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Asymmetric synthesis of *Sedum* alkaloids via lithium amide conjugate addition

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ABSTRACT

Conjugate addition of lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amide or lithium (*R*)-*N*-but-3-enyl-*N*-(α-methylbenzyl)amide to an alkyl hexa-2,4-dienoate or alkyl hepta-2,6-dienoate, followed by ring-closing metathesis of the olefin functionalities within the resultant β-amino ester, generates a range of diastereoisomerically pure azacycles in good yield. These homochiral templates are readily transformed to a range of piperidine alkaloids of the *Sedum* family, and the corresponding five-, seven- and eight-membered ring homologues.

1. Introduction

The *Sedum* alkaloids have been isolated from some 60 species of the genus *Sedum*.[1] The most commonly occurring members of this alkaloid family are 2-substituted piperidines,[2] e.g., norsedamine **1**, allosedridine **2**, sedamine **3** and allosedamine **4**, which differ in the presence or absence of a methyl group on the piperidine nitrogen atom, the relative stereochemistry of the amino-alcohol moiety and the identity of the alcohol-containing side chain. Pyrrolidine members of the family have also been isolated, e.g., pyrrolsedamine **5**,[1] pseudohygroline **6**[3] and pyrrolallosedamine **7**,[1] along with the less commonly occurring ketone derivatives, e.g., pelletierine **8** (Fig. 1). Sedamine **3** is perhaps the best known *Sedum* alkaloid: it was the first member of the family to be isolated from the *Sedum acre*.[4] Both enantiomers have subsequently been found in many other *Sedum* species,[1] and the C(1)-epimeric compound allosedamine **4** has been isolated from the Indian tobacco plant *Lobelia inflate*.[5] Sedamine **3** and allosedamine **4** have been shown to exhibit interesting and desirable biological properties: sedamine **3** may be of use for cognitive disorders[6] and allosedamine **4** is useful for the treatment of various respiratory illnesses, including asthma, bronchitis and pneumonia.[7] The synthesis of a variety of *Sedum* alkaloids, both in racemic and homochiral form, has been actively pursued over the past 50 years: strategies based upon manipulation of chiral pool starting materials, as well as asymmetric methods, have been reported.[8]

Previous investigations from this laboratory have shown extensively that the conjugate addition of a homochiral, secondary lithium amide derived from α-methylbenzylamine to an

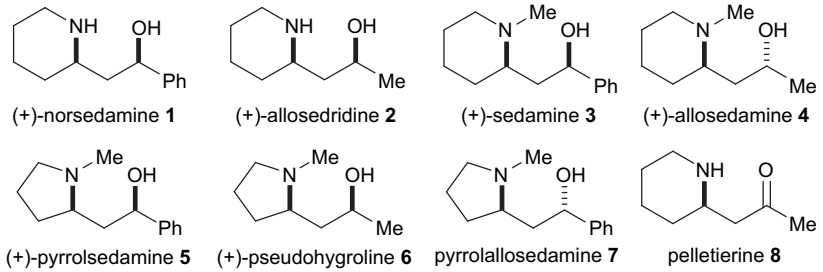

Figure 1. Structures of representative *Sedum* alkaloids **1**–**8**.

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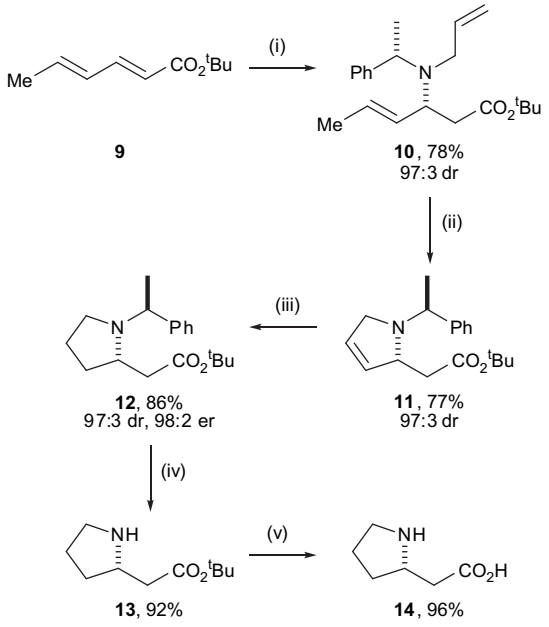
α,β-unsaturated ester represents an efficient strategy for the synthesis of acyclic and cyclic β-amino esters and derivatives.[9] We have reported that the conjugate addition of lithium (*S*)-*N*-allyl-*N*-(α-methylbenzyl)amide[10] to a suitable α,β-unsaturated ester can be coupled with subsequent ring-closing metathesis to generate homochiral pyrrolidine and piperidine scaffolds, as exemplified through the synthesis of homoproline **14** (Scheme 1).[11] Herein the further application of this lithium amide conjugate addition/ring-closing metathesis protocol to facilitate a general strategy towards the asymmetric synthesis of a range of *Sedum* alkaloids and derivatives employing the highly diastereoselective conjugate addition of lithium (*R*)-*N*-but-3-enyl-*N*-(α-methylbenzyl)amide is delineated.

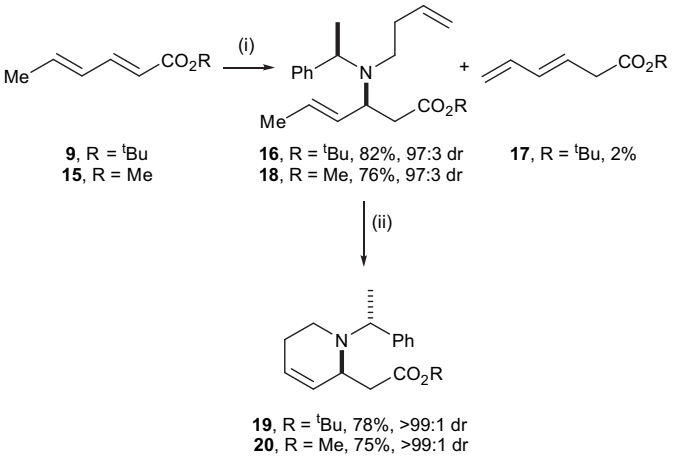


Scheme 1. *Reagents and conditions*: (i) lithium (*S*)-*N*-allyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h; (ii) Grubbs I (4 mol %), CH_2Cl_2, 30 °C, 6 h; (iii) H_2 (2 atm), $RhCl(PPh_3)_3$ (5 mol %), C_6H_6, rt, 12 h; (iv) H_2 (5 atm), $Pd(OH)_2/C$ (50% w/w), MeOH, rt, 12 h; (v) TFA, CH_2Cl_2, rt, 12 h, then HCl (6 M, aq), then Dowex 50WX8-200.

2. Results and discussion

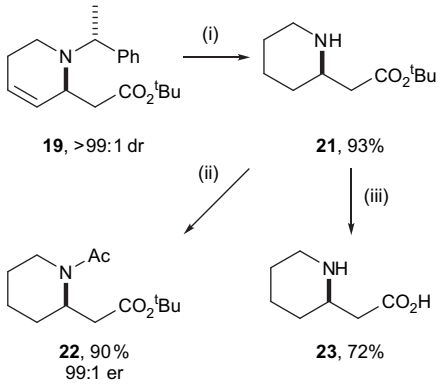
2.1. Asymmetric synthesis of cyclic β-amino acids

Conjugate addition of lithium (*R*)-*N*-but-3-enyl-*N*-(α-methylbenzyl)amide[12] to *tert*-butyl and methyl hexa-2,4-dienoate **9** and **15** gave the corresponding β-amino esters (3*S*,α*R*)-**16** and (3*S*,α*R*)-**17** in 97:3 dr in each case.[13] Conjugate addition to **9** was accompanied by small amounts of competing ε-deprotonation (6%) resulting in the formation of β,γ,δ,ε-unsaturated ester **17** upon protonation.[14] Chromatography furnished the desired β-amino ester **16** in 82% yield and 97:3 dr, and β,γ,δ,ε-unsaturated ester **17** in 2% yield. Addition to **15** also resulted in the formation of several minor, unidentified side-products, with chromatographic purification giving β-amino ester **18** in 76% yield and 97:3 dr. The absolute (3*S*)-stereochemistry within β-amino esters **16** and **18** was assigned from the known (*R*)-configuration of the α-methylbenzyl stereocentre by reference to the transition state mnemonic that was developed by us to rationalise the exceptional facial bias of this class of lithium amide.[15] Ring-closing metathesis of the olefin functionalities within β-amino esters **16** and **18** was achieved upon treatment with Grubbs I, followed by removal of the spent catalyst with tris(hydroxymethyl)phosphine[16] and purification by chromatography giving tetrahydropyridines **19** and **20** in 78 and 75% yield, respectively, and in >99:1 dr in each case (Scheme 2).



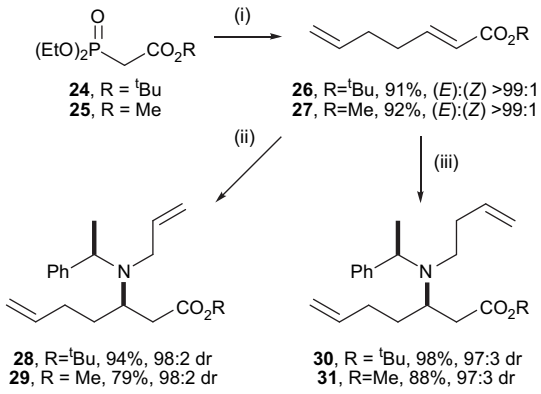
Scheme 2. *Reagents and conditions*: (i) lithium (*R*)-*N*-but-3-enyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h; (ii) Grubbs I (4 mol %), CH_2Cl_2, rt, 12 h, then $P(CH_2OH)_3$, Et_3N, SiO_2, CH_2Cl_2, rt, 2 h; (iii) H_2 (4 atm), $RhCl(PPh_3)_3$ (5 mol %), EtOAc, rt, 12 h.

Deprotection of tetrahydropyridine **19** to the corresponding cyclic β-amino acid, homopipecolic acid **23**, was next probed. Tandem hydrogenation/hydrogenolysis of **19** gave piperidine **21** in 93% isolated yield, which was shown to be of 99:1 er by chiral GC analysis of the corresponding *N*-acetate **22** and comparison with an authentic racemic standard.[17] Hydrolysis of the *tert*-butyl ester within **21** was achieved upon treatment with TFA, giving, after ion-exchange chromatography, homopipecolic acid **23**[11,18] in 72% yield, 43% overall from *tert*-butyl hexa-2,4-dienoate **9**. The spectroscopic properties of **23** were in excellent agreement with those previously reported {$[\alpha]_D^{24}$ −23.4 (*c* 0.5 in H_2O); lit.[11] for enantiomer $[\alpha]_D^{26}$ +24.0 (*c* 0.9 in H_2O)} (Scheme 3).



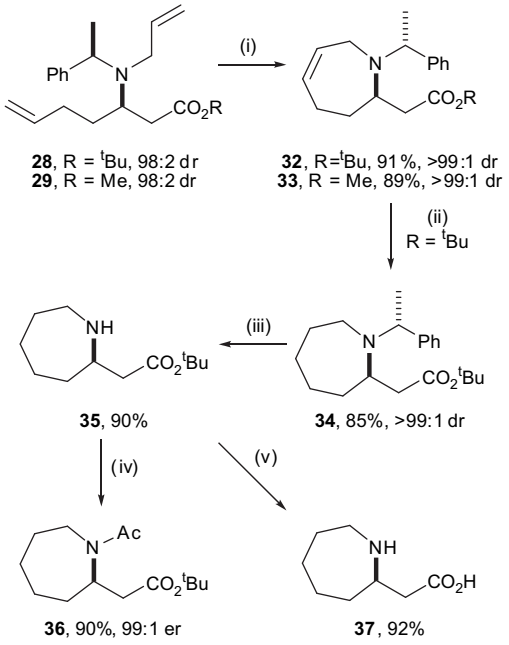
Scheme 3. *Reagents and conditions*: (i) H_2 (5 atm), $Pd(OH)_2/C$ (50% w/w), EtOAc, rt, 12 h; (ii) Ac_2O, DMAP, pyridine, rt, 12 h; (iii) TFA, CH_2Cl_2, rt, 12 h, then HCl (6 M, aq), then Dowex 50WX8-200.

Having demonstrated that this protocol represents an efficient procedure for the synthesis of functionalised piperidine scaffolds, application to the corresponding seven- and eight-membered skeletons was investigated. Olefination of 4-pentenal upon treatment with either *tert*-butyl or methyl diethylphosphonoacetate **24** and **25** and MeMgBr[19] gave the corresponding (*E*)-α,β-unsaturated esters **26** and **27** in good yields and with total control of the geometry of the olefin [(*E*):(*Z*) >99:1]. Subsequent conjugate additions of lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amide and lithium (*R*)-*N*-but-3-enyl-*N*-(α-methylbenzyl)amide to α,β-unsaturated esters **26** and **27** proceeded, in each case, to give the corresponding (3*R*,α*R*)-β-amino esters **28**–**31** in ≥97:3 dr, which were isolated in good yield. The absolute stereochemistry within β-amino esters **28**–**31** was assigned by reference to the transition state mnemonic previously described[15] (Scheme 4).



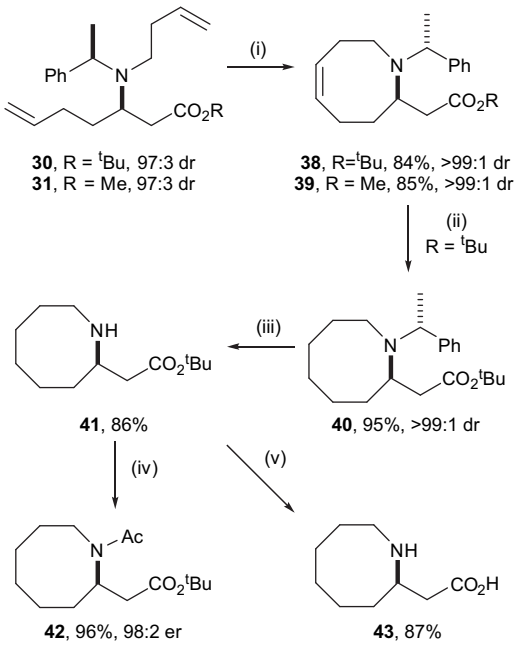
Scheme 4. *Reagents and conditions*: (i) MeMgBr, THF, −78 °C, then 4-pentenal, THF, −78 °C to rt, 4 h; (ii) lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h; (iii) lithium (*R*)-*N*-but-3-enyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h.

The ring-closing metathesis reactions of **28** and **29** required treatment with 8 mol % Grubbs I over 12 h at room temperature to achieve quantitative conversion to the corresponding tetrahydroazepines **32** and **33**, which were isolated in good yield and >99:1 dr. Attempted tandem hydrogenation/hydrogenolysis of **32** upon treatment with Pearlman's catalyst under a hydrogen atmosphere resulted in the formation of a complex mixture of products from which the desired azepane **35** was isolated in only 34% yield. A two-step protocol was therefore implemented. Treatment of tetrahydroazepine **32** with Wilkinson's catalyst in EtOAc gave azepane **34** in 85% yield and >99:1 dr; subsequent hydrogenolysis mediated by Pearlman's catalyst gave the desired azepane **35** in 90% yield, which was shown to be of 99:1 er by chiral GC analysis of the corresponding *N*-acetate **36** and comparison with an authentic racemic standard.[17] Hydrolysis of the *tert*-butyl ester within **35** and ion-exchange chromatography gave cyclic β-amino acid **37** in 92% yield (Scheme 5).



Scheme 5. *Reagents and conditions*: (i) Grubbs I (8 mol %), CH_2Cl_2, rt, 12 h, then $P(CH_2OH)_3$, Et_3N, SiO_2, CH_2Cl_2, rt, 2 h; (ii) H_2 (4 atm), $RhCl(PPh_3)_3$ (5 mol %), EtOAc, rt, 12 h; (iii) H_2 (5 atm), $Pd(OH)_2/C$ (50% w/w), EtOAc, rt, 12 h; (iv) Ac_2O, DMAP, pyridine, rt, 12 h; (v) TFA, CH_2Cl_2, rt, 12 h, then HCl (6 M, aq), then Dowex 50WX8-200.

In the eight-membered ring series, formation of hexahydroazocines **38** and **39** from the β-amino ester precursors **30** and **31** was achieved after treatment with 8 mol % Grubbs I over 12 h at 30 °C, with **38** and **39** being isolated in good yield and >99:1 dr. Hydrogenation of hexahydroazocine **38** promoted by Wilkinson's catalyst was followed by hydrogenolysis in the presence of Pearlman's catalyst, giving azocane **41** in 82% yield over two steps, which was shown to be of 98:2 er by chiral GC analysis of the corresponding *N*-acetate **42** and comparison with an authentic racemic standard.[17] Hydrolysis of the *tert*-butyl ester and ion-exchange chromatography gave cyclic β-amino acid **43** in 87% yield (Scheme 6).

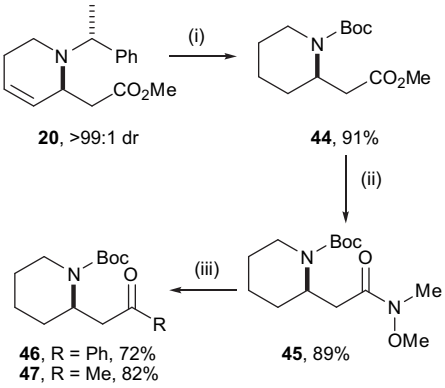


Scheme 6. *Reagents and conditions*: (i) Grubbs I (8 mol %), CH_2Cl_2, 30 °C, 12 h, then $P(CH_2OH)_3$, Et_3N, SiO_2, CH_2Cl_2, rt, 2 h; (ii) H_2 (4 atm), $RhCl(PPh_3)_3$ (5 mol %), EtOAc, rt, 12 h; (iii) H_2 (5 atm), $Pd(OH)_2/C$ (50% w/w), EtOAc, rt, 12 h; (iv) Ac_2O, DMAP, pyridine, rt, 12 h; (v) TFA, CH_2Cl_2, rt, 12 h, then HCl (6 M, aq), then Dowex 50WX8-200.

2.2. Synthetic application: asymmetric synthesis of a range of *Sedum* alkaloids and homologues

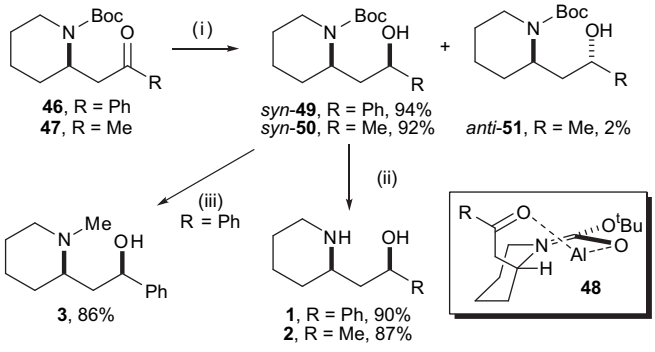
Having shown that this lithium amide conjugate addition/ring-closing metathesis protocol allows the rapid assembly of azocyclic structures comprising six-, seven- and eight-membered rings, the utility of this methodology for the synthesis of a family of *Sedum* alkaloid natural products and homologues was next demonstrated. Tandem hydrogenation/hydrogenolysis of tetrahydropyridine **20** in the presence of Boc_2O gave *N*-Boc piperidine **44**[20] in 91% yield. Conversion to Weinreb amide **45**[21] was effected upon treatment with *N*,*O*-dimethylhydroxylamine hydrochloride and isopropylmagnesium chloride,[22] giving **45** in 89% isolated yield. Subsequent addition of phenylmagnesium bromide or methylmagnesium bromide gave the corresponding ketones **46**[23] and **47** in good yields (Scheme 7).

