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Cyclic β-amino acid derivatives: synthesis *via* lithium amide promoted tandem asymmetric conjugate addition–cyclisation reactions

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The product distribution upon conjugate addition of homochiral lithium *N*-benzyl-*N*-α-methylbenzylamide to dimethyl-(*E*,*E*)-nona-2,7-dienedioate can be controlled to give either the cyclic 1,2-*anti*-1,6-*anti*-β-amino ester (derived from conjugate addition and intramolecular enolate cyclisation) or the acyclic bis-β-amino ester derivative (derived from double conjugate addition) in high de. The introduction of a protected nitrogen functionality into the diester skeleton facilitates, after conjugate addition and intramolecular enolate cyclisation, the asymmetric construction of piperidines in high de; variation in the *N*-protecting group indicates that the highest stereoselectivity is observed with α-branched *N*-substituents. Tandem conjugate addition–aldol reactions can also be achieved stereoselectively, with lithium amide conjugate addition to ε- and ζ-oxo-α,β-unsaturated esters giving the corresponding five and six membered cyclic β-amino esters in high de. *N*-deprotection by hydrogenolysis of the products arising from these reactions furnishes a range of polyfunctionalised transpentacin and transhexacin derivatives in high de and ee.

Introduction

Synthetic design in organic chemistry demands efficiency in terms of minimisation of the number of steps required for the preparation of molecules of structural complexity. Tandem reaction sequences permit relatively complex structures to be constructed in a small number of synthetic steps.[1] Within this area, the conjugate addition of a nucleophile to an α,β-unsaturated system and intramolecular cyclisation of the resultant enolate onto an internal electrophilic site has been studied extensively as a method for the stereocontrolled construction of three- to seven-membered cyclic systems from acyclic precursors.[2] A variety of synthetic protocols have been developed that use this strategy for the preparation of enantiomerically pure cyclic derivatives.[3] In this area, Yamamoto *et al.* have previously demonstrated that addition of achiral lithium *N*-benzyl-*N*-trimethylsilylamide to dimethyl-(*E*,*E*)-nona-2,7-dienedioate facilitates tandem conjugate addition and diastereoselective intramolecular cyclisation,[4] while conjugate addition to the enantiomerically pure dimethyl ester derivative promotes the transformation in a diastereo- and enantioselective fashion.[5] Previous work from this laboratory has demonstrated extensively that the conjugate addition of homochiral lithium amides derived from α-methylbenzylamine to α,β-unsaturated esters allows the highly diastereoselective preparation of *N*-protected β-amino esters.[6] This methodology has been extended recently to the conjugate addition and concomitant intramolecular cyclisation of diester derivatives of (*E*,*E*)-octa-2,6-dienedioic acid, allowing the preparation of the stereoisomers of 2-amino-5-carboxymethyl-cyclopentane-1-carboxylate **3**–**6** in enantiomerically pure form (Fig. 1).[7]

In order to demonstrate further the versatility of this lithium amide methodology, a study concerned with the compatability of a range of ε- and ζ-functionalised α,β-unsaturated esters to participate in conjugate addition–cyclisation reactions was undertaken.[8] It was envisaged that lithium amide conjugate addition and subsequent intramolecular cyclisation of the *in situ*-formed β-amino enolate onto either an α,β-unsaturated ester or aldehyde functionality would give rise to a range of polysubstituted carbocyclic pentacin and hexacin derivatives that would be of interest as scaffolds for synthetic peptide design and for incorporation into novel β-peptide architectures.[9] Furthermore, the incorporation of a protected nitrogen functionality within the acceptor framework would lead, after conjugate addition and cyclisation, to the synthesis of homochiral piperidines (Fig. 2).

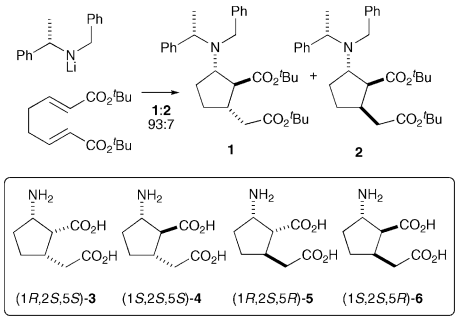

Fig. 1 Conjugate addition and cyclisation for the synthesis of the stereoisomers of 2-amino-5-carboxymethyl-cyclopentane-1-carboxylate.

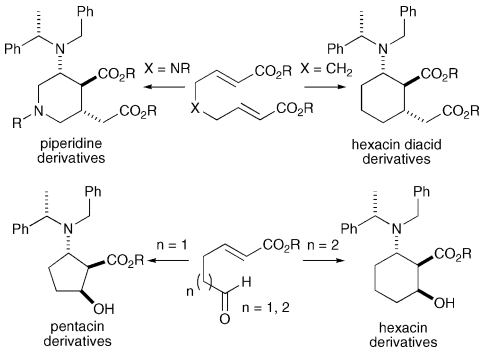

Fig. 2 Proposed conjugate addition–cyclisation reactions for the synthesis of the pentacin, hexacin and piperidine derivatives.

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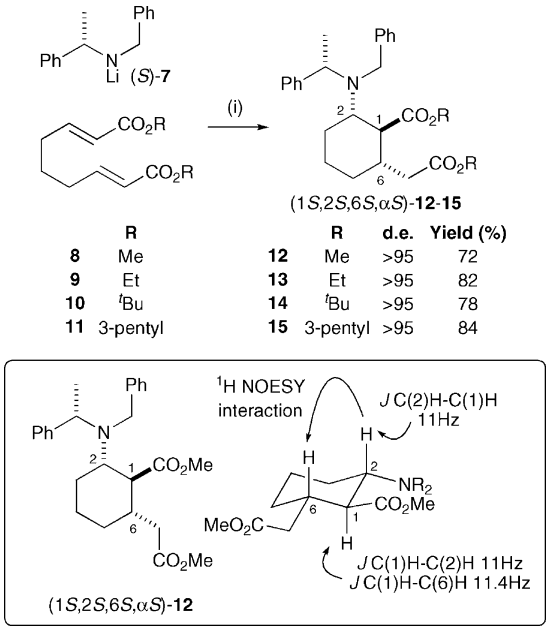
We report herein our full results in this area, in which we delineate the scope and limitations of this methodology, part of which has been communicated previously.[10]

Results and discussion

Lithium amide addition to (*E*,*E*)-nona-2,7- and (*E*,*E*)-deca-2,8-dienedioate esters; promoting tandem conjugate addition–cyclisation or double conjugate addition reactions

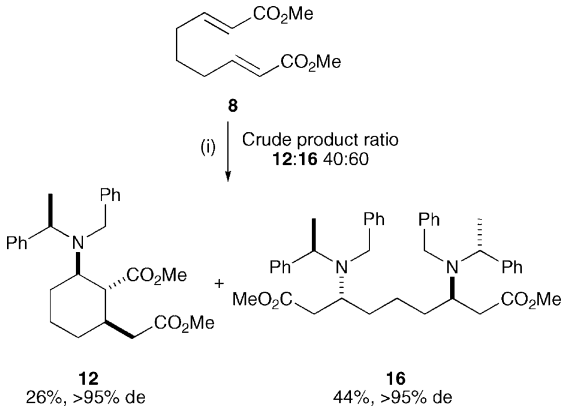
Initial studies concentrated upon the propensity for lithium amides to promote the conjugate addition and cyclisation of a range of diester derivatives of (*E*,*E*)-nona-2,7-dienedioic acid. Addition of dimethyl, diethyl, di-*tert*-butyl or di-3-pentyl-(*E*,*E*)-nona-2,7-dienedioate **8**–**11** to lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (**7**, 1.6 eq.) gave, in each case, the corresponding 1,2-*anti*-1,6-*anti*-cyclic β-amino esters **12**–**15** as the sole reaction products in >95% de and in 72–84% yield after purification (Scheme 1). The relative configuration within β-amino ester **12** was assigned using ^{1}H NMR spectroscopic analysis, using a combination of coupling constant analysis and NOESY experiments. The absolute configuration at C(2) within **12** was assigned relative to the *N*-α-methylbenzyl stereocentre by analogy with previous authenticated models developed to explain the stereoselectivity observed during addition of lithium amide (*S*)-**7** to α,β-unsaturated acceptors,[11] while the configuration at C(1) is consistent with the established *anti*-alkylation preference of lithium (*Z*)-β-amino enolates.[12] The 1,2-*anti*-1,6-*anti*-arrangement within β-amino esters **13**–**15** was assigned by analogy to **12**, and was verified independently by ^{1}H NMR analysis in each case.



	R		R	d.e.	Yield (%)
8	Me	**12**	Me	>95	72
9	Et	**13**	Et	>95	82
10	^{t}Bu	**14**	^{t}Bu	>95	78
11	3-pentyl	**15**	3-pentyl	>95	84

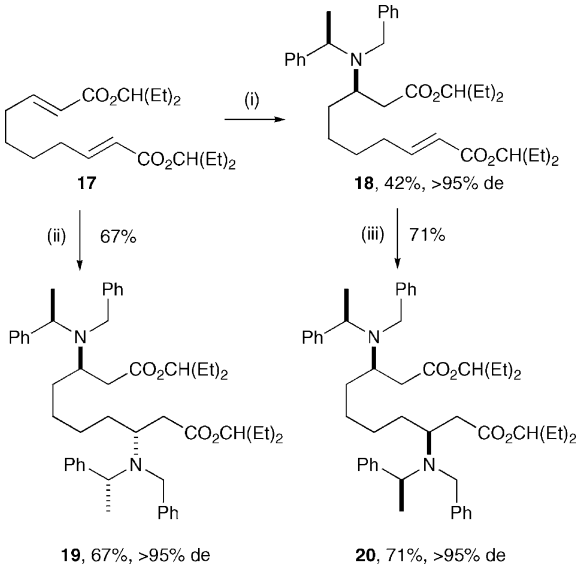
Scheme 1 Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (**7**, 1.6 eq.), THF, −78 °C.

It was envisaged that an alternative reaction manifold may be realised in this system if, following initial lithium amide conjugate addition to dimethyl-(*E*,*E*)-nona-2,7-dienedioate, the rate of a second intermolecular lithium amide conjugate addition could compete effectively with the intramolecular cyclisation of the *in situ* formed β-amino enolate. In order to bias the system toward the di-addition reaction manifold, addition of dienoate **8** to a large excess of lithium amide (*R*)-**7** (12 eq.) was investigated, giving a separable 40 : 60 mixture of the 1,2-*anti*-1,6-*anti*-cyclic β-amino ester **12** (>95% de) to the bis-β-amino ester **16** (>95% de), in 26 and 44% isolated yields, respectively, after chromatography (Scheme 2).



Scheme 2 Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide (**7**, 12 eq.), THF, −78 °C.

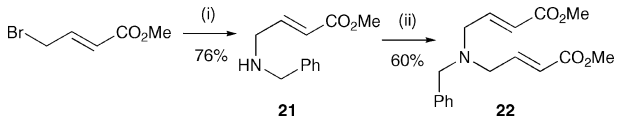
Having shown that the product distribution upon lithium amide addition to (*E*,*E*)-nona-2,7-dienedioate esters can be biased towards either the conjugate addition–cyclisation or diaddition reaction manifolds, lithium amide addition to a homologous (*E*,*E*)-deca-2,8-dienedioic acid derivative was investigated. Addition of lithium amide (*R*)-**7** (1.2 eq.) to di-3-pentyl-(*E*,*E*)-deca-2,8-dienedioate **17** gave, at approximately 45% conversion, mono β-amino ester **18** in 42% isolated yield and >95% de, while addition of diester **17** to an excess of lithium amide (*R*)-**7** (10 eq.) gave the bis-β-amino ester **19** as the sole reaction product in 67% isolated yield and >95% de. Furthermore, addition of lithium amide (*S*)-**7** to the mono-β-amino ester **18** gave the *meso*-di-β-amino ester **20** in >95% de and 71% yield (Scheme 3). Comparison of the ratio of products arising from the additions of 2,7-dienedioate **8** and 2,8-dienedioate **17** to an excess of lithium amide indicates that intermolecular conjugate addition can compete effectively with intramolecular cyclisation for formation of the six-membered carbocycle, but that bis-addition is favoured upon addition to the deca-2,8-dienoate. This product ratio presumably reflects the relative rates of cyclisation to form the six and seven membered rings, respectively, or that the reaction is reversible.



Scheme 3 Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide (**7**, 1.2 eq.), THF, −78 °C; (ii) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide (**7**, 10 eq.), THF, −78 °C; (iii) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (**7**, 4 eq.), THF, −78 °C.

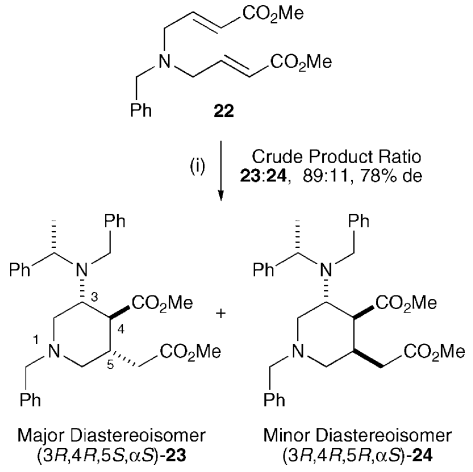
Having shown that tandem conjugate addition–cyclisation allows the effective stereoselective synthesis of six-membered carbocycles, the extension of this methodology for the preparation of piperidine derivatives was investigated. It was envisaged that

lithium amide conjugate addition to a 2,7-dienoate containing a protected nitrogen at C(5) and subsequent intramolecular cyclisation would proceed to give a functionalised piperidine skeleton. *N*-benzyl protection was initially chosen, as it was envisaged that global *N*-deprotection of the β-amino piperidine product could be realised by hydrogenolysis. The desired *N*-benzyl protected dienoate for this protocol, methyl-(*E*,*E*)-4-(*N*-benzyl-*N*-methoxycarbonylallylamino)-but-2-enoate **22**, was prepared by a simple two step procedure. Based upon a literature protocol,[13] benzylamine (2 eq.) was added to a solution of methyl 4-bromocrotonate to give the known *N*-benzyl amino ester **21** in 76% yield. Subsequent treatment of **21** with excess methyl 4-bromocrotonate in the presence of NEt_3 gave the desired diester **22** in 60% yield (Scheme 4).



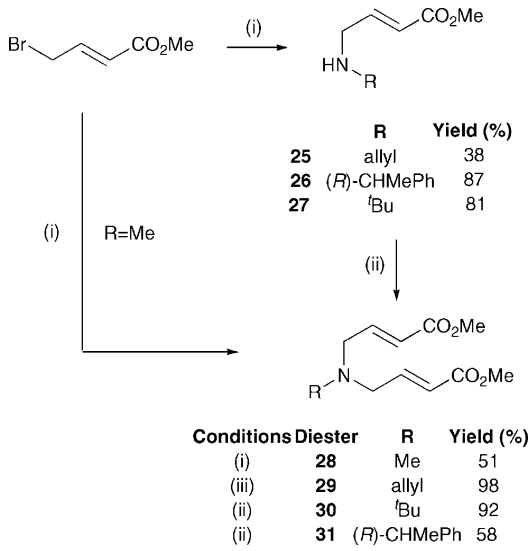
Scheme 4 Reagents and conditions: (i) $BnNH_2$ (2 eq.), DCM, rt; (ii) methyl 4-bromocrotonate (2 eq.), NEt_3, DCM, rt.

Addition of diester **22** to lithium amide (*S*)-**7** (1.2 eq.) gave a partially separable 89 : 11 mixture of two diastereoisomers **23** and **24** (78% de) in 76% overall yield. The relative configuration within both diastereoisomers **23** and **24** was elucidated through a combination of DQF-COSY, NOE difference and ^{1}H NMR coupling constant analysis, which were consistent with the piperidine skeleton adopting a chairlike conformation, with the *N*-alkyl group assumed to occupy an equatorial position.[14] The absolute configuration at C(3) within **23** and **24** was assigned relative to the *N*-α-methylbenzyl stereocentre by analogy with the model developed previously to explain the stereoselectivity observed during conjugate addition of lithium amide **7** to α,β-unsaturated acceptors, allowing the (3*R*,4*S*,5*S*,α*S*)- and (3*R*,4*S*,5*R*,α*S*)-configurations within **23** and **24** to be derived (Scheme 5).



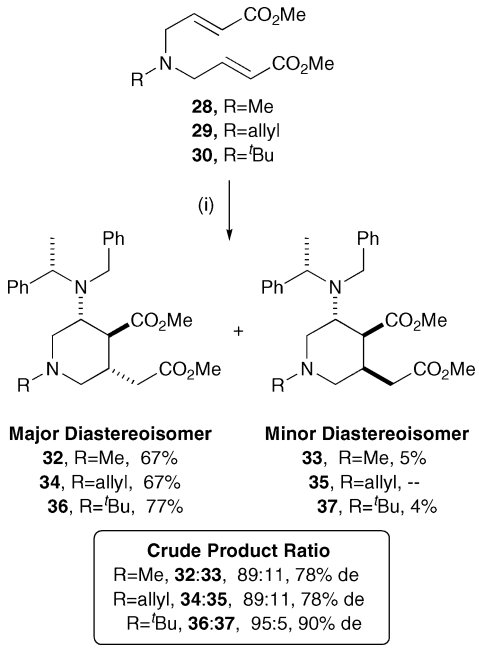
Scheme 5 Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (**7**, 1.2 eq.), THF, −78 °C.

The stereoselectivity observed upon conjugate addition–cyclisation of *N*-benzyl protected diester **22** is significantly lower than the selectivity (>95% de) observed in the analogous carbocyclic analogue. Notably, the 89 : 11 mixture of diastereoisomers **23** and **24** (78% de) that are epimeric at C(5) is consistent with the expected high stereocontrol upon lithium amide conjugate addition, but incomplete stereocontrol in the C–C bond forming cyclisation step of the reaction. The effect of changing the nature of the *N*-protecting group within the diester upon the stereoselectivity of the cyclisation reaction was next investigated, with a range of diesters containing linear and α-branched *N*-protecting groups used to probe this reaction manifold. The linear *N*-methyl and *N*-allyl protected diesters **28** and **29**, and the α-branched *N*-*tert*-butyl and the known (*R*)-*N*-α-methylbenzyl protected diesters **30** and **31** were therefore prepared by standard procedures (Scheme 6).



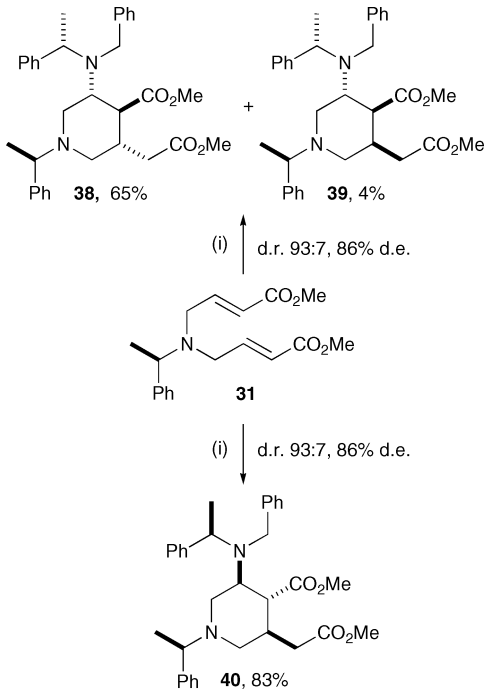
Scheme 6 Reagents and conditions: (i) RNH_2 (2 eq.), DCM, rt; (ii) methyl 4-bromocrotonate (2 eq.), $NEt(^iPr)_2$, DCM, rt.

Investigations initially focused upon the addition of *N*-methyl and *N*-allyl diesters **28** and **29** to lithium amide (*S*)-**7**. Treatment of *N*-methyl **28** with lithium amide (*S*)-**7** (1.2 eq.) gave an 89 : 11 mixture of diastereoisomers **32** : **33** (78% de), with chromatographic purification allowing the isolation of **32** in 67% yield and **33** in 5% yield and in >98% de in each case. Similarly, addition of *N*-allyl **29** to lithium amide (*S*)-**7** (1.2 eq.) gave an 89 : 11 mixture of diastereoisomers **34** : **35**, with chromatographic purification allowing the isolation of **34** in 81% yield. Furthermore, treatment of *N*-*tert*-butyl **30** with lithium amide (*S*)-**7** (1.2 eq.) gave a 95 : 5 mixture of diastereoisomers **36** : **37** (90% de), giving **36** and **37** in 77 and 4% yields, respectively, after purification (Scheme 7).[15]



Scheme 7 Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (**7**, 1.2 eq.), THF, −78 °C.

Treatment of the homochiral branched (*R*)-*N*-α-methylbenzyl protected diester **31** with lithium amide (*S*)-**7** was next investigated, giving a separable 93 : 7 mixture of diastereoisomers **38** and **39** (86% de), isolated in 65 and 4% yield, respectively. To test if this level of stereoselectivity was a result of "matched" double diastereoinduction operating in the reaction,[16] addition of diester (*R*)-**31** to the enantiomeric lithium amide (*R*)-**7** was evaluated, which also gave a 93 : 7 mixture of diastereoisomers (86% de). Purification yielded the major diastereoisomer **40** in 83% isolated yield and >98% de (Scheme 8). Analysis of the product distributions arising from conjugate addition–cyclisation of the *N*-containing diesters **22** and **28–31** indicate that increased branching in the *N*-protecting group has a small positive effect upon the stereoselectivity of the reaction. Notably the linear *N*-methyl, *N*-allyl and *N*-benzyl protected dienoates give an 89 : 11 mixture of diastereoisomers (78% de) upon cyclisation, while the *N*-*tert*-butyl protected dienoate gives the highest diastereoselectivity upon cyclisation, giving a 95 : 5 mixture of diastereoisomers (90% de).



Scheme 8 Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (**7**, 1.2 eq.), THF, −78 °C.

