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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 1793–1811

Homochiral lithium amides for the asymmetric synthesis of β-amino acids

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Received 10 April 2006; accepted 15 May 2006
Available online 18 July 2006

Abstract—Secondary homochiral lithium amides derived from α-methylbenzylamine undergo highly diastereoselective conjugate additions to a range of α,β-unsaturated esters. The corresponding β-amino acids are readily liberated by successive N-debenzylation and ester hydrolysis, furnishing (*R*)-β-amino butyric acid, (*R*)-β-amino pentanoic acid, (*S*)-β-leucine, (*R*)-β-amino octanoic acid, (*S*)-β-phenylalanine, (*S*)-β-tyrosine methyl ether, (*S*)-β-tyrosine hydrochloride and (*S*)-β-(2-methoxyphenyl)-β-amino propanoic acid in high yields and high ee. The application of this procedure to the synthesis of the natural products (*R*)-β-DOPA and (*R*)-β-lysine is demonstrated. The development of a simplified one-pot reaction protocol applicable to the multi-gram scale synthesis of homochiral β-amino esters is also delineated.

1. Introduction

β-Amino acids are components of a variety of naturally occurring products of biological significance, including alkaloids and peptides. For example, the β-phenylalanine unit is found in celacinnine, a member of the spermidine alkaloids,[1] while Taxol®, a potent anti-cancer agent, contains α-hydroxy-β-phenylalanine as an essential component of its anti-tumour activity.[2] (*R*)-β-Tyrosine is the β-amino acid component of the cyclodepsipeptide, jasplakinolide,[3] while its enantiomer has been identified as a component of the antibiotic edeine A.[4] β-Lysine residues have been identified as key components of a range of antibiotics such as streptothrycin F,[5] the racemomycins[6] and viomycin,[7] while β-arginine is a component of blasticidin S.[8] While the pharmacological activity of these compounds has often been the focus of these studies, the importance of β-amino acid derivatives as tools to probe the secondary and tertiary structures of proteins and β-peptides has been receiving increasing recognition.[9] The favourable biological and conformational activities of β-amino acids and peptides has stimulated the development of methodology for their asymmetric synthesis.[10] While Arndt–Eistert homologation of α-amino acids[11] and enzymatic resolution[12] are popular routes to specific β-amino target molecules, the development of general and reliable methodology for their asymmetric synthesis is of widespread synthetic interest. Many asymmetric routes to β-amino acids have been developed, including the stereoselective addition of homochiral enolates to imines,[13] the conjugate addition of amines to homochiral α,β-unsaturated esters,[14] the diastereo- and enantioselective addition of *N*-benzylhydroxylamines to imides,[15] the catalytic reduction of β-amino crotonates[16] or (*E*)-β-(acylamino)acrylic acids[17] and the dipolar cycloaddition of homochiral nitrones[18] among others.[19] Chiral auxiliary approaches involving the use of sulfinimines,[20] hydropyrimidines[21] and pyrimidinones[22] have also been developed specifically for the synthesis of β-amino acids.

Despite these advances, the simplest and most elegant approach to the preparation of β-amino acids undoubtedly involves the conjugate addition of a homochiral ammonia source to an α,β-unsaturated ester.[23] Although the use of lithium amides as strong bases has been extensively studied and is universally recognised, their ability to act as nucleophiles in Michael additions has received relatively little attention. Within this field, Schlessinger et al. first observed that LDA adds in a conjugate manner to ethyl crotonate in

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doi:10.1016/j.tetasy.2006.05.008

near quantitative yield over 30 years ago.[24] Yamamoto et al. demonstrated the potential utility of this transformation by showing that lithium benzyltrimethylsilyl amide (LSA) **1** adds in a conjugate fashion to methyl crotonate[25] and extended this methodology to the conjugate addition of amido cuprates to homochiral α,β-unsaturated acceptors.[26] Hawkins et al. reported the first diastereoselective conjugate addition of a homochiral lithium amide, showing that lithium amide **2** undergoes highly diastereoselective conjugate addition to a range of α,β-unsaturated acceptors.[27] However, deprotection of the *N*-naphthyl protecting groups of the resultant β-amino esters requires forcing conditions, using 500% (w/w) of palladium hydroxide catalyst for removal by hydrogenolysis.[28] We subsequently communicated that chiral lithium amides such as **3** derived from readily available α-methylbenzylamine undergo highly diastereoselective conjugate additions to α,β-unsaturated esters, with deprotection of the resultant β-amino esters readily achieved by hydrogenolysis under mild conditions.[29] A variety of uses of this methodology have since been reported.[30] Both Bovy[31] and Sewald[32] subsequently showed that lithium *N*-trimethylsilyl-*N*-α-methylbenzylamide **4** can undergo stereoselective conjugate addition reactions, while Enders et al. have introduced lithiated TMS-SAMP **5** as a chiral ammonia equivalent.[33] Recent advances within this area include the catalytic use of homochiral diethers to confer stereocontrol in the conjugate addition of lithium amide **1** to α,β-unsaturated esters (Fig. 1).[34]

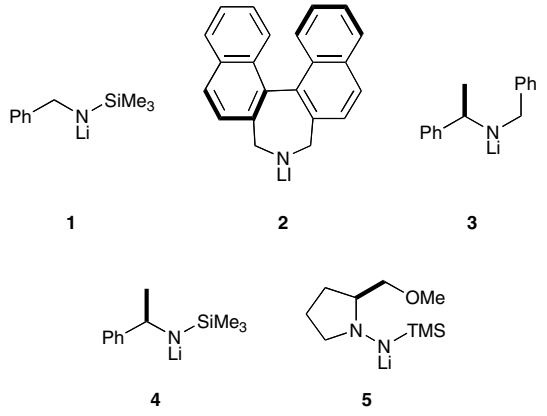


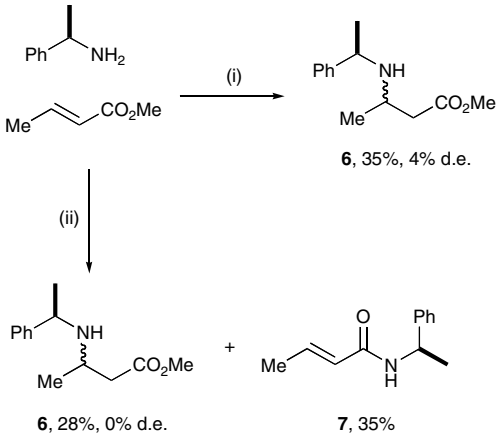
Figure 1. Lithium amides for conjugate addition.

Herein, we wish to delineate the full details of the generality of our lithium amide methodology and its application to the synthesis of a variety of simple β-amino acids and selected natural product targets. Moreover, we also demonstrate a simplified one-pot reaction protocol that is applicable to the multi-gram scale synthesis of homochiral β-amino esters.

2. Results and discussion

2.1. Conjugate addition of chiral lithium amides

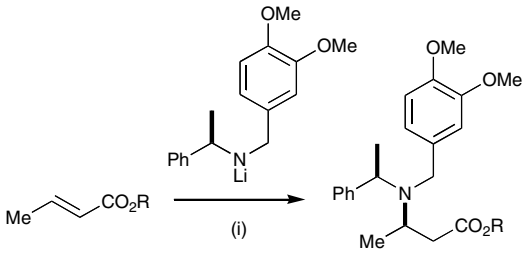
The thermal 1,4 conjugate addition of (*R*)-α-methylbenzylamine to methyl crotonate was first examined to assay the level of diastereoselectivity upon conjugate addition of a primary amine to an α,β-unsaturated acceptor. Treatment of (*R*)-α-methylbenzylamine with methyl crotonate in refluxing ethanol gave the secondary β-amino ester **6** in a moderate 35% yield and with 4% de, in slight favour of the (3*S*,α*R*)-diastereoisomer, consistent with the results previously reported by Furukawa et al.[14] Similarly, conjugate addition of lithium (*R*)-α-methylbenzylamide to methyl crotonate at −78 °C in THF gave secondary β-amino ester **6** in 28% yield as a 1:1 mixture of (3*S*,α*R*)- and (3*R*,α*R*)-diastereoisomers, along with *N*-α-methylbenzyl crotonamide **7**, the product of 1,2-addition, in 35% yield (Scheme 1).



Scheme 1. Reagents and conditions: (i) EtOH, Δ; (ii) *n*-BuLi (0.95 equiv), THF, −78 °C then methyl crotonate (0.65 equiv), THF, −78 °C.

The conjugate addition reactions of chiral secondary lithium amides were subsequently investigated as previous chiral recognition studies from this laboratory imply that lithium (*RS*)-*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamide exerts a powerful stereodirecting influence upon the β-centre of an α,β-unsaturated acceptor upon conjugate addition.[35] Lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamide was therefore added to methyl, benzyl and *tert*-butyl crotonate at −78 °C, resulting in exclusive 1,4-addition and furnishing the β-amino esters (3*R*,α*R*)-**8**–**10** in good yield and with high levels of diastereoselectivity (>95% de). However, addition of lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamide to benzyl or *tert*-butyl crotonate at 15 °C resulted in a substantial decrease in the observed levels of diastereoselectivity (70% and 66% de, respectively), indicating that low temperature is essential for high diastereoselectivity in this reaction (Scheme 2).

A notable reduction in stereoselectivity and reactivity for this conjugate addition process was observed upon reaction of either lithium (*R*)-*N*-(2-methoxybenzyl)-*N*-α-methylbenzylamide or lithium (*R*)-*N*-(2,4-dimethoxybenzyl)-*N*-α-methylbenzylamide with *tert*-butyl cinnamate. Under standard reaction conditions at −78 °C, these additions proceeded to only 36% and 42% conversion, respectively, furnishing a 50:50 mixture of β-amino ester diastereoisomers **11** and **12** in each case. Presumably, the reduced



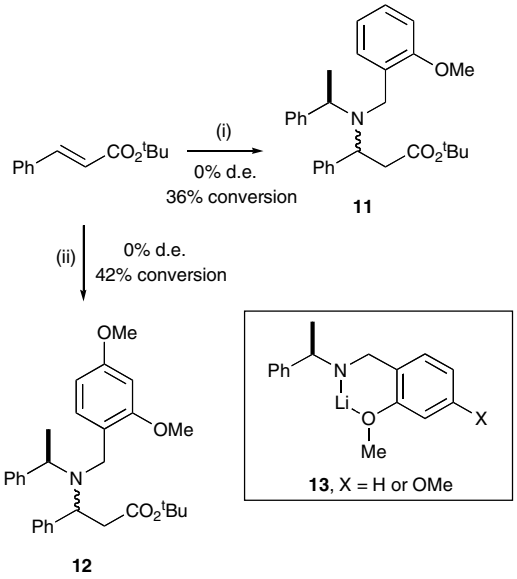
(3*R*,α*R*)-**8-10**

R	T (°C)	β-amino ester	Yield(%)	d.e.*
Me	-78	**8**	68	>95
Bn	-78	**9**	74	>95
^{t}Bu	-78	**10**	75	>95
Bn	15	**9**	56	70
^{t}Bu	15	**10**	94	66

* As shown by ^{1}H NMR spectroscopic analysis of the crude reaction mixture

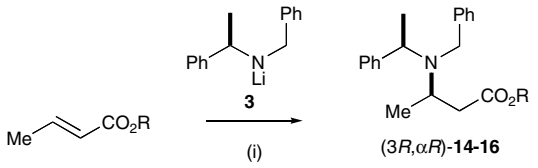
Scheme 2. Reagents and conditions: (i) lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamide, THF, −78 °C or 15 °C.

reactivity and low stereoselectivity observed in these reactions arises from the formation of a chelated lithium amide species such as **13**, resulting in disruption of the normal chelation controlled lithium amide transition state and a corresponding decrease in stereoselectivity (Scheme 3).

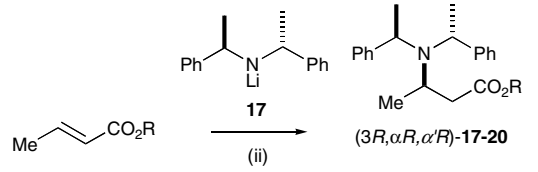


Scheme 3. Reagents and conditions: (i) lithium *N*-(2-methoxybenzyl)-*N*-α-methylbenzylamide, THF, −78 °C; (ii) lithium *N*-(2,4-dimethoxybenzyl)-*N*-α-methylbenzylamide, THF, −78 °C.

As methoxy-substituted *N*-benzyl groups are highly susceptible to oxidative cleavage[36] while being relatively inert towards hydrogenolysis compared to an *N*-benzyl group,[37,38] this conjugate addition methodology was extended to the use of homochiral lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **3** and C_2 symmetric lithium (*R*,*R*)-*N*,*N*-bis(α-methylbenzyl)amide **17**. Tertiary β-amino esters derived from conjugate addition of these lithium amides were predicted to prove amenable to global N-deprotection by hydrogenolysis and realise an efficient synthetic route to β-amino acids. Addition of methyl, benzyl and *tert*-butyl crotonate to lithium amide (*R*)-**3** at −78 °C gave β-amino esters (3*R*,α*R*)-**14–16** in good isolated yield (>80%) and in consistently high de. Addition of methyl, benzyl and *tert*-butyl crotonate to lithium amide (*R*,*R*)-**17** at −78 °C was also evaluated, giving β-amino esters (3*R*,α*R*,α′*R*)-**18–20**, respectively. Although high levels of stereoselectivity (>97% de) using lithium amide (*R*,*R*)-**17** were observed, both the rate of reaction and yield of the isolated β-amino ester products were noticeably attenuated in comparison to the corresponding products derived from lithium amide (*R*)-**3** (Scheme 4).



R	β-amino ester	Yield (%)	d.e. (%)
Me	**14**	85	95
Bn	**15**	88	95
^{t}Bu	**16**	82	>98



R	β-amino ester	Yield (%)	d.e. (%)
Me	**18**	57	>99
Bn	**19**	23	>97
Bu	**20**	60	>98

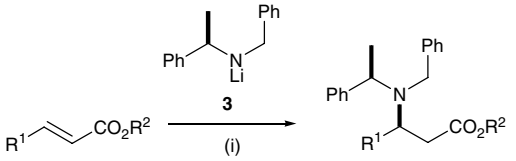
Scheme 4. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **3** or lithium (*R*,*R*)-*N*,*N*-bis(α-methylbenzyl)amide **17**, THF, −78 °C.

As a result of the lower isolated yields of the β-amino esters derived from reaction with lithium amide (*R*,*R*)-**17**, the synthetic generality of this protocol was evaluated using lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **3**.

2.2. Addition of lithium *N*-benzyl-*N*-α-methylbenzylamide to a range of β-substituted α,β-unsaturated esters

To investigate the scope of this methodology, a range of β-aryl and β-alkyl substituted α,β-unsaturated acceptors were added to homochiral lithium amide (*R*)-**3**. In each case, the reaction proceeded to give the desired β-amino ester **21–35** in high de (91%–>95%). In each case, the configuration of the major diastereoisomer was assigned by analogy with the model previously developed to explain the stereoselectivity observed during addition of lithium *N*-benzyl-*N*-α-methylbenzylamide to α,β-unsaturated acceptors (Scheme 5).[39]

Within this series, it is noticeable that the yield of the isolated β-amino ester is considerably enhanced with the use of *tert*-butyl esters when compared to other ester protecting groups. With sterically unencumbered ester protecting

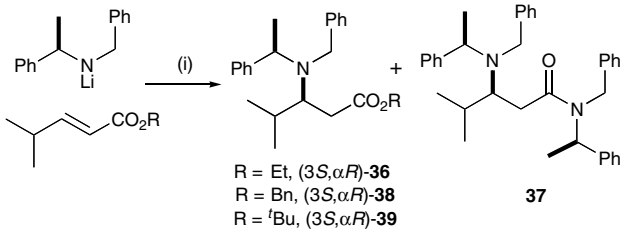


R^1	R^2	β-amino ester	Yield (%)	d.e. (%)
Et	Bn	**21**	67	95
Et	^{t}Bu	**22**	92	>95
n-pent	Bn	**23**	75	>95
n-pent	^{t}Bu	**24**	81	>95
Ph	Me	**25**	68	94
Ph	Bn	**26**	39	91
Ph	^{t}Bu	**27**	96	>95
2-MeOC$_6$H$_4$	Bn	**28**	31	92
2-MeOC$_6$H$_4$	^{t}Bu	**29**	95	>95
4-MeOC$_6$H$_4$	Bn	**30**	72	90
4-MeOC$_6$H$_4$	^{t}Bu	**31**	96	>95
4-BnOC$_6$H$_4$	Me	**32**	63	>95
4-BnOC$_6$H$_4$	Bn	**33**	64	91
3,4-(OCH$_2$O)C$_6$H$_3$[#]	^{t}Bu	**34**	73	>95
3,4-(MeO)$_2$C$_6$H$_3$[#]	^{t}Bu	**35**	79	>95

[#] Performed in the enantiomeric series

Scheme 5. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **3**, THF, −78 °C.

groups (Bn, Et, Me), conjugate addition and 1,2 addition to the ester carbonyl can compete, resulting in a mixture of products. For example, addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **3** to ethyl or benzyl (*E*)-4-methyl-pent-2-enoate gave 56% and 38% of the required β-amino esters **36** (95% de) and **38** (95% de), respectively, together with 25% and 29%, respectively, of amide **37**, resulting from sequential 1,2- and then 1,4-lithium amide addition. Addition to *tert*-butyl (*E*)-4-methyl-pent-2-enoate resulted in exclusive formation of *tert*-butyl β-amino ester **39**, which was isolated in 91% yield and 95% de (Scheme 6).

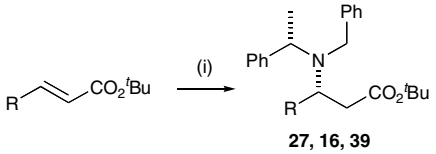


R	β-amino ester	Yield (%)	β-amino amide	Yield(%)
Et	**36**	56	**37**	25
Bn	**38**	38	**37**	29
^{t}Bu	**39**	91	--	0

Scheme 6. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **3**, THF, −78 °C.

