Organic & Biomolecular Chemistry

PAPER

View Article Online
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Cite this: *Org. Biomol. Chem.*, 2014, **12**, 2702

Diastereoselective Ireland–Claisen rearrangements of substituted allyl β-amino esters: applications in the asymmetric synthesis of C(5)-substituted transpentacins†

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Received 6th February 2014,
Accepted 11th March 2014

DOI: 10.1039/c4ob00274a

www.rsc.org/obc

The diastereoselective Ireland–Claisen rearrangement of a range of substituted allyl β-amino esters gave the corresponding enantiopure α-substituted-β-amino esters with good diastereoselectivity. The application of this methodology in the asymmetric synthesis of a range of C(5)-substituted 1,2-*anti*-1,5-*syn*-transpentacins was demonstrated by the rearrangement of a range of β-amino esters derived from sorbic acid, followed by esterification, ring-closing metathesis, hydrogenolytic deprotection/reduction, and hydrolysis, which gave the C(5)-substituted transpentacins in only 9 steps from commercially available starting materials.

Introduction

Since its introduction in 1972, the Ireland–Claisen rearrangement[1] of allyl esters (as the corresponding silyl ketene acetals) has shown considerable utility in synthesis. Its popularity is principally due to the high levels of diastereoselectivity which are typically observed during this reaction, in which two adjacent stereogenic centers are produced in a single step. This methodology has been extensively reviewed,[2] and several asymmetric variants have been developed.[3,4]

Previous investigations from our laboratory have demonstrated that the conjugate addition of enantiopure secondary lithium amides (derived from α-methylbenzylamines) to α,β-unsaturated esters represents a general and efficient synthetic protocol for the synthesis of β-amino esters and their derivatives.[5] This methodology has found numerous applications, including the total syntheses of natural products,[6] molecular recognition phenomena[7] and resolution protocols,[8] and has been reviewed.[9] As part of our ongoing research programme to extend the scope and utility of this methodology, we envisaged that the diastereoselective Ireland–Claisen rearrangement of enantiopure allyl β-amino esters, prepared using this methodology, would create up to two new stereogenic centres within the β-amino acid scaffold and provide access to substrates that are not accessible by enolate alkylation. It was envisaged that the requisite substrates **3** could either be prepared by conjugate addition of lithium amide (*S*)-**6** to an α,β-unsaturated allyl ester **4**, or by transesterification of the known *tert*-butyl β-amino esters **2** (Fig. 1). Part of this work has been communicated previously.[10]

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†Electronic supplementary information (ESI) available: Experimental procedures, characterisation data, copies of ^{1}H and ^{13}C NMR spectra, and crystallographic data. CCDC 982697–982706. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob00274a

Results and discussion

Ireland–Claisen rearrangement of allyl β-amino esters: model studies

Allyl β-amino esters **10**, **11** and **13** were selected as model substrates with which to optimise the conditions for an Ireland–Claisen rearrangement. Unfortunately, attempted conjugate addition of lithium amide reagents to simple allyl α,β-unsaturated esters [*i.e.*, those lacking substitution at the C(1′) position] resulted the competitive formation of amide products resulting from 1,2-addition of the lithium amide reagent. Compounds **10**, **11** and **13** were therefore prepared *via* transesterification of the corresponding *tert*-butyl β-amino esters **8**, **9** and **12**. Conjugate addition of lithium *N*,*N*-dibenzylamide and lithium *N*-isopropyl-*N*-benzylamide to *tert*-butyl cinnamate **7** gave racemic β-amino esters **8** and **9** in 73 and 80% yield, respectively.[11] Similarly, conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **6** to **7** gave enantiopure β-amino ester **12** in 82% yield and >99 : 1 dr.[11] Transesterification of all three substrates upon treatment with

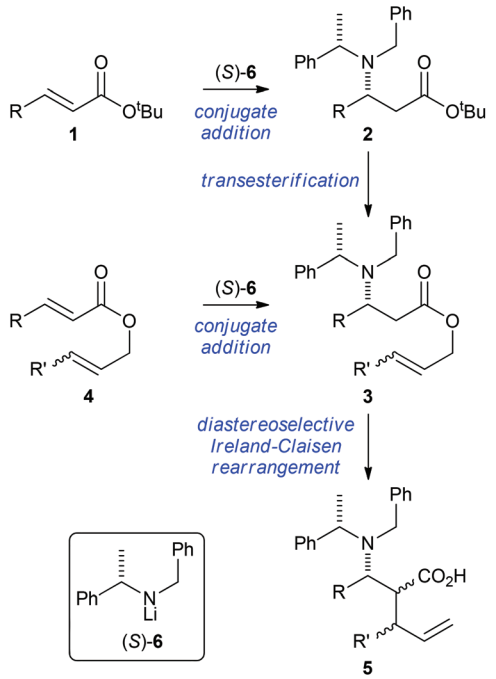
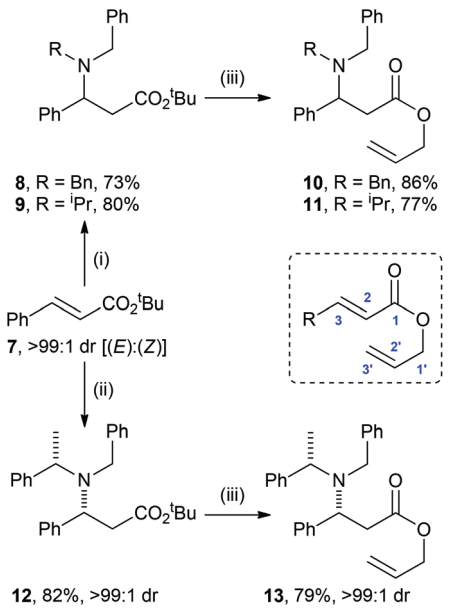


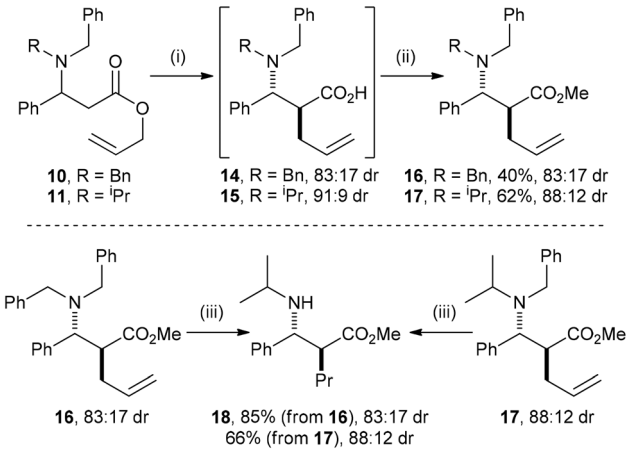
Fig. 1 Ireland–Claisen rearrangement of substituted allyl β-amino esters.



Scheme 1 *Reagents and conditions*: (i) LiN^{i}PrBn or LiNBn$_2$, THF, −78 °C, 2 h; (ii) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **6**, THF, −78 °C, 2 h; (iii) $SOCl_2$, allyl alcohol, 50 °C, 3 h.

$SOCl_2$ in allyl alcohol gave **10**, **11** and **13** in good yield (Scheme 1).

Following a screen of different reaction conditions (varying the temperature, solvent, base, equivalents of reagents, *etc.*), a reproducible procedure for the Ireland–Claisen rearrangement of **10**, **11** and **13** was developed: deprotonation of **10** (R = Bn) with LiHMDS followed by reaction of the resultant lithium (*E*)-β-amino enolate[12] with TMSCl produced the corresponding silyl ketene acetal which was heated at reflux in PhMe to give β-amino acid **14** in 83 : 17 dr. Subsequent esterification of **14** (for ease of handling and isolation) upon treatment with $SOCl_2$ in MeOH produced β-amino ester **16** in 40% yield (from **10**) and 83 : 17 dr (Scheme 2).[13] The relative configuration within the major diastereoisomer **16** was unambiguously determined by single crystal X-ray diffraction analysis (Fig. 2);[14] this analysis also secured the relative configuration within β-amino acid **14**. Ireland–Claisen rearrangement of **11** (R = ^{i}Pr) following an identical procedure produced β-amino acid **15** in 91 : 9 dr, which was converted into β-amino ester **17** upon treatment with $SOCl_2$ and MeOH; after purification **17** was isolated in 62% yield and 88 : 12 dr.[13] The configurations within **15** and **17** were assigned by chemical correlation: hydrogenolysis of **16** (83 : 17 dr) in the presence of acetone effected removal of the *N*-benzyl groups and *in situ* reductive alkylation to give *N*-isopropyl substituted β-amino ester **18** in 85% yield



Scheme 2 *Reagents and conditions*: (i) TMSCl, PhMe, −78 °C, 10 min then LiHMDS, −78 °C, 30 min then reflux, 1 h; (ii) $SOCl_2$, MeOH, 50 °C, 48 h; (iii) H_2 (1 atm), $Pd(OH)_2$/C, MeOH–acetone (9 : 1), rt, 16 h.

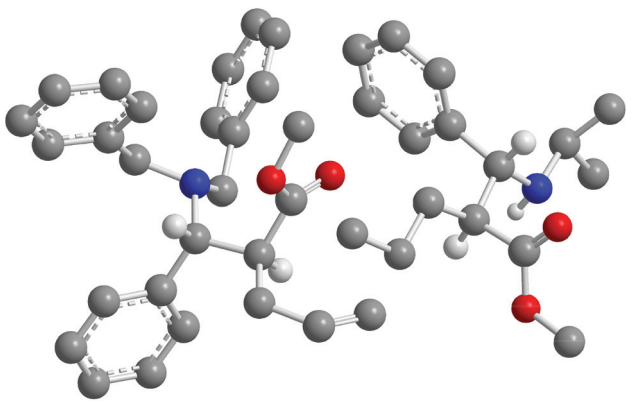
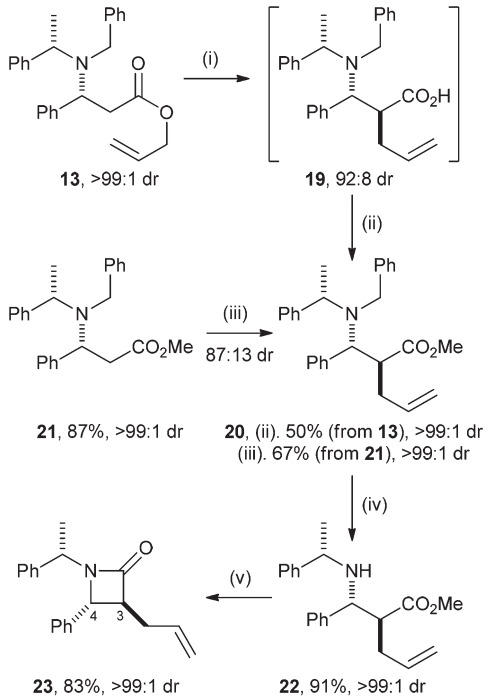


Fig. 2 X-ray crystal structures of (*RS*,*SR*)-**16** [*left*] and (*RS*,*SR*)-**18** [*right*] (selected H-atoms are omitted for clarity).



Scheme 3 *Reagents and conditions*: (i) TMSCl, PhMe, −78 °C, 10 min then LiHMDS, −78 °C, 30 min then reflux, 1 h; (ii) $SOCl_2$, MeOH, 50 °C, 48 h; (iii) LiHMDS, THF, −78 °C, 2 h then allyl bromide, −78 °C to rt, 16 h; (iv) CAN, MeCN–H_2O (5 : 1), rt, 16 h; (v) MeMgBr, Et_2O, 0 °C, 30 min.

and 83 : 17 dr. Hydrogenolysis of **17** (88 : 12 dr), under identical conditions, gave **18** in 66% yield and 88 : 12 dr (Scheme 2).[15] The relative configuration within **18** was subsequently confirmed unambiguously *via* single crystal X-ray diffraction analysis (Fig. 2).[14]

Ireland–Claisen rearrangement of the corresponding enantiopure substrate **13** [derived from conjugate addition of enantiopure lithium amide (*S*)-**6** to α,β-unsaturated ester **7**, followed by transesterification] produced β-amino acid **19** in 92 : 8 dr. Esterification of **19** upon treatment with $SOCl_2$ in MeOH gave β-amino ester **20** in 92 : 8 dr, which was then isolated in 50% yield and >99 : 1 dr. An authentic sample of **20** was prepared upon alkylation of the known[5b] β-amino ester **21** with allyl bromide, which gave **20** in 87 : 13 dr, and 67% yield and >99 : 1 dr after chromatographic purification. β-Amino ester **20** was subsequently converted into the corresponding β-lactam **23** *via* (i) oxidative monodebenzylation with CAN, and (ii) MeMgBr-mediated cyclisation of **22** to give β-lactam **23** in 76% overall yield for the two step procedure (Scheme 3). The relative configuration within **23** (and therefore also those within **19**, **20** and **22**) was assigned from the value of the ^{1}H NMR ^3J coupling constant observed between the C(3)*H* and C(4)*H* protons ($^3J_{3,4}$ = 2.1 Hz), which is known to be diagnostic of the relative stereochemical configuration within β-lactams.[16] These assignments were all confirmed unambiguously by subsequent single crystal X-ray diffraction analyses of both **19** and **20** (Fig. 3);[14] in both cases the absolute configurations within (2*S*,3*R*,α*S*)-**19** and (2*S*,3*R*,α*S*)-**20** were assigned relative to the known (*S*)-configuration of the α-methylbenzyl fragment and were confirmed by determination of Flack *x* parameters[17] of −0.02(18) and −0.02(15), respectively.

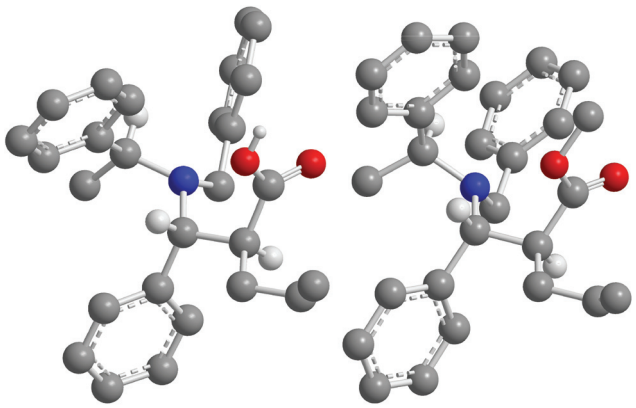
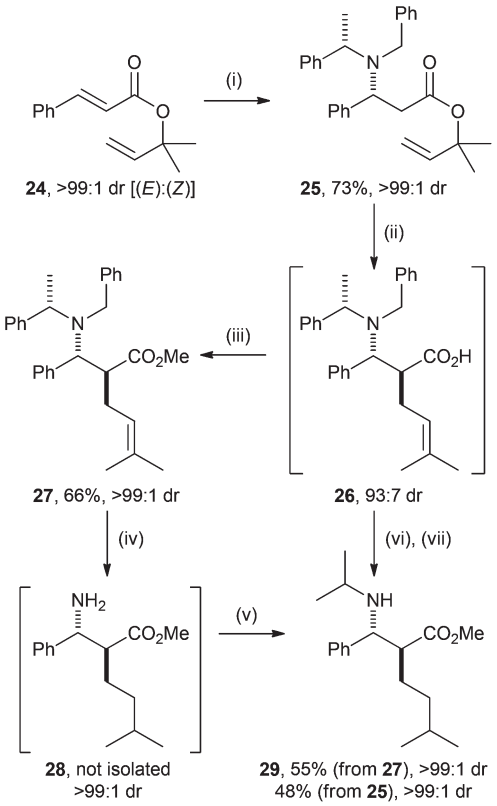


Fig. 3 X-ray crystal structures of (2*S*,3*R*,α*S*)-**19** [*left*] and (2*S*,3*R*,α*S*)-**20** [*right*] (selected H-atoms are omitted for clarity).

The rearrangement of isoprenyl β-amino ester **25** was investigated next. As 1,2-addition of the lithium amide reagent was not expected to present a problem upon conjugate addition to isoprenyl cinnamate **24**, β-amino ester **25** was prepared from **24**[18] upon conjugate addition of enantiopure lithium amide (*S*)-**6**, which gave **25** as the only reaction product in 73% isolated yield and >99 : 1 dr after chromatographic purification (Scheme 4).[19] The relative configuration within **25** was assigned unambiguously *via* single crystal X-ray diffraction analysis and the absolute (3*R*,α*S*)-configuration within **25** was assigned relative to the known (*S*)-configuration of the α-methylbenzyl fragment (Fig. 4); furthermore, the determination of a Flack *x* parameter[17] of −0.09(10) confirmed this assignment.[14] Ireland–Claisen rearrangement of **25** gave β-amino acid **26** in 93 : 7 dr. Subsequent esterification of **26**, upon treatment with DBU and MeI,[20,21] gave β-amino ester **27** in 93 : 7 dr, which was isolated in 66% yield and >99 : 1 dr. The relative configuration within **27** was then established by X-ray diffraction analysis of a derivative: hydrogenolysis of **27** followed by reductive N-alkylation of **28** gave **29** in 55% yield and >99 : 1 dr. Alternatively, **29** was accessed directly from **25** in 3 steps and 48% overall yield (Scheme 4). Subsequent single crystal X-ray diffraction analysis of **29** allowed the relative configurations within **26–28** to be established unambiguously (Fig. 4).[14]

The Ireland–Claisen rearrangement of prenyl β-amino ester **30** [which was expected to generate a quaternary centre at the C(1′)-position upon rearrangement] was investigated next. β-Amino ester **30** was prepared by hydrolysis of *tert*-butyl ester **12** followed by treatment of the resultant β-amino acid with prenyl bromide in the presence of DBU. Ireland–Claisen rearrangement of **30** produced β-amino acid **31** in 90 : 10 dr, and esterification with DBU and MeI gave methyl ester **32** in 90 : 10 dr, which was isolated in 50% yield and >99 : 1 dr (Scheme 5). The stereochemical outcome of this



Scheme 4 *Reagents and conditions*: (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **6**, THF, −78 °C, 2 h; (ii) TMSCl, PhMe, −78 °C, 10 min then LiHMDS, −78 °C, 30 min then reflux, 1 h; (iii) DBU, MeCN, MeI, rt, 4 h; (iv) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 15 h; (v) acetone, $NaBH_3CN$, MeOH, rt, 22 h; (vi) H_2 (1 atm), $Pd(OH)_2/C$, MeOH–acetone (9 : 1), rt, 22 h; (vii) $SOCl_2$, MeOH, 50 °C, 48 h.

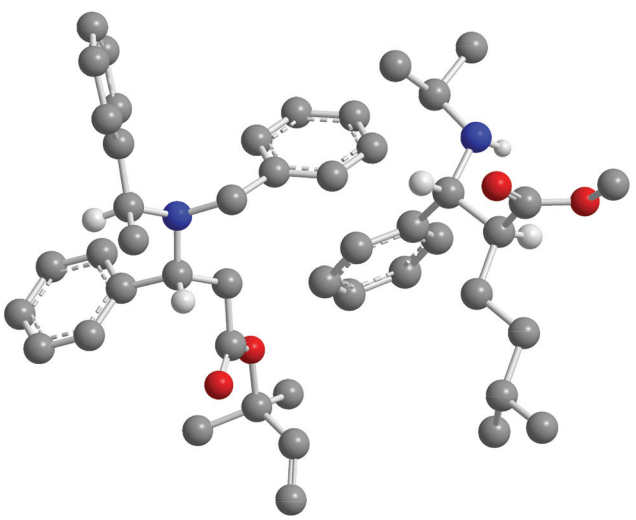
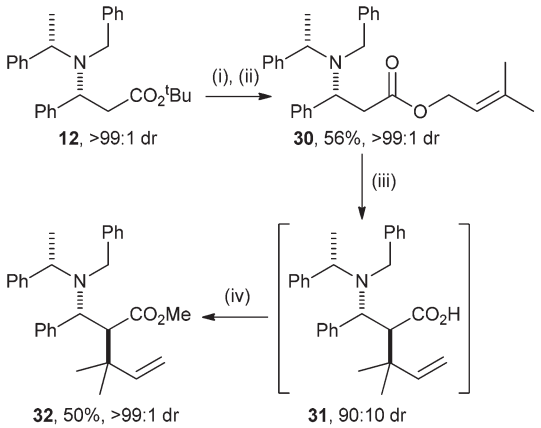


Fig. 4 X-ray crystal structures of (3*R*,α*S*)-**25** [*left*] and (2*S*,3*R*)-**29** [*right*] (selected H-atoms are omitted for clarity).

rearrangement was assigned by analogy to the stereochemical outcomes observed upon rearrangement of substrates **10**, **11**, **13** and **25**.



Scheme 5 *Reagents and conditions*: (i) TFA, CH_2Cl_2, rt, 16 h; (ii) prenyl bromide, DBU, MeCN, rt, 17 h; (iii) TMSCl, PhMe, −78 °C then LiHMDS, −78 °C, 30 min then reflux, 1 h; (iv) DBU, MeCN, MeI, rt, 8 h.

Ireland–Claisen rearrangement of *cis*- and *trans*-configured allyl β-amino esters: asymmetric synthesis of β-amino acids bearing chiral C(2)-substituents

As the Ireland–Claisen rearrangement of stereodefined allyl esters bearing only one substituent at the C(3′)-position would create an additional stereogenic centre at the C(1′)-position of the product, representative substrates derived from *cis*- or *trans*-crotyl and cinnamyl alcohols were evaluated in this reaction manifold; the rearrangement of the *trans*-configured substrates **33** and **34** were investigated first. Both substrates were again prepared by transesterification of *tert*-butyl ester **12**. In the case of *trans*-crotyl alcohol derived substrate **33** (R = Me), the Ireland–Claisen rearrangement proceeded with poor diastereoselectivity to give a 54 : 46 mixture of diastereoisomeric β-amino acids **35**.[22] Improved diastereoselectivity was observed upon rearrangement of the *trans*-cinnamyl alcohol derived substrate **34** (R = Ph), which gave a 70 : 30 mixture of diastereoisomeric β-amino acids **37** and **38**, respectively. The configuration within the major diastereoisomer **37** was determined unambiguously by single crystal X-ray diffraction analysis (Fig. 5),[14] and the absolute (2*S*,3*R*,1′*S*,α*S*)-configuration within **37** was assigned relative to the known configuration of the (*S*)-α-methylbenzyl fragment; furthermore, the determination of a Flack *x* parameter[17] of 0.02(16) for the crystal structure of **37** confirmed this assignment. Subsequent esterification gave β-amino esters **39** and **40** in 38 and 13% yield, respectively, and >99 : 1 dr in both cases (Scheme 6).