The diastereoselectivity observed in the tandem conjugate addition–cyclisation reactions of the 2,7-carbocyclic dienoates **8–11** and the analogous *N*-containing systems **22** and **28–31** is consistent with the initially formed lithium (*Z*)-β-amino enolate[17] arising from conjugate addition occupying a pseudo-equatorial position in a chair-like transition state. Subsequent intramolecular reaction with the tethered α,β-unsaturated system preferentially in a pseudo-equatorial position gives the 1,2-*anti*-1,6-*anti* arrangement (carbocyclic system) or 3,4-*anti*-4,5-*anti* arrangement (piperidine system) of the major diastereoisomer. The minor 3,4-*anti*-4,5-*syn* arrangement of the piperidine diastereoisomer is presumably formed *via* the tethered α,β-unsaturated system occupying a pseudo-axial position in the transition state (Fig. 3).[18]

Conjugate addition and cyclisation onto ε- and ζ-oxo-α,β-unsaturated esters

To extend further the scope of this methodology, the lithium amide promoted conjugate addition and cyclisation of ε- and ζ-oxo-α,β-unsaturated esters was investigated. *tert*-Butyl-(*E*)-7-oxohept-2-enoate (**41**) was chosen as a model system for

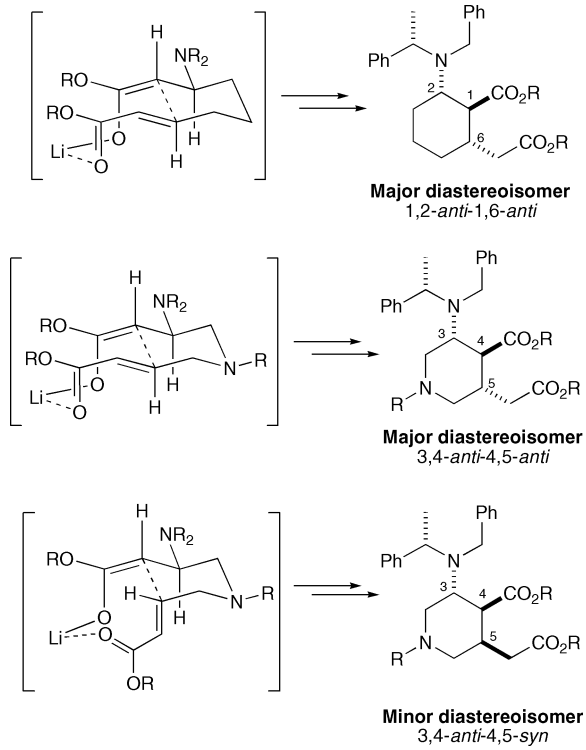
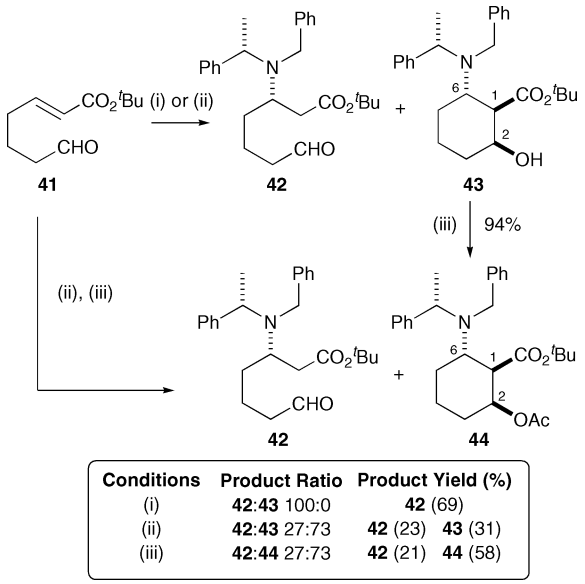


Fig. 3 Proposed transition state models for conjugate addition–cyclisation reactions.

reaction optimisation and prepared in three steps by a modified literature procedure from δ-valerolactone.[6b] Addition of **41** to lithium amide (*S*)-**7** (1.6 eq.) returned starting material, although addition to an excess of lithium amide (*S*)-**7** (2.4 eq.) gave the uncyclised β-amino-ζ-aldehyde ester (3*S*,α*S*)-**42** in 69% isolated yield and in >98% de. Having shown that conjugate addition to **41**, but not cyclisation of the resultant β-amino enolate was feasible at −78 °C, the effect of raising the reaction temperature to promote the cyclisation reaction was investigated.[19] Addition of ester **41** to lithium amide (*S*)-**7** at −78 °C and subsequent warming to −20 °C gave a 27 : 73 mixture of β-amino ester **42** (>98% de) to the cyclic 1,2-*syn*-1,6-*anti*-β-amino ester **43** (>98% de). Chromatographic purification allowed the isolation of (3*S*,α*S*)-**42** in 23% yield, and the amino alcohol (1*R*,2*S*,6*S*,α*S*)-**43** in 31% yield and >98% de. The low isolated yield of amino alcohol **43** was ascribed to decomposition during chromatography, so *in situ* protection of the alcohol was investigated. In this manner, acetylation of the crude reaction product, followed by chromatography gave aldehyde **42** in 21% yield (>98% de) and the 1,2-*syn*-1,6-*anti*-acetate (1*R*,2*S*,6*S*,α*S*)-**44** in 58% yield and >98% de (Scheme 9). An authentic sample of acetate **44** was also prepared from the purified alcohol **43** in 94% yield. The (1*R*,2*S*,6*S*,α*S*) configuration within both cyclic β-amino esters **43** and **44** was assigned on the basis of NMR spectroscopic analysis and NOE difference analysis relative to the assumed sense of asymmetric induction at C(6) arising from lithium amide conjugate addition.

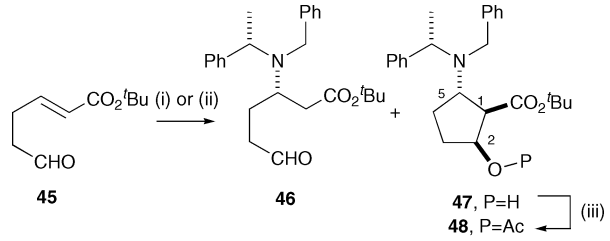
Subsequent studies were concerned with the analogous cyclisation upon lithium amide addition to *tert*-butyl-(*E*)-6-oxo-hex-2-enoate **45**, which was prepared in three steps from γ-valerolactone. Addition of **45** to a solution of lithium amide (*S*)-**7** (2.4 eq.) at −78 °C gave a 57 : 43 mixture of β-amino-ε-aldehyde ester **46** and the 1,2-*syn*-1,5-*anti*-cyclic β-amino ester **47**, with purification giving **46** in 54% yield (>98% de) and **47** in 18% yield (>98% de). Warming the reaction to −20 °C after initial addition of **45** to lithium amide (*S*)-**7** at −78 °C gave a 9 : 91 mixture of **46** : **47**, furnishing **46** in 7% yield (>98% de) and cyclic β-amino ester **47** in 66% yield (>98% de), with subsequent *O*-acetylation of **47** giving the 1,2-*syn*-1,5-*anti*-acetate **48** in 97% yield (Scheme 10). The relative configuration within **48** was confirmed by NOE



Conditions	Product Ratio	Product Yield (%)
(i)	**42**:**43** 100:0	**42** (69)
(ii)	**42**:**43** 27:73	**42** (23) **43** (31)
(iii)	**42**:**44** 27:73	**42** (21) **44** (58)

Scheme 9 Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (**7**, 2.4 eq.), THF, −78 °C, 2 h; (ii) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (**7**, 2.4 eq.), THF, −78 °C, 2 h then −20 °C, 2 h; (iii) Ac_2O, DMAP, pyridine, DCM, rt, 5 h.

difference analysis, with the absolute configuration assumed relative to the known sense of asymmetric induction at C(5) arising from lithium amide addition.



Conditions	Product Ratio	Product Yield (%)
(i)	**46**:**47** 57:43	**46** (54) **47** (18)
(ii)	**46**:**47** 9:91	**46** (7) **47** (66)

Scheme 10 Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (**7**, 2.4 eq.), THF, −78 °C, 2 h; (ii) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (**7**, 2.4 eq.), THF, −78 °C, 2 h then −20 °C, 2 h; (iii) Ac_2O, pyridine, DMAP, DCM, rt.

With the relative 1,2-*syn*-1,6-*anti*- and 1,2-*syn*-1,5-*anti*-configuration of the cyclic products **43** and **47** elucidated, possible transition states for their formation can be postulated. Diastereoselective conjugate addition of lithium amide (*S*)-**7** to **41** and **45** is assumed to generate the corresponding lithium (*Z*)-β-amino enolates. Allowing lithium chelation between the enolate oxygen and remote aldehyde, the bicyclic transition states **49** and **50** are consistent with the observed stereoselectivity. Minimization of 1,3-allylic strain predicts preferential alkylation *anti*-to the C(3)-amino functionality of the β-amino enolate in each case, with intramolecular aldol reaction proceeding *via* either a chair (six ring) or envelope (five ring) transition state. Assuming that the large C(3)-amino group occupies an equatorial position within the transition state, the aldehyde offers preferentially its *Re* face to nucleophilic attack (Fig. 4).

Deprotection reactions: asymmetric synthesis of polyfunctionalised transpentacin and transhexacin derivatives

Having demonstrated that both tethered aldehyde and α,β-unsaturated ester functional groups may participate in conjugate addition–cyclisation reactions, deprotection of the polyfunctionalised scaffolds was investigated. *N*-deprotection of the carbocyclic β-amino esters **13** and **14** (>98% de) by hydrogenolysis gave the corresponding amino esters **51** and **52** in >98% de and in 96% yield in each case, with ester hydrolysis under basic or acidic conditions, respectively, and subsequent purification by Dowex ion exchange chromatography, giving the β-amino diacid **53** (>98% de) in 74 and 71% yield, respectively (Scheme 11).

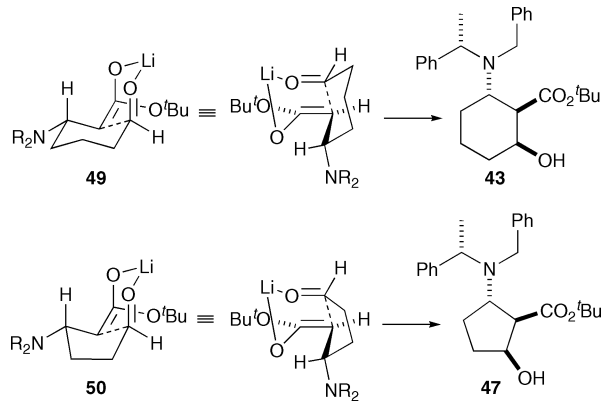
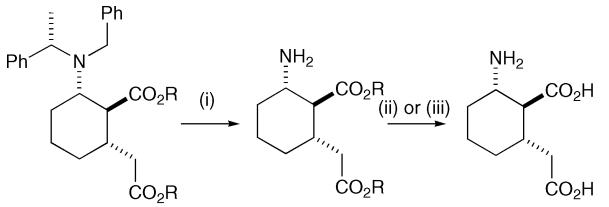


Fig. 4 Proposed transition state for tandem cyclisation of five and six membered aldehydes.

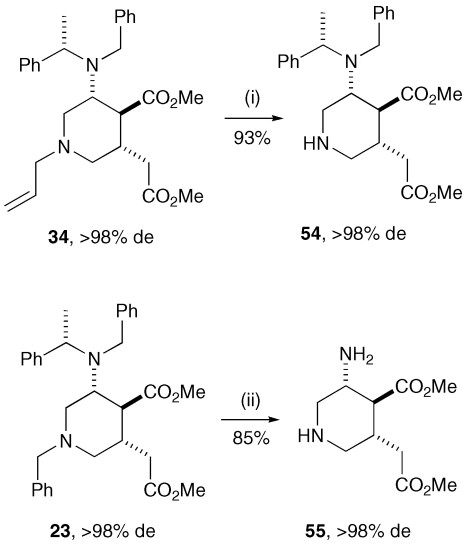


Scheme 11 Reagents and conditions: (i) $Pd(OH)_2/C$, MeOH, H_2 (5 atm); (ii) LiOH, THF : H_2O, rt then DOWEX ion exchange chromatography; (iii) TFA : DCM (1 : 1), rt then DOWEX ion exchange chromatography.

The differential and global deprotection of the *N*-benzyl and *N*-allyl protected piperidine β-amino esters **34** and **23** was next investigated. The ability to deprotect selectively the *N*-allyl functionality within β-amino ester **34** using palladium catalysis[20] allowed the selective unmasking of the piperidine nitrogen, giving **54** in 93% yield and >98% de and >98% ee.[21] Global *N*-deprotection of *N*-benzyl piperidine **23** was readily achieved by hydrogenolysis, giving **55** in 92% yield (>98% de) (Scheme 12).

Further studies were directed toward deprotection and functionalisation of the products arising from conjugate addition to the ε- and ζ-oxo-α,β-unsaturated esters. It was envisaged that deprotection of both the uncyclised β-amino-ε- or ζ-oxo esters **42** and **46** and cyclised β-amino ester products **43**, **44**, **47** and **48** arising from these reactions would furnish useful scaffolds for incorporation into pseudopeptides. While β-amino-ε- and ζ-oxo esters **42** and **46** may be prepared selectively by conjugate addition in reasonable yield at low temperature, an alternative, selective synthesis of these products was investigated that would prove amenable to large scale synthesis. Thus, addition of α,β-unsaturated esters **56** and **57** to an excess of lithium amide (*S*)-**7** gave the corresponding β-amino-ε- and ζ-alcohols **58** and **59** in 79 and 82% yield and in >98% de, with Swern oxidation giving the aldehydes **46** and **42** in 87 and 91% yield respectively. Subsequent treatment of **46** and **42** with $Pd(OH)_2$ on C under H_2 (5 atm) gave (*S*)-homoproline *tert*-butyl ester **60** and (*S*)-homopipecolic acid *tert*-butyl ester **61** in 96 and 86% yield respectively (Scheme 13).

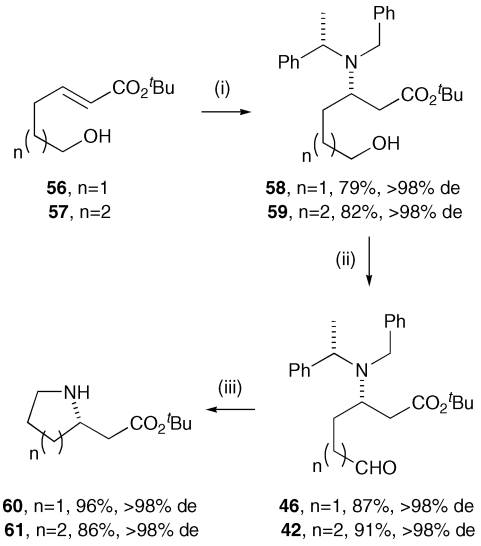
Finally, deprotection of the cyclic β-amino esters **43**, **44**, **47** and **48** derived from tandem conjugate addition and intramolecular aldol reaction was investigated. In the pentacin



34, >98% de **54**, >98% de

23, >98% de **55**, >98% de

Scheme 12 Reagents and conditions: (i) $Pd(PPh_3)_4$, 1,3-dimethylbarbituric acid, DCM, rt; (ii) $Pd(OH)_2$ on C, MeOH, H_2 (5 atm).



56, n=1
57, n=2

58, n=1, 79%, >98% de
59, n=2, 82%, >98% de

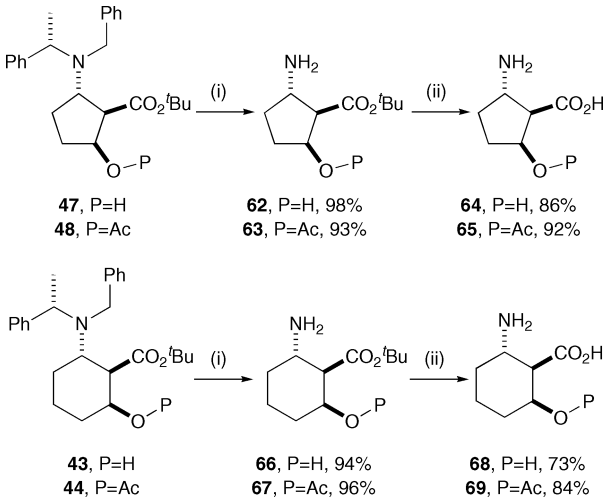
60, n=1, 96%, >98% de
61, n=2, 86%, >98% de

46, n=1, 87%, >98% de
42, n=2, 91%, >98% de

Scheme 13 Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (**7**, 3.5 eq.), THF, −78 °C; (ii) $(COCl)_2$, DMSO, Et_3N, −78 °C, 1 h, then rt, 30 min; (iii) $Pd(OH)_2$ on C, MeOH, H_2 (5 atm).

series, *N*-deprotection of **47** and **48** by hydrogenolysis gave the corresponding 2-hydroxy- or 2-acetoxy protected β-amino esters **62** and **63**, with subsequent ester hydrolysis and purification by Dowex ion exchange chromatography giving 2-hydroxy-transpentacin **64** and 2-acetoxy-transpentacin **65** in high yield and >98% de in each case. Similarly, in the hexacin series, *N*-deprotection of **43** and **44** by hydrogenolysis gave the corresponding β-amino esters **66** and **67** (>98% de) with ester hydrolysis and Dowex ion exchange chromatography giving 2-hydroxy-transhexacin **68** and 2-acetoxy-transhexacin **69** in high yield and >98% de (Scheme 14). As enantiomerically pure lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **7** was used to initiate the formation of **43**, **44**, **47** and **48**, and the subsequent deprotection steps proceeded without epimerisation, an ee of >98% was ascribed to the β-amino acids **64**, **65**, **68** and **69**.

In conclusion, we have demonstrated that the conjugate addition of homochiral lithium amides and subsequent intramolecular cyclisation of the *in situ*-formed lithium (*Z*)-β-amino enolate onto an α,β-unsaturated ester or aldehyde functionality gives access to a range of polysubstituted carbocyclic transhexacin, transpentacin and piperidine derivatives. The application of this methodology to the synthesis of a range of scaffolds for incorporation into pseudopeptides and for the total synthesis



47, P=H
48, P=Ac

62, P=H, 98%
63, P=Ac, 93%

64, P=H, 86%
65, P=Ac, 92%

43, P=H
44, P=Ac

66, P=H, 94%
67, P=Ac, 96%

68, P=H, 73%
69, P=Ac, 84%

Scheme 14 Reagents and conditions: (i) $Pd(OH)_2$/C, MeOH, H_2 (5 atm); (ii) TFA : DCM (1 : 1), rt then DOWEX ion exchange chromatography.

of a range of natural products is under investigation in our laboratory.

Experimental

General experimental

All reactions involving organometallic or other moisture-sensitive reagents were performed under an atmosphere of dry nitrogen using standard vacuum line techniques. All glassware was flame-dried and allowed to cool under vacuum. In all cases, the reaction diastereoselectivity was assessed by peak integration in the ^{1}H NMR spectrum of the crude reaction mixture. THF and Et_2O were distilled from sodium–benzophenone ketyl under an atmosphere of dry nitrogen. DCM was distilled from CaH_2 under dry nitrogen, all other solvents were used as supplied (analytical or HPLC grade) without prior purification. *n*-Butyllithium (BuLi) was used as a solution in hexane and was titrated against diphenylacetic acid prior to use. DIBAL-H was used as supplied (Aldrich), as a 1.0 M solution in hexane. Allylamine was distilled from and stored over potassium hydroxide pellets. All other reagents were used as supplied, without further purification. Unless otherwise stated, all aqueous solutions were saturated, and all organic layers were dried with $MgSO_4$. Column chromatography was performed on silica gel (Kieselgel 60) or basic alumina. TLC was performed on Merck plates, aluminium sheets coated with silica gel 60 F_{254}. Plates were visualized either by UV light (254 nm), iodine, Dragendorff's reagent,[22] ammonium molybdate (7% in 10% ethanolic sulfuric acid) or 1% aqueous $KMnO_4$. Nuclear magnetic resonance (NMR) spectra were recorded on Varian Gemini 200 (^{1}H: 200 MHz), Bruker AM-200 (^{1}H:200 MHz and ^{13}C:50.3 MHz), Bruker DPX-400 (^{1}H:400 MHz and ^{13}C:100.6 MHz), or Bruker AM-500 (^{1}H:500 MHz and ^{13}C:125.78 MHz) spectrometers in the deuterated solvents stated. All chemical shifts (δ_H) are reported in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants (*J*) are measured in Hz and are calculated using a first order approximation. Carbon chemical shifts (δ_C) are quoted in ppm and are referenced using residual solvent signals. Proton and carbon assignment was performed with the aid of COSY and DQF-COSY to establish the ^{1}H–^{1}H coupling and APT, HMQC and HMBC to establish the ^{1}H–^{13}C coupling. NOE spectra were obtained on the Bruker DRX-500 (500 MHz) spectrometer. Infrared spectra were recorded on a Perkin-Elmer 1750 IR Fourier Transform spectrophotometer using either KBr disc (KBr) or as thin film (film). Selected peaks are reported in cm^{-1}. Low resolution mass spectra (*m*/*z*) were recorded on VG Masslab

20–250 or Micromass Platform 1 spectrometers and high-resolution mass spectra (HRMS) on a Micromass Autospec 500 OAT spectrometer. Techniques used were chemical ionisation (CI, NH_3), atmospheric pressure chemical ionisation (APCI) using partial purification by HPLC with methanol : acetonitrile : water (40 : 40 : 20) as eluent or electrospray ionisation (ESI). Major peaks are listed with intensities quoted as percentages of the base peak. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter, using a path length of 10 cm, with concentrations (*c*) given in g/100 mL solvent and temperature as recorded. Values are quoted in units of 10^{-1}deg cm^2 g^{-1}. Melting points were recorded on a Leica VMTG Galen III apparatus and are uncorrected. Elemental analysis was performed by the microanalysis service of the Inorganic Chemistry Laboratory, Oxford.

General procedure 1a (standard addition) and 1b (inverse addition) for lithium amide reaction

n-BuLi was added dropwise to a stirred solution of secondary amine in THF at −78 °C under N_2 atmosphere and the resulting solution stirred for 30 min. Subsequently (a) a solution of the α,β-unsaturated ester in THF at −78 °C was added dropwise to the lithium amide solution *via* cannula and stirred at −78 °C for 2 h before addition of saturated aqueous NH_4Cl and warming to rt or (b) the lithium amide solution was added dropwise *via* cannula to a solution of the α,β-unsaturated ester in THF at −78 °C and stirred at −78 °C for 2 h before addition of saturated aqueous NH_4Cl and warming to rt. The crude reaction mixture was partitioned between DCM and brine and the organics concentrated *in vacuo*. This residue was partitioned between DCM and 10% citric acid solution, organic layer washed in succession with aqueous $NaHCO_3$ solution and brine, dried and concentrated *in vacuo* before purification *via* column chromatography.

General procedure 2

Phosphorus ylide was added portion-wise to a stirred solution of the aldehyde in DCM at rt and left stirring for 16 h. The resultant solution was then diluted with DCM, dried and concentrated *in vacuo* before purification *via* column chromatography.