2.3. The development of a one-pot lithium amide conjugate addition protocol

The standard experimental protocol for this highly diastereoselective conjugate addition reaction involves pre-forming the lithium amide by deprotonation of the corresponding amine in THF with *n*-BuLi at −78 °C, followed by addition of a solution of the α,β-unsaturated ester in THF at −78 °C. This protocol ensures that alternative reaction manifolds such as conjugate addition, 1,2-addition or γ-deprotonation of the α,β-unsaturated ester by *n*-BuLi does not compete with lithium amide addition. In order to simplify this reaction procedure, the viability of a one-pot reaction protocol was investigated to enable competition between deprotonation of the amine by *n*-BuLi followed by lithium amide conjugate addition with any of the many alternative reactions to be evaluated.[40] Using the conjugate addition to *tert*-butyl cinnamate as a model, a solution of *n*-BuLi (1.55 equiv) in hexanes at −78 °C was added to a solution of (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (1.6 equiv) and *tert*-butyl cinnamate (1.0 equiv) in THF at −78 °C, giving, after addition of saturated aqueous NH_4Cl and standard workup, the desired β-amino ester (3*R*,α*S*)-**27** in >98% de and in 82% isolated yield. This reaction protocol is readily reproduceable on a multi-gram scale and has been used for the preparation of over 15 g of β-amino ester **27**. This one-pot reaction protocol was next tested with *tert*-butyl crotonate and methyl (*E*)-4-methyl-pent-2-enoate as representative α,β-unsaturated esters containing γ-acidic protons, giving exclusively the corresponding β-amino esters (3*S*,α*S*)-**16** and (3*R*,α*S*)-**39** in >98% de and in 93% and 89% yield, respectively (Scheme 7). Further optimisation of this reaction protocol indicated that similar levels of reaction efficiency could be achieved using *n*-BuLi (1.05 equiv), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (1.1 equiv) and the α,β-unsaturated ester (1.0 equiv). In each case, the conjugate addition reaction proceeded to complete conversion, giving the corresponding β-amino esters in >98% de.



	R	d.e. (%)	Yield (%)
27	Ph	>98	82
16	Me	>98	93
39	CH(Me)$_2$	>98	89

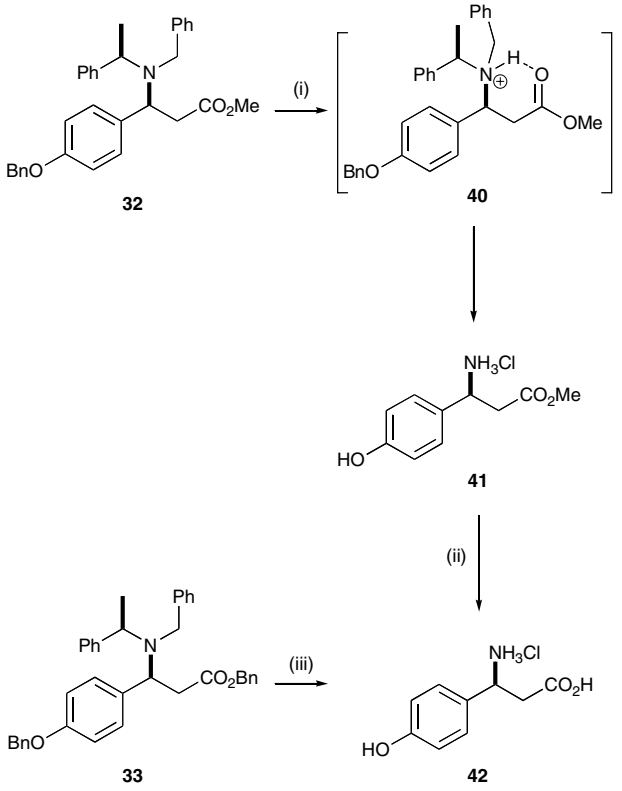
Scheme 7. Reagents and conditions: (i) *n*-BuLi (1.55 equiv), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (1.6 equiv), α,β-unsaturated ester (1.0 equiv), THF, −78 °C.

Having demonstrated the generality of this conjugate addition approach and the viability of a one-pot reaction protocol, deprotection of the *N*-benzyl and ester protecting groups to the parent β-amino acids was investigated.

2.4. Deprotection of β-amino esters

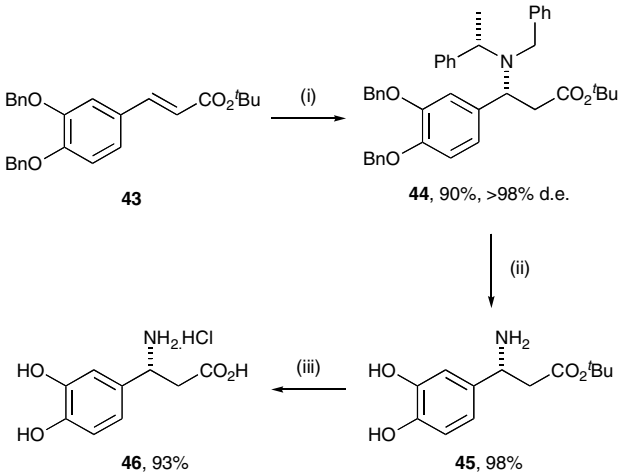
Initial investigations for deprotection of the *N*-benzyl and *N*-α-methylbenzyl protecting groups of tertiary β-amino esters concentrated upon the susceptibility of *N*-benzylic bonds to hydrogenolysis. Treatment of β-amino ester (3*S*,α*R*)-**32** (>95% de) with $Pd(OH)_2$ on C in MeOH/

H_2O/AcOH under 1 atm of H_2 furnished, after treatment with aqueous HCl, (*S*)-β-tyrosine methyl ester hydrochloride **41** in quantitative yield. In this debenzylation reaction, there are four possible benzylic bonds that could be cleaved; however, only the *N*-benzyl, *N*-α-methylbenzyl and the *O*-benzyl ether are susceptible to hydrogenolysis. This remarkable chemoselective debenzylation is proposed to arise from the intermediacy of a hydrogen bonded intermediate **40** that holds the C(3)-β-aryl group in a conformation that disfavours hydrogenolysis and cleavage of the benzylic C(3)–*N* bond. The enantiomeric purity (>95% ee) of (*S*)-**41** was confirmed by ^{1}H NMR spectroscopic analysis in the presence of (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol and comparison with an authentic racemic sample, with acidic hydrolysis yielding (*S*)-β-tyrosine hydrochloride **42**. Similarly, treatment of benzyl (3*S*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-(4-benzyloxyphenyl)propanoate **33** (91% de) with $Pd(OH)_2$ on C in EtOH under 5 atm H_2 gave (*S*)-β-tyrosine hydrochloride **42** after treatment of the crude reaction mixture with aqueous HCl (Scheme 8).



Scheme 8. Reagents and conditions: (i) $Pd(OH)_2$/C, H_2 (1 atm), MeOH/H_2O/AcOH then HCl (aq); (ii) HCl (aq), Δ; (iii) $Pd(OH)_2$/C, H_2 (5 atm), EtOH then HCl (aq).

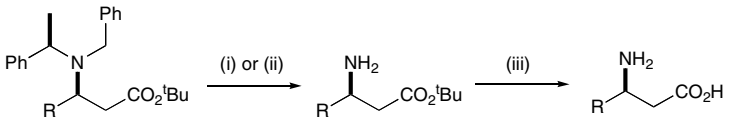
This methodology was next applied to the synthesis of the hydrochloride salt of (*R*)-3,4-dihydroxy-β-phenylalanine {(*R*)-β-DOPA} **46**, a naturally occurring β-amino acid recently isolated from *Cortinarius violaceus*.[41] Conjugate addition of lithium amide (*S*)-**3** to *tert*-butyl (*E*)-3-(3,4-dibenzyloxyphenyl)prop-2-enoate **43** (prepared in 81% yield and >98% de by Horner Wadsworth Emmons reaction of the corresponding aldehyde and the lithium anion of *tert*-butyl diethylphosphonoacetate) gave β-amino ester **44** in >98% de and in 90% isolated yield. *N*-Benzyl deprotection was readily achieved by hydrogenolysis, giving β-amino ester **45** in 98% yield, with subsequent treatment of **45** with HCl (g) for 5 min in cold Et_2O affording (*R*)-β-DOPA·HCl **46** in 93% yield (Scheme 9).



Scheme 9. Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **3**, THF, −78 °C; (ii) $Pd(OH)_2$/C, H_2 (1 atm), MeOH/H_2O/AcOH; (iii) HCl (g), Et_2O.

Having shown that tertiary *N*-benzyl-*N*-α-methylbenzyl-protected β-amino esters are susceptible to hydrogenolysis, *tert*-butyl β-amino esters **22**, **24**, **27**, **29**, **31** and **39** were treated with Pd/C under 6 atm of H_2, either in AcOH or MeOH, furnishing the corresponding primary β-amino esters **47**–**52** in uniformly good yields. Deprotection of the resulting β-amino *tert*-butyl esters by consecutive treatment with TFA and 2 N HCl, followed by purification via ion-exchange chromatography, gave the corresponding β-amino acids **53**–**58** in excellent yields. Comparison of the sign and magnitude of the specific rotations of the known β-amino acids prepared using this protocol with the literature values allowed unambiguous assignment of their absolute configurations. The ees of (*S*)-β-phenylalanine **55** (>95% ee), (*S*)-β-tyrosine methyl ether **56** (97% ee) and (*S*)-β-(2-methoxyphenyl)-β-phenylpropionic acid **57** (>95% ee) were determined by derivatisation to the corresponding methyl esters and ^{1}H NMR chiral shift experiments with *O*-acetylmandelic acid and comparison with authentic racemic samples. As the ees of β-amino acids **55**–**57** are equivalent to the des of the corresponding β-amino esters **27**, **29** and **31**, this indicates that racemisation does not occur during the deprotection procedure. Although the ee of β-amino acids **53**, **54** and **58** were not determined, similar high levels of enantiomeric excess are assured (Scheme 10).

As an alternative deprotection procedure, direct global deprotection of the benzyl β-amino esters **15**, **21**, **23**, **28**, **30** and **38** facilitated direct conversion to the corresponding β-amino acid hydrochloride salts by hydrogenolysis followed by treatment with aqueous HCl. Purification via ion-exchange chromatography gave the corresponding β-amino acids **53**–**54** and **56**–**59** with comparable spectroscopic



22, 24, 27, 29, 31, 39 **47-52** **53-58**

	R	(i) or (ii)	β-amino ester	Yield (%)	β-amino acid	Yield (%)
22	Et	(i)	**47**	95%	**53**	89%
24	*n*-pent	(i)	**48**	83%	**54**	95%
27	Ph	(ii)	**49**	84%	**55**	96%
29	2-$MeOC_6H_4$	(ii)	**50**	91%	**56**	85%
31	4-$MeOC_6H_4$	(ii)	**51**	91%	**57**	96%
39	^{i}Pr	(ii)	**52**	88%	**58**	97%

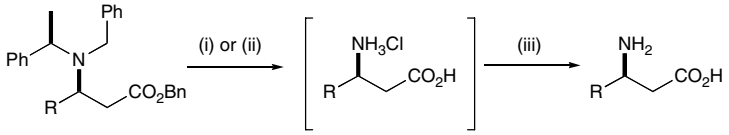
Scheme 10. Reagents and conditions: (i) Pd/C, H_2 (5 atm), MeOH; (ii) Pd/C, H_2 (5 atm), AcOH; (iii) TFA, DCM (1:1) then 2 N HCl, then Dowex 50WX-200.

properties and specific rotations to the literature. The ee of (*R*)-β-amino butyric acid **59** (97% ee) was determined by derivatisation to the methyl ester and ^{1}H NMR chiral shift experiments with *O*-acetylmandelic acid and comparison with an authentic racemic sample (Scheme 11).

2.5. Application: asymmetric synthesis of (*R*)-β-lysine

Having demonstrated the generality of this lithium amide methodology for the synthesis of a range of simple β-substituted-β-amino acids, the application of this strategy to the synthesis of (*R*)-β-lysine **65** was investigated. β-Lysine is one of the most important naturally occurring β-amino acids, the (*S*)-enantiomer being produced in the anaerobic catabolism of (*S*)-α-lysine in *Clostridia*[42] by the lysine 2,3-aminomutase enzyme,[43] which has been used for the in vitro preparation of multi-gram quantities of this enantiomer.[44] Furthermore, (*S*)-β-lysine is a building block in a number of natural products, including the streptothricin (or racemomycin) family of antibiotics,[45] lysinomicin,[46] tuberactinomycins B and O,[47] capreomycins 1A and 1B,[48] and 3-*epi*-deoxynegamycin.[49] Although less common, (*R*)-β-lysine is a constituent of the *anti*-HIV agent bellenamine,[50] with the (*S*)-enantiomer showing little bioactivity. Previous synthetic strategies towards the preparation of β-lysine include the use of Arndt–Eistert homologation from ornithine[51] and a nitrone cycloaddition.[52] Our strategy centred around the incorporation of the C-6 amino group into the α,β-unsaturated ester prior to conjugate addition. In this manner, reduction of commercially available *N*-Boc pyrolidinone **60** with DIBAL-H,[53] subsequent Wittig olefination[54] and further *N*-Boc protection gave (*E*)-**61** in 56% overall yield over three steps. Addition of **61** to lithium amide (*R*)-**3** gave a 77:23 mixture of β-amino ester **63** in >95% de[55] and by-product **62**, which could be separated by exhaustive chromatography, although in practice this crude material was immediately deprotected by transfer hydrogenolysis, affording β-amino ester **64** in 51% yield over two steps and in 96% ee.[56] Subsequent treatment of β-amino ester **64** with TFA in dichloromethane, followed by purification by ion-exchange chromatography, afforded (*R*)-β-lysine **65** in quantitative yield $[\alpha]_D^{21} = -19.3$ (*c* 0.63, 1 M HCl), lit.[50] $[\alpha]_D = -19.5$ (*c* 1.0, 1 M HCl) (Scheme 12). The asymmetric synthesis of (*R*)-β-lysine **65** has therefore been achieved in six steps, 29% overall yield and in 96% ee.

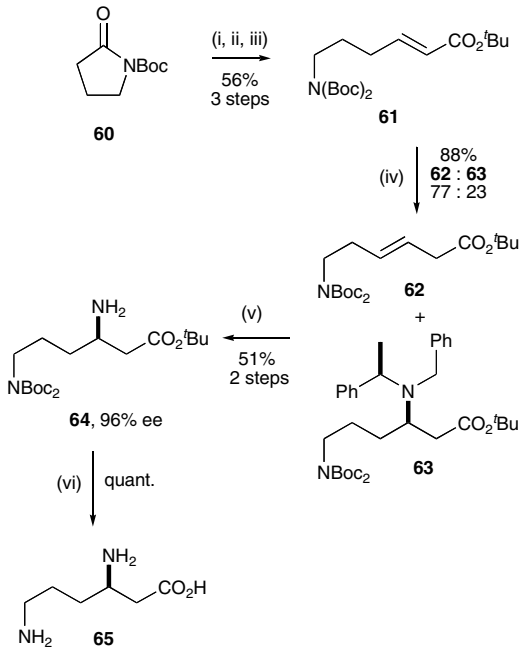
In conclusion, homochiral lithium amides derived from α-methylbenzylamine undergo diastereoselective conjugate addition to a range of β-alkyl and β-aryl α,β-unsaturated esters with high and predictable levels of stereoinduction. The resulting tertiary β-amino esters are readily deprotected by N-debenzylation via hydrogenolysis and subsequent ester hydrolysis to afford the corresponding β-amino acids in high yields and in high ee. Furthermore, the development of a new, simplified one-pot reaction protocol applicable to the multi-gram scale synthesis of homochiral β-amino esters has been achieved. The further application



15, 21, 23, 28, 30, 38 **53-54, 56-59**

β-amino ester	R	Conditions	β-amino acid	Yield (%)
15	Me	(i)	**59**	68%
21	Et	(ii)	**53**	90%
23	*n*-pent	(ii)	**54**	88%
28	2-$MeOC_6H_4$	(ii)	**56**	87%
30	4-$MeOC_6H_4$	(ii)	**57**	58%
38	^{i}Pr	(ii)	**58**	86%

Scheme 11. Reagents and conditions: (i) $Pd(OH)_2/C$, H_2 (5 atm), EtOH; (ii) Pd/C, H_2 (5 atm), AcOH then 2 N HCl; (iii) Dowex 50WX-200.



Scheme 12. Reagents and conditions: (i) DIBAL-H, THF −78 °C; (ii) $Ph_3P{=}CHCO_2{}^tBu$, toluene, 110 °C; (iii) Boc_2O, DMAP, MeCN; (iv) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **3**, THF, −78 °C; (v) NH_4HCO_2, Pd/C, MeOH, 65 °C; (vi) TFA, DCM, then Dowex 50WX-200.

of this methodology for complex natural product synthesis is currently ongoing within our laboratory.

3. Experimental

3.1. General experimental

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. THF was distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl. Water was distilled. *n*-Butyllithium was used as a solution in hexanes at the molarity stated. All other solvents and reagents were used as supplied (Analytical or HPLC grade), without prior purification. The reactions were dried with $MgSO_4$. Thin layer chromatography (TLC) was performed on aluminium sheets coated with 60 F_{254} silica. The sheets were visualised using iodine, UV light or 1% aqueous $KMnO_4$ solution. Flash chromatography was performed on Kieselgel 60 silica. Nuclear magnetic resonance (NMR) spectra were recorded on Bruker DPX 400 (^1H: 400 MHz and ^{13}C: 100.6 MHz), AMX 500 (^1H: 500 MHz and ^{13}C: 125.3 MHz), Bruker W-H 300 (^1H: 300 MHz) or Varian 200 (^1H: 200 MHz) spectrometers in the deuterated solvent stated. All chemical shifts (δ) are quoted in parts per million and coupling constants (J) in Hertz. 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. In all cases, the reaction's diastereoselectivity was assessed by peak integration of the ^1H NMR spectrum of the crude reaction mixture. 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. Low resolution mass spectra (m/z) were recorded on B.G. micromass ZAB 2F instrument, 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. The 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. Specific optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a water-jacketed 10 cm cell and are given in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are quoted in g/100 mL. Melting points were recorded on a Leica VMTG Galen III apparatus and are uncorrected. Elemental analyses were performed by the microanalysis services of the Dyson Perrins Laboratory or the Inorganic Chemistry Laboratory, Oxford.