Ireland–Claisen rearrangement of the corresponding *cis*-configured substrates **41** and **42** (derived from transesterification of *tert*-butyl ester **12** with either *cis*-crotyl alcohol or *cis*-cinnamyl alcohol, respectively) proceeded with far greater diastereoselectivity than the *trans*-configured substrates **33** and **34**, giving β-amino acids **43** and **37** in 96 : 4 and 90 : 10 dr, respectively. Conversion of **43** and **37** to the corresponding methyl esters gave **44** in 85% yield (from **41**) and 96 : 4 dr, and **39** in 48% yield (from **42**) and >99 : 1 dr. It is interesting to note that the major diastereoisomer resulting from the

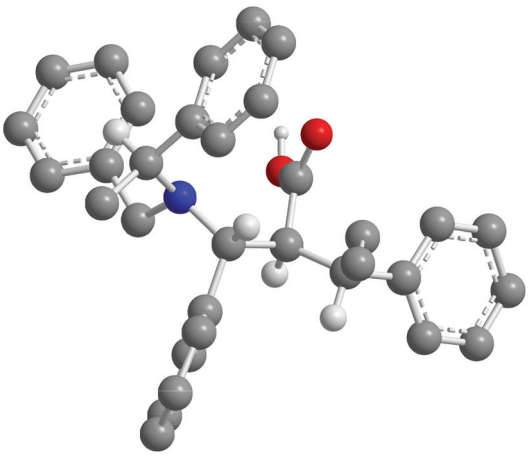
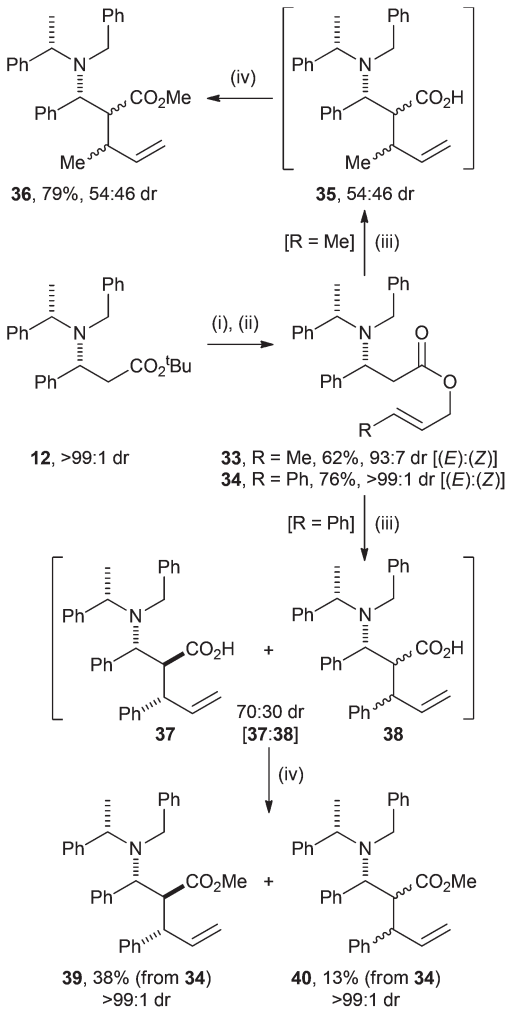
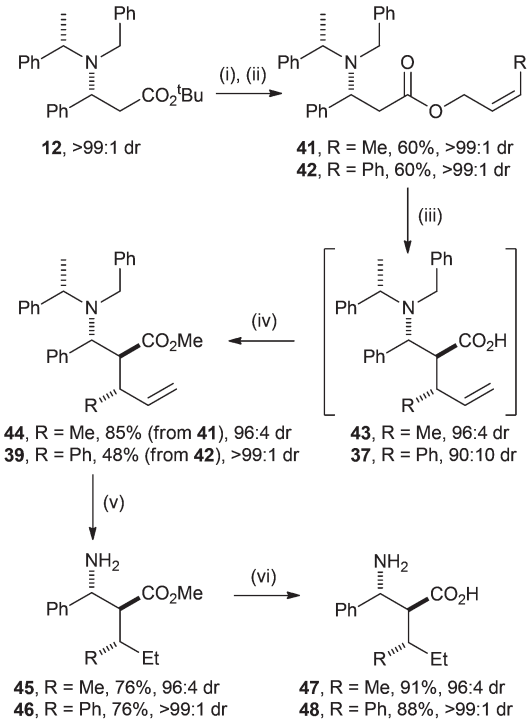


Fig. 5 X-ray crystal structure of (2*S*,3*R*,1′*S*,α*S*)-**37** (selected H-atoms are omitted for clarity).



Scheme 6 *Reagents and conditions*: (i) TFA, CH_2Cl_2, rt, 16 h; (ii) $(COCl)_2$, CH_2Cl_2, DMF, 0 °C to rt, 1 h then crotyl alcohol [96 : 4 dr (*E*):(*Z*)] or cinnamyl alcohol [>99 : 1 dr (*E*):(*Z*)], CH_2Cl_2, 0 °C to rt, 16 h; (iii) LiHMDS, TMSCl, PhMe, −78 °C then reflux, 1 h; (iv) DBU, MeI, MeCN, rt, 16 h.



Scheme 7 *Reagents and conditions*: (i) TFA, CH_2Cl_2, rt, 16 h; (ii) $(COCl)_2$, CH_2Cl_2, DMF, 0 °C to rt, 1 h then crotyl alcohol [>99 : 1 dr (*Z*):(*E*)] or cinnamyl alcohol [>99 : 1 dr (*Z*):(*E*)], CH_2Cl_2, 0 °C to rt, 16 h; (iii) LiHMDS, TMSCl, PhMe, −78 °C then reflux, 1 h; (iv) DBU, MeI, MeCN, rt, 16 h; (v) $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt, 24 h; (vi) HCl (6.0 M aq), reflux, 5 days then DOWEX 50WX8.

Ireland–Claisen rearrangement of the *cis*-cinnamyl alcohol derived substrate **42** is identical to the major diastereoisomer resulting from the rearrangement of the *trans*-cinnamyl alcohol derived substrate **34**. The configurations within **43** and **44** were assigned by analogy to those within **37** and **39**. Tandem hydrogenation/hydrogenolysis of both **44** and **39**, and subsequent hydrolysis of **45** and **46** gave β-amino acids **47** and **48** in good overall yield after purification on DOWEX 50WX8 ion exchange resin (Scheme 7).

The origin of diastereoselectivity in the Ireland–Claisen rearrangement of allyl β-amino esters

The levels of diastereoselectivity observed upon Ireland–Claisen rearrangement of this range of allyl β-amino esters have proven to be somewhat variable, with the substrates lacking substitution on the allyl fragment, and the *cis*-configured substrates bearing a substituent on the allyl fragment, displaying superior levels of diastereoselectivity to the corresponding *trans*-configured substrates. It is also curious that the formation of β-amino acid **37** occurs as the major diastereoisomer resulting from Ireland–Claisen rearrangement of *both* β-amino esters *trans*-**34** (giving **37** in 70 : 30 dr) and *cis*-**42** (giving **37** in 90 : 10 dr).[23] These data can be explained by considering the possible transition states for rearrangement: it can be expected that rearrangement of the *cis*-configured substrates, such as **42** (R^1 = H, R^2 = Ph), would proceed *via*

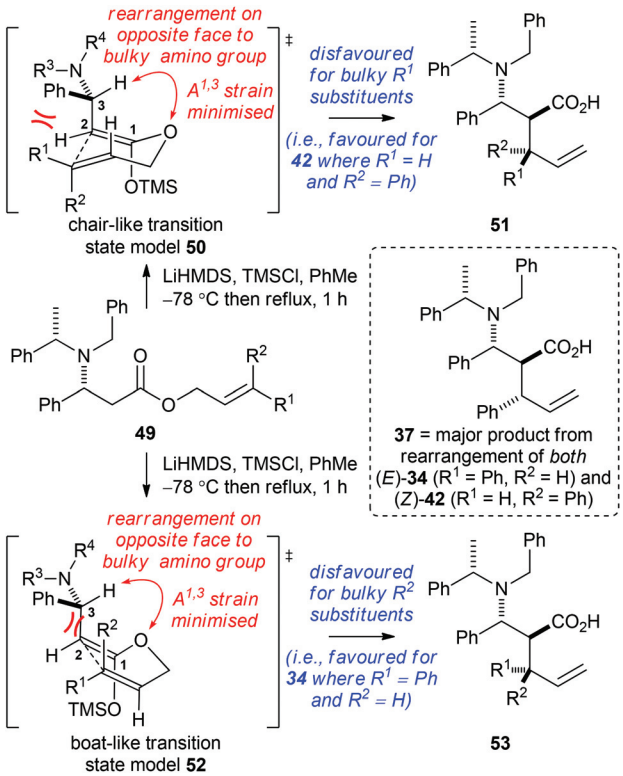


Fig. 6 Proposed transition state models for rearrangement.

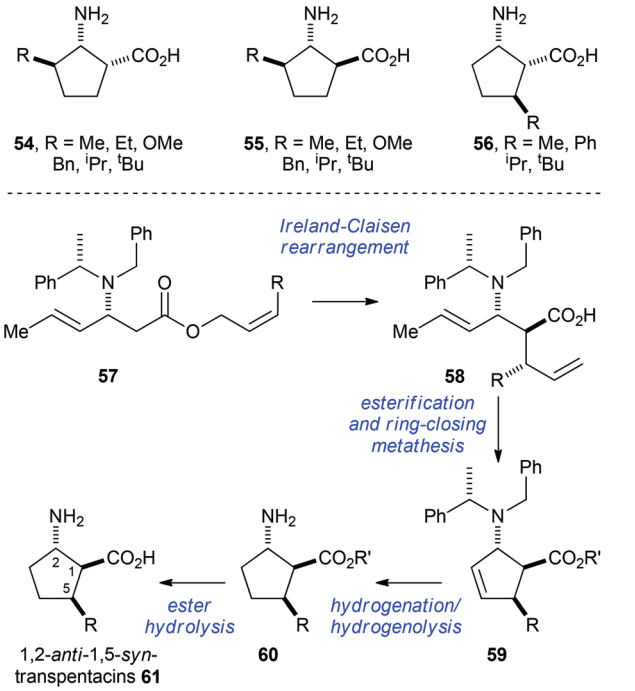


Fig. 7 Proposed asymmetric synthesis of enantiopure 1,2-*anti*-1,5-*syn*-transpentacins **63**.

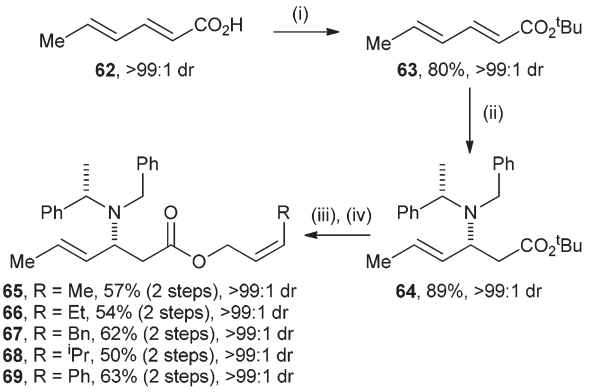
chair-like transition state **50** in which 1,3-allylic strain between the C(3)-substituents and the C(1)–O bond is minimised and the reaction occurs on the face opposite the bulky *N*-benzyl-*N*-(α-methylbenzyl) group. A chair-like transition state is disfavoured for substrates such as **34** (R^1 = Ph, R^2 = H) when significant steric interactions between R^1 and the C(3)-phenyl group are encountered; in this case a boat-like transition state **52**,[24] in which 1,3-allylic strain between the C(3)-substituents and the C(1)–O bond is minimised and the reaction occurs on the face opposite the bulky *N*-benzyl-*N*-(α-methylbenzyl) group, would be favoured as the R^1 substituent occupies a far less sterically congested position (Fig. 6). This analysis is also consistent with the rearrangement of **41** (R^1 = H, R^2 = Me; 96 : 4 dr) being more highly diastereoselective than that of **42** (R^1 = H, R^2 = Ph; 90 : 10 dr), and the rearrangement of **33** (R^1 = Me, R^2 = H; 54 : 46 dr) being essentially non-selective.

Application to the asymmetric synthesis of C(5)-substituted transpentacins

The development of routes to access enantiopure substituted derivatives of the cyclic β-amino acid transpentacin (*trans*-2-aminocyclopentanecarboxylic acid) is of considerable importance as oligomers of these β-amino acids display interesting secondary structural characteristics.[25,26] In order to enhance the structural diversity of enantiopure monomeric cispentacin and transpentacin derivatives available we have previously developed efficient parallel kinetic resolution (PKR) procedures for the asymmetric syntheses of C(3)- and C(5)-substituted analogues **54–56**,[27] and subsequently investigated the secondary structural characteristics of some of their oligomers.[28] It was therefore envisaged that an alternative procedure for the syntheses of 1,2-*anti*-1,5-*syn*-diastereoisomers **61**, which are not accessible using the PKR protocol, could be developed employing the diastereoselective Ireland–Claisen rearrangement of enantiopure *cis*-substituted allyl esters **57**. The resultant α-substituted β-amino acid products **58** could then be elaborated to the corresponding C(5)-substituted transpentacins **61** *via* a three step protocol involving ring-closing metathesis, hydrogenolytic deprotection/reduction, and finally hydrolysis (Fig. 7).

Esterification of commercially available sorbic acid **62** upon treatment with isobutylene in the presence of H_2SO_4 gave α,β-unsaturated ester **63** in 80% isolated yield. Conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **6** to **63** produced the known[19,29] β-amino ester **64** as a single diastereoisomer (>99 : 1 dr), which was isolated in 89% yield and >99 : 1 dr. Hydrolysis of **64** upon treatment with TFA, conversion of the resultant carboxylic acid to the corresponding acid chloride, and treatment with the requisite *cis*-allylic alcohols (R = Me, Et, Bn, ^{i}Pr, Ph) gave β-amino esters **65–69** in good yield (Scheme 8).

In each case, Ireland–Claisen rearrangement of **65–69** produced the corresponding β-amino acids **70–79** in ~80 : 20 dr. Following esterification of **70–79**, upon treatment with DBU and MeI, and chromatographic purification, the major diastereoisomers **80–84** were isolated in 38–69% yield, and the minor diastereoisomers **85–89** were isolated in 7–16% yield,[30] as single diastereoisomers (>99 : 1 dr) in each case (Scheme 9). The configurations within **84**, **86**, **87** and **89** were established



Scheme 8 *Reagents and conditions*: (i) isobutylene, H_2SO_4, CH_2Cl_2, 0 °C to rt, 48 h; (ii) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**6**, THF, −78 °C, 2 h; (iii) CH_2Cl_2–TFA (2 : 1), rt, 16 h; (iv) $(COCl)_2$, CH_2Cl_2, DMF, 0 °C to rt, 1 h then *cis*-RCH=CHCH$_2$OH [>99 : 1 dr (*E*) : (*Z*)], CH_2Cl_2, 0 °C to rt, 16 h.

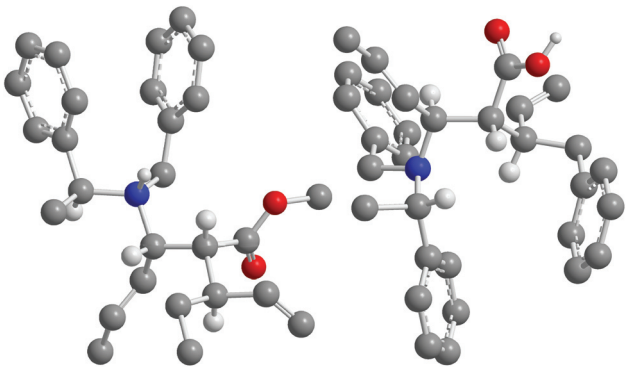
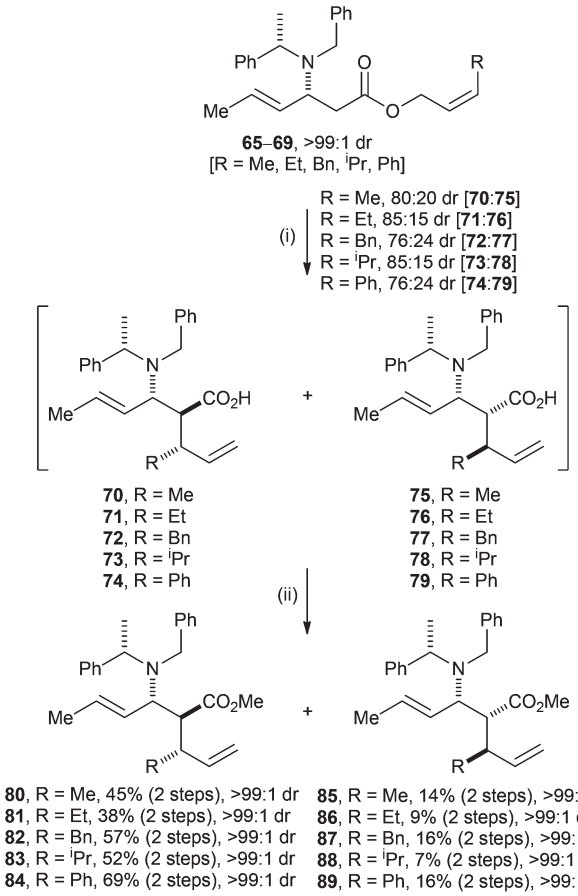


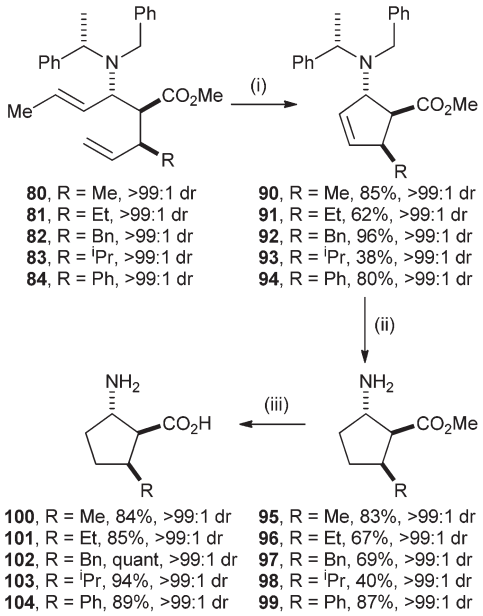
Fig. 8 X-ray crystal structures of (*S*,*S*,*S*,*E*)-**86**·HBF_4 [*left*] and (2*R*,3*S*,1′-*R*,α*S*,*E*)-**87** [*right*] (the BF_4^- counterion and selected H-atoms are omitted for clarity).



Scheme 9 *Reagents and conditions*: (i) LiHMDS, TMSCl, PhMe, −78 °C, 15 min, then reflux, 1 h; (ii) DBU, MeI, MeCN, rt, 16 h.

by single crystal X-ray diffraction analyses (Fig. 8),[14,31] and the configurations within **80–83, 85** and **88** were then assigned by analogy.

Ring-closing metathesis of **80–84** (the major diastereoisomers resulting from Ireland–Claisen rearrangement of **65–69**) gave the corresponding cyclic β-amino esters **90–94** in 38–96% yield. Subsequent tandem hydrogenation/hydrogenolysis of **90–94** gave primary β-amino esters **95–99** as single diastereoisomers (>99 : 1 dr) in 40–87% yield (Scheme 10). The configurations within **95, 96** and **99** were established by single crystal X-ray diffraction analyses (Fig. 9),[14,31] and the configurations within **97** and **98** were then assigned by analogy. Finally, hydrolysis of the methyl ester functionalities within **95–99**, upon treatment with 6.0 M aq. HCl at reflux for 16 h, gave β-amino acids **100–104** which were isolated in 84% to quantitative yield and >99 : 1 dr after purification on Dowex 50WX8 ion exchange resin (Scheme 10).



Scheme 10 *Reagents and conditions*: (i) Grubbs I, CH_2Cl_2, 40 °C, 24–48 h; (ii) H_2 (1 atm), $Pd(OH)_2$/C, MeOH, rt, 24 h; (iii) HCl (6.0 M aq), reflux, 16 h then DOWEX 50WX8.

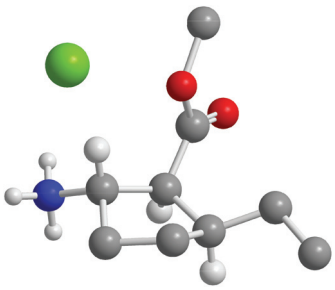


Fig. 9 X-ray crystal structure of (*S*,*S*,*S*)-**96**·HCl (selected H-atoms are omitted for clarity).

Conclusions

In conclusion, a diastereoselective Ireland–Claisen rearrangement protocol has been developed for the asymmetric synthesis of α-substituted-β-amino acids. The rearrangement precursors were typically prepared upon conjugate addition of enantiopure lithium amides to *tert*-butyl α,β-unsaturated esters, followed by transesterification to give the requisite allyl β-amino ester substrates. Subsequent Ireland–Claisen rearrangement gave the corresponding enantiopure β-amino acids in good yield. The stereochemical outcomes of these reactions were considered and transition state models to account for this diastereoselectivity were proposed. The application of this methodology in the asymmetric synthesis of a range of C(5)-substituted 1,2-*anti*-1,5-*syn*-transpentacins was demonstrated by the rearrangement of β-amino esters derived from sorbic acid, followed by esterification of the rearrangement products, ring-closing metathesis, hydrogenolytic deprotection/reduction, and hydrolysis which provided access to the C(5)-substituted transpentacins in only 9 steps from commercially available starting materials. Further applications of this methodology are under investigation within our laboratory.

Experimental

General experimental details

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[32] BuLi was purchased as a solution in hexanes and titrated against diphenylacetic acid before use. $Pd(OH)_2/C$ (20 wt % dry basis) was used for all hydrogenolysis reactions. All other reagents were used as supplied without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), 1% aq. $KMnO_4$ or Dragendorff's reagent. Flash column chromatography was performed on Kieselgel 60 silica. Melting points are uncorrected. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g per 100 mL. IR spectra were recorded using an ATR module. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded in the deuterated solvent stated. Spectra were recorded at rt unless otherwise stated. The field was locked by external referencing to the relevant deuteron resonance. ^1H–^1H COSY, ^1H–^{13}C HMQC, and ^1H–^{13}C HMBC analyses were used to establish atom connectivity. Accurate mass measurements were run on a TOF spectrometer internally calibrated with polyalanine.

Prop-2′-en-1′-yl (*RS*)-3-(*N*,*N*-dibenzylamino)-3-phenylpropanoate 10

$SOCl_2$ (2.15 mL, 29.9 mmol) was added dropwise to a stirred solution of **8**[11] (4.00 g, 9.96 mmol) in allyl alcohol (40 mL) at 0 °C and the resultant mixture was stirred at 50 °C for 3 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*, the residue was dissolved in CH_2Cl_2 (150 mL), and the resultant solution was washed with satd aq. $NaHCO_3$ (3 × 150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 98 : 2) gave **10** as a colourless oil (3.30 g, 86%); ν_{max} (ATR) 2934 (C–H), 1735 (C=O), 1602 (C=C); δ_H (400 MHz, $CDCl_3$) 2.69 (1H, dd, *J* 14.4, 7.3, C(2)H_A), 3.07 (1H, dd, *J* 14.4, 7.3, C(2)H_B), 3.11 (2H, d, *J* 13.9, N(C$H_A$$H_B$Ph)$_2$), 3.69 (2H, d, *J* 13.9, N(C$H_A$$H_B$Ph)$_2$), 4.25 (1H, t, *J* 7.3, C(3)*H*), 4.38–4.55 (2H, m, C(1′)H_2), 5.09–5.17 (2H, m, C(3′)H_2), 5.69–5.79 (1H, m, C(2′)*H*), 7.12–7.31 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 36.6 (*C*(2)), 53.7 (N(*C*H_2Ph)$_2$), 58.9 (*C*(3)), 65.3 (*C*(1′)), 118.3 (*C*(3′)), 126.9, 127.5, 128.1, 128.2, 128.6, 128.8 (*o*,*m*,*p*-*Ph*), 132.1 (*C*(2′)), 137.4, 139.5 (*i*-*Ph*), 171.3 (*C*(1)); *m*/*z* (ESI$^+$) 408 ([M + Na]$^+$, 100%), 386 ([M + H]$^+$, 70%); HRMS (ESI$^+$) $C_{26}H_{28}NO_2^+$ ([M + H]$^+$) requires 386.2115; found 386.2101.

Prop-2′-en-1′-yl (*RS*)-3-(*N*-isopropyl-*N*-benzylamino)-3-phenylpropanoate 11

$SOCl_2$ (2.44 mL, 33.9 mmol) was added dropwise to a stirred solution of **9**[11] (4.00 g, 11.3 mmol) in allyl alcohol (40 mL) at 0 °C and the resultant mixture was stirred at 50 °C for 3 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*, the residue was dissolved in CH_2Cl_2 (150 mL), and the resultant solution was washed with satd aq. $NaHCO_3$ (3 × 150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 98 : 2) gave **11** as a colourless oil (2.94 g, 77%); ν_{max} (ATR) 2965, 2934 (C–H), 1735 (C=O), 1601 (C=C); δ_H (400 MHz, $CDCl_3$) 0.71 (3H, d, *J* 6.6, CH*Me*$_A$Me$_B$), 0.98 (3H, d, *J* 6.6, CHMe$_A$*Me*$_B$), 2.55 (1H, dd, *J* 14.4, 8.5, C(2)H_A), 2.87 (1H, dd, *J* 14.4, 6.9, C(2)H_B), 3.01 (1H, septet, *J* 6.6, C*H*Me$_2$), 3.61 (2H, d, *J* 15.1, NCH_2Ph), 4.25 (1H, dd, *J* 8.5, 6.9, C(3)*H*), 4.29–4.40 (2H, m, C(1′)H_2), 5.04–5.10 (2H, m, C(3′)H_2), 5.62–5.71 (1H, m, C(2′)*H*), 7.12–7.31 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.4, 21.4 (CH*Me*$_2$), 38.9 (*C*(2)), 47.9 (*C*HMe$_2$), 49.3 (N*C*H_2Ph), 60.0 (*C*(3)), 65.0 (*C*(1′)), 118.0 (*C*(3′)), 126.5, 127.1, 128.0, 128.1 (*o*,*m*,*p*-*Ph*), 132.1 (*C*(2′)), 141.3, 141.8 (*i*-*Ph*), 171.5 (*C*(1)); *m*/*z* (ESI$^+$) 360 ([M + Na]$^+$, 100%), 338 ([M + H]$^+$, 90%); HRMS (ESI$^+$) $C_{22}H_{28}NO_2^+$ ([M + H]$^+$) requires 338.2115; found 338.2104.

