.3 Hz, C(1′)*H*), 4.79 (1H, sept, J=6.3 Hz, $OCH(CH_3)_2$), 7.14–7.42 (19H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.1, 21.5, 21.6, 22.2, 28.0, 37.7, 43.8, 50.8, 54.6, 56.8, 57.0, 59.3, 67.4, 80.4, 126.5, 126.8, 126.8, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 140.7, 141.6, 141.7, 144.0, 146.0, 171.0, 171.3; *m/z* ($APCI^+$) 649.9 (MH^+, 100%), 672.0 (MNa^+, 80%), 545.4 ($MH^+-C_4H_8$, 30%); HRMS (CI^+) $C_{42}H_{53}N_2O_4$ requires 649.4005; found 649.4008; ν_{max} (film) 2976 (C–H), 1727 (C=O), 1149 (C–O); $[\alpha]_D^{23}=-7.6$ (*c* 1.0, $CHCl_3$).

4.5.11. (3*S*,α*R*,1′*S*,α′*R*)-*tert*-Butyl 3-(*N*-α-methylbenzylamino)-3-[4-*iso*-propoxy-3′-oxo-1′-(*N*-benzyl-*N*-α-methylbenzylamino)propanoate)phenyl]propanoate 34. $Rh(PPh_3)_3Cl$ (120 mg, 0.13 mmol) was added to a stirred solution of **31** (900 mg, 1.3 mmol) in MeCN/H_2O (8.5:1.5) (15 mL) under nitrogen and heated at reflux for 8 h. The volatiles were removed, and the residue passed through a small plug of alumina (eluent Et_2O), before purification by column chromatography on silica gel (pentane/Et_2O 4:1) to give **34** (782 mg, 92%) as a colourless oil in 95% de; δ_H (400 MHz, $CDCl_3$) δ_H 0.99, 1.05 (2×3H, d, J=6.2 Hz, OCH(*Me*)$_2$), 1.26 (3H, d, J=6.7 Hz, C(α′)*Me*), 1.34 (3H, d, J=6.5 Hz, C(α)*Me*), 1.35 (9H, s, $CO_2C(Me)_3$), 1.76 (1H, br s, N*H*), 2.50–2.66 (4H, m, C(2)H_2 and C(2′)H_2), 3.59 (1H, q, J=6.5 Hz, C(α)*H*), 3.67 (2H, app s, NCH_2Ph), 3.97 (1H, q, J=6.7 Hz, C(α′)*H*), 4.14 (1H, dd, $J_{3A,2}$=7.7 Hz, $J_{3B,2}$=6.5 Hz, C(3)*H*), 4.42 (1H, dd, $J_{1',2'A}$ = 9.5 Hz, $J_{1',2'B}$=5.7 Hz, C(1′)*H*), 4.81 (1H, sept, J=6.2 Hz, $OCH(CH_3)_2$), 7.16–7.49 (19H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.5, 21.6, 21.6, 22.3, 28.0, 37.4, 43.8, 50.9, 54.6, 56.8, 57.1, 59.2, 67.4, 80.4, 126.5, 126.8, 126.8, 127.8, 127.9, 128.1, 128.1, 128.2, 128.3, 140.7, 141.6, 141.7, 144.0, 146.0, 171.0, 171.4; *m/z* ($APCI^+$) 649.3 (MH^+, 100%), 593.3 ($MH^+-C_4H_8$, 10%); HRMS (EI) $C_{42}H_{53}N_2O_4$ requires 649.4005; found 649.4005; ν_{max} (film) 2976, 2930 (C–H), 1726 (C=O), 1150 (C–O); $[\alpha]_D^{23}=+8.4$ (*c* 1.6, $CHCl_3$).