3.2. Representative procedure 1

n-Butyllithium (1.6 M, 1.55 equiv) was added dropwise to a stirred solution of the amine (1.6 equiv) in anhydrous THF at −78 °C under nitrogen. After 30 min, a solution of the α,β-unsaturated ester (1.0 equiv) in anhydrous THF was added dropwise via a cannula and stirred at −78 °C for the specified time prior to the addition of saturated aqueous ammonium chloride and warmed to rt. The resultant solution was partitioned between brine and 1:1 DCM/Et_2O, and the combined organic extracts were dried, filtered and concentrated in vacuo before purification by column chromatography.

3.3. Representative procedure 2

Pd/C was added to a stirred solution of conjugate addition product in AcOH or MeOH and stirred under hydrogen (6 atm) at rt in a Fischer–Porter bottle. After filtration through Celite®, the residue was concentrated in vacuo, dissolved in DCM (200 mL), washed with 10% aqueous $NaHCO_3$, dried and concentrated in vacuo before purification.

3.4. Representative procedure 3

TFA (2 mL) was added to a stirred solution of the *tert*-butyl β-amino stirred for 2 h at rt. After concentration in vacuo, treatment with 1 M HCl (5 mL) and concentration in vacuo gave the β-amino acid hydrochloride, which was purified by ion-exchange chromatography on Dowex 50WX200 to give the free amino acid.

3.5. Representative procedure 4

Pd/C was added to a stirred solution of the conjugate addition product in AcOH or EtOH and stirred under

hydrogen (6 atm) at rt in a Fischer–Porter bottle. After filtration through Celite®, the residue was concentrated in vacuo, dissolved in 2 M HCl, washed (Et_2O) and concentrated in vacuo before purification via ion-exchange chromatography on Dowex 50WX200 to give the free amino acid.

3.6. Preparation of methyl (3*R*,α*R*)- and methyl (3*S*,α*R*)-3-(*N*-α-methylbenzylamino)butanoate 6

A solution of (*R*)-α-methylbenzylamine (2.42 g, 20 mmol) and methyl crotonate (2.0 g, 20 mmol) in EtOH (100 mL) was heated at reflux for 18 h before concentration in vacuo. Purification via column chromatography on silica gel (Et_2O) gave **6** (1.56 g, 35%) as a 48:52 mixture of diastereoisomers: δ_H (200 MHz, $CDCl_3$) 1.06 and 1.08 (2 × 3H, d, *J* 6.4, C(4)H_3), 1.34 (2 × 3H, d, *J* 5.9, C(α)*Me*), 2.25–2.53 (2 × 2H, m, C(2)H_2), 2.90 and 3.00 (2 × 1H, m, C(3)*H*), 3.65, 3.68 (2 × 3H, s, CO_2Me), 3.88 and 3.93 (2 × 1H, q, *J* 5.9, C(α)*H*), 7.20–7.28 (2 × 5H, m, *Ph*).[26]

3.7. Preparation of methyl (3*R*,α*R*)- and methyl (3*S*,α*R*)-3-(*N*-α-methylbenzylamino)butanoate 6 and (*R*)-*N*-(α-methylbenzyl)crotonamide 7

Following representative procedure 1, *n*-BuLi (1.6 M, 19.4 mL, 31 mmol), (*R*)-α-methylbenzylamine (3.78 g, 32 mmol) in THF (100 mL) and methyl crotonate (2.0 g, 20 mmol) in THF (30 mL) gave, after 30 min, and subsequent recrystallisation (hexane/Et_2O 3:1), **7** (1.32 g, 35%) as white needles: $[\alpha]_D^{25} = +155.0$ (*c* 1.7, $CHCl_3$), lit.[57] (*ent*) $[\alpha]_D = -121.4$ (*c* 1.8, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 1.52 (3H, d, *J* 7.0, C(α)*Me*), 1.84 (3H, dd, $J_{4,3}$ 6.9, $J_{4,2}$ 1.6, C(4)H_3), 5.21 (1H, app quin, *J* 7.3, C(α)*H*), 5.66 (1H, br s, N*H*), 5.80 (1H, dd, $J_{2,3}$ 15.1, $J_{2,4}$ 1.6, C(2)*H*), 6.87 (1H, dq, $J_{3,2}$ 15.1, $J_{3,4}$ 6.9, C(3)*H*), 7.21–7.39 (5H, m, *Ph*). The mother liquor was concentrated and purified by chromatography on silica gel (Et_2O) to give an inseparable 1:1 mixture of (3*R*,α*R*)- and (3*S*,α*R*)-**6** as a colourless oil (1.23 g, 28%) with identical spectroscopic properties to those previously reported.

3.8. Preparation of methyl (3*R*,α*R*)-3-(*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamino)butanoate 8

Following representative procedure 1, *n*-BuLi (1.6 M, 10.7 mL, 17.0 mmol), (*R*)-*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamine (4.7 g, 17.6 mmol) in THF (20 mL) and methyl crotonate (1.1 g, 11.0 mmol) in THF (20 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 2:1), **8** (2.8 g, 68%) as a colourless oil: $C_{22}H_{29}NO_4$ requires C, 71.1; H, 7.9; N, 3.8%, found C, 71.4; H, 8.15; N, 3.7%; $[\alpha]_D^{20} = -5.2$ (*c* 1.1, CH_2Cl_2); δ_H (500 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.6, C(4)H_3), 1.38 (3H, d, *J* 6.8, C(α)*Me*), 2.14 (1H, dd, $J_{2A,2B}$ 14.4, $J_{2A,3}$ 7.2, C(2)H_AH_B), 2.40 (1H, dd, $J_{2B,2A}$ 14.4, $J_{2B,3}$ 7.2, C(2)H_AH_B), 3.42–3.52 (1H, m, C(3)*H*), 3.44 (3H, s, CO_2Me), 3.49 (2H, ABq, NCH_2), 3.88 and 3.91 (2 × 3H, s, O*Me*), 3.83–3.96 (1H, m, C(α)*H*), 6.78–7.03 (3H, m, *Ph*), 7.20–7.31 (5H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 16.4, 18.2, 40.3, 49.0, 49.6, 51.3, 56.9, 110.6, 111.7, 120.4, 126.7, 128.0, 134.2, 144.5, 147.9, 149.1, 172.9; *m*/*z* (CI^+) 372 (MH^+, 35%); ν_{max}/cm^{-1} (film) 2970, 2830 (C–H), 1735 (C=O).

3.9. Preparation of benzyl (3*R*,α*R*)-3-(*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamino)butanoate 9

Following representative procedure 1, *n*-BuLi (1.6 M, 1.1 mL, 1.8 mmol), (*R*)-*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamine (487 mg, 1.8 mmol) in THF (10 mL) and benzyl crotonate (200 mg, 1.1 mmol) in THF (5 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 2:1), **9** (378 mg, 74%) as a colourless oil: $C_{28}H_{33}NO_4$ requires C, 75.1; H, 7.4; N, 3.1%, found: C, 75.4; H, 7.7; N, 3.0%; $[\alpha]_D^{20} = +13.3$ (*c* 1.3, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.7, C(4)H_3), 1.37 (3H, d, *J* 6.9, C(α)*Me*), 2.19 (1H, dd, $J_{2A,2B}$ 14.2, $J_{2A,3}$ 7.7, C(2)H_AH_B), 2.42 (1H, dd, $J_{2B,2A}$ 14.2, $J_{2B,3}$ 6.3, C(2)H_AH_B), 3.52 (1H, m, C(3)*H*), 3.66 (2H, app s, NCH_2), 3.87 and 3.89 (2 × 3H, s, O*Me*), 3.89 (1H, q, *J* 6.9, C(α)*H*), 4.83 (1H, ABq, *J* 12.4, OCH_AH_B), 5.02 (1H, ABq, *J* 12.4, OCH_AH_B), 6.76–7.01 (3H, m, *Ph*), 7.19–7.37 (5H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 17.1, 18.4, 40.1, 49.1, 49.9, 57.3, 65.9, 110.7, 111.6, 120.3, 126.8, 127.9, 128.1, 128.2, 128.4, 128.6, 134.3, 144.5, 147.9, 149.1, 172.3; *m*/*z* (CI^+) 448 (MH^+, 60%); ν_{max}/cm^{-1} (film) 2985, 2830 (C–H), 1725 (C=O).

3.10. Preparation of *tert*-butyl (3*R*,α*R*)-3-(*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamino)butanoate 10

Following representative procedure 1, *n*-BuLi (1.4 M, 1.5 mL, 2.15 mmol), (*R*)-*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamine (602 mg, 2.23 mmol) in THF (10 mL) and *tert*-butyl crotonate (200 mg, 1.39 mmol) in THF (5 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 1:1), **10** (478 mg, 83%) as a colourless oil: $C_{25}H_{35}NO_4$ requires C, 72.6; H, 8.5; N, 3.9%, found C, 72.8; H, 8.8; N, 3.7%; $[\alpha]_D^{20} = +2.3$ (*c* 1.7, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 1.13 (3H, d, *J* 6.8, C(α)*Me*), 1.37 (3H, d, *J* 7.1, C(4)H_3), 1.39 (9H, s, O^t*Bu*), 2.04 (1H, dd, $J_{2A,2B}$ 14.1, $J_{2A,3}$ 9.1, C(2)H_AH_B), 2.42 (1H, dd, $J_{2B,2A}$ 14.1, $J_{2B,3}$ 4.7, C(2)H_AH_B), 3.42–3.51 (1H, m, C(3)*H*), 3.57 (1H, ABq, *J* 14.8, NCH_AH_B), 3.70 (1H, ABq, *J* 14.8, NCH_AH_B), 3.89 and 3.90 (2 × 3H, s, O*Me*), 3.92 (1H, q, *J* 6.8, C(α)*H*), 6.79–6.96 (3H, m, *Ph*), 7.22–7.39 (5H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 18.2, 18.6, 27.9, 40.7, 49.3, 50.1, 55.7, 55.8, 58.1, 80.1, 110.8, 111.1, 120.3, 126.8, 127.8, 128.2, 134.8, 144.6, 147.9, 149.0, 172.2; *m*/*z* (CI^+) 414 (MH^+, 57%); ν_{max}/cm^{-1} (film) 2970, 2930 (C–H), 1725 (C=O).

3.11. Preparation of *tert*-butyl (α*R*,3*S*)- and *tert*-butyl (α*R*,3*R*)-3-[*N*-(2-methoxybenzyl)-*N*-(α-methylbenzyl)-amino]-3-phenyl-propionate 11

Following representative procedure 1, *n*-BuLi (0.31 mL, 0.76 mmol), (*R*)-*N*-2-methoxybenzyl-*N*-α-methylbenzylamine (189 mg, 0.79 mmol) in THF (10 mL) and *tert*-butyl cinnamate (100 mg, 0.49 mmol) in THF (5 mL) gave, after column chromatography on silica gel (pentane/Et_2O 100:1), an inseparable 50:50 mixture of *tert*-butyl (α*R*,3*S*)- and *tert*-butyl (α*R*,3*R*)-3-*N*-(2-methoxybenzyl)-*N*-α-methylbenzylamino-3-phenylpropanoate **11** (13 mg, 6%); δ_H (400 MHz, $CDCl_3$) 1.20 (9H, s, O^t*Bu*), 1.22 (9H, s, O^t*Bu*), 1.27 (3H, d, *J* 6.9, C(α)*Me*), 1.28 (3H, d, *J* 6.8,

C(α)*Me*), 2.49–2.60 (2H, m, C(2)H_2), 2.68 (1H, dd, *J* 14.6, *J* 10.5, C(2)H_AH_B), 2.87 (1H, dd, *J* 14.4, *J* 5.0, C(2)H_AH_B), 3.57 (1H, ABq, *J* 16.2, NCH_AH_B), 3.73 (2H, app s, NCH_2), 3.78 (3H, s, O*Me*), 3.80 (3H, s, O*Me*), 3.91 (1H, q, *J* 6.8, C(α)*H*), 3.95–3.99 (1H, obsc q, C(α)*H*), 4.02 (1H, ABq, *J* 16.1, NCH_AH_B), 4.32–4.37 (2H, m, 2 × C(3)*H*), 6.78 (1H, dd, *J* 8.3, *J* 1.0, *Ar*), 6.81 (1H, dd, *J* 8.4, *J* 1.0, *Ar*), 6.89 (1H, app td, *J* 7.6, *J* 1.1, *Ar*), 6.97 (1H, app td, *J* 7.7, *J* 1.0, *Ar*), 7.12–7.36 (19H, m, *Ph*, *Ar*), 7.43–7.48 (4H, m, *Ph*, *Ar*), 7.65 (1H, app dd, *J* 7.6, *J* 1.8, Ar); δ_C (100 MHz, $CDCl_3$) 15.9, 19.6, 22.8, 38.4, 39.4, 43.2, 43.7, 55.1, 57.6, 58.6, 60.1, 60.6, 80.0, 80.1, 109.7, 120.3, 126.6, 126.7, 126.9, 127.0, 127.1, 127.8, 127.9, 128.0, 128.4, 128.6, 129.5, 129.6, 129.9, 130.5, 144.4, 144.7, 156.6, 171.1, 171.3; *m*/*z* (ESI^+) 446 (100%, MH^+); HRMS $C_{29}H_{36}NO_3$ (MH^+) requires 446.2695, found 446.2696; ν_{max}/cm^{-1} (film) 160 (C═C), 1726 (C═O).

3.12. Preparation of *tert*-butyl (α*R*,3*S*)- and *tert*-butyl (α*R*,3*R*)-3-*N*-(2,4-dimethoxybenzyl)-*N*-α-methylbenzylamino-3-phenylpropanoate 12

Following representative procedure 1, *n*-BuLi (0.31 mL, 0.76 mmol), (*R*)-*N*-2,4-dimethoxybenzyl-*N*-α-methylbenzylamine (213 mg, 0.79 mmol) in THF (10 mL) and *tert*-butyl cinnamate (100 mg, 0.49 mmol) in THF (5 mL) gave, after column chromatography on silica gel (pentane/Et_2O 100:1), an inseparable 50:50 mixture of *tert*-butyl (α*R*,3*S*)- and *tert*-butyl (α*R*,3*R*)-3-*N*-(2,4-dimethoxybenzyl)-*N*-α-methylbenzylamino-3-phenylpropanoate **12** (38 mg, 16%): δ_H (400 MHz, $CDCl_3$) 1.21 (3H, s, O^t*Bu*), 1.24 (3H, s, O^t*Bu*), 1.26 (3H, d, *J* 6.9, C(α)*Me*), 1.31 (3H, d, *J* 6.8, C(α)*Me*), 2.48–2.59 (2H, m, C(2)H_2), 2.71 (1H, dd, *J* 14.3, *J* 10.3, C(2)H_AH_B), 2.89 (1H, dd, *J* 14.5, *J* 4.7, C(2)H_AH_B), 3.49 (1H, ABq, *J* 15.7, NCH_AH_B), 3.66 (2H, app d, *J* 2.6, NCH_2), 3.75 (3H, s, O*Me*), 3.78 (3H, s, O*Me*), 3.79 (3H, s, O*Me*), 3.82 (3H, s, O*Me*), 3.89–4.00 (3H, m, CH_AH_BNC(α)*H*, NC(α)*H*), 4.31–4.37 (2H, m, 2 × C(3)*H*), 6.39 (2H, app dd, *J* 9.8, *J* 2.7, *Ar*), 6.44 (1H, app dd, *J* 8.3, *J* 2.4, *Ar*), 6.51 (1H, app dd, *J* 8.4, *J* 2.7, *Ar*), 7.20–7.48 (22H, m, *Ph*, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.9, 19.0, 27.8, 38.4, 39.0, 42.8, 43.3, 55.1, 55.2, 55.3, 55.3, 57.3, 58.0, 59.8, 60.3, 79.9, 80.0, 97.8, 104.0, 122.1, 122.6, 126.5, 126.6, 126.8, 126.9, 127.8, 127.9, 127.9, 128.0, 128.3, 128.6, 130.1, 130.3, 141.0, 142.2, 144.6, 144.8, 157.5, 157.7, 159.2, 159.3, 171.2, 171.3; *m*/*z* (ESI^+) 476 [100%, MH^+]; HRMS $C_{30}H_{38}NO_4$ (MH^+) requires 476.2801, found 476.2802; ν_{max}/cm^{-1} (film) 1588 (C═C), 1613 (C═C), 1726 (C═O).

3.13. Preparation of methyl (3*R*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)butanoate 14

Following representative procedure 1, *n*-BuLi (1.4 M, 2.2 mL, 3.1 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (678 mg, 3.2 mmol) in THF (10 mL) and methyl crotonate (200 mg, 2.0 mmol) in THF (5 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 4:1), **14** (527 mg, 85%) as a colourless oil: $C_{20}H_{26}NClO_2$ (**14**·HCl) requires C, 69.05; H, 7.5; N, 4.0%, found C, 69.1; H, 7.9; N, 4.2%; $[\alpha]_D^{20} = -3.4$ (*c* 1.2, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.7, C(4)H_3), 1.36 (3H, d, *J* 6.9, C(α)*H*), 2.19 (1H, dd, $J_{2A,2B}$ 14.2, $J_{2A,3}$ 7.8, C(2)H_AH_B), 2.46 (1H, dd, $J_{2B,2A}$ 14.2, $J_{2B,3}$ 6.3, C(2)H_AH_B), 3.47–3.59 (1H, m, C(3)*H*), 3.57 (3H, s, CO_2Me), 3.78 (2H, ABq, NCH_2), 3.97 (1H, q, *J* 6.9, C(α)*H*), 7.25–7.50 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 17.5, 18.6, 39.7, 49.6, 49.9, 51.4, 57.6, 126.7, 127.1, 127.8, 128.1, 128.4, 128.8, 141.7, 144.3, 172.7; *m*/*z* (CI^+) 312 (MH^+, 100%); ν_{max}/cm^{-1} (film) 2970 (C–H), 1735 (C═O).