General Procedure 3

The requisite phosphonoacetate was added dropwise to a solution of glutaraldehyde followed by 6.5 M aqueous K_2CO_3 solution (5 eq.). The reaction mixture was stirred at rt for 16 h and then extracted with ether. The combined organic extracts were washed with brine, dried, filtered and concentrated *in vacuo* before purification *via* column chromatography.

General Procedure 4

$Pd(OH)_2/C$ was added to a solution of substrate in degassed MeOH and the resultant suspension stirred under hydrogen (5 atm) for 16 h. The reaction mixture was then filtered through celite® (eluent MeOH), concentrated *in vacuo*, and the residue purified *via* column chromatography on activated basic alumina.

General Procedure 5

A 1 : 1 mixture of TFA–DCM solution was added dropwise to the requisite substrate at 0 °C. Solution was then vigorously stirred for 16 h at rt, after which the mixture was concentrated *in vacuo*, and purified *via* ion-exchange chromatography.

Preparation of dimethyl-(2*E*,7*E*)-2,7-nonadienedioate (8)

Following the general procedure 3, glutaraldehyde (40% w/w, 3.0 mL, 12.7 mmol), methyl triphenylphosphoranylidene acetate (6.75 g, 31.9 mmol) and K_2CO_3 solution (5 M, 12.8 mL, 64.0 mmol) gave the crude reaction product as yellow oil. Purification *via* column chromatography on silica (1 : 5, Et_2O : pentane) gave **8** as a clear oil (1.43 g, 54%) with spectroscopic properties consistent with the literature;[23] δ_H (400 MHz, $CDCl_3$) 1.62–1.64 (2H, m, C(5)H_2), 2.24 (4H, dt, $J_{4,3}$ 11.5, $J_{4,5}$ 6.1, C(4)H_2 and C(6)H_2), 3.72 (6H, s, 2x CO_2CH_3), 5.85 (2H, dt, $J_{2,3}$ 13.0, $J_{2,4}$ 1.1, C(2)*H* and C(8)*H*), 6.95 (2H, td, $J_{3,2}$ 13.0, $J_{3,4}$ 6.1, C(3)*H* and C(7)*H*).

Preparation of diethyl-(2*E*,7*E*)-2,7-nonadienedioate (9)

Following the general procedure 3, glutaraldehyde (40% w/w, 3.0 mL, 12.7 mmol), ethyl triphenylphosphoranylidene acetate (6.30 mL, 31.8 mmol) and EtOH (5 mL) gave the crude reaction product as a yellow oil. Purification *via* column chromatography on silica (1 : 5, Et_2O : pentane) gave **9** as a clear oil (678 mg, 81%) with spectroscopic properties consistent with the literature;[24] δ_H (400 MHz, $CDCl_3$) 1.29 (6H, t, $J_{1',2'}$ 7.1, 2x CH_2CH_3), 1.64 (2H, m, C(5)H_2), 2.21 (4H, app q, $J_{4,3;4,5}$ 6.6, C(4)H_2 and C(6)H_2), 4.19 (4H, q, $J_{2',1'}$ 7.1, 2x CH_2CH_3), 5.85 (2H, d, $J_{2,3}$ 15.6, C(2)*H* and C(8)*H*), 6.92 (2H, dt, $J_{3,2}$ 15.6, $J_{3,4}$ 6.6, C(3)*H* and C(7)*H*).

Preparation of di-*tert*-butyl-(2*E*,7*E*)-2,7-nonadienedioate (10)

Following the general procedure 2, phosphorane (5.0 g, 13.3 mmol), glutaraldehyde (25% w/w, 5.0 mL, 53.2 mmol) and THF (150 mL) were reacted to afford the crude product as a colourless oil. Purification *via* column chromatography on silica (1 : 5, Et_2O : pentane) furnished **10** (2.57 g, 65%) as a white solid; mp 61–63 °C (Et_2O); ν_{max} (film) 1654, 1706; δ_H (400 MHz, $CDCl_3$) 1.48 (18H, s, 2x C(CH_3)$_3$), 1.61–1.63 (2H, m, C(5)H_2), 2.30–2.33 (4H, m, C(4)H_2 and C(6)H_2), 5.76 (2H, d, $J_{2,3}$ 15.6, C(2)*H* and C(8)*H*), 6.83 (2H, dt, $J_{3,2}$ 15.5, $J_{3,4}$ 6.9, C(3)*H* and C(7)*H*); δ_C (100 MHz, $CDCl_3$), 28.1 2x(C(CH_3)$_3$), 29.7 (*C*(5)H_2), 30.3 (*C*(4)H_2 and *C*(6)H_2), 80.2 2x(*C*(CH_3)$_3$), 123.8 (*C*(2)H and *C*(8)H), 145.8 (*C*(3)H and *C*(7)H), 165.8 2x(*C*O); *m*/*z* (CI$^+$) 300.2333 ($C_{17}H_{32}NO_4^+$. Requires 300.2331); 300 (MNH_4^+, 27%), 244 (72).

Preparation of methyl-(1*S*,2*S*,6*S*,α*S*)-2-*N*-benzyl-*N*-α-methylbenzylamino-6-(methyloxycarbonylmethyl)-cyclohexanecarboxylate (12)

Following the general procedure 1a, *n*-BuLi (1.6 M, 2.0 mL, 3.22 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (0.70 mL, 3.34 mmol) in THF (8 mL) and diester **8** (0.48 g, 2.0 mmol) in THF (5 mL) gave the crude reaction product as a red oil. Purification *via* column chromatography on silica (1 : 4, Et_2O : pentane) gave **12** (0.65 g, 72%) as a clear oil; $[\alpha]_D^{24}$ −4.1 (*c* 1.00, $CHCl_3$); ν_{max} (film) 2974, 1738, 1435, 1028; δ_H (400 MHz, $CDCl_3$) 0.80–0.92 (1H, m, C(4)H_AH$_B$), 1.20–1.30 (1H, m, C(3)H_AH$_B$), 1.36 (3H, d, *J* 6.9, C(α)CH_3), 1.25–1.40 (1H, m, C(5)H_AH$_B$), 1.60–1.70 (1H, m, C(4)H$_A$$H_B$), 1.68–1.80 (1H, m, C(3)H$_A$$H_B$), 1.92–2.05 (3H, m, C(5)H$_A$$H_B$, C(6)*H* and C$H_AH_BCO_2$), 2.10–2.18 (1H, m, CH$_A$$H_BCO_2$), 2.29 (1H, dd, $J_{1,2}$ 9.8, $J_{1,6}$ 9.2, C(1)*H*), 3.02 (1H, td, $J_{1,2;1,6}$ 9.8, $J_{1,6}$ 3.6, C(2)*H*), 3.40, 3.59 (3H, s, 2x CO_2CH_3), 3.72 (1H, AB d, $J_{A,B}$ 12.8, CH_AH$_B$Ph), 3.82 (1H, AB d, $J_{A,B}$ 12.8, CH$_A$$H_B$Ph), 3.96 (1H, q, *J* 6.9, C(α)*H*), 7.13–7.32 (10H, m, 2x *o*/*m*/*p*-*Ph*); δ_C (100 MHz, $CDCl_3$) 16.1 (C(α)CH_3), 24.5 (*C*(3)H_2), 28.5 (*C*(5)H_2), 30.1 (*C*(4)H_2), 37.3 (*C*(6)H_2), 39.4 (C(6)CH_2), 49.9 (CH_2Ph), 51.2 (CO_2CH_3), 51.4 (CO_2CH_3'), 54.5 (*C*(1)H), 56.8 (*C*(α)H), 58.6 (*C*(2)H), 126.4, 126.7, 127.7, 127.9, 129.1 2x(*o*/*m*/*p*-*Ph*), 140.6, 144.1 (*i*-*Ph*), 172.4 (CH_2CO_2), 174.1 (C(1)CO_2); *m*/*z* (CI$^+$) 424.2490 (MH$^+$, $C_{26}H_{34}NO_4$ requires 424.2488); 423 (M$^+$, 7), 250 (25), 146 (30), 105 (90), 91 (100), 79 (25).

Preparation of ethyl-(1*S*,2*S*,6*S*,α*S*)-2-*N*-benzyl-*N*-α-methylbenzylamino-6-(ethyloxycarbonylmethyl)-cyclohexanecarboxylate (13)

Following the general procedure 1a, *n*-BuLi (1.6 M in hexane, 1.0 mL, 1.61 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine

(0.35 mL, 1.67 mmol) in THF (5 mL) and diester **9** (0.25 g, 1.0 mmol) in THF (5 mL) gave the crude reaction product as a red oil. Purification *via* column chromatography on silica (1 : 4, Et_2O : pentane) gave **13** (0.49 g, 82%) as a red oil; $[\alpha]_D^{24}$ −5.1 (*c* 1.00, $CHCl_3$); (Found: C, 74.3; H, 8.2; N, 3.2. Calc. for $C_{28}H_{37}NO_4$: C, 73.4; H, 8.2; N, 3.2%); ν_{max} (film) 1730, 1736, 2859, 2978; δ_H (400 MHz, $CDCl_3$) 0.84–0.97 (1H, m, C(5)H_AH_B), 1.15 (3H, t, $J_{1',2'}$ 7.0, CH_2CH_3), 1.21 (3H, t, $J_{1',2'}$ 7.0, CH_2CH_3'), 1.21–1.40 (2H, m, C(5)H_AH_B and C(3)H_AH_B), 1.39 (3H, d, *J* 6.9, C(α)CH_3), 1.70–1.81 (2H, m, C(4)H_2), 1.90–2.06 (3H, m, C(3)H_AH_B, C(6)*H* and C(6)CH_AH_B), 2.15–2.22 (1H, m, C(6)CH_AH_B), 2.25 (1H, app t, $J_{1,2;1,6}$ 9.5, C(1)*H*), 3.08–3.10 (1H, m, C(2)*H*), 3.70 (1H, AB d, $J_{A,B}$ 12.9, CH_AH_BPh), 3.89 (1H, AB d, *J* 12.9, CH_AH_BPh), 3.89–3.91 (1H, m, C(α)*H*), 3.95–4.13 (4H, m, CH_2CH_3 and CH_2CH_3'), 7.13–7.50 (10H, m, 2x *o/m/p-Ph*); δ_C (100 MHz, $CDCl_3$) 14.0, 14.2 2x(CH_2CH_3), 16.6 (C(α)CH_3), 24.6 ($C(4)H_2$), 28.4 ($C(5)H_2$), 30.9 ($C(6)H_2$), 37.5 (*C*(3)H), 39.5 (C(6)CH_2), 50.0 (CH_2Ph), 54.4, 57.1, 59.0 (*C*(1)H, *C*(2)H, *C*(α)H), 60.1, 60.2 2x(CH_2CH_3) 126.4, 126.7, 127.7, 128.0, 129.2 2x(*o/m/p-Ph*), 140.8, 144.2 2x(*i-Ph*), 172.1, 174.0 2x(CO_2); *m/z* (CI^+) 452.2807 (MH^+, $C_{34}H_{38}NO_4$ requires 452.2801); 455 (12%), 454 (21), 452 ((MH)$^+$, 100), 348 (12).

Preparation of *tert*-butyl-(1*S*,2*S*,6*S*,α*S*)-2-*N*-benzyl-*N*-α-methylbenzylamino-6-(*tert*-butyloxycarbonylmethyl)-cyclohexanecarboxylate (14)

Following the general procedure 1a, *n*-BuLi (2.5 M, 1.11 mL, 2.77 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (0.60 mL, 2.86 mmol) in THF (10 mL) and diester **10** (0.50 g, 1.79 mmol) in THF (8 mL) gave the crude reaction product. Purification *via* column chromatography on silica (1 : 10, EtOAc : pentane) furnished **14** (710 mg, 78%) as a clear oil; $[\alpha]_D^{24}$ −4.5 (*c* 1.35, $CHCl_3$); ν_{max} (film) 1602, 1727, 2933, 2976, 3062; δ_H (400 MHz, $CDCl_3$) 0.90 (1H, app q, $J_{5,4;5,6}$ 9.5, C(5)H_AH_B), 1.21–1.24 (1H, m, C(4)H_AH_B), 1.39 (3H, d, *J* 6.9, C(α)CH_3), 1.41 (9H, s, C(CH_3)$_3$), 1.48 (9H, s, C(CH_3)$_3'$), 1.45–1.50 (1H, m, C(6)CH_AH_B), 1.61–1.72 (2H, m, C(5)H_AH_B, C(6)CH_AH_B), 1.72–1.79 (1H, m, C(4)H_AH_B), 1.84–1.93 (2H, m, C(3)H_AH_B, C(6)*H*), 2.10 (1H, app t, $J_{1,2;1,6}$ 8.7, C(1)*H*), 2.23 (1H, app q, $J_{3,4;3,5}$ 6.5, C(3)H_AH_B), 3.06 (1H, dt, $J_{2,1}$ 8.7, $J_{2,3}$ 3.1, C(2)*H*), 3.71 (1H, AB d, $J_{A,B}$ 13.3, CH_AH_BPh), 3.78 (1H, AB d, $J_{A,B}$ 13.3, CH_AH_BPh), 3.81 (1H, q, *J* 6.9, C(α)*H*), 7.13–7.39 (10H, m, 2x *o/m/p-Ph*); δ_C (125 MHz, $CDCl_3$) 21.0 (C(α)CH_3), 25.1 ($C(4)H_2$), 28.3, 28.6 2x(C(CH_3)$_3$), 29.1 ($C(5)H_2$), 30.9 ($C(3)H_2$), 38.8 (*C*(6)H), 40.8 (C(6)CH_2), 50.1 (CH_2Ph), 55.4 (*C*(1)H), 58.7 (*C*(α)H), 60.9 (*C*(2)H), 80.6, 80.7 2x ($C(CH_3)_3$), 126.9, 128.2 2x(*p-Ph*), 128.4, 128.5, 128.9, 129.2, 129.5 2x(*o/m-Ph*), 141.9, 144.8 2x(*i-Ph*), 172.0, 174.3 2x(CO_2); *m/z* (CI^+) 508.3413 (MH^+, $C_{32}H_{46}NO_4^+$ requires 508.3427); (EI^+) 530 (21%), 508 ((MH)$^+$, 100).

Preparation of 3-pentyl-(1*S*,2*S*,6*S*,α*S*)-2-*N*-benzyl-*N*-α-methylbenzylamino-6-(pent-3-yloxycarbonylmethyl)-cyclohexanecarboxylate (15)

Following the general procedure 1a, (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (239 mg, 2.1 mmol) in THF (10 mL), *n*-BuLi (1.25 mL, 2.0 mmol) and diene **11** (219 mg, 0.67 mmol) in THF (2 mL) gave, after purification *via* column chromatography on silica (1 : 24, EtOAc : pentane), **15** (303 mg, 84%) as a colourless oil; $[\alpha]_D^{26}$ −2.5 (*c* 1.35, $CHCl_3$); ν_{max} (film) 750, 912, 1030, 1260, 1465, 1732, 2971; δ_H (400 MHz, $CDCl_3$) 0.75–0.82 (1H, m, C(4)H_AH_B), 0.83 (6H, t, $J_{3',2'}$ 7.4, CH(CH_2CH_3)$_2$), 0.91 (3H, t, $J_{3',2'}$ 7.4, CH(CH_2CH_3)), 0.93 (3H, t, $J_{3',2'}$ 7.4, CH(CH_2CH_3)′), 1.12–1.30 (2H, m, C(3)H_AH_B and C(5)H_AH_B) 1.32 (3H, d, *J* 6.9, C(α)CH_3), 1.45–1.75 (11H, m, C(3)H_AH_B, C(4)H_AH_B, C(5)H_AH_B and 2x CH(CH_2CH_3)$_2$), 1.92–2.08 (2H, m, C(6)*H* and C(6)H_AH_B), 2.14 (1H, app t, $J_{1,2;1,6}$ 10.6, C(1)*H*), 2.27 (1H, d, $J_{B,A}$ 11.8, C(6)H_AH_B), 3.16 (1H, td, $J_{2,1;2,3}$ 10.6, $J_{2,3}$ 3.3, C(2)*H*), 3.74 (2H, s, CH_2Ph), 4.04 (1H, q, *J* 6.9, C(α)*H*), 4.68, 4.69 (1H, quin, $J_{1',2'}$ 6.2, 2x CH(CH_2CH_3)$_2'$), 7.15–7.40 (10H, m, 2x *o/m/p-Ph*); δ_C (100 MHz, $CDCl_3$) 9.4, 9.5 2x (CH(CH_2CH_3)$_2$), 19.5 (C(α)CH_3), 24.6 ($C(3)H_2$), 25.2, 25.3, 26.4 2x(CH(CH_2CH_3)$_2$), 28.1 ($C(5)H_2$), 30.9 ($C(4)H_2$), 38.0 (*C*(6)H), 39.7 (C(6)CH_2), 49.7 (CH_2Ph), 54.7 (*C*(1)H), 60.4 (*C*(α)H), 60.9 (*C*(2)H), 76.6, 76.9 2x(CH(CH_2CH_3)$_2$), 126.5, 126.6, 127.6, 127.8, 129.1 2x(*o/m/p-Ph*), 141.6, 144.4 2x(*i-Ph*), 171.6, 174.2 2x(CO_2); *m/z* (CI^+) 536.3724 (MH^+, $C_{34}H_{50}NO_4$ requires 536.3740); 539 (12%), 538 (68), 536 ((MH)$^+$, 100);

Preparation of dimethyl-(3*R*,α*R*,7*R*,α′*R*)-3,7-*bis*-*N*-benzyl-*N*-α-methylbenzylamino-nonadioate (16)

Following the general procedure 1b, (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (1.2 g, 5.5 mmol) in THF (10 mL), *n*-BuLi (3.4 mL, 5.4 mmol) and diene **8** (98 mg, 0.46 mmol) in THF (1 mL) gave, after purification *via* column chromatography on silica (1 : 24, EtOAc : pentane), **12** (50 mg, 26%) as a colourless oil; $[\alpha]_D^{26}$ +3.9 (*c* 1.86 $CHCl_3$); Further elution furnished diester **16** (128 mg, 44%) as a colourless oil; $[\alpha]_D^{26}$ +7.5 (*c* 2.00, $CHCl_3$); ν_{max} (film) 702, 1152, 1204, 1377, 1452, 1738, 2949; δ_H (400 MHz, $CDCl_3$): 1.21–1.32 (2H, m, C(5)H_2), 1.36 (6H, d, *J* 7.0, C(α)CH_3), 1.45–1.65 (4H, m, C(4)H_2 and C(6)H_2), 2.02 (2H, dd, $J_{A,B}$ 14.6, $J_{2,3}$ 8.2, C(2)H_AH_B and C(8)H_AH_B), 2.08 (2H, dd, $J_{B,A}$ 14.6, $J_{2,3}$ 4.8, C(2)H_AH_B and C(8)H_AH_B), 3.34–3.38 (2H, m, C(3)*H* and C(7)*H*), 3.54 (6H, s, 2x CO_2CH_3), 3.57 (2H, AB d, $J_{A,B}$ 14.8, CH_AH_BPh), 3.78 (2H, AB d, $J_{A,B}$ 14.8, CH_AH_BPh), 3.86 (2H, q, *J* 7.0, C(α)*H*), 7.21–7.42 (20H, m, 4x *o/m/p-Ph*); δ_C (50 MHz, $CDCl_3$) 19.9 (C(α)CH_3), 24.9 ($C(5)H_2$), 34.1 ($C(4)H_2$ and $C(6)H_2$), 36.8 ($C(2)H_2$ and $C(8)H_2$), 50.2 (CH_2Ph), 51.0 2x(CO_2CH_3), 54.7 (*C*(3)H and *C*(7)H), 58.2 (*C*(α)H), 126.6, 126.9, 128.0, 128.1, 128.3 4x(*o/m/p-Ph*), 141.7, 143.6 4x(*i-Ph*), 173.1 2x(CO_2Me); *m/z* (EI^+) 635.3862 (MH^+, $C_{41}H_{51}O_4N_2^+$ requires 635.3849); 635 ((MH)$^+$, 100%), 561 (8), 424 (12).

Preparation of di-3-pentyl-(3*R*,α*R*,8*E*)-3-*N*-benzyl-*N*-α-methylbenzylamino-dec-8-enedioate (18)

Following the general procedure 1b, (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (352 mg, 1.7 mmol) in THF (15 mL), *n*-BuLi (0.9 mL, 1.4 mmol) and diene **17** (430 mg, 1.27 mmol) in THF (2 mL), gave after chromatographic purification on silica (1 : 49, EtOAc : pentane), **18** (295 mg, 42%) as a colourless oil; $[\alpha]_D^{26}$ +6.2 (*c* 2.62, $CHCl_3$); ν_{max} (film) 700, 1460, 1500, 1640, 1714, 3000–2800; δ_H (400 MHz, $CDCl_3$) 0.81 (6H, t, $J_{3',2'}$ 7.4, CH(CH_2CH_3)$_2$), 0.85 (6H, t, $J_{3',2'}$ 7.4, CH(CH_2CH_3)$_2'$), 1.33 (3H, d, *J* 7.0, C(α)CH_3), 1.48–1.52 (8H, m, 2x CH(CH_2CH_3)$_2$), 1.60 (6H, m, C(4)H_2 and C(5)H_2 and C(6)H_2), 1.96 (1H, dd, $J_{2,2}$ 14.6, $J_{2,3}$ 3.0, C(2)H_AH_B), 2.04 (1H, dd, $J_{2,2}$ 14.6, $J_{2,3}$ 6.0, C(2)H_AH_B), 2.17 (2H, app q, *J* 6.9, C(7)H_2), 3.31–3.35 (1H, m, C(3)*H*), 3.50 (1H, AB d, *J* 15.0, CH_AH_BPh), 3.81 (1H, AB d, *J* 15.0, CH_AH_B), 3.81 (1H, q, *J* 7.0, C(α)*H*), 4.67 (1H, quin, $J_{1',2'}$ 6.8, CH(CH_2CH_3)$_2$), 4.82 (1H, quin, $J_{1',2'}$ 6.8, CH(CH_2CH_3)$_2$), 5.81 (1H, d, $J_{9,8}$ 15.6, C(9)*H*), 6.95 (1H, dt, $J_{8,9}$ 15.6, $J_{8,7}$ 6.9, C(8)*H*), 7.22–7.43 (10H, m, 2x *o/m/p-Ph*); δ_C (50 MHz, $CDCl_3$) 9.5 (CH(CH_2CH_3)$_2$), 20.7 (C(α)CH_3), 26.3 ($C(4)H_2$), 26.5 2x(CH(CH_2CH_3)$_2$), 27.8 ($C(5)H_2$), 32.1 ($C(6)H_2$), 33.4 ($C(7)H_2$), 36.6 ($C(2)H_2$), 50.2 (CH_2Ph), 53.9 (*C*(3)H), 58.6 (*C*(α)H), 76.4 2x(CH(CH_2CH_3)$_2$), 121.7 (*C*(9)H), 126.6, 126.9, 127.8, 128.0, 128.2 2x(*o/m/p-Ph*), 141.9, 143.2 2x(*i-Ph*), 148.8 (*C*(8)H), 166.6, 172.6 2x(CO_2); *m/z* (EI^+) 549.3837 (MH^+, $C_{35}H_{51}O_4N^+$ requires 549.3818); (CI^+) 549 ((MH)$^+$. 60%), 420 (12), 352 (30), 262 (35), 181 (70), 105 (100).