4.5.12. (3*R*,α*S*,1′*S*,α′*R*)-*tert*-Butyl 3-(*N*-allyl-*N*-α-methylbenzylamino)-3-[4-*iso*-propoxy-3′-oxo-1′-(*N*-α-methylbenzylamino)propanoate)phenyl]propanoate 33. CAN (670 mg, 1.22 mmol) was added to a stirred solution of **28** (400 mg, 0.58 mmol) in MeCN/H_2O (5:1, 20 mL) at room temperature. After 12 h, saturated aqueous sodium bicarbonate solution (20 mL) was added and the resultant mixture partitioned between brine and Et_2O (3×50 mL), dried and concentrated in vacuo. Purification by column chromatography (hexane/Et_2O 6:1 to 4:1) gave **33** (275 mg, 79%) as a pale yellow oil in 95% de; δ_H (400 MHz, $CDCl_3$) 1.15–1.21 (9H, m, OCH(*Me*)$_2$ and C(α)*Me*), 1.32 (9H, s, $CO_2C(Me)_3$), 1.37 (3H, d, J=6.5 Hz, C(α′)*Me*), 1.90 (1H, br s, N*H*), 2.57–2.81 (4H, m, C(2)H_2 and C(2′)H_2), 3.16 (2H, app d, NCH_2), 3.64 (1H, q, J=6.5 Hz, C(α′)*H*), 4.02 (1H, q, J=6.7 Hz, C(α)*H*), 4.22 (1H, dd, J=7.8, 6.4 Hz, C(1′)*H*), 4.45 (1H, dd, J=8.7, 6.3 Hz, C(3)*H*), 4.98 (1H, sept, J=6.2 Hz, $OCH(CH_3)_2$), 5.04–5.19 (2H, m, $NCH_2CH{=}CH_2$), 5.77–5.85 (1H, m, $NCH_2CH{=}CH_2$), 7.18–7.45 (14H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.4, 21.8, 21.8, 22.2, 28.0, 39.2, 43.1, 49.7, 54.6, 56.1, 56.7, 58.8, 67.7, 80.1, 115.7, 126.5, 126.7, 126.8, 127.5, 128.0, 128.2, 128.3, 138.9, 140.6, 141.5, 144.9, 146.0, 171.2; ν_{max} (film) 2975, 2930 (C–H), 1727 (C=O), 1150 (C–O); *m/z* ($APCI^+$) 599.3 (MH^+, 100%); HRMS (EI) $C_{38}H_{50}N_2O_4$ requires 599.3849; found 599.3848; $[\alpha]_D^{23}=+7.2$ (*c* 1.0, $CHCl_3$).

4.5.13. (3*S*,α*R*,1′*S*,α′*R*)-*tert*-Butyl 3-(*N*-allyl-*N*-α-methylbenzylamino)-3-[4-*iso*-propoxy-3′-oxo-1′-(*N*-α-methylbenzylamino)propanoate)phenyl]propanoate 35. CAN (602 mg, 1.1 mmol) was added to a stirred solution of **31** (350 mg, 0.53 mmol) in MeCN/H_2O (5:1, 20 mL) at room temperature. After 12 h, saturated aqueous sodium bicarbonate solution (20 mL) was added and the resultant mixture partitioned between brine and Et_2O (3×50 mL), dried and concentrated in vacuo. Purification by column chromatography (hexane/Et_2O 7:1 to 4:1) gave **35** (265 mg, 87%) as a colourless oil in 95% de; δ_H (400 MHz, $CDCl_3$) 1.15–1.20 (9H, m, OCH(*Me*)$_2$ and C(α)*Me*), 1.31 (9H, s, $CO_2C(Me)_3$), 1.35 (3H, d, J=6.6 Hz, C(α′)*Me*), 1.85 (1H, br s, N*H*), 2.55–2.79 (4H, m, C(2)H_2 and C(2′)H_2), 3.14 (2H, app d, NCH_2), 3.64 (1H, q, J=6.6 Hz, C(α′)*H*), 4.01 (1H, q, J=6.6 Hz, C(α)*H*), 4.20 (1H, dd, J=7.8, 6.5 Hz, C(1′)*H*), 4.44 (1H, dd, J=8.8, 6.3 Hz, C(3)*H*), 4.98 (1H, sept, J=6.3 Hz, $OCH(CH_3)_2$), 5.03–5.17 (2H, m, $NCH_2CH{=}CH_2$), 5.76–5.86 (1H, m, $NCH_2CH{=}CH_2$), 7.17–7.34 (12H, m, *Ph*), 7.41–7.43 (2H, m, *Ph*); δ_C (100 MHz,