3.14. Preparation of benzyl (3*R*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)butanoate 15

Following representative procedure 1, *n*-BuLi (1.6 M, 4.4 mL, 7.0 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (1.53 g, 7.2 mmol) in THF (10 mL) and benzyl crotonate (792 mg, 4.5 mmol) in THF (5 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 7:3), **15** (1.55g, 88%) as a colourless oil: $C_{26}H_{29}NO_2$ requires C, 80.6; H, 7.5; N, 3.6%, found C, 80.8; H, 7.9; N, 3.7%; $[\alpha]_D^{20} = +12.0$ (*c* 1.2 in CH_2Cl_2); δ_H (300 MHz) 1.16 (3H, d, *J* 6.7, C(4)H_3), 1.36 (3H, d, *J* 6.8, C(α)*Me*), 2.19 (1H, dd, $J_{2A,2B}$ 14.2, $J_{2A,3}$ 8.0, C(2)H_AH_B), 2.42 (1H, dd, $J_{2B,2A}$ 14.2, $J_{2B,3}$ 5.8, C(2)H_AH_B), 3.47–3.52 (1H, m, C(3)*H*), 3.68 (1H, ABq, *J* 14.8, NCH_AH_B), 3.84 (1H, ABq, *J* 14.8, NCH_AH_B), 3.91 (1H, q, *J* 6.8, C(α)*H*), 4.93 (1H, ABq, *J* 12.4, OCH_AH_B), 5.05 (1H, ABq, *J* 12.4, OCH_AH_B), 7.16–7.47 (15H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 17.8, 18.5, 39.6, 49.6, 50.0, 57.8, 66.0, 126.8, 127.1, 127.9, 128.2, 128.3, 128.5, 128.6, 136.2, 141.9, 144.4, 172.5; *m*/*z* (CI^+) 388 (MH^+, 37%); ν_{max}/cm^{-1} (film) 3015, 2970 (C–H), 1735 (C═O).

3.15. Preparation of *tert*-butyl (3*R*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)butanoate 16

Following representative procedure 1, *n*-BuLi (1.6 M, 1.35 mL, 2.15 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (472 mg, 2.2 mmol) in THF (10 mL) and *tert*-butyl crotonate (200 mg, 1.39 mmol) in THF (5 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 7:3), **16** (403 mg, 82%) as a colourless oil: $C_{23}H_{31}NO_2$ requires C, 78.15; H, 8.8; N, 4.0%, found C, 78.3; H, 8.9; N, 3.8%; $[\alpha]_D^{20} = -3.7$ (*c* 1.1, CH_2Cl_2); δ_H (500 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.3, C(4)H_3), 1.36 (3H, d, *J* 6.8, C(α)*Me*), 1.40 (9H, s, O^t*Bu*), 2.02 (1H, dd, $J_{2A,2B}$ 14.3, $J_{2A,3}$ 8.2, C(2)H_AH_B), 2.42 (1H, dd, $J_{2B,2A}$ 14.3, $J_{2B,3}$ 5.1, C(2)H_AH_B), 3.33–3.53 (1H, m, C(3)*H*), 3.62 (1H, ABq, *J* 16.0, NCH_AH_B), 3.78 (1H, ABq, *J* 16.0, NCH_AH_B), 3.91 (1H, q, *J* 6.8, C(α)*H*), 7.16–7.48 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 18.3, 19.0, 27.9, 40.4, 49.7, 50.3, 58.5, 79.9, 126.6, 126.8, 127.1, 127.9, 128.3, 142.3, 144.5, 172.2; *m*/*z* (CI^+) 354 (MH^+, 100%); ν_{max}/cm^{-1} (film) 2970 (C–H), 1720 (C═O).

3.16. One-pot reaction protocol for the preparation of *tert*-butyl (3*S*,α*S*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)butanoate 16

n-BuLi (2.5 M, 31.5 mL, 78.7 mmol) at −78 °C was added dropwise to a stirred solution of (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (17.14 g, 17.0 mL, 81.2 mmol) and *tert*-butyl crotonate (7.21 g, 50.8 mmol) in anhydrous THF

(100 mL) at −78 °C under nitrogen and stirred for 2 h prior to the addition of saturated aqueous ammonium chloride (10 mL) and warmed to rt. The resultant solution was partitioned between brine and DCM (3 × 100 mL), and the combined organic extracts were concentrated in vacuo. The residue was re-dissolved in DCM (200 mL), washed successively with 10% aqueous citric acid solution (2 × 100 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried and concentrated in vacuo before purification by column chromatography on silica gel (Et_2O/pentane 1:20) to give **16** (16.7 g, 93%) as a colourless oil $[\alpha]_D^{24} = +3.6$ (*c* 0.8, $CHCl_3$) with spectroscopic properties consistent with those reported above.

3.17. Preparation of methyl (3*R*,α*R*,α′*R*)-3-(*N*,*N*-bis-(α-methylbenzyl)amino)butanoate 18

Following representative procedure 1, *n*-BuLi (1.6 M, 2.6 mL, 4.1 mmol), (*R*,*R*)-*N*,*N*-bis-(α-methylbenzyl)amine (954 mg, 4.2 mmol) in THF (5 mL) and methyl crotonate (265 mg, 2.7 mmol) in THF (5 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 4:1), **18** (492 mg, 57%) as a pale yellow oil: $[\alpha]_D^{20} = -7.6$ (*c* 1.1, CH_2Cl_2); $C_{21}H_{27}NO_2$ requires C, 77.5; H, 8.4; N, 4.3%, found C, 77.3; H, 8.5; N, 4.2%; δ_H (500 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.8, C(4)H_3), 1.54 (6H, d, *J* 7.0, C(α)*Me*), 2.10–2.26 (2H, m, C(2)H_2), 3.40 (3H, s, CO_2Me), 3.42–3.50 (1H, m, C(3)*H*), 4.19 (2H, q, *J* 7.0, C(α)*H*), 7.14–7.30 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 18.8, 20.9, 42.3, 48.3, 51.1, 53.6, 126.5, 127.0, 128.0, 145.5, 172.8; *m*/*z* (CI^+) 326 (MH^+, 100%); ν_{max}/cm^{-1} (film) 2970 (C–H), 1735 (C=O).

3.18. Preparation of benzyl (3*R*,α*R*,α′*R*)-3-(*N*,*N*-bis-(α-methylbenzyl)amino)butanoate 19

Following representative procedure 1, *n*-BuLi (1.6 M, 1.9 mL, 3.1 mmol), (*R*,*R*)-*N*,*N*-bis-(α-methylbenzyl)amine (709 mg, 3.2 mmol) in THF (5 mL) and benzyl crotonate (347 mg, 2.0 mmol) in THF (5 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 4:1), **19** (180 mg, 23%) as a pale yellow oil; $[\alpha]_D^{20} = +9.6$ (*c* 1.1, CH_2Cl_2); $C_{27}H_{31}NO_2$ requires C, 80.8; H 7.8; N, 3.5%, found C, 80.6; H, 7.7; N, 3.6%; δ_H (500 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.8, C(4)H_3), 1.54 (6H, d, *J* 7.0, C(α)*Me*), 2.18–2.27 (2H, m, C(2)H_2), 3.47–3.52 (1H, m, C(3)*H*), 4.19 (2H, q, *J* 7.0, C(α)*H*), 4.86 (1H, ABq, *J* 11.5, OC$H_A$$H_B$Ph), 4.90 (1H, ABq, *J* 11.5, OC$H_A$$H_B$Ph), 7.14–7.42 (15H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 18.9, 20.9, 42.6, 48.3, 53.9, 65.8, 126.5, 128.0, 128.2, 128.4, 128.6, 136.3, 145.5, 172.2; *m*/*z* (CI^+) 402 (MH^+, 100%); ν_{max}/cm^{-1} (film) 1730 (C=O).

3.19. Preparation of *tert*-butyl (3*R*,α*R*,α′*R*)-3-(*N*,*N*-bis-(α-methylbenzyl)amino)butanoate 20

Following representative procedure 1, *n*-BuLi (1.6 M, 1.0 mL, 1.64 mmol), (*R*,*R*)-*N*,*N*-bis-(α-methylbenzyl)amine (382 mg, 1.70 mmol) in THF (5 mL) and *tert*-butyl crotonate (150 mg, 1.1 mmol) in THF (5 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 4:1), **20** (234 mg, 60%) as a colourless oil: $[\alpha]_D^{20} = +2.6$ (*c* 1.2, CH_2Cl_2); $C_{24}H_{33}NO_2$ requires C, 78.4; H, 9.05; N, 3.8%, found C, 78.35; H, 9.3; N, 3.8%; δ_H (300 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.8, C(4)H_3), 1.35 (9H, s, O^t*Bu*), 1.53 (6H, d, *J* 6.4, C(α)*Me*), 1.97–2.21 (2H, m, C(2)H_2), 3.40–3.58 (1H, m, C(3)*H*), 4.17 (2H, q, *J* 6.8, C(α)*H*), 7.14–7.28 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 19.1, 20.4, 27.9, 43.9, 48.1, 53.9, 79.7, 126.4, 127.9, 128.0, 128.2, 128.4, 145.6, 171.9; *m*/*z* (CI^+) 368 (MH^+, 78%); ν_{max}/cm^{-1} (film) 2970 (C–H), 1725 (C=O).

3.20. Preparation of benzyl (3*R*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)pentanoate 21

Following representative procedure 1, *n*-BuLi (1.6 M, 9.1 mL, 14.6 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (3.2 g, 15.0 mmol) in THF (25 mL) and benzyl (*E*)-2-pentenoate (1.8 g, 9.4 mmol) in THF (25 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 1:1), **21** (2.53 g, 67%) as a colourless oil: $C_{27}H_{31}NO_2$ requires C, 80.8; H, 7.8; N, 3.5%, found C, 80.5; H, 7.8; N, 3.3%; $[\alpha]_D^{20} = +23.6$ (*c* 1.1, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.01 (3H, t, *J* 7.3, C(5)H_3), 1.37 (3H, d, *J* 7.0, C(α)*Me*), 1.34–1.40 (1H, m, C(4)$H_A$$H_B$), 1.51–1.58 (1H, m, C(4)$H_A$$H_B$), 2.08–2.10 (2H, m, C(2)H_2), 3.28–3.33 (1H, m, C(3)*H*), 3.57 (1H, ABq, *J* 14.8, NC$H_A$$H_B$), 3.81 (1H, ABq, *J* 14.8, NC$H_A$$H_B$), 3.87 (1H, q, *J* 7.0, C(α)*H*), 4.91 (1H, ABq, *J* 12.3, OC$H_A$$H_B$), 5.08 (1H, ABq, *J* 12.3, OC$H_A$$H_B$), 7.20–7.46 (15H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 11.8, 19.6, 26.3, 36.6, 50.0, 55.7, 57.7, 66.1, 126.9, 127.2, 128.1, 128.4, 128.5, 128.7, 141.9, 143.2, 173.1; *m*/*z* (CI^+) 402 (MH^+, 100%); ν_{max}/cm^{-1} (film) 3062, 3029 (C–H), 1733 (C=O).

3.21. Preparation of *tert*-butyl (3*R*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)pentanoate 22

Following representative procedure 1, *n*-BuLi (1.6 M, 1.3 mL, 2.1 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (500 mg, 2.4 mmol) in THF (25 mL) and *tert*-butyl (*E*)-pent-2-enoate (210 mg, 1.34 mmol) in THF (25 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 9:1), **22** (456 mg, 92%) as a colourless oil: $C_{24}H_{33}NO_2$ requires C, 78.4; H, 9.05; N, 3.8%, found C, 78.3; H, 9.3; N, 3.55%; $[\alpha]_D^{20} = +22.4$ (*c* 1.1, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.04 (3H, t, *J* 7.3, C(5)H_3), 1.38 (3H, d, *J* 7.0, C(α)*Me*), 1.43 (9H, s, O^t*Bu*), 1.36–1.53 (2H, m, C(4)H_2), 1.88–1.96 (2H, m, C(2)H_2), 3.28 (1H, m, C(3)*H*), 3.53 (1H, ABq, *J* 14.9, NC$H_A$$H_B$), 3.81 (1H, ABq, *J* 14.9, NC$H_A$$H_B$), 3.86 (1H, q, *J* 7.0, C(α)*H*), 7.24–7.47 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 11.9, 20.2, 26.3, 28.0, 37.7, 50.1, 55.5, 58.0, 79.9, 126.8, 127.1, 128.2, 128.3, 128.4, 142.1, 143.2, 172.6; *m*/*z* (CI^+) 367 (MH^+, 100%); ν_{max}/cm^{-1} (film) 3062, 3027 (C–H), 1728 (C=O).

3.22. Preparation of benzyl (3*R*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)octanoate 23

Following representative procedure 1, *n*-BuLi (1.6 M, 6.49 mL, 10.4 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (2.27 g, 10.7 mmol) in THF (15 mL) and benzyl (*E*)-oct-2-enoate (1.56 g, 6.7 mmol) in THF (20 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 4:1), **23** (2.22 g, 75%) as a colourless oil:

$[\alpha]_D^{20} = +11.9$ (*c* 1.6, $CHCl_3$); $C_{30}H_{37}NO_2$ requires C, 81.2; H, 8.4; N, 3.2%, found C, 81.1; H, 8.4, N, 3.0%; δ_H (500 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.3, C(8)H_3), 1.16–1.38 (6H, m, $CH_3C(7)H_2C(6)H_2C(5)H_2$), 1.35 (3H, d, *J* 7.0, C(α)*Me*), 1.49–1.59 (2H, m, C(4)H_2), 2.08 (1H, dd, $J_{2A,2B}$ 14.5, $J_{2A,3}$ 8.5, C(2)H_AH_B), 1.98 (1H, dd, $J_{2B,2A}$ 14.5, $J_{2B,3}$ 4.3, C(2)H_AH_B), 3.33–3.39 (1H, m, C(3)*H*), 3.56 (1H, ABq, *J* 14.9, NCH_AH_B), 3.82 (1H, ABq, *J* 14.9, NCH_AH_B), 3.86 (1H, q, *J* 7.0, C(α)*H*), 4.98 (1H, ABq, *J* 12.3, OCH_AH_B), 5.07 (1H, ABq, *J* 12.3, OCH_AH_B), 7.20–7.45 (15H, m, *Ph*); δ_C (50 MHz) 14.0, 19.7, 22.6, 26.6, 31.7, 33.5, 36.8, 50.0, 54.1, 58.0, 66.1, 126.9, 127.1, 128.2, 128.4, 128.5, 128.7, 136.4, 142.1, 143,4, 173.1; *m*/*z* (CI^+) 444 (MH^+, 90%); ν_{max}/cm^{-1} (film) 3063, 3030 (C–H), 1733 (C=O), 1146 (C–O).

3.23. Preparation of *tert*-butyl (3*R*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)octanoate 24

Following representative procedure 1, *n*-BuLi (1.6 M, 1.5 mL, 2.3 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (509 mg, 2.4 mmol) in THF (25 mL) and *tert*-butyl (*E*)-oct-2-enoate (300 mg, 1.51 mmol) in THF (25 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 9:1), **24** (501 mg, 81%) as a colourless oil: $[\alpha]_D^{20} = +7.6$ (*c* 1.4, $CHCl_3$); $C_{27}H_{39}NO_2$ requires C, 79.2; H, 9.6; N, 3.4%, found: C, 79.1; H, 9.9; N, 3.3%; δ_H (500 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.2, C(8)H_3), 1.15–1.60 (8H, m, $CH_3C(7)H_2C(6)H_2C(5)H_2C(4)H_2$), 1.34 (3H, d, *J* 7.0, C(α)*Me*), 1.41 (9H, s, O^t*Bu*), 1.99 (1H, dd, $J_{2A,2B}$ 14.5, $J_{2A,3}$ 9.4, C(2)H_AH_B), 1.98 (1H, dd, $J_{2B,2A}$ 14.5, $J_{2B,3}$ 3.5, C(2)H_AH_B), 3.28–3.33 (1H, m, C(3)*H*), 3.50 (1H, ABq, *J* 15.0, NCH_AH_B), 3.81 (1H, ABq, *J* 15.0, NCH_AH_B), 3.83 (1H, q, *J* 7.0, C(α)*H*), 7.22–7.42 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 13.9, 20.3, 22.5, 26.4, 27.9, 31.7, 33.3, 37.7, 50.0, 53.8, 58.3, 79.9, 126.6, 127.0, 127.1, 128.0, 128.3, 142.3, 143.3, 172.5; *m*/*z* (CI^+) 409 (MH^+, 100%); ν_{max}/cm^{-1} (film) 3062, 3027 (C–H), 1728 (C=O), 1147 (C–O).