Preparation of di-3-pentyl-(3*R*,α*R*,8*R*,α′*R*)-3,8-bis-*N*-benzyl-*N*-α-methylbenzylamino-decadioate (19)

Following the general procedure 1a, (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (1.81 g, 8.6 mmol) in THF (20 mL), *n*-BuLi (5.3 mL, 8.6 mmol) and diester **17** (290 mg, 0.86 mmol) in

THF (1 mL) gave, after chromatographic purification on silica (1 : 19, EtOAc : pentane), **19** (427 mg, 67%) as a colourless oil; $[\alpha]_D^{26}$ +7.1 (*c* 0.86, $CHCl_3$); ν_{max} (film) 903, 964, 1460, 1493, 1726, 1807, 1948, 1975, 2971; δ_H (400 MHz, $CDCl_3$) 0.82 (6H, t, $J_{3',2'}$ 7.4, $CH(CH_2CH_3)_2$), 0.86 (6H, t, $J_{3',2'}$ 7.4, $CH(CH_2CH_3)_{2'}$), 1.20–1.30 (4H, m, C(5)H_2 and C(6)H_2), 1.33 (6H, d, *J* 7.0, 2x C(α)CH_3), 1.42–1.75 (12H, m, 2x $CH(CH_2CH_3)_2$, C(4)H_2 and C(7)H_2), 1.97 (4H, m, C(2)H_2 and C(9)H_2), 3.35–3.38 (2H, m, C(3)*H* and C(8)*H*), 3.49 (2H, AB d, *J* 15.0, CH_AH_BPh), 3.81 (2H, AB d, *J* 15.0, CH_AH_BPh), 3.82 (2H, q, *J* 7.0, 2x C(α)*H*), 4.69 (2H, quin, $J_{1',2'}$ 6.7, 2x $CH(CH_2CH_3)_2$), 7.23–7.46 (20H, m, 4x *o/m/p-Ph*); δ_C (50 MHz, $CDCl_3$) 9.6 ($CH(CH_2CH_3)_2$), 20.4 (C(α)CH_3), 26.4 ($CH(CH_2CH_3)_2$), 27.4 (*C*(5)H_2 and *C*(6)H_2), 33.9 (*C*(4)H_2 and *C*(7)H_2), 37.0 (*C*(2)H_2 and *C*(9)H_2), 50.2 2x(CH_2Ph), 54.3 (*C*(3)H and *C*(8)H), 58.4 2x(*C*(α)H), 76.4 2x($CH(CH_2CH_3)_2$), 126.6, 126.9. 127.9, 128.2 4x(*o/m/p-Ph*), 141.9, 143.2 4x(*i-Ph*), 172.6 2x(CO_2); *m/z* (EI^+) 761.5251 (MH^+, $C_{50}H_{69}O_4N_2^+$ requires 761.5257); 762 ($(MH_2)^+$, 100%), 747 (6), 631 (8).

Preparation of di-3-pentyl-(3*R*,α*R*,8*S*,α′*S*)-3,8-bis-*N*-benzyl-*N*-α-methylbenzylamino-decadioate (20)

Following the general procedure 1a, (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (127 mg, 0.6 mmol) in THF (5 mL), *n*-BuLi (0.4 mL, 0.6 mmol) and diester **17** (82 mg, 0.4 mmol) in THF (1 mL) gave, after chromatographic purification on silica (1 : 49, EtOAc : pentane), **20** (82 mg, 71%) as a colourless oil; $[\alpha]_D^{26}$ −0.3 (*c* 0.86, $CHCl_3$); ν_{max} (film) 903, 964, 1460, 1493, 1726, 1807, 1948, 1975, 2971, 3020, 3060, 3080; δ_H (200 MHz, $CDCl_3$) 0.80 (6H, t, $J_{3',2'}$ 7.4, $CH(CH_2CH_3)_2$), 0.87 (6H, t, $J_{3',2'}$ 7.4, $CH(CH_2CH_3)_2$), 1.20–1.30 (4H, m, C(5)H_2 and C(6)H_2), 1.33 (6H, d, *J* 7.0, 2x C(α)CH_3), 1.42–1.75 (8H, m, 2x $CH(CH_2CH_3)_2$), C(4)H_2 and C(7)H_2), 1.97 (4H, m, C(2)H_2 and C(9)H_2), 3.30–3.43 (2H, m, C(3)*H* and C(8)*H*), 3.49 (2H, AB d, *J* 15.0, CH_AH_BPh), 3.81 (2H, AB d, *J* 15.0, CH_AH_BPh), 3.82 (2H, q, *J* 7.0, 2x C(α)*H*), 4.69 (2H, quin, $J_{1',2'}$ 6.7, 2x $CH(CH_2CH_3)_2$), 7.23–7.46 (20H, m, 4x *o/m/p-Ph*); δ_C (50 MHz, $CDCl_3$) 9.5 ($CH(CH_2CH_3)_2$), 20.4 (C(α)CH_3), 26.3 ($CH(CH_2CH_3)_2$), 27.3 (*C*(5)H_2 and *C*(6)H_2), 33.7 (*C*(4)H_2 and *C*(7)H_2), 37.0 (*C*(2)H_2 and *C*(9)H_2), 50.2 (CH_2Ph), 54.2 (*C*(3)H and *C*(8)H), 58.3 (*C*(α)H), 76.4 ($CH(CH_2CH_3)_2$), 126.5, 126.7, 127.9, 128.2 4x(*o/m/p-Ph*), 141.9, 143.1 4x(*i-Ph*), 172.6 2x(CO_2); *m/z* (EI^+) 761.5252 (MH^+, $C_{50}H_{69}O_4N_2^+$ requires 761.5257); 762 ($(MH_2)^+$, 100%), 550 (5).

Preparation of (*E*)-methyl-4-(*N*-benzylamino)-but-2-enoate (21)

Benzylamine (4.28 g, 40.0 mmol) was added dropwise to a stirred solution of methyl 4-bromocrotonate (3.07 g, 20.0 mmol) and stirred at rt under nitrogen for 3 h before being washed with aqueous saturated $NaHCO_3$ solution. The resultant solution was extracted with DCM, dried and concentrated *in vacuo* and the residue purified *via* column chromatography on silica (1 : 4, Et_2O : pentane) to give the **21** (3.10 g, 76%) as a colourless oil with spectroscopic properties consistent with the literature; δ_H (200 MHz, $CDCl_3$) 1.44 (1H, br s, N*H*), 3.44 (2H, dd, $J_{4,3}$ 5.4, $J_{4,2}$ 1.8, C(4)H_2), 3.75 (3H, s, CO_2CH_3), 3.82 (2H, s, CH_2Ph), 6.05 (1H, dt, $J_{2,3}$ 15.7, $J_{2,4}$ 1.8, C(2)*H*), 7.04 (1H, dt, $J_{3,2}$ 15.7, $J_{3,4}$ 5.4, C(3)*H*), 7.24–7.35 (5H, m, *o/m/p-Ph*).[25]

Preparation of dimethyl-(*E*,*E*)-4-(*N*-benzyl-*N*-methoxycarbonylallylamino)-but-2-enoate (22)

Methyl 4-bromocrotonate (1.3 mL, 10.7 mmol) was added to a solution of methyl-(*E*)-4-(*N*-benzylamino)-but-2-enoate **21** (2.0 g, 9.8 mmol) in DCM (15 mL) at 0 °C, followed by triethylamine (3.1 mL, 20.0 mmol) and stirred overnight. After purification *via* column chromatography on silica (1 : 5, Et_2O : pentane), diene **22** was isolated as an orange oil (1.77 g, 60%) with spectroscopic properties consistent with the literature;[26] δ_H (400 MHz, $CDCl_3$) 3.24–3.26 (4H, m, 2x C(4)H_2), 3.61 (2H, s, CH_2Ph), 3.75 (6H, s, 2x CO_2CH_3), 6.06 (2H, d, $J_{2,3}$ 15.7, 2x C(2)*H*), 6.95 (2H, dt, $J_{3,2}$ 15.7, $J_{3,4}$ 5.8, C(3)*H*), 7.30–7.40 (5H, m, *o/m/p-Ph*).

Preparation of (3*R*,4*R*,5*S*,α*S*)- and (3*R*.4*R*,5*R*,α*S*)-1-benzyl-3-(*N*-benzyl-*N*-α-methylbenzylamino)-4-methoxycarbonyl-5-methoxycarbonylmethyl-piperidine (23 and 24)

Following the general procedure 1a, *n*-BuLi (2.5 M, 0.3 mL, 0.76 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (170 mg, 0.80 mmol) in THF (3 mL) and diene **22** (200 mg, 0.67 mmol) in THF (5 mL) gave, after purification *via* column chromatography on silica (1 : 3, Et_2O : pentane), a partially separable mixture of diastereoisomers (261 mg, 76% overall). The least polar fraction gave piperidine **24** (15 mg, 5%) as a colourless oil; $[\alpha]_D^{23}$ +14.5 (*c* 0.75, $CHCl_3$); ν_{max} (film) 2948, 1737, 1170; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.9, C(α)CH_3), 1.97 (1H, br d, C(6)H_{ax}), 2.05 (1H, t, $J_{2,1;2,3}$ 10.7, C(2)H_{ax}), 2.49–2.67 (5H, m, C(4)H_{ax}, C(5)H_{eq}, C(6)H_{eq}, and C(1′)H_2), 2.95–2.96 (1H, m, C(2)H_{eq}), 3.35–3.49 (3H, m, C(3)*H* and CH_2Ph'), 3.50, 3.55 (3H, s, 2x CO_2CH_3), 3.67 (1H, AB d, $J_{A,B}$ 14.5, CH_AH_BPh), 3.78 (1H, AB d, $J_{A,B}$ 14.5, CH_AH_BPh), 4.05 (1H, q, *J* 6.9, C(α)*H*), 7.16–7.34 (15H, m, 3x *o/m/p-Ph*); δ_C (100 MHz, $CDCl_3$) 18.4 (C(α)CH_3), 33.0 (*C*(1′)H_2), 33.4 (*C*(5)H), 49.4 (*C*(4)H), 49.5 (CH_2Ph), 51.2, 51.4 2x(CO_2CH_3), 53.9 (*C*(3)H), 55.6 (*C*(2)H_2), 57.2, (*C*(6)H_2), 58.7 (*C*(α)H), 62.6 (CH_2Ph'), 126.5, 126.6, 126.9, 127.1, 127.7, 127.8, 128.0, 128.1, 128.2, 128.4, 128.6 3x(*o/m/p-Ph*), 138.6, 141.0, 144.2 3x(*i-Ph*), 173.4, 173.6 2x(CO_2); *m/z* (CI^+) 527 (5%), 515 ($(MH)^+$, 100).

Further elution furnished the major piperidine diastereoisomer **23** (210 mg, 61%) as a colourless oil; $[\alpha]_D^{23}$ +11.0 (*c* 1.00, $CHCl_3$); ν_{max} (film) 1737, 1159; δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.9, C(α)CH_3), 1.73 (1H, m, C(6)H_{ax}), 1.99 (1H, app t, $J_{2ax,2eq;2ax,3ax}$ 10.8, C(2)H_{ax}), 2.07 (1H, dd, $J_{A,B}$ 15.7, $J_{A,5}$ 8.3, C(1′)H_AH_B), 2.21 (1H, dd, $J_{B,A}$ 15.7, $J_{B,5}$ 2.9, C(1′)H_AH_B), 2.33–2.38 (2H, m, C(4)H_{ax} and C(5)H_{ax}), 2.93 (1H, ddd, $J_{6eq,6ax}$ 11.3, $J_{6eq,5ax}$ 3.4, $J_{6eq,2eq}$ 1.4, C(6)H_{eq}), 3.10 (1H, ddd, $J_{2eq,2ax}$ 10.8, $J_{2eq,3ax}$ 2.6, $J_{2eq,6eq}$ 1.4, C(2)H_{eq}), 3.26–3.30 (1H, m, C(3)H_{ax}), 3.42–3.45 (4H, m, CO_2CH_3 and CH_AH_BPh'), 3.57–3.60 (4H, m, CO_2CH_3 and CH_AH_BPh'), 3.66 (1H, AB d, *J* 13.5, CH_AH_BPh), 3.88 (1H, AB d, *J* 13.5, CH_AH_BPh), 3.95 (1H, q, *J* 6.9, C(α)*H*), 7.18–7.40 (15H, m, 3x *o/m/p-Ph*); δ_C (100 MHz, $CDCl_3$) 15.9 (C(α)CH_3), 35.8 (*C*(5)H), 36.8 (*C*(1′)H_2), 50.0 (CH_2Ph), 51.4, 51.5 2x(CO_2CH_3), 52.8 (*C*(4)H), 56.6, 56.7 (*C*(3)H and *C*(α)H), 55.0, 58.2, 62.5 (*C*(2)H_2, *C*(6)H_2 and CH_2Ph'), 126.5, 126.8, 127.1, 127.8, 128.0, 128.3, 129.1 3x(*o/m/p-Ph*), 138.3, 140.4, 143.7 3x(*i-Ph*), 172.0, 173.6 2x(CO_2); *m/z* (CI^+) 515.2912 (MH^+, $C_{32}H_{38}N_2O_4^+$ requires 515.2910); 537 (10%), 515 ($(MH)^+$, 100).

Preparation of methyl-(*E*)-4-allylamino-but-2-enoate (25)

Methyl 4-bromocrotonate (9.6 mL, 70 mmol) was added to a solution of allylamine (4.68 mL, 63.0 mmol) in DCM (50 mL) at 0 °C, followed by NEt_3 (10.0 mL, 71.5 mmol) and stirred overnight before the addition of saturated aqueous K_2CO_3 solution. The resultant solution was extracted with DCM, dried and concentrated *in vacuo*. After purification *via* column chromatography (1 : 5, Et_2O : pentane) on silica, the more polar mono-ester **25** (3.71 g, 38%) was isolated as an orange oil; (Found C, 62.3; H, 8.7; N, 8.8. Calc. for $C_8H_{13}NO_2$: C, 61.9; H, 8.4; N, 9.0%); ν_{max} (film) 1659, 1724, 3311; δ_H (400 MHz, $CDCl_3$) 3.25 (2H, d, *J* 8.7, $NCH_{2-allyl}$), 3.41 (2H, dd, $J_{4,3}$ 5.4, $J_{4,2}$ 1.7, C(4)H_2), 3.74 (3H, CO_2CH_3), 5.11 (1H, dd, *J* 14.5, 1.2, $CHCH_{cis}H_{trans-allyl}$), 5.19 (1H, dd, *J* 14.5, 1.5, $C(3)H_{cis}H_{trans-allyl}$), 5.81–5.92 (1H, m, NCH_2CH_{allyl}), 6.00 (1H, dd, $J_{2,3}$ 14.4, $J_{2,4}$ 1.7, C(2)*H*), 6.99 (1H, dt, $J_{3,2}$ 14.4, $J_{3,4}$ 5.4, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 49.5 (*C*(4)H_2), 51.5 (CO_2CH_3), 51.7 ($NCH_{2-allyl}$), 116.3 ($CHCH_{2-allyl}$), 121.1 (*C*(2)H), 136.3

($CHCH_{2-allyl}$), 146.9 (C(3)H), 166.9 (CO_2); m/z (CI^+) 156.1011 (MH^+, $C_8H_{14}NO_2^+$ requires 156.1024); (EI^+) 156 ($(MH)^+$, 100%), 114 (61).

Diester **29** was isolated as the least polar component (5.13 g, 32%) as a yellow oil; ν_{max} (film) 1660, 1726, 3069; δ_H (400 MHz, $CDCl_3$) 3.09 (2H, d, J 16.3, $NCH_{2-allyl}$), 3.22 (4H, dd, $J_{4,3}$ 15.7, $J_{4,2}$ 1.5, 2x C(4)H_2), 3.71 (6H, s, 2x CO_2CH_3), 5.16 (1H, dd, J 13.6, 1.5, $CHCH_{cis}H_{trans-allyl}$), 5.19 (1H, dd, J 13.6, 1.5, $CHCH_{cis}H_{trans-allyl}$), 5.71–5.88 (1H, m, $CHCH_{2-allyl}$), 6.03 (2H, dd, $J_{2,3}$ 15.7, $J_{2,4}$ 1.5, 2x C(2)H), 6.91 (2H, dt, $J_{3,2}$ 15.7, $J_{3,4}$ 5.8, 2x C(3)H); δ_C (100 MHz, $CDCl_3$) 51.6 (CO_2CH_3), 54.4 (C(4)H_2), 57.0 ($NCH_{2-allyl}$), 118.2 ($CHCH_{2-allyl}$), 122.6 (C(2)H), 134.8 ($CHCH_{2-allyl}$), 145.8 (C(3)H), 166.7 (CO_2); m/z (CI^+) 254.1397 (MH^+, $C_{13}H_{20}NO_4^+$ requires 254.1392); (EI^+) 255 (34%), 254 ($(MH)^+$, 100).

Preparation of (2*E*,α*R*)-methyl 4-(*N*-α-methylbenzylamino)-but-2-enoate (26)

(*R*)-*N*-Benzyl-*N*-α-methylbenzylamine (88.5 mL, 66.0 mmol) was added dropwise to a solution of methyl 4-bromocrotonate (5.26 mL, 33.0 mmol) and stirred at rt under nitrogen for 3 h before being washed with aqueous saturated $NaHCO_3$ solution. The resultant solution was extracted with DCM, dried and concentrated *in vacuo*, and the residue purified *via* column chromatography on silica (1 : 2, Et_2O : pentane) to give the ester **26** (6.3 g, 87%) as a colourless oil with spectroscopic properties consistent with the literature; $[\alpha]_D^{23}$ +61.9 (c 1.00, $CHCl_3$); (lit. *ent.*,[27] $[\alpha]_D^{23}$ −48.5 (c 1.00, $CHCl_3$)); δ_H (200 MHz, $CDCl_3$) 1.37 (3H, d, J 6.6, C(α)CH_3), 1.53 (1H, br s, NH), 3.26 (2H, dd, $J_{4,3}$ 5.5, $J_{4,2}$ 1.8, C(4)H_2), 3.75 (3H, s, CO_2CH_3), 3.81 (1H, q, J 6.6, C(α)H), 5.98 (1H, dt, $J_{2,3}$ 15.8, $J_{2,4}$ 1.8, C(2)H), 6.99 (1H, dt, $J_{3,2}$ 15.8, $J_{3,4}$ 5.5, C(3)H), 7.23–7.39 (5H, m, *o*/*m*/*p*-*Ph*).

Preparation of (*E*)-methyl 4-(*N*-*tert*-butylamino)-but-2-enoate (27)

tert-Butyl amine (5.9 mL, 55.7 mmol) was added dropwise to a stirred solution of methyl 4-bromocrotonate (3.9 mL, 27.9 mmol) under nitrogen at rt and left to stir overnight. The products were partitioned between aqueous saturated $NaHCO_3$ solution and DCM, organic layers dried and concentrated *in vacuo*. The residue was purified *via* column chromatography on silica (1 : 3, Et_2O : pentane) to furnish the ester **27** (3.85 g, 81%) as a yellow oil, with spectroscopic properties consistent with these quoted in the literature;[28] δ_H (200 MHz, $CDCl_3$) 1.08 (9H, s, C(CH_3)$_3$), 3.38 (2H, dd, $J_{4,3}$ 5.2, $J_{4,2}$ 1.6, C(4)H_2), 3.72 (3H, s, CO_2CH_3), 6.01 (1H, dt, $J_{2,3}$ 15.6, $J_{2,4}$ 1.6, C(2)H), 7.05 (1H, dt, $J_{3,2}$ 15.6, $J_{3,4}$ 5.2, C(3)H).

Preparation of methyl-(2*E*,2′*E*)-4-(*N*-methyl-*N*-methoxycarbonylallylamino)-but-2-enoate (28)

Methylamine (2.0 M, 27.9 mL, 55.7 mmol) was added dropwise to a stirred solution of methyl 4-bromocrotonate (3.9 mL, 27.9 mmol) at 0 °C under nitrogen. After 30 min the mixture was warmed to rt and left to stir for 5 h. Aqueous saturated $NaHCO_3$ solution was added, solution partitioned between brine and DCM, organic layers dried and concentrated *in vacuo*. The residue was purified *via* column chromatography on silica gel (1 : 2, Et_2O : pentane) to give the diene **28** (1.77 g, 51%) as a colourless oil; ν_{max} (film) 1660, 1727, 2793, 2950; δ_H (200 MHz, $CDCl_3$) 2.26 (3H, s, NCH_3), 3.16 (4H, dd, $J_{4,3}$ 6.0, $J_{4,2}$ 1.6, C(4)H_2), 3.75 (6H, s, 2x CO_2CH_3), 5.99 (2H, dt, $J_{2,3}$ 15.7, $J_{2,4}$ 1.6, C(2)H), 6.95 (2H, dt, $J_{3,2}$ 15.7, $J_{3,4}$ 6.0, C(3)H); δ_C (100 MHz, $CDCl_3$) 42.4 (NCH_3), 51.4 (C(4)H_2), 58.0 (CO_2CH_3), 122.9 (C(2)H), 145.7 (C(3)H), 166.7 (CO_2); m/z (CI^+) 228.1231 (MH^+, $C_{11}H_{18}NO_4^+$ requires 228.1236); 250 (60%), 228 ($(MH)^+$, 100).

Preparation of methyl-(2*E*,2′*E*)-4-(*N*-allyl-*N*-methoxycarbonylallylamino)-but-2-enoate (29)

Methyl-(*E*)-4-bromocrotonate (0.25 mL, 3.52 mmol) was added dropwise to methyl-(*E*)-4-allylamino-but-2-enoate **25** (500 mg, 3.2 mmol) in DCM (10 mL) at 0 °C and allowed to warm to rt overnight before the addition of saturated aqueous K_2CO_3 solution. The resultant solution was extracted with DCM, dried and concentrated *in vacuo*. Purification *via* column chromatography on silica (1 : 8, Et_2O : pentane) furnished diester **29** (0.81 g, 98%) as a yellow oil with spectroscopic properties same as above.