Prop-2′-en-1′-yl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-phenylpropanoate 13

$SOCl_2$ (0.94 mL, 13.1 mmol) was added dropwise to a solution of **12**[11] (1.82 g, 4.38 mmol, >99 : 1 dr) in allyl alcohol (18 mL) at 0 °C and the resultant mixture was stirred at 50 °C for 3 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (100 mL) and the resultant solution was washed with satd aq. $NaHCO_3$ (3 × 150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 98 : 2) gave **13** as a colourless oil (1.39 g, 79%, >99 : 1 dr); $[\alpha]_D^{20}$ −4.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2971, 2935 (C–H), 1733 (C=O), 1601 (C=C); δ_H (400 MHz, $CDCl_3$) 1.14 (3H, d, *J* 6.8, C(α)*Me*), 2.52 (1H, dd, *J* 14.6, 9.6, C(2)H_A), 2.61 (1H, dd, *J* 14.6, 5.4, C(2)H_B), 3.58 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 3.65 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 3.92 (1H, q, *J* 6.8, C(α)*H*), 4.24–4.32 (2H, m, C(1′)H_2), 4.38 (1H, dd, *J* 9.6, 5.4, C(3)*H*), 5.00–5.04 (2H, m, C(3′)H_2), 5.56–5.66 (1H, m, C(2′)*H*), 7.07–7.32 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.8 (C(α)*Me*), 37.5 (*C*(2)), 50.7 (N*C*H_2Ph), 56.7 (*C*(α)), 59.3 (*C*(3)), 64.9 (*C*(1′)), 118.0 (*C*(3′)), 126.6, 126.8, 127.2, 127.8, 128.0, 128.0, 128.1, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 132.0 (*C*(2′)), 141.3, 141.6, 143.9 (*i*-*Ph*), 171.4 (*C*(1)); *m*/*z* (ESI^+) 422 ($[M + Na]^+$, 100%), 400 ($[M + H]^+$, 90%); HRMS (ESI^+) $C_{27}H_{29}NNaO_2^+$ ($[M + Na]^+$) requires 422.2091; found 422.2091.

Methyl (*RS*,*SR*)-2-(prop-2′-en-1′-yl)-3-(*N*,*N*-dibenzylamino)-3-phenylpropanoate 16

Method A. TMSCl (0.9 mL, 7.8 mmol) was added dropwise to a solution of **10** (1.00 g, 2.59 mmol) in PhMe (10 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 7.8 mL, 7.8 mmol) was added dropwise and the resultant solution was stirred at −78 °C for 30 min. The reaction mixture was heated at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (100 mL) and 1.0 M aq. HCl (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo*. The residue was then dissolved in MeOH (20 mL), the resultant solution was cooled to 0 °C, and $SOCl_2$ (5.6 mL, 77.8 mmol) was added dropwise. The reaction mixture was heated at 50 °C for 48 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (100 mL) and the resultant solution was washed with satd aq. $NaHCO_3$ (3 × 100 mL). The organic extract was then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 99 : 1) gave **16** as a pale yellow oil (51 mg, 40%, 83 : 17 dr). Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.69–1.73 (1H, m, C(1′)H_A), 1.90–1.99 (1H, m, C(1′)H_B), 2.86 (2H, d, *J* 13.6, N(C$H_A$$H_B$Ph)$_2$), 3.33 (1H, app td, *J* 11.5, 3.3, C(2)*H*), 3.67 (3H, s, O*Me*), 3.83–3.89 (3H, m, C(3)*H*, N($CH_A$$H_B$Ph)$_2$), 4.79–4.82 (2H, m, C(3′)H_2), 5.47–5.57 (1H, m, C(2′)*H*), 7.08–7.36 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 34.8 (*C*(1′)), 48.4 (*C*(2)), 51.4 (O*Me*), 53.7 (N(*C*H_2Ph)$_2$), 64.5 (*C*(3)), 116.6 (*C*(3′)), 126.9, 127.7, 128.1, 128.2, 128.9, 129.4 (*o*,*m*,*p*-*Ph*), 133.9 (*i*-*Ph*), 135.0 (*C*(2′)), 139.3 (*i*-*Ph*), 174.0 (*C*(1)). Data for minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) 2.22 (1H, ddd, *J* 14.0, 10.9, 8.1, C(1′)H_A), 2.93 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 3.08–3.12 (1H, m, C(1′)H_B), 3.14 (3H, s, O*Me*), 3.24 (1H, td, *J* 10.9, 3.5, C(2)*H*), 3.75–3.82 (3H, m, C(3)*H*, N($CH_A$$H_B$Ph)$_2$), 4.91–5.02 (2H, m, C(3′)H_2), 5.64–5.74 (1H, m, C(2′)*H*), 7.07–7.35 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 35.0 (*C*(1′)), 48.1 (*C*(2)), 51.0 (O*Me*), 53.8 (N(*C*H_2Ph)$_2$), 63.4 (*C*(3)), 116.6 (*C*(3′)), 127.0, 127.8, 128.0, 128.4, 128.8, 129.4 (*o*,*m*,*p*-*Ph*), 134.7 (*i*-*Ph*), 135.6 (*C*(2′)), 139.4 (*i*-*Ph*), 174.0 (*C*(1)). Data for mixture: ν_{max} (ATR) 2948, 2839 (C–H), 1738 (C=O), 1603 (C=C); *m*/*z* (ESI^+) 422 ($[M + Na]^+$, 40%), 400 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{30}NO_2^+$ ($[M + H]^+$) requires 400.2271; found 400.2253.

Method B. LiHMDS (1.0 M in THF, 3.56 mL, 3.56 mmol) was added dropwise to a solution of methyl (*RS*)-3-(*N*,*N*-dibenzylamino)-3-phenylpropanoate[33] (508 mg, 1.19 mmol) in THF (5 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 2 h. Allyl bromide (465 μL, 5.35 mmol) was then added dropwise, and the resultant solution was allowed to warm to rt over 16 h. Satd aq. NH_4Cl (0.5 mL) was then added and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with brine (20 mL), then dried and concentrated *in vacuo* to give **16** in 54 : 46 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 93 : 7) gave **16** as a colourless oil (72 mg, 15%, 98 : 2 dr).

X-ray crystal structure determination for 16

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation, using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions.

X-ray crystal structure data for **16** [$C_{27}H_{29}NO_2$]: M = 399.53, triclinic, $P\bar{1}$, a = 10.0503(2) Å, b = 10.9520(2) Å, c = 11.2054(3) Å, α = 74.3842(8)°, β = 68.6115(8)°, γ = 80.1552(12)°, V = 1102.40(4) Å^3, Z = 2, μ = 0.075 mm^{-1}, colourless block, crystal dimensions = 0.17 × 0.22 × 0.27 mm^3. A total of 5018 unique reflections were measured for 5 < θ < 27 and 3448 reflections were used in the refinement. The final parameters were wR_2 = 0.109 and R_1 = 0.053 [$I > -3.0\sigma(I)$]. CCDC 982697.†

Methyl (*RS*,*SR*)-2-(prop-2′-en-1′-yl)-3-(*N*-isopropyl-*N*-benzylamino)-3-phenylpropanoate 17

Method A. TMSCl (1.12 mL, 8.89 mmol) was added dropwise to a solution of **11** (1.00 g, 2.96 mmol) in PhMe (10 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 8.89 mL, 8.89 mmol) was added dropwise and the resultant solution was stirred at −78 °C for 30 min. The reaction mixture was allowed to warm to rt then heated at reflux for 1 h, before being allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (100 mL) and 1.0 M aq. HCl (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL).

The combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo*. The residue was then dissolved in MeOH (10 mL), the resultant solution was cooled to 0 °C, and $SOCl_2$ (6.39 mL, 88.9 mmol) was added dropwise. The reaction mixture was then heated at 50 °C for 48 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (100 mL), the resultant solution was washed with satd aq. $NaHCO_3$ (3 × 100 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 99 : 1) gave **17** as a pale yellow oil (640 mg, 62%, 88 : 12 dr). Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 0.42 (3H, d, *J* 6.6, CH*Me*$_A$Me$_B$), 1.01 (3H, d, *J* 6.6, CHMe$_A$*Me*$_B$), 1.70–1.74 (1H, m, C(1′)H_A), 1.87–1.95 (1H, m, C(1′)H_B), 3.22–3.30 (2H, m, C(2)*H*, C*H*Me$_2$), 3.28 (1H, d, *J* 14.2, NCH$_A$$H_B$Ph), 3.60 (3H, s, O*Me*), 3.80 (1H, d, *J* 14.2, NCH_AH$_B$Ph), 3.84 (1H, d, *J* 11.6, C(3)*H*), 4.78–4.82 (2H, m, C(3′)H_2), 5.47–5.57 (1H, m, C(2′)*H*), 7.17–7.30 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.8, 22.7 (CH*Me*$_2$), 34.7 (*C*(1′)), 47.4 (*C*(2)), 49.2 (*C*HMe$_2$), 49.5 (N*C*H$_2$Ph), 51.2 (O*Me*), 64.3 (*C*(3)), 116.4 (*C*(3′)), 126.7, 127.4, 127.9, 128.3, 129.0, 129.1 (*o*,*m*,*p*-*Ph*), 135.2 (*C*(2′)), 137.8, 140.4 (*i*-*Ph*), 174.4 (*C*(1)). Data for minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) 0.46 (3H, d, *J* 6.7, CH*Me*$_A$Me$_B$), 1.06 (3H, d, *J* 6.7, CHMe$_A$*Me*$_B$), 2.00–2.06 (1H, m, C(1′)H_A), 2.86–2.92 (1H, m, C(1′)H_B), 3.08 (1H, dt, *J* 11.2, 3.4, C(2)*H*), 3.14–3.19 (1H, m, C*H*Me$_2$), 3.15 (3H, s, O*Me*), 3.34 (1H, d, *J* 14.2, NCH_AH$_B$Ph), 3.72–3.76 (2H, m, NCH$_A$$H_B$Ph, C(3)*H*), 4.87–4.96 (2H, m, C(3′)H_2), 5.58–5.68 (1H, m, C(2′)*H*), 7.15–7.34 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.4, 22.8 (CH*Me*$_2$), 35.5 (*C*(1′)), 47.7 (*C*(2)), 48.8 (C*H*Me$_2$), 49.2 (N*C*H$_2$Ph), 50.9 (O*Me*), 63.3 (*C*(3)), 116.2 (*C*(3′)), 126.8, 127.2, 127.8, 128.2, 128.9 (*o*,*m*,*p*-*Ph*), 136.0 (*C*(2′)), 138.4, 140.6 (*i*-*Ph*), 174.4 (*C*(1)). Data for mixture: ν_{max} (ATR) 2964 (C–H), 1738 (C=O), 1602 (C=C); *m*/*z* (ESI^+) 374 ($[M + Na]^+$, 50%), 352 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{30}NO_2^+$ ($[M + H]^+$) requires 352.2271; found 352.2260.

Method B – step 1. $SOCl_2$ (0.31 mL, 4.24 mmol) was added dropwise to a solution of **9** (500 mg, 9.96 mmol) in MeOH (12 mL) at 0 °C and the reaction mixture was then stirred at 50 °C for 16 h. The resultant mixture was concentrated *in vacuo*, and the residue was dissolved in CH_2Cl_2 (20 mL). The resultant solution was washed with satd aq. $NaHCO_3$ (3 × 25 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 99 : 1) gave methyl (*RS*)-3-(*N*-isopropyl-*N*-benzylamino)-3-phenylpropanoate as a colourless oil (330 mg, 75%); ν_{max} (ATR) 2964 (C–H), 1738 (C=O); δ_H (400 MHz, $CDCl_3$) 0.68 (3H, d, *J* 6.6, CH*Me*$_A$), 0.98 (3H, d, *J* 6.6, CH*Me*$_B$), 2.51 (1H, dd, *J* 14.5, 7.7, C(2)H_A), 2.86 (1H, dd, *J* 14.5, 7.7, C(2)H_B), 3.02 (1H, septet, *J* 6.6, C*H*Me$_2$), 3.43 (3H, s, O*Me*), 3.59 (2H, app d, *J* 15.2, NCH_2Ph), 4.22 (1H, app t, *J* 7.7, C(3)*H*), 7.12–7.30 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.4, 21.5 (CH*Me*$_2$), 38.7 (*C*(2)), 47.7 (*C*HMe$_2$), 49.3 (N*C*H$_2$Ph), 51.4 (O*Me*), 59.8 (*C*(3)), 126.5, 127.1, 128.0, 128.1, 128.1, 128.1 (*o*,*m*,*p*-*Ph*), 141.2, 141.7 (*i*-*Ph*), 172.2 (*C*(1)); *m*/*z* (ESI^+) 312 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{26}NO_2^+$ ($[M + H]^+$) requires 312.1958; found 312.1949.

Method B – step 2. LiHMDS (1.0 M in THF, 2.27 mL, 2.27 mmol) was added dropwise to a solution of methyl (*RS*)-3-(*N*-isopropyl-*N*-benzylamino)-3-phenylpropanoate (236 mg, 0.76 mmol) in THF (2.5 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 2 h. Allyl bromide (198 μL, 2.27 mmol) was then added dropwise, and the resultant solution was allowed to warm to rt over 16 h. Satd aq. NH_4Cl (0.5 mL) was then added and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with brine (20 mL), then dried and concentrated *in vacuo* to give **17** in 81 : 19 dr. Purification *via* flash column chromatography (eluent, 30–40 °C petrol–Et_2O, 98 : 2) gave **17** as a colourless oil (30 mg, 11%, >99 : 1 dr).

Methyl (*RS*,*SR*)-2-propyl-3-(*N*-isopropylamino)-3-phenylpropanoate 18

Method A. $Pd(OH)_2$/C (50 mg, 50% w/w) was added to a degassed solution of **16** (100 mg, 0.25 mmol, 83 : 17 dr) in MeOH–acetone (9 : 1, 2.5 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 16 h. The reaction mixture was then filtered through Celite® (eluent EtOAc) and the filtrate was washed with satd aq. $NaHCO_3$ (10 mL), then dried and concentrated *in vacuo* to give **18** in 83 : 17 dr. Purification *via* flash column chromatography (eluent, 30–40 °C petrol–Et_2O, 93 : 7) gave **18** as a colourless oil (56 mg, 85%, 83 : 17 dr). Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 0.67 (3H, t, *J* 7.2, C(3′)H_3), 0.81 (3H, d, *J* 6.2, CH*Me*$_A$Me$_B$), 0.86 (3H, d, *J* 6.2, CHMe$_A$*Me*$_B$), 0.91–1.18 (3H, m, C(1′)H_A, C(2′)H_2), 1.32–1.42 (1H, m, C(1′)H_B), 1.51 (1H, br s, N*H*), 2.40 (1H, dt, *J* 12.4, 6.2, C*H*Me$_2$), 2.51 (1H, dt, *J* 10.1, 3.5, C(2)*H*), 3.64 (3H, s, O*Me*), 3.70 (1H, d, *J* 10.1, C(3)*H*), 7.13–7.19 (3H, m, *Ph*), 7.24–7.27 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.7 (*C*(3′)), 20.6 (*C*(1′)), 21.6, 24.2 (CH*Me*$_2$), 32.1 (*C*(2′)), 45.2 (*C*HMe$_2$), 51.3 (O*Me*), 53.6 (*C*(2)), 62.4 (*C*(3)), 127.2, 127.3, 128.4 (*o*,*m*,*p*-*Ph*), 142.3 (*i*-*Ph*), 175.7 (*C*(1)). Data for minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.57–1.65 (2H, m, C(1′)H_2), 3.34 (3H, s, O*Me*), 3.79 (1H, d, *J* 7.8, C(3)*H*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 13.9 (*C*(3′)), 20.9 (*C*(1′)), 21.7 (CH*Me*$_A$Me$_B$), 30.8 (*C*(2′)), 45.5 (*C*HMe$_2$), 51.0 (O*Me*), 53.4 (*C*(2)), 61.8 (*C*(3)), 127.0, 128.0 (*o*,*m*,*p*-*Ph*), 142.2 (*i*-*Ph*), 174.8 (*C*(1)). Data for mixture: ν_{max} (ATR) 3326 (N–H), 2960, 2872 (C–H), 1735 (C=O), 1602 (C=C); *m*/*z* (ESI^+) 286 ($[M + Na]^+$, 5%), 264 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{16}H_{26}NO_2^+$ ($[M + H]^+$) requires 264.1958; found 264.1956.

Method B. $Pd(OH)_2$/C (120 mg, 50% w/w) was added to a degassed solution of **17** (240 mg, 0.68 mmol, 88 : 12 dr) in MeOH–acetone (9 : 1, 6 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 17 h. The reaction mixture was then filtered through Celite® (eluent EtOAc) and the filtrate was washed with satd aq. $NaHCO_3$ (10 mL), then dried and concentrated *in vacuo* to give **18** in 88 : 12 dr. Purification *via* flash column chromatography (eluent, 30–40 °C petrol–Et_2O, 93 : 7) gave **18** as a colourless oil (101 mg, 66%, 88 : 12 dr).

Method C. $Pd(OH)_2$/C (87 mg, 50% w/w by substrate) was added to a degassed solution of **20** (173 mg, 0.42 mmol,

>99 : 1 dr) in MeOH–acetone (4 mL, 9 : 1) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 16 h. The reaction mixture was then filtered through Celite® (eluent EtOAc) and the filtrate was washed with satd aq. $NaHCO_3$ (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent, 30–40 °C petrol–Et_2O, 93 : 7) gave **18** as a colourless oil which solidified upon standing (75 mg, 68%, >99 : 1 dr); mp 47–50 °C; $[\alpha]_D^{20}$ +23.4 (*c* 1.0 in $CHCl_3$).

X-ray crystal structure determination for 18

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation, using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions.

X-ray crystal structure data for **18** [$C_{16}H_{25}NO_2$]: M = 263.38, orthorhombic, $P2_12_12_1$, a = 8.66504(13) Å, b = 9.9818(2) Å, c = 18.4067(4) Å, V = 1592.04(5) Å^3, Z = 4, μ = 0.562 mm^{-1}, colourless plate, crystal dimensions = 0.05 × 0.19 × 0.21 mm^3. A total of 1913 unique reflections were measured for $5 < \theta < 76$ and 7067 reflections were used in the refinement. The final parameters were wR_2 = 0.083 and R_1 = 0.034 [$I > -3.0\sigma(I)$]. CCDC 982698.†

Methyl (2*S*,3*R*,α*S*)-2-(prop-2′-en-1′-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 20

Method A. LiHMDS (1.0 M in THF, 4.0 mL, 4.0 mmol) was added dropwise to a solution of **21**[12a] (500 mg, 1.34 mmol, >99 : 1 dr) in THF (5 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 2 h. Allyl bromide (525 μL, 6.03 mmol) was then added dropwise, and the resultant solution was allowed to warm to rt over 16 h. Satd aq. NH_4Cl (0.5 mL) was added and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with brine (20 mL), then dried and concentrated *in vacuo* to give **20** in 83 : 17 dr. Purification *via* flash column chromatography (eluent, 30–40 °C petrol–Et_2O, 98 : 2) gave **20** as a colourless oil which solidified upon standing (370 mg, 67%, >99 : 1 dr); mp 79–81 °C; $[\alpha]_D^{20}$ +27.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977 (C–H), 1737 (C═O), 1642 (C═C); δ_H (400 MHz, $CDCl_3$) 0.83 (3H, d, *J* 7.0, C(α)*Me*), 1.60–1.64 (1H, m, C(1′)H_A), 1.80–1.88 (1H, m, C(1′)H_B), 3.21 (1H, dt, *J* 11.3, 3.4, C(2)*H*), 3.45 (3H, s, O*Me*), 3.56 (1H, d, *J* 13.7, NCH_AH$_B$Ph), 3.92 (1H, d, *J* 11.3, C(3)*H*), 4.07–4.14 (1H, m, C(α)*H*), 4.12 (1H, d, *J* 13.7, NCH$_A$$H_B$Ph), 4.73–4.78 (2H, m, C(3′)H_2), 5.39–5.49 (1H, m, C(2′)*H*), 7.13–7.32 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.9 (C(α)*Me*), 34.8 (*C*(1′)), 49.3 (*C*(2)), 50.7 (N*C*H$_2$Ph), 51.2 (O*Me*), 55.3 (*C*(α)), 63.4 (*C*(3)), 116.4 (*C*(3′)), 126.4, 126.8, 127.5, 127.7, 128.0, 128.2, 128.4, 129.0, 129.1 (*o*,*m*,*p*-*Ph*), 135.0 (*C*(2′)), 138.8, 139.8, 144.0 (*i*-*Ph*), 174.0 (*C*(1)); *m*/*z* (ESI$^+$) 436 ([M + Na]$^+$, 100%), 414 ([M + H]$^+$, 80%); HRMS (ESI$^+$) $C_{28}H_{31}NNaO_2^+$ ([M + Na]$^+$) requires 436.2247; found 436.2234. Data for minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* 6.8, C(α)*Me*), 1.80–1.91 (2H, m, C(1′)H_2), 3.09 (1H, td, *J* 11.2, 3.2, C(2)*H*), 3.14 (3H, s, O*Me*), 3.54 (1H, d, *J* 13.8, NCH_AH$_B$Ph), 3.83 (1H, d, *J* 11.4, C(3)*H*), 3.87 (1H, d, *J* 13.8, NCH$_A$$H_B$Ph), 4.06–4.11 (1H, m, C(α)*H*), 4.86–4.91 (2H, m, C(3′)H_2), 5.56 (1H, ddt, *J* 17.1, 10.0, 7.1, C(2′)*H*), 7.14–7.32 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 35.3 (*C*(1′)), 49.3 (*C*(2)), 50.6 (N*C*H$_2$Ph), 50.9 (O*Me*), 55.9 (*C*(α)), 62.5 (*C*(3)), 116.3 (*C*(3′)), 126.7, 127.0, 127.3, 127.8, 128.0, 128.2, 128.3, 128.9, 129.1 (*o*,*m*,*p*-*Ph*), 135.9 (*C*(2′)), 138.8, 140.0, 144.5 (*i*-*Ph*), 174.3 (*C*(1)).

Method B – step 1. TMSCl (1.3 mL, 10.4 mmol) was added dropwise to a solution of **13** (1.39 g, 3.48 mmol, >99 : 1 dr) in PhMe (14 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 10.4 mL, 10.4 mmol) was then added dropwise and the resultant solution was stirred at −78 °C for 30 min. The reaction mixture was stirred at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (100 mL) and 1.0 M aq. HCl (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo* to give **19** as an orange oil (1.39 g, 92 : 8 dr). Purification of an aliquot *via* flash column chromatography (eluent, 30–40 °C petrol–acetone, 93 : 7) gave **19** as a white solid; $[\alpha]_D^{20}$ +73.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3100–2600 (O–H), 2934, 2849 (C–H), 1708 (C═O), 1603 (C═C); δ_H (400 MHz, $CDCl_3$) 1.05 (3H, d, *J* 7.1, C(α)*Me*), 1.62–1.69 (1H, m, C(1′)H_A), 2.31–2.35 (1H, m, C(1′)H_B), 3.04 (1H, ddd, *J* 11.3, 6.8, 3.8, C(2)*H*), 3.60 (1H, d, *J* 13.5, NCH_AH$_B$Ph), 4.07 (1H, app q, *J* 6.8, C(3)*H*), 4.16–4.20 (1H, m, C(α)*H*), 4.18 (1H, d, *J* 13.5, NCH$_A$$H_B$Ph), 4.57–4.76 (2H, m, C(3′)H_2), 5.38–5.48 (1H, m, C(2′)*H*), 7.16–7.41 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.9 (C(α)*Me*), 32.9 (*C*(1′)), 44.5 (*C*(2)), 51.0 (N*C*H$_2$Ph), 57.6 (*C*(3)), 61.6 (*C*(α)), 117.4 (*C*(3′)), 127.7, 127.8, 128.4, 128.4, 128.6, 128.7, 129.4, 129.7 (*o*,*m*,*p*-*Ph*), 134.1 (*C*(2′)), 135.8, 136.3, 140.2 (*i*-*Ph*), 175.9 (*C*(1)); *m*/*z* (ESI$^+$) 422 ([M + Na]$^+$, 100%), 400 ([M + H]$^+$, 30%); *m*/*z* (ESI$^-$) 398 ([M − H]$^-$, 40%); HRMS (ESI$^+$) $C_{27}H_{30}NO_2^+$ ([M + H]$^+$) requires 400.2271; found 400.2268.