3.24. Preparation of methyl (3*S*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-phenylpropanoate 25

Following representative procedure 1, *n*-BuLi (1.6 M, 1.5 mL, 2.3 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (509 mg, 2.4 mmol) in THF (25 mL) and methyl cinnamate (300 mg, 1.85 mmol) in THF (25 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 9:1), **25** (467 mg, 68%) as a colourless oil: $[\alpha]_D^{20} = -4.2$ (*c* 1.1, CH_2Cl_2); $C_{25}H_{28}NClO_2$ (**25**·HCl) requires C, 73.25; H, 6.9; N, 3.4%, found: C, 73.5; H, 7.1; N, 3.5%; δ_H (300 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.9, C(α)*Me*), 2.55 (1H, dd, $J_{2A,2B}$ 14.9, $J_{2A,3}$ 9.2, C(2)H_AH_B), 2.68 (1H, dd, $J_{2B,2A}$ 14.9, $J_{2B,3}$ 5.7, C(2)H_AH_B), 3.46 (3H, s, CO_2Me), 3.65 (1H, ABq, *J* 14.6, NCH_AH_B), 3.74 (1H, ABq, *J* 14.6, NCH_AH_B), 4.00 (1H, q, *J* 6.8, C(α)*H*), 4.43 (1H, dd, $J_{3,2A}$ 9.3, $J_{3,2B}$ 5.7, C(3)*H*), 7.16–7.42 (15H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 15.6, 37.4, 50.6, 51.4, 56.6, 59.2, 126.7, 126.8, 127.0, 127.1, 127.4, 127.7, 128.0, 128.2, 128.3, 141.5, 141.9, 144.2, 172.5; *m*/*z* (CI^+) 374 (MH^+, 85%); ν_{max}/cm^{-1} (film) 3060, 3020, 2845 (C–H), 1740 (C=O), 1490, 1450.

3.25. Preparation of benzyl (3*S*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-phenylpropanoate 26

Following representative procedure 1, *n*-BuLi (1.6 M, 1.2 mL, 1.95 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (427 mg, 2.0 mmol) in THF (10 mL) and benzyl cinnamate (300 mg, 1.26 mmol) in THF (5 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 4:1), **26** (221 mg, 39%) as a colourless oil: $[\alpha]_D^{20} = +3.8$ (*c* 1.0, CH_2Cl_2); $C_{31}H_{32}NClO_2$ (**26**·HCl) requires C, 76.6; H, 6.6; N, 2.9%, found C, 76.3; H, 6.9; N, 2.8%; δ_H (300 MHz, $CDCl_3$) 1.23 (3H, d, *J* 6.8, C(α)*Me*), 2.62 (1H, dd, $J_{2A,2B}$ 14.9, $J_{2A,3}$ 9.1, C(2)H_AH_B), 2.68 (1H, dd, $J_{2B,2A}$ 14.9, $J_{2B,3}$ 5.8, C(2)H_AH_B), 3.68 (2H, ABq, NCH_2), 3.99 (1H, q, *J* 6.8, C(α)*H*), 4.48 (1H, dd, $J_{3,2A}$ 9.1, $J_{3,2B}$ 5.8, C(3)*H*), 4.90 (2H, s, OCH_2), 7.08–7.42 (20H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 15.9, 37.4, 50.7, 56.8, 59.4, 66.1, 126.8, 127.0, 127.4, 128.0, 128.2, 128.5, 128.6, 128.8, 136.0, 141.6, 141.8, 144.2, 171.9; *m*/*z* (CI^+) 450 (MH^+, 71%); ν_{max}/cm^{-1} (film) 3030, 2920 (C–H), 1710 (C=O).

3.26. Preparation of *tert*-butyl (3*S*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-phenylpropanoate 27

Following representative procedure 1, *n*-BuLi (1.6 M, 5.7 mL, 9.1 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (2.0 g, 9.5 mmol) in THF (10 mL) and *tert*-butyl cinnamate (1.21 g, 5.9 mmol) in THF (10 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 4:1), **27** (2.37 g, 96%) as a colourless oil: $[\alpha]_D^{20} = +3.9$ (*c* 0.7, $CHCl_3$); $C_{28}H_{33}NO_2$ requires C, 80.9; H, 8.0; N, 3.4%, found: C, 80.6; H, 7.8; N, 3.2%; δ_H (500 MHz, $CDCl_3$) 1.24 (9H, s, O^t*Bu*), 1.29 (3H, d, *J* 6.8, C(α)*Me*), 2.45–2.60 (2H, m, C(2)H_2), 3.71 (2H, ABq, NCH_2), 4.03 (1H, q, *J* 6.8, C(α)*H*), 4.43 (1H, dd, $J_{3,2A}$ 9.9, $J_{3,2B}$ 5.2, C(3)*H*), 7.18–7.47 (15H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 16.1, 27.7, 38.5, 50.8, 57.0, 59.9, 126.7, 127.0, 127.2, 127.5, 128.0, 128.3, 141.9, 142.0, 144.4, 171.4; *m*/*z* (MH^+) 416 (MH^+, 100%); ν_{max}/cm^{-1} (film) 2970, 2930 (C–H), 1710 (C=O).

3.27. One-pot reaction protocol for the preparation of *tert*-butyl (3*R*,α*S*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-phenylpropanoate 27

n-BuLi (2.5 M, 23.5 mL, 58.8 mmol) at −78 °C was added dropwise to a stirred solution of (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (13.5 g, 13.3 mL, 64.0 mmol) and *tert*-butyl cinnamate (10.0 g, 49.0 mmol) in anhydrous THF (100 mL) at −78 °C under nitrogen and stirred for 2 h prior to the addition of saturated aqueous ammonium chloride (10 mL) and warmed to rt. The resultant solution was partitioned between brine and DCM (3 × 100 mL) and the combined organic extracts were concentrated in vacuo. The residue was re-dissolved in DCM (200 mL), washed successively with 10% aqueous citric acid solution (2 × 100 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried and concentrated in vacuo before purification by chromatography on silica gel (Et_2O/pentane 1:20) to give **27** (16.7 g, 82%) as a colourless oil; $[\alpha]_D^{24} = -3.4$ (*c* 1.1, $CHCl_3$) with spectroscopic properties consistent with those reported above.

3.28. Preparation of benzyl (3*S*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-(2-methoxyphenyl) propanoate 28

Following representative procedure 1, *n*-BuLi (1.6 M, 0.5 mL, 0.84 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (183 mg, 0.86 mmol) in THF (15 mL) and benzyl (*E*)-3-(2-methoxyphenyl)prop-2-enoate (145 mg, 0.54 mmol) in THF (10 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 4:1), **28** (80 mg, 31%) as a colourless oil: $[\alpha]_D^{20} = +8.6$ (*c* 0.6, $CHCl_3$); $C_{32}H_{33}NO_3$ requires C, 80.1; H, 6.9; N, 2.9%, found C, 79.9; H, 7.1; N, 2.7%; δ_H (500 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.7, C(α)*Me*), 2.76 (1H, dd, $J_{2A,2B}$ 14.6, $J_{2A,3}$ 9.1, C(2)H_AH_B), 2.68 (1H, dd, $J_{2B,2A}$ 14.6, $J_{2B,3}$ 6.5, C(2)H_AH_B), 3.76 (2H, ABq, NCH_2), 3.81 (3H, s, O*Me*), 4.11 (1H, q, *J* 6.7, C(α)*H*), 4.84 (1H, ABq, *J* 12.5, OCH_AH_B), 4.93 (1H, ABq, *J* 12.5, OCH_AH_B), 4.96 (1H, dd, $J_{3,2A}$ 9.1, $J_{3,2B}$ 6.5, C(3)*H*), 6.89–6.96 (2H, m, *Ar*), 7.09–7.46 (17H, m, *Ar*, *Ph*); δ_C (50 MHz, $CDCl_3$) 14.3, 38.9, 50.7, 53.5, 55.2, 56.4, 65.9, 111.1, 120.6, 126.7, 126.8, 128.1, 128.2, 128.4, 128.6, 128.9, 129.1, 129.9, 136.3, 142.2, 144.8, 158.1, 172.0; *m*/*z* (CI^+) 480 (MH^+, 60%); ν_{max}/cm^{-1} (film) 3062, 3028 (C–H), 1735 (C=O).

3.29. Preparation of *tert*-butyl (3*S*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-(2-methoxyphenyl)propanoate 29

Following representative procedure 1, *n*-BuLi (1.6 M, 1.3 mL, 2.05 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (448 mg, 2.11 mmol) in THF (15 mL) and *tert*-butyl (*E*)-3-(2-methoxyphenyl)prop-2-enoate (310 mg, 1.32 mmol) in THF (10 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 9:1), **29** (558 mg, 95%) as a colourless oil: $[\alpha]_D^{20} = +15.0$ (*c* 0.9, $CHCl_3$); $C_{29}H_{35}NO_3$ requires C, 78.2; H, 7.9; N, 3.1%, found: C, 78.35; H, 7.6; N, 3.3%; δ_H (500 MHz, $CDCl_3$) 1.18 (9H, s, O^t*Bu*), 1.25 (3H, d, *J* 6.8, C(α)*Me*), 2.62 (2H, app d, C(2)H_2), 3.73 (2H, ABq, NCH_2), 3.84 (3H, s, O*Me*), 4.08 (1H, q, *J* 6.8, C(α)*H*), 4.86 (1H, t, *J* 8.0, C(3)*H*), 6.89–6.94 (2H, m, *Ar*), 7.14–7.43 (12H, m, *Ar*, *Ph*); δ_C (50 MHz, $CDCl_3$) 14.2, 27.6, 40.1, 45.8, 53.9, 55.1, 56.5, 79.8, 110.8, 120.4, 126.5, 126.7, 128.0, 128.2, 128.4, 129.3, 130.0, 142.5, 144.9, 158.2, 171.4; *m*/*z* (CI^+) 445 (MH^+, 100%); ν_{max}/cm^{-1} (film) 3061, 3027 (C–H), 1728 (C=O).

3.30. Preparation of benzyl (3*S*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-(4-methoxyphenyl)propanoate 30

Following representative procedure 1, *n*-BuLi (1.6 M, 3.0 mL, 4.8 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (1.0 g, 4.9 mmol) in THF (15 mL) and benzyl (*E*)-3-(4-methoxyphenyl)prop-2-enoate (825 mg, 3.1 mmol) in THF (10 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 4:1), **30** (1.06 g, 72%) as a colourless oil: $[\alpha]_D^{20} = +7.1$ (*c* 1.0, $CHCl_3$); $C_{32}H_{33}NO_3$ requires C, 80.1; H, 6.9; N, 2.9%, found: C, 80.2; H, 6.6; N, 2.6%; δ_H (500 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.8, C(α)*Me*), 2.62 (1H, dd, $J_{2A,2B}$ 14.7, $J_{2A,3}$ 9.9, C(2)H_AH_B), 2.68 (1H, dd, $J_{2B,2A}$ 14.7, $J_{2B,3}$ 5.3, C(2)H_AH_B), 3.71 (2H, ABq, NCH_2), 3.82 (3H, s, O*Me*), 4.03 (1H, q, *J* 6.8, C(α)*H*), 4.46 (1H, dd, $J_{3,2A}$ 9.9, $J_{3,2B}$ 5.3, C(3)*H*), 4.93 (2H, ABq, OCH_2), 6.86–6.91 (2H, m, Ar(3)*H*, Ar(5)*H*), 7.12–7.33 (10H, m, *Ph*), 7.43 (2H, m, *Ar*); δ_C (50 MHz, $CDCl_3$) 16.0, 37.8, 50.7, 55.2, 56.8, 59.0, 66.1, 113.8, 126.8, 127.1, 127.8, 128.1, 128.2, 128.4, 133.8, 136.1, 141.9, 144.4, 159.1, 172.1; *m*/*z* (CI^+) 479 (MH^+, 30%); ν_{max}/cm^{-1} (film) 3062, 3030 (C–H), 1734 (C=O).

3.31. Preparation of *tert*-butyl (3*S*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-(4-methoxyphenyl)propanoate 31

Following representative procedure 1, *n*-BuLi (1.6 M, 1.0 mL, 1.6 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (360 mg, 1.7 mmol) in THF (15 mL) and *tert*-butyl (*E*)-3-(4-methoxyphenyl)prop-2-enoate (249 mg, 1.1 mmol) in THF (10 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 4:1), **31** (453 mg, 96%) as a colourless oil: $[\alpha]_D^{20} = +2.2$ (*c* 1.0, $CHCl_3$); $C_{29}H_{35}NO_3$ requires C, 78.2; H, 7.9; N, 3.1%, found: C, 78.4; H, 7.9; N, 2.9%; δ_H (500 MHz, $CDCl_3$) 1.24 (9H, s, O^t*Bu*), 1.26 (3H, d, *J* 6.8, C(α)*Me*), 2.46 (1H, dd, $J_{2A,2B}$ 14.4, $J_{2A,3}$ 10.2, C(2)H_AH_B), 2.68 (1H, dd, $J_{2B,2A}$ 14.4, $J_{2B,3}$ 5.0, C(2)H_AH_B), 3.67 (2H, app s, NCH_2), 3.81 (3H, s, O*Me*), 3.99 (1H, q, *J* 6.8, C(α)*H*), 4.35 (1H, dd, $J_{3,2A}$ 10.3, $J_{3,2B}$ 5.0, C(3)*H*), 6.85–6.89 (2H, m, Ar(3)*H*, Ar(5)*H*), 7.16–7.42 (12H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 16.4, 27.8, 38.6, 50.8, 55.2, 57.1, 59.2, 80.2, 113.6, 126.7, 127.0, 128.1, 128.2, 128.4, 129.6, 134.1, 142.2, 144.6, 159.0, 171.6; *m*/*z* (CI^+) 445 (MH^+, 50%); ν_{max}/cm^{-1} (film) 3061 (C–H), 1726 (C=O).

3.32. Preparation of methyl (3*S*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-(4-benzyloxyphenyl)propanoate 32

Following representative procedure 1, *n*-BuLi (1.6 M, 1.3 mL, 2.1 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (1.6 g, 7.4 mmol) in THF (15 mL) and methyl (*E*)-3-(4-benzyloxyphenyl)prop-2-enoate (1.2 g, 4.6 mmol) in THF (10 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 4:1), **32** (1.38 g, 63%) as a pale yellow oil: $[\alpha]_D^{20} = -0.8$ (*c* 2.0, CH_2Cl_2); $C_{32}H_{33}NO_3$ requires C, 80.1; H, 6.9; N, 2.9%, found C, 80.2; H, 7.2; N, 3.1%; δ_H (500 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.8, C(α)*Me*), 2.55 (1H, dd, $J_{2A,2B}$ 14.9, $J_{2A,3}$ 9.4, C(2)H_AH_B), 2.68 (1H, dd, $J_{2B,2A}$ 14.9, $J_{2B,3}$ 6.3, C(2)H_AH_B), 3.49 (3H, s, CO_2Me), 3.70 (2H, ABq, NCH_2), 4.02 (1H, q, *J* 6.8, C(α)*H*), 4.40 (1H, dd, $J_{3,2A}$ 9.4, $J_{3,2B}$ 6.0, C(3)*H*), 5.07 (2H, s, OCH_2), 7.20–7.49 (19H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 15.7, 37.6, 50.6, 51.4, 56.6, 58.7, 70.0, 114.7, 126.8, 127.0, 127.7, 128.0, 128.1, 128.3, 128.7, 129.3, 134.2, 137.4, 141.7, 144.4, 158.2, 172.6; *m*/*z* (CI^+) 480 (MH^+, 46%); ν_{max}/cm^{-1} (film) 1730 (C=O).

3.33. Preparation of benzyl (3*S*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-(4-benzyloxyphenyl)propanoate 33

Following representative procedure 1, *n*-BuLi (1.6 M, 5.6 mL, 9.0 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (2.0 g, 9.3 mmol) in THF (15 mL) and benzyl (*E*)-3-(4-benzyloxyphenyl)prop-2-enoate (2.0 g, 5.8 mmol) in THF (10 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 4:1), **33** (2.1 g, 64%) as a pale yellow oil: $[\alpha]_D^{20} = -3.5$ (*c* 1.7, CH_2Cl_2); $C_{38}H_{37}NO_3$ requires C, 82.1; H, 6.7; N, 2.5%, found: C, 82.25; H, 7.0; N, 2.5%; δ_H (300 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.9, C(α)*Me*), 2.60

(1H, dd, $J_{2A,2B}$ 14.7, $J_{2A,3}$ 9.7, C(2)H_AH$_B$), 2.72 (1H, dd, $J_{2B,2A}$ 14.7, $J_{2B,3}$ 5.5, C(2)H$_A$$H_B$), 3.73 (2H, ABq, NC$H_2$), 4.01 (1H, q, J 6.8, C(α)H), 4.45 (1H, dd, $J_{3,2A}$ 9.7, $J_{3,2B}$ 5.5, C(3)H), 4.92 (2H, s, OCH_2Ph), 5.06 (2H, s, OCH_2Ph), 7.10–7.48 (24H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 15.9, 37.6, 50.7, 56.8, 58.9, 66.0, 70.0, 114.5, 114.7, 123.5, 127.0, 127.4, 127.7, 128.0, 128.8, 128.3, 128.6, 128.8, 129.1, 129.4, 134.1, 136.0, 137.2, 141.8, 144.3, 158.2, 172.2; *m*/*z* (CI^+) 556 (MH^+, 13%); ν_{max}/cm^{-1} (film) 3030, 2930 (C–H), 1730 (C=O).

3.34. Preparation of *tert*-butyl (3*R*,α*S*)-3-(3,4-methylenedioxyphenyl)-3-(*N*-benzyl-*N*-α-methylbenzylamino)propanoate 34

Following representative procedure 1, *n*-BuLi (2.5 M, 1.8 mL, 4.7 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (2.6 g, 12.1 mmol) in THF (15 mL) and *tert*-butyl (*E*)-3-(3,4-methylenedioxyphenyl)prop-2-enoate (1.5 g, 6.0 mmol) in THF (15 mL) gave, after column chromatography on silica gel (hexane/Et_2O 1:9), **34** (2.0 g, 73%) as a colourless oil: $[\alpha]_D^{23} = -0.3$ (*c* 1.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.26 (9H, s, O^t*Bu*), 1.28 (3H, d, *J* 6.8, C(α)*Me*), 2.37–2.53 (2H, m, C(2)H_2), 3.67 (2H, app s, NCH_2), 3.99 (1H, q, *J* 6.8, C(α)H), 4.29–4.33 (1H, m, C(3)H), 5.96 (2H, s, OCH_2O), 6.74–7.43 (13H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.2, 27.8, 38.6, 50.8, 57.0, 59.6, 80.2, 100.9, 107.6, 108.7, 121.2, 126.5, 126.8, 127.8, 127.9, 128.1, 128.4, 135.9, 141.7, 144.1, 146.5, 147.5, 171.1; *m*/*z* (APCI$^+$) 460 (MH^+, 10%); HRMS $C_{29}H_{34}NO_4^+$ requires 460.2498, found 460.2488; ν_{max}/cm^{-1} (film) 3027, 2975 (C–H), 1728 (C=O).