Preparation of methyl-(2*E*,2′*E*)-4-(*N*-*tert*-butyl-*N*-methoxycarbonylallylamino)-but-2-enoate (30)

Methyl 4-bromocrotonate (2.46 g, 11.7 mmol) was added dropwise to a stirred solution of amino ester **27** (1.0 g, 5.8 mmol) and DIPEA (0.83 g, 6.4 mmol). The mixture was placed under nitrogen in DCM (20 mL) at rt and left to stir overnight. This solution was partitioned between aqueous saturated $NaHCO_3$ and DCM, organic layers dried and concentrated *in vacuo*. The residue was purified *via* column chromatography on silica (1 : 4, Et_2O : pentane) and then recrystallised (Et_2O : hexane) to give the diester **30** (1.46 g, 92%) as white solid; mp 48–49 °C (Et_2O : hexane); ν_{max} (KBr) 1160, 1660, 1723, 2886, 2977; δ_H (400 MHz, $CDCl_3$) 1.08 (9H, s, C(CH_3)$_3$), 3.30 (4H, dd, $J_{4,3}$ 5.7, $J_{4,2}$ 1.6, C(4)H_2), 3.72 (6H, s, 2x CO_2CH_3), 5.98 (2H, dt, $J_{2,3}$ 15.6, $J_{2,4}$ 1.6, C(2)H), 6.94 (2H, dt, $J_{3,2}$ 15.6, $J_{3,4}$ 5.7, C(3)H); δ_C (100 MHz, $CDCl_3$) 27.4 (C(CH_3)$_3$), 50.5 (CO_2CH_3), 51.4 (C(4)H_2), 55.1 (C(CH_3)$_3$), 121.2 (C(2)H), 149.0 (C(3)H), 168.9 (CO_2); m/z (CI^+) 292.1513 (MNa^+. $C_{14}H_{21}NaNO_4^+$ requires 292.1525); 292 (80%), 270 ($(MH)^+$, 40), 214 (100).

Preparation of methyl-(2*E*,2′*E*,α*R*)-4-(*N*-α-methylbenzyl-*N*-methoxycarbonylallylamino)-but-2-enoate (31)

Methyl 4-bromocrotonate (1.5 mL, 9.2 mmol) was added dropwise to a stirred solution of ester **26** (1.0 g, 4.6 mmol) in DCM (5 mL) at 0 °C followed by the dropwise addition of NEt_3 (0.63 mL, 4.6 mmol). The solution was allowed to warm slowly to rt overnight before being partitioned between aqueous saturated $NaHCO_3$ solution and DCM, organic layers combined, dried and concentrated *in vacuo*. The residue was purified *via* column chromatography on silica (1 : 4, Et_2O : pentane) to give diester **31** (0.85 g, 58%) as a colourless oil; $[\alpha]_D^{23}$ +157.7 (c 1.00, $CHCl_3$); ν_{max} (film) 1172, 1659, 1724, 2821, 2951; δ_H (200 MHz, $CDCl_3$) 1.36 (3H, d, J 6.8, C(α)CH_3), 3.10–3.37 (4H, m, C(4)H_2), 3.74 (6H, s, 2x CO_2CH_3), 3.85 (1H, q, J 6.8, C(α)H), 6.01 (2H, dt, $J_{2,3}$ 15.8, $J_{2,4}$ 1.6, C(2)H), 6.97 (2H, dt, $J_{3,2}$ 15.8, $J_{3,4}$ 5.7, C(3)H), 7.22–7.35 (5H, m, *o*/*m*/*p*-*Ph*); δ_C (50 MHz, $CDCl_3$) 17.1 (C(α)CH_3), 51.1 (C(4)H_2), 51.4 (CO_2CH_3), 59.2 (C(α)H), 122.2 (C(2)H), 127.1 (*p*-*Ph*), 127.3, 128.3 (*o*/*m*-*Ph*), 142.9 (*i*-*Ph*), 146.7 (C(3)H), 166.5 2x(CO_2); m/z (CI^+) 318.1704 (MH^+, $C_{18}H_{24}NO_4^+$ requires 318.1705); 340 (10%), 318 ($(MH)^+$, 20), 214 (100).

Preparation of (3*R*,4*R*,5*S*,α*S*)- and (3*R*,4*R*,5*R*,α*S*)-1-methyl-3-(*N*-benzyl-*N*-α-methylbenzylamino)-4-methoxycarbonyl-5-methoxycarbonylmethyl-piperidine (32 and 33)

Following the general procedure 1a, *n*-BuLi (2.5 M, 3.4 mmol, 1.4 mL), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (0.75 g, 3.5 mmol) in THF (5 mL) and diene **28** (0.50 g, 2.2 mmol) in THF (10 mL) gave, after purification *via* chromatography on silica (1 : 2, Et_2O : pentane) a separable mixture of diastereoisomers (0.69 g, 72%). The minor piperidine diastereoisomer **33** was isolated as a 11 : 1 mixture of piperidine **33** (51 mg, 5%) colourless oil and starting material **28**; ν_{max} (film) 1171, 1737, 2947; δ_H (400 MHz, $CDCl_3$) 1.41 (3H, d, J 7.0, C(α)CH_3), 1.90 (1H, dd, $J_{6ax,6eq}$ 11.5, $J_{6ax,5eq}$ 2.1, C(6)H_{ax}), 1.97 (1H, app t, $J_{2ax,2eq;2ax,3ax}$ 10.8, C(2)H_{ax}), 2.20 (3H, s, NCH_3), 2.50–2.63 (5H, m, C(4)H_{ax}, C(5)H_{eq}, C(6)H_{eq}, and C(1′)H_2), 2.91 (1H, dd, $J_{2eq,2ax}$ 10.8, $J_{2eq,3ax}$

3.4, C(2)H_{eq}), 3.39 (1H, td, $J_{3ax,2ax;3ax,4ax}$ 11.2, $J_{3ax,2eq}$ 4.1, C(3)H_{ax}), 3.48, 3.62 (3H, s, 2x CO_2CH_3), 3.79 (2H, AB q, J 14.5, CH_2Ph), 4.07 (1H, q, J 7.0, C(α)H), 7.19–7.33 (10H, m, 2x *o/m/p-Ph*); δ_C (100 MHz, $CDCl_3$) 18.2 (C(α)CH_3), 33.0 (C(1′)H_2), 33.3 (C(5)H), 46.6 (NCH_3), 48.8 (C(4)H), 49.6 (CH_2Ph), 51.3, 51.5 2x(CO_2CH_3), 53.3 (C(3)H), 58.1 (C(2)H_2), 58.5 (C(α)H), 59.7 (C(6)H_2), 125.5, 125.7, 127.0, 127.8, 127.9, 128.0, 128.1, 128.4 (*o/m/p-Ph*), 141.0, 144.2 2x(*i-Ph*), 173.4, 173.7 2x(CO_2); *m/z* (CI^+) 439.2603 (MH^+, $C_{26}H_{35}N_2O_4^+$ requires 439.2597); 461 (75%), 439 ($(MH)^+$, 40).

Further elution gave the major product piperidine **32** (0.64 g, 67%) as a colourless oil; $[\alpha]_D^{23}$ +14.4 (*c* 1.00, $CHCl_3$); ν_{max} (film) 1736, 2845, 2947; δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, J 7.0, C(α)CH_3), 1.56 (1H, app t, $J_{6ax,6eq;6ax,5ax}$ 10.9, C(6)H_{ax}), 2.01 (1H, app t, $J_{2ax,2eq;2ax,3ax}$ 11.0, C(2)H_{ax}), 2.05 (1H, dd, $J_{1'A,1'B}$ 15.7, $J_{1'A,5}$ 9.2, C(1′)H_A), 2.20 (1H, dd, $J_{1'B,1'A}$ 15.7, $J_{1'B,5}$ 3.2, C(1′)H_B), 2.27–2.32 (5H, m, C(4)H and C(5)H and NCH_3), 2.86 (1H, dd, $J_{6eq,6ax}$ 16.9, $J_{6eq,5ax}$ 2.8, C(6)H_{eq}), 3.08 (1H, dd, $J_{2eq,2ax}$ 11.6, $J_{2eq,3ax}$ 2.0, C(2)H_{eq}), 3.28–3.34 (1H, m, C(3)H), 3.39, 3.62 (3H, s, 2x CO_2CH_3), 3.68 (1H, AB d, J 13.8, CH_AH$_B$Ph), 3.92 (1H, AB d, J 13.8, CH$_A$$H_B$Ph), 3.96 (1H, q, J 7.0, C(α)H), 7.17–7.35 (10H, m, 2x *o/m/p-Ph*); δ_C NMR (100 MHz, $CDCl_3$) 15.9 (C(α)CH_3), 35.7 (NCH_3), 36.7 (C(1′)H_2), 46.4 (C(5)H), 50.1 (CH_2Ph), 51.5, 51.6 2x(CO_2CH_3), 52.2 (C(4)H), 56.3 (C(3)H), 56.7 (C(α)H), 58.2 (C(2)H_2), 59.8 (C(6)H_2), 126.6, 126.8 2x(*p-Ph*) 127.8, 128.1, 129.0 2x(*o/m-Ph*), 140.4, 143.6 2x(*i-Ph*), 171.9, 173.5 2x(CO_2); *m/z* (CI^+) 439.2601 (MH^+, $C_{26}H_{35}N_2O_4^+$ requires 439.2597); 461 (70%), 439 ($(MH)^+$, 50).

Preparation of (3*S*,4*S*,5*S*,α*S*)-1-allyl-3-(*N*-benzyl-*N*-α-methylbenzylamino)-4-methoxycarbonyl-5-methoxycarbonylmethyl-piperidine (34)

Following the general procedure 1a, *n*-BuLi (2.5 M, 5.8 mL, 14.5 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (3.13 mL, 15.0 mmol) in THF (17 mL) and diester **29** (2.54 g, 10.0 mmol) in THF (10 mL) gave the crude reaction product **34** in (78% de) after 2 h. Purification *via* column chromatography on silica (3 : 10, Et_2O : pentane) gave the piperidine **34** (3.76 g, 81%) as a yellow oil; $[\alpha]_D^{23}$ +14.9 (*c* 2.23, $CHCl_3$); ν_{max} (film) 1634, 1731, 2765; δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, J 6.8, C(α)CH_3), 1.56–1.66 (1H, m, C(6)H_AH$_B$), 1.94 (1H, dd, $J_{2ax,2eq}$ 11.0, $J_{2ax,3eq}$ 2.0, C(2)H_AH$_B$), 2.04 (1H, dd, $J_{A,B}$ 15.8, $J_{A,5}$ 8.9, CH_AH$_B$$CO_2$), 2.20 (1H, dd, $J_{B,A}$ 15.8, $J_{B,5}$ 3.0, CH$_A$$H_B$$CO_2$), 2.24–2.36 (2H, m, C(4)H, C(5)H), 2.88 (1H, dd, $J_{6ax,5ax}$ 12.1, $J_{6ax,6eq}$ 1.4, C(6)H$_A$$H_B$), 2.94 (1H, dd, $J_{A,B}$ 13.5, $J_{A,CH}$ 10.1, CH_AH$_B$(CH=CH$_2$)), 3.04 (1H, dd, $J_{B,A}$ 13.5, $J_{B,CH}$ 9.9, CH$_A$$H_B$(CH=CH$_2$)), 3.15 (1H, dd, $J_{2eq,2ax}$ 11.0, $J_{2eq,3eq}$ 1.4, C(2)H$_A$$H_B$), 3.26 (1H, dt, $J_{3eq,4ax}$ 7.4, $J_{3eq,2ax;}$ 2.0, C(3)H), 3.39 (3H, s, CO_2CH_3), 3.61 (3H, s, $CO_2CH_{3'}$), 3.66 (1H, AB d, J 13.8, CH_AH$_B$Ph), 3.91 (1H, AB d, J 13.8, CH$_A$$H_B$Ph), 3.98 (1H, q, J 6.8, C(α)H), 5.18 (1H, dd, J 4.1, 1.1, CH_{cis}H=CH), 5.21 (1H, dd, J 10.0, 1.1, CH_{tr}H=CH), 5.69–5.92 (1H, m, CH=CH$_2$), 7.13–7.43 (10H, m, *o/m/p-Ph*); δ_C (100 MHz, $CDCl_3$) 15.9 (C(α)CH_3), 35.6 (C(5)H), 36.8 (CH_2CO_2), 50.1 (CH_2Ph), 51.4, 51.6 2x(CO_2CH_3), 52.7 (C(4)H), 55.4 (C(2)H), 56.4 (C(3)H), 56.7 (C(α)H), 57.9 (C(6)H_2), 61.5 (CH_2CH=CH$_2$), 118.0 (CH=CH_2), 126.6, 126.9 2x(*p-Ph*), 127.8, 128.1, 129.1, 129.4 2x(*o/m-Ph*), 140.5, 143.6 2x(*i-Ph*), 151.4 (CH=CH$_2$), 171.9, 173.5 2x(CO_2); *m/z* (CI^+) 465.2749 (MH^+, $C_{28}H_{37}N_2O_4^+$ requires 465.2753); (EI^+) 523 (36%), 466 (29), 465 ($(MH)^+$, 100).

Preparation of (3*R*,4*R*,5*S*,α*S*)- and (3*R*,4*R*,5*R*,α*S*)-1-*tert*-butyl-3-(*N*-benzyl-*N*-α-methylbenzylamino)-4-methoxycarbonyl-5-methoxycarbonylmethyl-piperidine (36 and 37)

Following the general procedure 1a, *n*-BuLi (2.5 M, 2.0 mmol, 0.8 mL), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (0.44 g, 2.1 mmol) in THF (5 mL) and diester **30** (0.50 g, 1.7 mmol) in THF (10 mL) gave, after purification *via* column chromatography on silica (1 : 2, Et_2O : pentane) a separable mixture of diastereoisomers (0.68 g, 81%). The minor piperidine diastereoisomer **37** was isolated as an 8 : 1 mixture of piperidine **37** (36 mg, 4%) and starting material **30** as a colourless oil; ν_{max} (film) 1168, 1737, 2805, 2970; δ_H (400 MHz, $CDCl_3$) 0.94 (9H, s, C(CH_3)$_3$), 1.39 (3H, d, J 7.0, C(α)CH_3), 1.94 (1H, dd, $J_{6eq,6ax}$ 11.7, $J_{6eq,5eq}$ 2.4, C(6)H_{ax}), 2.02 (1H, app t, $J_{2ax,2eq;2ax,3ax}$ 10.7, C(2)H_{ax}), 2.42–2.47 (2H, m, C(5)H_{eq} and C(1′)H_A), 2.54 (1H, dd, $J_{4ax,3ax}$ 11.7, $J_{4ax,5eq}$ 4.5, C(4)H_{ax}), 2.67 (1H, dd, $J_{B,A}$ 17.8, $J_{B,5}$ 10.0, C(1′)H_B), 2.84 (1H, dt, $J_{6eq,6ax}$ 11.7, $J_{6eq,5eq;6eq,2eq}$ 2.5, C(6)H_{eq}), 3.05 (1H, ddd, $J_{2eq,2ax}$ 10.7, $J_{2eq,3ax}$ 4.1, $J_{2eq,6eq}$ 2.3, C(2)H_{eq}), 3.24 (1H, ddd, $J_{3ax,4ax}$ 11.7, $J_{3ax,2ax}$ 10.7, $J_{3ax,2eq}$ 4.1, C(3)H), 3.51, 3.62 (3H, s, 2x CO_2CH_3), 3.78 (2H, AB q, J 14.5, CH_2Ph), 4.09 (1H, q, J 7.0, C(α)H), 7.20–7.29 (10H, m, 2x *o/m/p-Ph*); δ_C (100 MHz, $CDCl_3$) 18.8 (C(α)CH_3), 26.1 (C(CH_3)$_3$), 32.7 (C(1′)H_2), 33.3 (C(5)H), 48.6 (C(2)H_2), 49.3 (CH_2Ph), 50.1 (C(4)H), 50.4 (C(6)H_2), 51.1, 51.3 2x(CO_2CH_3), 53.1 (C(CH_3)$_3$), 55.2 (C(3)H), 59.4 (C(α)H), 126.6, 127.7, 127.9, 128.5 2x(*o/m/p-Ph*), 141.4, 144.3 2x(*i-Ph*), 173.7, 173.9 2x(CO_2); *m/z* (CI^+) 481.3068 (MH^+, $C_{29}H_{41}N_2O_4^+$ requires 481.3066); 503 (20%), 481 ($(MH)^+$, 100).

Further elution furnished the major piperidine diastereoisomer **36** (0.65 g, 77%) as a colourless oil; $[\alpha]_D^{21}$ +16.1 (*c* 1.00, $CHCl_3$); ν_{max} (film) 1171, 1738, 2806; δ_H (400 MHz, $CDCl_3$) 1.08 (9H, s, C(CH_3)$_3$), 1.40 (3H, d, J 7.0, C(α)CH_3), 1.66 (1H, app t, J 10.5, C(6)H_{ax}), 2.04 (1H, app t, $J_{2ax,2eq;2ax,3ax}$ 10.5, C(2)H_{ax}), 2.08 (1H, dd, $J_{A,B}$ 15.7, $J_{A,5}$ 8.8, C(1′)H_A), 2.19–2.32 (3H, m, C(5)H_{eq}, C(4)H and C(1′)H_B), 3.10 (1H, br d, C(6)H_{eq}), 3.22–3.29 (2H, m, C(2)H_{eq} and C(3)H), 3.42, 3.62 (3H, s, 2x CO_2CH_3), 3.70 (1H, AB d, J 13.7, CH_AH$_B$Ph), 3.93 (1H, AB d, J 13.7, CH$_A$$H_B$Ph), 4.00 (1H, q, J 7.0, C(α)H), 7.17–7.37 (10H, m, 2x *o/m/p-Ph*); δ_C (100 MHz, $CDCl_3$) 16.2 (C(α)CH_3), 26.1 (C(CH_3)$_3$), 36.4 (C(5)H), 37.0 (C(1′)H_2), 48.8 (CH_2Ph), 50.0 (C(2)H_2), 51.0 (C(6)H_2), 51.3, 51.5 2x(CO_2CH_3), 53.3 (C(4)H), 53.7 (C(CH_3)$_3$), 57.0 (C(3)H), 57.9 (C(α)H), 126.5, 126.8, 127.8, 128.0, 129.1 2x(*o/m/p-Ph*), 140.7, 143.8 2x(*i-Ph*), 172.1, 173.8 2x(CO_2); *m/z* (CI^+) 481.3061 (MH^+, $C_{29}H_{41}N_2O_4^+$ requires 481.3066); 503 (100%), 481 ($(MH)^+$, 90).

Preparation of (3*R*,4*R*,5*S*,α*R*,α′*S*)- and (3*R*,4*R*,5*R*,α*R*,α′*S*)-1-α-methylbenzyl-3-(*N*-benzyl-*N*-α′-methylbenzylamino)-4-methoxycarbonyl-5-methoxycarbonylmethyl-piperidine (38 and 39)

Following the general procedure 1a, *n*-BuLi (1.6 M, 0.8 mL, 1.3 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (0.28 g, 1.3 mmol) in THF (3 mL) and diester **31** (0.35 mg, 1.1 mmol) in THF (5 mL) gave, after purification *via* column chromatography on silica (1 : 3, Et_2O : pentane), a separable mixture of diastereoisomers (0.36 g, 69% overall). The least polar fraction gave **39** (18 mg, 4%) as a colourless oil; $[\alpha]_D^{23}$ +18.0 (*c* 0.90, $CHCl_3$); ν_{max} (film) 1171, 1732, 1738, 2949, 3028; δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, J 6.7, C(α)CH_3), 1.35 (3H, d, J 7.0, C(α)C$H_{3'}$), 1.88 (1H, dd, $J_{6ax,6eq}$ 11.7, $J_{6ax,5eq}$ 1.7, C(6)H_{ax}), 1.98 (1H, app t, J 10.7, C(2)H_{ax}), 2.42–2.67 (5H, m, C(4)H_{ax}, C(5)H_{eq}, C(6)H_{eq}, and C(1′)H_2), 3.02 (1H, dd, $J_{2eq,2ax}$ 10.5, $J_{2eq,3ax}$ 2.3, C(2)H_{eq}), 3.32–3.39 (2H, m, C(3)H and C(α)H), 3.50, 3.55 (2 × 3H, s, CO_2CH_3), 3.74 (2H, ABq, J 14.5, NCH_2), 4.07 (1H, q, J 7.0, C(α)H'), 7.19–7.35 (15H, m, *o/m/p-Ph*); δ_C (100 MHz, $CDCl_3$) 18.3, 18.6 2x(C(α)CH_3), 32.8 (C(1′)H_2), 33.4 (C(5)H), 49.4, 51.6 (C(2)H_2 and C(6)H_2), 49.6 (C(4)H), 51.2, 51.4 2x(CO_2CH_3), 54.5 (C(3)H), 55.1 (NCH_2), 63.7 2x(C(α)H), 126.6, 126.8, 127.3, 127.7, 127.9, 128.1, 128.3, 128.6 (*o/m/p-Ph*), 141.2, 144.0, 144.2 3x(*i-Ph*), 173.5, 173.6 2x(CO_2CH_3); *m/z* (CI^+) 529.3076 (MH^+, $C_{33}H_{41}N_2O_4^+$ requires 529.3066); 551 (25%), 529 ($(MH)^+$,100).

The major diastereoisomer **38** was next eluted, and isolated as a colourless oil (0.35 g, 65%); $[\alpha]_D^{23}$ +48.6 (*c* 1.00, $CHCl_3$); ν_{max} (film) 1737, 2949; δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, J 7.0, C(α)CH_3), 1.37 (3H, d, J 6.7, C(α)C$H_{3'}$), 1.70–1.76 (1H, m, C(6)H_{ax}), 2.00–2.09 (2H, m, C(1′)H_A and C(2)H_{ax}), 2.15

(1H, dd, $J_{1'B,1'A}$ 15.0, $J_{1'B,5}$ 3.2, C(1′)H_B), 2.28–2.35 (2H, m, C(4)H and C(5)H), 2.86 (1H, ddd, $J_{6eq,6ax}$ 11.4, $J_{6eq,5ax}$ 3.4, $J_{6eq,2eq}$ 1.7, C(6)H_{eq}), 3.14 (1H, ddd, $J_{2eq,2ax}$ 10.9, $J_{2eq,3ax}$ 3.8, $J_{2eq,6eq}$ 1.7, C(2)H_{eq}), 3.25 (1H, m, C(3)H), 3.43, 3.55 2x(3H, s, CO_2CH_3 × 2), 3.58–3.65 (2H, m, NCH_A and C(α)H), 3.88 (1H, d, J 13.7, NCH_AH_B), 3.95 (1H, q, J 7.0, C(α)H), 7.19–7.40 (15H, m, *o/m/p-Ph*); δ_C (100 MHz, $CDCl_3$) 15.9, 17.1 2x(C(α)CH_3), 35.9 (C(5)H), 36.9 (C(1′)H_2), 50.0 (NCH_2), 51.0 (C(2)H_2), 51.4, 51.5 2x(CO_2CH_3) 53.1 (C(4)H), 55.4 (C(6)H_2), 56.6 (C(3)H) 56.9 (C(α)H′), 62.9 (C(α)H), 126.5, 126.8, 126.9, 127.5, 127.8, 128.1, 128.2, 129.1 3x(*o/m/p-Ph*), 140.5, 143.6, 143.8 3x(*i-Ph*), 172.1, 173.8 2x(CO_2); *m/z* (CI^+) 529.3060 (MH^+, $C_{33}H_{41}N_2O_4^+$ requires 529.3066); 551 (25%), 529 ($(MH)^+$,100), 425 (10).