The reduction of a range of *N*-protected α-(piperidin-2′-yl)-ketones with various reducing agents has been the subject of several investigations, with the observed levels of selectivity varying widely from poor (~50:50) to very good (>90:10).[24] Reduction of ketone **46** with various hydride sources (e.g., $LiAlH_4$, $LiBH_4$, $NaBH_4$, DIBAL-H, L-Selectride) was investigated although in general poor levels of selectivity, resulting in near 50:50 mixtures of diastereoisomers, were observed.[25] Employing $LiAl(O^tBu)_3H$,[24d,g,i,j] however, gave the known amino-alcohol *syn*-**49**[21,24e,26] in >99:1 dr, which was isolated in 94% yield and >99:1 dr. Application to ketone **47** gave a 96:4 mixture of the corresponding *syn*- and *anti*-diastereoisomers **50** and **51**, with purification furnishing *syn*-**50** in



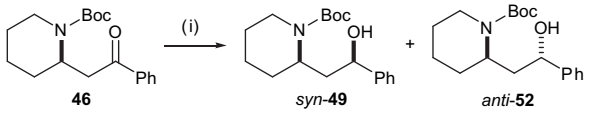
Scheme 7. *Reagents and conditions*: (i) H_2 (5 atm), $Pd(OH)_2/C$ (50% w/w), Boc_2O, EtOAc, rt, 12 h; (ii) (MeO)(Me)NH·HCl, ^iPrMgCl, THF, −20 to 0 °C, 6 h; (iii) RMgBr, Et_2O, 6 h.

92% yield and >99:1 dr, and *anti*-**51** in 2% yield and >99:1 dr. The configurations within *syn*-**50** and *anti*-**51** could not be assigned a priori; they were subsequently determined through conversion of *syn*-**50** to (+)-allosedridine **2**. The very high levels of stereoselectivity arising upon reduction of ketones **46** and **47** with $LiAl(O^tBu)_3H$ may be explained by invoking transition state **48**, in which chelation of the aluminium atom between the carbamate and ketone carbonyls directs hydride delivery to the least hindered face of the ketone (*Si* face of **46**, *Re* face of **47**).[27] Removal of the *tert*-butoxycarbonyl protecting group from *syn*-**50** gave (+)-allosedridine **2** in 87% yield and >99:1 dr {$[\alpha]_D^{25}$ +20.1 (*c* 1.0 in MeOH); lit.[28] $[\alpha]_D^{29}$ +16.2 (*c* 4.0 in MeOH); lit.[29] $[\alpha]_D^{25}$ +17.1 (*c* 1.55 in MeOH)}. Under identical conditions, hydrolysis of *syn*-**49** gave (+)-norsedamine **1** in 90% yield and >99:1 dr {$[\alpha]_D^{23}$ +24.6 (*c* 1.0 in MeOH); lit.[30] $[\alpha]_D^{17}$ +33.2 (*c* 2.0 in MeOH)}, with carbamate reduction upon treatment with $LiAlH_4$ giving (+)-sedamine **3** {$[\alpha]_D^{22}$ +81.5 (*c* 1.1 in MeOH); $[\alpha]_D^{25}$ +82.1 (*c* 1.0 in EtOH); lit. for enantiomer[30] $[\alpha]_D^{21}$ −81.7 (*c* 3.0 in MeOH); lit.[31] $[\alpha]_D^{32}$ +87.0 (*c* 1.1 in EtOH)} in 86% yield and >99:1 dr (Scheme 8).



Scheme 8. *Reagents and conditions*: (i) $LiAl(O^tBu)_3H$, THF, 0 °C, 6 h; (ii) HCl (3 M, aq), MeOH, 50 °C, 3 h; (iii) $LiAlH_4$, THF, reflux, 6 h. [All compounds were isolated as single diastereoisomers (>99:1 dr).].

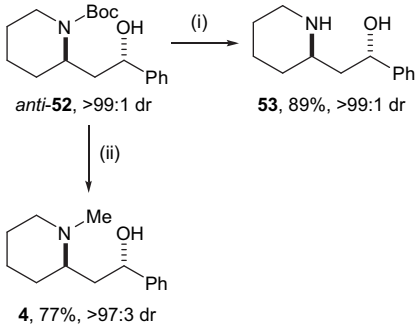
In order to access the corresponding *anti*-diastereoisomers, an alternative reduction protocol employing the homochiral CBS reagent[32] was probed. Reduction of phenyl ketone **46** with BH_3·THF gave a 56:44 mixture of *syn*-**49**:*anti*-**52**,[21,24e,26] indicating a slight substrate preference for formation of the *syn*-diastereoisomer **49**. In the doubly diastereoselectively 'matched' case,[33] reduction promoted by (*S*)-*B*-Me-CBS gave a 92:8 mixture of *syn*-**49**:*anti*-**52**. In the 'mismatched' case, the homochiral (*R*)-*B*-Me-CBS reagent exerted the dominant stereocontrol to furnish a 25:75 mixture of *syn*-**49**:*anti*-**52**, from which *syn*-**49** and *anti*-**52** were isolated in 19 and 67% yield, respectively, and as single diastereoisomers in both cases (Scheme 9).



Hydride Source	Crude dr *syn*-49:*anti*-52	*syn*-49 Yield %[a]	*anti*-52 Yield %[a]
BH_3·THF	56:44	-	-
(*S*)-*B*-Me-CBS/BH_3·THF	92:8	82	3
(*R*)-*B*-Me-CBS/BH_3·THF	**25:75**	19	**67**

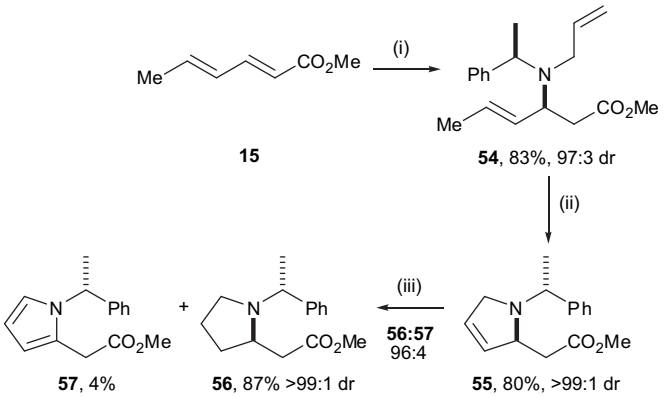
Scheme 9. *Reagents and conditions*: (i) (*R*)-*B*-Me-CBS (5 mol %), BH_3·THF, THF, 0 °C, 2 h; (ii) (*S*)-*B*-Me-CBS (5 mol %), BH_3·THF, THF, 0 °C, 2 h; (iii) BH_3·THF, THF, 0 °C, 2 h. [[a]Isolated yields refer to single diastereoisomers (>99:1 dr).]

Removal of the *tert*-butoxycarbonyl protecting group from *anti*-**52** gave (−)-norallosedamine **53** in 89% yield and >99:1 dr {$[\alpha]_D^{22}$ −23.0 (*c* 2.0 in EtOH); lit. for enantiomer[30] $[\alpha]_D^{21}$ +37.2 (*c* 3.0 in EtOH)}, and reduction of **52** with $LiAlH_4$ gave (+)-allosedamine **4** in 77% yield and 98:2 dr {$[\alpha]_D^{22}$ +29.7 (*c* 1.0 in MeOH); lit.[30] $[\alpha]_D^{21}$ +32.0 (*c* 2.0 in MeOH)} (Scheme 10).



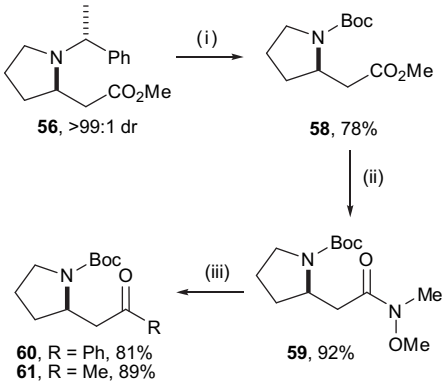
Scheme 10. *Reagents and conditions*: (i) HCl (3 M, aq), MeOH, 50 °C, 3 h; (ii) $LiAlH_4$, THF, reflux, 6 h.

The application of this strategy to the synthesis of pyrrolidine members of the *Sedum* alkaloid family[1] was explored. Conjugate addition of lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amide to α,β-unsaturated ester **15** proceeded in 97:3 dr, furnishing β-amino ester (3*S*,α*R*)-**54** in 83% isolated yield and 97:3 dr after purification. The absolute (3*S*,α*R*)-configuration within β-amino ester **54** was assigned by reference to the transition state mnemonic for the lithium amide conjugate addition reaction.[15] Subsequent ring-closing metathesis with Grubbs I furnished dihydropyrrole **55** in 80% yield. Hydrogenation of **55** in benzene furnished pyrrolidine **56** and pyrrole **57** in a 96:4 ratio, respectively, which were separated via flash column chromatography, giving pyrrolidine **56** in 87% yield and >99:1 dr, and pyrrole **57** in 4% yield (Scheme 11).



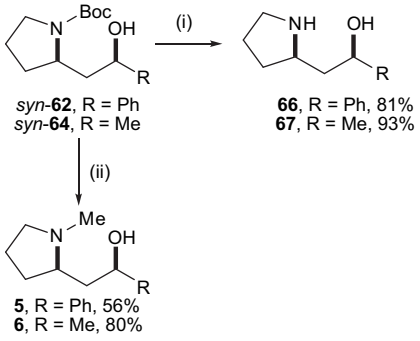
Scheme 11. Reagents and conditions: (i) lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amide (1.6 equiv), THF, −78 °C, 2 h; (ii) Grubbs I (4 mol %), CH_2Cl_2, rt, 12 h, then $P(CH_2OH)_3$, Et_3N, SiO_2, CH_2Cl_2, rt, 2 h; (iii) H_2 (4 atm), $RhCl(PPh_3)_3$ (5 mol %), C_6H_6, rt, 12 h.

Hydrogenolysis of **56** in the presence of Boc_2O gave *N*-Boc pyrrolidine **58**,[34] with subsequent treatment with (MeO)(Me)NH·HCl and ^{i}PrMgCl[22] giving Weinreb amide **59**. Conversion to the phenyl and methyl ketones **60** and **61**, respectively, was achieved upon reaction with the requisite Grignard reagent (Scheme 12).

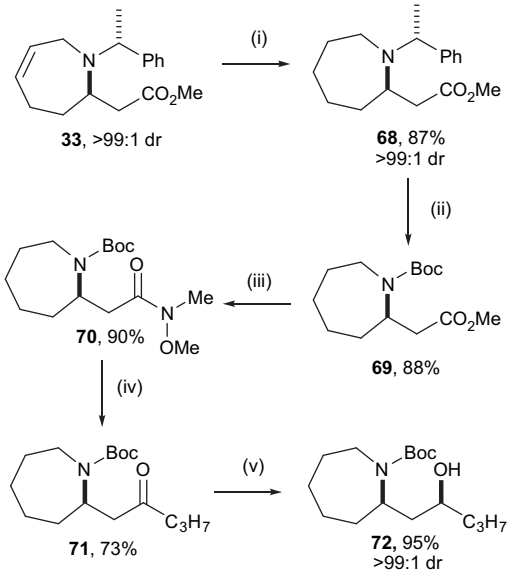


Scheme 12. *Reagents and conditions*: (i) H_2 (5 atm), $Pd(OH)_2/C$ (50% w/w), Boc_2O, EtOAc, rt, 12 h; (ii) (MeO)(Me)NH·HCl, ^{i}PrMgCl, THF, −20 to 0 °C, 6 h; (iii) RMgBr, Et_2O, −78 to 0 °C, 6 h.

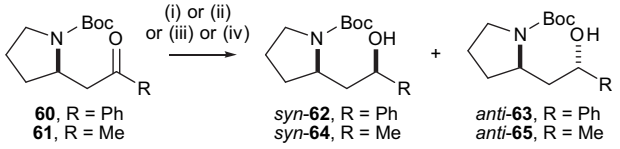
Reduction of both ketones with $LiAl(O^{t}Bu)_3H$ proceeded to give the corresponding *syn*-diastereoisomer as the major product in each case (*syn*:*anti* >99:1 for **60**, R=Ph; *syn*:*anti* 97:3 for **61**, R=Me). The stereoselectivity of these reductions was subsequently established by chemical correlation of *syn*-**62** and *syn*-**64** with pyrrolsedamine **5** and (+)-pseudohygroline **6**, and is consistent with a transition state similar to **48**, invoked to rationalise the selectivity observed in the analogous six-membered ring compounds **46** and **47**. In an effort to form the corresponding *anti*-diastereoisomers stereoselectively in the five-membered ring system, reduction promoted by the CBS reagent was investigated. In these investigations, treatment of phenyl ketone **60** with (*R*)-*B*-Me-CBS proceeded to give a 15:85 ratio of *syn*-**62**:*anti*-**63**, and reduction of methyl ketone **61** with (*S*)-*B*-Me-CBS gave a 24:76 ratio of *syn*-**64**:*anti*-**65**. The desired *anti*-diastereoisomers **63** and **65** were isolated in 71 and 68% yield, respectively, after chromatographic purification (Scheme 13).



Scheme 14. *Reagents and conditions*: (i) HCl (3 M, aq), MeOH, 50 °C, 3 h; (ii) $LiAlH_4$, THF, reflux, 6 h. [All compounds are single diastereoisomers (>99:1 dr).]



Scheme 15. *Reagents and conditions*: (i) H_2 (4 atm), $RhCl(PPh_3)_3$ (5 mol %), EtOAc, rt, 12 h; (ii) H_2 (5 atm), $Pd(OH)_2/C$ (50% w/w), Boc_2O, EtOAc, rt, 12 h; (iii) (MeO)(Me)NH·HCl, ^{i}PrMgCl, THF, −20 to 0 °C, 6 h; (iv) C_3H_7MgCl, Et_2O, −78 to 0 °C, 6 h; (v) $LiAl(O^{t}Bu)_3H$, THF, 0 °C, 6 h.



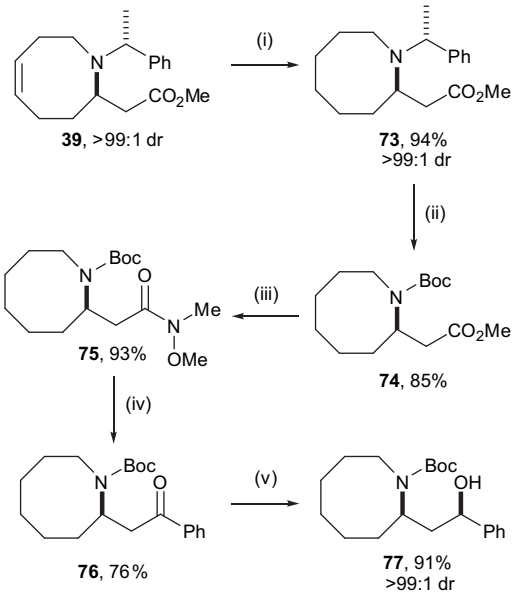
Ketone	Hydride Source	Ratio *syn*:*anti*	*syn* Yield %[a]	*anti* Yield %[a]
60, R = Ph	$LiAl(O^{i}Bu)_3H$	**>99:1**	**96**	0
60, R = Ph	BH_3·THF	50:50	-	-
60, R = Ph	(*S*)-*B*-Me-CBS/BH_3·THF	88:12	78	10
60, R = Ph	(*R*)-*B*-Me-CBS/BH_3·THF	**15:85**	12	**71**
61, R = Me	$LiAl(O^{i}Bu)_3H$	**97:3**	**94**	1
61, R = Me	BH_3·THF	50:50*	-	-
61, R = Me	(*S*)-*B*-Me-CBS/BH_3·THF	**24:76**	18	**68**
61, R = Me	(*R*)-*B*-Me-CBS/BH_3·THF	84:16	70	12

Scheme 13. *Reagents and conditions*: (i) $LiAl(O^{t}Bu)_3H$, THF, 0 °C, 6 h; (ii) BH_3·THF, THF, 0 °C, 2 h; (iii) (*S*)-*B*-Me-CBS, BH_3·THF, THF, 0 °C, 2 h; (iv) (*R*)-*B*-Me-CBS, BH_3·THF, THF, 0 °C, 2 h. [*50% conversion. [a]Isolated yields refer to single diastereoisomers (>99:1 dr).]

Hydrolysis of *syn*-**62** and *syn*-**64** gave the corresponding pyrrolidines **66**[35] and **67**, whilst carbamate reduction upon treatment with $LiAlH_4$ gave pyrrolsedamine **5**[1] and (+)-pseudohygroline **6**[3] {$[\alpha]_D^{22}$ +105.2 (*c* 1.0 in EtOH); lit.[3] $[\alpha]_D^{20}$ +84.4 (*c* 3.4 in EtOH); lit.[36] $[\alpha]_D^{25}$ +97.0 (*c* 1.0 in EtOH); lit.[37] $[\alpha]_D^{20}$ +78.8 (*c* 0.9 in EtOH)}, respectively. The specific rotation of pyrrolsedamine **5** {$[\alpha]_D^{23}$ +73.7 (*c* 2.0 in EtOH)} allowed assignment of (1*R*,2′*R*)-**5** as the (+)-enantiomer[38] (Scheme 14).

The generality of this protocol to medium ring systems was also demonstrated. In the seven-membered azepine system, tetrahydroazepine **33** was derivatised to the corresponding *n*-propyl ketone **71** in four steps. Reduction of **71** with $LiAl(O^{t}Bu)_3H$ proceeded to give **72** as a single diastereoisomer with high levels of selectivity (Scheme 15). An analogous sequence of reactions applied to hexahydroazocine **39** resulted in the highly selective formation of *syn*-

77 (Scheme 16). In both of these ring systems the *syn*-configurations within **72** and **77** resulting from $LiAl(O^tBu)_3H$ reduction were assigned by analogy to those unambiguously proven in the pyrrolidine and piperidine systems.



Scheme 16. *Reagents and conditions*: (i) H_2 (4 atm), $RhCl(PPh_3)_3$ (5 mol%), EtOAc, rt, 12 h; (ii) H_2 (5 atm), $Pd(OH)_2/C$ (50% w/w), Boc_2O, EtOAc, rt, 12 h; (iii) (MeO)(Me)NH·HCl, ^{i}PrMgCl, THF, −20 to 0 °C, 6 h; (iv) PhMgBr, Et_2O, −78 to 0 °C, 6 h; (v) $LiAl(O^tBu)_3H$, THF, 0 °C, 6 h.

3. Conclusion

In conclusion, conjugate addition of lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amide or lithium (*R*)-*N*-but-3-enyl-*N*-(α-methylbenzyl) amide to an alkyl hexa-2,4-dienoate or alkyl hepta-2,6-dienoate, followed by ring-closing metathesis of the olefin functionalities within the resultant β-amino ester, generates a range of diastereoisomerically pure azacycles in good yield. These homochiral templates are readily transformed to a range of piperidine alkaloids of the *Sedum* family, and the corresponding five-, seven- and eight-membered ring homologues.

4. Experimental

4.1. General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon 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.[39] Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) 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), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, UK. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers 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. In cases where methylene carbon atoms of ring systems could not be unambiguously assigned, the descriptor 'CH_2' is employed throughout. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m×0.25 mm) using amyl acetate as a lock mass.

4.2. General procedure 1: lithium amide conjugate addition

BuLi (2.5 M in hexanes, 1.55 equiv) was added dropwise via syringe to a stirred solution of the requisite amine (1.6 equiv) in THF at −78 °C under nitrogen. After stirring for 30 min, a solution of the requisite α,β-unsaturated ester (1.0 equiv) in THF at −78 °C was added dropwise via cannula. After stirring for a further 2 h at −78 °C the reaction mixture was quenched with satd aq NH_4Cl. After warming to rt over 15 min the reaction mixture was concentrated in vacuo. The residue was partitioned between CH_2Cl_2 and 10% aq citric acid. The organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed sequentially with satd aq $NaHCO_3$ and brine, before being dried and concentrated in vacuo to give the crude reaction mixture.

4.3. General procedure 2: ring-closing metathesis

Grubbs I (4 mol% or 8 mol%) was added to a stirred solution of the substrate (1.0 equiv) in dry, degassed CH_2Cl_2 at rt. After stirring at the temperature stated for 12 h the reaction mixture was concentrated in vacuo. The residue was redissolved in CH_2Cl_2, stirred, and tris(hydroxymethyl)phosphine (100 equiv w.r.t. Grubbs I) and Et_3N (2.0 equiv) were added sequentially. After stirring for 10 min, excess silica (>10 equiv) was added and stirring continued for a further 2 h. The mixture was then filtered and concentrated in vacuo to give the crude reaction mixture.

4.4. General procedure 3: hydrogenation with Wilkinson's catalyst

Wilkinson's catalyst (5 mol%) was added to a vigorously stirred solution of the substrate in the solvent stated and placed under a hydrogen atmosphere (4 atm). Stirring continued for 12 h, after which time the reaction mixture was concentrated in vacuo to give the crude reaction mixture.