3.35. Preparation of *tert*-butyl (3*R*,α*S*)-3-(3,4-dimethoxyphenyl)-3-(*N*-benzyl-*N*-α-methylbenzylamino)propanoate 35

Following representative procedure 1, *n*-BuLi (2.5 M, 8.9 mL, 22.2 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (4.5 g, 23.6 mmol) in THF (15 mL) and *tert*-butyl (*E*)-3-(3,4-methoxyphenyl)prop-2-enoate (3.0 g, 6.0 mmol) in THF (15 mL) gave, after column chromatography on silica gel (hexane/Et_2O 2:1), **35** (4.2 g, 79%) as a colourless oil: $[\alpha]_D^{22} = -0.07$ (*c* 0.95, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.26 (9H, s, O^t*Bu*), 1.27 (3H, d, *J* 6.8, C(α)*Me*), 2.47 (1H, dd, $J_{2A,2B}$ 14.6, $J_{2A,3}$ 10.1, C(2)H_AH$_B$), 2.55 (1H, dd, $J_{2B,2A}$ 14.6, $J_{2B,3}$ 4.9, C(2)H$_A$$H_B$), 3.67 (2H, ABq, *J* 14.9, NCH_2), 3.87, 3.90 (2 × 3H, s, O*Me*), 4.01 (1H, q, *J* 6.8, C(α)H), 4.35 (1H, dd, $J_{3,2A}$ 10.1, $J_{3,2B}$ 4.9, C(3)H), 6.80–6.96 (3H, m, *Ar*), 7.17–7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.1, 27.9, 38.2, 50.7, 55.7, 55.8, 57.4, 59.3, 80.2, 110.4, 111.7, 119.9, 126.5, 126.8, 127.8, 128.0, 128.1, 128.1, 134.5, 141.3, 144.3, 147.9, 148.5, 171.3; *m*/*z* (APCI$^+$) 476 (MH^+, 5%), 265 ($MH^+ - C_{15}H_{16}N$, 100%); HRMS $C_{30}H_{38}NO_4^+$ requires 476.2801, found 476.2807; ν_{max}/cm^{-1} (film) 2975 (C–H), 1724 (C=O).

3.36. Preparation of ethyl (3*S*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-4-methyl-pentanoate 36 and (3*S*,α*R*,α′*R*)-*N*-benzyl-*N*-α-methylbenzyl 3-(*N*-benzyl-*N*-α-methylbenzylamino)-4-methyl pentamide 37

Following representative procedure 1, *n*-BuLi (1.6 M, 6.7 mL, 10.7 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (2.34 g, 11.0 mmol) in THF (25 mL) and ethyl (*E*)-4-methyl-pent-2-enoate (980 mg, 6.9 mmol) in THF (25 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 9:1), 36 (1.37 g, 56%) as a colourless oil: $[\alpha]_D^{20} = -2.5$ (*c* 1.0, $CHCl_3$); $C_{23}H_{31}NO_2$ requires C, 78.15; H, 8.8; N, 4.0%, found C, 78.0; H, 8.9; N, 4.0%; δ_H (500 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.7, C(4)*Me*), 1.10 (3H, d, *J* 6.7, C(4)*Me*), 1.22 (3H, t, *J* 7.0, OCH_2CH_3), 1.40 (3H, d, *J* 7.0, C(α)*Me*), 1.73 (1H, m, C(4)H), 1.92 (1H, dd, $J_{2A,2B}$ 15.9, $J_{2A,3}$ 2.5, C(2)H_AH$_B$), 2.13 (1H, dd, $J_{2B,2A}$ 15.9, $J_{2B,3}$ 9.0, C(2)H$_A$$H_B$), 3.25 (1H, m, C(3)$H$), 3.52 (1H, ABq, *J* 14.9, NCH_AH$_B$), 3.80 (1H, ABq, *J* 14.9, NCH$_A$$H_B$), 3.81 (1H, q, *J* 7.0, C(α)H), 4.06 (2H, q, *J* 7.0, OCH_2CH$_3$), 7.22–7.48 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 14.0, 19.5, 20.1, 20.9, 32.7, 34.8, 51.2, 57.9, 58.4, 60.1, 126.8, 127.2, 128.2, 128.4, 128.5, 141.7, 142.4, 173.7; *m*/*z* (CI^+) 354 (MH^+, 100%); ν_{max}/cm^{-1} (film) 1733 (C=O). Further elution afforded **37** (894 mg, 25%) as a white solid: mp 97–100 °C; $[\alpha]_D^{21} = +89.3$ (*c* 1.8, $CHCl_3$); $C_{36}H_{42}N_2O$ requires C, 83.4; H, 8.2; N, 5.4%, found: C, 83.5; H, 8.2; N, 5.3%; δ_H (300 MHz, DMSO-d_6, 353 K) two rotamers 0.78 and 0.93 (2 × 3H, m, C(4)*Me*), 1.32 (6H, d, *J* 6.7, C(α)*Me*), 1.65 (1H, m, C(4)H), 1.83–1.96 (1H, m, C(2)H_AH$_B$), 2.00–2.32 (1H, m, C(2)H$_A$$H_B$), 3.41–3.48 (1H, br s, C(α)H), 3.51 (1H, app t, *J* 6.1, C(3)H), 3.73–3.86 and 4.18–4.26 (2 × 2H, br s, NCH_2), 7.15–7.49 (20H, m, *Ph*); δ_C (125 MHz, DMSO-d_6) two rotamers 17.0, 18.8, 20.0, 20.1, 20.2, 20.4, 20.5, 32.1, 33.0, 33.7, 45.6, 46.8, 51.1, 51.2, 51.6, 54.5, 56.7, 56.9, 57.5, 57.7, 126.1, 126.3, 126.5, 126.7, 126.8, 127.1, 127.2, 127.3, 127.9, 128.9, 128.5, 138.8, 139.9, 141.3, 141.5, 141.6, 141.7, 142.1, 142.2, 171.8, 172.1; *m*/*z* (CI^+) 519 (MH^+, 100%); ν_{max}/cm^{-1} (KBr) 3051, 3045 (C–H), 1646 (C=O).

3.37. Preparation of benzyl (3*S*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-4-methyl-pentanoate 38

Following representative procedure 1, *n*-BuLi (1.6 M, 1.7 mL, 2.8 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (611 mg, 2.9 mmol) in THF (10 mL) and benzyl (*E*)-4-methyl-pent-2-enoate (370 mg, 1.8 mmol) in THF (5 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 9:1), 38 (283 mg, 38%) as a colourless oil: $[\alpha]_D^{20} = -4.8$ (*c* 1.3, $CHCl_3$); $C_{28}H_{33}NO_2$ requires C, 80.9; H, 8.0; N, 3.4%, found C, 80.9; H, 8.3; N, 3.35%; δ_H (500 MHz, $CDCl_3$) 0.84 (3H, d, *J* 6.8, C(4)*Me*), 1.09 (3H, d, *J* 6.6, C(4)*Me*), 1.38 (3H, d, *J* 6.8, C(α)*Me*), 1.71 (1H, m, C(4)H), 1.95 (1H, dd, $J_{2A,2B}$ 16.0, $J_{2A,3}$ 2.5, C(2)H_AH$_B$), 2.13 (1H, dd, $J_{2B,2A}$ 16.0, $J_{2B,3}$ 9.1, C(2)H$_A$$H_B$), 3.27 (1H, m, C(3)$H$), 3.51 (1H, ABq, *J* 15.0, NCH_AH$_B$), 3.78 (1H, ABq, *J* 15.0, NCH$_A$$H_B$), 3.77 (1H, q, *J* 6.8, C(α)H), 5.01 (1H, ABq, *J* 12.3, OCH_AH$_B$), 5.05 (1H, ABq, *J* 12.3, OCH$_A$$H_B$), 7.18–7.46 (15H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 19.5, 20.1, 20.9, 32.6, 34.7, 51.2, 57.8, 58.3, 66.1, 126.8, 127.2, 128.2, 128.4, 128.5, 128.7, 136.3, 141.7, 142.2, 173.4; *m*/*z* (CI^+) 416 (MH^+, 100%); ν_{max}/cm^{-1} (film) 3063, 3029 (C–H), 1734 (C=O), 1146 (C–O). Further elution afforded **37** (271 mg, 29%) as a white solid with spectroscopic properties consistent with those reported above.

3.38. Preparation of *tert*-butyl (3*S*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-4-methyl-pentanoate 39

Following representative procedure 1, *n*-BuLi (1.6 M, 1.25 mL, 2.0 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (450 mg, 2.1 mmol) in THF (25 mL) and *tert*-butyl (*E*)-4-methyl-pent-2-enoate (220 mg, 1.3 mmol) in THF (25 mL) gave, after column chromatography on silica gel (petrol 40–60/Et_2O 4:1), **39** (450 mg, 91%) as a colourless oil: $[\alpha]_D^{24} = -1.9$ (*c* 1.4, $CHCl_3$); $C_{25}H_{35}NO_2$ requires C, 78.7; H, 9.25; N, 3.7%, found: C, 78.8; H, 9.2; N, 3.8%; δ_H (500 MHz, $CDCl_3$) 0.90 (3H, d, *J* 6.8, C(4)*Me*), 1.12 (3H, d, *J* 6.8, C(4)*Me*), 1.41 (3H, d, *J* 7.1, C(α)*Me*), 1.42 (9H, s, O^t*Bu*), 1.67–1.72 (1H, m, C(4)*H*), 1.82 (1H, dd, $J_{2A,2B}$ 16.1, $J_{2A,3}$ 2.1, C(2)H_AH_B), 1.98 (1H, dd, $J_{2B,2A}$ 16.1, $J_{2B,3}$ 9.5, C(2)H_AH_B), 3.24–3.28 (1H, m, C(3)*H*), 3.49 (1H, ABq, *J* 14.2, NCH_AH_B), 3.77 (1H, ABq, *J* 14.2, NCH_AH_B), 3.77 (1H, q, *J* 7.1, C(α)*H*), 7.23–7.48 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 19.5, 20.1, 21.0, 28.0, 32.8, 36.2, 51.2, 57.7, 57.9, 79.9, 126.8, 127.2, 128.5, 141.8, 142.1, 172.8; *m*/*z* (CI^+) 381 (MH^+, 100%); ν_{max}/cm^{-1} (film) 3062, 3027 (C–H), 1729 (C=O).

3.39. One-pot reaction protocol for the preparation of *tert*-butyl (3*R*,α*S*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-4-methyl-pentanoate 39

n-BuLi (2.5 M, 21.9 mL, 54.7 mmol) was added dropwise to a stirred solution of (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (11.9 g, 11.8 mL, 56.5 mmol) and *tert*-butyl (*E*)-4-methyl-pent-2-enoate (6.0 g, 35.3 mmol) in anhydrous THF (100 mL) at −78 °C under nitrogen and stirred for 2 h prior to the addition of saturated aqueous ammonium chloride (10 mL) and warmed to rt. The resultant solution was partitioned between brine and DCM (3 × 100 mL), and the combined organic extracts were concentrated in vacuo. The residue was re-dissolved in DCM (200 mL), washed successively with 10% aqueous citric acid solution (2 × 100 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried and concentrated in vacuo before purification by column chromatography on silica gel (Et_2O/pentane 1:10) to give **39** (12.0 g, 89%) as a colourless oil $[\alpha]_D^{24} = +1.9$ (*c* 1.1, $CHCl_3$) with spectroscopic properties consistent with those reported above.

3.40. Preparation of (*S*)-β-tyrosine methyl ester hydrochloride 41

$Pd(OH)_2$ on carbon (150 mg) was added to a stirred solution of **32** (375 mg, 0.81 mmol) in MeOH/H_2O/AcOH (40:4:1, 11.2 mL) and stirred under a hydrogen atmosphere (1 atm) at rt overnight. After filtration through Celite® (eluent MeOH) and concentration in vacuo, the residue was treated with 1 M aqueous HCl and concentrated in vacuo to give **41** (72 mg, quant) as a white solid; $[\alpha]_D^{20} = +10.6$ (*c* 1.9, H_2O); $C_{10}H_{14}NClO_3$ requires C, 51.8; H, 6.0; N, 6.05%, found C, 52.0; H, 6.2; N, 5.75%; δ_H (200 MHz, D_2O) 2.88 (1H, dd, $J_{2A,2B}$ 16.0, $J_{2A,3}$ 8.1, C(2)H_AH_B), 2.96 (1H, dd, $J_{2B,2A}$ 16.0, $J_{2B,3}$ 6.9, C(2)H_AH_B), 3.45 (3H, s, CO_2Me), 4.53 (1H, m, C(3)*H*), 7.27–6.69 (4H, m, *Ph*); δ_C (50 MHz, D_2O) 37.4, 50.8, 52.4, 116.0, 126.7, 128.8, 156.7, 172.3; *m*/*z* (CI^+) 196 (MH^+−HCl, 15%); ν_{max}/cm^{-1} (film) 1720 (C=O).

3.41. Preparation of (*S*)-β-tyrosine hydrochloride 42

Compound **41** (245 mg, 1.06 mmol) was dissolved in 5 M aqueous HCl (5 mL) and heated to reflux overnight. Concentration in vacuo gave **42** (227 mg, 99%) as a white solid: $[\alpha]_D^{25} = +3.6$ (*c* 1.4, H_2O); lit.[58] (*ent*) $[\alpha]_D^{24} = -3.1$ (*c* 1.65, H_2O); δ_H (200 MHz, D_2O) 2.88 (2H, m, C(2)H_2), 4.44–4.53 (1H, m, C(3)*H*), 7.11–7.25 (4H, m, *Ph*); δ_C (63 MHz, D_2O) 37.6, 115.8, 126.8, 128.6, 156.3, 173.5.

3.42. Alternative preparation of (*S*)-β-tyrosine hydrochloride 42

Following representative procedure 4, **33** (1.56 g, 2.9 mmol) in MeOH (5 mL) and $Pd(OH)_2$/C (1.4 g) at rt gave **42** (441 mg, 76%) as a white powder, which displayed identical spectroscopic properties as those reported above $[\alpha]_D^{25} = +3.2$ (*c* 0.6, H_2O).

3.43. Preparation of *tert*-butyl (*E*)-3-(3,4-dibenzyloxyphenyl)prop-2-enoate 43

n-BuLi (2.5 M, 12.0 mL, 30.0 mmol) was added to a stirred solution of *tert*-butyl diethylphosphonoacetate (7.93 g, 31.4 mmol) in THF (20 mL) and stirred for 30 min before the addition of 3,4-dibenzyloxybenzaldehyde (8.00 g, 25.1 mmol) and allowed to warm to rt overnight. Saturated aqueous ammonium chloride (10 mL) was added and the resultant solution partitioned between brine and DCM (3 × 100 mL) and the combined organic extracts were dried, filtered and concentrated in vacuo. Recrystallisation from Et_2O/hexanes afforded (*E*)-**43** (8.50 g, 81%) as white crystals: mp 59–61 °C; δ_H (400 MHz, $CDCl_3$) 1.27 (9H, s, O^t*Bu*), 4.85 (2 × 2H, s, OCH_2Ph), 5.94 (1H, d, *J* 15.9, C(2)*H*), 6.60–7.18 (13H, m, *Ar*, *Ph*), 7.22 (1H, d, *J* 15.9, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 27.9, 70.5, 70.9, 81.6, 113.2, 113.9, 117.8, 122.4, 126.9, 127.0, 127.6, 127.8, 128.2, 136.5, 136.6, 143.0, 148.6, 150.5, 166.2; *m*/*z* (CI^+) 417.5 (MH^+, 25%), 361.1 (MH^+−C_4H_8, 100); HRMS $C_{27}H_{28}O_4^+$ requires 416.1987, found 416.1993; ν_{max}/cm^{-1} (film) 1694 (C=O), 1640 (C=C).

3.44. Preparation of *tert*-butyl (3*R*,α*S*)-3-(3,4-dibenzyloxyphenyl)-3-(*N*-benzyl-*N*-α-methylbenzylamino)propanoate 44

Following representative procedure 1, *n*-BuLi (2.5 M, 14.2 mL, 35.4 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (7.61 g, 36.0 mmol) in THF (15 mL) and (*E*)-**43** (5.0 g, 12.0 mmol) in THF (15 mL) gave, after column chromatography on silica gel (hexane/Et_2O, 9:1), **44** (7.11 g, 90%) as a colourless oil: $[\alpha]_D^{22} = -2.0$ (*c* 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.19 (3H, d, *J* 6.8, C(α)*Me*), 1.25 (9H, s, O^t*Bu*), 2.40–2.55 (2H, m, C(2)H_2), 3.60 (2H, app s, NCH_2), 3.85 (1H, q, *J* 6.8, C(α)*H*), 4.28–4.31 (1H, m, C(3)*H*), 5.20 (2 × 2H, s, OCH_2Ph), 6.89–7.52 (23H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.6, 27.8, 38.4, 50.7, 57.1, 59.2, 71.2, 71.3, 80.1, 114.3, 115.5, 120.8, 126.4, 126.7, 127.2, 127.3, 127.7, 128.0, 128.1, 128.4, 128.5, 135.1, 137.3, 137.5, 144.2, 147.9, 148.5, 172.0; *m*/*z*

(CI^+) 628.2 (MH^+, 25%); HRMS $C_{42}H_{45}NO_4^+$ requires 628.3427, found 628.3422; ν_{max}/cm^{-1} (film) 1724 (C=O), 1505 (OCH_2Ph).