Preparation of (3*S*,4*S*,5*R*,α*R*,α′*R*)-1-*N*-α-methylbenzyl-3-(*N*-benzyl-*N*-α′-methylbenzylamino)-4-methoxycarbonyl-5-methoxycarbonylmethyl-piperidine (40)

Following the general procedure 1a, *n*-BuLi (1.6 M, 0.5 mL, 0.7 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (161 mg, 0.8 mmol) in THF (3 mL) and diester **31** (0.20 g, 0.6 mmol) in THF (5 mL) gave, after purification *via* column chromatography on silica (1 : 3, Et_2O : pentane) piperidine **40** (0.28 g, 83%) as a colourless oil; $[\alpha]_D^{23}$ −8.5 (*c* 1.00, $CHCl_3$); ν_{max} (film) 1737, 2971; δ_H (400 MHz, $CDCl_3$) 1.14 (3H, d, J 7.0, C(α)CH_3), 1.37 (3H, d, J 6.7, C(α)CH_3′), 1.63 (1H, app t, $J_{6ax,6eq;6ax,5ax}$ 10.6, C(6)H_{ax}), 1.87 (1H, t, J 10.9, C(2)H_{ax}), 2.09 (1H, dd, $J_{1'A,1'B}$ 15.7, $J_{1'B,5}$ 8.8, C(1′)H_A), 2.22 (1H, dd, $J_{1'B,1'A}$ 15.7, $J_{1'B,5}$ 3.6, C(1′)H_B), 2.29–3.38 (2H, m, C(4)H and C(5)H), 3.09–3.20 (3H, m, C(6)H_{eq}, C(2)H_{eq} and C(3)H), 3.43 (4H, m, CO_2CH_3 and C(α)H′), 3.51 (1H, AB d, J 13.6, C$H_A$$H_B$Ph), 3.63 (3H, s, CO_2CH_3), 3.84 (1H, AB d, J 13.6, CH_AH_BPh), 3.90 (1H, q, J 7.0, C(α)H), 7.18–7.42 (15H, m, 3x *o/m/p-Ph*); δ_C (100 MHz, $CDCl_3$) 15.2, 20.2 2x(C(α)CH_3), 36.0 (C(5)H), 37.0 (C(1′)H_2), 49.9 (CH_2Ph), 51.4, 51.6 2x(CO_2CH_3), 52.9 (C(4)H), 53.3 (C(2)H_2), 54.8 (C(6)H_2), 56.3 (C(3)H) 56.7 (C(α)H), 64.2 (C′(α)H), 126.5, 126.7, 126.8, 126.9, 127.0, 127.4, 127.8, 128.0, 128.1, 128.3, 128.5, 129.1 3x(*o/m/p-Ph*), 140.5, 143.7, 144.0 3x(*i-Ph*), 172.1, 173.7 2x(CO_2); *m/z* (CI^+) 529.3069 (MH^+, $C_{33}H_{41}N_2O_4^+$ requires 529.3066); 551 (25%), 529 ($(MH)^+$,100), 424 (10).

Preparation of *tert*-butyl-(2*E*)-7-oxohept-2-enoate (41)

PCC (0.30 g, 1.3 mmol) was added to a solution of alcohol **57** (0.10 g, 0.50 mmol) and NaOAc (0.11 g, 1.3 mmol) in DCM (10 mL) at 0 °C. After 2 h Et_2O was added and the resultant solution concentrated *in vacuo*, partitioned between water and DCM, organic layers dried and re-concentrated *in vacuo* after being passed through a pad of silica (eluent Et_2O), aldehyde **41** (54 mg, 56%) was obtained as a colourless oil with spectroscopic data consistent with that quoted in the literature;[29] δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, C(CH_3)$_3$), 1.82–1.86 (2H, m, C(5)H_2), 2.24–2.26 (2H, m, C(4)H_2), 2.49 (2H, t, $J_{6,5}$ 6.0, C(6)H_2), 5.77 (1H, d, $J_{2,3}$ 15.6, C(2)H), 6.83 (1H, dt, $J_{3,2}$ 15.6, $J_{3,4}$ 7.0, C(3)H), 9.79 (1H, s, COH).

Preparation of *tert*-butyl-(3*S*,α*S*)-3-(*N*-benzyl-*N*-(α-methylbenzylamino)-7-oxoheptanoate (42)

Following the general procedure 1a, *n*-BuLi (2.5 M, 0.9 mL, 2.3 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (0.5 mL, 2.5 mmol) in THF (5 mL) and α,β-unsaturated ester **41** (100 mg, 0.50 mmol) in THF (6 mL) gave the crude reaction mixture as a brown oil. After purification *via* column chromatography on silica (1 : 5, EtOAc : pentane), amino ester **41** (107 mg, 69%) was obtained as a colorless oil; $[\alpha]_D^{24}$ −2.9 (*c* 0.85, $CHCl_3$); ν_{max} (film) 1601, 1724, 2816, 2975, 3427; δ_H (400 MHz, $CDCl_3$) 1.22–1.27 (1H, m, C(4)$H_A$$H_B$), 1.33 (3H, d, J 4.9, C(α)CH_3), 1.40 (9H, s, C(CH_3)$_3$), 1.50–1.53 (1H, m, C(4)$H_A$$H_B$), 1.70–1.74 (2H, m, C(5)H_2), 1.85–1.89 (1H, m, C(2)$H_A$$H_B$), 1.98–2.04 (1H, m, C(2)$H_A$$H_B$), 2.30 (2H, dt, $J_{6,5}$ 7.8, $J_{6,7}$ 1.6 C(6)H_2), 3.30–3.32 (1H, m, C(3)H), 3.50 (2H, AB d, $J_{A,B}$ 15.0, CH_2Ph), 3.84 (1H, q, J 4.9, C(α)H), 7.35–7.52 (10H, m, 2x *o/m/p-Ph*), 9.71 (1H, br s, CHO); δ_C (100 MHz, $CDCl_3$) 19.4 (C(5)H_2), 20.7 (C(α)CH_3), 28.0 (C(CH_3)$_3$), 32.8 (C(4)H_2), 43.6 (C(6)H_2), 50.1 (CH_2Ph), 53.4 (C(3)H), 58.5 (C(α)CH_3), 65.9 (C(2)H_2), 80.2 (C(CH_3)$_3$), 126.7, 127.0 2x(*p-Ph*), 127.9, 128.0, 128.2, 128.3 2x(*o/m-Ph*), 141.7, 143.0 2x(*i-Ph*), 172.0 (CO_2), 202.7 (CHO); *m/z* (CI^+) 410.2710 (MH^+, $C_{26}H_{36}NO_3^+$ requires 410.2695); 411 (27%), 410 ($(MH)^+$, 100), 354 (52), 249 (26).

Preparation of *tert*-butyl-(1*R*,2*S*,6*S*,α*S*)-2-hydroxy-6-(*N*-benzyl-*N*-(α-methylbenzylamino)cyclohexanoate (43)

Following the general procedure 1a, *n*-BuLi (2.5 M, 0.5 mL, 1.2 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (0.24 mL, 1.2 mmol) in THF (7 mL) and ester **41** (100 mg, 0.5 mmol) in THF (7 mL) were allowed to react for 2 h. The solution was then warmed to −20 °C for 2 h, and following the work-up procedure gave the crude reaction product as a brown oil. Purification *via* column chromatography (1 : 5, Et_2O : pentane) on silica gave the cyclic ester **43** (52 mg, 31%, >98% de) as a more polar component as a colorless oil; $[\alpha]_D^{24}$ +10.4 (*c* 1.00, $CHCl_3$); (Found: C, 75.8; H, 8.9; N, 2.9. Calc. for $C_{26}H_{35}NO_3$: C, 76.2; H, 8.7; N, 3.4%); ν_{max} (film) 1602, 1703, 2248, 2866, 2935, 2974, 3027, 3480; δ_H (500 MHz, $CDCl_3$) 1.19 (1H, app t, $J_{4ax,5eq;4ax,3ax}$ 9.2, C(4)$H_A$$H_B$), 1.40 (3H, d, J 6.9, C(α)CH_3), 1.41–1.45 (1H, m, C(4)$H_A$$H_B$), 1.48 (9H, s, C(C$H_3$)$_3$), 1.51–1.53 (1H, m, C(3)$H_A$$H_B$), 1.81–1.84 (3H, m, C(5)H_2, C(3)$H_A$$H_B$), 2.45 (1H, dd, $J_{1ax,6ax}$ 9.9, $J_{1ax,2eq}$ 3.9, C(1)H), 3.44 (1H, app. dt, $J_{6ax,1ax;6ax,5ax}$ 9.9, $J_{6ax,5eq}$ 3.3, C(6)H), 3.73 (1H, AB d, J 14.2, C$H_A$$H_B$Ph), 3.84 (1H, AB d, J 14.1, CH_AH_BPh), 4.01 (1H, q, J 6.9, C(α)H), 4.08 (1H, br s, C(2)H), 7.14–7.42 (10H, m, 2x *o/m/p-Ph*); δ_C (100 MHz, $CDCl_3$) 17.8 (C(α)CH_3), 19.4 (C(4)H_2), 28.1 (C(CH_3)$_3$), 28.8 (C(5)H_2), 31.2 (C(3)H_2), 49.7 (CH_2Ph), 53.0 (C(1)H), 54.2 (C(6)H), 58.7 (C(α)H), 68.0 (C(2)H), 81.2 (C(CH_3)$_3$), 126.5, 126.6, 127.8, 127.9, 128.3, 129.0 2x(*o/m/p-Ph*), 141.3, 144.2 2x(*i-Ph*), 175.3 (CO_2); *m/z* (CI^+) 410.2694 (MH^+, $C_{26}H_{36}NO_3^+$ requires 410.2695); (EI^+) 411 (34%), 410 ($(MH)^+$, 100).

This reaction also gave amino ester **42** as a less polar fraction (62 mg, 23%, >98% de), with spectroscopic data consistent with that reported above; $[\alpha]_D^{24}$ −2.8 (*c* 0.96, $CHCl_3$).

Preparation of *tert*-butyl-(1*R*,2*S*,6*S*,α*S*)-2-acetoxy-6-(*N*-benzyl-*N*-(α-methylbenzylamino)cyclohexanoate (44)

Following the general procedure 1a, *n*-BuLi (2.5 M, 0.5 mL, 1.2 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (0.24 mL, 1.2 mmol) in THF (7 mL) and acceptor **41** (100 mg, 0.5 mmol) in THF (7 mL), followed by subsequent warming to −20 °C for 2 h and work up gave the crude reaction product containing amino esters **42** and **43**. Acetic anhydride (2.0 mL, 21.7 mmol) followed by pyridine (2.0 mL, 30.0 mmol) and DMAP (5 mg, 0.04 mmol) were added to this crude reaction mixture at rt in DCM (10 mL). After 16 h stirring, mixture was diluted with Et_2O, washed with aqueous saturated $CuSO_4$ solution and brine, dried and concentrated *in vacuo*. Purification *via* column chromatography (1 : 10, Et_2O : pentane) on silica gave the more polar fraction acetate **44** (114 mg, 58%, >98% de) as a viscous green oil; $[\alpha]_D^{24}$ +9.8 (*c* 1.00, $CHCl_3$); ν_{max} (film) 1602, 1741, 2256, 2869, 2934, 3035; δ_H (400 MHz, $CDCl_3$) 1.17–1.21 (1H, app d, $J_{3ax,2eq}$ 2.9, C(3)$H_A$$H_B$), 1.24–1.32 (1H, m, C(4)$H_A$$H_B$), 1.30–1.39 (1H, m, C(5)$H_A$$H_B$), 1.40 (3H, d, J 6.8, C(α)CH_3), 1.47 (9H, s, C(CH_3)$_3$), 1.48–1.52 (2H, m, C(4)$H_A$$H_B$ and C(5)$H_A$$H_B$), 1.66 (1H, br d, $J_{3ax,4ax}$ 12.0, C(3)$H_A$$H_B$), 2.04 (3H, s, C$H_3$$CO_2$), 2.14 (1H, dd, $J_{1ax,6ax}$ 10.2, $J_{1ax,2eq}$ 2.9, C(1)H), 3.50–3.54 (1H, m, C(6)H), 3.59 (1H, AB d, J 12.2, C$H_A$$H_B$Ph), 3.81 (1H, AB d, J 14.7, CH_AH_BPh), 4.18 (1H, q, J 6.8, C(α)H), 5.26–5.31 (1H, m, C(2)H), 7.13–7.38 (10H, m, 2x *o/m/p-Ph*); δ_C (100 MHz, $CDCl_3$) 19.8 (C(α)CH_3), 20.4 (C(4)H_2),

21.2 (CH_3CO_2), 27.0 (C(5)H_2), 28.0 (C(CH_3)$_3$), 29.9 (C(3)H_2), 48.6 (CH_2Ph), 52.8 (C(1)H), 57.0 (C(6)H), 63.0 (C(α)H), 70.5 (C(2)H), 79.9 ($C(CH_3)_3$), 126.6, 126.4 2x(*p-Ph*), 127.7, 127.8, 127.9, 128.6, 128.7 2x(*o/m-Ph*), 142.3, 144.3 2x(*i-Ph*), 170.1, 170.9 2x(CO_2); *m/z* (CI^+) 452.2795 (MH^+, $C_{28}H_{38}NO_4^+$ requires 452.2801); (EI^+) 474 (15%), 453 (34), 452 ($(MH)^+$, 100).

Less polar aldehyde **42** (56 mg, 23%, >98% de) was isolated as a colorless oil with spectroscopic data consistent with that reported above; $[\alpha]_D^{24}$ −3.3 (*c* 0.78, $CHCl_3$).

Alternatively, acetic anhydride (2.0 mL, 21.7 mmol) followed by pyridine (2.0 mL, 30.0 mmol) and DMAP (5 mg, 0.04 mmol) were added to the cyclic β-amino ester **42** (75 mg, 0.2 mmol) in DCM (10 mL) and stirred under nitrogen at rt. After 16 h, mixture was partitioned between Et_2O and aqueous saturated $CuSO_4$ solution and brine, organic layer dried and concentrated *in vacuo*. Purification *via* column chromatography on silica (1 : 10, Et_2O : pentane) gave acetate **44** (77 mg, 94%, >98% de) as a viscous green oil with spectroscopic data consistent with that reported above; $[\alpha]_D^{24}$ +8.9 (*c* 0.96, $CHCl_3$).

Preparation of *tert*-butyl-(*E*)-6-oxohex-2-enoate (45)

PCC (0.30 g, 1.3 mmol) was added to a solution of alcohol **56** (0.10 g, 0.5 mmol) and NaOAc (0.11 g, 1.3 mmol) in DCM (10 mL) at 0 °C. After 2 h Et_2O was added and the resultant solution concentrated *in vacuo*, re-dissolved in DCM, dried and concentrated *in vacuo* after being passed through a pad of silica (eluent Et_2O) to furnish aldehyde **45** (54 mg, 56%) as a colourless oil; ν_{max} (film) 1634, 1728, 2718; δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, C(CH_3)$_3$), 2.43–2.46 (2H, m, C(4)H_2), 2.56–2.58 (2H, m, C(5)H_2), 5.72 (1H, dt, $J_{2,3}$ 15.6, $J_{2,4}$ 1.9, C(2)*H*), 6.81 (1H, dt, $J_{3,2}$ 15.6, $J_{3,4}$ 6.7, C(3)*H*), 9.83 (1H, s, C*H*O); δ_C (100 MHz, $CDCl_3$) 28.3 (C(CH_3)$_3$), 30.3 (C(5)H_2), 31.7 (C(4)H_2), 62.3 (C(6)H_2), 62.6 (C(CH_3)$_3$), 123.6 (C(2)H), 146.8 (C(3)H), 173.1 (CO_2), 203.1 (*C*HO); *m/z* (GCMS, CI^+) 185.1178 (MH^+, $C_{10}H_{17}O_3^+$ requires 185.1176); (GCMS, CI^+) 208 (44%), 185 ((MH^+), 100).

Preparation of *tert*-butyl-(3*S*,α*S*)-3-(*N*-benzyl-*N*-(α-methylbenzylamino)-6-oxohexanoate (46) and (1*R*,2*S*,5*S*,α*S*)-2-hydroxy-5-(*N*-benzyl-*N*-(α-methylbenzylamino)-cyclopentanoate (47)

Following the general procedure 1a, *n*-BuLi (2.5 M, 0.3 mL, 0.6 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (0.14 mL, 0.7 mmol) in THF (5 mL) and acceptor **45** (50 mg, 0.3 mmol) in THF (5 mL) were reacted together to give the crude reaction product as a brown oil. Purification *via* column chromatography (1 : 20, Et_2O : pentane) on silica gave **46** (58 mg, 54%) as a colourless oil; $[\alpha]_D^{24}$ −6.6 (*c* 1.12, $CHCl_3$); ν_{max} (film) 1601, 1723, 2718, 2931, 2975, 3027, 3061; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.9, C(α)CH_3), 1.49 (9H, s, C(CH_3)$_3$), 1.68–1.70 (2H, m, C(4)H_2), 1.82–1.85 (2H, m, C(2)H_2), 2.61 (1H, dt, $J_{5,4}$ 6.5, $J_{5',4'}$ 4.2 C(5)H_AH$_B$), 2.73 (1H, dt, $J_{5,4}$ 6.6, $J_{5',4'}$ 4.0, C(5)H$_A$$H_B$), 3.33–3.34 (1H, m, C(3)*H*), 3.50 (1H, AB d, *J* 14.6, CH_AH$_B$Ph), 3.69 (1H, AB d, *J* 14.9, CH$_A$$H_B$Ph), 3.72 (1H, obst q, C(α)*H*), 7.22–7.40 (10H, 2x *o/m/p-Ph*), 9.76 (1H, br s, C*H*O); δ_C (100 MHz, $CDCl_3$) 19.2 (C(α)CH$_3$), 26.0 (C(4)H_2), 28.0 (C(CH_3)$_3$), 37.2 (C(2)H_2), 42.4 (C(5)H_2), 50.0 (CH_2Ph), 52.8 (C(α)H), 57.7 (C(3)H), 81.6 ($C(CH_3)_3$), 126.8, 127.0 2x(*p-Ph*), 127.9, 128.0, 128.1, 128.2, 128.4 2x(*o/m-Ph*), 142.4, 144.1 2x(*i-Ph*), 186.1 (CO_2), 204.0 (*C*HO); *m/z* (CI^+) 428.2807 (MH^++MeOH. $C_{26}H_{39}NO_4^+$ requires 428.2801); (EI^+) 429 (28%), 428 (100), 396 ($(MH)^+$, 10).

The more polar cyclic ester **47** (29 mg, 18%) was obtained as a colorless oil; $[\alpha]_D^{24}$ +3.2 (*c* 1.15, $CHCl_3$); ν_{max} (film) 1622, 1698, 2875, 2890, 3463; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.9, C(α)CH_3), 1.44 (9H, s, C(CH_3)$_3$), 1.70–1.75 (2H, m, C(4)H_AH$_B$, C(3)H_AH$_B$), 1.74–1.77 (1H, m, C(4)H$_A$$H_B$), 1.92–1.94 (1H, m, C(3)H$_A$$H_B$), 2.70 (1H, dd, $J_{1ax,6ax}$ 8.0, $J_{1ax,2ax}$ 4.4, C(1)*H*), 3.69 (1H, AB d, *J* 14.6, CH_AH$_B$Ph), 3.74 (1H, AB d, *J* 14.7, CH$_A$$H_B$Ph), 3.84 (1H, q, *J* 6.9, C(α)CH$_3$), 3.83–3.85 (1H, m, C(2)*H*), 4.20–4.22 (1H, m, C(5)*H*), 7.12–7.50 (10H, m, 2x *o/m/p-Ph*); δ_C (100 MHz, $CDCl_3$) 17.9 (C(α)CH$_3$), 24.5 (C(4)H_2), 28.2 (C(CH_3)$_3$), 33.8 (C(3)H_2), 36.2 (C(1)H), 52.8 (CH_2Ph), 53.1 (C(2)H), 61.4 (C(α)CH$_3$), 72.7 (C(5)H), 83.9 ($C(CH_3)_3$), 126.6, 126.9 2x(*p-Ph*), 127.8, 127.9, 128.1, 128.2, 128.6 2x(*o/m-Ph*), 143.7, 144.6 2x(*i-Ph*), 195.1 (CO_2); *m/z* (CI^+) 396.2538 (MH^+, $C_{25}H_{34}NO_3^+$ requires 396.2539); (EI^+) 397 (34%), 396 ($(MH)^+$, 100).

Using the effect of temperature on the reaction: following the general procedure 1, *n*-BuLi (2.5 M, 0.3 mL, 0.6 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (0.14 mL, 0.7 mmol) in THF (5 mL) and α,β-unsaturated ester **45** (50 mg, 0.3 mmol) in THF (5 mL) were reacted at −78 °C. After 2 h, the reaction was warmed to −20 °C, stirred for further 2 h. After purification *via* column chromatography (1 : 10, Et_2O : pentane) on silica, aldehyde **46** (8 mg, 7%) was isolated as a colorless oil (>98% de) with spectroscopic data consistent to that above; $[\alpha]_D^{24}$ −5.9 (*c* 1.00, $CHCl_3$); After further elution, cyclic ester **47** (59 mg, 66%) was obtained as a colourless oil and (>98% de) with spectroscopic data consistent with that above; $[\alpha]_D^{24}$ +3.4 (*c* 1.15, $CHCl_3$).