Method B – step 2. The residue of **19** (92 : 8 dr) was dissolved in MeOH (15 mL) and the resultant solution was cooled to 0 °C. $SOCl_2$ (7.5 mL, 104 mmol) was then added dropwise and the reaction mixture was allowed to warm to rt, then heated at 50 °C for 48 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (100 mL) and the resultant solution was washed with satd aq. $NaHCO_3$ (3 × 100 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent, 30–40 °C petrol–Et_2O, 98 : 2) gave **20** as a colourless oil which solidified upon standing (718 mg, 50%, >99 : 1 dr); $[\alpha]_D^{20}$ +26.1 (*c* 1.0 in $CHCl_3$). Further elution gave second (44 mg, 3%, 62 : 38 dr) and third (30 mg, 5%, 58 : 42 dr) fractions of **20** as colourless oils.

X-ray crystal structure determination for 19

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation, using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were

refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions.

X-ray crystal structure data for **19** [$C_{27}H_{29}NO_2$]: M = 399.53, trigonal, $P3_12$, a = b = 11.2376(1) Å, c = 31.9939(3) Å, V = 3498.98(6) Å^3, Z = 6, μ = 0.553 mm^{-1}, colourless block, crystal dimensions = 0.23 × 0.24 × 0.27 mm^3. A total of 4879 unique reflections were measured for 5 < θ < 77 and 4158 reflections were used in the refinement. The final parameters were wR_2 = 0.085 and R_1 = 0.034 [$I > -3.0\sigma(I)$]], with Flack enantiopole = −0.02(18).[17] CCDC 982699.†

X-ray crystal structure determination for 20

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation, using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions.

X-ray crystal structure data for **20** [$C_{28}H_{31}NO_2$]: M = 413.56, monoclinic, $P2_1$, a = 9.7215(3) Å, b = 13.5384(2) Å, c = 10.1187(3) Å, β = 116.959(3)°, V = 1187.05(6) Å^3, Z = 2, μ = 0.559 mm^{-1}, colourless block, crystal dimensions = 0.25 × 0.31 × 0.40 mm^3. A total of 2574 unique reflections were measured for 5 < θ < 77 and 9573 reflections were used in the refinement. The final parameters were wR_2 = 0.101 and R_1 = 0.038 [$I > -3.0\sigma(I)$], with Flack enantiopole = −0.02(15).[17] CCDC 982700.†

Methyl (2*S*,3*R*,α*S*)-2-(prop-2′-en-1′-yl)-3-[*N*-(α-methyl-benzyl)-amino]-3-phenylpropanoate 22

CAN (696 mg, 1.27 mmol) was added to a stirred solution of **20** (250 mg, 0.60 mmol, >99 : 1 dr) in MeCN–H_2O (5 : 1, 7 mL) at rt and the resultant mixture was stirred at rt for 16 h. Satd aq. $NaHCO_3$ (15 mL) and Et_2O (20 mL) were then added and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with brine (50 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent, 30–40 °C petrol–Et_2O, 95 : 5) gave **22** as a colourless oil (179 mg, 91%, >99 : 1 dr); $[\alpha]_D^{20}$ −5.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3320 (N–H), 2970, 2949 (C–H), 1735 (C=O), 1642, 1603 (C=C); δ_H (400 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.3, C(α)*Me*), 1.74 (1H, br s, N*H*), 1.83–1.88 (1H, m, C(1′)H_A), 2.10–2.17 (1H, m, C(1′)H_B), 2.62 (1H, app td, *J* 9.9, 6.9, C(2)*H*), 3.43 (1H, q, *J* 6.3, C(α)*H*), 3.63 (3H, s, O*Me*), 3.83 (1H, d, *J* 9.9, C(3)*H*), 4.83–4.88 (2H, m, C(3′)H_2), 5.49–5.59 (1H, m, C(2′)*H*), 7.08–7.25 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 21.8 (C(α)*Me*), 34.2 (*C*(1′)), 51.3 (O*Me*), 53.3 (*C*(2)), 54.4 (*C*(α)), 61.9 (*C*(3)), 116.6 (*C*(3′)), 126.5, 126.8, 127.3, 127.4, 128.2, 128.5 (*o*,*m*,*p*-*Ph*), 135.0 (*C*(2′)), 141.3, 146.2 (*i*-*Ph*), 174.7 (*C*(1)); *m*/*z* (ESI$^+$) 346 ([M + Na]$^+$, 100%), 324 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{26}NO_2^+$ ([M + H]$^+$) requires 324.1958; found 324.1949.

(3*S*,4*R*,α*S*)-*N*(1)-(α-Methylbenzyl)-3-(prop-2′-en-1′-yl)-4-phenylazetidin-2-one 23

MeMgBr (90 μL, 2.0 M in Et_2O, 0.18 mmol) was added dropwise to a solution of **22** (50.0 mg, 0.15 mmol, >99 : 1 dr) in Et_2O (2 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 30 min. Satd aq. NH_4Cl (2 mL) was then added and the aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent, 30–40 °C petrol–Et_2O, 80 : 20) gave **23** as a colourless oil (30 mg, 83%, >99 : 1 dr); $[\alpha]_D^{20}$ +34.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2979, 2934 (C–H), 1746 (C=O), 1603 (C=C); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, d, *J* 7.3, C(α)*Me*), 2.20–2.29 (1H, m, C(1′)H_A), 2.38–2.45 (1H, m, C(1′)H_B), 3.00 (1H, ddd, *J* 8.8, 5.1, 2.0, C(3)*H*), 3.87 (1H, d, *J* 2.0, C(4)*H*), 4.85–4.90 (2H, m, C(3′)H_2), 4.97 (1H, q, *J* 7.3, C(α)*H*), 5.57–5.67 (1H, m, C(2′)*H*), 7.14–7.27 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.6 (C(α)*Me*), 32.3 (*C*(1′)), 51.9 (*C*(α)), 58.4 (*C*(3)), 59.8 (*C*(4)), 117.1 (*C*(3′)), 127.3, 127.7, 128.3, 128.5, 128.6, 128.8 (*o*,*m*,*p*-*Ph*), 134.1 (*C*(2′)), 139.5, 140.0 (*i*-*Ph*), 170.0 (*C*(2)); *m*/*z* (ESI$^+$) 314 ([M + Na]$^+$, 100%), 292 ([M + H]$^+$, 40%); HRMS (ESI$^+$) $C_{20}H_{21}NNaO^+$ ([M + Na]$^+$) requires 314.1515; found 314.1509.

2′-Methylbut-3′-en-2′-yl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methyl-benzyl)amino]-3-phenylpropanoate 25

BuLi (2.0 M in hexanes, 14.3 mL, 28.7 mmol) was added dropwise to a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (6.25 g, 29.6 mmol) in THF (132 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **24** (4.00 g, 18.5 mmol, >99 : 1 dr) in THF (52 mL) at −78 °C was then added dropwise *via* cannula, and the resultant mixture was stirred at −78 °C for 2 h. Satd aq. NH_4Cl (20 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic extracts were washed sequentially with 10% aq. citric acid (100 mL), satd aq. $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo* to give **25** in >95 : 5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 99 : 1) gave **25** as a colourless oil which solidified upon standing (5.78 g, 73%, >99 : 1 dr); mp 60–62 °C; $[\alpha]_D^{20}$ −8.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2976, 2934 (C–H), 1728 (C=O), 1602 (C=C); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 7.0, C(α)*Me*), 1.35 (3H, s, C(2′)*Me*$_A$), 1.37 (3H, s, C(2′)*Me*$_B$), 2.61–2.64 (2H, m, C(2)H_2), 3.76 (2H, app s, NCH_2Ph), 4.07 (1H, q, *J* 7.0, C(α)*H*), 4.51 (1H, dd, *J* 8.3, 6.6, C(3)*H*), 4.98–5.04 (2H, m, C(4′)H_2), 5.87 (1H, dd, *J* 17.4, 10.9, C(3′)*H*), 7.22–7.42 (11H, m, *Ph*), 7.49–7.51 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.2 (C(α)*Me*), 26.1 (C(2′)*Me*$_2$), 38.2 (*C*(2)), 50.8 (N*C*H$_2$Ph), 57.0 (*C*(α)), 59.6 (*C*(3)), 80.5 (*C*(2′)), 112.2 (*C*(4′)), 126.5, 126.8, 127.1, 127.8, 127.9, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 141.6, 141.6 (*i*-*Ph*), 142.4 (*C*(3′)), 144.0 (*i*-*Ph*), 170.6 (*C*(1)); *m*/*z* (ESI$^+$) 428 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{34}NO_2^+$ ([M + H]$^+$) requires 428.2584; found 428.2569.

X-ray crystal structure determination for 25

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation, using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions.

X-ray crystal structure data for **25** [$C_{29}H_{33}NO_2$]: M = 427.59, monoclinic, $P2_1$, a = 10.27494(11) Å, b = 10.27815(10) Å, c = 12.21513(16) Å, β = 107.2702(13)°, V = 1231.85(3) Å^3, Z = 2, μ = 0.554 mm^{-1}, colourless block, crystal dimensions = 0.15 × 0.18 × 0.19 mm^3. A total of 2711 unique reflections were measured for $4 < \theta < 77$ and 10 142 reflections were used in the refinement. The final parameters were wR_2 = 0.076 and R_1 = 0.029 [$I > -3.0\sigma(I)$], with Flack enantiopole = −0.09(10).[17] CCDC 982701.†

Methyl (2*S*,3*R*,α*S*)-2-(3′-methylbut-2′-en-1′-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 27

Step 1. TMSCl (89 μL, 0.70 mmol) was added dropwise to a solution of **25** (100 mg, 0.23 mmol, >99 : 1 dr) in PhMe (1 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 0.70 mL, 0.70 mmol) was then added dropwise and the resultant mixture was stirred at −78 °C for 30 min. The reaction mixture was then allowed to warm to rt, then heated at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 1.0 M aq. HCl (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine (25 mL), then dried and concentrated *in vacuo* to give **26** as a pale orange solid (100 mg, 93 : 7 dr). Purification of an aliquot *via* flash column chromatography (eluent 30–40 °C petrol–acetone, 93 : 7) gave **26** as a white solid (>99 : 1 dr); mp 146–148 °C; $[\alpha]_D^{20}$ +58.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2969, 2929 (C–H), 1706 (C═O), 1602 (C═C); δ_H (400 MHz, $CDCl_3$) 1.03 (3H, d, *J* 7.0, C(α)*Me*), 1.05 (3H, s, C(3′)*Me*$_A$), 1.42 (3H, s, C(3′)*Me*$_B$), 1.68–1.75 (1H, m, C(1′)*H*$_A$), 2.16 (1H, app d, *J* 14.4, C(1′)*H*$_B$), 2.98–3.04 (1H, m, C(2)*H*), 3.60 (1H, d, *J* 13.2, NC*H*$_A$H$_B$Ph), 4.08 (1H, q, *J* 7.0, C(α)*H*), 4.15 (1H, d, *J* 11.6, C(3)*H*), 4.17 (1H, d, *J* 13.2, NCH$_A$*H*$_B$Ph), 4.69–4.72 (1H, m, C(2′)*H*), 7.16–7.27 (10H, m, *Ph*), 7.31–7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.8 (C(α)*Me*), 17.6 (C(3′)*Me*$_A$), 25.6 (C(3′)*Me*$_B$), 27.4 (*C*(1′)), 45.2 (*C*(2)), 50.9 (N*C*H$_2$Ph), 57.4 (*C*(α)), 61.7 (*C*(3)), 119.9 (*C*(2′)), 127.7, 127.7, 128.3, 128.3, 128.5, 128.6, 129.4, 129.8 (*o*,*m*,*p*-*Ph*), 133.8 (*C*(3′)), 136.2, 136.4, 140.3 (*i*-*Ph*), 176.6 (*C*(1)); *m*/*z* (ESI$^+$) 450 ([M + Na]$^+$, 10%), 428 ([M + H]$^+$, 100%); *m*/*z* (ESI$^-$) 426 ([M − H]$^-$ 100%); HRMS (ESI$^+$) $C_{29}H_{34}NO_2^+$ ([M + H]$^+$) requires 428.2584; found 428.2573.

Step 2. The residue of **26** (50 mg, 93 : 7 dr) was dissolved in MeCN (500 μL) and the resultant solution was treated sequentially with DBU (18 μL, 0.12 mmol) and MeI (9 μL, 0.14 mmol), and the resultant mixture was stirred at rt for 4 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 mL) and 2.0 M aq. HCl (5 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were then washed sequentially with satd aq. $NaHCO_3$ (15 mL) and brine (15 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 98 : 2) gave **27** as a colourless oil (34 mg, 66% from **25**, >99 : 1 dr); $[\alpha]_D^{20}$ +4.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2969, 2946 (C–H), 1737 (C═O), 1602 (C═C); δ_H (400 MHz, $CDCl_3$) 0.81 (3H, d, *J* 7.1, C(α)*Me*), 1.23 (3H, s, C(3′)*Me*$_A$), 1.46 (3H, s, C(3′)*Me*$_B$), 1.49–1.55 (1H, m, C(1′)*H*$_A$), 1.77–1.86 (1H, m, C(1′)*H*$_B$), 3.11 (1H, app td, *J* 11.3, 3.4, C(2)*H*), 3.42 (3H, s, O*Me*), 3.53 (1H, d, *J* 13.9, NC*H*$_A$H$_B$Ph), 3.91 (1H, d, *J* 11.3, C(3)*H*), 4.06–4.11 (1H, m, C(α)*H*), 4.09 (1H, d, *J* 13.9, NCH$_A$*H*$_B$Ph), 4.76–4.80 (1H, m, C(2′)*H*), 7.09–7.30 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (C(α)*Me*), 17.4 (C(3′)*Me*$_A$), 25.6 (C(3′)*Me*$_B$), 29.3 (*C*(1′)), 49.7 (*C*(2)), 50.6 (N*C*H$_2$Ph), 51.1 (O*Me*), 55.2 (*C*(α)), 63.3 (*C*(3)), 120.6 (*C*(2′)), 126.3, 126.8, 127.4, 127.7, 127.9, 128.1, 128.3, 128.9, 129.0 (*o*,*m*,*p*-*Ph*), 133.4 (*C*(3′)), 139.0, 139.8, 144.1 (*i*-*Ph*), 174.4 (*C*(1)); *m*/*z* (ESI$^+$) 464 ([M + Na]$^+$, 40%), 442 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{36}NO_2^+$ ([M + H]$^+$) requires 442.2741; found 442.2734. Further elution gave **27** as a colourless oil (6 mg, 12% from **25**, 43 : 57 dr). Data for minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) 0.85 (3H, d, *J* 6.9, C(α)*Me*), 1.41 (3H, s, C(3′)*Me*$_A$), 1.57 (3H, s, C(3′)*Me*$_B$), 1.79–1.87 (1H, m, C(1′)*H*$_A$), 2.70–2.73 (1H, m, C(1′)*H*$_B$), 3.01 (1H, app td, *J* 11.1, 3.6, C(2)*H*), 3.13 (3H, s, O*Me*), 3.54 (1H, d, *J* 13.9, NC*H*$_A$H$_B$Ph), 3.83 (1H, d, *J* 11.1, C(3)*H*), 3.89 (1H, d, *J* 13.9, NCH$_A$*H*$_B$Ph), 4.07–4.10 (1H, m, C(α)*H*), 4.86–4.89 (1H, m, C(2′)*H*), 7.12–7.33 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.6 (C(α)*Me*), 17.6 (C(3′)*Me*$_A$), 25.8 (C(3′)*Me*$_B$), 29.8 (*C*(1′)), 49.5 (*C*(2)), 50.6 (N*C*H$_2$Ph), 51.0 (O*Me*), 55.6 (*C*(α)), 62.6 (*C*(3)), 121.2 (*C*(2′)), 126.7, 127.0, 127.2, 127.9, 128.0, 128.1, 128.3, 129.0, 129.2 (*o*,*m*,*p*-*Ph*), 133.3 (*C*(3′)), 139.1, 140.1, 144.6 (*i*-*Ph*), 174.7 (*C*(1)). Data for mixture: ν_{max} (ATR) 2929, 2853 (C–H), 1736 (C═O), 1603 (C═C); *m*/*z* (ESI$^+$) 464 ([M + Na]$^+$, 60%), 442 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{36}NO_2^+$ ([M + H]$^+$) requires 442.2741; found 442.2742.

Methyl (2*S*,3*R*)-2-(3′-methylbutyl)-3-(*N*-isopropylamino)-3-phenylpropanoate 29

Method A – step 1. $Pd(OH)_2$/C (75 mg, 50% w/w) was added to a degassed solution of **27** (150 mg, 0.34 mmol, >99 : 1 dr) in MeOH (3.4 mL) at rt. The resultant mixture was stirred vigorously under H_2 (1 atm) at rt for 15 h. The reaction mixture was then filtered through Celite® (eluent EtOAc) and the filtrate was washed with satd aq. $NaHCO_3$ (10 mL), then dried and concentrated *in vacuo* to give **28** as a yellow solid (76 mg, >99 : 1 dr).

Method A – step 2. Acetone (44 μL, 0.61 mmol) and $NaBH_3CN$ (77 mg, 1.22 mmol) were added sequentially to a solution of the residue of **28** (76 mg, >99 : 1 dr) in MeOH (4 mL) at rt, and the resultant mixture was stirred at rt for 22 h. The reaction mixture was then concentrated *in vacuo*, the residue was partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 93 : 7) gave **29** as a colourless oil which solidified upon standing (49 mg, 55% from **27**, >99 : 1 dr); mp 47–49 °C; $[\alpha]_D^{20}$ +12.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3324 (N–H), 2956, 2870 (C–H), 1735 (C═O); δ_H (400 MHz, $CDCl_3$) 0.63 (3H, d, *J* 6.7, C(3′)*Me*$_A$), 0.66 (3H, d, *J* 6.7, C(3′)*Me*$_B$), 0.81 (3H, d, *J* 6.2, NHCH*Me*$_A$Me$_B$), 0.86 (3H, d, *J* 6.2, NHCHMe$_A$*Me*$_B$), 0.90–0.96 (2H, m, C(2′)*H*$_2$), 0.97–1.06 (1H, m, C(1′)*H*$_A$), 1.24–1.32 (1H, m, C(3′)*H*), 1.33–1.41 (1H, m, C(1′)*H*$_B$), 2.44–2.51 (1H, m, NHC*H*Me$_2$), 2.46 (1H, td, *J* 10.0, 3.4, C(2)*H*), 3.64 (3H, s, O*Me*), 3.71 (1H, d, *J* 10.0, C(3)*H*), 7.17–7.20 (3H, m, *Ph*), 7.24–7.27 (2H, m, *Ph*); δ_C (100 MHz,

$CDCl_3$) 21.6, 21.9, 22.7, 24.2 (C(3′)*Me*$_2$, NHCH*Me*$_2$), 27.7 (*C*(3′)), 27.8 (*C*(1′)), 36.4 (*C*(2′)), 45.2 (NH*C*HMe$_2$), 51.4 (O*Me*), 53.9 (*C*(2)), 62.3 (*C*(3)), 127.2, 127.3, 128.4 (*o*,*m*,*p*-*Ph*), 142.3 (*i*-*Ph*), 175.7 (*C*(1)); *m*/*z* (ESI$^+$) 314 ([M + Na]$^+$, 10%), 292 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{30}NO_2^+$ ([M + H]$^+$) requires 292.2271; found 292.2263.

Method B – step 1. TMSCl (443 μL, 3.51 mmol) was added dropwise to a solution of **25** (500 mg, 1.17 mmol, >99 : 1 dr) in PhMe (5 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 3.5 mL, 3.51 mmol) was then added dropwise and the resultant mixture was stirred at −78 °C for 30 min. The reaction mixture was then allowed to warm to rt, then heated at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 1.0 M aq. HCl (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine (25 mL), then dried and concentrated *in vacuo* to give **26** as a pale orange solid (63 mg, 93 : 7 dr).

Method B – step 2. $Pd(OH)_2$/C (32 mg, 50% w/w) was added to a degassed solution of the residue of **26** (63 mg, 93 : 7 dr) in MeOH–acetone (9 : 1, 1.6 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 22 h. The reaction mixture was then filtered through Celite® (eluent EtOAc) and the filtrate was washed with satd aq. $NaHCO_3$ (10 mL), then dried and concentrated *in vacuo* to give a yellow oil (39 mg).

Method B – step 3. The residue (39 mg) was dissolved in MeOH (0.4 mL), and the resultant solution was cooled to 0 °C then $SOCl_2$ (300 μL, 4.25 mmol) was added dropwise. The resultant mixture was allowed to warm to rt then heated at 50 °C for 48 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then dissolved in CH_2Cl_2 (10 mL) and the resultant solution was washed with satd aq. $NaHCO_3$ (3 × 10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent, 30–40 °C petrol–Et_2O, 92 : 8) gave **29** as a colourless oil (20 mg, 48% from **25**, >99 : 1 dr); $[\alpha]_D^{20}$ +11.1 (*c* 1.0 in $CHCl_3$).

X-ray crystal structure determination for 29

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation, using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions.

X-ray crystal structure data for **29** [$C_{18}H_{29}NO_2$]: M = 291.43, monoclinic, $P2_1$, a = 12.4852(2) Å, b = 9.9345(2) Å, c = 15.0329(3) Å, β = 100.0163(9)°, V = 1836.17(6) Å^3, Z = 4, μ = 0.067 mm^{-1}, colourless block, crystal dimensions = 0.27 × 0.33 × 0.38 mm^3. A total of 4416 unique reflections were measured for $5 < \theta < 27$ and 4002 reflections were used in the refinement. The final parameters were wR_2 = 0.109 and R_1 = 0.049 [$I > -3.0\sigma(I)$]. CCDC 982702.†

3′-Methylbut-2′-en-1′-yl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 30

Step 1. TFA (0.9 mL) was added to a stirred solution of **12**[11] (200 mg, 0.48 mmol, >99 : 1 dr) in CH_2Cl_2 (1.9 mL) at rt, and the resultant mixture was stirred at rt for 16 h. Satd aq. $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) were then added and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic extracts were then concentrated *in vacuo* to give an orange oil (109 mg, >99 : 1 dr).

Step 2. A solution of the residue (109 mg, >99 : 1 dr) in MeCN (2 mL) was treated sequentially with DBU (144 μL, 0.96 mmol) and 3,3-dimethylallyl bromide (134 μL, 1.16 mmol) at rt. The resultant mixture was stirred at rt for 17 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and 2.0 M aq. HCl (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then washed sequentially with satd aq. $NaHCO_3$ (30 mL) and brine (30 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 99 : 1) gave **30** as a colourless oil (115 mg, 56% from **12**, >99 : 1 dr); $[\alpha]_D^{20}$ −9.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2971, 2933 (C–H), 1731 (C═O); δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.7, C(α)*Me*), 1.51 (3H, s, C(3′)*Me*$_A$), 1.61 (3H, s, C(3′)*Me*$_B$), 2.48 (1H, dd, *J* 14.8, 9.6, C(2)*H*$_A$), 2.58 (1H, dd, *J* 14.8, 5.4, C(2)*H*$_B$), 3.56–3.66 (2H, m, NC*H*$_2$Ph), 3.92 (1H, q, *J* 6.7, C(α)*H*), 4.24–4.34 (2H, m, C(1′)*H*$_2$), 4.37 (1H, dd, *J* 9.6, 5.4, C(3)*H*), 5.02–5.06 (1H, m, C(2′)*H*), 7.07–7.26 (11H, m, *Ph*), 7.31–7.34 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.8 (C(α)*Me*), 17.9 (C(3′)*Me*$_A$), 25.7 (C(3′)*Me*$_B$), 37.7 (*C*(2)), 50.7 (N*C*H$_2$Ph), 56.8 (*C*(α)), 59.5 (*C*(3)), 61.1 (*C*(1′)), 118.5 (*C*(2′)), 126.5, 126.8, 127.1, 127.8, 128.0, 128.1, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 138.7 (*C*(3′)), 141.4, 141.7, 144.0 (*i*-*Ph*), 171.8 (*C*(1)); *m*/*z* (ESI$^+$) 450 ([M + Na]$^+$, 10%), 428 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{34}NO_2^+$ ([M + H]$^+$) requires 428.2584; found 428.2567.