$CDCl_3$) 16.5, 21.7, 21.8, 22.2, 27.8, 39.0, 43.0, 49.7, 54.6, 56.2, 56.7, 58.8, 67.7, 80.1, 115.6, 126.5, 126.7, 126.8, 127.5, 128.0, 128.2, 128.3, 138.9, 140.7, 141.5, 144.9, 146.0, 171.2; ν_{max} (film) 2977, 2931 (C–H), 1729 (C=O), 1149 (C–O); *m/z* ($APCI^+$) 599.3 (MH^+, 100%); HRMS (EI) $C_{38}H_{51}N_2O_4$ requires 599.3849; found 599.3860; $[\alpha]_D^{23}$ = +9.7 (*c* 1.0, $CHCl_3$).

4.5.14. (3*R*,α*S*,1′*S*,α′*R*)-*tert*-Butyl 3-(*N*-benzyloxycarbonyl-*N*-α-methylbenzylamino)-3-[4-*iso*-propoxy-3′-oxo-1′-(*N*-benzyl-*N*-α-methylbenzylamino)propanoate)-phenyl]propanoate 36. Dibenzyl dicarbonate (400 mg, 1.39 mmol) was added neat to **32** (300 mg, 0.46 mmol) and the mixture stirred under high vacuum at rt for three days. The resultant oil was purified by column chromatography on silica gel (hexane/Et_2O 4:1) to give **36** (255 mg, 70%); δ_H (500 MHz, toluene-d_8, 363 K) 0.94, 0.95 (2×3H, d, *J*=6.3 Hz, OCH*(Me)*$_2$), 1.20 (3H, d, *J*=6.9 Hz, C(α)*Me*), 1.24 (9H, s, CO_2C*(Me)*$_3$), 1.37 (3H, d, *J*=6.9 Hz, C(α)*Me*), 2.63–2.70 (3H, m, C(2)H_2 and C(2′)H_A), 3.10 (1H, dd, $J_{2'B,2'A}$=16.0 Hz, $J_{2'B,3'}$=8.8 Hz, C(2′)H_B), 3.68 (2H, ABq, *J*=15.0 Hz, NCH_2Ph), 4.01 (1H, q, *J*=6.9 Hz, C(α′)*H*), 4.62 (1H, dd, $J_{3',2'B}$=8.5 Hz, $J_{3',2'A}$=6.5 Hz, C(1′)*H*), 4.80 (1H, sept, *J*=6.3 Hz, OC*H*$(CH_3)_2$), 4.97–5.06 (3H, m, OCH_2Ph and C(α)*H*), 5.51 (1H, dd, $J_{3,2B}$=8.8 Hz, $J_{3,2A}$=5.3 Hz, C(3)*H*), 7.03–7.40 (24H, m, *Ph*); δ_C (125 MHz, toluene-d_8, 363 K) (some aromatic C obscured by toluene) 17.8, 18.5, 21.6, 28.0, 37.4, 40.5, 51.4, 55.5, 56.1, 58.3, 59.5, 67.2, 80.0, 125.3, 126.8, 127.0, 127.4, 127.5, 127.6, 128.2, 128.3, 128.4, 128.4, 129.0, 140.5, 141.5, 141.9, 142.8, 144.8, 156.0, 169.9, 170.5; *m/z* ($APCI^+$) 784.0 (MH^+, 50%), 805.9 (MNa^+, 100%); HRMS (CI^+) $C_{50}H_{58}N_2O_6$ requires 783.4373; found 783.4374; ν_{max} (film) 2977, 2933 (C–H), 1727, 1695 (C=O), 1148 (C–O); $[\alpha]_D^{23}$ = +4.5 (*c* 1.0, $CHCl_3$).