Preparation of *tert*-butyl-(1*R*,2*S*,5*S*,α*S*)-2-acetoxy-5-(*N*-benzyl-*N*-(α-methylbenzylamino)-cyclopentanoate (48)

Following the general procedure 1a, *n*-BuLi (2.5 M, 0.3 mL, 0.6 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (0.14 mL, 0.7 mmol) in THF (5 mL) and α,β-unsaturated ester **45** (50 mg, 0.3 mmol) in THF (5 mL) were reacted at −78 °C. After 2 h, the reaction was warmed to −20 °C and stirred for a further 2 h before work up. Acetic anhydride (2.0 ml, 21.7 mmol) followed by pyridine (2.0 mL, 30.0 mmol) and DMAP (5 mg, 0.04 mmol) were added to this crude reaction mixture at rt in DCM (10 mL). After 16 h stirring, mixture was diluted with Et_2O, washed with aqueous saturated $CuSO_4$ solution and brine, dried and concentrated *in vacuo*. After purification *via* column chromatography (1 : 10, Et_2O : pentane) on silica, acetate **48** (88 mg, 94%) was isolated as a white crystalline solid; mp 152–153 °C (DCM : heptane); $[\alpha]_D^{24}$ +6.7 (*c* 1.21, $CHCl_3$); ν_{max} (KBr) 1493, 1602, 1740, 2931, 2974, 3028, 3641; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.5, C(α)CH_3), 1.39 (9H, s, C(CH_3)$_3$), 1.61–1.64 (1H, m, C(3)H_AH$_B$), 1.71–1.74 (1H, m, C(4)H_AH$_B$), 1.81–1.93 (2H, m, C(3)H$_A$$H_B$, C(4)H$_A$$H_B$), 1.96 (3H, s, C$H_3CO_2$), 2.88 (1H, app t, $J_{1ax,6ax;1ax,2ax}$ 4.4, C(1)*H*), 3.71 (1H, AB d, *J* 14.3, CH_AH$_B$Ph), 3.74 (1H, AB d, *J* 14.6, CH$_A$$H_B$Ph), 3.89 (1H, q, *J* 6.5, C(α)*H*), 3.94 (1H, app q, $J_{2ax,3ax;2ax,3eq}$ 8.1, C(2)*H*), 5.20–5.25 (1H, m, C(5)*H*), 7.18–7.43 (10H, m, 2x *o/m/p-Ph*); δ_C (100 MHz, $CDCl_3$) 17.7 (C(α)CH$_3$), 21.1 (CH_3CO_2), 28.0 (C(CH_3)$_3$), 30.3 (C(3)H_2), 30.9 (C(4)H_2), 50.0 (CH_2Ph), 52.2 (C(1)H), 60.0 (C(α)H), 61.7 (C(2)H), 75.1 (C(5)H), 80.3 ($C(CH_3)_3$), 126.6, 126.7 2x(*p-Ph*), 127.6, 127.8, 128.0, 128.2, 128.3, 128.6 2x(*o/m-Ph*), 141.9, 144.4 2x(*i-Ph*), 170.4, 170.5 2x(CO_2); *m/z* (CI^+) 438.2648 (MH^+, $C_{27}H_{36}NO_4^+$ requires 438.2644); (EI^+) 460 (60%), 438 ($(MH)^+$, 100).

Alternatively, Ac_2O (0.07 mL, 0.76 mmol) followed by pyridine (0.03 mL, 0.5 mmol) and DMAP (5 mg, 0.04 mmol) were added to a stirred solution of alcohol **47** (150 mg, 0.4 mmol) at rt in DCM (5 mL). After 16 h of stirring, the reaction mixture was diluted with Et_2O, partitioned between aqueous saturated $CuSO_4$ solution and DCM, and the organic layer dried and concentrated *in vacuo*. After column chromatography (1 : 2, Et_2O : pentane) on silica, acetate **48** (158 mg, 97%) was isolated as a white crystalline solid with spectroscopic properties as above; mp 151–152 °C (DCM : heptane); $[\alpha]_D^{24}$ +6.7 (*c* 1.21, $CHCl_3$).

Preparation of (1*S*,2*S*,6*S*)-1-ethylcarboxylate-2-amino-6-ethylcyclohexane-ethanoate (51)

Following the general procedure 4, $Pd(OH)_2$/C (0.1 g, 46% w/w), β-amino ester **13** (0.22 g, 0.5 mmol) and MeOH (5 mL) gave the cyclic ester **51** (0.12 g, 96%) as a clear oil without further purification; $[\alpha]_D^{24}$ +4.0 (*c* 0.51, $CHCl_3$); ν_{max} (film) 1727,

3373, 3428; δ_H (400 MHz, $CDCl_3$) 1.11 (1H, app t, $J_{3ax,4ax;3ax,2ax}$ 10.2, C(3)H_AH_B), 1.24, 1.29 (3H, t, J 6.9, 2x CH_2CH_3), 1.39 (1H, m, C(4)H_AH_B), 1.63 (1H, m, C(5)H_AH_B), 1.80 (2H, m, C(3)H_AH_B and C(4)H_AH_B), 2.03 (2H, br d, J 13.6, C(2)NH_2), 2.12 (1H, m, C(6)CH_AH_B), 2.29 (1H, m, C(5)H_AH_B), 2.41 (1H, m, C(6)CH_AH_B), 2.54 (1H, app t, $J_{1ax,2ax;1ax,6eq}$ 7.7, C(1)H), 3.03 (1H, m, C(2)H), 3.42 (1H, m, C(6)H), 4.08 (2H, q, J 6.9, CH_2CH$_3$), 4.27 (2H, q, J 6.9, CH_2'CH$_3$); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_2CH_3), 14.2 (CH_2CH_3'), 23.1 (C(4)H$_2$), 29.4 (C(5)H$_2$), 30.4 (C(3)H$_2$), 33.5 (C(2)HN), 36.1 (C(6)CH_2), 52.4 (C(1)CO$_2$), 52.6 (C(6)H), 60.2 (CH_2CH_3), 62.1 (CH_2CH_3), 171.6 (CO_2Et), 172.4 (CO_2Et'); m/z (CI$^+$) 258.1711 (MH$^+$, $C_{13}H_{24}NO_4^+$ requires 258.1705); 258 ((MH)$^+$, 100%), 212 (50).

Preparation of (1*S*,2*S*,6*S*)-1-*tert*-butyl-carboxylate-2-amino-6-*tert*-butylcyclohexane-ethanoate (52)

Following the general procedure 4, Pd(OH)$_2$/C (40 mg, 10% w/w), β-amino ester **14** (0.40 g, 0.8 mmol) and MeOH (5 mL) gave the cyclic ester **52** (0.24 g, 96%) as a clear oil without further purification; $[\alpha]_D^{24}$ +4.1 (*c* 1.00, $CHCl_3$); ν_{max} (film) 1726, 2876, 2954, 3012, 3379; δ_H (400 MHz, $CDCl_3$) 1.00 (1H, dq, $J_{5ax,6ax}$ 4.9, $J_{5ax,4eq}$ 2.0, C(5)H_AH_B), 1.12 (1H, app q, $J_{4,3;4,5'}$ 2.0, C(4)H_AH_B), 1.32–1.38 (1H, m, C(4)H$_A$H$_B$), 1.41 (9H, s, C(CH_3)$_3$), 1.48 (9H, s, C(CH_3)$_3'$), 1.48–1.53 (1H, m, C(3)H_AH_B), 1.71 (1H, dq, $J_{5eq,6eq}$ 4.9, $J_{5eq,4eq}$ 2.0, C(5)H$_A$H$_B$), 1.82 (1H, app t, $J_{6eq,1ax;6eq,1A}$ 3.6, C(6)H), 1.94 (1H, q, $J_{2ax,1ax;2ax,3ax}$ 8.8, C(2)H), 2.00 (1H, q, $J_{A,6;A,B}$ 11.1, C(6)CH_AH_B), 2.12–2.18 (1H, m, C(3)H$_A$H$_B$), 2.24 (1H, dd, $J_{B,A}$ 11.1, $J_{B,6}$ 8.7, C(6)CH$_A$H$_B$), 2.81–2.89 (1H, m, C(1)H); δ_C (100 MHz, $CDCl_3$) 24.6 (C(4)H$_2$), 28.5, 28.6 2x(C(CH_3)$_3$), 31.0 (C(5)H$_2$), 35.2 (C(6)H), 35.4 (C(3)H$_2$), 37.0 (C(2)H), 40.7 (C(5)CH_2), 53.1 (C(1)H), 80.8, 81.4 2x(C(CH$_3$)$_3$), 172.0, 174.1 2x(CO_2); m/z (CI$^+$) 314.2345 (MH$^+$, $C_{17}H_{32}NO_4^+$ requires 314.2331); (EI$^+$) 336 (52%), 314 (MH$^+$, 100).

Preparation of (1*S*,2*S*,6*S*,α*S*)-1-carboxyl-2-amino-6-ethanoate-cyclohexanoic acid (53)

Following the general procedure 5, β-amino ester **52** (75 mg, 0.24 mmol) and TFA–DCM (5 mL) gave the cyclic ester **53** (34 mg, 71%) as a yellow solid after ion exchange chromatography (Dowex 50WX8-200, 1 M $NH_4OH_{(aq)}$ eluent); (Found C, 53.7; H, 7.5; N, 6.9. Calc. for $C_9H_{15}NO_4$: C, 53.7; H, 7.5; N, 7.0%); mp 169–171 °C (MeOH); $[\alpha]_D^{24}$ −0.8 (*c* 0.50, MeOH); ν_{max} (film) 1645, 2502, 3369; δ_H (400 MHz, MeOD) 1.04 (1H, br d, $J_{4,3;4,5}$ 7.1, C(4)H_AH_B), 1.11–1.24 (1H, m, C(5)H_AH_B), 1.31–1.42 (2H, m, C(6)H, C(5)H$_A$H$_B$), 1.48–1.56 (1H, m, C(4)H$_A$H$_B$), 1.71–1.99 (2H, m, C(3)H_2), 2.10 (1H, dd, $J_{A,B}$ 11.1, $J_{A,6}$ 4.3, C(6)CH_AH_B), 2.19–2.26 (2H, m, C(6)CH$_A$H$_B$, C(2)H), 2.32 (1H, dd, $J_{1ax,2ax}$ 8.6, $J_{1ax,6eq}$ 6.3, C(1)H), 2.81 (2H, br s, NH_2); δ_C (100 MHz, MeOD) 12.1 (C(4)H$_2$), 22.2 (C(5)H$_2$), 29.1 (C(3)H$_2$), 35.9 (C(6)H), 51.6 (C(6)CH_2), 52.0 (C(1)H), 56.3 (C(2)H), 176.1, 178.4 2x(CO_2); m/z (CI$^+$) 265.1160 (MH$^+$, $C_{11}H_{18}N_2O_4Na^+$ required 265.1164); (EI$^+$) 267 (21%), 265 ((MH)$^+$, 100).

Alternatively, β-amino ester **52** (100 mg, 0.39 mmol) was dissolved in 1 : 1 THF : aqueous 5 M LiOH solution and stirred overnight, after which the solution was neutralised with 1 M HCl and concentrated *in vacuo*. Purification *via* ion exchange chromatography (Dowex 50WX8-200, 1 M $NH_4OH_{(aq)}$ eluent) gave **53** (76 mg, 74%) as a yellow solid with spectroscopic properties same as above.

Preparation of (3*S*,4*S*,5*S*,α*S*)-3-(*N*-benzyl-*N*-(α-methylbenzylamino)-4-methoxycarbonyl-5-(methylethanoate)-piperidine (54)

Tetrakis–palladium Pd(PPh$_3$)$_4$ (31.1 mg, 0.20 mmol) was added to a solution of *N*-allyl-piperidine **34** (0.93 g, 2.0 mmol) and 1,3-dimethylbarbituric acid (0.93 g, 6.0 mmol) in DCM (20 mL) followed by vigorous stirring. After 16 h saturated aqueous K_2CO_3 was added, and the resultant solution partitioned between DCM and brine, organic layers combined, dried and concentrated *in vacuo*. Purification *via* column chromatography on silica (1 : 3, Et$_2$O : pentane) gave the piperidine **54** (0.79 g, 93%) as an orange oil; $[\alpha]_D^{24}$ −3.2 (*c* 0.81, $CHCl_3$); ν_{max} (film) 1638, 1734, 2941, 3341; δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, J 7.0, C(α)CH_3), 1.99 (1H, obst dd, $J_{A,B}$ 10.2, $J_{A,5}$ 4.1, C(5)CH_AH_B), 2.06–2.20 (3H, m, C(5)H, C(6)H_AH_B and C(5)CH$_A$H$_B$), 2.41 (1H, app t, $J_{4ax,3ax;4ax,5ax}$ 6.5, C(4)H), 2.64 (1H, app t, $J_{2ax,2eq;2ax.3ax}$ 11.9, C(2)H_AH_B), 3.02–3.09 (2H, m, C(6)H$_A$H$_B$, C(3)H), 3.31 (1H, dd, $J_{2eq,2ax}$ 11.9, $J_{2eq,3ax}$ 4.1, C(2)H$_A$H$_B$), 3.43 (3H, s, CO$_2$CH_3), 3.64 (3H, s, CO$_2$CH_3'), 3.71 (1H, AB d, J 13.8, CH_AH_BPh), 3.92 (1H, AB d, J 13.8, CH$_A$H$_B$Ph), 3.99 (1H, q, J 7.0, C(α)H), 7.16–7.39 (10H, m, 2x *o*/*m*/*p*-*Ph*); δ_C (125 MHz, $CDCl_3$) 15.9 (C(α)CH_3), 36.5 (C(5)CH_2), 37.8 (C(5)H), 49.9 (C(6)H$_2$), 50.4 (C(2)H$_2$), 51.4, 51.5 2x(CO$_2$CH_3), 51.7 (CH_2Ph), 53.0 (C(4)H), 56.3 (C(α)H), 57.4 (C(3)H), 126.5, 126.8 2x(*p*-*Ph*), 127.8, 127.9, 128.0, 128.2, 128.4, 128.5, 128.9 2x(*o*/*m*-*Ph*), 140.3, 143.6 2x(*i*-*Ph*), 171.9, 173.2 2x(CO_2); m/z (CI$^+$) 425.2450 (MH$^+$, $C_{25}H_{33}N_2O_4^+$ requires 425.2440); (EI$^+$) 604 (7%), 483 (10), 425 ((MH)$^+$, 100).

Preparation of (3*S*,4*S*,5*S*)-3-amino-4-methoxycarbonyl-5-methylethanoate-piperidine (55)

Following the general procedure 4, Pd(OH)$_2$/C (100 mg, 40% w/w), protected piperidine **23** (250 mg, 0.5 mmol) and MeOH (5 mL) gave the piperidine **55** (89 mg, 85%) as a clear oil without further purification; $[\alpha]_D^{24}$ −5.21 (*c* 0.94, $CHCl_3$); ν_{max} (film) 1651, 1732, 2955, 3360; δ_H (400 MHz, $CDCl_3$) 1.25 (3H, br s, NH and NH_2), 1.96 (1H, app t, $J_{2,3}$ 6.9, C(5)CH_AH_B), 2.09–2.42 (5H, m, C(5)CH$_A$H$_B$, C(6)H_2, C(5)H, C(4)H), 2.94 (1H, dt, $J_{3,4}$ 10.2, $J_{3,2}$ 4.5, C(3)H), 3.11–3.18 (2H, m, C(2)H_2), 3.64 (3H, s, CO$_2$CH_3), 3.71 (3H, s, CO$_2$CH_3'); δ_C (100 MHz, $CDCl_3$) 36.6 (C(5)H), 50.5 (C(4)H), 50.6 (C(6)H$_2$), 51.62, 51.64 (CO$_2$CH_3 and CO$_2$CH_3'), 51.7 (C(3)H), 54.3 (C(2)H$_2$), 57.6 (C(5)CH_2), 172.0, 173.9 2x(CO_2CH$_3$); m/z (CI$^+$) 231.1346 (MH$^+$, $C_{10}H_{19}N_2O_4^+$ requires 231.1345); 461 (33%), 339 (38), 231 ((MH)$^+$, 100), 273 (34).

Preparation of *tert*-butyl-(2*E*)-6-hydroxyhex-2-enoate (56)

n-BuLi (1.6 M in hexane, 14.1 mL, 22.5 mmol) was added dropwise to a solution of *tert*-butyl triphenylphosphoranylidene acetate (5.80 g, 23.0 mmol) in THF (15 mL) under N$_2$ and stirred at −78 °C. After 30 min a solution of γ-lactone (1.8 mL, 20.9 mmol) in THF (5 mL) at −78 °C was added *via* cannula followed by the dropwise addition of DIBAL-H (1.0 M in hexane, 20.5 mL, 20.5 mmol). The solution was then warmed to rt and stirred overnight, before the addition of aqueous sodium potassium tartrate solution; the resultant solution was partitioned between EtOAc and 0.5 M HCl, the organic layer washed with aqueous saturated K_2CO_3 solution and brine, dried and concentrated *in vacuo* to furnish the crude product **56** in 86% de. Purification by column chromatography on silica (1 : 1, Et$_2$O : pentane) gave alcohol **56** (1.92 g, 49%, 89% de) as a colorless oil; ν_{max} (film) 1457, 1653, 1715, 2934, 2980, 3428; δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, C(CH_3)$_3$), 1.72 (2H, tt, $J_{5,4}$ 7.2, $J_{5,6}$ 6.5, C(5)H_2), 2.28 (2H, dt, $J_{4,5}$ 7.2, $J_{4,3}$ 6.0, C(4)H_2), 3.66 (2H, t, $J_{6,5}$ 6.5, C(6)H_2), 5.78 (1H, d, $J_{2,3}$ 15.1, C(2)H), 6.84 (1H, dt, $J_{3,2}$ 15.1, $J_{3,4}$ 6.0, C(3)H); δ_C (100 MHz, $CDCl_3$) 28.1 (C(CH_3)$_3$), 28.3 (C(5)H$_2$), 31.0 (C(4)H$_2$), 62.0 (C(6)H$_2$), 62.5 (C(CH$_3$)$_3$), 123.5 (C(2)H), 147.0 (C(3)H), 173.1 (CO_2); m/z (GCMS, CI$^+$) 187.1335 (MH$^+$, $C_{10}H_{19}O_3^+$requires 187.1334); (GCMS, CI$^+$) 204 (60%), 187 ((MH$^+$), 100).

Preparation of *tert*-butyl-(2*E*)-7-hydroxyhept-2-enoate (57)

n-BuLi (2.5 M in hexane, 8.9 mL, 22.2 mmol) was added dropwise to a solution of *tert*-butyl triphenylphosphoranylidene acetate (5.54 g, 22.0 mmol) in THF (15 mL) at −78 °C. After 30 min a solution of δ-valerolactone (1.9 mL, 20.0 mmol) in

THF (5 mL) at −78 °C was added *via* cannula followed by the dropwise addition of DIBAL-H (1.0 M in hexane, 19.6 mL, 19.6 mmol). The solution was then warmed to rt overnight, before the addition of saturated aqueous sodium potassium tartrate solution; the resultant solution was partitioned between EtOAc and 0.5 M HCl, organic layer partitioned between aqueous saturated K_2CO_3 solution and brine, dried and concentrated *in vacuo*. Purification *via* column chromatography on silica (1 : 1, Et_2O : pentane) gave alcohol **57** as a clear oil (1.42 g, 36%, 92% de) with spectroscopic properties consistent with those quoted in the literature;[6b] δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, C(CH_3)$_3$), 1.58–1.61 (4H, m, C(5)H_2 and C(6)H_2), 2.23 (2H, dt, $J_{4,3}$ 5.7, $J_{4,5}$ 5.6, C(4)H_2), 3.67 (2H, t, $J_{7,6}$ 6.2, C(7)H_2), 5.78 (1H, dt, $J_{3,2}$ 15.4, $J_{3,4}$ 5.6, C(3)*H*), 6.86 (1H, d, $J_{2,3}$ 15.4, C(2)*H*), 7.37 (1H, s, CH_2OH).

Preparation of *tert*-butyl-(3*S*,α*S*)-3-(*N*-benzyl-*N*-(α-methylbenzylamino)-6-hydroxyhexanoate (58)

Following the general procedure 1, *n*-BuLi (2.5 M, 5.6 mL, 13.9 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (3.0 mL, 14.1 mmol) in THF (8 mL) and alcohol **56** (0.75 g, 4.0 mmol) in THF (8 mL) gave the crude reaction product. Purification *via* column chromatography (1 : 5, Et_2O : pentane) on silica gave **58** (1.27 g, 79%) as a colourless oil; $[\alpha]_D^{24}$ −12.6 (*c* 1.23, $CHCl_3$); ν_{max} (film) 1723, 3415; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.8, C(α)CH_3), 1.36–1.38 (1H, m, C(4)H_AH$_B$), 1.39 (9H, s, C(CH_3)$_3$), 1.48–1.50 (1H, m, C(4)H$_A$$H_B$), 1.63–1.66 (1H, m, C(5)H_AH$_B$), 1.81–1.83 (1H, m, C(5)H$_A$$H_B$), 1.90–1.92 (2H, m, C(2)H_2), 3.31–3.33 (1H, m, C(3)*H*), 3.49 (1H, AB d, *J* 14.9, CH_AH$_B$Ph), 3.54–3.57 (2H, m, C(6)H_2), 3.80 (1H, AB d, *J* 14.9, CH$_A$$H_B$Ph), 3.81 (1H, q, *J* 6.8, C(α)*H*), 7.20–7.43 (10H, 2x *o*/*m*/*p*-*Ph*); δ_C (100 MHz, $CDCl_3$) 20.5 (C(α)CH_3), 28.0 (C(CH_3)$_3$), 29.6 (*C*(5)H$_2$), 30.0 (*C*(4)H$_2$), 37.3 (*C*(2)H$_2$), 50.1 (*C*H$_2$Ph), 53.2 (*C*(3)H), 58.3 (*C*(α)H), 62.6 (*C*(6)H$_2$), 80.2 (*C*(CH$_3$)$_3$), 126.7, 127.0 2x(*p*-*Ph*), 127.9, 128.0, 128.1, 128.2, 128.5 2x(*o*/*m*-*Ph*), 141.7, 142.8 2x(*i*-*Ph*), 172.4 (*C*O$_2$); *m*/*z* (CI$^+$) 398.2695 (MH$^+$, $C_{25}H_{36}NO_3^+$ requires 398.2695); (EI$^+$) 421 (51%), 398 ((MH)$^+$, 100).