Methyl (2*S*,3*R*,α*S*)-2-(2′-methylbut-3′-en-2′-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 32

Step 1. TMSCl (101 μL, 0.81 mmol) was added dropwise to a solution of **30** (115 mg, 0.27 mmol, >99 : 1 dr) in PhMe (1 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 0.8 mL, 0.80 mmol) was then added dropwise and the resultant mixture was stirred at −78 °C for 30 min. The reaction mixture was heated at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 1.0 M aq. HCl (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine (25 mL), then dried and concentrated *in vacuo* to give **31** as a pale orange solid (117 mg, 90 : 10 dr). Purification of an aliquot *via* flash column chromatography (eluent 30–40 °C petrol–acetone, 95 : 5) gave **31** as a white solid (>99 : 1 dr); ν_{max} (ATR) 2969 (C–H), 1737 (C═O), 1638, 1602 (C═C); δ_H (400 MHz, $CDCl_3$) 0.74 (3H, s, C(2′)*Me*$_A$), 0.75 (3H, s, C(2′)*Me*$_B$), 0.82 (3H, d, *J* 7.1, C(α)*Me*), 3.21 (1H, d, *J* 11.1, C(2)*H*), 3.64 (1H, d, *J* 13.1, NC*H*$_A$H$_B$Ph), 3.95–4.01 (1H, m, C(α)*H*), 4.14 (1H, d, *J* 11.1, C(3)*H*), 4.38 (1H, d, *J* 13.1, NCH$_A$*H*$_B$Ph),

4.42–4.46 (2H, m, C(4′)H_2), 5.47 (1H, dd, *J* 17.2, 11.1, C(3′)*H*), 7.12–7.41 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.1 (C(α)*Me*), 24.9, 26.3 (C(2′)Me_2), 38.3 (*C*(2′)), 51.3 (N*C*H_2Ph), 56.4 (*C*(α)), 58.5 (*C*(2)), 59.9 (*C*(3)), 110.7 (*C*(4′)), 127.0, 127.1, 127.7, 127.7, 128.3, 129.1, 129.3 (*o*,*m*,*p-Ph*), 138.7, 139.1, 141.5 (*i-Ph*), 145.5 (*C*(3′)), 178.3 (*C*(1)); *m*/*z* (ESI^+) 450 ($[M + Na]^+$, 5%), 428 ($[M + H]^+$, 100%); *m*/*z* (ESI^-) 426 ($[M - H]^-$, 100%); HRMS (ESI^+) $C_{29}H_{34}NO_2^+$ ($[M + H]^+$) requires 428.2584; found 428.2570.

Step 2. A solution of the residue of **31** (117 mg, 90 : 10 dr) in MeCN (1.2 mL) was treated sequentially with DBU (40 μl, 0.27 mmol) and MeI (40 μL, 0.64 mmol) at rt. The reaction mixture was stirred at rt for 8 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 mL) and 2.0 M aq. HCl (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were then washed sequentially with satd aq. $NaHCO_3$ (15 mL) and brine (15 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 98 : 2) gave **32** as a colourless oil (60 mg, 50% from **30**, >99 : 1 dr); $[\alpha]_D^{20}$ +21.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2969 (C–H), 1737 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 0.58 (3H, s, C(2′)Me_A), 0.65 (3H, s, C(2′)Me_B), 0.78 (3H, d, *J* 7.1, C(α)*Me*), 3.21 (1H, d, *J* 11.4, C(2)*H*), 3.27 (3H, br s, O*Me*), 3.53 (1H, d, *J* 13.6, NCH_AH_BPh), 4.10 (1H, d, *J* 11.4, C(3)*H*), 4.11–4.16 (2H, m, NCH_AH_BPh, C(α)*H*), 4.34–4.41 (2H, m, C(4′)H_2), 5.48 (1H, dd, *J* 17.3, 10.7, C(3′)*H*), 7.10–7.40 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.5 (C(α)*Me*), 25.7 (C(2′)Me_2), 38.5 (*C*(2′)), 50.6 (O*Me*), 51.0 (N*C*H_2Ph), 53.4 (*C*(α)), 55.5 (*C*(2)), 60.1 (*C*(3)), 110.3 (*C*(4′)), 126.2, 126.7, 127.4, 127.6, 127.8, 128.2, 128.9 (*o*,*m*,*p-Ph*), 139.1, 139.6 (*i-Ph*), 145.7 (*C*(3′)), 173.0 (*C*(1)); *m*/*z* (ESI^+) 464 ($[M + Na]^+$, 20%), 442 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{30}H_{36}NO_2^+$ ($[M + H]^+$) requires 442.2741; found 442.2724.

(*E*)-But-2′-en-1′-yl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-phenylpropanoate 33

Step 1. TFA (4.6 mL) was added to a solution of **12**[11] (1.00 g, 2.41 mmol, >99 : 1 dr) in CH_2Cl_2 (9.3 mL) at rt, and the resultant mixture was stirred at rt for 16 h. Satd aq. $NaHCO_3$ (100 mL) and CH_2Cl_2 (100 mL) were then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give a yellow oil (1.05 g, >99 : 1 dr).

Step 2. A solution of the residue (1.05 g, >99 : 1 dr) in CH_2Cl_2 (10 mL) was treated sequentially with $(COCl)_2$ (0.22 mL, 2.53 mmol) and DMF (8 μL, 0.10 μmol) at 0 °C. The reaction mixture was allowed to warm to rt over 1 h then concentrated *in vacuo*. A solution of (*E*)-but-2-en-1-ol (240 mg, 3.37 mmol, 96 : 4 dr) was then added to a solution of the residue in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq. $NaHCO_3$ (100 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 0% → 6% Et_2O in 30–40 °C petrol) gave **33** as a colourless oil (613 mg, 62%, 93 : 7 dr); $[\alpha]_D^{20}$ −16.1 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3028 (C–H), 1732 (C=O), 1493 (C=C); δ_H (400 MHz, $CDCl_3$) 1.14 (3H, d, *J* 6.8, C(α)*Me*), 1.56 (3H, d, *J* 6.8, C(4′)H_3), 2.48 (1H, dd, *J* 14.6, 9.4, C(2)H_A), 2.59 (1H, dd, *J* 14.6, 5.4, C(2)H_B), 3.57 (1H, d, *J* 14.6, NCH_AH_BPh), 3.65 (1H, d, *J* 14.6, NCH_AH_BPh), 3.92 (1H, q, *J* 6.8, C(α)*H*), 4.19–4.24 (2H, m, C(1′)H_2), 4.36 (1H, dd, *J* 9.4, 5.4, C(3)*H*), 5.23–5.30 (1H, m, C(2′)*H*), 5.47–5.55 (1H, m, C(3′)*H*), 7.06–7.26 (11H, m, *Ph*), 7.31–7.34 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.7 (C(α)*Me*), 17.7 (*C*(4′)), 37.7 (*C*(2)), 50.7 (N*C*H_2Ph), 56.7 (*C*(α)), 59.4 (*C*(3)), 64.9 (*C*(1′)), 124.9 (*C*(2′)), 126.5, 126.8, 127.2, 127.8, 128.0, 128.1, 128.1, 128.1, 128.2 (*o*,*m*,*p-Ph*), 130.9 (*C*(3′)), 141.4, 141.7, 144.0 (*i-Ph*), 171.5 (*C*(1)); *m*/*z* (ESI^+) 414 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{28}H_{32}NO_2^+$ ($[M + H]^+$) requires 414.2428; found 414.2418.

(*E*)-3′-Phenylprop-2′-en-1′-yl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 34

Step 1. TFA (8 mL) was added to a solution of **12**[11] (1.70 g, 4.09 mmol, >99 : 1 dr) in CH_2Cl_2 (16 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a yellow oil (1.75 g, >99 : 1 dr).

Step 2. A solution of the residue (1.75 g, >99 : 1 dr) in CH_2Cl_2 (18 mL) was treated sequentially with $(COCl)_2$ (0.37 μL, 4.29 mmol) and DMF (14 μL, 0.18 μmol) at 0 °C. The reaction mixture was allowed to warm to rt over 1 h then concentrated *in vacuo*. A solution of (*E*)-3-phenylprop-2-en-1-ol (770 mg, 5.73 mmol, >99 : 1 dr) was then added to a solution of the residue in CH_2Cl_2 (18 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq. $NaHCO_3$ (100 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 0% → 6% Et_2O in 30–40 °C petrol) gave **34** as a colourless oil (1.47 g, 76%, >99 : 1 dr); $[\alpha]_D^{20}$ −14.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2935 (C–H), 1732 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.9, C(α)*Me*), 2.72 (1H, dd, *J* 14.6, 9.6, C(2)H_A), 2.82 (1H, dd, *J* 14.6, 5.8, C(2)H_B), 3.77 (1H, d, *J* 14.6, NCH_AH_BPh), 3.85 (1H, d, *J* 14.6, NCH_AH_BPh), 4.12 (1H, q, *J* 6.9, C(α)*H*), 4.57–4.67 (3H, m, C(3)*H*, C(1′)H_2), 6.09–6.16 (1H, dt, *J* 15.8, 6.4, C(2′)*H*), 6.56 (1H, d, *J* 15.8, C(3′)*H*), 7.25–7.44 (16H, m, *Ph*), 7.52–7.54 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.8 (C(α)*Me*), 37.7 (*C*(2)), 50.7 (N*C*H_2Ph), 56.7 (*C*(α)), 59.4 (*C*(3)), 64.8 (*C*(1′)), 123.1 (*C*(2′)), 126.5, 126.6, 126.8, 127.2, 127.8, 127.9, 128.0, 128.0, 128.1, 128.1, 128.2, 128.5, (*o*,*m*,*p-Ph*), 133.8 (*C*(3′)), 136.2, 141.3, 141.6, 144.0 (*i-Ph*), 171.5 (*C*(1)); *m*/*z* (ESI^+) 476 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{33}H_{33}NNaO_2^+$ ($[M + Na]^+$) requires 498.2404; found 498.2388.

Methyl (2*S*,3*R*,1′*S*,α*S*)-2-(1′-phenylprop-2′-en-1′-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 39

Method A (from 42) – step 1. TMSCl (780 μL, 6.18 mmol) was added dropwise to a solution of **42** (980 mg, 2.06 mmol,

>99 : 1 dr) in PhMe (9.8 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 6.31 mL, 6.31 mmol) was added dropwise at −78 °C and the resultant mixture was stirred at −78 °C for 15 min. The reaction mixture was then heated at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (200 mL) and 1.0 M aq. HCl (150 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo* to give **37** as an off-white solid (962 mg, 90 : 10 dr).

Method A – step 2 (for 37). A solution of the residue of **37** (962 mg, 90 : 10 dr) in MeCN (9.8 mL) was treated sequentially with DBU (0.62 mL, 4.12 mmol) and MeI (0.28 mL, 4.53 mmol) at rt. The resultant mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 2.0 M aq. HCl (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then washed sequentially with satd aq. $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 98 : 2) gave **39** as a colourless oil (487 mg, 48% from **42**, >99 : 1 dr); $[\alpha]_D^{20}$ +28.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2946 (C–H), 1736 (C═O), 1494 (C═C); δ_H (400 MHz, $CDCl_3$) 0.83 (3H, d, *J* 6.9, C(α)*Me*), 2.96 (1H, dd, *J* 9.6, 4.4, C(1′)*H*), 3.20 (3H, s, O*Me*), 3.49 (1H, d, *J* 14.0, NC$H_A$$H_B$Ph), 3.53 (1H, dd, *J* 11.7, 4.4, C(2)*H*), 4.01 (1H, d, *J* 14.0, NCH$_A$$H_B$Ph), 4.15 (1H, d, *J* 11.7, C(3)*H*), 4.16 (1H, q, *J* 6.9, C(α)*H*), 4.36 (1H, dd, *J* 16.9, 1.7, C(3′)H_A), 4.80 (1H, dd, *J* 10.0, 1.7, C(3′)H_B), 6.22 (1H, app dt, *J* 16.9, 10.0, C(2′)*H*), 6.87–6.89 (2H, m, *Ph*), 6.99–7.33 (18H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.1 (C(α)*Me*), 49.3 (*C*(1′)), 50.8 (O*Me*), 50.9 (N*C*H$_2$Ph), 54.5 (*C*(2)), 55.5 (*C*(α)), 61.7 (*C*(3)), 117.7 (*C*(3′)), 126.3, 126.4, 126.8, 127.3, 127.6, 127.7, 127.9, 128.1, 128.3, 128.3, 129.0, 129.6 (*o*,*m*,*p*-*Ph*), 135.5 (*C*(2′)), 137.4, 139.6, 142.7, 144.3 (*i*-*Ph*), 172.6 (*C*(1)); *m*/*z* (ESI$^+$) 490 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{35}NNaO_2^+$ ([M + Na]$^+$) requires 512.2560; found 512.2541.

Method B (from 34) – step 1. TMSCl (956 μL, 7.57 mmol) was added dropwise to a solution of **34** (1.20 g, 2.52 mmol, >99 : 1 dr) in PhMe (12 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 7.57 mL, 7.57 mmol) was added dropwise at −78 °C and the resultant mixture was stirred at −78 °C for 15 min. The reaction mixture was heated at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (200 mL) and 1.0 M aq. HCl (150 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo* to give a 70 : 30 mixture of **37** and **38**. Purification *via* flash column chromatography (gradient elution, 0% → 8% acetone in 30–40 °C petrol) gave **37** as a white solid (632 mg, >99 : 1 dr); mp 77–79 °C; $[\alpha]_D^{20}$ +57.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3028, 2971 (C–H), 1704 (C═O), 1494 (C═C); δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, *J* 7.0, C(α)*Me*), 3.03 (1H, dd, *J* 9.9, 3.4, C(1′)*H*), 3.51 (1H, dd, *J* 11.7, 3.4, C(2)*H*), 3.58 (1H, d, *J* 13.5, NC$H_A$$H_B$Ph), 4.07 (1H, q, *J* 7.0, C(α)*H*), 4.19 (1H, d, *J* 13.5, NCH$_A$$H_B$Ph), 4.23 (1H, d, *J* 11.7, C(3)*H*), 4.52 (1H, dd, *J* 17.1, 1.8, C(3′)H_A), 4.87 (1H, dd, *J* 9.9, 1.8, C(3′)H_B), 6.09 (1H, app dt, *J* 17.1, 9.9, C(2′)*H*), 6.98–7.01 (3H, m, *Ph*), 7.06–7.14 (5H, m, *Ph*), 7.16–7.21 (3H, m, *Ph*), 7.36–7.39 (9H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.5 (C(α)*Me*), 48.6 (*C*(1′)), 51.0 (N*C*H$_2$Ph), 52.3 (*C*(2)), 56.9 (*C*(α)), 61.5 (*C*(3)), 118.0 (*C*(3′)), 126.3, 127.3, 127.3, 127.4, 128.0, 128.1, 128.3, 128.5, 128.5, 128.6, 129.2, 129.9 (*o*,*m*,*p*-*Ph*), 135.9 (*C*(2′)), 136.8, 137.5, 141.2, 142.6 (*i*-*Ph*), 176.1 (*C*(1)); *m*/*z* (ESI$^+$) 476 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{34}NO_2^+$ ([M + H]$^+$) requires 476.2584; found 476.2571. Further elution (eluent 30–40 °C petrol–acetone, 92 : 8) gave **38** as a yellow oil (175 mg, >99 : 1 dr); $[\alpha]_D^{20}$ +39.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3029, 2928 (C–H), 1707 (C═O), 1494 (C═C); δ_H (400 MHz, $CDCl_3$) 0.96 (3H, d, *J* 7.0, C(α)*Me*), 3.05 (1H, dd, *J* 7.7, 3.6, C(1′)*H*), 3.33 (1H, dd, *J* 11.4, 3.6, C(2)*H*), 3.55 (1H, d, *J* 13.2, NC$H_A$$H_B$Ph), 4.03 (1H, q, *J* 7.0, C(α)*H*), 4.12 (1H, d, *J* 13.2, NCH$_A$$H_B$Ph), 4.16 (1H, app d, *J* 11.4, C(3)*H*), 4.55 (1H, app d, *J* 17.1, C(3′)H_A), 4.77 (1H, d, *J* 10.0, C(3′)H_B), 6.30–6.38 (1H, m, C(2′)*H*), 6.75–6.78 (2H, m, *Ph*), 6.94–7.02 (3H, m, *Ph*), 7.09–7.28 (12H, m, *Ph*), 7.35–7.41 (3H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.7 (C(α)*Me*), 49.5 (*C*(1′)), 50.5 (*C*(2)), 51.1 (N*C*H$_2$Ph), 57.9 (*C*(α)), 60.9 (*C*(3)), 113.9 (*C*(3′)), 126.4, 128.0, 128.0, 128.1, 128.4, 128.6, 128.6, 128.8, 128.8, 128.8, 129.5, 130.1 (*o*,*m*,*p*-*Ph*), 135.0, 135.2, 138.9, 139.5 (*i*-*Ph*), 141.2 (*C*(2′)), 174.0 (*C*(1)); *m*/*z* (ESI$^+$) 476 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{34}NO_2^+$ ([M + H]$^+$) requires 476.2584; found 476.2579.

Method B – step 2 (for 37). A solution of **37** (472 mg) in MeCN (4.7 mL) was treated sequentially with DBU (296 μL, 1.98 mmol) and MeI (135 μL, 2.18 mmol) at rt. The reaction mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 2.0 M aq. HCl (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then washed sequentially with satd aq. $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 98 : 2) gave **39** as a colourless oil (350 mg, 38% from **34**, >99 : 1 dr).

Method B – step 2 (for 38). A solution of **38** (150 mg) in MeCN (1.5 mL) was treated sequentially with DBU (94 μL, 0.63 mmol) and MeI (43 μL, 0.69 mmol) at rt. The reaction mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 2.0 M aq. HCl (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then washed sequentially with satd aq. $NaHCO_3$ (40 mL) and brine (40 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 98 : 2) gave **40** as a colourless oil (133 mg, 13% from **34**, >99 : 1 dr); $[\alpha]_D^{20}$ +33.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3028, 2946 (C–H), 1739 (C═O), 1494 (C═C); δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.9, C(α)*Me*), 3.28 (3H, s, O*Me*), 3.38 (1H, app t, *J* 8.1, C(1′)*H*), 3.67 (1H, d, *J* 13.9, NC$H_A$$H_B$Ph), 3.83 (1H, dd, *J* 11.2, 8.1, C(2)*H*), 4.18 (1H, d, *J* 13.9, NCH$_A$$H_B$Ph), 4.24 (1H, d, *J* 11.2, C(3)*H*), 4.32 (1H, q, *J* 6.9, C(α)*H*), 4.58–4.68 (2H, m, C(3′)H_2), 5.55–5.64

(1H, m, C(2′)*H*), 7.01–7.03 (2H, m, *Ph*), 7.15–7.47 (18H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.4 (C(α)*Me*), 50.8 (O*Me*), 50.9 (N*C*H_2Ph), 51.4 (*C*(1′)), 54.0 (*C*(2)), 55.9 (*C*(α)), 62.3 (*C*(3)), 114.4 (*C*(3′)), 126.2, 126.3, 126.6, 127.4, 127.7, 127.7, 127.8, 128.0, 128.1, 128.4, 128.9, 129.9 (*o*,*m*,*p*-*Ph*), 138.2, 139.0, 139.6 (*i*-*Ph*), 141.1 (*C*(2′)), 144.4 (*i*-*Ph*), 172.6 (*C*(1)); *m*/*z* (ESI^+) 490 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{34}H_{36}NO_2^+$ ($[M + H]^+$) requires 490.2741; found 490.2750.

X-ray crystal structure determination for 37

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation, using standard procedures at 150 K. The structures was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions.

X-ray crystal structure data for **37** [$C_{34.5}H_{36}NO_{2.5}$]: M = 504.67, orthorhombic, $P2_12_12_1$, a = 12.3150(1) Å, b = 15.4817(2) Å, c = 29.8308(3) Å, V = 5687.45(10) Å^3, Z = 8, μ = 0.571 mm^{-1}, colourless plate, crystal dimensions = 0.15 × 0.21 × 0.26 mm^3. A total of 11 951 unique reflections were measured for $3 < \theta < 77$ and 11 907 reflections were used in the refinement. The final parameters were wR_2 = 0.118 and R_1 = 0.045 [$I > -3.0\sigma(I)$], with Flack enantiopole = 0.02(16).[17] CCDC 982703.†

(*Z*)-But-2′-en-1′-yl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-phenylpropanoate 41

Step 1. TFA (7 mL) was added to a solution of **12**[11] (1.60 g, 3.85 mmol, >99 : 1 dr) in CH_2Cl_2 (15 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a yellow oil (1.58 g, >99 : 1 dr).

Step 2. A solution of the residue (1.58 g, >99 : 1 dr) in CH_2Cl_2 (16 mL) was treated sequentially with $(COCl)_2$ (0.35 mL, 4.05 mmol) and DMF (13 μL, 0.17 μmol) at 0 °C. The reaction mixture was allowed to warm to rt over 1 h then concentrated *in vacuo*. A solution of (*Z*)-but-2-en-1-ol[10,34] (0.39 g, 5.39 mmol, >99 : 1 dr) was then added to a solution of the residue in CH_2Cl_2 (16 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq. $NaHCO_3$ (100 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 0% → 7% Et_2O in 30–40 °C petrol) gave **41** as a colourless oil (960 mg, 60%, >99 : 1 dr); $[\alpha]_D^{20}$ −8.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3028 (C–H), 1732 (C═O), 1493 (C═C); δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, *J* 6.8, C(α)*Me*), 1.61–1.63 (3H, m, C(4′)H_3), 2.59 (1H, dd, *J* 14.6, 9.4, C(2)H_A), 2.69 (1H, dd, *J* 14.6, 5.6, C(2)H_B), 3.68 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.75 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 4.02 (1H, q, *J* 6.8, C(α)*H*), 4.40–4.51 (3H, m, C(3)*H*, C(1′)H_2), 5.31–5.38 (1H, m, C(2′)*H*), 5.61–5.70 (1H, m, C(3′)*H*), 7.17–7.37 (11H, m, *Ph*), 7.41–7.45 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.0 (*C*(4′)), 15.8 (C(α)*Me*), 37.6 (*C*(2)), 50.7 (N*C*H_2Ph), 56.7 (*C*(α)), 59.4 (*C*(3)), 59.9 (*C*(1′)), 124.1 (*C*(2′)), 126.5, 126.8, 127.1, 127.8, 128.0, 128.0, 128.1, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 129.3 (*C*(3′)), 141.4, 141.7, 144.0 (*i*-*Ph*), 171.6 (*C*(1)); *m*/*z* (ESI^+) 414 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{28}H_{31}NNaO_2^+$ ($[M + Na]^+$) requires 436.2247; found 436.2234.

(*Z*)-3′-Phenylprop-2′-en-1′-yl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 42

Step 1. TFA (2 mL) was added to a solution of **12**[11] (500 mg, 1.20 mmol, >99 : 1 dr) in CH_2Cl_2 (4 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (50 mL) and washed with $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a yellow oil (475 mg, >99 : 1 dr).