4.5. General procedure 4: hydrogenation/hydrogenolysis with Pearlman's catalyst

Pearlman's catalyst (50% w/w of substrate) was added to a vigorously stirred solution of the requisite substrate in the solvent stated and placed under a hydrogen atmosphere (5 atm). Stirring continued for 12 h, after which time the reaction mixture was filtered through Celite® (eluent EtOAc) and concentrated in vacuo to give the crude reaction mixture.

4.6. General procedure 5: cleavage of esters with TFA

TFA was added dropwise to a stirred solution of the requisite *tert*-butyl ester in CH_2Cl_2 at rt and the reaction mixture was stirred for 12 h. After this time the reaction mixture was concentrated in vacuo and the residue was co-evaporated with 6 M aq HCl. The residue was then further co-evaporated with 6 M aq HCl solution to give the crude reaction mixture.

4.7. General procedure 6: Wadsworth–Emmons reaction

The requisite base was added dropwise via syringe to a stirred solution of the requisite phosphonate in THF at −78 °C and stirring continued for 30 min. A solution of the requisite aldehyde in THF at −78 °C was added dropwise via cannula, and stirring continued for a further 30 min at −78 °C before the reaction mixture was allowed to warm to rt over the stated amount of time. After this time, the reaction mixture was quenched with satd aq NH_4Cl and allowed to warm to rt over 15 min. Brine was added, the organic layer was separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried and concentrated in vacuo to give the crude reaction mixture.

4.8. General procedure 7: hydride reduction

A solution of the requisite hydride reagent was added to a solution of the requisite substrate in the stated solvent at the stated temperature under nitrogen and allowed to stir for the stated amount of time. The reaction was quenched by addition of a few drops of ice-cold water. EtOAc was added and the mixture stirred for a further hour. After this time, the reaction mixture was filtered through Celite® (eluent EtOAc) and the filtrate was concentrated in vacuo to give the crude reaction mixture.

4.9. General procedure 8: preparation of Weinreb amides from methyl esters

^{i}PrMgCl (2.0 M in THF, 3.0 equiv) was added dropwise via syringe to a vigorously stirred slurry of the requisite methyl ester (1.0 equiv) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.55 equiv) in THF at −20 °C. The reaction mixture was allowed to warm to 0 °C and stirring continued at 0 °C for 4 h. The reaction was quenched with a few drops of water and EtOAc was added. The slurry was filtered through Celite® (eluent EtOAc) and the filtrate was concentrated in vacuo to give the crude reaction mixture.

4.10. General procedure 9: preparation of ketones from Weinreb amides

The requisite Grignard reagent (2.0 equiv as a solution in Et_2O at the molarity stated) was added dropwise via syringe to a vigorously stirred solution of the requisite Weinreb amide (1.0 equiv) in Et_2O at −78 °C. The reaction mixture was allowed to warm to 0 °C and stirring continued at 0 °C for 6 h. The reaction was quenched with a few drops of water and EtOAc was added. The slurry was filtered through Celite® (eluent EtOAc) and the filtrate was concentrated in vacuo to give the crude reaction mixture.

4.11. General procedure 10: tandem hydrogenation/hydrogenolysis and *N*-Boc protection

Pearlman's catalyst (50% w/w of substrate) was added to a vigorously stirred solution of the requisite substrate (1.0 equiv) and Boc_2O (1.3 equiv) in EtOAc and placed under a hydrogen atmosphere (5 atm). Stirring continued for 12 h, after which time the reaction mixture was filtered through Celite® (eluent EtOAc) and concentrated in vacuo.

4.12. General procedure 11: ketone reduction with *B*-methyl CBS

B-Methyl CBS reagent (1.0 M in PhMe, 5 mol%) was added via syringe to a stirred solution of BH_3·THF complex (1.0 M in THF, 1.0 equiv) in THF at 0 °C. After stirring for 5 min, a solution of the requisite ketone (1.0 equiv) in THF at 0 °C was added dropwise via cannula. Stirring was continued at 0 °C for 2 h. The reaction was quenched with a few drops of MeOH and concentrated in vacuo to give the crude reaction mixture.

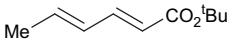
4.13. General procedure 12: *N*-Boc deprotection with HCl

3 M aq HCl was added to a stirred solution of the requisite substrate in MeOH and heated at 50 °C for 3 h. After cooling to rt the reaction mixture was concentrated in vacuo. The residue was partitioned between CH_2Cl_2 and satd aq $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried and concentrated in vacuo to give the crude reaction mixture.

4.14. General procedure 13: *N*-Boc reduction with $LiAlH_4$

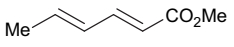
$LiAlH_4$ powder (5.0 equiv) was added portionwise to a stirred solution of the requisite substrate in THF at 0 °C. The reaction mixture was heated at 65 °C for 6 h and then cooled to 0 °C. The mixture was quenched by sequential addition of 10% aq NaOH and H_2O. The mixture was extracted with CH_2Cl_2 and the combined organic layers were dried, filtered and concentrated in vacuo to give the crude reaction mixture.

4.14.1. *tert*-Butyl (*E*,*E*)-hexa-2,4-dienaote **9**.



Condensed isobutylene gas (125 g, 2.23 mol) at −78 °C was added to a stirred solution of (*E*,*E*)-hexa-2,4-dienoic acid (25.0 g, 223 mmol), and a catalytic amount of 10 M aq H_2SO_4 (~1 mL), in CH_2Cl_2 (1 L) at 0 °C. The reaction mixture was allowed to warm to rt over 48 h. The reaction mixture was washed with satd aq $NaHCO_3$ (5×200 mL), and the combined aqueous washings were then extracted with CH_2Cl_2 (2×200 mL). The combined organic extracts were washed with brine (200 mL), dried and concentrated in vacuo. Purification of the residue via flash column chromatography (eluent pentane/Et_2O, 100:1) gave **9** as a colourless oil (27.8 g, 74%); δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, C*Me*$_3$), 1.85 (3H, d, *J* 6.2, C(6)*H*$_3$), 5.71 (1H, d, *J* 15.4, C(2)*H*), 6.07–6.21 (2H, m, C(4)*H*, C(5)*H*), 7.14 (1H, dd, *J* 15.4, 10.0, C(3)*H*).

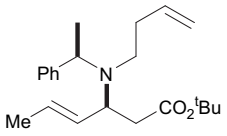
4.14.2. Methyl (*E*,*E*)-hexa-2,4-dienoate **15**.



$SOCl_2$ (4.23 mL, 58.0 mmol) was added dropwise to MeOH (50 mL) stirring at −10 °C. (*E*,*E*)-Hexa-2,4-dienoic acid (5.00 g, 44.6 mmol) was then added in one portion and the reaction mixture was refluxed for 2 h before being concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL) and the resultant solution

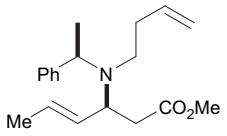
washed with satd aq $NaHCO_3$ (5×50 mL), dried and concentrated in vacuo. Purification via flash column chromatography (eluent pentane/Et_2O, 100:1) gave **15** as a colourless oil (4.78 g, 85%); δ_H (400 MHz, $CDCl_3$) 1.77 (3H, d, *J* 5.4, C(6)H_3), 3.66 (3H, s, O*Me*), 5.72 (1H, d, *J* 15.2, C(2)*H*), 6.03–6.16 (2H, m, C(4)*H*, C(5)*H*), 7.17–7.26 (1H, m, C(3)*H*).

4.14.3. tert-Butyl (3S,4E,αR)-3-[N-but-3′-enyl-N-(α-methylbenzyl)-amino]hex-4-enoate ***16****.*



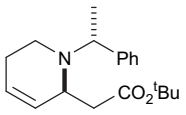
Following General Procedure 1, BuLi (2.5 M in hexanes, 3.69 mL, 9.21 mmol), *N*-but-3-enyl-*N*-(α-methylbenzyl)amine (1.67 g, 9.51 mmol) in THF (20 mL) at −78 °C, and **9** (1.00 g, 5.94 mmol) in THF (20 mL) at −78 °C gave a 96:4 mixture of **16**:**17**. Purification via flash column chromatography (eluent pentane/Et_2O, 50:1) gave **17** as a colourless oil (23 mg, 2%)[40]; ν_{max} (film) 2978, 2931 (C–H), 1733 (C=O); δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, CMe_3), 3.04 (2H, d, *J* 7.2, C(2)H_2), 5.04–5.18 (2H, m, C(6)H_2), 5.78 (1H, dt, *J* 15.4, 7.2, C(3)*H*), 6.10–6.16 (1H, m, C(4)*H*), 6.35 (1H, app dt, *J* 17.1, 10.2, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 28.5 (CMe_3), 39.5 (*C*(2)), 80.9 (*C*Me_3), 116.8 (*C*(6)), 126.7 (*C*(3)), 134.4 (*C*(4)), 136.9 (*C*(5)), 170.9 (*C*(1)); *m*/*z* (CI^+) 169 ([M+H]$^+$, 100%); HRMS (CI^+) $C_{10}H_{17}O_2^+$ ([M+H]$^+$) requires 169.1229; found 169.1230. Further elution gave **16** as a colourless oil (1.67 g, 82%, 97:3 dr); $C_{22}H_{33}NO_2$ requires C, 76.9; H, 9.7; N, 4.1%; found C, 76.4; H, 9.9; N, 4.0%; $[\alpha]_D^{24}$ −11.3 (*c* 2.5 in $CHCl_3$); ν_{max} (film) 2977 (C–H), 1733 (C=O); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, *J* 6.8, C(α)*Me*), 1.41 (9H, s, CMe_3), 1.70–1.72 (3H, m, C(6)H_3), 2.00–2.07 (2H, m, NCH_2CH_2), 2.29 (1H, dd, *J* 14.1, 8.4, C(2)H_A), 2.42 (1H, dd, *J* 14.1, 6.6, C(2)H_B), 2.48–2.57 (2H, m, N*C*H_2), 3.76–3.82 (1H, m, C(3)*H*), 3.94 (1H, q, *J* 6.8, C(α)*H*), 4.88–4.94 (2H, m, CH=CH_2), 5.46–5.57 (2H, m, C(4)*H*, C(5)*H*), 5.60–5.70 (1H, m, C*H*=CH_2), 7.19–7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.9 (C(6)), 18.6 (C(α)*Me*), 28.1 (CMe_3), 35.0 (NCH_2CH_2), 40.1 (*C*(2)), 46.5 (NCH_2), 57.6 (*C*(3)), 58.0 (*C*(α)), 80.0 (*C*Me_3), 115.0 (CH=CH_2), 126.5, 126.7, 127.7, 127.9, 130.7 (*C*(4), *C*(5), *p-Ph*, *m-Ph*, *o-Ph*), 137.1 (*C*H=CH_2), 145.6 (*i-Ph*), 171.4 (*C*(1)); *m*/*z* (ESI^+) 344 ([M+H]$^+$, 100%); HRMS (ESI^+) $C_{22}H_{34}NO_2^+$ ([M+H]$^+$) requires 344.2590; found 344.2592.

4.14.4. Methyl (3S,4E,αR)-3-[N-but-3′-enyl-N-(α-methylbenzyl)amino] hex-4-enoate ***18****.*



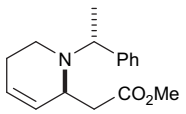
Following General Procedure 1, BuLi (2.5 M in hexanes, 4.91 mL, 12.3 mmol), *N*-but-3-enyl-*N*-(α-methylbenzyl)amine (2.22 g, 12.7 mmol) in THF (20 mL) at −78 °C, and **15** (1.00 g, 7.93 mmol) in THF (20 mL) at −78 °C gave **18** in 97:3 dr. Purification via flash column chromatography (eluent pentane/Et_2O, 50:1) gave **18** as a colourless oil (1.81 g, 76%, 97:3 dr); $C_{19}H_{27}NO_2$ requires C, 75.7; H, 9.0; N, 4.65%; found C, 75.6; H, 9.0; N, 4.4%; $[\alpha]_D^{24}$ −20.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2973 (C–H), 1741 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.8, C(α)*Me*), 1.70–1.71 (3H, m, C(6)H_3), 2.05–2.09 (2H, m, NCH_2CH_2), 2.37 (1H, dd, *J* 14.3, 7.6, C(2)H_A), 2.48–2.62 (3H, m, C(2)H_B, N*C*H_2), 3.59 (3H, s, O*Me*), 3.80–3.85 (1H, m, C(3)*H*), 3.98 (1H, q, *J* 6.8, C(α)*H*), 4.90–4.98 (2H, m, CH=CH_2), 5.52–5.54 (2H, m, C(4)*H*, C(5)*H*), 5.58–5.73 (1H, m, C*H*=CH_2), 7.19–7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.0 (*C*(6), C(α)*Me*), 34.7 (NCH_2CH_2), 38.9 (*C*(2)), 46.3 (NCH_2), 51.3 (O*Me*), 57.1 (*C*(3)), 57.6 (*C*(α)), 115.1 (CH=CH_2), 126.5, 126.9, 127.7, 127.9, 130.6 (*C*(4), *C*(5), *p-Ph*, *m-Ph*, *o-Ph*), 137.1 (*C*H=CH_2), 145.3 (*i-Ph*), 172.4 (*C*(1)); *m*/*z* (ESI^+) 302 ([M+H]$^+$, 100%); HRMS (ESI^+) $C_{19}H_{28}NO_2^+$ ([M+H]$^+$) requires 302.2120; found 302.2120.

4.14.5. tert-Butyl (2′S,αR)-2-[N(1′)-(α-methylbenzyl)-1′,2′,5′,6′-tetrahydropyridin-2′-yl]ethanoate ***19****.*



Following General Procedure 2, Grubbs I (95.8 mg, 0.116 mmol) and **16** (1.00 g, 2.91 mmol) in CH_2Cl_2 (300 mL) at rt gave the crude reaction mixture. Purification by treatment with $P(CH_2OH)_3$ (1.44 g, 11.6 mmol), Et_3N (0.81 mL, 5.82 mmol) and silica in CH_2Cl_2 (∼30 mL) followed by filtration through a short plug of silica gel (eluent pentane/Et_2O, 20:1) gave **19** as a colourless oil (683 mg, 78%, >99:1 dr); $C_{19}H_{27}NO_2$ requires C, 75.7; H, 9.0; N, 4.65%; found C, 75.5; H, 9.0; N, 4.6%; $[\alpha]_D^{25}$ +41.8 (*c* 1.5 in $CHCl_3$); ν_{max} (film) 2931 (C–H), 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.6, C(α)*Me*), 1.49 (9H, s, CMe_3), 1.68–1.75 (1H, m, C(5′)H_A), 2.07–2.15 (1H, m, C(5′)H_B), 2.38 (1H, dd, *J* 14.2, 6.9, C(2)H_A), 2.45–2.51 (1H, m, C(6′)H_A), 2.60 (1H, dd, *J* 14.2, 7.3, C(2)H_B), 2.86 (1H, ddd, *J* 13.3, 9.5, 4.8, C(6′)H_B), 3.73–3.76 (1H, m, C(2′)*H*), 3.90 (1H, q, *J* 6.6, C(α)*H*), 5.64–5.68 (1H, m, C(3′)*H*), 5.80–5.85 (1H, m, C(4′)*H*), 7.21–7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.8 (C(α)*Me*), 22.0 (*C*(5′)), 28.2 (CMe_3), 40.0 (*C*(6′)), 40.5 (*C*(2)), 52.1 (*C*(2′)), 57.9 (*C*(α)), 80.1 (*C*Me_3), 126.3, 126.8, 127.6, 128.1, 128.9 (*C*(3′), *C*(4′), *p-Ph*, *m-Ph*, *o-Ph*), 144.5 (*i-Ph*), 171.4 (*C*(1)); *m*/*z* (ESI^+) 302 ([M+H]$^+$, 100%); HRMS (ESI^+) $C_{19}H_{28}NO_2^+$ ([M+H]$^+$) requires 302.2120; found 302.2115.

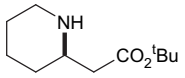
4.14.6. (2′S,αR)-Methyl 2-[N(1′)-(α-methylbenzyl)-1′,2′,5′,6′-tetrahydropyridin-2′-yl]ethanoate ***20****.*



Following General Procedure 2, Grubbs I (109 mg, 0.133 mmol) and **18** (1.00 g, 3.32 mmol) in CH_2Cl_2 (300 mL) at rt gave the crude reaction mixture. Purification by treatment with $P(CH_2OH)_3$ (1.65 g, 13.3 mmol), Et_3N (0.92 mL, 6.64 mmol) and silica in CH_2Cl_2 (∼30 mL) followed by filtration through a short plug of silica gel (eluent pentane/Et_2O, 20:1) gave **20** as a colourless oil (647 mg, 75%, >99:1 dr); $C_{16}H_{21}NO_2$ requires C, 74.1; H, 8.2; N, 5.4%; found C, 73.9; H, 8.0; N, 5.3%; $[\alpha]_D^{16}$ +42.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2972 (C–H), 1738 (C=O); δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.6, C(α)*Me*), 1.65–1.72 (1H, m, C(5′)H_A), 2.08–2.18 (1H, m, C(5′)H_B), 2.49 (1H, dd, *J* 14.4, 6.3, C(2)H_A), 2.49–2.55 (1H, m, C(6′)H_A), 2.69 (1H, dd, *J* 14.4, 7.8, C(2)H_B), 2.84 (1H, ddd, *J* 13.6, 10.1, 4.5, C(6′)H_B), 3.65 (3H, s, O*Me*), 3.83–3.87 (1H, m, C(2′)*H*), 3.88 (1H, q, *J* 6.6, C(α)*H*), 5.65–

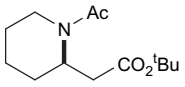
5.69 (1H, m, C(3′)*H*), 5.84–5.88 (1H, m, C(4′)*H*), 7.21–7.33 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.5 (*C*(5′)), 22.0 (C(α)*Me*), 39.3 (*C*(2)), 40.0 (*C*(6′)), 51.5 (O*Me*), 51.7 (*C*(2′)), 58.0 (*C*(α)), 126.8 (*C*(4′), *p-Ph*), 127.4, 128.2 (*o-Ph*, *m-Ph*), 128.6 (*C*(3′)), 144.9 (*i-Ph*), 172.6 (*C*(1)); *m*/*z* (ESI$^+$) 260 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{22}NO_2^+$ ([M+H]$^+$) requires 260.1651; found 260.1649.

*4.14.7. tert-Butyl (R)-2-(piperidin-2′–yl)ethanoate **21**.*



Following General Procedure 4, Pearlman's catalyst (250 mg) and **19** (500 mg) in EtOAc (5 mL) under H_2 (5 atm) at rt gave the crude reaction mixture. Purification via flash column chromatography (eluent pentane/Et_2O/Et_3N, 80:20:1) gave **21** as a colourless oil (307 mg, 93%)[41]; $[\alpha]_D^{25}$ −6.8 (*c* 1.5 in CH_2Cl_2); lit. for enantiomer $[\alpha]_D^{24}$ +8.3 (*c* 1.4 in CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 1.13–1.51 (3H, m, C(3′)H_A, C(4′)H_A, C(5′)H_A) overlapping 1.45 (9H, s, C*Me*$_3$), 1.58–1.62 (2H, m, C(3′)H_B, C(5′)H_B), 1.75–1.79 (1H, m, C(4′)H_B), 2.11 (1H, br s, N*H*), 2.30 (2H, app d, *J* 6.4, C(2)H_2), 2.64–2.70 (1H, m, C(6′)H_A), 2.84–2.91 (1H, m, C(2′)*H*), 3.04–3.07 (1H, m, C(6′)H_B).