Preparation of *tert*-butyl-(3*S*,α*S*)-3-(*N*-benzyl-*N*-(α-methylbenzylamino)-7-hydroxyheptanoate (59)

Following the general procedure 1, *n*-BuLi (1.6 M, 1.10 mL, 2.6 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (0.4 mL, 2.5 mmol) in THF (5 mL) and alcohol **57** (100 mg, 0.8 mmol) in THF (5 mL) gave the crude reaction product. Purification *via* column chromatography (1 : 5, Et_2O : pentane) on silica gave **59** (221 mg, 82%) as a colourless oil; $[\alpha]_D^{24}$ −12.8 (*c* 1.00, $CHCl_3$); ν_{max} (film) 1602, 1723, 2876, 2912, 3341; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.9, C(α)CH_3), 1.33–1.42 (2H, m, C(5)H_2), 1.38 (2H, app d, $J_{4,3;4,5}$ 5.5, C(4)H_2), 1.39 (9H, s, C(CH_3)$_3$), 1.44–1.46 (2H, m, C(6)H_2), 1.88 (1H, dd, $J_{2,2}$ 14.7, $J_{2,3}$ 9.5, C(2)H_AH$_B$), 1.96 (1H, dd, $J_{2,2}$ 14.7, $J_{2,3}$ 3.4, C(2)H$_A$$H_B$), 3.31–3.33 (1H, m, C(3)*H*), 3.51 (1H, AB d, *J* 15.0, CH_AH$_B$Ph), 3.60–3.68 (3H, m, C(7)H_2OH), 3.81 (1H, AB d, *J* 15.0, CH$_A$$H_B$Ph), 3.84 (1H, q, *J* 6.9, C(α)*H*), 7.35–7.52 (10H, m, 2x *o*/*m*/*p*-*Ph*); δ_C (100 MHz, $CDCl_3$) 20.6 (C(α)CH_3), 22.9 (*C*(4)H$_2$), 28.1 (C(CH_3)$_3$), 32.6 (*C*(5)H$_2$), 33.2 (*C*(6)H$_2$), 37.6 (*C*(2)H$_2$), 50.1 (*C*H$_2$Ph), 53.8 (*C*(3)H), 58.5 (*C*(α)H), 63.0 (*C*(7)H$_2$), 80.0 (*C*(CH$_3$)$_3$), 126.6, 126.8 2x(*p*-*Ph*), 127.9, 128.0, 128.1, 128.3, 128.5 2x(*o*/*m*-*Ph*), 142.0, 143.1 2x(*i*-*Ph*), 172.2 (*C*O$_2$); *m*/*z* (CI$^+$) 412.2849 (MH$^+$, $C_{26}H_{38}NO_3^+$ requires 412.2852); (EI$^+$) 413 (49%), 412 ((MH)$^+$, 100).

Preparation of *tert*-butyl-(3*S*,α*S*)-3-(*N*-benzyl-*N*-(α-methylbenzylamino)-6-oxohexanoate (46)

Anhydrous DMSO (0.36 mL, 5.04 mmol) was added to a solution of oxalyl chloride (0.2 mL, 2.5 mmol) in DCM (5 mL) at −78 °C and stirred for 20 min followed by the addition of the alcohol **58** (0.43 g, 1.3 mmol) *via* cannula in DCM (5 mL). After further stirring for 20 min, NEt_3 (1.1 mL, 7.6 mmol) was added, reaction stirred for 30 min and allowed to reach rt over another 30 min, extracted with DCM, washed with brine and concentrated *in vacuo*. Residue was re-dissolved in Et_2O, washed with aqueous saturated $NaHCO_3$ and brine solutions, dried and re-concentrated *in vacuo* to afford the aldehyde **46** (0.37 g, 87%) as a colourless oil after passing through a pad of silica (eluent Et_2O) with spectroscopic data consistent with that above; $[\alpha]_D^{24}$ −6.1 (*c* 1.00, $CHCl_3$).

Preparation of *tert*-butyl-(3*S*,α*S*)-3-(*N*-benzyl-*N*-(α-methylbenzylamino)-7-oxoheptanoate (42)

Anhydrous DMSO (0.14 mL, 1.95 mmol) was added to a solution of oxalyl chloride (0.9 mL, 1.0 mmol) in DCM (5 mL) at −78 °C and stirred for 20 min followed by the addition of alcohol **59** (0.20 g, 0.5 mmol) *via* cannula in DCM (5 mL). After further stirring for 20 min, NEt_3 (0.4 mL, 2.9 mmol) was added, reaction stirred for 30 min and allowed to reach rt over another 30 min, extracted with DCM, washed with brine, concentrated, re-dissolved in Et_2O, washed with aqueous saturated $NaHCO_3$ and brine solutions, dried and concentrated *in vacuo* to afford the aldehyde **42** (182 mg, 91%) as a colourless oil after column chromatography (eluent Et_2O) with spectroscopic data consistent with that above; $[\alpha]_D^{25}$ −2.8 (*c* 1.00, $CHCl_3$).

Preparation of *tert*-butyl-(*S*)-pyrrolidin-2-ylacetate (60)

Following the general procedure 4, Pd(OH)$_2$/C (0.1 g, 0.5 eq. w/w), β-amino ester **46** (221 mg, 0.60 mmol) and MeOH (5 mL) gave the cyclic ester **60** (109 mg, 96%) with spectroscopic properties consistent with the literature as a clear oil without further purification; $[\alpha]_D^{24}$ −1.5 (*c* 1.00, $CHCl_3$);[30] δ_H (400 MHz, $CDCl_3$) 1.32–1.41 (1H, m, C(3)H_AH$_B$), 1.41 (9H, s, C(CH_3)$_3$), 1.70–1.76 (2H, m, C(4)H_2), 1.89–1.93 (1H, m, C(3)H$_A$$H_B$), 2.42 (2H, app d, $J_{AB,5}$ 6.5, CH_2CO$_2$), 2.90 (1H, dt, $J_{5,AB}$ 7.9, $J_{5,4}$ 7.7, C(5)H_AH$_B$), 3.03 (1H, dt, $J_{5,AB;5,4}$ 7.9, 7.7, C(5)H$_A$$H_B$), 3.38–3.42 (1H, m, C(2)*H*).

Preparation of *tert*-butyl-(*S*)-piperidine-2-acetate (61)

Following the general procedure 4, Pd(OH)$_2$/C (50 mg, 40% w/w), β-amino ester **42** (120 mg, 0.29 mmol) and MeOH (5 mL) gave the crude cyclic ester **61** as a yellow oil. Purification *via* column chromatography on silica (4 : 6 : 0.1, Et_2O : pentane : NEt_3) gave **61** as a yellow oil (78 mg, 86%) with spectroscopic properties consistent with the literature;[6b] $[\alpha]_D^{24}$ +5.1 (*c* 0.92, $CHCl_3$); (lit.,[6b] $[\alpha]_D^{26}$ +8.3 (*c* 1.35 $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.11–1.18 (1H, m, C(5)H_AH$_B$), 1.21–1.49 (2H, m, C(4)H_AH$_B$, C(3)H_AH$_B$), 1.42 (9H, s, C(CH_3)$_3$), 1.59 (2H, app d, *J* 8.1, C(3)H$_A$$H_B$, C(5)H$_A$$H_B$), 1.72–1.76 (1H, app d, *J* 5.1, C(4)H$_A$$H_B$), 2.09 (1H, br s, N*H*), 2.28 (2H, app d, *J* 7.1, C(2′)H_2), 2.64 (1H, dt., *J* 6.3, 2.6, C(6)H_AH$_B$), 2.70–2.89 (1H, m, C(2)*H*), 3.04 (1H, d, *J* 6.3, C(6)H$_A$$H_B$).

Preparation of *tert*-butyl-(1*R*,2*S*,5*S*)-2-hydroxy-5-amino-cyclopentanoate (62)

Following the general procedure 4, Pd(OH)$_2$/C (75 mg, 50% w/w), β-amino ester **47** (150 mg, 0.35 mmol) and MeOH (5 mL) gave the amino alcohol **62** (79 mg, 98%) as a clear oil without further purification; $[\alpha]_D^{24}$ +2.9 (*c* 0.55, $CHCl_3$); ν_{max} (film) 1718, 2872, 3003, 3364; δ_H (400 MHz, MeOD) 1.44–1.49 (1H, m, C(4)H_AH$_B$), 1.49 (9H, s, C(CH_3)$_3$), 1.63–1.72 (1H, m, C(3)H_AH$_B$), 2.06–2.13 (1H, m, C(3)H$_A$$H_B$), 2.18–2.28 (1H, m, C(4)H$_A$$H_B$), 2.61 (1H, dd, $J_{1,2}$ 8.6, $J_{1,5}$ 3.6, C(1)*H*), 3.81 (1H, app q, *J* 8.6, C(2)*H*), 4.46–4.49 (1H, m, C(5)*H*), 7.31 (1H, app d, *J* 4.4, O-*H*); δ_C (100 MHz, MeOD) 27.5 (C(CH_3)$_3$), 29.8 (*C*(4)H$_2$), 32.9 (*C*(3)H$_2$), 52.1 (*C*(5)H), 58.8 (*C*(1)H), 73.6 (*C*(2)H), 81.2 (*C*(CH$_3$)$_3$), 171.2 (*C*O$_2$); *m*/*z* (CI$^+$) 202.1451 (MH$^+$, $C_{10}H_{20}NO_3^+$ requires 202.1443); (EI$^+$) 243 (100%), 202 ((MH)$^+$, 78).

Alternatively, acetate **63** (81 mg, 0.37 mmol) was stirred in 2.5 M LiOH dissolved in 1 : 3, H_2O : MeOH for 24 h, after which it was neutralised with 1 M HCl, passed through a silica frit (EtOAc as eluent) and concentrated *in vacuo* to furnish the amino alcohol **62** (71 mg, 88%) as a clear oil with spectroscopic properties consistent as these quoted above.

Preparation of *tert*-butyl-(1*R*,2*S*,5*S*)-2-acetoxy-5-amino-cyclopentanoate (63)

Following the general procedure 4, $Pd(OH)_2/C$ (75 mg, 50% w/w), β-amino ester **48** (150 mg, 0.33 mmol) and MeOH (5 mL) gave the cyclic acetate **63** (77 mg, 93%) as a clear oil without further purification; $[\alpha]_D^{24}$ +4.1 (*c* 0.90, MeOH); ν_{max} (film) 1604, 1739, 2987, 3310; δ_H (400 MHz, MeOD) 1.46 (9H, s, C(CH_3)$_3$), 1.46 (1H, obst dt, *J* 11.0, 7.9, C(4)H_AH$_B$), 1.68–1.74 (1H, m, C(4)H$_A$$H_B$), 2.01 (3H, s, C$H_3CO_2$), 2.10–2.24 (2H, m, C(3)H_2), 2.72 (1H, dd, *J* 8.5, 5.0, C(1)*H*), 3.75 (1H, app dd, *J* 8.5, 7.9, C(5)*H*), 5.39–5.50 (1H, m, C(2)*H*); δ_C (100 MHz, MeOD) 20.8 (*C*H$_3$CO$_2$), 27.3 (C(*C*H$_3$)$_3$), 29.6 (*C*(4)H$_2$), 30.6 (*C*(3)H$_2$), 56.3 (*C*(1)H), 56.9 (*C*(5)H), 76.4 (*C*(2)H), 81.4 (*C*(CH$_3$)$_3$), 176.4, 181.2 2x(*C*O$_2$); *m/z* (CI$^+$) 244.1553 (MH$^+$, $C_{12}H_{22}NO_4^+$ requires 244.1549); (EI$^+$) 267 (30%), 245 (34), 244 ((MH)$^+$, 100).

Preparation of (1*R*,2*S*,5*S*)-2-hydroxy-5-amino-cyclopentanoic acid (64)

Following the general procedure 5, amino-ester **62** (25 mg, 0.12 mmol) and TFA–DCM (5 mL) gave the β-amino acid **64** (12.3 mg, 86%) as a green solid after ion-exchange chromatography (Dowex 50WX8-200, 1 M $NH_4OH_{(aq)}$ eluent); mp 84–86 °C (1 M NH_3); $[\alpha]_D^{24}$ +64.4 (*c* 0.41, H_2O); ν_{max} (film) 1731, 3209, 3318; δ_H (400 MHz, D_2O) 1.48–1.52 (1H, m, C(4)H_AH$_B$), 1.73–1.75 (1H, m, C(4)H$_A$$H_B$), 2.11–2.18 (2H, m, C(3)H_2), 2.89 (1H, dd, $J_{1,2}$ 7.1, $J_{1,5}$ 6.4, C(1)*H*), 3.11–3.21 (1H, m, C(5)*H*), 5.01–5.11 (1H, m, C(2)*H*); δ_C (125 MHz, D_2O) 29.5 (*C*(4)H$_2$), 32.6 (*C*(3)H$_2$), 52.9 (*C*(5)H), 58.6 (*C*(1)H), 73.2 (*C*(2)H), 173.2 (*C*O$_2$); *m/z* (CI$^+$) 146.0811 (MH$^+$, $C_6H_{12}NO_3^+$ requires 146.0817); (EI$^+$) 169 (70%), 146 ((MH)$^+$, 100).

Preparation of (1*R*,2*S*,5*S*)-2-acetoxy-5-amino-cyclopentanoic acid (65)

Following the general procedure 5, amino-ester **63** (20 mg, 0.08 mmol) and TFA–DCM (5 mL) gave the title compound **65** (14.1 mg, 92%) as a brown solid after ion-exchange chromatography (Dowex 50WX8-200, 1 M $NH_4OH_{(aq)}$ eluent); mp 92–94 °C (1 M NH_3); $[\alpha]_D^{24}$ +112.9 (*c* 0.55, H_2O); ν_{max} (film) 1736, 3211, 3318; δ_H (400 MHz, D_2O) 1.50–1.54 (1H, m, C(4)H_AH$_B$), 1.71–1.77 (1H, m, C(4)H$_A$$H_B$), 1.91 (3H, s, C$H_3CO_2$), 2.08–2.22 (2H, m, C(3)H_2), 2.79 (1H, dd, $J_{1,2}$ 6.7, $J_{1,5}$ 5.1, C(1)*H*), 3.80–3.88 (1H, m, C(5)*H*), 5.27–5.29 (1H, m, C(2)*H*); δ_C (125 MHz, D_2O) 21.4 (*C*H$_3$CO$_2$), 25.4 (*C*(4)H$_2$), 30.6 (*C*(3)H$_2$), 56.1 (*C*(5)H), 68.7 (*C*(1)H), 77.3 (*C*(2)H), 174.0, 180.9 2x(*C*O$_2$); *m/z* (CI$^+$) 188.0927 (MH$^+$, $C_8H_{14}NO_4^+$ requires 188.0923); (EI$^+$) 211 (41%), 188 ((MH)$^+$, 100).

Preparation of *tert*-butyl-(1*R*,2*S*,6*S*)-2-hydroxy-6-aminocyclohexanoate (66)

Following the general procedure 4, $Pd(OH)_2/C$ (50 mg, 20% w/w), protected cyclohexane **43** (250 mg, 0.59 mmol) and MeOH (5 mL) gave the **66** as an orange oil without further purification (121.5 mg, 94%); $[\alpha]_D^{24}$ +42.6 (*c* 0.80, MeOH); ν_{max} (film) 1719, 3214; δ_H (400 MHz, CD$_3$OD) 1.26 (1H, app d, *J* 5.9, C(5)H_AH$_B$), 1.49 (9H, s, C(CH_3)$_3$), 1.46–1.61 (2H, m, C(4)H_2), 1.78 (2H, br t, *J* 10.2, C(3)H_2), 1.92 (1H, br d, *J* 6.1, C(5)H$_A$$H_B$), 2.28 (1H, dd, $J_{1ax,6ax}$ 9.5, $J_{1ax,2eq}$ 3.0, C(1)*H*), 3.32 (1H, dt, *J* 3.0, 1.6, C(6)*H*), 4.39 (1H, br s, C(2)*H*); δ_C (125 MHz, CD$_3$OD) 18.4 (*C*(4)H$_2$), 27.5 (C(*C*H$_3$)$_3$), 31.6 (*C*(5)H$_2$), 32.6 (*C*(3)H$_2$), 46.7 (*C*(6)H), 55.4 (*C*(1)H), 68.0 (*C*(2)H), 81.5 (*C*(CH$_3$)$_3$), 172.6 (*C*O$_2$); *m/z* (CI$^+$) 216.1608 (MH$^+$, $C_{11}H_{22}NO_3^+$ requires 216.1600); (EI$^+$) 279 (100%), 216 ((MH)$^+$, 40).

Preparation of *tert*-butyl-(1*R*,2*S*,6*S*)-2-acetoxy-6-aminocyclohexanoate (67)

Following the general procedure 4, $Pd(OH)_2/C$ (50 mg, 17% w/w), protected acetate **44** (300 mg, 0.64 mmol) and MeOH (5 mL) gave the **67** as a brown oil without further purification (155 mg, 96%); $[\alpha]_D^{24}$ +97.1 (*c* 0.85, MeOH); ν_{max} (film) 1737, 3243; δ_H (400 MHz, CD$_3$OD) 1.23–1.25 (1H, m, C(5)H_AH$_B$), 1.31–1.36 (1H, m, C(4)H_AH$_B$), 1.41 (9H, s, C(CH_3)$_3$), 1.49–1.51 (1H, m, C(3)H_AH$_B$), 1.60–1.68 (1H, m, C(4)H$_A$$H_B$), 1.90–1.94 (1H, m, C(3)H$_A$$H_B$), 2.03 (3H, s, C$H_3CO_2$), 2.03–2.08 (1H, m, C(5)H$_A$$H_B$), 2.41 (1H, dd, $J_{1ax,6ax}$ 7.8, $J_{1ax,2eq}$ 3.0, C(1)*H*), 3.31–3.38 (1H, m, C(6)*H*), 5.50 (1H, br s, C(2)*H*); δ_C (125 MHz, CD$_3$OD) 18.8 (*C*(4)H$_2$), 21.2 (*C*H$_3$CO$_2$), 27.2 (C(*C*H$_3$)$_3$), 29.0 (*C*(3)H$_2$), 30.4 (*C*(5)H$_2$), 47.1 (*C*(6)H), 52.1 (*C*(1)H), 71.1 (*C*(2)H), 81.2 (*C*(CH$_3$)$_3$), 170.3 (CH$_3$*C*O$_2$), 171.0 (*C*O$_2$tBu); *m/z* (CI$^+$) 258.1715 (MH$^+$, $C_{13}H_{24}NO_4^+$ requires 258.1705); (EI$^+$) 258 ((MH)$^+$, 100%), 202 (95).

Preparation of (1*R*,2*S*,6*S*)-2-hydroxy-6-aminocyclohexanoic acid (68)

Following the general procedure **5**, amino-ester **66** (50 mg, 0.23 mmol) and TFA–DCM (5 mL) gave the title compound **68** (27 mg, 73%) as a yellow solid after ion-exchange chromatography (Dowex 50WX8-200, 1 M $NH_4OH_{(aq)}$ eluent); mp 139–141 °C (1 M NH_3); $[\alpha]_D^{24}$ +17.1 (*c* 0.55, H_2O); ν_{max} (film) 1579, 2984, 3317, 3321; δ_H (400 MHz, D_2O) 1.31–1.42 (3H, m, C(4)H_2, C(5)H_AH$_B$), 1.51–1.69 (2H, m, C(3)H_2), 2.01–2.09 (1H, m, C(5)H$_A$$H_B$), 2.31 (1H, dd, $J_{1ax,6ax}$ 10.8, $J_{1ax,2eq}$ 2.8, C(1)*H*), 3.33 (1H, dt, $J_{6ax,1ax}$ 10.8, $J_{6ax,6eq;6ax,5}$ 7.8, C(6)*H*), 4.44 (1H, br s, C(2)*H*); δ_C (100 MHz, D_2O) 18.2 (*C*(4)H$_2$), 30.6 (*C*(5)H$_2$), 32.8 (*C*(3)H$_2$), 46.8 (*C*(6)H), 55.8 (*C*(1)H), 68.2 (*C*(2)H), 174.1 (*C*O$_2$); *m/z* (CI$^-$) 158.0811 ((M–H)$^-$. $C_7H_{13}NO_3^-$ requires 158.0817); (EI$^-$) 158 ((M–H)$^-$, 100%).

Preparation of (1*R*,2*S*,6*S*)-2-acetoxy-6-aminocyclohexanoic acid (69)

Following the general procedure 5, amino-ester **67** (75 mg, 0.29 mmol) and TFA–DCM (5 mL) gave the title compound **69** (49 mg, 84%) as an off-white solid after ion-exchange chromatography (Dowex 50WX8-200, 1 M $NH_4OH_{(aq)}$ eluent); mp 131–133 °C (1 M NH_3); $[\alpha]_D^{24}$ +24.1 (*c* 1.05, H_2O); ν_{max} (KBr) 1646, 3020, 3431, 3444; δ_H (400 MHz, D_2O) 1.24–1.52 (3H, m, C(3)H_AH$_B$, C(4)H_AH$_B$, C(5)H_AH$_B$), 1.52–1.57 (1H, m, C(4)H$_A$$H_B$), 1.57–1.68 (1H, br s, C(5)H$_A$$H_B$), 2.04 (3H, s, C$H_3CO_2$), 2.03–2.06 (1H, m, C(3)H$_A$$H_B$), 2.32 (1H, app t, $J_{1,6;1,2}$ 8.9, C(1)*H*), 3.48 (1H, dt, $J_{6,1}$ 8.9, $J_{6,6;6,5}$ 7.6, C(6)*H*), 4.52 (1H, br s, C(2)*H*); δ_C (100 MHz, D_2O) 18.8 (*C*(4)H$_2$), 21.3 (*C*H$_3$CO$_2$), 29.2 (*C*(3)H$_2$), 30.7 (*C*(5)H$_2$), 47.2 (*C*(6)H), 52.2 (*C*(1)H), 71.3 (*C*(2)H), 170.4, 177.0 2x(*C*O$_2$); *m/z* (CI$^-$) 201.0925 ((M–H)$^-$. $C_9H_{15}NO_4^-$ requires 201.0923); (EI$^-$) 201 ((M–H)$^-$, 100).

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chromatography, samples of (*S*)-**60** prepared by the route described in this paper, and in our previous report,[31] gave (*S*)-homoproline with the same magnitude and sign of specific rotation {$[a]_D^{23}$ +3.4 (*c* 1.00, H_2O) and $[a]_D^{23}$ +3.7 (*c* 0.83, H_2O), respectively} as reported in the literature {$[a]_D^{25}$ +4.0 (*c* 1.00, H_2O)}.[33] The reasons for the discrepancy in the data for (*S*)-**60** is bewildering.

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