Step 2. A solution of the residue (475 mg, >99 : 1 dr) in CH_2Cl_2 (5 mL) was treated sequentially with $(COCl)_2$ (108 μL, 1.26 mmol) and DMF (4 μL, 0.05 μmol) at 0 °C. The reaction mixture was allowed to warm to rt over 1 h then concentrated *in vacuo*. A solution of (*Z*)-3-phenylprop-2-en-1-ol[10,35,36] (226 mg, 1.69 mmol, >99 : 1 dr) was then added to a solution of the residue in CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred at this temperature for 16 h. Sat aq. $NaHCO_3$ (50 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 0% → 10% Et_2O in 30–40 °C petrol) gave **42** as a colourless oil (342 mg, 60%, >99 : 1 dr); $[\alpha]_D^{20}$ −12.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2969 (C–H), 1733 (C═O), 1494 (C═C); δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.9, C(α)*Me*), 2.51 (1H, dd, *J* 14.7, 9.4, C(2)H_A), 2.60 (1H, dd, *J* 14.7, 5.6, C(2)H_B), 3.57 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.64 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.91 (1H, q, *J* 6.9, C(α)*H*), 4.37 (1H, dd, *J* 9.4, 5.6, C(3)*H*), 4.51–4.60 (2H, m, C(1′)H_2), 5.45 (1H, dt, *J* 11.7, 6.6, C(2′)*H*), 6.44–6.47 (1H, m, C(3′)*H*), 7.02–7.25 (16H, m, *Ph*), 7.31–7.33 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.9 (C(α)*Me*), 37.5 (*C*(2)), 50.7 (N*C*H_2Ph), 56.7 (*C*(α)), 59.3 (*C*(3)), 61.3 (*C*(1′)), 125.7 (*C*(2′)), 126.6, 126.8, 127.2, 127.4, 127.8, 128.0, 128.0, 128.1, 128.1, 128.2, 128.3, 128.6 (*o*,*m*,*p*-*Ph*), 132.6 (*C*(3′)), 135.9, 141.3, 141.6, 143.9 (*i*-*Ph*), 171.5 (*C*(1)); *m*/*z* (ESI^+) 476 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{33}H_{33}NNaO_2^+$ ($[M + Na]^+$) requires 498.2404; found 498.2382.

Methyl (2*S*,3*R*,1′*S*,α*S*)-2-(but-3′-en-2′-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 44

Step 1. TMSCl (541 μL, 5.08 mmol) was added dropwise to a solution of **41** (590 mg, 1.69 mmol, >99 : 1 dr) in PhMe (7 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 4.28 mL, 4.28 mmol) was added dropwise at −78 °C and the resultant mixture was stirred at −78 °C for 15 min. The reaction mixture was then heated at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2

(200 mL) and 1.0 M aq. HCl (150 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo* to give **43** as an orange oil (582 mg, 96 : 4 dr); $[\alpha]_D^{20}$ +59.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3029, 2965 (C–H), 1704 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 1.13–1.19 (6H, m, C(1′)H_3, C(α)*Me*), 1.94–2.02 (1H, m, C(2′)*H*), 3.11 (1H, dd, *J* 11.6, 2.5, C(2)*H*), 3.66 (1H, d, *J* 13.4, NC$H_A$$H_B$Ph), 4.16 (1H, q, *J* 6.9, C(α)*H*), 4.23–4.28 (2H, m, NC$H_A$$H_B$Ph, C(3)*H*), 4.47–4.51 (1H, m, C(4′)H_A), 4.70–4.73 (1H, m, C(4′)H_B), 5.58–5.67 (1H, m, C(3′)*H*), 7.25–7.49 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.9 (C(α)*Me*), 20.1 (*C*(1′)), 38.1 (*C*(2′)), 50.8 (*C*(2)), 51.1 (N*C*H_2Ph), 57.5 (*C*(α)), 61.4 (*C*(3)), 115.5 (*C*(4′)), 127.6, 128.2, 128.3, 128.6, 128.7, 129.4, 130.0 (*o*,*m*,*p*-*Ph*), 136.4, 136.6 (*i*-*Ph*), 139.2 (*C*(3′)), 140.4 (*i*-*Ph*), 175.5 (*C*(1)); *m*/*z* (ESI^+) 414 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{28}H_{32}NO_2^+$ ($[M + H]^+$) requires 414.2428; found 414.2432.

Step 2. A solution of the residue of **43** (582 mg, 96 : 4 dr) in MeCN (5.9 mL) was treated sequentially with DBU (0.51 mL, 3.39 mmol) and MeI (0.23 mL, 3.73 mmol) at rt. The resultant mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 2.0 M aq. HCl (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then washed sequentially with satd aq. $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 98 : 2) gave **44** as a colourless oil (517 mg, 85%, 96 : 4 dr); $[\alpha]_D^{20}$ +98.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2968 (C–H), 1736 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 0.78 (3H, d, *J* 7.1, C(1′)H_3), 0.85 (3H, d, *J* 6.9, C(α)*Me*), 1.79–1.88 (1H, m, C(2′)*H*), 3.22 (1H, dd, *J* 12.0, 4.2, C(2)*H*), 3.43 (3H, s, O*Me*), 3.46 (1H, d, *J* 14.2, NC$H_A$$H_B$Ph), 3.98 (1H, d, *J* 14.2, NC$H_A$$H_B$Ph), 4.06 (1H, d, *J* 12.0, C(3)*H*), 4.13 (1H, q, *J* 6.9, C(α)*H*), 4.22–4.27 (1H, m, C(4′)H_A), 4.62 (1H, dd, *J* 10.0, 2.0, C(4′)H_B), 5.62 (1H, app dt, *J* 17.2, 10.0, C(3′)*H*), 7.08–7.17 (4H, m, *Ph*), 7.19–7.29 (11H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.2 (C(α)*Me*), 19.6 (*C*(1′)), 37.5 (*C*(2′)), 50.7 (N*C*H_2Ph), 50.8 (O*Me*), 53.4 (*C*(2)), 55.8 (*C*(α)), 61.5 (*C*(3)), 115.2 (*C*(4′)), 126.3, 126.6, 127.3, 127.6, 127.9, 128.0, 128.1, 128.9, 129.5 (*o*,*m*,*p*-*Ph*), 137.7 (*i*-*Ph*), 138.8 (*C*(3′)), 139.8, 144.3 (*i*-*Ph*), 172.9 (*C*(1)); *m*/*z* (ESI^+) 428 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{34}NO_2^+$ ($[M + H]^+$) requires 428.2584; found 428.2583.

Methyl (2*S*,3*R*,1′*S*)-2-(but-2′-yl)-3-amino-3-phenylpropanoate 45

$Pd(OH)_2$/C (100 mg, 50% w/w by substrate) was added to a degassed solution of **44** (200 mg, 0.47 mmol, 96 : 4 dr) in MeOH (6 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (15 mL) and the resultant solution was washed with satd aq. $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$–MeOH, 99 : 1) gave **45** as a colourless oil (83 mg, 76%, 96 : 4 dr); $[\alpha]_D^{20}$ +33.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3386 (N–H), 2963 (C–H), 1727 (C=O), 1154; δ_H (400 MHz, $CDCl_3$) 0.81 (3H, t, *J* 7.4, C(4′)H_3), 0.96 (3H, d, *J* 6.7, C(1′)H_3), 0.99–1.07 (1H, m, C(3′)H_A), 1.45–1.60 (2H, m, C(2′)*H*, C(3′)H_B), 1.70 (2H, br s, NH_2), 2.57 (1H, dd, *J* 7.8, 6.7, C(2)*H*), 3.59 (3H, s, O*Me*), 4.26 (1H, d, *J* 7.8, C(3)*H*), 7.24–7.28 (3H, m, *Ph*), 7.30–7.36 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.6 (*C*(4′)), 17.2 (*C*(1′)), 25.8 (*C*(3′)), 34.2 (*C*(2′)), 51.0 (O*Me*), 55.1 (*C*(3)), 59.4 (*C*(2)), 126.3, 127.1, 128.4 (*o*,*m*,*p*-*Ph*), 144.2 (*i*-*Ph*), 174.6 (*C*(1)); *m*/*z* (ESI^+) 236 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{22}NO_2^+$ ($[M + H]^+$) requires 236.1645; found 236.1643.

Methyl (2*S*,3*R*,1′*S*)-2-(1′-phenylpropyl)-3-amino-3-phenylpropanoate 46

$Pd(OH)_2$/C (200 mg, 50% w/w by substrate) was added to a degassed solution of **39** (400 mg, 0.82 mmol, >99 : 1 dr) in MeOH (12 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (15 mL) and the resultant solution was washed with satd aq. $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), then the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$–^{i}PrOH, 99 : 1) gave **46** as a pale yellow oil (184 mg, 76%, >99 : 1 dr); $[\alpha]_D^{20}$ +4.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3397 (N–H), 3027, 2962 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 0.59 (3H, t, *J* 7.3, C(3′)H_3), 1.44–1.56 (2H, m, C(2′)H_2), 1.66 (2H, br s, NH_2), 2.89 (1H, app td, *J* 10.0, 4.4, C(2)*H*), 2.91–2.97 (1H, m, C(1′)*H*), 3.39 (3H, s, O*Me*), 3.66 (1H, d, *J* 4.4, C(3)*H*), 7.02–7.05 (2H, m, *Ph*), 7.08–7.12 (1H, m, *Ph*), 7.15–7.20 (5H, m, *Ph*), 7.25–7.29 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (*C*(3′)), 27.2 (*C*(2′)), 47.3 (*C*(1′)), 51.0 (O*Me*), 54.8 (*C*(3)), 59.4 (*C*(2)), 125.8, 126.7, 126.8, 128.0, 128.2, 128.6 (*o*,*m*,*p*-*Ph*), 141.7, 144.3 (*i*-*Ph*), 174.4 (*C*(1)); *m*/*z* (ESI^+) 298 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{23}NNaO_2^+$ ($[M + Na]^+$) requires 320.1621; found 320.1611.

(2*S*,3*R*,1′*S*)-2-(But-2′-yl)-3-amino-3-phenylpropanoic acid 47

A solution of **45** (63 mg, 0.27 mmol, 96 : 4 dr) in 6.0 M aq. HCl (8.8 mL) was heated at reflux for 5 days. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in H_2O (2 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq. NH_4OH) to give **47** as a white solid (54 mg, 91%, 96 : 4 dr); mp 190–192 °C; $[\alpha]_D^{20}$ +27.1 (*c* 0.3 in H_2O); ν_{max} (ATR) 3604, 2965 (C–H), 1649 (C=O), 1498 (C=C); δ_H (400 MHz, MeOH-d_4) 0.88 (3H, t, *J* 7.2, C(4′)H_3), 1.10 (3H, d, *J* 6.8, C(1′)H_3), 1.06–1.17 (1H, m, C(3′)H_A), 1.50–1.64 (2H, m, C(2′)*H*, C(3′)H_B), 2.49–2.52 (1H, m, C(2)*H*), 4.51 (1H, d, *J* 6.4, C(3)*H*), 7.38–7.52 (5H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 12.3 (*C*(4′)), 17.7 (*C*(1′)), 27.7 (*C*(3′)), 36.1 (*C*(2′)), 56.1 (*C*(3)), 59.1 (*C*(2)), 128.5, 130.0, 130.3 (*o*,*m*,*p*-*Ph*), 139.0 (*i*-*Ph*), 179.4 (*C*(1)); *m*/*z* (ESI^+) 222 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{19}NNaO_2^+$ ($[M + Na]^+$) requires 244.1308; found 244.1314.

(2*S*,3*R*,1′*S*)-2-(1′-Phenylpropyl)-3-amino-3-phenylpropanoic acid 48

A solution of **46** (73 mg, 0.24 mmol, >99 : 1 dr) in 6.0 M aq. HCl (10 mL) was heated at reflux for 5 days. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in H_2O (2 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq. NH_4OH) to give **48** as a white solid (61 mg, 88%, >99 : 1 dr); mp 209–211 °C (sub); $[\alpha]_D^{20}$ −19.6 (*c* 0.2 in H_2O); ν_{max} (ATR) 2957 (C–H), 1613, 1571, 1496; δ_H (500 MHz, D_2O) 0.57 (3H, t, *J* 7.3, C(3′)H_3), 1.47–1.56 (1H, m, C(2′)H_A), 1.60–1.67 (1H, m, C(2′)H_B), 2.71 (1H, td, *J* 10.8, 3.7, C(1′)*H*), 2.84 (1H, dd, *J* 10.8, 3.7, C(2)*H*), 4.05 (1H, d, *J* 3.7, C(3)*H*), 7.10–7.12 (2H, m, *Ph*), 7.27–7.34 (6H, m, *Ph*), 7.36–7.39 (2H, m, *Ph*); δ_C (125 MHz, D_2O) 11.1 (*C*(3′)), 27.1 (*C*(2′)), 47.1 (*C*(1′)), 54.1 (*C*(3)), 58.6 (*C*(2)), 126.0, 127.1, 128.5, 128.8, 129.0, 129.1 (*o*,*m*,*p*-*Ph*), 136.3, 141.3 (*i*-*Ph*), 179.1 (*C*(1)); *m*/*z* (ESI^+) 284 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{18}H_{22}NO_2^+$ ($[M + H]^+$) requires 284.1645; found 284.1645.

(*Z*)-Pent-2′-en-1′-yl (3*R*,α*S*,*E*)-3-[*N*-benzyl-*N*-(α-methyl-benzyl)-amino]hex-4-enoate 66

Step 1. TFA (8 mL) was added to a solution of **64**[29a] (2.00 g, 5.27 mmol, >99 : 1 dr) in CH_2Cl_2 (16 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a yellow oil (1.97 g, >99 : 1 dr).

Step 2. A solution of the residue (1.97 g, >99 : 1 dr) in CH_2Cl_2 (21 mL) was treated sequentially with $(COCl)_2$ (0.53 mL, 6.18 mmol) and DMF (18 μL, 0.24 μmol) at 0 °C. The reaction mixture was allowed to warm to rt over 1 h then concentrated *in vacuo*. A solution of (*Z*)-pent-2-en-1-ol[37] (0.72 g, 8.41 mmol, >99 : 1 dr) in CH_2Cl_2 (2 mL) was then added to a solution of the residue in CH_2Cl_2 (21 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq. $NaHCO_3$ (100 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 98 : 2) gave **66** as a colourless oil (1.30 g, 54%, >99 : 1 dr); $[\alpha]_D^{20}$ +5.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2966 (C–H), 1733 (C═O), 1494 (C═C); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.5, C(5′)H_3), 1.29 (3H, d, *J* 6.9, C(α)*Me*), 1.61 (3H, d, *J* 5.4, C(6)H_3), 1.99 (2H, qdd, *J* 7.5, 7.5, 1.3, C(4′)H_2), 2.23 (1H, dd, *J* 14.2, 8.2, C(2)H_A), 2.38 (1H, dd, *J* 14.2, 6.6, C(2)H_B), 3.57 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 3.62 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 3.69–3.74 (1H, m, C(3)*H*), 3.92 (1H, q, *J* 6.9, C(α)*H*), 4.34–4.39 (1H, m, C(1′)H_A), 4.44–4.49 (1H, m, C(1′)H_B), 5.26–5.33 (1H, m, C(2′)*H*), 5.39–5.55 (3H, m, C(4)*H*, C(5)*H*, C(3′)*H*), 7.09–7.14 (2H, m, *Ph*), 7.17–7.22 (4H, m, *Ph*), 7.24–7.29 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(5′)), 16.8 (C(α)*Me*), 18.0 (*C*(6)), 20.8 (*C*(4′)), 38.6 (*C*(2)), 50.3 (N*C*H_2Ph), 56.7 (*C*(3)), 56.8 (*C*(α)), 60.0 (*C*(1′)), 122.9 (*C*(2′)), 126.5, 126.6 (*o*,*m*,*p*-*Ph*), 127.1 (*C*(5)), 127.8, 127.9, 128.0, 128.3 (*o*,*m*,*p*-*Ph*), 131.1 (*C*(4)), 136.5 (*C*(3′)), 141.3, 144.3 (*i*-*Ph*), 171.7 (*C*(1)); *m*/*z* (ESI^+) 392 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{34}NO_2^+$ ($[M + H]^+$) requires 392.2584; found 392.2584.

(*Z*)-4′-Phenylbut-2′-en-1′-yl (3*R*,α*S*,*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 67

Step 1. TFA (18 mL) was added to a solution of **64**[29a] (4.13 g, 10.9 mmol, >99 : 1 dr) in CH_2Cl_2 (33 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and washed with $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a yellow oil (4.31 g, >99 : 1 dr).

Step 2. A solution of the residue (4.31 g, >99 : 1 dr) in CH_2Cl_2 (43 mL) was treated sequentially with $(COCl)_2$ (0.98 mL, 11.4 mmol) and DMF (33 μL, 0.43 μmol) at 0 °C. The reaction mixture was allowed to warm to rt over 1 h then concentrated *in vacuo*. A solution of (*Z*)-4-phenylbut-2-en-1-ol[38] (2.26 g, 15.3 mmol, >99 : 1 dr) was then added to a solution of the residue in CH_2Cl_2 (43 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq. $NaHCO_3$ (100 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 0% → 5% Et_2O in 30–40 °C petrol) gave **67** as a colourless oil (3.04 g, 62%, >99 : 1 dr); $[\alpha]_D^{20}$ +7.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2935 (C–H), 1733 (C═O), 1494 (C═C); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.8, C(α)*Me*), 1.62 (3H, d, *J* 5.2, C(6)H_3), 2.26 (1H, dd, *J* 14.2, 8.1 C(2)H_A), 2.41 (1H, dd, *J* 14.2, 6.6, C(2)H_B), 3.35 (2H, d, *J* 7.6, C(4′)H_2), 3.58 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 3.64 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 3.71–3.76 (1H, m, C(3)*H*), 3.94 (1H, q, *J* 6.8, C(α)*H*), 4.47 (1H, dd, *J* 12.8, 6.8, C(1′)H_A), 4.58 (1H, dd, *J* 12.8, 7.2, C(1′)H_B), 5.41–5.54 (3H, m, C(5)*H*, C(2′)*H*, C(4)*H*), 5.66–5.74 (1H, m, C(3′)*H*), 7.08–7.15 (5H, m, *Ph*), 7.19–7.24 (6H, m, *Ph*), 7.26–7.30 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.8 (C(α)*Me*), 18.0 (*C*(6)), 33.7 (*C*(4′)), 38.6 (*C*(2)), 50.3 (N*C*H_2Ph), 56.7 (*C*(3)), 56.8 (*C*(α)), 59.9 (*C*(1′)), 124.4 (*C*(2′)), 126.1, 126.5, 126.6, 127.8, 127.9, 128.0, 128.3, 128.3, 128.5 (*o*,*m*,*p*-*Ph*), 127.1 (*C*(5)), 131.0 (*C*(4)), 132.9 (*C*(3′)), 139.8, 141.3, 144.3 (*i*-*Ph*), 171.6 (*C*(1)); *m*/*z* (ESI^+) 454 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{31}H_{36}NO_2^+$ ($[M + H]^+$) requires 454.2741; found 454.2741.

(*Z*)-4′-Methylpent-2′-en-1′-yl (3*R*,α*S*,*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 68

Step 1. TFA (4 mL) was added to a solution of **64**[29a] (0.95 g, 2.50 mmol, >99 : 1 dr) in CH_2Cl_2 (8 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were then dried

and concentrated *in vacuo* to give a yellow oil (900 mg, >99 : 1 dr).

Step 2. A solution of the residue (900 mg, >99 : 1 dr) in CH_2Cl_2 (9 mL) was treated sequentially with $(COCl)_2$ (0.2 mL, 2.62 mmol) and DMF (8 μL, 0.10 μmol) at 0 °C. The reaction mixture was allowed to warm to rt over 1 h then concentrated *in vacuo*. A solution of (*Z*)-4-methylpent-2-en-1-ol[29a] (350 mg, 3.49 mmol, >99 : 1 dr) was then added to a solution of the residue in CH_2Cl_2 (9 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq. $NaHCO_3$ (100 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 0% → 5% Et_2O in 30–40 °C petrol) gave **68** as a colourless oil (510 mg, 50%, >99 : 1 dr); $[\alpha]_D^{20}$ +12.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2962 (C–H), 1734 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 0.87 (6H, app d, *J* 6.8, C(5′)H_3, C(4′)*Me*), 1.29 (3H, d, *J* 6.9, C(α)*Me*), 1.61–1.62 (3H, m, C(6)H_3), 2.23 (1H, dd, *J* 14.3, 6.6, C(2)H_A), 2.38 (1H, dd, *J* 14.3, 8.0, C(2)H_B), 2.47–2.56 (1H, m, C(4′)*H*), 3.57 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 3.62 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 3.69–3.74 (1H, m, C(3)*H*), 3.92 (1H, q, *J* 6.9, C(α)*H*), 4.37 (1H, ddd, *J* 12.7, 6.8, 1.2, C(1′)H_A), 4.47 (1H, ddd, *J* 12.7, 6.8, 1.2, C(1′)H_B), 5.17–5.23 (1H, m, C(2′)*H*), 5.31–5.37 (1H, m, C(3′)*H*), 5.39–5.46 (1H, m, C(5)*H*), 5.46–5.52 (1H, m, C(4)*H*), 7.09–7.15 (2H, m, *Ph*), 7.17–7.31 (8H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.8 (C(α)*Me*), 18.0 (*C*(6)), 23.0 (*C*(5′), C(4′)*Me*), 26.9 (*C*(4′)), 38.6 (*C*(2)), 50.3 (N*C*H_2Ph), 56.7 (*C*(3)), 56.8 (*C*(α)), 60.2 (*C*(1′)), 121.1 (*C*(2′)), 126.5, 126.6 (*o*,*m*,*p*-*Ph*), 127.1 (*C*(5)), 127.8, 127.9, 128.0, 128.3 (*o*,*m*,*p*-*Ph*), 131.0 (*C*(4)), 141.3 (*i*-*Ph*), 142.2 (*C*(3′)), 144.3 (*i*-*Ph*), 171.7 (*C*(1)); *m*/*z* (ESI^+) 406 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{36}NO_2^+$ ($[M + H]^+$) requires 406.2741; found 406.2745.

Methyl (*S*,*S*,*S*,*S*,*E*)-2-(pent-1′-en-3′-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 81

Step 1. TMSCl (1.94 mL, 15.3 mmol) was added dropwise to a solution of **66** (2.00 g, 5.11 mmol, >99 : 1 dr) in PhMe (20 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 15.3 mL, 15.3 mmol) was added dropwise at −78 °C and the resultant mixture was stirred at −78 °C for 15 min. The reaction mixture was stirred at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (200 mL) and 1.0 M aq. HCl (150 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo* to give a 85 : 15 mixture of **71** and **76**. Purification *via* flash column chromatography (gradient elution, 0% → 5% acetone in 30–40 °C petrol) gave **76** as a yellow oil (308 mg, >99 : 1 dr); $[\alpha]_D^{20}$ −7.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2965 (C–H), 1702 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 0.61 (3H, t, *J* 7.3, C(5′)H_3), 0.97–1.08 (1H, m, C(4′)H_A), 1.09–1.16 (1H, m, C(4′)H_B), 1.34 (3H, d, *J* 6.8, C(α)*Me*), 1.61 (3H, d, *J* 4.9, C(6)H_3), 2.17–2.24 (1H, m, C(3′)*H*), 2.39 (1H, app t, *J* 6.5, C(2)*H*), 3.47 (1H, dd, *J* 8.4, 7.5, C(3)*H*), 3.53 (1H, d, *J* 14.2, NC$H_A$$H_B$Ph), 3.74 (1H, d, *J* 14.2, NC$H_A$$H_B$Ph), 4.06 (1H, q, *J* 6.8, C(α)*H*), 4.65 (1H, dd, *J* 17.1, 1.7, C(1′)H_A), 4.83 (1H, dd, *J* 10.3, 1.7, C(1′)H_B), 5.38–5.45 (1H, m, C(2′)*H*), 5.47–5.56 (2H, m, C(4)*H*, C(5)*H*), 7.08–7.12 (3H, m, *Ph*), 7.14–7.18 (3H, m, *Ph*), 7.23–7.31 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.7 (*C*(5′)), 15.0 (C(α)*Me*), 18.0 (*C*(6)), 25.0 (*C*(4′)), 43.7 (*C*(3′)), 51.7 (N*C*H_2Ph), 52.0 (*C*(2)), 57.7 (*C*(α)), 62.0 (*C*(3)), 116.0 (*C*(1′)), 126.9, 127.1 (*o*,*m*,*p*-*Ph*), 127.5 (*C*(4)), 128.2, 128.2, 128.3, 128.8 (*o*,*m*,*p*-*Ph*), 130.6 (*C*(5)), 139.0 (*C*(2′)), 140.0, 143.0 (*i*-*Ph*), 177.3 (*C*(1)); *m*/*z* (ESI^+) 392 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{33}NNaO_2^+$ ($[M + Na]^+$) requires 414.2404; found 414.2404. Further elution (eluent 30–40 °C petrol–acetone, 95 : 5) gave **71** as a yellow oil (1.11 g, >99 : 1 dr); $[\alpha]_D^{20}$ +26.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2964 (C–H), 1703 (C=O), 1495 (C=C); δ_H (400 MHz, $CDCl_3$) 0.64 (3H, t, *J* 7.5, C(5′)H_3), 1.41–1.55 (1H, m, C(4′)H_A), 1.47 (3H, d, *J* 7.0, C(α)*Me*), 1.63–1.75 (1H, m, C(4′)H_B), 1.81 (3H, dd, *J* 6.5, 1.5, C(6)H_3), 1.86–1.93 (1H, m, C(3′)*H*), 2.13 (1H, dd, *J* 11.1, 1.8, C(2)*H*), 3.64 (1H, d, *J* 13.5, NC$H_A$$H_B$Ph), 3.72 (1H, app t, *J* 10.0, C(3)*H*), 3.85 (1H, d, *J* 13.5, NC$H_A$$H_B$Ph), 3.96 (1H, q, *J* 7.0, C(α)*H*), 4.65 (1H, dd, *J* 17.2, 2.1, C(1′)H_A), 4.78 (1H, dd, *J* 10.1, 2.1, C(1′)H_B), 5.38 (1H, app ddd, *J* 15.4, 10.0, 1.5, C(4)*H*), 5.51 (1H, app dt, *J* 17.2, 10.1, C(2′)*H*), 5.67 (1H, dq, *J* 15.4, 6.5, C(5)*H*), 7.15–7.25 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.3 (*C*(5′)), 17.2 (C(α)*Me*), 18.3 (*C*(6)), 26.5 (*C*(4′)), 46.0 (*C*(3′)), 47.1 (*C*(2)), 51.1 (N*C*H_2Ph), 59.9 (*C*(α)), 60.6 (*C*(3)), 116.6 (*C*(1′)), 126.0 (*C*(4)), 128.0, 128.1, 128.3, 128.6, 128.6, 129.6 (*o*,*m*,*p*-*Ph*), 133.9 (*C*(5)), 135.2 (*i*-*Ph*), 138.8 (*C*(4′)), 140.0 (*i*-*Ph*), 174.0 (*C*(1)); *m*/*z* (ESI^+) 392 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{33}NNaO_2^+$ ($[M + Na]^+$) requires 414.2404; found 414.2404.