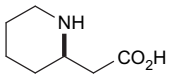
*4.14.8. tert-Butyl (RS)- and (R)-[N(1′)-acetylpiperidin-2′-yl]ethanoate **22**.*



Ac_2O (0.14 mL, 1.51 mmol) was added dropwise to a stirred solution of (*R*)-**21** (100 mg, 0.50 mmol) and DMAP (cat, 2 mg) in pyridine (2 mL) and the reaction mixture stirred at rt for 12 h. The reaction mixture was quenched with H_2O (1 mL) and Et_2O was added (2 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (2×2 mL). The combined organic extracts were washed sequentially with satd aq $CuSO_4$ (5 mL) and H_2O (2×5 mL) before being dried, and concentrated in vacuo. Purification via flash column chromatography (eluent pentane/EtOAc, 4:1) gave (*R*)-**22** as a colourless oil (107 mg, 88%); $[\alpha]_D^{22}$ +4.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2936 (C–H), 1725 (C=O, ester), 1646 (C=O, amide); δ_H (400 MHz, $CDCl_3$) [58:42 mixture of rotamers] 1.32–1.73 (m, C(3′)H_2, C(4′)H_2, C(5′)H_2), 1.42 (s, C*Me*$_3$), 1.43 (s, C*Me*$_3$), 2.06 (s, CO*Me*), 2.15 (s, CO*Me*), 2.42 (dd, *J* 13.9, 7.9, C(2)H_A), 2.48 (dd, *J* 14.6, 6.8, C(2)H_A), 2.52 (dd, *J* 13.9, 8.0, C(2)H_B), 2.56–2.64 (m, C(6′)H_A), 2.68 (dd, *J* 14.6, 8.2, C(2)H_B), 3.11–3.20 (m, C(6′)H_A), 3.57–3.65 (m, C(6′)H_B), 4.38–4.45 (m, C(2′)*H*), 4.52–4.59 (m, C(6′)H_B), 5.17–5.23 (m, C(2′)*H*); δ_H (500 MHz, DMSO-d_6, 373 K) 1.32–1.65 (6H, m, C(3′)H_2, C(4′)H_2, C(5′)H_2) overlapping 1.41 (9H, s, C(CH_3)$_3$), 2.01 (3H, s, COCH_3), 2.45–2.58 (2H, m, C(2)H_2), 3.02 (1H, br s, C(6′)H_A), 3.5–5.0 (2H, br, C(2′)*H*, C(6′)H_B); δ_C (125 MHz, DMSO-d_6, 373 K) [resonances attributable to C(2′) and C(6′) were not observed] 19.0 (*C*H$_2$), 21.6 (CO*Me*), 25.7 (*C*H$_2$), 27.6 (*C*H$_2$), 28.2 (C*Me*$_3$), 36.9 (*C*(2)), 80.4 (*C*Me$_3$), 168.5 (NCO), 170.6 (*C*(1)); *m*/*z* (ESI$^+$) 300 ([M+59]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{24}NO_3^+$ ([M+H]$^+$) requires 242.1756; found 242.1760. An analogous procedure applied to (*RS*)-**21**[17] (100 mg) gave (*RS*)-**22** as a colourless oil (109 mg, 90%).

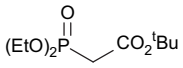
(*RS*)-**22** was analysed by chiral GC, giving complete resolution of enantiomers (run conditions: 70 °C, 60 min; 4.0 °C/min ramp; 130 °C, 120 min; (*R*)-**22** t_R=156.2 min; (*S*)-**22** t_R=159.2 min). (*R*)-**22** was therefore assessed to be 99:1 er.

*4.14.9. (R)-2-(Piperidin-2′-yl)ethanoic acid **23**.*



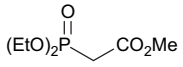
Following General Procedure 5, TFA (0.1 mL) and (*R*)-**21** (100 mg) in CH_2Cl_2 (1 mL) at rt gave the crude reaction mixture. Co-evaporation with 6 M aq HCl and purification of the residue via ion-exchange chromatography on Dowex 50WX8-200 resin (eluent 1 M aq NH_4OH) gave **23** as a white solid (52 mg, 72%)[18]; mp 215–217 °C; {lit.[18] mp 218–221 °C}; $[\alpha]_D^{24}$ −23.4 (*c* 0.5 in H_2O); {lit.[11] for enantiomer $[\alpha]_D^{26}$ +24.0 (*c* 0.9 in H_2O)}; δ_H (400 MHz, D_2O) 1.39–1.85 (6H, m, C(3′)H_2, C(4′)H_2, C(5′)H_2), 2.45 (2H, app d, *J* 6.6, C(2)H_2), 2.88–2.90 (1H, m, C(6′)H_A), 3.25–3.39 (2H, m, C(2′)*H*, C(6′)H_B).

*4.14.10. tert-Butyl diethylphosphonoacetate **24**.*



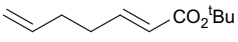
A stirred mixture of *tert*-butyl bromoacetate (10.0 g, 51.3 mmol) and triethylphosphite (8.79 mL, 51.3 mmol) was heated at 50 °C for 2 h. After this time volatiles were removed in vacuo to give **24** as a colourless liquid (12.9 g, quant); δ_H (200 MHz, $CDCl_3$) 1.24 (6H, t, *J* 7.2, P(OCH$_2$CH_3)$_2$), 1.37 (9H, s, C*Me*$_3$), 2.77 (2H, d, *J* 21.5, PCH_2), 4.02–4.08 (4H, m, P(OCH_2CH$_3$)$_2$).

*4.14.11. Methyl diethylphosphonoacetate **25**.*



A stirred mixture of methyl bromoacetate (10.0 g, 65.4 mmol) and triethylphosphite (11.2 mL, 65.4 mmol) was heated at 50 °C for 2 h. After this time volatiles were removed in vacuo to give **25** as a colourless liquid (13.7 g, quantitative); δ_H (200 MHz, $CDCl_3$) 1.31 (6H, t, *J* 7.0, P(OCH$_2$CH_3)$_2$), 2.95 (2H, d, *J* 21.5, PCH_2), 3.71 (3H, s, O*Me*), 4.07–4.21 (4H, m, P(OCH_2CH$_3$)$_2$).

*4.14.12. tert-Butyl (E)-hepta-2,6-dienoate **26**.*

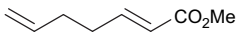


4.14.12.1. Olefination promoted by MeMgBr. Following General Procedure 6, MeMgBr (3.0 M in Et_2O, 5.94 mL, 17.8 mmol), **24** (4.50 g, 17.8 mmol) in THF (20 mL), and pent-4-enal (1.00 g, 11.9 mmol) in THF (10 mL) gave, after 4 h, (*E*)-**26** in >99:1 dr. Purification via flash column chromatography (eluent pentane/Et_2O, 100:1) gave (*E*)-**26** as a colourless oil (1.98 g, 91%, >99:1 dr); ν_{max} (film) 2975 (C–H), 1718 (C=O), 1652 (C=C); δ_H (400 MHz,

$CDCl_3$) 1.48 (9H, s, CMe_3), 2.18–2.30 (4H, m, C(4)H_2, C(5)H_2), 4.99–5.07 (2H, m, C(7)H_2), 5.74–5.86 (2H, m, C(2)*H*, C(6)*H*), 6.87 (1H, dt, *J* 15.5, 6.5, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.1 (CMe_3), 31.3 (*C*(5)), 32.1 (*C*(4)), 79.9 (*C*Me_3), 115.4 (*C*(7)), 123.3 (*C*(6)), 137.1 (*C*(3)), 146.9 (*C*(2)), 165.9 (*C*(1)); *m*/*z* (CI^+) 183 ($[M+H]^+$, 72%), 127 (100); HRMS (CI^+) $C_{11}H_{19}O_2^+$ ($[M+H]^+$) requires 183.1385; found 183.1382.

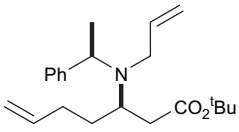
4.14.12.2. Olefination promoted by BuLi. Following General Procedure 6, BuLi (2.5 M in hexanes, 26.1 mL, 65.4 mmol), **24** (16.5 g, 65.4 mmol) in THF (50 mL), and pent-4-enal (5.00 g, 59.4 mmol) in THF (25 mL) gave, after 2 h, a 90:10 mixture of (*E*)-**26**:(*Z*)-**26**. Purification via flash column chromatography (eluent pentane/Et_2O, 100:1) gave (*Z*)-**26** as a colourless oil (214 mg, 2%, >99:1 dr); ν_{max} (film) 2977 (C–H), 1716 (C=O), 1645 (C=C); δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, CMe_3), 2.16–2.21 (2H, m, C(5)H_2), 2.69–2.74 (2H, m, C(4)H_2), 4.97–5.06 (2H, m, C(7)H_2), 5.67–5.70 (1H, m, C(2)*H*), 5.76–5.86 (1H, m, C(6)*H*), 6.10 (1H, dt, *J* 11.6, 7.2, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 27.8 (*C*(4)), 28.1 (CMe_3), 33.0 (*C*(5)), 80.0 (*C*Me_3), 115.2 (*C*(7)), 121.8 (*C*(6)), 137.5 (*C*(2)), 147.7 (*C*(3)), 165.8 (*C*(1)); *m*/*z* (CI^+) 183 ($[M+H]^+$, 45%), 127 (100); HRMS (CI^+) $C_{11}H_{19}O_2^+$ ($[M+H]^+$) requires 183.1385; found 183.1380. Further elution gave (*E*)-**26** as a colourless oil (8.93 g, 83%, >99:1 dr).[42]

*4.14.13. Methyl (E)-hepta-2,6-dienoate **27**.*



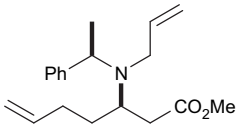
Following General Procedure 6, MeMgBr (3.0 M in Et_2O, 5.94 mL, 17.8 mmol), **25** (3.75 g, 17.8 mmol) in THF (20 mL), and pent-4-enal (1.00 g, 11.9 mmol) in THF (10 mL) gave, after 4 h, (*E*)-**27** in >99:1 dr. Purification via flash column chromatography (eluent pentane/Et_2O, 100:1) gave (*E*)-**27** as a colourless oil (1.54 g, 92%, >99:1 dr)[43]; δ_H (400 MHz, $CDCl_3$) 2.19–2.35 (4H, m, C(4)H_2, C(5)H_2), 3.73 (3H, s, O*Me*), 5.01–5.08 (2H, m, C(7)H_2), 5.75–5.87 (2H, m, C(2)*H*, C(6)*H*), 6.97 (1H, dt, *J* 15.7, 6.8, C(3)*H*).

*4.14.14. tert-Butyl (3R,αR)-3-[N-allyl-N-(α-methylbenzyl)amino]hept-6-enoate **28**.*



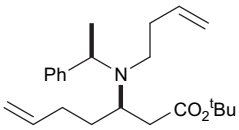
Following General Procedure 1, BuLi (2.5 M in hexanes, 3.35 mL, 8.50 mmol), (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amine (1.42 g, 8.78 mmol) in THF (20 mL) at −78 °C, and **26** (1.00 g, 5.49 mmol) in THF (20 mL) at −78 °C gave **28** in 98:2 dr. Purification via flash column chromatography (eluent pentane/Et_2O, 50:1) gave **28** as a colourless oil (1.76 g, 94%, 98:2 dr); $[\alpha]_D^{25}$ −20.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2977 (C–H), 1727 (C=O), 1641 (C=C); δ_H (400 MHz, $CDCl_3$) 1.32–1.42 (1H, m, C(4)H_A) overlapping 1.40 (9H, s, CMe_3) and 1.41 (3H, d, *J* 6.8, C(α)*Me*), 1.46–1.57 (1H, m, C(4)H_B), 1.94 (1H, dd, *J* 14.5, 8.8, C(2)H_A), 1.99–2.08 (1H, m, C(5)H_A) overlapping 2.03 (1H, dd, *J* 14.5, 4.4, C(2)H_B), 2.17–2.34 (1H, m, C(5)H_B), 3.05 (1H, dd, *J* 15.3, 6.9, NCH_A), 3.20–3.31 (2H, m, C(3)*H*, NCH_B), 3.93 (1H, q, *J* 6.8, C(α)*H*), 4.92–5.23 (4H, m, C(7)H_2, $NCH_2CH{=}CH_2$), 5.75–5.91 (2H, m, C(6)*H*, $NCH_2CH{=}CH_2$), 7.20–7.34 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.8 (C(α)*Me*), 28.1 (CMe_3), 31.0 (*C*(5)), 32.4 (*C*(4)), 37.8 (*C*(2)), 48.7 (NCH_2), 54.2 (*C*(3)), 58.4 (*C*(α)),79.9 (*C*Me_3), 114.3, 115.3 (*C*(7), $NCH_2CH{=}CH_2$), 126.8 (*p*-*Ph*), 127.8, 128.1 (*m*-*Ph*, *o*-*Ph*), 139.0, 139.2 (*C*(6), $NCH_2CH{=}CH_2$), 144.0 (*i*-*Ph*), 172.1 (*C*(1)); *m*/*z* (ESI^+) 344 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{22}H_{34}NO_2^+$ ($[M+H]^+$) requires 344.2590; found 344.2593.

*4.14.15. Methyl (3R,αR)-3-[N-allyl-N-(α-methylbenzyl)amino]hept-6-enoate **29**.*



Following General Procedure 1, BuLi (2.5 M in hexanes, 4.42 mL, 11.1 mmol), (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amine (1.84 g, 11.4 mmol) in THF (20 mL) at −78 °C, and **27** (1.00 g, 7.13 mmol) in THF (20 mL) at −78 °C gave **29** in 98:2 dr. Purification via flash column chromatography (eluent pentane/Et_2O, 50:1) gave **29** as a colourless oil (1.69 g, 79%, 98:2 dr); $[\alpha]_D^{25}$ −15.4 (*c* 1.5 in $CHCl_3$); ν_{max} (film) 2975 (C–H), 1737 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.32–1.43 (1H, m, C(4)H_A) overlapping 1.40 (3H, d, *J* 6.8, C(α)*Me*), 1.52–1.61 (1H, m, C(4)H_B), 1.97–2.18 (3H, m, C(2)H_2, C(5)H_A), 2.20–2.35 (1H, m, C(5)H_B), 3.10 (1H, dd, *J* 15.4, 6.8, NCH_A), 3.22–3.35 (2H, m, C(3)*H*, NCH_B), 3.58 (3H, s, O*Me*), 3.96 (1H, q, *J* 6.8, C(α)*H*), 4.94–5.23 (4H, m, C(7)H_2, $NCH_2CH{=}CH_2$), 5.76–5.92 (2H, m, C(6)*H*, $NCH_2CH{=}CH_2$), 7.20–7.31 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.3 (C(α)*Me*), 31.1 (*C*(5)), 32.4 (*C*(4)), 36.7 (*C*(2)), 48.7 (NCH_2), 51.3 (O*Me*), 54.3 (*C*(3)), 58.2 (*C*(α)), 114.3, 115.5 (*C*(7), $NCH_2CH{=}CH_2$), 126.8 (*p*-*Ph*), 127.6, 128.1 (*m*-*Ph*, *o*-*Ph*), 138.7, 139.0 (*C*(6), $NCH_2CH{=}CH_2$), 144.1 (*i*-*Ph*), 173.1 (*C*(1)); *m*/*z* (ESI^+) 302 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{28}NO_2^+$ ($[M+H]^+$) requires 302.2120; found 302.2122.

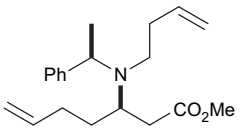
*4.14.16. tert-Butyl (3R,αR)-3-[N-but-3′-enyl-N-(α-methylbenzyl)amino]hept-6-enoate **30**.*



Following General Procedure 1, BuLi (2.5 M in hexanes, 3.40 mL, 8.50 mmol), (*R*)-*N*-but-3-enyl-*N*-(α-methylbenzyl)amine (1.54 g, 8.78 mmol) in THF (20 mL) at −78 °C, and **26** (1.00 g, 5.49 mmol) in THF (20 mL) at −78 °C gave **30** in 97:3 dr. Purification via flash column chromatography (eluent pentane/Et_2O, 50:1) gave **30** as a colourless oil (1.93 g, 98%, 97:3 dr)[44]; $C_{23}H_{35}NO_2$ requires C, 77.3; H, 9.9; N, 3.9%; found C, 77.6; H, 9.7; N, 3.8%; $[\alpha]_D^{25}$ −16.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2976 (C–H), 1727 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.31–1.42 (1H, m, C(4)H_A) overlapping 1.40 (9H, s, CMe_3) and 1.42 (3H, d, *J* 6.8, C(α)*Me*), 1.46–1.56 (1H, m, C(4)H_B), 1.94–2.08 (3H, m, C(2)H_2, C(5)H_A), 2.11–2.30 (3H, m, C(5)H_B, NCH_2CH_2), 2.51–2.56 (2H, m, NCH_2), 3.15–3.22 (1H, m, C(3)*H*), 3.88 (1H, q, *J* 6.8, C(α)*H*), 4.92–5.03 (4H, m, C(7)H_2, $NCH_2CH_2CH{=}CH_2$), 5.71–5.84 (2H, m, C(6)*H*, $NCH_2CH_2CH{=}CH_2$), 7.21–7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.0 (C(α)*Me*), 28.0 (CMe_3), 31.0 (*C*(5)), 32.2 (*C*(4)), 35.4 (NCH_2CH_2), 37.7 (*C*(2)), 45.7 (NCH_2), 54.8 (*C*(3)), 58.9 (*C*(α)), 79.9 (*C*Me_3), 114.2, 115.3 (*C*(7), $NCH_2CH_2CH{=}CH_2$), 126.8 (*p*-*Ph*), 127.7, 128.1 (*m*-*Ph*, *o*-*Ph*), 137.1, 139.0 (*C*(6), $NCH_2CH_2CH{=}CH_2$),

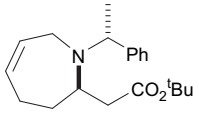
144.6 (*i-Ph*), 172.2 (*C*(1)); *m*/*z* (ESI$^+$) 358 ([M+H]$^+$, 78%), 302 (100); HRMS (ESI$^+$) $C_{23}H_{36}NO_2^+$ ([M+H]$^+$) requires 358.2746; found 358.2749.

4.14.17. Methyl (3R,αR)-3-[N-but-3′-enyl-N-(α-methylbenzyl)amino]-hept-6-enoate ***31****.*



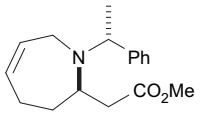
Following General Procedure 1, BuLi (2.5 M in hexanes, 4.42 mL, 11.1 mmol), (*R*)-*N*-but-3-enyl-*N*-(α-methylbenzyl)amine (2.00 g, 11.4 mmol) in THF (20 mL) at −78 °C, and **27** (1.00 g, 7.13 mmol) in THF (20 mL) at −78 °C gave **31** in 97:3 dr. Purification via flash column chromatography (eluent pentane/Et_2O, 50:1) gave **31** as a colourless oil (1.99 g, 88%, 97:3 dr); $[\alpha]_D^{25}$ −16.5 (*c* 1.5 in $CHCl_3$); ν_{max} (film) 2976 (C–H), 1737 (C═O), 1640 (C═C); δ_H (400 MHz, $CDCl_3$) 1.31–1.44 (1H, m, C(4)H_A) overlapping 1.41 (3H, d, *J* 6.8, C(α)*Me*), 1.51–1.60 (1H, m, C(4)H_B), 1.96–2.35 (5H, m, C(2)H_2, C(5)H_2, NCH_2CH_2), 2.53–2.62 (2H, m, NCH_2), 3.20–3.26 (1H, m, C(3)*H*), 3.57 (3H, s, O*Me*), 3.91 (1H, q, *J* 6.8, C(α)*H*), 4.94–5.09 (4H, m, C(7)H_2, $NCH_2CH_2CH{=}CH_2$), 5.72–5.88 (2H, m, C(6)*H*, $NCH_2CH_2CH{=}CH_2$), 7.21–7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.5 (C(α)*Me*), 31.3 (*C*(5)), 32.4 (*C*(4)), 35.2 (NCH_2CH_2), 36.6 (*C*(2)), 45.5 (NCH_2), 51.3 (O*Me*), 54.8 (*C*(3)), 58.6 (*C*(α)), 114.3, 115.4 (*C*(7), $NCH_2CH_2CH{=}CH_2$), 126.7 (*p-Ph*), 127.7, 128.1 (*m-Ph*, *o-Ph*), 137.0, 138.7 (*C*(6), $NCH_2CH_2CH{=}CH_2$), 144.6 (*i-Ph*), 173.2 (*C*(1)); *m*/*z* (ESI$^+$) 316 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{30}NO_2^+$ ([M+H]$^+$) requires 316.2277; found 316.2276.