4.5.15. (3*S*,α*R*,1′*S*,α′*R*)-*tert*-Butyl 3-(*N*-benzyloxycarbonyl-*N*-α-methylbenzylamino)-3-[4-*iso*-propoxy-3′-oxo-1′-(*N*-benzyl-*N*-α-methylbenzylamino)propanoate)phenyl] propanoate 37. Dibenzyl dicarbonate (661 mg, 2.31 mmol) was added neat to **34** (500 mg, 0.77 mmol) and the mixture stirred under high vacuum at rt for three days. The resultant oil was purified by column chromatography on silica gel (hexane/Et_2O 4:1) to give **37** (432 mg, 72%); δ_H (500 MHz, toluene-d_8, 363 K) 0.94, 0.95 (2×3H, d, *J*=6.2 Hz, OCH*(Me)*$_2$), 1.20 (3H, d, *J*=7.1 Hz, C(α)*Me*), 1.23 (9H, s, CO_2C*(Me)*$_3$), 1.35 (3H, d, *J*=7.0 Hz, C(α)*Me*), 2.60–2.70 (3H, m, C(2)H_2 and C(2′)H_A), 3.10 (1H, dd, $J_{2'B,2'A}$=15.7 Hz, $J_{2'B,3'}$=8.8 Hz, C(2′)H_B), 3.67 (2H, ABq, *J*=14.6 Hz, NCH_2Ph), 4.00 (1H, q, *J*=7.1 Hz, C(α′)*H*), 4.62 (1H, dd, $J_{3',2'B}$=9.7 Hz, $J_{3',2'A}$=5.9 Hz, C(1′)*H*), 4.80 (1H, sept, *J*=6.2 Hz, OC*H*$(CH_3)_2$), 4.98–5.05 (3H, m, OCH_2Ph and C(α)*H*), 5.51 (1H, dd, $J_{3,2B}$=8.8 Hz, $J_{3,2A}$=5.3 Hz, C(3)*H*), 6.99–7.40 (24H, m, *Ph*); δ_C (125 MHz, toluene-d_8, 363 K) (some aromatic C obscured by toluene) 17.7, 18.5, 21.6, 21.6, 28.0, 37.5, 40.5, 51.4, 55.5, 56.1, 58.2, 59.5, 67.2, 67.2, 80.0, 125.3, 126.8, 127.0, 127.6, 127.8, 127.9, 128.3, 128.4, 129.0, 140.5, 141.5, 141.9, 142.8, 144.8, 156.0, 169.8, 170.5; *m/z* ($APCI^+$) 783.2 (MH^+, 100%); HRMS (EI) $C_{50}H_{59}N_2O_6$ requires 783.4373; found 783.4373; ν_{max} (film) 2976, 2934 (C–H), 1727, 1693 (C=O), 1147 (C–O); $[\alpha]_D^{23}$=−13.9 (*c* 1.0, $CHCl_3$).

4.5.16. (3*S*,α*R*,1′*R*)-*iso*-Propyl 3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-{4-[1-(*N*-benzyloxycarbonyl)propionic acid]phenyl}propanoate 38. Formic acid (5 mL) was added to **36** (80 mg, 0.10 mmol) and heated at reflux for 3 h under nitrogen before cooling and concentration in vacuo. The resultant oil was purified by column chromatography on silica gel ($CHCl_3$/MeOH 50:1) to give **38** as a colourless oil (48 mg, 75%); δ_H (400 MHz, CD_3OD) 0.95, 1.01 (2×3H, d, *J*=6.2 Hz, OCH*(Me)*$_2$), 1.21 (3H, d, *J*=6.8 Hz, C(α)*Me*), 2.53–2.67 (2H, m, C(2)H_2), 2.71–2.82 (2H, m, C(2′)H_2), 3.70 (2H, app s, NCH_2Ph), 4.00 (1H, q, *J*=6.8 Hz, C(α)*H*), 4.39 (1H, dd, $J_{3',2'B}$=9.8 Hz, $J_{3',2'A}$=5.1 Hz, C(3)*H*), 4.72 (1H, sept, *J*=6.2 Hz, OC*H*$(CH_3)_2$), 5.05 (2H, s, OCH_2Ph), 5.13 (1H, app t, *J*=7.3 Hz, C(1′)*H*), 7.14–7.92 (20H, m, *Ph* and *NH*); δ_C (400 MHz, CD_3OD) 17.6, 22.3, 38.4, 42.5, 52.1, 53.5, 59.0, 61.1, 67.8, 69.4, 127.7, 128.0, 128.4, 129.1, 129.3, 129.4, 129.5, 129.7, 129.8, 130.0, 138.7, 142.5, 143.0, 143.4, 146.0, 158.4, 173.6; ν_{max} (film) 3027, 2979, 2929 (C–H), 1716, 1698 (C=O); *m/z* ($APCI^+$) 623.6 (MH^+, 25%), 645.4 (MNa^+, 20%); HRMS (ESI) $C_{38}H_{41}N_2O_6$ requires 621.2965; found 621.2957; $[\alpha]_D^{23}$=+10.5 (*c* 1.0, $CHCl_3$).