3.45. Preparation of *tert*-butyl (*R*)-3-(3,4-dihydroxyphenyl)-3-aminopropanoate 45

$Pd(OH)_2$ on carbon (0.25 g, 0.18 mmol) was added to a stirred solution of **44** (1.0 g, 4.0 mmol) in degassed methanol (10 mL) with AcOH (0.5 mL) under 1 atm H_2 and stirred for 16 h. The crude reaction mixture was filtered through Celite® (eluent MeOH) to yield **45** as a yellow oil. Purification via column chromatography on silica gel ($CHCl_3$/MeOH 3:1) afforded **45** (0.37 g, 98%) as yellow oil; $[\alpha]_D^{23} = +1.0$ (*c* 0.70, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.04 (9H, s, O^tBu), 2.58–2.87 (2H, m, C(2)H_2), 4.33–4.37 (C(3)*H*), 6.62–6.72 (3H, m, *Ar*), δ_C (100 MHz, $CDCl_3$) 27.2, 39.5, 51.6, 83.8, 115.3, 116.3, 120.1, 127.4, 144.6, 145.3, 170.6; *m*/*z* (ESI^+) 254 (MH^+, 100%); HRMS $C_{13}H_{19}NO_4^+$ requires 254.1392, found 254.1396; ν_{max}/cm^{-1} (film) 3018 (C–H), 1716 (C=O).

3.46. Preparation of (*R*)-β-DOPA hydrochloride 46·HCl

Ester **45** (0.25 g, 0.99 mmol) was added portionwise to a solution of HCl (g) in Et_2O (10 mL) at 0 °C and stirred for 5 min. The organic solvents were removed in vacuo to afford **46**·HCl (0.22 g, 93%) as an off white solid: $[\alpha]_D^{23} = -5.0$ (*c* 0.50, 6 M HCl); δ_H (400 MHz, CD_3OD) 2.93 (1H, dd, $J_{2A,2B}$ 17.7, $J_{2A,3}$ 6.1, C(2)H_AH_B), 2.95 (1H, dd, $J_{2B,2A}$ 17.7, $J_{2B,3}$ 8.3, C(2)H_AH_B), 4.54 (1H, dd, $J_{3,2B}$ 8.3, $J_{3,2A}$ 6.1, C(3)*H*), 6.78–6.90 (3H, m, *Ar*); δ_C (100 MHz, CD_3OD) 39.5, 53.3, 115.8, 117.1, 120.1, 129.0, 147.5, 148.0, 173.6; *m*/*z* (ESI^+) 198.1 (MH^+, 100); HRMS $C_9H_{12}NO_4^+$ requires 198.0766, found 198.0760; ν_{max}/cm^{-1} (KBr) 3042 (C–H), 1716 (C=O).

3.47. Preparation of *tert*-butyl (*R*)-3-aminopentanoate 47

Following representative procedure 2, **22** (550 mg, 1.5 mmol) in MeOH (5 mL) and Pd/C (305 mg) at 50 °C gave, after Kugelrohr distillation, **47** (245 mg, 95%) as a colourless oil: $[\alpha]_D^{20} = -22.3$ (*c* 1.5, $CHCl_3$); $C_9H_{19}NO_2$ requires C, 62.4; H, 11.05; N, 8.1%, found C, 62.3; H, 11.1; N 7.9%; δ_H (300 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.4, C(5)H_3), 1.45 (9H, s, O^tBu), 1.34–1.46 (2H, m, C(4)H_2), 2.14 (1H, dd, $J_{2A,2B}$ 15.5, $J_{2A,3}$ 8.9, C(2)H_AH_B), 2.37 (1H, dd, $J_{2B,2A}$ 15.5, $J_{2B,3}$ 4.0, C(2)H_AH_B), 3.06 (1H, m, C(3)*H*); δ_C (50 MHz, $CDCl_3$) 10.2, 27.9, 30.1, 43.3, 49.7, 80.3, 172.3; *m*/*z* (CI^+) 174 (MH^+, 36%); ν_{max}/cm^{-1} (film) 3400 (N–H), 1728 (C=O).

3.48. Preparation of *tert*-butyl (*R*)-3-aminoctanoate 48[59]

Following representative procedure 2, **24** (328 mg, 0.8 mmol) in MeOH (5 mL) and Pd/C (150 mg) at rt gave, after purification by column chromatography on silica gel (Et_2O/MeOH 4:1), **48** (142 mg, 83%) as a colourless oil: $[\alpha]_D^{20} = -14.3$ (*c* 0.7, $CHCl_3$); $C_{12}H_{25}NO_2$ requires C, 66.9; H, 11.7; N, 6.5%, found C, 66.6; H, 11.7; N, 6.8%; δ_H (500 MHz, $CDCl_3$) 0.87 (3H, t, *J* 6.9, C(8)H_3), 1.43 (9H, s, O^tBu), 1.52 (2H, br s, NH_2), 1.23–1.56 (8H, m, CH_3C(7)H_2C(6)H_2C(5)H_2C(4)H_2), 2.15 (1H, dd, $J_{2A,2B}$ 15.5, $J_{2A,3}$ 8.8, C(2)H_AH_B), 2.35 (1H, dd, $J_{2B,2A}$ 15.5, $J_{2B,3}$ 4.0, C(2)H_AH_B), 3.11 (1H, m, C(3)*H*); δ_C (50 MHz, $CDCl_3$) 13.8, 22.4, 25.6, 28.0, 31.7, 37.3, 43.7, 48.3, 80.5, 172.4; *m*/*z* (CI^+) 215 (MH^+, 50%); ν_{max}/cm^{-1} (film) 3383 (N–H), 1728 (C=O).

3.49. Preparation of *tert*-butyl (*S*)-3-phenyl-3-aminopropanoate 49

Following representative procedure 2, **27** (1.6 g, 3.8 mmol) in AcOH (8 mL) and Pd/C (510 mg) at rt gave, after purification by column chromatography on silica gel (petrol/Et_2O 1:1), **49** (705 mg, 84%) as a colourless oil: $[\alpha]_D^{20} = -21.0$ (*c* 1.0, $CHCl_3$); $C_{13}H_{19}NO_2$ requires C, 70.6; H, 8.65; N, 6.3%, found C, 70.55; H, 8.3; N, 6.4%; δ_H (300 MHz, $CDCl_3$) 1.42 (9H, s, O^tBu), 1.75 (2H, s, NH_2), 2.59 (2H, app d, C(2)H_2), 4.38 (1H, t, *J* 6.8, C(3)*H*), 7.25–7.38 (5H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 27.9, 45.2, 52.7, 80.7, 126.5, 127.4, 128.7, 144.9, 171.6; *m*/*z* (CI^+) 222 (MH^+, 50%); ν_{max}/cm^{-1} (film) 1724 (C=O).

3.50. Preparation of *tert*-butyl (*S*)-3-(2-methoxyphenyl)-3-aminopropanoate 50

Following representative procedure 2, **29** (525 mg, 1.2 mmol) in AcOH (5 mL) and Pd/C (155 mg) at rt gave, after purification by column chromatography on silica gel (DCM/MeOH 9:1), **50** (268 mg, 91%) as a colourless oil; $[\alpha]_D^{20} = -20.0$ (*c* 0.7, $CHCl_3$); $C_{14}H_{21}NO_3$ requires C, 66.9; H, 8.4; N, 5.6%, found C, 67.0; H, 8.7; N, 5.8%; δ_H (300 MHz, $CDCl_3$) 1.40 (9H, s, O^tBu), 1.93 (2H, br s, NH_2), 2.59 (1H, dd, $J_{2A,2B}$ 15.4, $J_{2A,3}$ 8.8, C(2)H_AH_B), 2.70 (1H, dd, $J_{2B,2A}$ 15.4, $J_{2B,3}$ 5.0, C(2)H_AH_B), 3.84 (3H, s, O*Me*), 4.56 (1H, dd, $J_{3,2A}$ 8.8, $J_{3,2B}$ 5.0, C(3)*H*), 6.83–6.94 (2H, m, Ar(3)*H*, Ar(5)*H*), 7.18–7.32 (2H, m, Ar(4)*H*, Ar(6)*H*); δ_C (50 MHz, $CDCl_3$) 27.9, 43.0, 48.4, 55.2, 80.5, 110.6, 120.8, 127.2, 128.3, 132.7, 157.0, 172.1; *m*/*z* (CI^+) 251(MH^+, 100%); ν_{max}/cm^{-1} (film) 1724 (C=O).

3.51. Preparation of *tert*-butyl (*S*)-3-(4-methoxyphenyl)-3-aminopropanoate 51

Following representative procedure 2, **31** (120 mg, 0.27 mmol) in AcOH (5 mL) and Pd/C (55 mg) at rt gave, after purification by column chromatography on silica gel (DCM/MeOH 95:5), **51** (62 mg, 91%) as a colourless oil: $[\alpha]_D^{20} = -14.1$ (*c* 0.8, $CHCl_3$); $C_{14}H_{21}NO_3$ requires C, 66.9; H, 8.4; N, 5.6%, found: C, 66.7; H, 8.7; N, 5.3%; δ_H (300 MHz, $CDCl_3$) 1.40 (9H, s, O^tBu), 1.84 (2H, s, NH_2), 2.55 (2H, m, C(2)H_2), 3.77 (3H, s, O*Me*), 4.32 (1H, t, *J* 7.4, C(3)*H*), 6.84 (2H, m, Ar(3)*H*, ArPh(5)*H*), 7.26 (2H, m, Ar(2)*H*, Ar(4)*H*); δ_C (50 MHz, $CDCl_3$) 27.9, 45.3, 50.0, 55.2, 80.7, 114.0, 127.6, 159.1, 171.7; *m*/*z* (CI^+) 251 (MH^+, 35%); ν_{max}/cm^{-1} (film) 1724 (C=O).

3.52. Preparation of *tert*-butyl (*S*)-4-methyl-3-aminopentanoate 52

Following representative procedure 2, **39** (1.3 g, 3.48 mmol) in AcOH (5 mL) and Pd/C (530 mg) at rt gave,

after Kugelrohr distillation, **52** (510 mg, 88%) as a colourless oil: $[\alpha]_D^{20} = -25.8$ (*c* 3.4, $CHCl_3$); $C_{10}H_{21}NO_2$ requires C, 64.1; H, 11.3; N, 7.5%, found C, 64.1; H, 11.2; N, 7.5%; δ_H (300 MHz, $CDCl_3$) 0.88 and 0.89 ($2 \times 3H$, d, *J* 6.8, C(4)*Me*$_2$), 1.44 (9H, s, O^t*Bu*), 1.58 (1H, m, C(4)*H*), 2.13 (1H, dd, $J_{2A,2B}$ 15.4, $J_{2A,3}$ 9.7, C(2)H_AH_B), 2.36 (1H, dd, $J_{2B,2A}$ 15.4, $J_{2B,3}$ 3.4, C(2)H_AH_B), 2.96 (1H, m, C(3)*H*); δ_C (50 MHz, $CDCl_3$) 17.6, 18.6, 27.9, 33.1, 40.8, 53.5, 80.4, 172.7; *m*/*z* (CI^+) 188 (MH^+, 50%); ν_{max}/cm^{-1} (film) 3385 (N–H), 1728 (C=O).

3.53. Preparation of (*R*)-β-aminopentanoic acid 53

Following representative procedure 3, **47** (120 mg, 0.7 mmol) and TFA (1 mL) gave, after purification by ion-exchange chromatography, **53** (73 mg, 89%) as a white solid with spectroscopic properties consistent with those of the literature: $[\alpha]_D^{20} = -40.8$ (*c* 0.8, H_2O), lit.[60] $[\alpha]_D^{23} = -37.0$ (*c* 0.7, H_2O).

3.54. Preparation of (*R*)-β-aminooctanoic acid 54

Following representative procedure 3, **48** (62 mg, 0.3 mmol) and TFA (1 mL) gave, after purification by ion-exchange chromatography, **54** (45 mg, 95%) as a white solid with spectroscopic properties consistent with those of the literature: $[\alpha]_D^{24} = -28.3$ (*c* 0.5, H_2O), lit.[61] $[\alpha]_D^{20} = -31.1$ (*c* 0.51, H_2O).

3.55. Preparation of (*S*)-β-phenylalanine 55

Following representative procedure 3, **49** (505 mg, 2.3 mmol) and TFA (3 mL) gave, after purification by ion-exchange chromatography, **55** (364 mg, 96%) as a white solid with spectroscopic properties consistent with those of the literature: mp 227–229 °C; $[\alpha]_D^{20} = -7.0$ (*c* 1.0, H_2O), lit.[62] $[\alpha]_D^{22} = -6.3$ (*c* 0.8, H_2O).

3.56. Preparation of (*S*)-β-(2-methoxyphenyl)-β-amino propionic acid 56

Following representative procedure 3, **50** (175 mg, 0.7 mmol) and TFA (1 mL) gave, after purification by ion-exchange chromatography, **56** (116 mg, 85%) as a white solid: mp 208–210 °C; $[\alpha]_D^{20} = +15.5$ (*c* 1.0, H_2O); δ_H (300 MHz, D_2O) 2.50–2.70 (2H, m, C(2)H_2), 3.67 (3H, s, O*Me*), 4.41–4.52 (1H, m, C(3)*H*), 6.7–7.3 (4H, m, *Ph*); δ_C (50 MHz, D_2O) 38.1, 40.5, 55.1, 111.6, 120.0, 123.1, 128.3, 130.0, 157.0, 178.0; *m*/*z* (ESI^-) 194 ($M-H^-$, 100%); HRMS $C_{10}H_{12}NO_3^-$ requires 194.0817, found 194.0816; ν_{max}/cm^{-1} (KBr) 2966 (N–H, O–H), 1612 (C=O).

3.57. Preparation of (*S*)-β-tyrosine methyl ether 57

Following representative procedure 3, **51** (280 mg, 1.1 mmol) and TFA (5 mL) gave, after purification by ion-exchange chromatography, **57** (206 mg, 96%) as a white solid with spectroscopic properties consistent with those of the literature: $[\alpha]_D^{20} = -1.4$ (*c* 0.2, H_2O), lit.[18] $[\alpha]_D^{20} = -7.2$ (*c* 1.0, H_2O).

3.58. Preparation of (*S*)-β-leucine 58

Following representative procedure 3, **52** (380 mg, 2.1 mmol) and TFA (3 mL) gave, after purification by ion-exchange chromatography, **58** (258 mg, 97%) as a white solid with spectroscopic properties consistent with those of the literature: $[\alpha]_D^{24} = -48.2$ (*c* 1.1, H_2O), lit.[33] (*ent*) $[\alpha]_D^{22} = +40.3$ (*c* 1.02, H_2O).

3.59. Preparation of (*R*)-β-aminobutanoic acid 59

Following representative procedure 4, **15** (2.11 g, 5.44 mmol) in EtOH (5 mL) and $Pd(OH)_2$ on C (1.0 g) at rt gave, after recrystallisation (MeOH), **59** (379 mg, 68%) as white needles with spectroscopic properties consistent with those of the literature: $[\alpha]_D^{19} = -39.8$ (*c* 0.5, H_2O), lit.[63] (*ent*) $[\alpha]_D^{18} = +38.8$ (*c* 0.48, H_2O).

3.60. Preparation 2 of (*R*)-3-aminopentanoic acid 53

Following representative procedure 4, **15** (370 mg, 0.96 mmol) in EtOH (5 mL) and Pd/C (190 mg) at rt gave (*R*)-3-aminopentanoic acid hydrochloride **53**·HCl (142 mg, 98%) as a white powder: mp 137–139 °C; $[\alpha]_D^{20} = -22.9$ (*c* 0.8, H_2O); $C_5H_{12}NO_2Cl$ requires C, 39.1; H, 7.9; N, 9.1%, found: C, 39.2; H, 8.1; N, 8.7%; δ_H (300 MHz, D_2O) 0.72 (3H, t, *J* .4, C(5)H_3), 1.46 (2H, app q, *J* 7.0, C(4)*H*), 2.43 (1H, dd, $J_{2A,2B}$ 17.7, $J_{2A,3}$ 8.1, C(2)H_AH_B), 2.58 (1H, dd, $J_{2B,2A}$ 17.7, $J_{2B,3}$ 4.4, C(2)H_AH_B), 3.31 (1H, m, C(3)*H*); δ_C (50 MHz, D_2O) 8.5, 24.9, 35.3, 49.3, 174.5; *m*/*z* (CI^+) 117 (MH^+, 100%); ν_{max}/cm^{-1} (film) 3400 (N–H), 1703 (C=O), 1613. Purification by ion-exchange chromatography gave (*R*)-3-aminopentanoic acid **53** (90 mg, 90%) as a white solid with spectroscopic properties consistent with those of the literature: $[\alpha]_D^{20} = -40.0$ (*c* 1.5, H_2O); lit.[60] $[\alpha]_D^{23} = -37.0$ (*c* 0.7, H_2O).