4.14.18. tert-Butyl (2′R,αR)-2-[N(1′)-(α-methylbenzyl)-2′,3′,4′,7′-tetrahydro-1H-azepin-2′-yl]ethanoate ***32****.*



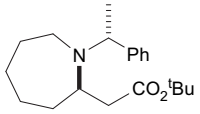
Following General Procedure 2, Grubbs I (192 mg, 0.233 mmol) and **28** (1.00 g, 2.91 mmol) in CH_2Cl_2 (300 mL) at rt gave the crude reaction mixture. Purification by treatment with $P(CH_2OH)_3$ (23.3 mmol, 2.89 g), Et_3N (5.82 mmol, 0.81 mL) and silica in CH_2Cl_2 (∼30 mL) followed by filtration through a short plug of silica gel (eluent pentane/Et_2O, 20:1) gave **32** as a colourless oil, which solidified on standing to a white solid (835 mg, 91%, >99:1 dr); $C_{20}H_{29}NO_2$ requires C, 76.15; H, 9.3; N, 4.4%; found C, 76.4; H, 9.5; N, 4.3%; mp 38–40 °C; $[\alpha]_D^{25}$ +33.2 (*c* 1.5 in $CHCl_3$); ν_{max} (KBr) 2976 (C–H), 1729 (C═O); δ_H (400 MHz, $CDCl_3$) 1.42 (3H, d, *J* 6.6, C(α)*Me*), 1.51 (9H, s, C*Me*$_3$), 1.66–1.75 (1H, m, C(3′)H_A), 1.91–1.98 (1H, m, C(3′)H_B), 2.16–2.27 (2H, m, C(4′)H_2), 2.32 (1H, dd, *J* 14.1, 6.3, C(2)H_A), 2.55 (1H, dd, *J* 14.1, 8.2, C(2)H_B), 2.85 (1H, dd, *J* 17.4, 6.3, C(7′)H_A), 3.40–3.44 (1H, m, C(7′)H_B), 3.81–3.88 (1H, m, C(2′)*H*), 4.06 (1H, q, *J* 6.6, C(α)*H*), 5.29–5.33 (1H, m, C(6′)*H*), 5.78–5.84 (1H, m, C(5′)*H*), 7.19–7.31 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.2 (C(α)*Me*), 26.4 (*C*(4′)), 28.2 (C*Me*$_3$), 32.4 (*C*(3′)), 41.1 (*C*(2)), 43.3 (*C*(7′)), 54.6 (*C*(2′)), 59.1 (*C*(α)), 80.0 (*C*Me$_3$), 126.5 (*p-Ph*), 127.2, 128.0 (*m-Ph*, *o-Ph*), 129.1 (*C*(6′)), 131.9 (*C*(5′)), 146.8 (*i-Ph*), 172.0 (*C*(1)); *m*/*z* (ESI$^+$) 316 ([M+H]$^+$, 90%), 260 (100); HRMS (ESI$^+$) $C_{20}H_{30}NO_2^+$ ([M+H]$^+$) requires 316.2277; found 316.2274.

4.14.19. Methyl (2′R,αR)-2-[N(1′)-(α-methylbenzyl)-2′,3′,4′,7′-tetrahydro-1H-azepin-2′-yl]ethanoate ***33****.*



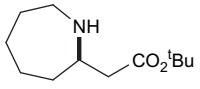
Following General Procedure 2, Grubbs I (218 mg, 0.265 mmol) and **29** (1.00 g, 3.32 mmol) in CH_2Cl_2 (300 mL) at rt gave the crude reaction mixture. Purification by treatment with $P(CH_2OH)_3$ (3.29 g, 26.5 mmol), Et_3N (0.92 mL, 6.64 mmol) and silica in CH_2Cl_2 (∼30 mL) followed by filtration through a short plug of silica gel (eluent pentane/Et_2O, 20:1) gave **33** as a colourless oil (806 mg, 89%, >99:1 dr); $[\alpha]_D^{22}$ −31.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2929 (C–H), 1739 (C═O); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.7, C(α)*Me*), 1.70–1.79 (1H, m, C(3′)H_A), 1.92–1.96 (1H, m, C(3′)H_B), 2.15–2.28 (2H, m, C(4′)H_2), 2.42 (1H, dd, *J* 14.0, 5.8, C(2)H_A), 2.60 (1H, dd, *J* 14.0, 8.9, C(2)H_B), 2.82 (1H, dd, *J* 17.4, 6.1, C(7′)H_A), 3.38–3.45 (1H, m, C(7′)H_B), 3.74 (3H, s, O*Me*), 3.85–3.92 (1H, m, C(2′)*H*), 4.06 (1H, q, *J* 6.7, C(α)*H*), 5.26–5.31 (1H, m, C(6′)*H*), 5.77–5.83 (1H, m, C(5′)*H*), 7.18–7.29 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.2 (C(α)*Me*), 26.6 (*C*(4′)), 33.4 (*C*(3′)), 40.2 (*C*(2)), 43.1 (*C*(7′)), 51.4 (O*Me*), 54.6 (*C*(2′)), 59.1 (*C*(α)), 126.5 (*p-Ph*), 127.1, 128.1 (*m-Ph*, *o-Ph*), 128.9 (*C*(6′)), 131.8 (*C*(5′)), 146.9 (*i-Ph*), 173.0 (*C*(1)); *m*/*z* (ESI$^+$) 274 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{24}NO_2^+$ ([M+H]$^+$) requires 274.1807; found 274.1802.

4.14.20. tert-Butyl (2′R,αR)-2-[N(1′)-(α-methylbenzyl)azepan-2′-yl]-ethanoate ***34****.*



Following General Procedure 3, Wilkinson's catalyst (14.7 mg, 0.016 mmol) and **32** (100 mg, 0.32 mmol) in EtOAc (5 mL) under H_2 (4 atm) at rt gave the crude reaction mixture. Purification via flash column chromatography (eluent pentane/Et_2O, 10:1) gave **34** as a colourless oil (86.2 mg, 85%, >99:1 dr); $[\alpha]_D^{22}$ −2.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2927 (C–H), 1725 (C═O); δ_H (400 MHz, $CDCl_3$) 1.32–1.50 (3H, m, CH_2) overlapping 1.38 (3H, d, *J* 6.7, C(α)*Me*) and 1.41 (9H, s, C*Me*$_3$), 1.51–1.69 (4H, m, CH_2), 1.80–1.88 (1H, m, CH_2), 2.15 (1H, dd, *J* 13.5, 8.9, C(2)H_A), 2.44 (1H, dd, *J* 13.5, 5.1, C(2)H_B), 2.67–2.70 (2H, m, C(7′)H_2), 3.29–3.53 (1H, m, C(2′)*H*), 3.97 (1H, q, *J* 6.7, C(α)*H*), 7.19–7.35 (5H, m *Ph*); δ_C (100 MHz, $CDCl_3$) 21.7 (C(α)*Me*), 24.3 (CH_2), 28.1 (C*Me*$_3$), 29.1, 29.4, 34.2 (CH_2), 39.6 (*C*(2)), 43.8 (*C*(7′)), 55.4 (*C*(2′)), 59.9 (*C*(α)), 79.8 (*C*Me$_3$), 126.5 (*p-Ph*), 127.4, 128.1 (*m-Ph*, *o-Ph*), 145.7 (*i-Ph*), 172.4 (*C*(1)); *m*/*z* (ESI$^+$) 318 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{32}NO_2^+$ ([M+H]$^+$) requires 318.2433; found 318.2430.

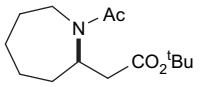
4.14.21. tert-Butyl (R)-2-(azepan-2′-yl)ethanoate ***35****.*



Following General Procedure 4, Pearlman's catalyst (250 mg) and **34** (500 mg) in EtOAc (5 mL) under H_2 (5 atm) at rt gave the

crude reaction mixture. Purification via flash column chromatography on silica gel (eluent pentane/Et_2O/Et_3N, 80:20:1) gave **35** as a colourless oil (301 mg, 90%); $[\alpha]_D^{20}$ −3.9 (*c* 1.5 in $CHCl_3$); ν_{max} (film) 3352 (N–H), 2927 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.25–1.78 (8H, m, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2), overlapping 1.42 (9H, s, CMe_3), 1.96 (1H, br s, N*H*), 2.27–2.30 (2H, m, C(2)H_2), 2.67–2.73 (1H, m, C(7′)H_A), 2.92–2.97 (1H, m, C(7′)H_B), 3.00–3.08 (1H, m, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 25.5, 27.1 (*C*H_2), 28.1 (CMe_3), 31.1, 36.4 (*C*H_2), 43.5 (*C*(2)), 47.1 (*C*(7′)), 56.0 *C*(2′), 80.3 (*C*Me_3), 171.9 (*C*(1)); *m*/*z* (ESI$^+$) 214 ($[M+H]^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{24}NO_2^+$ ($[M+H]^+$) requires 214.1807; found 214.1817.

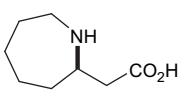
*4.14.22. tert-Butyl (R)- and (RS)-2-[N(1′)-acetlyazepan-2′-yl]ethanoate (R)- and (RS)-**36**.*



Ac_2O (0.13 mL, 1.41 mmol) was added dropwise to a stirred solution of (*R*)-**35** (100 mg, 0.47 mmol) and DMAP (cat, 2 mg) in pyridine (2 mL) and the reaction mixture stirred at rt for 12 h. The reaction mixture was quenched with H_2O (1 mL) and Et_2O was added (2 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (2×2 mL). The combined organic extracts were washed sequentially with satd aq $CuSO_4$ (5 mL) and H_2O (2×5 mL) before being dried and concentrated in vacuo. Purification via flash column chromatography (eluent pentane/EtOAc, 4:1) gave (*R*)-**36** as a colourless oil (114 mg, 95%); $[\alpha]_D^{20}$ +65.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2930 (C–H), 1727 (C=O, ester), 1644 (C=O, amide); δ_H (400 MHz, $CDCl_3$) [50:50 mixture of rotamers] 1.15–1.48 (m, CH_2) overlapping 1.43 (s, CMe_3) and 1.44 (s, CMe_3), 1.56–1.67 (m, CH_2), 1.75–1.83 (m, CH_2), 2.09–2.22 (m, CH_2) overlapping 2.12 (s, CO*Me*) and 2.29 (s, CO*Me*), 2.29 (dd, *J* 14.1, 7.7, C(2)H_A), 2.34 (dd, *J* 14.3, *J* 7.8, C(2)H_A), 2.41–2.46 (m, C(2)H_B), 2.56–2.61 (m, C(7′)H_A), 3.08–3.13 (m, C(7′)H_A), 3.50–3.54 (m, C(7′)H_B), 4.08–4.15 (m, C(2′)*H*, C(7′)H_B), 4.67–4.73 (m, C(2′)*H*); δ_C (125 MHz, $CDCl_3$) 21.8 (CO*Me*), 21.9 (NCO*Me*), 24.5, 25.0, 27.3 (*C*H_2), 27.9 (CMe_3), 29.1, 29.7, 30.1, 32.5, 34.5 (*C*H_2), 40.2, 40.5, 41.7, 43.9 (*C*(2), *C*(7′)), 51.3, 54.6 (*C*(2′)), 80.3, 81.0 (*C*Me_3), 170.1, 170.2, 170.4, 170.5 (*C*(1), NC*O*); *m*/*z* (ESI$^+$) 314 ($[M+59]^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{26}NO_3^+$ ($[M+H]^+$) requires 256.1913; found 256.1911. An analogous procedure applied to (*RS*)-**35**[17] (100 mg) gave (*RS*)-**36** (108 mg, 90%).

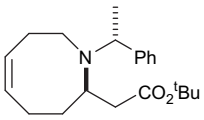
(*RS*)-**36** was analysed by chiral GC, giving complete resolution of enantiomers (run conditions: 70 °C, 60 min; 4.0 °C/min ramp; 130 °C, 180 min; (*R*)-**36** t_R=204.3 min; (*S*)-**36** t_R=210.9 min). (*R*)-**36** was therefore assessed to be 99:1 er.

*4.14.23. (R)-2-(Azepan-2′-yl)ethanoic acid **37**.*



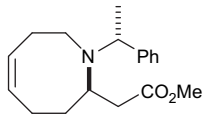
Following General Procedure 5, TFA (0.2 mL) and (*R*)-**35** (250 mg) in CH_2Cl_2 (2 mL) at rt gave the crude reaction mixture. Co-evaporation with 6 M aq HCl and purification via ion-exchange chromatography on Dowex 50WX8-200 resin (eluent 1 M aq NH_4OH) gave **37** as a white solid (169 mg, 92%); mp 180–182 °C; $[\alpha]_D^{20}$ −42.4 (*c* 2.0 in H_2O); ν_{max} (KBr) 3388 (NH_2^+, br), 2937 (C–H), 1584 (CO_2^- asymmetric), 1397 (CO_2^- symmetric); δ_H (400 MHz, D_2O) 1.40–1.86 (8H, m, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2), 2.36–2.43 (2H, m, C(2)H_2), 3.09 (1H, ddd, *J* 13.7, 7.6, 4.0, C(7′)H_A), 3.20 (1H, ddd, *J* 13.7, 7.3, 4.1 C(7′)H_B), 3.40–3.47 (1H, m, C(2′)*H*); δ_C (100 MHz, D_2O) 24.6, 25.0, 26.1, 31.2 (*C*(3′), *C*(4′), *C*(5′), *C*(6′)), 40.3 (*C*(2)), 45.4 (*C*(7′)), 56.9 *C*(2′), 178.3 (*C*(1)); *m*/*z* (ESI$^-$) 156 ($[M-H]^-$, 100%); HRMS (ESI$^-$) $C_8H_{14}NO_2^-$ ($[M-H]^-$) requires 156.1025; found 156.1022.

*4.14.24. tert-Butyl (2′R,αR)-2-[N(1′)-(α-methylbenzyl)-1′,2′,3′,4′,7′,8′-hexahydroazocin-2′-yl]ethanoate **38**.*



Following General Procedure 2, Grubbs I (184 mg, 0.224 mmol) and **30** (1.00 g, 2.80 mmol) in CH_2Cl_2 (300 mL) at 30 °C gave the crude reaction mixture. Purification by treatment with $P(CH_2OH)_3$ (22.4 mmol, 2.78 g), Et_3N (5.59 mmol, 0.78 mL) and silica in CH_2Cl_2 (~30 mL) followed by filtration through a short plug of silica gel (eluent pentane/Et_2O, 20:1) gave **38** as a white solid (812 mg, 88%, >99:1 dr); $C_{21}H_{31}NO_2$ requires C, 76.55; H, 9.5; N, 4.25%; found C, 76.5; H, 9.4; N, 4.2%; mp 50–52 °C; $[\alpha]_D^{25}$ +49.5 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 2922 (C–H), 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s, CMe_3), 1.40–1.48 (1H, m, C(3′)H_A), 1.49 (3H, d, *J* 7.1, C(α)*Me*), 1.80–1.88 (1H, m, C(3′)H_B), 1.91–1.99 (1H, m, C(7′)H_A) overlapping 1.98 (1H, dd, *J* 15.4, 7.1, C(2)H_A), 2.02–2.09 (1H, m, C(4′)H_A), 2.24 (1H, dd, *J* 15.4, 7.1, C(2)H_B), 2.36–2.48 (2H, m, C(4′)H_B, C(7′)H_B), 2.87–2.94 (1H, m, C(8′)H_A), 3.24–3.30 (1H, m, C(8′)H_B), 3.52–3.59 (1H, m, C(2′)*H*), 4.08 (1H, q, *J* 7.1, C(α)*H*), 5.67–5.73 (1H, m, C(5′)*H*), 5.79–5.85 (1H, m, C(6′)*H*), 7.16–7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.7 (C(α)*Me*), 25.1 (*C*(4′)), 28.0 (CMe_3), 30.2 (*C*(7′)), 33.8 (*C*(3′)), 40.5 (*C*(2)), 49.2 (*C*(8′)), 55.4 (*C*(α)), 56.2 (*C*(2′)), 79.8 (*C*Me_3), 126.1 (*p-Ph*), 126.8, 128.1 (*m-Ph*, *o-Ph*), 129.8 (*C*(6′)), 130.7 (*C*(5′)), 148.0 (*i-Ph*), 172.2 (*C*(1)); *m*/*z* (ESI$^+$) 330 ($[M+H]^+$, 78%), 274 (100); HRMS (ESI$^+$) $C_{21}H_{32}NO_2^+$ ($[M+H]^+$) requires 330.2433; found 330.2434.

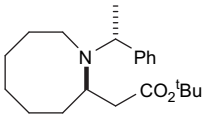
*4.14.25. Methyl (2′R,αR)-2-[N(1′)-(α-methylbenzyl)-1′,2′,3′,4′,7′,8′-hexahydroazocin-2′-yl]ethanoate **39**.*



Following General Procedure 2, Grubbs I (209 mg, 0.254 mmol) and **31** (1.00 g, 3.17 mmol) in CH_2Cl_2 (300 mL) at 30 °C gave the crude reaction mixture. Purification by treatment with $P(CH_2OH)_3$ (3.15 g, 25.4 mmol), Et_3N (0.88 mL, 6.34 mmol) and silica in CH_2Cl_2 (~30 mL) followed by filtration through a short plug of silica gel (eluent pentane/Et_2O, 20:1) gave **39** as a white solid (778 mg, 85%, >99:1 dr); mp 40–42 °C; $[\alpha]_D^{22}$ −45.5 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 2920 (C–H), 1736 (C=O); δ_H (400 MHz, $CDCl_3$) 1.35–1.44 (1H, m, C(3′)H_A), 1.49 (3H, d, *J* 7.2, C(α)*Me*), 1.81–1.90 (1H, m, C(3′)H_B), 1.93–2.00 (1H, m, C(7′)H_A), 2.00–2.08 (1H, m, C(4′)H_A) overlapping 1.98 (1H, dd, *J* 15.7, 6.5, C(2)H_A), 2.28 (1H, dd, *J* 15.7, 8.2, C(2)H_B), 2.34–2.46 (2H, m, C(4′)H_B, C(7′)H_B), 2.91–2.98 (1H, m, C(8′)H_A), 3.34–3.40 (1H, m, C(8′)H_B), 3.49 (3H, s, O*Me*), 3.54–3.65 (1H, m, C(2′)*H*), 4.08 (1H, q, *J* 7.2, C(α)*H*), 5.65–5.72 (1H, m, C(5′)*H*), 5.80–5.87 (1H, m, C(6′)*H*), 7.15–7.34 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.9 (C(α)*Me*),

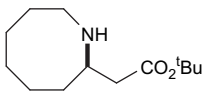
25.0 (*C*(4′)), 30.4 (*C*(7′)), 33.8 (*C*(3′)), 39.1 (*C*(2)), 49.4 (*C*(8′)), 51.2 (O*Me*), 55.1 (*C*(2′)), 56.2 (*C*(α)), 126.1 (*p-Ph*), 126.5, 128.0 (*m-Ph*, *o-Ph*), 130.0 (*C*(6′)), 130.6 (*C*(5′)), 148.4 (*i-Ph*), 173.1 (*C*(1)); *m*/*z* (ESI$^+$) 288 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{26}NO_2^+$ ([M+H]$^+$) requires 288.1964; found 288.1955.

4.14.26. tert-Butyl (2′R,αR)-2-[N(1′)-(α-methylbenzyl)azocan-2′-yl]-ethanoate ***40***.



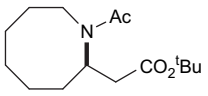
Following General Procedure 3, Wilkinson's catalyst (14.0 mg, 0.015 mmol) and **38** (100 mg, 0.30 mmol) in EtOAc (5 mL) under H_2 (4 atm) at rt gave the crude reaction mixture. Purification via flash column chromatography (eluent pentane/Et_2O, 10:1) gave **40** as a colourless oil (96 mg, 95%, >99:1 dr); $[\alpha]_D^{22}$ +4.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2975 (C–H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.30–1.47 (4H, m, C*H*$_2$) overlapping 1.32 (9H, s, C*Me*$_3$) and 1.38 (3H, d, *J* 6.9, C(α)*Me*), 1.52–1.69 (4H, m, C*H*$_2$), 1.83–1.95 (2H, m, C(2)H_A, C*H*$_2$), 1.99–2.13 (1H, m, C*H*$_2$), 2.42 (1H, dd, *J* 13.2, 3.1, C(2)H_B), 2.53–2.61 (1H, m, C(8′)H_A), 2.70–2.77 (1H, m, C(8′)H_B), 2.87–2.96 (1H, m, C(2′)*H*), 3.72 (1H, q, *J* 6.9, C(α)*H*), 7.20–7.36 (5H, m *Ph*); δ_C (100 MHz, $CDCl_3$) 23.5 (C(α)*Me*), 25.8, 26.5 (*C*H$_2$), 28.0 (C*Me*$_3$), 28.8, 31.4, 32.8 (*C*H$_2$), 34.8 (*C*(2)), 43.3 (*C*(8′)), 56.3 (*C*(2′)), 61.8 (*C*(α)), 79.6 (*C*Me$_3$), 126.7 (*p-Ph*), 127.4, 128.3 (*m-Ph*, *o-Ph*), 146.0 (*i-Ph*), 172.7 (*C*(1)); *m*/*z* (ESI$^+$) 332 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{34}NO_2^+$ ([M+H]$^+$) requires 332.2590; found 330.2590.