Step 2 (for 71). A solution of **71** (906 mg) in MeCN (4 mL) was treated sequentially with DBU (692 μl, 4.63 mmol) and MeI (317 μL, 5.09 mmol) at rt. The reaction mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (80 mL) and 2.0 M aq. HCl (80 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts were then washed sequentially with satd aq. $NaHCO_3$ (150 mL) and brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 98 : 2) gave **81** as a colourless oil (791 mg, 38% from **66**, >99 : 1 dr); $[\alpha]_D^{20}$ +4.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2967 (C–H), 1733 (C=O), 1495 (C=C); δ_H (400 MHz, $CDCl_3$) 0.70 (3H, t, *J* 7.3, C(5′)H_3), 0.98–1.09 (1H, m, C(4′)H_A), 1.18–1.28 (1H, m, C(4′)H_B), 1.31 (3H, d, *J* 6.9, C(α)*Me*), 1.68–1.70 (3H, m, C(6)H_3), 1.84 (1H, m, C(3′)*H*), 2.68 (1H, dd, *J* 11.5, 4.5, C(2)*H*), 3.35 (3H, s, O*Me*), 3.43–3.48 (1H, m, C(3)*H*), 3.47 (1H, d, *J* 14.2, NC$H_A$$H_B$Ph), 3.71 (1H, d, *J* 14.2, NC$H_A$$H_B$Ph), 4.03 (1H, q, *J* 6.9, C(α)*H*), 4.63 (1H, dd, *J* 17.1, 2.1, C(1′)H_A), 4.81 (1H, dd, *J* 10.1, 2.1, C(1′)H_B), 5.22–5.28 (1H, m, C(4)*H*), 5.34–5.42 (1H, m, C(5)*H*), 5.50 (1H, dt, *J* 17.1, 10.1, C(2′)*H*) 7.05–7.13 (2H, m, *Ph*), 7.14–7.22 (8H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.9 (*C*(5′)), 16.9 (C(α)*Me*), 18.0 (*C*(6)), 26.4 (*C*(4′)), 45.6 (*C*(3′)), 50.3 (N*C*H_2Ph), 50.6 (O*Me*), 52.3 (*C*(2)), 56.3 (*C*(α)), 60.4 (*C*(3)), 116.4 (*C*(1′)), 127.9 (*C*(4)), 126.2, 126.4, 127.6, 127.8, 128.1, 128.9 (*o*,*m*,*p*-*Ph*), 130.1 (*C*(5)), 137.5 (*C*(2′)), 140.3, 144.7 (*i*-*Ph*), 173.2 (*C*(1)); *m*/*z* (ESI^+) 406 ($[M + H]^+$,

100%); HRMS (ESI^+) $C_{27}H_{36}NO_2^+$ ($[M + H]^+$) requires 406.2741; found 406.2746.

Step 2 (for 76). A solution of **76** (256 mg) in MeCN (1.0 mL) was treated sequentially with DBU (196 μL, 1.31 mmol) and MeI (90 μL, 1.44 mmol) at rt. The reaction mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 2.0 M aq. HCl (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then washed sequentially with satd aq. $NaHCO_3$ (150 mL) and brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 98 : 2) gave **86** as a white solid (179 mg, 9% from **66**, >99 : 1 dr); $[\alpha]_D^{20}$ −19.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2966 (C–H), 1732 (C═O), 1494 (C═C); δ_H (400 MHz, $CDCl_3$) 0.55 (3H, t, *J* 7.5, C(5′)H_3), 0.84–0.95 (1H, m, C(4′)H_A), 0.97–1.06 (1H, m, C(4′)H_B), 1.30 (3H, d, *J* 6.9, C(α)*Me*), 1.63 (3H, dd, *J* 6.4, 1.5, C(6)H_3), 2.18–2.25 (1H, m, C(3′)*H*), 2.45 (1H, dd, *J* 8.6, 6.1, C(2)*H*), 3.39–3.42 (1H, m, C(3)*H*), 3.44 (3H, s, O*Me*), 3.57 (1H, d, *J* 14.0, NC$H_A$$H_B$Ph), 3.65 (1H, d, *J* 14.0, NCH$_A$$H_B$Ph), 3.90 (1H, q, *J* 6.9, C(α)*H*), 4.64 (1H, dd, *J* 17.1, 2.0, C(1′)H_A), 4.80 (1H, dd, *J* 10.3, 2.0, C(1′)H_B), 5.34–5.40 (1H, m, C(2′)*H*), 5.40–5.47 (1H, m, C(5)*H*), 5.55–5.61 (1H, m, C(4)*H*), 7.09–7.14 (2H, m, *Ph*), 7.17–7.24 (6H, m, *Ph*), 7.30–7.31 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.4 (*C*(5′)), 16.6 (C(α)*Me*), 18.1 (*C*(6)), 24.9 (*C*(4′)), 44.0 (*C*(3′)), 50.7 (O*Me*), 50.9 (N*C*H$_2$Ph), 53.6 (*C*(2)), 57.9 (*C*(α)), 59.9 (*C*(3)), 116.1 (*C*(1′)), 127.9 (*C*(4)), 126.5, 126.6, 128.0, 128.0, 128.1, 128.8 (*o*,*m*,*p*-*Ph*), 129.3 (*C*(5)), 138.7 (*C*(2′)), 141.3, 144.6 (*i*-*Ph*), 173.9 (*C*(1)); *m*/*z* (ESI^+) 406 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{36}NO_2^+$ ($[M + H]^+$) requires 406.2741; found 406.2745.

X-ray crystal structure determination for 86·HBF$_4$

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation, using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions.

X-ray crystal structure data for **86**·HBF_4 [$C_{27}H_{36}BF_4NO_2$]: *M* = 493.39, monoclinic, $P2_1$, *a* = 8.93933(11) Å, *b* = 14.19427(18) Å, *c* = 10.40085(16) Å, *β* = 98.8420(13)°, *V* = 1304.05(3) Å^3, *Z* = 2, *μ* = 0.808 mm^{-1}, colourless block, crystal dimensions = 0.08 × 0.10 × 0.19 mm^3. A total of 5399 unique reflections were measured for 4 < *θ* < 76 and 5377 reflections were used in the refinement. The final parameters were wR_2 = 0.070 and R_1 = 0.029 [$I > -3.0\sigma(I)$], with Flack enantiopole = 0.03(9).[17] CCDC 982704.†

Methyl (*S*,*S*,*S*,*S*,*E*)-2-(1′-phenylbut-3′-en-2′-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 82

Step 1. TMSCl (1.11 mL, 8.80 mmol) was added dropwise to a solution of **67** (1.33 g, 2.93 mmol, >99 : 1 dr) in PhMe (13 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 8.80 mL, 8.80 mmol) was then added dropwise and the resultant mixture was stirred at −78 °C for 15 min. The reaction mixture was allowed to warm to rt then heated at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (150 mL) and 1.0 M aq. HCl (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL). The combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo* to give a 76 : 24 mixture of **72** and **77**. Purification *via* flash column chromatography (gradient elution, 0% → 12% acetone in 30–40 °C petrol) gave **77** as a yellow oil (360 mg, >99 : 1 dr); $[\alpha]_D^{20}$ −21.3 (*c* 0.8 in $CHCl_3$); ν_{max} (ATR) 2928 (C–H), 1704 (C═O), 1494 (C═C); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.6, C(α)*Me*), 1.58–1.59 (3H, m, C(6)H_3), 2.42–2.47 (1H, m, C(1′)H_A), 2.49–2.57 (1H, m, C(2′)*H*), 2.67–2.69 (1H, m, C(2)*H*), 2.78 (1H, dd, *J* 12.8, 6.5, C(1′)H_B), 3.40 (1H, dd, *J* 10.0, 5.9, C(3)*H*), 3.55 (1H, d, *J* 14.0, NC$H_A$$H_B$Ph), 3.63 (1H, d, *J* 14.0, NCH$_A$$H_B$Ph), 4.11 (1H, q, *J* 6.6, C(α)*H*), 4.54 (1H, app d, *J* 17.5, C(4′)H_A), 4.82 (1H, app d, *J* 10.2, C(4′)H_B), 5.25–5.32 (1H, m, C(4)*H*), 5.48–5.57 (1H, m, C(5)*H*), 5.67 (1H, ddd, *J* 17.5, 10.2, 8.2, C(3′)*H*), 6.91–6.93 (2H, m, *Ph*), 7.04–7.28 (13H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.2 (C(α)*Me*), 17.9 (*C*(6)), 39.3 (*C*(1′)), 44.2 (*C*(2)), 50.2 (*C*(2′)), 51.2 (N*C*H$_2$Ph), 56.9 (*C*(α)), 62.4 (*C*(3)), 116.1 (*C*(4′)), 125.9, 126.9, 127.2 (*o*,*m*,*p*-*Ph*), 127.9 (*C*(4)), 128.1, 128.2, 128.2, 128.3, 128.8, 129.4 (*o*,*m*,*p*-*Ph*), 130.8 (*C*(5)), 138.5 (*C*(3′)), 139.4, 140.2, 142.0 (*i*-*Ph*), 176.6 (*C*(1)); *m*/*z* (ESI^+) 454 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{31}H_{36}NO_2^+$ ($[M + H]^+$) requires 454.2741; found 454.2754. Further elution (eluent 30–40 °C petrol–acetone, 88 : 12) gave **72** as a yellow oil (1.15 g, >99 : 1 dr); $[\alpha]_D^{20}$ +13.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2933 (C–H), 1704 (C═O), 1495 (C═C); δ_H (400 MHz, $CDCl_3$) 1.43 (3H, d, *J* 6.9, C(α)*Me*), 1.76 (3H, dd, *J* 6.4, 0.9, C(6)H_3), 2.02 (1H, app d, *J* 11.0, C(2)*H*), 2.29 (1H, app q, *J* 8.0, C(2′)*H*), 2.79 (1H, dd, *J* 13.4, 6.6, C(1′)H_A), 3.14 (1H, dd, *J* 13.4, 9.3, C(1′)H_B), 3.54 (1H, d, *J* 13.6, NC$H_A$$H_B$Ph), 3.65–3.70 (2H, m, NCH$_A$$H_B$Ph, C(3)*H*), 3.89 (1H, q, *J* 6.9, C(α)*H*), 4.64 (1H, app d, *J* 17.1, C(4′)H_A), 4.77 (1H, dd, *J* 10.2, 1.7, C(4′)H_B), 5.07 (1H, dd, *J* 14.8, 10.1, C(4)*H*), 5.53–5.61 (1H, m, C(5)*H*), 5.61–5.70 (1H, m, C(3′)*H*), 7.02–7.03 (2H, m, *Ph*), 7.07–7.11 (3H, m, *Ph*), 7.14–7.25 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.9 (C(α)*Me*), 18.4 (*C*(6)), 40.0 (*C*(1′)), 44.4 (*C*(2)), 46.1 (*C*(2′)), 51.0 (N*C*H$_2$Ph), 59.9 (*C*(α)), 60.4 (*C*(3)), 116.9 (*C*(4′)), 125.7 (*C*(4)), 125.9, 128.1, 128.2, 128.3, 128.4, 128.8, 128.9, 129.5, 129.6 (*o*,*m*,*p*-*Ph*), 134.3 (*C*(5)), 134.6 (*i*-*Ph*), 138.5 (*C*(3′)), 139.6, 140.6 (*i*-*Ph*), 174.0 (*C*(1)); *m*/*z* (ESI^+) 454 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{31}H_{36}NO_2^+$ ($[M + H]^+$) requires 454.2741; found 454.2763.

Step 2 (for 72). A solution of **72** (1.15 g, >99 : 1 dr) in MeCN (12 mL) was treated sequentially with DBU (758 μl, 5.07 mmol) and MeI (347 μL, 5.58 mmol) at rt. The resultant mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (80 mL) and 2.0 M aq. HCl (80 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then washed sequentially with satd aq. $NaHCO_3$ (150 mL) and brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 98 : 2) gave **82** as a pale yellow oil (777 mg, 57% from **67**, >99 : 1 dr); $[\alpha]_D^{20}$ −12.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2935

(C–H), 1734 (C═O), 1495 (C═C); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.9, C(α)*Me*), 1.67 (3H, dd, *J* 6.4, 1.5, C(6)H_3), 2.26–2.33 (1H, m, C(2′)*H*), 2.38 (1H, dd, *J* 13.4, 8.2, C(1′)H_A), 2.55 (1H, dd, *J* 13.4, 6.6, C(1′)H_B), 2.72 (1H, dd, *J* 11.4, 3.8, C(2)*H*), 3.42 (3H, s, O*Me*), 3.45 (1H, d, *J* 14.0, NC$H_A$$H_B$Ph), 3.46–3.52 (1H, m, C(3)*H*), 3.66 (1H, d, *J* 14.0, NCH$_A$$H_B$Ph), 3.98 (1H, q, *J* 6.9, C(α)*H*), 4.50 (1H, dd, *J* 17.1, 2.1, C(4′)H_A), 4.74 (1H, dd, *J* 10.2, 2.1, C(4′)H_B), 5.15–5.22 (1H, m, C(4)*H*), 5.36 (1H, app dq, *J* 15.3, 6.4, C(5)*H*), 5.57–5.66 (1H, m, C(3′)*H*), 6.98–7.01 (2H, m, *Ph*), 7.06–7.22 (13H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.9 (C(α)*Me*), 18.0 (*C*(6)), 40.1 (*C*(1′)), 45.6 (*C*(2′)), 50.3 (N*C*H$_2$Ph), 50.7 (O*Me*), 51.6 (*C*(2)), 56.3 (*C*(α)), 60.4 (*C*(3)), 116.6 (*C*(4′)), 125.8, 126.2, 126.4, 127.6, 127.8, 127.9 (*o*,*m*,*p-Ph*), 127.9 (*C*(4)), 128.0, 128.9, 129.2 (*o*,*m*,*p-Ph*), 130.3 (*C*(5)), 137.0 (*C*(3′)), 139.9, 140.2, 144.6 (*i-Ph*), 173.0 (*C*(1)); *m*/*z* (ESI$^+$) 468 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{38}NO_2^+$ ([M + H]$^+$) requires 468.2897; found 468.2907.

Step 2 (for 77). A solution of **77** (359 mg, >99 : 1 dr) in MeCN (3.6 mL) was treated sequentially with DBU (237 μL, 1.58 mmol) and MeI (108 μL, 1.74 mmol) at rt. The resultant mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 2.0 M aq. HCl (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then washed sequentially with satd aq. $NaHCO_3$ (150 mL) and brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2% Et_2O in 30–40 °C petrol) gave **87** as a yellow oil (221 mg, 16% from **67**, >99 : 1 dr); $[\alpha]_D^{20}$ +15.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3028, 2950 (C–H), 1732 (C═O), 1496 (C═C); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 7.0, C(α)*Me*), 1.63–1.65 (3H, m, C(6)H_3), 2.25 (1H, dd, *J* 13.7, 8.8, C(1′)H_A), 2.39 (1H, dd, *J* 13.7, 6.4, C(1′)H_B), 2.56 (1H, dd, *J* 8.8, 5.4, C(2)*H*), 2.63–2.70 (1H, m, C(2′)*H*), 3.43–3.49 (1H, m, C(3)*H*), 3.48 (3H, s, O*Me*), 3.51 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 3.58 (1H, d, *J* 14.4, NCH$_A$$H_B$Ph), 3.85 (1H, q, *J* 7.0, C(α)*H*), 4.35–4.40 (1H, m, C(4′)H_A), 4.66 (1H, dd, *J* 10.4, 2.1, C(4′)H_B), 5.37–5.45 (1H, m, C(3′)*H*), 5.40–5.48 (1H, m, C(5)*H*), 5.51–5.57 (1H, m, C(4)*H*), 6.87–6.89 (2H, m, *Ph*), 7.02–7.27 (13H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.0 (C(α)*Me*), 18.1 (*C*(6)), 38.7 (*C*(1′)), 43.8 (*C*(2′)), 50.7 (N*C*H$_2$Ph), 50.8 (O*Me*), 53.0 (*C*(2)), 57.0 (*C*(α)), 59.6 (*C*(3)), 116.1 (*C*(4′)), 125.8 (*C*(4)), 126.6 (*C*(5)), 127.9, 128.0, 128.0, 128.1, 128.1, 128.3, 129.0, 129.3, 129.3 (*o*,*m*,*p-Ph*), 138.0 (*C*(3′)), 140.0, 140.9, 144.4 (*i-Ph*), 173.4 (*C*(1)); *m*/*z* (ESI$^+$) 468 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{38}NO_2^+$ ([M + H]$^+$) requires 468.2897; found 468.2904.

X-ray crystal structure determination for 87

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation, using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions.

X-ray crystal structure data for **87** [$C_{31}H_{35}NO_2$]: *M* = 453.62, orthorhombic, $P22_12_1$, *a* = 10.7026(7) Å, *b* = 15.0868(9) Å, *c* = 16.8872(8) Å, *V* = 2726.8(3) Å^3, *Z* = 4, *μ* = 0.527 mm^{-1}, colourless prism, crystal dimensions = 0.08 × 0.11 × 0.19 mm^3. A total of 5681 unique reflections were measured for $3 < \theta < 77$ and 5154 reflections were used in the refinement. The final parameters were wR_2 = 0.205 and R_1 = 0.079 [$I > -3.0\sigma(I)$], with Flack enantiopole = −0.7(4).[17] CCDC 982705.†

Methyl (*S*,*S*,*S*,*S*,*E*)-2-(4′-methylpent-1′-en-3′-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 83

Step 1. TMSCl (476 μL, 3.77 mmol) was added dropwise to a solution of **68** (509 mg, 1.26 mmol, >99 : 1 dr) in PhMe (5 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 3.76 mL, 3.76 mmol) was added dropwise at −78 °C and the resultant mixture was stirred at −78 °C for 15 min. The reaction mixture was then stirred at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (200 mL) and 1.0 M aq. HCl (150 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo* to give an 85 : 15 mixture of **73** and **78**. Purification *via* flash column chromatography (gradient elution, 0% → 6% acetone in 30–40 °C petrol) gave **78** as a yellow oil (81 mg, >99 : 1 dr); $[\alpha]_D^{20}$ −9.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2962 (C–H), 1701 (C═O), 1494 (C═C); δ_H (400 MHz, $CDCl_3$) 0.34 (3H, d, *J* 6.7, C(4′)*Me*$_A$), 0.54 (3H, d, *J* 6.7, C(4′)*Me*$_B$), 1.25 (3H, d, *J* 6.8, C(α)*Me*), 1.33–1.43 (1H, m, C(4′)*H*), 1.57 (3H, d, *J* 6.4, C(6)H_3), 1.91–1.97 (1H, m, C(3′)*H*), 2.47 (1H, app t, *J* 7.0, C(2)*H*), 3.34 (1H, dd, *J* 9.4, 7.0, C(3)*H*), 3.47 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 3.69 (1H, d, *J* 14.4, NCH$_A$$H_B$Ph), 3.93 (1H, q, *J* 6.8, C(α)*H*), 4.51–4.56 (1H, m, C(1′)H_A), 4.74–4.77 (1H, m, C(1′)H_B), 5.38–5.47 (2H, m, C(5)*H*, C(2′)*H*), 5.54–5.61 (1H, m, C(4)*H*), 7.03–7.20 (8H, m, *Ph*), 7.27–7.29 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.6 (C(α)*Me*), 17.6 (*C*(4′)*Me*$_A$), 17.9 (*C*(6)), 21.2 (C(4′)*Me*$_B$), 27.6 (*C*(4′)), 49.0 (*C*(3′)), 51.1 (*C*(2)), 51.5 (N*C*H$_2$Ph), 57.3 (*C*(α)), 61.0 (*C*(3)), 117.5 (*C*(1′)), 126.7, 126.8 (*o*,*m*,*p-Ph*), 127.6 (*C*(4)), 128.0, 128.1, 128.3, 128.8 (*o*,*m*,*p-Ph*), 130.2 (*C*(5)), 136.1 (*C*(2′)) 140.6, 143.7 (*i-Ph*), 179.2 (*C*(1)); *m*/*z* (ESI$^+$) 406 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{36}NO_2^+$ ([M + H]$^+$) requires 406.2741; found 406.2748. Further elution (eluent 30–40 °C petrol–acetone, 94 : 6) gave **73** as a yellow oil (382 mg, >99 : 1 dr); $[\alpha]_D^{20}$ +5.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2960 (C–H), 1702 (C═O), 1495 (C═C); δ_H (400 MHz, $CDCl_3$) 0.57 (3H, d, *J* 6.7, C(4′)*Me*$_A$), 0.64 (3H, d, *J* 6.7, C(4′)*Me*$_B$), 1.40 (1H, app td, *J* 10.0, 1.7, C(3′)*H*), 1.48 (3H, d, *J* 7.1, C(α)*Me*), 1.83 (3H, dd, *J* 6.5, 1.8, C(6)H_3), 2.14–2.24 (C(2)*H*, C(4′)*H*), 3.67 (1H, d, *J* 13.4, NC$H_A$$H_B$Ph), 3.74–3.79 (1H, m, C(3)*H*), 3.78 (1H, d, *J* 13.4, NCH$_A$$H_B$Ph), 3.91 (1H, q, *J* 7.1, C(α)*H*), 4.59 (1H, dd, *J* 17.3, 2.5, C(1′)H_A), 4.79 (1H, dd, *J* 10.0, 2.5, C(1′)H_B), 5.33 (1H, app ddd, *J* 15.5, 9.6, 1.8, C(4)*H*), 5.52 (1H, ddd, *J* 17.3, 10.2, 10.0, C(2′)*H*), 5.66 (1H, dq, *J* 15.5, 6.5, C(5)*H*), 7.15–7.27 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.9 (C(α)*Me*), 18.3 (*C*(6)), 20.6, 22.1 (C(4′)*Me*$_2$), 28.4 (*C*(4′)), 43.9 (*C*(2)), 51.4 (N*C*H$_2$Ph), 52.2 (*C*(3′)), 60.6 (*C*(α)), 60.6 (*C*(3)), 117.0 (*C*(1′)), 125.7 (*C*(4)), 128.0, 128.1, 128.1, 128.7, 128.7, 129.6 (*o*,*m*,*p-Ph*), 134.2 (*C*(5)), 135.1 (*i-Ph*), 138.5 (*C*(2′)), 140.3 (*i-Ph*), 174.0 (*C*(1)); *m*/*z* (ESI$^+$) 406 ([M + H]$^+$,

100%); HRMS (ESI$^+$) $C_{27}H_{36}NO_2^+$ ([M + H]$^+$) requires 406.2741; found 406.2747.