4.5.17. (3*S*,α*R*,1′*S*)-*iso*-Propyl 3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-{4-[1′-(*N*-benzyloxycarbonyl)propionic acid]phenyl}propanoate 39. Formic acid (5 mL) was added to **37** (200 mg, 0.25 mmol) and heated at reflux for 3 h under nitrogen before cooling and concentration in vacuo. The resultant oil was purified by column chromatography on silica gel ($CHCl_3$/MeOH 50:1) to give **39** as a colourless oil (112 mg, 71%); δ_H (400 MHz, CD_3OD) 0.96, 1.01 (2×3H, d, *J*=6.2 Hz, OCH*(Me)*$_2$), 1.22 (3H, d, *J* = 6.8 Hz, C(α)*Me*), 2.56 (1H, dd, $J_{2A,2B}$=14.6 Hz, $J_{2A,3}$ = 10.1 Hz, C(2)H_A), 2.63 (1H, dd, $J_{2B,2A}$=14.6 Hz, $J_{2B,3}$ = 5.1 Hz, C(2)H_B), 2.68–2.79 (2H, m, C(2′)H_2), 3.70 (2H, app s, NCH_2Ph), 3.99 (1H, q, *J*=6.8 Hz, C(α)*H*), 4.40 (1H, dd, $J_{3',2'B}$=9.7 Hz, $J_{3',2'A}$=6.0 Hz, C(3)*H*), 4.72 (1H, sept, *J*=6.2 Hz, OC*H*$(CH_3)_2$), 5.05 (2H, s, OCH_2Ph), 5.12–5.15 (1H, br m, C(1′)*H*), 7.14–7.50 (19H, m, *Ph*); δ_C (400 MHz, CD_3OD) 17.7, 22.2, 22.3, 38.5, 42.5, 52.1, 53.5, 59.0, 61.0, 67.9, 69.4, 127.7, 128.0, 128.4, 129.1, 129.3, 129.4, 129.5, 129.6, 129.8, 130.0, 130.2, 138.7, 142.5, 143.0, 143.4, 146.0, 158.4, 173.6; ν_{max} (film) 3027, 2976 (C–H), 1736, (br, C=O); *m/z* ($APCI^+$) 623.0 (MH^+, 10%); HRMS (ESI) $C_{38}H_{43}N_2O_6$ requires 623.3121; found 621.3124; $[\alpha]_D^{23}$=−11.9 (*c* 1.25, $CHCl_3$).

4.6. X-Ray crystal structure data for 23

Data were collected using an Enraf Nonius Kappa CCD diffractometer with graphite monochromated Cu Kα radiation using standard procedures at 190 K. The structure was solved by direct methods (Sir92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[37]

Crystal Data for **23**: [$C_{25}H_{30}NO_2$], colourless block, *M* = 376.52, monoclinic, space group *P*121/*a*1, *a*=14.3547(4), *b*=10.4856(1), *c*=15.6342(5) Å, β=114.9141(11)°, *U* = 2134.2 Å^3, *Z*=4, μ=0.073, crystal dimensions 0.2×0.2×0.2 mm, A total of 4840 unique reflections were

measured for $5.23<\theta<27.50$ and 3289 reflections were used in the refinement. The final parameters were $wR_2 = 0.0251$ and $R_1=0.0422$ [$I>3\sigma(I)$].

Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC175460. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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