4.14.27. tert-Butyl (R)-2-(azocan-2′-yl)ethanoate ***41***.



Following General Procedure 4, Pearlman's catalyst (250 mg) and **40** (500 mg) in EtOAc (5 mL) under H_2 (5 atm) at rt gave the crude reaction mixture. Purification via flash column chromatography (eluent pentane/Et_2O/Et_3N, 80:20:1) gave (*R*)-**41** as a colourless oil (294 mg, 86%); $[\alpha]_D^{22}$ −1.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3364 (N–H), 2920 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.28–1.74 (11H, m, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2, C(7′)H_2, N*H*) overlapping 1.44 (9H, s, C*Me*$_3$), 2.21–2.30 (2H, m, C(2)H_2), 2.66–2.73 (1H, m, C(8′)H_A), 2.92–2.99 (1H, m, C(8′)H_B), 3.06–3.13 (1H, m, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 23.4, 25.3, 27.8 (*C*H$_2$), 28.1 (C*Me*$_3$), 29.5, 33.8 (*C*H$_2$), 43.8 (*C*(2)), 47.0 (*C*(8′)), 54.4 (*C*(2′)), 80.2 (*C*Me$_3$), 172.1 (*C*(1)); *m*/*z* (ESI$^+$) 228 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{26}NO_2^+$ ([M+H]$^+$) requires 228.1964; found 228.1965.

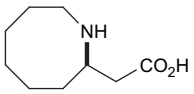
4.14.28. tert-Butyl (R)- and (RS)-2-(N-acetylazocan-2′-yl)ethanoate ***42***.



Ac_2O (0.12 mL, 1.32 mmol) was added dropwise to a stirred solution of (*R*)-**41** (100 mg, 0.44 mmol) and DMAP (cat, 2 mg) in pyridine (2 mL) and the reaction mixture stirred at rt for 12 h. The reaction mixture was quenched with H_2O (1 mL) and Et_2O was added (2 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (2×2 mL). The combined organic extracts were washed sequentially with satd aq $CuSO_4$ (5 mL) and H_2O (2×5 mL) before being dried and concentrated in vacuo. Purification via flash column chromatography (eluent pentane/EtOAc, 4:1) gave (*R*)-**42** as a colourless oil (109 mg, 92%); $[\alpha]_D^{22}$ −9.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2930 (C–H), 1727 (C=O, ester), 1644 (C=O, amide); δ_H (400 MHz, $CDCl_3$) [65:35 mixture of rotamers] 1.32–1.93 (m, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2, C(7′)H_2) overlapping 1.43 (s, C*Me*$_3$), 1.98–2.12 (m, C(7′)H_B) overlapping 2.10 (s, CO*Me*), 2.17 (s, CO*Me*), 2.30–2.41 (m, C(2)H_2), 2.54–2.65 (m, C(2)H_B), 2.72–2.80 (m, C(8′)H_A), 3.28–3.43 (m, C(8′)H_2), 3.81–3.87 (m, C(8′)H_B), 4.07–4.15 (m, C(2′)*H*), 4.47–4.58 (m, C(2′)*H*); δ_C (125 MHz, $CDCl_3$) 22.1 (CO*Me*), 22.4 (CO*Me*), 24.2, 24.8, 25.4, 25.9, 26.0, 26.1, 26.4 (*C*H$_2$), 27.9, 28.0 (C*Me*$_3$), 28.3, 29.4, 29.9 (*C*H$_2$), 40.1 (*C*(2)), 40.6 (*C*(8′)), 41.4 (*C*(2), *C*(8′)), 55.6 (*C*(2′)), 80.3, 81.1 (*C*Me$_3$), 170.3, 170.4 (NCO), 170.8, 170.9 (*C*(1)); *m*/*z* (ESI$^+$) 328 ([M+59]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{28}NO_3^+$ ([M+H]$^+$) requires 270.2069; found 270.2074. An analogous procedure applied to (*RS*)-**41**[17] (100 mg) gave (*RS*)-**42** (113 mg, 96%).

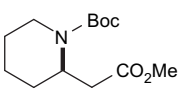
(*RS*)-**42** was analysed by chiral GC, giving complete resolution of enantiomers (run conditions: 70 °C, 90 min; 4.0 °C/min ramp; 130 °C, 240 min; (*R*)-**42** t_R=319.6 min; (*S*)-**42** t_R=324.3 min). (*R*)-**42** was therefore assessed to be 98:2 er.

4.14.29. (R)-2-(Azocan-2′-yl)ethanoic acid ***43***.



Following General Procedure 5, TFA (0.2 mL) and (*R*)-**41** (250 mg) in CH_2Cl_2 (2 mL) at rt gave the crude reaction mixture. Co-evaporation with 6 M aq HCl and purification via ion-exchange chromatography on Dowex 50WX8-200 resin (eluent 1 M aq NH_4OH) gave **43** as a white solid (163 mg, 87%); mp 197–199 °C; $[\alpha]_D^{20}$ −13.3 (*c* 1.0 in H_2O); ν_{max} (KBr) 3367 (NH_2^+, br), 2933 (C–H), 1582 (CO_2^- asymmetric), 1402 (CO_2^- symmetric); δ_H (400 MHz, D_2O) 1.45–1.84 (10H, m, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2, C(7′)H_2), 2.50–2.55 (2H, m C(2)H_2), 3.13 (1H, ddd, *J* 14.0, 7.8, 3.8, C(8′)H_A), 3.28 (1H, ddd, *J* 14.0, 7.5, 4.1, C(8′)H_A), 3.52–3.60 (1H, m, C(2′)*H*); δ_C (100 MHz, D_2O) 23.5, 24.2, 24.3, 25.0, 29.5 (*C*(3′), *C*(4′), *C*(5′), *C*(6′), *C*(7′)), 40.3 (*C*(2)), 45.1 (*C*(8′)), 55.3 (*C*(2′)), 178.5 (*C*(1)); *m*/*z* (ESI$^+$) 172 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_9H_{18}NO_2^+$ ([M+H]$^+$) requires 172.1338; found 172.1334.

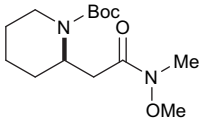
4.14.30. Methyl (R)-[N(1′)-(tert-butoxycarbonyl)piperidin-2′-yl]ethanoate ***44***.



Following General Procedure 10, Pearlman's catalyst (250 mg), **20** (500 mg, 1.93 mmol) and Boc_2O (547 mg, 2.51 mmol) in EtOAc (5 mL) under H_2 (5 atm) at rt gave the crude reaction mixture. Purification via flash column chromatography (eluent pentane/Et_2O, 20:1; increased to pentane/Et_2O, 10:1) gave **44** as a colourless oil (450 mg, 91%)[20]; $[\alpha]_D^{22}$ +8.1 (*c* 2.0 in $CHCl_3$); {lit.[20] for enantiomer $[\alpha]_D^{20}$ −8.3 (*c* 4.5 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.37–1.70 (6H,

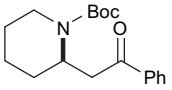
m, C(3′)H_2, C(4′)H_2, C(5′)H_2) overlapping 1.44 (9H, s, CMe_3), 2.51 (1H, dd, *J* 14.2, 7.8, C(2)H_A), 2.62 (1H, dd, *J* 14.2, 7.3, C(2)H_B), 2.74–2.77 (1H, m, C(6′)H_A), 3.65 (3H, s, O*Me*), 3.97–3.99 (1H, m, C(6′)H_B), 4.66–4.68 (1H, m, C(2′)*H*).

4.14.31. N-Methoxy-N-methyl (R)-[N(1′)-(tert-butoxycarbonyl)piperidin-2′-yl]ethanamide ***45***.



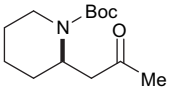
Following General Procedure 8, ^{i}PrMgCl (2.0 M in THF, 0.58 mL, 1.17 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (59 mg, 0.60 mmol) and **44** (100 mg, 0.39 mmol) in THF (5 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent pentane/EtOAc, 5:1) gave **45** as a colourless oil (99 mg, 89%)[21]; $[\alpha]_D^{22}$ +3.3 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.38–1.65 (6H, m, C(3′)H_2, C(4′)H_2, C(5′)H_2) overlapping 1.44 (9H, s, CMe_3), 2.59–2.72 (2H, m, C(2)H_2), 2.79–2.86 (1H, m, C(6′)H_A), 3.13 (3H, s, N*Me*), 3.70 (3H, s, O*Me*), 3.98–4.01 (1H, m, C(6′)H_B), 4.71–4.73 (1H, m, C(2′)*H*).

4.14.32. (R)-1-Phenyl-2-[N(1′)-(tert-butoxycarbonyl)piperidin-2′-yl]ethanone ***46***.



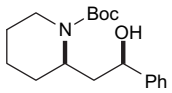
Following General Procedure 9, PhMgBr (3.0 M in Et_2O, 0.23 mL, 0.70 mmol) and **45** (100 mg, 0.35 mmol) in Et_2O (2 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent pentane/Et_2O, 10:1) gave **46** as a colourless oil, which solidified on standing to a white solid (81 mg, 76%)[23]; mp 52–54 °C; $[\alpha]_D^{22}$ −17.8 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.22–1.68 (6H, m, C(3′)H_2, C(4′)H_2, C(5′)H_2) overlapping 1.37 (9H, s, CMe_3), 2.86–2.93 (1H, m, C(6′)H_A), 3.15 (1H, dd, *J* 14.3, 6.1, C(2)H_A), 3.24 (1H, dd, *J* 14.3, 8.5, C(2)H_B), 4.04–4.08 (1H, m, C(6′)H_B), 4.83–4.86 (1H, m, C(2′)*H*).

4.14.33. (R)-[N(1′)-(tert-butoxycarbonyl)piperidin-2′-yl]propanone ***47***.



Following General Procedure 9, MeMgBr (3.0 M in Et_2O, 0.23 mL, 0.70 mmol) and **45** (100 mg, 0.35 mmol) in Et_2O (2 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent pentane/Et_2O, 10:1) gave **47** as a colourless oil (69 mg, 82%); $[\alpha]_D^{23}$ +8.2 (*c* 2.0 in $CHCl_3$); ν_{max} (film) 2935 (C–H), 1713 (C=O, ketone), 1694 (C=O, carbamate); δ_H (400 MHz, $CDCl_3$) 1.34–1.68 (6H, m, C(3′)H_2, C(4′)H_2, C(5′)H_2) overlapping 1.43 (9H, s, CMe_3), 2.17 (3H, s, C(3)H_3), 2.58–2.68 (2H, m, C(1)H_2), 2.72–2.82 (1H, m, C(6′)H_A), 3.88–4.03 (1H, m, C(6′)H_B), 4.68–4.77 (1H, m, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 18.9, 25.3 (*C*H_2), 28.4 (CMe_3), 28.5 (*C*H_2), 30.0 (*C*(3)), 39.5 (*C*(6′)), 44.3 (*C*(1)), 47.3 (*C*(2′)), 79.6 (*C*Me_3), 154.7 (*NC*O), 207.1 (*C*(2)); *m*/*z* (ESI^+) 300 ($[M+59]^+$, 100%); HRMS (ESI^+) $C_{13}H_{24}NO_3^+$ requires 242.1756; found 242.1761.

4.14.34. (1R,2′R)-1-Phenyl-2-[N(1′)-(tert-butoxycarbonyl)piperidin-2′-yl]ethanol syn- ***49***.



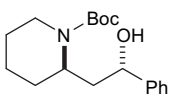
Following General Procedure 7, LiAl(O^tBu_3)H (210 mg, 0.82 mmol) and **46** (100 mg, 0.33 mmol) in THF (5 mL) at 0 °C for 6 h gave *syn*-**49** in >99:1 dr. Purification via flash column chromatography (eluent pentane/EtOAc, 10:1) gave *syn*-**49** as a colourless oil (95 mg, 94%, >99:1 dr)[21,24e,26]; $[\alpha]_D^{22}$ +48.6 (*c* 1.0 in EtOH); {lit.[26] $[\alpha]_D^{25}$ +44.8 (*c* 0.6 in EtOH)}; δ_H (400 MHz, $CDCl_3$) 1.37–1.71 (6H, m, C(3′)H_2, C(4′)H_2, C(5′)H_2) overlapping 1.46 (9H, s, CMe_3), 1.85–1.91 (1H, m, C(2)H_A), 2.06–2.15 (1H, m, C(2)H_B), 2.74–2.82 (1H, m, C(6′)H_A), 3.81–3.99 (1H, app br s, C(6′)H_B), 4.35–4.46 (1H, app br s, C(2′)*H*), 4.76–4.80 (1H, app br s, C(1)*H*), 7.25–7.39 (5H, m, *Ph*).

4.14.35. (2S,2′R)- and (2R,2′R)-1-[N(1′)-(tert-butoxycarbonyl)piperidin-2′-yl]propan-2-ol syn- ***50*** *and anti-* ***51***.

syn-**50** *anti*-**51**

Following General Procedure 7, LiAl(O^tBu)$_3$H (211 mg, 0.83 mmol) and **47** (100 mg, 0.41 mmol) in THF (5 mL) at 0 °C for 6 h gave a 96:4 mixture of *syn*-**50**:*anti*-**51**. Purification via flash column chromatography (eluent pentane/EtOAc, 10:1) gave *anti*-**51** as a colourless oil (2 mg, 2%, >99:1 dr); $[\alpha]_D^{23}$ +25.6 (*c* 0.6 in $CHCl_3$); ν_{max} (film) 3446 (O–H), 2934 (C–H), 1688, 1659 (carbamate); δ_H (400 MHz, $CDCl_3$) 1.14–1.76 (7H, m, C(1)H_2, C(3′)H_A, C(4′)H_2, C(5′)H_2) overlapping 1.20 (3H, d, *J* 6.3, C(3)H_3) and 1.45 (9H, s, CMe_3), 1.99 (1H, t, *J* 13.4, C(3′)H_B), 2.68 (1H, t, *J* 12.7, C(6′)H_A), 3.52 (1H, br s, C(2)*H*), 3.90–4.00 (1H, m, C(6′)H_B), 4.35 (1H, br s, O*H*), 4.46 (1H, m, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 19.2 (*C*H_2), 22.5 (*C*(3)), 25.5 (*C*H_2), 28.4 (CMe_3), 29.3, 39.4, 39.6 (*C*H_2), 46.5 (*C*(2′)), 63.3 (*C*(2)), 80.1 (*C*Me$_3$), 156.2 (*NC*O); *m*/*z* (ESI^+) 302 ($[M+59]^+$, 100%); HRMS (ESI^+) $C_{13}H_{26}NO_3^+$ requires 244.1913; found 244.1911. Further elution gave *syn*-**50** as a colourless oil (93 mg, 92%, >99:1 dr); $[\alpha]_D^{23}$ +35.5 (*c* 0.8 in $CHCl_3$); ν_{max} (film) 3431 (O–H), 2933 (C–H), 1690, 1667 (carbamate); δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.3, C(3)H_3), 1.32–1.92 (8H, m, C(1)H_2, C(3′)H_2, C(4′)H_2, C(5′)H_2) overlapping 1.46 (9H, s, CMe_3), 2.83 (1H, t, *J* 12.7, C(6′)H_A), 3.79–3.88 (1H, m, C(2)*H*), 3.90–4.03 (1H, m, C(6′)H_B), 4.28–4.37 (1H, m, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 19.1 (*C*H_2), 23.5 (*C*(3)), 25.5 (*C*H_2), 28.5 (CMe_3), 30.9, 39.8, 40.0 (*C*H_2), 48.6 (*C*(2′)), 66.6 (*C*(2)), 79.8 (*C*Me$_3$), 155.8 (*NC*O); *m*/*z* (ESI^+) 302 ($[M+59]^+$, 100%); HRMS (ESI^+) $C_{13}H_{26}NO_3^+$ requires 244.1913; found 244.1913.

4.14.36. (1S,2′R)-1-Phenyl-2-[N-(tert-butoxycarbonyl)piperidin-2′-yl]-ethanol anti- ***52***.

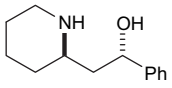


Following General Procedure 11, BH_3·THF complex (1.0 M in THF, 0.33 mL, 0.33 mmol), (*R*)-*B*-Me-CBS (1.0 M in PhMe, 0.02 mL,

0.016 mmol) in THF (2 mL) at 0 °C, and **46** (100 mg, 0.33 mmol) in THF (2 mL) at 0 °C gave a 25:75 ratio of *syn*-**49**:*anti*-**52**. Purification via flash column chromatography (eluent pentane/EtOAc, 10:1) gave *anti*-**52** as a colourless oil, which solidified on standing to a white solid (68 mg, 67%, >99:1 dr)[21,24e,26]; mp 58–60 °C; $[\alpha]_D^{22}$ +30.1 (*c* 1.0 in EtOH); {lit.[26] $[\alpha]_D^{25}$ +26.5 (*c* 0.6 in EtOH)}; δ_H (400 MHz, $CDCl_3$) 1.30–1.68 (6H, m, C(3′)H_2, C(4′)H_2, C(5′)H_2) overlapping 1.50 (9H, s, CMe_3), 1.71–1.83 (1H, m, C(2)H_A), 2.17–2.27 (1H, m, C(2)H_B), 2.73–2.86 (1H, m, C(6′)H_A), 3.95–4.11 (1H, m, C(6′)H_B), 4.35–4.50 (1H, m, C(2′)*H*), 4.54–4.66 (1H, m, C(1)*H*), 7.24–7.39 (5H, m *Ph*). Further elution gave *syn*-**49** as a colourless oil (19 mg, 19%, >99:1 dr).

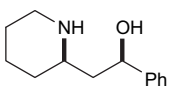
Under identical conditions, reduction of **46** (100 mg) with BH_3·THF complex alone gave a 56:44 mixture of *syn*-**49**:*anti*-**52**, and reduction with BH_3·THF complex in the presence of (*S*)-*B*-Me-CBS gave a 92:8 mixture of *syn*-**49**:*anti*-**52**. This crude reaction mixture was purified via flash column chromatography to give *syn*-**49** (83 mg, 82%, >99:1 dr) and *anti*-**52** (4 mg, 3%, >99:1 dr).

4.14.37. (1S,2′R)-1-Phenyl-2-(piperidine-2′-yl)ethanol [(−)-norallosedamine] ***53****.*



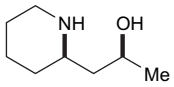
Following General Procedure 12, 3 M aq HCl (1 mL) and *anti*-**52** (100 mg, 0.33 mmol) in MeOH (5 mL) at 50 °C gave the crude reaction mixture. The crude mixture was dissolved in 1 M aq HCl (10 mL), and washed with CH_2Cl_2 (2×10 mL). The aqueous layer was basified with 1 M aq. NaOH and extracted with CH_2Cl_2 (5×10 mL). The combined organics were dried, filtered and concentrated in vacuo to give **53** as white solid (60 mg, 89%, >99:1 dr); mp 80–81 °C; $[\alpha]_D^{23}$ −23.0 (*c* 2.0 in EtOH); {lit.[30] for enantiomer $[\alpha]_D^{21}$ +37.2 (*c* 3.0 in EtOH)}; ν_{max} (KBr) 3258 (O–H, N–H, br), 2924 (C–H), 1472; δ_H (400 MHz, $CDCl_3$) 1.05–1.16 (1H, m, C(3′)H_A), 1.25–1.57 (1H, m, C(5′)*HA*), 1.50–1.75 (5H, m, C(2)H_2, C(3′)*HB*, C(4′)H_A, C(5′)H_B), 1.79–1.86 (1H, m, C(4′)H_B), 2.65–2.72 (1H, ddd, *J* 3.0, 11.8, 13.6, C(6′)H_A), 2.98 (1H, app. tt, *J* 10.8, 2.8, C(2′)*H*), 3.04–3.10 (1H, m, C(6′)H_B), 3.80–4.10 (2H, br s, O*H* and N*H*), 4.93 (1H, dd, *J* 8.1, 2.5, C(1)*H*), 7.22–7.40 (5H, m *Ph*); δ_C (100 MHz, $CDCl_3$) 24.5 (*C*(4′)), 27.2 (*C*(5′)), 37.2 (*C*(3′)), 45.1 (*C*(2)), 46.0 (*C*(6′)), 58.2 (*C*(2′)), 75.4 (*C*(1)), 125.6, 126.9, 128.2, 128.3, (*m*-, *p*-, *o*-*Ph*), 145.3 (*i*-*Ph*); *m*/*z* (ESI$^+$) 206 ($[M+H]^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{20}NO^+$ ($[M+H]^+$) requires 206.1539; found 206.1542.