Step 2 (for 73). A solution of **73** (382 mg, >99 : 1 dr) in MeCN (3.9 mL) was treated sequentially with DBU (281 μL, 1.88 mmol) and MeI (129 μL, 2.07 mmol) at rt. The reaction mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 2.0 M aq. HCl (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts were then washed sequentially with satd aq. $NaHCO_3$ (150 mL) and brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 98 : 2) gave **83** as a colourless oil (272 mg, 52% from **68**, >99 : 1 dr); $[\alpha]_D^{20}$ +1.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2958 (C–H), 1737 (C═O), 1495 (C═C); δ_H (400 MHz, $CDCl_3$) 0.65 (3H, d, *J* 6.6, C(4′)*Me*$_A$), 0.80 (3H, d, *J* 6.6, C(4′)*Me*$_B$), 1.22–1.29 (1H, m, C(4′)*H*), 1.31 (3H, d, *J* 6.9, C(α)*Me*), 1.58 (1H, app td, *J* 9.5, 3.8, C(3′)*H*), 1.69 (3H, dd, *J* 6.4, 1.2, C(6)H_3), 2.83 (1H, dd, *J* 11.4, 3.8, C(2)*H*), 3.34 (3H, s, O*Me*), 3.42–3.48 (1H, m, C(3)*H*), 3.48 (1H, d, *J* 13.9, NCH_AH_BPh), 3.71 (1H, d, *J* 13.9, NCH$_A H_B$Ph), 4.03 (1H, q, *J* 6.9, C(α)*H*), 4.58 (1H, dd, *J* 17.1, 2.5, C(1′)H_A), 4.80 (1H, dd, *J* 10.2, 2.5, C(1′)H_B), 5.17–5.24 (1H, m, C(4)*H*), 5.31–5.40 (1H, m, C(5)*H*), 5.51 (1H, dt, *J* 17.1, 10.2, C(2′)*H*), 7.05–7.12 (2H, m, *Ph*), 7.13–7.23 (8H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.2 (C(α)*Me*), 18.1 (*C*(6)), 21.0 (C(4′)*Me*$_B$), 21.3 (C(4′)*Me*$_A$), 30.0 (*C*(4′)), 49.6 (*C*(2)), 50.5 (N*C*H$_2$Ph), 50.6 (O*Me*), 51.2 (*C*(3′)), 56.5 (*C*(α)), 60.7 (*C*(3)), 116.8 (*C*(1′)), 126.1, 126.4, 127.6, 127.8, 127.9, 129.0 (*o*,*m*,*p*-*Ph*), 128.1 (*C*(4)), 130.2 (*C*(5)), 136.9 (*C*(2′)), 140.3, 144.8 (*i*-*Ph*), 173.3 (*C*(1)); *m*/*z* (ESI$^+$) 420 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{38}NO_2^+$ ([M + H]$^+$) requires 420.2897; found 420.2900.

Step 2 (for 78). A solution of **78** (72 mg, >99 : 1 dr) in MeCN (0.7 mL) was treated sequentially with DBU (53 μL, 0.36 mmol) and MeI (24 μL, 0.39 mmol) at rt. The reaction mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 2.0 M aq. HCl (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then washed sequentially with satd aq. $NaHCO_3$ (40 mL) and brine (40 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 98 : 2) gave **88** as a white solid (44 mg, 7% from **68**, >99 : 1 dr); $[\alpha]_D^{20}$ −27.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2960 (C–H), 1731 (C═O), 1494 (C═C); δ_H (400 MHz, $CDCl_3$) 0.30 (3H, d, *J* 6.7, C(4′)*Me*$_A$), 0.57 (3H, d, *J* 6.7, C(4′)*Me*$_B$), 1.28 (3H, d, *J* 6.7, C(α)*Me*), 1.34 (1H, dd, *J* 11.9, 6.7, C(4′)*H*), 1.65 (3H, dd, *J* 6.4, 1.5, C(6)H_3), 2.00 (1H, ddd, *J* 9.9, 7.6, 5.2, C(3′)*H*), 2.56 (1H, app t, *J* 7.6, C(2)*H*), 3.36 (1H, dd, *J* 9.9, 7.6, C(3)*H*), 3.44 (3H, s, O*Me*), 3.56 (1H, d, *J* 14.2, NCH_AH_BPh), 3.69 (1H, d, *J* 14.2, NCH$_A H_B$Ph), 3.90 (1H, q, *J* 6.7, C(α)*H*), 4.61 (1H, dd, *J* 17.1, 2.3, C(1′)H_A), 4.84 (1H, dd, *J* 9.9, 2.3, C(1′)H_B), 5.40–5.52 (2H, m, C(5)*H*, C(2′)*H*), 5.68–5.75 (1H, m, C(4)*H*), 7.10–7.13 (2H, m, *Ph*), 7.17–7.27 (6H, m, *Ph*), 7.33–7.35 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.2 (C(α)*Me*), 17.2 (C(4′)*Me*$_A$), 18.1 (*C*(6)), 21.2 (C(4′)*Me*$_B$), 27.5 (*C*(4′)), 49.3 (*C*(3′)), 50.8 (O*Me*), 51.1 (N*C*H$_2$Ph), 52.1 (*C*(2)), 57.2 (*C*(α)), 59.8 (*C*(3)), 117.4 (*C*(1′)), 126.6, 126.6 (*o*,*m*,*p*-*Ph*), 127.9 (*C*(4)), 128.0, 128.1, 128.2, 128.8 (*o*,*m*,*p*-*Ph*), 129.5 (*C*(5)), 136.1 (*C*(2′)), 141.3, 144.5 (*i*-*Ph*), 174.5 (*C*(1)); *m*/*z* (ESI$^+$) 420 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{38}NO_2^+$ ([M + H]$^+$) requires 420.2897; found 420.2898.

Methyl (*S*,*S*,*S*,*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-ethylcyclopent-3-ene-1-carboxylate 91

Grubbs I catalyst (292 mg, 0.36 mmol) was added to a degassed solution of **81** (360 mg, 0.89 mmol, >99 : 1 dr) in CH_2Cl_2 (36 mL) at rt and the resultant mixture was heated at 40 °C for 24 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 98 : 2) gave **91** as a colourless oil (200 mg, 62%, >99 : 1 dr); $[\alpha]_D^{20}$ +198.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2965 (C–H), 1729 (C═O), 1493 (C═C); δ_H (400 MHz, $CDCl_3$) 0.75 (3H, t, *J* 7.3, C(2′)H_3), 0.97–1.08 (1H, m, C(1′)H_A), 1.18–1.29 (1H, m, C(1′)H_B), 1.27 (3H, d, *J* 7.0, C(α)*Me*), 2.67–2.75 (1H, m, C(5)*H*), 2.89 (1H, dd, *J* 9.4, 6.0, C(1)*H*), 3.37 (3H, s, O*Me*), 3.58 (1H, d, *J* 15.4, NCH_AH_BPh), 3.62 (1H, d, *J* 15.4, NCH$_A H_B$Ph), 3.77 (1H, q, *J* 7.0, C(α)*H*), 4.35–4.38 (1H, m, C(2)*H*), 5.64–5.66 (1H, m, C(4)*H*), 5.70–5.73 (1H, m, C(3)*H*), 7.09–7.25 (8H, m, *Ph*), 7.31–7.33 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.5 (*C*(2′)), 16.3 (C(α)*Me*), 24.5 (*C*(1′), 48.4 (*C*(5)), 50.1 (N*C*H$_2$Ph), 50.6 (*C*(1)), 51.1 (O*Me*), 57.8 (*C*(α)), 67.5 (*C*(2)), 126.5, 126.5, 127.7, 127.8, 128.1, 128.1 (*o*,*m*,*p*-*Ph*), 132.5 (*C*(4)), 134.8 (*C*(3)), 141.7, 144.0 (*i*-*Ph*), 174.1 (*C*O$_2$Me); *m*/*z* (ESI$^+$) 364 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{30}NO_2^+$ ([M + H]$^+$) requires 364.2271; found 364.2275.

Methyl (*S*,*S*,*S*,*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-benzylcyclopent-3-ene-1-carboxylate 92

Grubbs I catalyst (282 mg, 0.34 mmol) was added to a degassed solution of **82** (400 mg, 0.86 mmol, >99 : 1 dr) in CH_2Cl_2 (40 mL) at rt and the resultant mixture was heated at 40 °C for 48 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 98 : 2) gave **92** as a colourless oil (349 mg, 96%, >99 : 1 dr); $[\alpha]_D^{20}$ +185.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2946 (C–H), 1730 (C═O), 1494 (C═C); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.9, C(α)*Me*), 2.23 (1H, dd, *J* 13.2, 10.6, C(1′)H_A), 2.58 (1H, dd, *J* 13.2, 5.6, C(1′)H_B), 2.95 (1H, dd, *J* 9.4, 5.6, C(1)*H*), 3.11–3.19 (1H, m, C(5)*H*), 3.34 (3H, s, O*Me*), 3.60 (2H, app s, NCH_2Ph), 3.78 (1H, q, *J* 6.9, C(α)*H*), 4.43–4.46 (1H, m, C(2)*H*) 5.45 (1H, app dt, *J* 5.6, 2.1, C(4)*H*), 5.66 (1H, app dt, *J* 5.6, 2.1, C(3)*H*), 6.98–7.01 (2H, m, *Ph*), 7.05–7.25 (11H, m, *Ph*), 7.30–7.33 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.2 (C(α)*Me*), 37.7 (*C*(1′)), 47.9 (*C*(5)), 50.1 (N*C*H$_2$Ph), 50.3 (*C*(1)), 51.2 (O*Me*), 57.7 (*C*(α)), 67.8 (*C*(2)), 126.0, 126.6, 126.6, 127.7, 127.9, 128.1, 128.1, 128.2, 128.8 (*o*,*m*,*p*-*Ph*), 132.6 (*C*(3)), 134.6 (*C*(4)), 140.1, 141.6, 144.0 (*i*-*Ph*), 174.0 (*C*O$_2$Me); *m*/*z* (ESI$^+$) 426 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{32}NO_2^+$ ([M + H]$^+$) requires 426.2428; found 426.2439.

Methyl (*S*,*S*,*S*,*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-isopropylcyclopent-3-ene-1-carboxylate 93

Grubbs I catalyst (197 mg, 0.24 mmol) was added to a degassed solution of **83** (251 mg, 0.60 mmol, >99 : 1 dr) in CH_2Cl_2 (25 mL) at rt and the resultant mixture was heated at 40 °C for 48 h then concentrated *in vacuo*. The residue was dissolved in degassed CH_2Cl_2 (25 mL) and Grubbs I catalyst (197 mg, 0.24 mmol) was added to the resultant solution. The reaction mixture was heated at 40 °C for 48 h then concentrated *in vacuo.* Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 98 : 2) gave **93** as a colourless oil (85 mg, 38%, >99 : 1 dr); $[\alpha]_D^{20}$ +204.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2958 (C–H), 1734 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 0.68 (3H, d, *J* 6.6, C(1′)*Me*$_A$), 0.75 (3H, d, *J* 6.6, C(1′)*Me*$_B$), 1.26 (3H, d, *J* 6.9, C(α)*Me*), 1.55–1.63 (1H, m, C(1′)*H*), 2.65 (1H, app t, *J* 8.0, C(5)*H*), 2.96 (1H, dd, *J* 9.2, 5.9, C(1)*H*), 3.38 (3H, s, O*Me*), 3.62 (2H, app s, NCH_2Ph), 3.81 (1H, q, *J* 6.9, C(α)*H*), 4.28 (1H, d, *J* 5.9, C(2)*H*), 5.68–5.71 (2H, m, C(3)*H*, C(4)*H*), 7.10–7.15 (2H, m, *Ph*), 7.18–7.25 (6H, m, *Ph*), 7.31–7.33 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.5 (C(α)*Me*), 20.0 (C(1′)*Me*$_A$), 22.7 (C(1′)*Me*$_B$), 28.8 (*C*(1′)), 50.0 (N*C*H_2Ph), 50.5 (*C*(1)), 51.2 (O*Me*), 54.1 (*C*(5)), 58.2 (*C*(α)), 68.3 (*C*(2)), 126.5, 127.7, 127.8, 128.0, 128.1 (*o*,*m*,*p*-*Ph*), 133.1 (*C*(3)), 133.4 (*C*(4)), 141.9, 144.3 (*i*-*Ph*), 174.4 (*C*O_2Me); *m*/*z* (ESI$^+$) 378 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{32}NO_2^+$ ([M + H]$^+$) requires 378.2428; found 378.2437.

Methyl (*S*,*S*,*S*)-2-amino-5-ethylcyclopentane-1-carboxylate 96

$Pd(OH)_2$/C (87 mg, 50% w/w) was added to a degassed solution of **91** (173 mg, 0.48 mmol, >99 : 1 dr) in MeOH (12 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (15 mL) and the resultant solution was washed with satd aq. $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$–MeOH, 94 : 6) gave **96** as a white solid (55 mg, 67%, >99 : 1 dr); mp 64–66 °C; $[\alpha]_D^{20}$ +15.7 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3344 (N–H), 2959, 2932 (C–H), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 0.80 (3H, t, *J* 7.3, C(2′)*H*$_3$), 1.01–1.12 (1H, m, C(1′)*H*$_A$), 1.23–1.39 (3H, m, C(3)*H*$_A$, C(4)*H*$_A$, C(1′)*H*$_B$), 1.81–1.91 (1H, m, C(4)*H*$_B$), 2.00–2.09 (3H, m, C(3)*H*$_B$, N*H*$_2$), 2.13–2.23 (1H, m, C(5)*H*), 2.53 (1H, dd, *J* 9.1, 7.1, C(1)*H*), 3.54–3.65 (1H, m, C(2)*H*), 3.62 (3H, s, O*Me*); δ_C (100 MHz, $CDCl_3$) 12.4 (*C*(2′)), 24.7 (*C*(1′)), 29.2 (*C*(4)), 34.0 (*C*(3)), 42.9 (*C*(5)), 51.2 (O*Me*), 54.9 (*C*(2)), 57.4 (*C*(1)), 174.5 (*C*O_2Me); *m*/*z* (ESI$^+$) 172 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_9H_{18}NO_2^+$ ([M + H]$^+$) requires 172.1332; found 172.1336.

X-ray crystal structure determination for 96·HCl

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation, using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions.

X-ray crystal structure data for **96**·HCl [$C_9H_{18}ClNO_2$]: *M* = 207.70, monoclinic, $P2_1$, *a* = 5.4210(1) Å, *b* = 8.9375(3) Å, *c* = 11.4409(3) Å, β = 101.8270(12)°, *V* = 542.55(3) Å^3, *Z* = 2, μ = 0.323 mm^{-1}, colourless block, crystal dimensions = 0.21 × 0.23 × 0.24 mm^3. A total of 2115 unique reflections were measured for 5 < θ < 27 and 2115 reflections were used in the refinement. The final parameters were wR_2 = 0.056 and R_1 = 0.025 [$I > -3.0\sigma(I)$], with Flack enantiopole = 0.03(5).[17] CCDC 982706.†

Methyl (1*S*,2*S*,5*R*)-2-amino-5-benzylcyclopentane-1-carboxylate 97

$Pd(OH)_2$/C (99 mg, 50% w/w by substrate) was added to a degassed solution of **92** (197 mg, 0.46 mmol, >99 : 1 dr) in MeOH (14 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (15 mL) and the resultant solution was washed with satd aq. $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$–MeOH, 98 : 2) gave **97** as a white solid (74 mg, 69%, >99 : 1 dr); mp 65–67 °C; $[\alpha]_D^{20}$ +32.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3365 (N–H), 2950 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.18–1.29 (1H, m, C(3)*H*$_A$), 1.36–1.45 (3H, m, C(4)*H*$_A$, N*H*$_2$), 1.64–1.72 (1H, m, C(4)*H*$_B$), 2.02–2.09 (1H, m, C(3)*H*$_B$), 2.26–2.33 (1H, m, C(1′)*H*$_A$), 2.52–2.58 (1H, m, C(1)*H*), 2.59–2.68 (2H, m, C(1′)*H*$_B$, C(5)*H*), 3.59 (3H, s, O*Me*), 3.62–3.68 (1H, m, C(2)*H*), 7.06–7.12 (3H, m, *Ph*), 7.17–7.21 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 29.4 (*C*(4)), 34.1 (*C*(3)), 37.7 (*C*(1′)), 42.5 (*C*(5)), 51.3 (O*Me*), 55.1 (*C*(2)), 57.5 (*C*(1)), 125.9, 128.2, 128.8 (*o*,*m*,*p*-*Ph*), 140.5 (*i*-*Ph*), 174.4 (*C*O_2Me); *m*/*z* (ESI$^+$) 234 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{20}NO_2^+$ ([M + H]$^+$) requires 234.1489; found 234.1495.

Methyl (1*S*,2*S*,5*R*)-2-amino-5-isopropylcyclopentane-1-carboxylate 98

$Pd(OH)_2$/C (43 mg, 50% w/w by substrate) was added to a degassed solution of **93** (85 mg, 0.23 mmol, >99 : 1 dr) in MeOH (6 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (15 mL) and the resultant solution was washed with satd aq. $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$–MeOH, 99 : 1) gave **98** as a colourless oil (17 mg, 40%, >99 : 1 dr); $[\alpha]_D^{20}$ +16.1 (*c* 0.2 in $CHCl_3$); ν_{max} (ATR) 3392 (N–H), 2956 (C–H), 1721 (C=O), 1477; δ_H (700 MHz, $CDCl_3$) 0.81 (3H, d, *J* 3.6, C(1′)*Me*$_A$), 0.85 (3H, d, *J* 3.6, C(1′)*Me*$_B$), 1.24–1.30 (1H, m, C(3)*H*$_A$), 1.44–1.53 (2H, m, C(4)*H*$_A$, C(1′)*H*), 1.71 (2H, br s, N*H*$_2$), 1.79–1.83 (1H, m, C(4)*H*$_B$), 1.93–1.98 (1H,

m, C(5)*H*), 2.15–2.19 (1H, m, C(3)H_B), 2.59 (1H, dd, *J* 8.1, 3.2, C(1)*H*), 3.53–3.55 (1H, m, C(2)*H*), 3.59 (3H, s, O*Me*); δ_C (176 MHz, $CDCl_3$) 21.5 (C(1′)*Me*$_A$), 22.3 (C(1′)*Me*$_B$), 28.5 (*C*(4)), 29.7 (*C*(1′)), 34.8 (*C*(3)), 49.9 (*C*(5)), 51.2 (O*Me*), 56.6 (*C*(2)), 56.8 (*C*(1)), 175.0 (*C*O_2Me); *m*/*z* (ESI$^+$) 186 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{20}NO_2^+$ ([M + H]$^+$) requires 186.1489; found 186.1493.

(*S*,*S*,*S*)-2-Amino-5-ethylcyclopentane-1-carboxylic acid 101

A solution of **96** (35 mg, 0.20 mmol, >99 : 1 dr) in 6.0 M aq. HCl (5 mL) was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in H_2O (2 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq. NH_4OH) to give **101** as a white solid (27 mg, 85%, >99 : 1 dr); mp 202–204 °C; $[\alpha]_D^{20}$ +73.3 (*c* 1.0 in H_2O); ν_{max} (ATR) 3399 (O–H, N–H), 2960 (C–H), 1629 (C═O), 1570; δ_H (400 MHz, D_2O) 0.75 (3H, t, *J* 7.3, C(2′)H_3), 0.92–1.03 (1H, m, C(1′)H_A), 1.23–1.33 (1H, m, C(1′)H_B), 1.35–1.43 (1H, m, C(4)H_A), 1.44–1.53 (1H, m, C(3)H_A), 1.81–1.89 (1H, m, C(4)H_B), 2.08–2.17 (2H, m, C(3)H_B, C(5)*H*), 2.65 (1H, dd, *J* 8.8, 7.7, C(1)*H*), 3.71 (1H, app q, *J* 7.7, C(2)*H*); δ_C (100 MHz, D_2O) 11.8 (*C*(2′)), 23.5 (*C*(1′)), 28.2 (*C*(4)), 28.9 (*C*(3)), 42.6 (*C*(5)), 53.8 (*C*(2)), 55.8 (*C*(1)), 179.5 (*C*O_2H); *m*/*z* (ESI$^+$) 158 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_8H_{16}NO_2^+$ ([M + H]$^+$) requires 158.1176; found 158.1173.

(1*S*,2*S*,5*R*)-2-Amino-5-benzylcyclopentane-1-carboxylic acid 102

A solution of **97** (28 mg, 0.12 mmol, >99 : 1 dr) in 6.0 M aq. HCl (4 mL) was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in H_2O (2 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq. NH_4OH) to give **102** as a white solid (26 mg, quant, >99 : 1 dr); mp 213–215 °C; $[\alpha]_D^{20}$ +4.7 (*c* 1.0 in H_2O); ν_{max} (ATR) 3363 (N–H), 3045 (C–H), 1571 (C═O), 1402; δ_H (400 MHz, D_2O) 1.35–1.45 (1H, m, C(4)H_A), 1.45–1.54 (1H, m, C(3)H_A), 1.58–1.66 (1H, m, C(4)H_B), 2.15–2.24 (2H, m, C(3)H_B, C(1′)H_A), 2.52–2.61 (1H, m, C(5)*H*), 2.72 (1H, dd, *J* 13.2, 4.0, C(1′)H_B), 2.77 (1H, app t, *J* 7.9, C(1)*H*), 3.83 (1H, app q, *J* 7.9, C(2)*H*), 7.15–7.21 (3H, m, *Ph*), 7.24–7.28 (2H, m, *Ph*); δ_C (176 MHz, D_2O) 27.8 (*C*(4)), 28.6 (*C*(3)), 36.2 (*C*(1′)), 42.5 (*C*(5)), 53.8 (*C*(2)), 55.8 (*C*(1)), 126.2, 128.6, 129.1 (*o*,*m*,*p*-*Ph*), 141.1 (*i*-*Ph*), 179.0 (*C*O_2H); *m*/*z* (ESI$^+$) 220 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{18}NO_2^+$ ([M + H]$^+$) requires 220.1332; found 220.1337.

(1*S*,2*S*,5*R*)-2-Amino-5-isopropylcyclopentane-1-carboxylic acid 103

A solution of **98** (20 mg, 0.11 mmol, >99 : 1 dr) in 6.0 M aq. HCl (2.8 mL) was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in H_2O (2 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq. NH_4OH) to give **103** as a white solid (17 mg, 94%, >99 : 1 dr); mp 200–204 °C (dec.); $[\alpha]_D^{20}$ +6.0 (*c* 0.2 in H_2O); ν_{max} (ATR) 3419 (N–H), 2953 (C–H), 1634 (C═O), 1510; δ_H (700 MHz, D_2O) 0.79 (3H, d, *J* 6.6, C(1′)*Me*$_A$), 0.87 (3H, d, *J* 6.6, C(1′)*Me*$_B$), 1.48–1.58 (3H, m, C(3)H_A, C(4)H_A, C(1′)*H*), 1.83–1.87 (1H, m, C(4)H_B), 1.92–1.97 (1H, m, C(5)*H*), 2.21–2.25 (1H, m, C(3)H_B), 2.73 (1H, dd, *J* 8.6, 4.4, C(1)*H*), 3.75 (1H, app td, *J* 7.3, 4.4, C(2)*H*); δ_C (176 MHz, D_2O) 20.3 (C(1′)*Me*$_A$), 21.8 (C(1′)*Me*$_B$), 27.4 (*C*(4)), 29.1 (*C*(1′)), 30.1 (*C*(3)), 49.4 (*C*(5)), 55.0 (*C*(1)), 55.2 (*C*(2)), 180.3 (*C*O_2H); *m*/*z* (ESI$^+$) 172 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_9H_{18}NO_2^+$ ([M + H]$^+$) requires 172.1332; found 172.1335.

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14 Crystallographic data (excluding structure factors) for compounds **16**, **18–20**, **25**, **29**, **37**, **86**·HBF_4, **87** and **96**·HCl have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 982697–982706, respectively.

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