3.61. Preparation 2 of (*R*)-β-aminoctanoic acid 54

Following representative procedure 4, **23** (432 mg, 1.08 mmol) in AcOH (5 mL) and Pd/C (228 mg) at rt gave (*R*)-β-aminoctanoic acid hydrochloride **54**·HCl (190 mg, quantitative) as a white powder: mp 103–104 °C; $[\alpha]_D^{20} = -16.6$ (*c* 1.1, H_2O); $C_8H_{18}NO_2Cl$ requires C, 49.1; H, 9.3; N, 7.2%, found C, 49.0; H, 9.45; N, 6.95%; δ_H (200 MHz, D_2O) 0.62 (3H, t, *J* 6.3, C(8)H_3), 0.99–1.21 (6H, m, $CH_3C(7)H_2C(6)H_2C(5)H_2$), 1.44 (2H, m, C(4)$H_2$), 2.43 (1H, dd, $J_{2A,2B}$ 17.5, $J_{2A,3}$ 7.9, C(2)H_AH_B), 2.60 (1H, dd, $J_{2B,2A}$ 17.5, $J_{2B,3}$ 4.6, C(2)H_AH_B), 3.37 (1H, m, C(3)*H*); δ_C (50 MHz, D_2O) 13.0, 21.4, 23.7, 30.3, 31.5, 35.6, 48.1, 174.4; *m*/*z* 159 (MH^+, 100%); ν_{max}/cm^{-1} (KBr) 1710 (C=O), 1605. Purification by ion-exchange chromatography gave (*R*)-β-aminoctanoic acid **54** (111 mg, 88%) as a white solid with spectroscopic properties consistent with those of the literature: $[\alpha]_D^{20} = -28.6$ (*c* 0.4, H_2O); lit.[61] $[\alpha]_D^{20} = -31.1$ (*c* 0.51, H_2O).

3.62. Preparation 2 of (*S*)-β-(2-methoxyphenyl)-β-amino-propionic acid 56

Following representative procedure 4, **28** (35 mg, 0.07 mmol) in AcOH (5 mL) and Pd/C (45 mg) at rt gave

(*S*)-β-(2-methoxyphenyl)-β-aminopropionic acid hydrochloride **56**·HCl (20 mg, 92%) as a white powder: $[\alpha]_D^{20} = +20.0$ (*c* 0.5, H_2O); $C_{10}H_{14}NO_3Cl$ requires C, 51.8; H, 6.1; N, 6.05%, found: C, 51.9; H, 6.0; N, 6.0%; δ_H (300 MHz, D_2O) 2.87 (1H, dd, $J_{2A,2B}$ 17.1, $J_{2A,3}$ 6.5, C(2)H_AH_B), 3.00 (1H, dd, $J_{2B,2A}$ 17.1, $J_{2B,3}$ 6.1, C(2)H_AH_B), 3.69 (3H, s, O*Me*), 4.65 (1H, m, C(3)*H*), 6.83–7.22 (4H, m, *Ph*); δ_C (50 MHz, D_2O) 35.8, 48.9, 55.5, 111.7, 121.0, 122.2, 128.9, 131.3, 157.1, 173.9; *m*/*z* (CI^+) 196 (MH^+, 100%); ν_{max}/cm^{-1} (KBr) 1715 (C=O), 1605. Purification by ion-exchange chromatography gave (*S*)-3-(2-methoxyphenyl)-β-phenylpropionic acid **56** (95%) with spectroscopic properties consistent with those reported above: $[\alpha]_D^{20} = +14.1$ (*c* 1.0, H_2O).

3.63. Preparation of (*S*)-β-tyrosine methyl ether 57

Following representative procedure 4, **30** (431 mg, 0.9 mmol) in AcOH (5 mL) and Pd/C (80 mg) at rt gave (*S*)-β-(4-methoxyphenyl)-β-aminopropionic acid hydrochloride **57**·HCl[64] (153 mg, 87%) as a white powder: mp 166–168 °C (decomp); $[\alpha]_D^{20} = +2.7$ (*c* 0.5, H_2O); $C_{10}H_{14}NO_3Cl$ requires C, 51.8; H, 6.1; N, 6.05%, found C, 51.6; H, 6.2; N, 6.25%; δ_H (500 MHz, D_2O) 2.96 (1H, dd, $J_{2A,2B}$ 17.1, $J_{2A,3}$ 6.8, C(2)H_AH_B), 3.08 (1H, dd, $J_{2B,2A}$ 17.1, $J_{2B,3}$ 7.8, C(2)H_AH_B), 3.72 (3H, s, O*Me*), 4.56 (1H, m, C(3)*H*), 6.95 (2H, d, *J* 8.8, Ar(3)*H* and Ar(5)*H*), 7.32 (2H, d, *J* 8.8, Ar(2)*H* and Ar(6)*H*); δ_C (50 MHz, D_2O) 37.4, 50.7, 55.1, 114.6, 125.5, 128.7, 159.6, 173.7; *m*/*z* 195 (MH^+, 55%), ν_{max}/cm^{-1} (KBr) 1723 (C=O), 1616. Purification by ion-exchange chromatography gave (*S*)-β-tyrosine methyl ether **57** (63%) with spectroscopic properties consistent with those reported above: $[\alpha]_D^{20} = -1.0$ (*c* 0.3, H_2O).

3.64. Preparation 2 of (*S*)-β-Leucine 58

Following representative procedure 4, **38** (225 mg, 0.61 mmol) in AcOH (5 mL) and Pd/C (80 mg) at rt gave (*S*)-β-leucine hydrochloride **58**·HCl (90 mg, 87%) as a white powder: $C_6H_{14}NO_2Cl$ requires C, 43.0; H, 8.4; N, 8.4%, found C, 43.0; H, 8.65; N, 8.0%; δ_H (200 MHz, D_2O) 0.77, 0.78 (2 × 3H, d, *J* 6.8, C(4)(CH_3)$_2$), 1.79 (1H, m, C(4)*H*), 2.47 (1H, dd, $J_{2A,2B}$ 17.7, $J_{2A,3}$ 8.9, C(2)H_AH_B), 2.63 (1H, dd, $J_{2B,2A}$ 17.7, $J_{2B,3}$ 8.9, C(2)H_AH_B) 3.27 (1H, m, C(3)*H*); δ_C (50 MHz, D_2O) 16.6, 17.0, 29.6, 33.1, 53.2, 174.8; *m*/*z* (CI^+) 131 (MH^+, 100); ν_{max}/cm^{-1} (KBr) 1710 (C=O), 1603. Purification by ion-exchange chromatography gave (*S*)-β-leucine **58** (97%) with spectroscopic properties consistent with those reported above: $[\alpha]_D^{20} = -48.6$ (*c* 1.0, H_2O).

3.65. Preparation of *tert*-butyl (*E*)-6-(*N*,*N*-di-*tert*-butoxycarbonylamino)hex-2-enoate 61

To a stirred solution of pyrrolidinone **2** (2.00 g, 10.8 mmol) in THF (40 mL) under N_2 at −78 °C was added DIBAL-H (1.0 M in hexanes, 16.2 mL, 16.2 mmol) dropwise. The resulting solution was stirred at −78 °C for 2 h and then saturated aqueous KOAc (20 mL) was added. The mixture was poured into Et_2O/saturated aqueous NH_4Cl (3:1, 200 mL) and stirred at rt for 18 h. The resulting slurry was filtered through Celite®, the phases were separated, and the aqueous phase was extracted with further Et_2O (2 × 100 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (2 × 100 mL), dried (K_2CO_3), filtered and the solvent was removed in vacuo. Purification via column chromatography (EtOAc/40–60 petrol 1:4) afforded *N*-*tert*-butoxycarbonyl-2-hydroxypyrrolidine (1.70 g, 84%) as a colourless oil with spectroscopic properties consistent with those of the literature:[52] δ_H (400 MHz, $CDCl_3$) rotamers 1.39 and 1.42 (2 × 9H, s, O^t*Bu*), 1.72–204 (4H, m, C(2)H_2C(3)H_2), 3.14–3.26 (1H, m, C(4)H_AH_B), 3.35–3.47 (1H, m, C(4)H_AH_B), 5.27–5.41 (1H, m, C(1)*H*); *m*/*z* (CI^+) 170 ($(M-OH)^+$, 40%), 114 ($(M-O^tBu)^+$, 12), 70 (100); ν_{max}/cm^{-1} (film) 3431 (O–H), 2977 (C–H), 1684 (C=O). To a stirred solution of *N*-*tert*-butoxycarbonyl-2-hydroxypyrrolidine (1.00 g, 5.35 mmol) in toluene (50 mL) under Ar was added (*tert*-butoxycarbonylmethyl)triphenylphosphorane (2.01 g, 5.35 mmol), and the mixture heated to reflux for 18 h. After concentration in vacuo, purification via column chromatography (Et_2O/pentane 15:85) afforded *tert*-butyl (*E*)-6-(*N*-*tert*-butoxycarbonylamino)hex-2-enoate (1.16 g, 76%, >99:1 *E*:*Z*) as a colourless oil that solidified on standing: mp 59–60 °C; δ_H (400 MHz, $CDCl_3$) 1.40 and 1.44 (2 × 9H, s, O^t*Bu*), 1.57–1.64 (2H, m, C(5)H_2), 2.14–2.20 (2H, m, C(4)H_2), 3.42–3.47 (2H, m, C(6)H_2), 4.65 (1H, br s, N*H*), 5.72 (1H, dt, *J* 15.7, 1.5, C(2)*H*), 6.79 (1H, dt, *J* 15.7, 7.0, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.1, 28.3, 28.5, 29.2, 40.0, 79.1, 80.1, 123.5, 146.6, 155.9, 165.8; *m*/*z* (EI^+) 349 ($(MNaMeCN)^+$, 100%), 308 (MNa^+, 55), 286 (MH^+, 10); HRMS $C_{14}H_{27}NO_4Na^+$ requires 308.1838, found 308.1832; ν_{max}/cm^{-1} (film) 3365 (N–H), 2978 (C–H), 1715 (C=O), 1695 (C=O), 1652 (C=C), 1520 (C=O). To a stirred solution of *tert*-butyl (*E*)-6-(*N*-*tert*-butoxycarbonylamino)hex-2-enoate (800 mg, 2.81 mmol) in MeCN (7 mL) under Ar were added Boc_2O (1.22 g, 5.61 mmol) and DMAP (84 mg, 0.70 mmol). The mixture was stirred at rt for 18 h, after which time the volatile material was removed in vacuo. Purification via column chromatography on silica gel (Et_2O/pentane 1:10) afforded **61** (953 mg, 88%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, O^t*Bu*), 1.50 (18H, s, 2 × O^t*Bu*), 1.72 (2H, quintet, *J* 7.4, C(5)H_2), 2.15–2.20 (2H, m, C(4)H_2), 3.58 (2H, t, *J* 7.3, C(6)H_2), 5.74 (1H, dt, *J* 15.6, 1.4, C(2)*H*), 6.83 (1H, dt, *J* 16.0, 6.8, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 27.4, 28.0, 28.1, 29.2, 45.8, 80.1, 82.2, 123.4, 146.6, 152.5, 165.8; *m*/*z* (EI^+) 793 (M_2Na^+, 100%), 408 (MNa^+, 35), 403 (MNH_4^+, 20); HRMS $C_{18}H_{35}NO_6Na^+$ requires 408.2362, found 408.2358; ν_{max}/cm^{-1} (film) 2980 (C–H), 1793, 1751, 1718, 1701 (C=O), 1654 (C=C).

3.66. Preparation of *tert*-butyl (3*R*,α*R*)-3-(*N*-benzyl-*N*-[α-methylbenzyl]amino)-6-(*N*′,*N*′-di-*tert*-butoxycarbonylamino)hexanoate 63 and *tert*-butyl (*E*)-6-(*N*,*N*-di-*tert*-butoxycarbonylamino)hex-3-enoate 62

Following representative procedure 1, *n*-BuLi (1.6 M, 0.45 mL, 0.72 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (164 mg, 0.78 mmol) in THF (10 mL) and **61** (100 mg, 0.26 mmol) in THF (10 mL) gave, after column chromatography on silica gel (30–40 petrol/Et_2O 19:1), **62** (6 mg, 6%) as a colourless oil: δ_H (400 MHz; $CDCl_3$)

1.45, (9H, s, O^t*Bu*), 1.52 (18H, s, 2 × O^t*Bu*), 2.31–2.36 (2H, m, *J* 7.4, C(5)H_2), 3.03 (2H, dd, *J* 7.0, 1.1, C(2)H_2), 3.58–3.62 (2H, m, C(6)H_2), 5.54 (1H, m, C(4)*H*), 5.64 (1 H, m, C(3)*H*); δ_C (100 MHz; $CDCl_3$) 27.2, 28.1, 34.1, 45.5, 80.5, 82.2, 124.2, 128.4, 152.5; *m*/*z* (ESI$^+$) 793 (M_2Na^+, 68%), 408 (MNa^+, 100); HRMS $C_{18}H_{35}NO_6Na^+$ requires 408.2362, found 408.2360; ν_{max}/cm^{-1} (film) 2979 (C–H), 1790, 1732, 1695 (C=O), 1602 (C=C). Further elution afforded a mixed fraction of β-amino ester **63** and alkene **62** (4 mg, 74:26). Further elution then afforded **63** (67 mg, 44%, >95% de) as a colourless oil: $[\alpha]_D^{22} = +6.4$ (*c* 0.75, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 1.25–1.63 (3H, m obscured, C(5)H_AH_B and C(4)H_2), 1.35 (3H, d, *J* 7.0, C(α)*Me*), 1.40 (9H, s, O^t*Bu*), 1.51 (18H, s, 2 × O^t*Bu*), 1.83–1.88 (2H, m, C(2)H_2), 1.96 (1H, m, C(5)H_AH_B), 3.33 (1H, m, C(3)*H*), 3.48 (1H, d, *J* 14.9, PhCH_AH_B), 3.53–3.63 (2H, m, C(6)H_2), 3.77 (1H, d, *J* 14.5, PhCH_AH_B), 3.81 (1H, q, *J* 6.9, C(α)*H*), 7.21–7.43 (10H, m, *Ph*); δ_C (100 MHz; $CDCl_3$) 20.1, 27.2, 28.0, 28.1, 30.9, 37.9, 46.6, 50.1, 53.8, 57.8, 79.9, 81.9, 126.6, 126.9, 127.9, 128.1, 128.2, 141.5, 142.6, 152.6, 171.9; *m*/*z* (ESI$^+$) 619 (MNa^+, 45%), 597 (MH^+, 100); HRMS $C_{35}H_{53}N_2O_6^+$ requires 597.3904, found 597.3898; ν_{max}/cm^{-1} (film) 2977 (C–H), 1950, 1876, 1789, 1747, 1723, 1694 (C=O).

3.67. Preparation of *tert*-butyl (*R*)-3-amino-6-(*N*,*N*-di-*tert*-butoxycarbonylamino)hexanoate 64

Following representative procedure 1, *n*-BuLi (2.5 M, 0.67 mL, 1.66 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (395 mg, 1.87 mmol) in THF (10 mL) and **61** (400 mg, 1.04 mmol) in THF (20 mL) gave a 77:23 mixture of β-amino ester **63** and alkene **62**. This material was then dissolved in MeOH (20 mL) under N_2, NH_4HCO_2 (500 mg, 7.94 mmol) and 10% Pd on C (250 mg) were added, and the mixture was stirred and heated to reflux for 48 h. The mixture was allowed to cool, aqueous NaOH (1 M, 10 mL) added, and the mixture filtered through Celite®, eluting with MeOH (300 mL). The MeOH was removed in vacuo, further aqueous NaOH (1 M, 50 mL) was added, and the organic material was extracted with DCM (3 × 75 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered and the solvent was removed in vacuo. Purification via column chromatography on silica gel (EtOAc/30–40 petrol 1:9, then MeOH/DCM 1:9) afforded **64** as a pale yellow oil (211 mg, 51%): $[\alpha]_D^{23} = -5.7$ (*c* 1.08, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 1.32–1.43 (2H, m, C(5)H_2), 1.44 (9H, s, O^t*Bu*), 1.49 (18H, s, 2 × O^t*Bu*), 1.53–1.73 (2H, m, C(4)H_2), 2.04 (2H, br s, NH_2), 2.19 and 2.39 (2H, ABX system, AB part, J_{AB} 15.8, J_{AX} 9.1, J_{BX} 3.8, C(2)H_2), 3.16 (1H, m, C(3)*H*), 3.52–3.70 (2H, m, C(6)H_2); δ_C (100 MHz; $CDCl_3$) 25.5, 28.1, 34.2, 43.4, 46.2, 48.1, 80.7, 82.2, 152.6, 171.8; *m*/*z* (EI$^+$) 827 (M_2Na^+, 20%), 805 (M_2H^+, 100), 403 (MH^+, 95), 303 ((MH−Boc)$^+$, 25); HRMS $C_{20}H_{39}N_2O_6^+$ requires 403.2808, found 403.2810; ν_{max}/cm^{-1} (film) 3380 (N–H), 2978 (C–H), 1784, 1728, 1697 (C=O).

3.68. Preparation of (*R*)-β-lysine 65

To a stirred solution of **64** (61 mg, 0.15 mmol) in DCM (1 mL) was added TFA (1 mL) and the mixture stirred at rt for 1 h, after which time the volatile material was removed in vacuo. The residue was dissolved in water (1 mL), the pH adjusted to 8 with aqueous NaOH (1 M), and this material was purified by ion-exchange chromatography to afford the title compound **65** as a pale yellow viscous oil (23 mg, quant): $[\alpha]_D^{21} = -19.3$ (*c* 0.63, 1 M HCl), lit.[50] $[\alpha]_D = -19.5$ (*c* 1.0, 1 M HCl); δ_H (400 MHz; D_2O) 1.46–1.67 (4H, m, C(5)H_2C(4)H_2), 2.26 and 2.36 (2H, ABX system, AB part, J_{AB} 15.6, J_{AX} 7.5, J_{BX} 6.6, C(2)H_2), 2.88 (2H, t, *J* 7.4, C(6)H_2), 3.25 (1H, m, C(3)*H*); δ_C (100 MHz; D_2O) 24.2, 31.4, 39.7, 42.1, 48.8, 179.9; *m*/*z* (CI$^+$) 147 (MH^+, 30%), 129 ((M−OH)$^+$, 80), 112 (44), 70 (100); ν_{max}/cm^{-1} (film) 3352 (N–H), 2160 (NH_3^+), 1637 (N–H bending), 1562 (CO_2^-), 1401 (CO_2^-).

Acknowledgements

We thank the Ministerio de Educacion y Ciencias and the British Council for a Fleming Fellowship (N.M.G.) and New College, Oxford, for a Junior Research Fellowship (A.D.S.).

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