4.14.38. (1R,2′R)-1-Phenyl-2-(piperidin-2′-yl)ethanol [(+)-norsedamine] ***1****.*



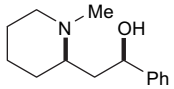
Following General Procedure 12, 3 M aq HCl (2 mL) and *syn*-**49** (250 mg, 0.82 mmol) in MeOH (8 mL) at 50 °C gave the crude reaction mixture. The crude mixture was dissolved in 1 M aq HCl (20 mL), and washed with CH_2Cl_2 (2×20 mL). The aqueous layer was basified with 1 M aq NaOH and extracted with CH_2Cl_2 (5×20 mL). The combined organic layers were dried, filtered and concentrated in vacuo to give **1** as a colourless crystalline solid (151 mg, 90%, >99:1 dr); mp 82–84 °C; $[\alpha]_D^{23}$ +24.6 (*c* 1.0 in MeOH); {lit.[30] $[\alpha]_D^{17}$ +33.2 (*c* 2.0 in MeOH)}; ν_{max} (KBr) 3363 (O–H, N–H, br), 2934 (C–H), 1450, 1061; δ_H (400 MHz, $CDCl_3$) 1.31–1.40 (3H, m, C(3′)H_A, C(4′)H_A, C(5′)H_A), 1.54–1.61 (2H, m, C(3′)H_B, C(4′)H_B), 1.69–1.75 (1H, m, C(2)H_A), 1.79–1.88 (2H, m, C(2)H_B, C(5′)H_B), 2.52–2.58 (1H, m, C(6′)H_A), 2.75–2.80 (1H, m, C(2′)*H*), 3.03–3.07 (1H, m, C(6′)H_B), 3.70–3.85 (2H, br s, N*H*, O*H*), 5.03 (1H, dd, *J* 7.5, 4.1, C(1)*H*), 7.22–7.40 (5H, m *Ph*); δ_C (100 MHz, $CDCl_3$) 21.5 (*C*(5′)), 26.4, 32.0 (*C*(3′), *C*(4′),), 44.1 (*C*(2)), 46.6 (*C*(6′)), 54.4 (*C*(2′)), 71.8 (*C*(1′)), 125.7, 126.7, 128.2 (*p*-, *m*-, *o*-*Ph*), 145.5 (*i*-*Ph*); *m*/*z* (ESI$^+$) 206 ($[M+H]^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{20}NO^+$ ($[M+H]^+$) requires 206.1539; found 206.1536.

4.14.39. (2S,2′R)-1-(Piperidin-2′-yl)propan-2-ol [(+)-allosedridine] ***2****.*



Following General Procedure 12, 3 M aq HCl (0.5 mL) and *syn*-**50** (50 mg, 0.21 mmol) in MeOH (2 mL) at 50 °C gave the crude reaction mixture. Basification and purification via flash column chromatography (eluent $CHCl_3$/MeOH/Et_3N, 98:2:1) gave **2** as a colourless crystalline solid (26 mg, 87%); mp 79–81 °C; $[\alpha]_D^{25}$ +20.1 (*c* 1.0 in MeOH); {lit.[28] $[\alpha]_D^{29}$ +16.2 (*c* 4.0 in MeOH); lit.[29] $[\alpha]_D^{25}$ +17.1 (*c* 1.55 in MeOH)}; ν_{max} (KBr) 3284 (O–H, N–H, br), 2932 (C–H); δ_H (400 MHz, $CDCl_3$) 1.07–1.20 (1H, m, C(3′)H_A) overlapping 1.13 (3H, d, *J* 6.3, C(3)H_3), 1.24–1.39 (2H, m, C(1)H_A, C(5′)H_A), 1.43–1.55 (2H, m, C(1)H_B, C(4′)H_A), 1.57–1.68 (2H, m, C(3′)H_B, C(5′)H_B), 1.76–1.85 (1H, m, C(4′)H_B), 2.55–2.65 (1H, m, C(6′)H_A), 2.70–2.78 (1H, m, C(2′)H_A), 3.02–3.09 (1H, m, C(6′)H_B), 3.42 (2H, br s, O*H*, N*H*), 3.95–4.03 (1H, m, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 23.9 (*C*(3)), 24.4 (*C*(4′)), 27.0 (*C*(5′)), 34.0 (*C*(3′)), 44.1 (*C*(1)), 45.9 (*C*(6′)), 58.2 (*C*(2′)), 69.0 (*C*(2)); *m*/*z* (ESI$^+$) 143 ($[M+H]^+$, 100%); HRMS (ESI$^+$) $C_8H_{18}NO^+$ ($[M+H]^+$) requires 143.1388; found 143.1391.

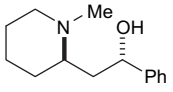
4.14.40. (1R,2′R)-1-Phenyl-2-[N(1′)methylpiperidin-2′-yl]ethanol [(+)-sedamine] ***3****.*



Following General Procedure 13, *syn*-**49** (280 mg, 0.91 mmol), lithium aluminium hydride (175 mg, 4.5 mmol) in THF (13 mL) gave the crude reaction mixture. The crude mixture was dissolved in 1 M aq HCl (10 mL), and washed with CH_2Cl_2 (2×10 mL). The aqueous layer was basified with 1 M aq NaOH and extracted with CH_2Cl_2 (5×10 mL). The combined organics were dried, filtered and concentrated in vacuo to give **3** as a colourless oil, which solidified on standing to a white solid (171 mg, 86%, >99:1 dr); $[\alpha]_D^{22}$ +81.5 (*c* 1.1 in MeOH); $[\alpha]_D^{25}$ +82.1 (*c* 1.0 in EtOH); {lit. for enantiomer[30] $[\alpha]_D^{21}$ −81.7 (*c* 3.0 in MeOH); lit.[31] $[\alpha]_D^{32}$ +87.0 (*c* 1.1 in EtOH)}; ν_{max} (film) 3356 (O–H, N–H, br), 2934 (C–H), 1451; δ_H (400 MHz, $CDCl_3$) 1.30–1.37 (1H, m, C(3′)H_A), 1.46–1.50 (3H, m, C(2)H_A, C(4′)H_A, C(5′)H_A), 1.55–1.68 (2H, m, C(4′)H_B, C(5′)H_B), 1.75–1.80 (1H, m, C(3′)H_B), 2.09–2.17 (1H, m, C(2)H_B), 2.49 (3H, s, NCH_3), 2.53–2.58 (1H, m, C(6′)H_A), 2.83–2.87 (1H, m, C(2′)H_B) and 3.05–3.09 (1H, m, C(6′)H_B), 4.90 (1H,

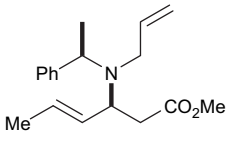
dd, *J* 2.8, 10.7, C(1)*H*), 7.23–7.27 (1H, m *Ph*), 7.32–7.40 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.6 (*C*(5′)), 22.4 (*C*(4′)), 25.9 (*C*(3′)), 39.8 (*C*(2)), 40.0 (NCH_3), 51.5 (*C*(6′)), 60.9 (*C*(2′)), 74.5 (*C*(1)), 125.6 (*p-Ph*), 127.0, 128.3 (*m-Ph*, *o-Ph*), 145.6 (*i-Ph*); *m*/*z* (ESI^+) 220 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{21}NO^+$ ($[M+H]^+$) requires 220.1696; found 220.1702.

4.14.41. (1S,2′R)-1-Phenyl-2-[N(1′)-methylpiperidin-2′-yl]ethanol [(+)-allosedamine] ***4***.



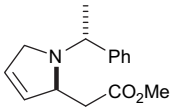
Following General Procedure 13, *anti*-**52** (200 mg, 0.65 mmol), lithium aluminium hydride (124 mg, 3.3 mmol) in THF (9.5 mL) gave the crude reaction mixture. The crude mixture was dissolved in 1 M aq HCl (10 mL), and washed with CH_2Cl_2 (2×10 mL). The aqueous layer was basified with 1 M aq NaOH and extracted with CH_2Cl_2 (5×10 mL). The combined organics were dried, filtered and concentrated in vacuo to give **4** as a colourless oil, which solidified on standing to a white solid (110 mg, 77%, 98:2 dr); mp 76–78 °C; $[\alpha]_D^{22}$ +29.7 (*c* 1.0 in MeOH); {lit.[30] $[\alpha]_D^{21}$ +32.0 (*c* 2.0 in MeOH)}; ν_{max} (KBr) 3319 (O–H, N–H, br), 2934 (C–H), 1451; δ_H (400 MHz, $CDCl_3$) 1.26–1.36 (1H, m, C(4′)H_A), 1.60–1.70 (4H, m, C(2)H_A, C(3′)H_A, C(5′)H_2), 1.79–1.89 (2H, m, C(3′)H_B, C(4′)H_B), 2.09–2.18 (2H, m, C(2)H_B, C(6′)H_A), 2.40–2.43 (1H, m, C(2′)*H*), 2.46 (3H, s, NCH_3), 2.96–3.01 (1H, m, C(6′)H_B), 5.07 (1H, dd, *J* 10.6, 3.5, C(1)*H*), 7.23–7.38 (5H, m *Ph*); δ_C (100 MHz, $CDCl_3$) 23.8 (*C*(4′)), 24.6 (*C*(5′)), 28.9(*C*(3′)), 39.6 (*C*(2)), 42.8 (NCH_3), 56.6 (*C*(6′)), 62.4 (*C*(2′)), 71.3 (*C*(1)), 125.6 (*p-Ph*), 126.9, 128.2 (*m-Ph*, *o-Ph*), 145.2 (*i-Ph*); *m*/*z* (ESI^+) 220 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{22}NO^+$ ($[M+H]^+$) requires 220.1696; found 220.1703.

4.14.42. Methyl (3S,4E,αR)-3-[N-allyl-N-(α-methylbenzyl)amino]hex-4-enoate ***54***.



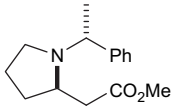
Following General Procedure 1, BuLi (2.5 M in hexanes, 4.91 mL, 12.3 mmol), (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amine (2.05 g, 12.7 mmol) in THF (10 mL) at −78 °C, and **15** (1.00 g, 7.93 mmol) in THF (10 mL) at −78 °C gave **54** in 97:3 dr. Purification via flash column chromatography (eluent pentane/Et_2O, 50:1) gave **54** as a colourless oil (1.89 g, 83%, 97:3 dr); $[\alpha]_D^{13}$ −2.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2958 (C–H), 1740 (C═O), 1640 (C═C); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.8, C(α)*Me*), 1.72 (3H, d, *J* 5.3, C(6)H_3), 2.37 (1H, dd, *J* 14.3, 7.6, C(2)H_A), 2.53 (1H, dd, *J* 14.3, 7.6, C(2)H_B), 3.11–3.23 (2H, m, NCH_2), 3.58 (3H, s, O*Me*), 3.84–3.90 (1H, m, C(3)*H*), 4.05 (1H, q, *J* 6.8, C(α)*H*), 5.02–5.15 (2H, m, CH═CH_2), 5.48–5.56 (2H, m, C(4)*H*, C(5)*H*), 5.80–5.87 (1H, m, C*H*═CH_2), 7.20–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.9, 18.0 (*C*(6), C(α)*Me*), 38.8 (*C*(2)), 49.4 (NCH_2), 51.3 (O*Me*), 56.7, 56.7 (*C*(3), *C*(α)), 115.7 (CH═CH_2), 126.5 (*p-Ph*), 127.0, 127.6, 128.0, 130.6 (*C*(4), *C*(5), *m-Ph*, *o-Ph*), 138.8 (CH═CH_2), 145.1 (*i-Ph*), 172.4 (*C*(1)); *m*/*z* (ESI^+) 288 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{18}H_{26}NO_2^+$ ($[M+H]^+$) requires 288.1964; found 288.1959.

4.14.43. Methyl (2′S,αR)-2-[N(1′)-(α-methylbenzyl)-2′,5′-dihydro-1H-pyrrol-2′-yl]ethanoate ***55***.



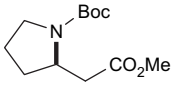
Following General Procedure 2, Grubbs I (115 mg, 0.139 mmol) and **54** (1.00 g, 3.48 mmol) in CH_2Cl_2 (300 mL) gave the crude reaction mixture. Purification by treatment with $P(CH_2OH)_3$ (1.73 g, 13.9 mmol), Et_3N (0.97 mL, 6.96 mmol) and silica in CH_2Cl_2 (~30 mL) and filtration through a short plug of silica gel (eluent pentane/Et_2O, 20:1) gave **55** as a colourless oil (685 mg, 80%, >99:1 dr); $[\alpha]_D^{20}$ +142.1 (*c* 0.7 in $CHCl_3$); ν_{max} (film) 2953 (C–H), 1738 (C═O); δ_H (400 MHz, $CDCl_3$) 1.45 (3H, d, *J* 6.8, C(α)*Me*), 2.46 (1H, dd, *J* 14.9, 8.8, C(2)H_A), 2.69 (1H, dd, *J* 14.9, 4.3, C(2)H_B), 3.38–3.44 (1H, m, C(5′)H_A), 3.60–3.65 (1H, m, C(5′)H_B), 3.68 (3H, s, O*Me*), 3.86 (1H, q, *J* 6.8, C(α)*H*), 4.18–4.24 (1H, m, C(2′)*H*), 5.72–5.78 (2H, m, C(3′)*H*, C(4′)*H*), 7.21–7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.8 (C(α)*Me*), 41.6 (*C*(2)), 51.4 (O*Me*), 58.5 (*C*(5′)), 62.2 (*C*(α)), 64.5 (C(2′)), 126.8 (*p-Ph*), 127.4, 128.3, 130.5 (*C*(3′), *C*(4′), *m-Ph*, *o-Ph*), 145.1 (*i-Ph*), 172.4 (*C*(1)); *m*/*z* (ESI^+) 246 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{15}H_{20}NO_2^+$ ($[M+H]^+$) requires 246.1494; found 244.1499.

4.14.44. Methyl (2′R,αR)-2-[N(1′)-(α-methylbenzyl)pyrrolidin-2′-yl]-ethanoate ***56***.



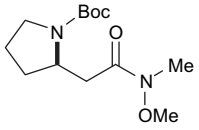
Following General Procedure 3, Wilkinson's catalyst (94.2 mg, 0.102 mmol) and **55** (500 mg, 2.04 mmol) in benzene (5 mL) under H_2 (4 atm) at rt gave a 96:4 mixture of **56**:**57**. Purification via flash column chromatography on silica gel (eluent pentane/Et_2O, 10:1) gave **57** as a colourless oil (20 mg, 4%); $[\alpha]_D^{21}$ +20.8 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 2934 (C–H), 1739 (C═O); δ_H (400 MHz, $CDCl_3$) 1.83 (3H, d, *J* 7.0, C(α)*Me*), 3.53 (2H, AB system, J_{AB} 16.4, C(2)H_2), 3.57 (3H, s, O*Me*), 5.42 (1H, q, *J* 7.0, C(α)*H*), 6.12–6.15 (1H, m, *Ar*), 6.21 (1H, app t, *J* 3.3, *Ar*), 6.87–6.88 (1H, m, *Ar*), 7.00–7.02 (2H, m, *Ph*), 7.22–7.33 (3H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.6 (C(α)*Me*), 32.5 (*C*(2)), 52.0 (O*Me*), 55.0 (*C*(α)), 107.4, 109.3, 118.4 (*Ar*), 124.9 (*i-Ar*), 125.7 (*p-Ph*), 127.2, 128.7 (*m-Ph*, *o-Ph*), 143.4 (*i-Ph*), 171.0 (*C*(1)); *m*/*z* (ESI^+) 302 ($[M+59]^+$, 100%); HRMS (ESI^+) $C_{15}H_{18}NO_2^+$ ($[M+H]^+$) requires 244.1338; found 244.1339. Further elution gave **56** as a colourless oil (440 mg, 87%, >99:1 dr); $[\alpha]_D^{21}$ +65.2 (*c* 3.0 in $CHCl_3$); ν_{max} (film) 2971 (C–H), 1737 (C═O); δ_H (400 MHz, $CDCl_3$) 1.44 (3H, d, *J* 6.8, C(α)*Me*), 1.54–1.66 (2H, m, C(3′)H_A, C(4′)H_A), 1.69–1.76 (1H, m, C(4′)H_B), 1.83–1.93 (1H, m, C(3′)H_B), 2.32 (1H, dd, *J* 14.6, 9.8, C(2)H_A), 2.39–2.45 (1H, m, C(5′)H_A), 2.66 (1H, dd, *J* 14.6, 3.6, C(2)H_B), 2.78–2.83 (1H, m, C(5′)H_B), 3.12–3.18 (1H, m, C(2′)*H*), 3.66 (3H, s, O*Me*), 3.76 (1H, q, *J* 6.8, C(α)*H*), 7.22–7.34 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.2 (C(α)*Me*), 22.8 (*C*(4′)), 30.9 (*C*(3′)), 40.1 (*C*(2)), 50.1 (*C*(5′)), 51.4 (O*Me*), 56.8 (*C*(2′)), 60.8 (*C*(α)), 126.9 (*p-Ph*), 127.8, 128.1 (*m-Ph*, *o-Ph*), 143.1 (*i-Ph*), 172.9 (*C*(1)); *m*/*z* (ESI^+) 248 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{15}H_{22}NO_2^+$ ($[M+H]^+$) requires 248.1651; found 248.1648.

*4.14.45. Methyl (R)-2-[N(1′)-(tert-butoxycarbonyl)pyrrolidin-2′-yl]-ethanoate **58**.*



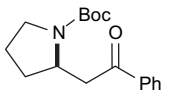
Following General Procedure 10, Pearlman's catalyst (250 mg), **56** (500 mg, 2.02 mmol) and Boc_2O (574 mg, 2.63 mmol) in EtOAc (5 mL) under H_2 (5 atm) at rt gave the crude reaction mixture. Purification via flash column chromatography (eluent pentane/Et_2O, 20:1; increased to pentane/Et_2O, 10:1) gave **58** as a colourless oil (385 mg, 78%)[34]; $[\alpha]_D^{22}$ +31.5 (*c* 2.0 in $CHCl_3$); ν_{max} (film) 2975 (C–H), 1740 (C=O, ester), 1695 (C=O, carbamate); δ_H (400 MHz, CDCl3) 1.44 (9H, s, C*Me*$_3$), 1.72–1.90 (3H, m, C(3′)H_2, C(4′)H_A), 1.90–2.11 (1H, m, C(4′)H_B), 2.35 (1H, dd, *J* 15.0, 9.7, C(2)H_A), 2.80 and 2.92 (1H, br d, *J* 15.0, C(2)H_B), 3.25–3.40 (2H, m, C(5′)H_2), 3.65 (3H, s, O*Me*), 4.08–4.22 (1H, m, C(2′)*H*); δ_H (500 MHz, DMSO-d_6, 373 K) 1.43 (9H, s, C*Me*$_3$), 1.69–1.85 (3H, m, C(3′)H_2, C(4′)H_A), 1.99–2.03 (1H, m, C(4′)H_B), 2.39 (1H, dd, *J* 14.8, 8.8, C(2)H_A), 2.72 (1H, dd, *J* 14.8, 3.8, C(2)H_B), 3.21–3.31 (2H, m, C(5′)H_2), 3.62 (3H, s, O*Me*), 4.00–4.03 (1H, m, C(2′)*H*); δ_C (125 MHz, DMSO-d_6, 373 K) 23.1 (*C*(3′)), 28.6 (C*Me*$_3$), 31.0 (*C*(4′)), 39.0 (*C*(2)), 46.5 (*C*(5′)), 51.5 (O*Me*), 54.3 (*C*(2′)), 79.0 (*C*Me$_3$), 153.9 (N*C*O), 171.6 (*C*(1)); *m*/*z* (ESI$^+$) 302 ([M+59]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{22}NO_4^+$ ([M+H]$^+$) requires 244.1549; found 244.1541.

*4.14.46. N-Methoxy-N-methyl (R)-2-[N(1′)-(tert-butoxycarbonyl)-pyrrolidin-2′-yl]ethanamide **59**.*



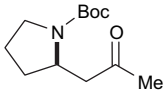
Following General Procedure 8, ^{i}PrMgCl (2.0 M in THF, 1.23 mL, 2.47 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (124 mg, 1.27 mmol) and **58** (200 mg, 0.82 mmol) in THF (5 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent pentane/EtOAc, 5:1) gave **59** as a colourless oil (205 mg, 92%); $[\alpha]_D^{22}$ +42.5 (*c* 4.5, in $CHCl_3$); ν_{max} (film) 2973 (C–H), 1694 (C=O, carbamate), 1667 (C=O, amide); δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, C*Me*$_3$), 1.73–1.90 (3H, m, C(3′)H_A, C(4′)H_2), 2.02–2.12 (1H, m, C(3′)H_B), 2.40–2.48 (1H, m, C(2)H_A), 2.96 (1H, app br s, C(2)H_B), 3.17 (3H, s, N*Me*), 3.30–3.40 (2H, app br s, C(5′)H_2), 3.69 (3H, s, O*Me*), 4.17–4.25 (1H, br m, C(2′)*H*); δ_H (500 MHz, DMSO-d_6, 373 K) 1.42 (9H, s, C*Me*$_3$), 1.67–1.89 (3H, m, C(3′)H_A, C(4′)H_2), 1.94–2.01 (1H, m, C(3′)H_B), 2.44 (1H, dd, *J* 15.1, 9.5, C(2)H_A), 2.83 (1H, dd, *J* 15.1, 3.8, C(2)H_B), 3.06 (3H, s, N*Me*), 3.24–3.32 (2H, m, C(5′)H_2), 3.67 (3H, s, O*Me*), 4.04–4.09 (1H, br m, C(2′)*H*); δ_C (125 MHz, DMSO-d_6, 373 K) 23.1 (*C*(3′)), 28.7 (C*Me*$_3$), 31.1 (*C*(4′)), 32.6 (N*Me*), 36.6 (*C*(2)), 46.5 (*C*(5′)), 54.3 (*C*(2′)), 61.4 (O*Me*), 78.8 (*C*Me$_3$), 153.9 (N′*C*O), 171.7 (*C*(1)); *m*/*z* (ESI$^+$) 331 ([M+59]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{24}N_2NaO_4^+$ ([M+Na]$^+$) requires 295.1634; found 295.1648.

*4.14.47. (R)-1-Phenyl-2-[N(1′)-(tert-butoxycarbonyl)pyrrolidin-2′-yl]ethanone **60**.*



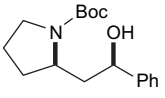
Following General Procedure 9, PhMgBr (3.0 M in Et_2O, 0.24 mL, 0.73 mmol) and **59** (100 mg, 0.37 mmol) in Et_2O (2 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent pentane/Et_2O, 10:1) gave **60** as a colourless oil (85 mg, 81%); $[\alpha]_D^{23}$ +20.7 (*c* 3.0 in $CHCl_3$); ν_{max} (film) 2975 (C–H), 1692 (C=O, carbamate), 1683 (C=O, ketone); δ_H (400 MHz, CDCl3) 1.46 (9H, s, C*Me*$_3$), 1.72–1.91 (3H, m, C(3′)H_A, C(4′)H_2), 1.98–2.14 (1H, br m, C(3′)H_B), 2.75–2.91 (1H, br m, C(2)H_A), 3.26–3.45 (2H, br m, C(5′)H_2), 3.51–3.76 (1H, m, C(2)H_B), 4.30–4.36 (1H, m, C(2′)*H*), 7.42–7.50 (2H, br m, *Ph*), 7.50–7.60 (1H, br m, *Ph*), 7.94–8.07 (2H, br m, *Ph*); δ_H (500 MHz, DMSO-d_6, 373 K) 1.39 (9H, s, C*Me*$_3$), 1.66–1.71 (1H, m, C(3′)H_A), 1.76–1.82 (1H, m, C(4′)H_A), 1.85–1.94 (1H, m, C(4′)H_B), 1.98–2.06 (1H, m, C(3′)H_B), 3.03 (1H, dd, *J* 15.5, 8.9, C(2)H_A), 3.27–3.35 (2H, m, C(5′)H_2), 3.43 (1H, dd, *J* 15.5, 3.5, C(2)H_B), 4.19–4.24 (1H, m, C(2′)*H*), 7.51–7.54 (2H, m, *Ph*), 7.61–7.65 (1H, m, *Ph*), 7.97–7.99 (2H, m, *Ph*); δ_C (125 MHz, DMSO-d_6, 373 K) 23.2 (*C*(3′)), 28.7 (C*Me*$_3$), 31.2 (*C*(4′)), 43.5 (*C*(2)), 46.5 (*C*(5′)), 54.5 (*C*(2′)), 79.0 (*C*Me$_3$), 128.4, 128.9, 133.4 (*p-Ph*, *m-Ph*, *o-Ph*), 137.6 (*i-Ph*), 153.9 (NCO), 199.0 (*C*(1)); *m*/*z* (ESI$^+$) 312 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{24}NO_3^+$ ([M+H]$^+$) requires 290.1756; found 290.1756.

*4.14.48. (R)-[N(1′)-(tert-butoxycarbonyl)pyrrolidin-2′-yl]propanone **61**.*



Following General Procedure 9, MeMgBr (3.0 M in Et_2O, 0.24 mL, 0.73 mmol) and **59** (100 mg, 0.37 mmol) in Et_2O (2 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent pentane/Et_2O, 10:1) gave **61** as a colourless oil (74 mg, 89%); $[\alpha]_D^{23}$ +31.6 (*c* 2.5 in $CHCl_3$); ν_{max} (film) 2974 (C–H), 1713 (C=O, ketone), 1693 (C=O, carbamate); δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, C*Me*$_3$), 1.57–1.64 (1H, m, C(3′)H_A), 1.76–1.82 (2H, m, C(4′)H_2), 2.00–2.09 (1H, m, C(3′)H_B), 2.12 (3H, s, C(3)H_3), 2.32–2.42 (1H, m, C(1)H_A), 2.89–3.10 (1H, m, C(1)H_B), 3.26–3.35 (2H, m, C(5′)H_2), 4.06–4.16 (1H, m, C(2′)*H*); δ_H (500 MHz, DMSO-d_6, 373 K) 1.42 (9H, s, C*Me*$_3$), 1.55–1.61 (1H, m, C(3′)H_A), 1.72–1.86 (2H, m, C(4′)H_2), 1.95–2.03 (1H, m, C(3′)H_B), 2.10 (3H, s, C(3)H_3), 2.50 (1H, dd, *J* 15.8, 9.1, C(1)H_A), 2.84 (1H, dd, *J* 15.8, 4.0, C(1)H_B), 3.21–3.31 (2H, m, C(5′)H_2), 4.01–4.06 (1H, m, C(2′)*H*); δ_C (125 MHz, DMSO-d_6, 373 K) 23.2 (*C*(3′)), 28.7 (C*Me*$_3$), 30.6 (*C*(3)), 31.3 (*C*(4′)), 46.4 (*C*(5′)), 48.2 (*C*(1)), 53.7 (*C*(2′)), 78.9 (*C*Me$_3$), 153.9 (NCO), 206.9 (*C*(2)); *m*/*z* (ESI$^+$) 250 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{22}NO_3^+$ ([M+H]$^+$) requires 228.1600; found 228.1606.

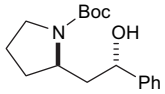
*4.14.49. (1R,2′R)-1-Phenyl-2-[N(1′)-(tert-butoxycarbonyl)pyrrolidin-2′-yl]ethanol syn-**62**.*



Following General Procedure 7, LiAl(O^{t}Bu)$_3$H (220 mg, 0.86 mmol) and **60** (100 mg, 0.35 mmol) in THF (5 mL) at 0 °C for 6 h gave *syn*-**62** in >99:1 dr. Purification via flash column chromatography (eluent pentane/EtOAc, 10:1) gave *syn*-**62** as a colourless oil (97 mg, 96%, >99:1 dr); $[\alpha]_D^{23}$ +87.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3412 (O–H), 2974 (C–H), 1692, 1668 (carbamate); δ_H

(400 MHz, $CDCl_3$) 1.46 (9H, s, CMe_3), 1.63–2.23 (6H, m, C(2)H_2, C(3′)H_2, C(4′)H_2), 3.30–3.38 (2H, m, C(5′)H_2), 4.05–4.15 (1H, m, C(2′)*H*), 4.72–4.83 (1H, m, C(1)*H*), 7.22–7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.8 (*C*(3′)), 28.5 (CMe_3), 32.4 (*C*(4′)), 46.3, 46.4 (*C*(2), *C*(5′)), 55.7 (*C*(2′)), 72.7 (*C*(1)), 79.8 (*C*Me$_3$), 125.6 (*p-Ph*), 127.0, 128.3 (*m-Ph*, *o-Ph*), 144.3 (*i-Ph*), 155.3 (NCO); *m*/*z* (ESI$^+$) 350 ([M+59]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{25}NNaO_3^+$ ([M+Na]$^+$) requires 314.1732; found 314.1734.

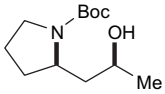
*4.14.50. (1S,2′R)-1-Phenyl-2-[N(1′)-(tert-butoxycarbonyl)pyrrolidin-2′-yl]ethanol anti-**63**.*



Following General Procedure 11, BH_3·THF complex (1.0 M in THF, 0.35 mL, 0.35 mmol), (*R*)-*B*-Me-CBS (1.0 M in PhMe, 0.02 mL, 0.017 mmol) in THF (2 mL) at 0 °C, and **60** (100 mg, 0.35 mmol) in THF (2 mL) at 0 °C, gave a 15:85 mixture of *syn*-**62**:*anti*-**63**. Purification via flash column chromatography (eluent pentane/EtOAc, 10:1) gave *anti*-**63** as a colourless oil, which solidified on standing to a colourless solid (72 mg, 71%, >99:1 dr); mp 70–72 °C; $[\alpha]_D^{23}$ +23.6 (*c* 0.6 in $CHCl_3$); ν_{max} (film) 3366 (O–H), 2975 (C–H), 1682, 1659 (carbamate); δ_H (400 MHz, $CDCl_3$) 1.50 (9H, s, CMe_3), 1.55–2.07 (6H, m, C(2)H_2, C(3′)H_2, C(4′)H_2), 3.34–3.45 (2H, m, C(5′)H_2), 4.27–4.35 (1H, m, C(2′)*H*), 4.59–4.68 (1H, m, C(1)*H*), 5.47 (1H, br s, O*H*), 7.22–7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.6 (*C*(3′)), 28.5 (CMe_3), 31.2 (*C*(4′)), 46.4, 46.7 (*C*(2), *C*(5′)), 53.9 (*C*(2′)), 70.0 (*C*(1)), 80.1 (*C*Me$_3$), 125.7 (*p-Ph*), 126.8, 128.2 (*m-Ph*, *o-Ph*), 144.3 (*i-Ph*), 156.8 (NCO); *m*/*z* (ESI$^+$) 350 ([M+59]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{26}NO_3^+$ ([M+H]$^+$) requires 292.1913; found 292.1915. Further elution gave *syn*-**62** as a colourless oil (12 mg, 12%, >99:1 dr).

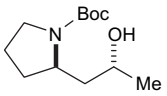
Under identical conditions, reduction of **60** (100 mg) with BH_3·THF complex alone gave a 50:50 mixture of *syn*-**62**:*anti*-**63**, and reduction with BH_3·THF complex in the presence of (*S*)-*B*-Me-CBS gave an 88:12 mixture of *syn*-**62**:*anti*-**63**. This crude reaction mixture was purified via flash column chromatography to give *syn*-**62** (79 mg, 78%, >99:1 dr) and *anti*-**63** (11 mg, 10%, >99:1 dr).

*4.14.51. (2S,2′R)-1-[N(1′)-(tert-butoxycarbonyl)pyrrolidin-2′-yl]propan-2-ol syn-**64**.*



Following General Procedure 7, $LiAl(O^tBu)_3H$ (280 mg, 1.10 mmol) and **61** (100 mg, 0.35 mmol) in THF (2 mL) at 0 °C for 6 h gave a 97:3 mixture of *syn*-**64**:*anti*-**65**. Purification via flash column chromatography (eluent pentane/EtOAc, 10:1) gave *anti*-**65** as a colourless oil (1 mg, 1%, >99:1 dr). Further elution gave *syn*-**64** as a colourless oil (95 mg, 94%, >99:1 dr); $[\alpha]_D^{23}$ +78.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3426 (O–H), 2971 (C–H), 1694, 1673 (carbamate); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 5.3, C(3)H_3), 1.40–2.02 (6H, m, C(1)H_2, C(3′)H_2, C(4′)H_2) overlapping 1.46 (9H, s, CMe_3), 3.27–3.39 (2H, m, C(5′)H_2), 3.87 (1H, br s, C(2)*H*), 3.98 (1H, br s, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 23.8 (*C*(3′)), 23.9 (*C*(3)), 28.5 (CMe_3), 32.5 (*C*(4′)), 45.8, 46.4 (*C*(1), *C*(5′)), 55.7 (*C*(2′)), 66.5 (*C*(2)), 79.7 (*C*Me$_3$), 155.6 (NCO); *m*/*z* (ESI$^+$) 288 ([M+59]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{24}NO_3^+$ ([M+H]$^+$) requires 230.1756; found 230.1750.

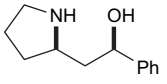
*4.14.52. (2R,2′R)-1-[N(1′)-(tert-butoxycarbonyl)pyrrolidin-2′-yl]propan-2-ol anti-**65**.*



Following General Procedure 11, BH_3·THF complex (1.0 M in THF, 0.44 mL, 0.44 mmol), (*S*)-*B*-Me-CBS (1.0 M in PhMe, 0.02 mL, 0.022 mmol) in THF (2 mL) at 0 °C, and **61** (100 mg, 0.44 mmol) in THF (2 mL) at 0 °C, gave a 24:76 mixture of *syn*-**64**:*anti*-**65**. Purification via flash column chromatography (eluent pentane/EtOAc, 10:1) gave *anti*-**65** as a colourless oil (68 mg, 68%, >99:1 dr); $[\alpha]_D^{23}$ +10.9 (*c* 0.7 in $CHCl_3$); ν_{max} (film) 3440 (O–H), 2971 (C–H), 1694, 1669 (carbamate); δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.3, C(3)H_3), 1.32–2.01 (6H, m, C(1)H_2, C(3′)H_2, C(4′)H_2) overlapping 1.46 (9H, s, CMe_3), 3.26–3.37 (2H, m, C(5′)H_2), 3.65–3.76 (1H, m, C(2)*H*), 4.13–4.22 (1H, m, C(2′)*H*), 5.01 (1H, br s, O*H*); δ_C (100 MHz, $CDCl_3$) 22.6 (*C*(3′)), 23.5 (*C*(3)), 28.5 (CMe_3), 31.1 (*C*(4′)), 45.6, 46.5 (*C*(1), *C*(5′)), 53.8 (*C*(2′)), 63.6 (*C*(2)), 79.8 (*C*Me$_3$), 156.6 (NCO); *m*/*z* (ESI$^+$) 288 ([M+59]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{24}NO_3^+$ ([M+H]$^+$) requires 230.1756; found 230.1761. Further elution gave *syn*-**64** as a colourless oil (18 mg, 18%, >99:1 dr).

Under identical conditions, reduction of **61** (100 mg) with BH_3·THF complex alone gave 50% conversion to a 50:50 mixture of *syn*-**64**:*anti*-**65**, and reduction with BH_3·THF complex in the presence of (*R*)-*B*-Me-CBS gave an 84:16 mixture of *syn*-**64**:*anti*-**65**. This crude reaction mixture was purified via flash column chromatography to give *syn*-**64** (71 mg, 70%, >99:1 dr) and *anti*-**65** (12 mg, 12%, >99:1 dr).

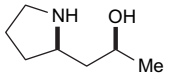
*4.14.53. (1R,2′R)-1-Phenyl-2-(pyrrolidin-2′-yl)ethanol **66**.*



Following General Procedure 12, 3 M aq HCl (2 mL) and *syn*-**62** (280 mg, 0.96 mmol) in MeOH (8 mL) at 50 °C gave the crude reaction mixture. The crude mixture was dissolved in 1 M aq HCl (20 mL), and washed with CH_2Cl_2 (2×20 mL). The aqueous layer was basified with 1 M aq NaOH and extracted with CH_2Cl_2 (5×20 mL). The combined organics were dried, filtered and concentrated in vacuo to give **66** as pale yellow oil (149 mg, 81%, >99:1 dr); $[\alpha]_D^{23}$ +40.0 (*c* 1.1 in MeOH); {lit.[35] $[\alpha]_D^{25}$ +36.8 (*c* 0.9 in MeOH)}; ν_{max} (film) 3258 (O–H, N–H, br), 2924 (C–H), 1472; δ_H (400 MHz, $CDCl_3$) 1.05–1.35 (1H, m, C(3′)H_A), 1.54–1.70 (3H, m, C(2)H_2, C(4′)H_A), 1.79–1.85 (1H, m, C(4′)H_B), 1.90–1.97 (1H, m, C(3′)H_B), 2.85 (1H, dt, *J* 12.0, 7.5, C(5′)H_A), 2.97–3.02 (1H, m, C(5′)H_B), 3.53–3.58 (1H, m, C(2′)*H*), 4.79–4.80 (2H, br s, O*H* and N*H*), 4.86 (1H, dd, *J* 10.4, 2.2, C(1)*H*), 7.22–7.39 (5H, m *Ph*); δ_C (100 MHz, $CDCl_3$) 25.7 (*C*(4′)), 32.7 (*C*(3′)), 43.3 (*C*(2)), 45.6 (*C*(5′)), 59.2 (*C*(2′)), 74.7 (*C*(1)), 125.6, 126.9, 128.2 (*m-*, *p-*, *o-Ph*), 145.4 (*i-Ph*); *m*/*z* (ESI$^+$) 192 ([M+H]$^+$,

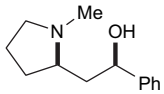
100%); HRMS (ESI$^+$) $C_{12}H_{18}NO^+$ ([M+H]$^+$) requires 192.1310; found 192.1314.

4.14.54. (2S,2′R)-1-(Pyrrolidin-2′-yl)propan-2-ol ***67****.*



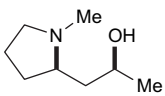
Following General Procedure 12, 3 M aq HCl (2 mL) and *syn*-**64** (230 mg, 1.00 mmol) in MeOH (8 mL) at 50 °C gave the crude reaction mixture. The crude mixture was dissolved in 1 M aq HCl (20 mL), and washed with CH_2Cl_2 (2×20 mL). The aqueous layer was basified with 1 M aq NaOH and extracted with CH_2Cl_2 (5×20 mL). The combined organics were dried, filtered and concentrated in vacuo to give **67** as pale yellow oil (120 mg, 93%, >99:1 dr); $[\alpha]_D^{23}$ +36.2 (*c* 2.6 EtOH); ν_{max} (film) 3258 (O–H, N–H, br), 2924 (C–H), 1472; δ_H (400 MHz, $CDCl_3$) 1.10 (3H, d, *J* 6.0, CH_3), 1.22–1.24 (1H, m, C(1)H_A), 1.29–1.34 (1H, m, C(3′)H_A), 1.42–1.44 (1H, m, C(1)H_B), 1.56–1.59 (1H, m, C(4′)H_A), 1.76–1.78 (1H, m, C(4′)H_B), 1.83–1.90 (1H, m, C(3′)H_B), 2.75 (1H, dt, *J* 11.7, 7.5, C(5′)H_A), 2.94–2.97 (1H, m, C(5′)H_B), 3.32–3.37 (1H, m, C(2′)*H*), 3.88–3.92 (1H, m, C(2)*H*), 4.10–4.25 (2H, br s, O*H* and N*H*); δ_C (100 MHz, $CDCl_3$) 23.7 (*C*H$_3$), 25.7 (*C*(4′)), 32.8 (*C*(3′)), 42.4 (*C*(1)), 45.6 (*C*(5′)), 59.2 (*C*(2′)), 68.3 (*C*(2)); *m*/*z* (ESI$^+$) 130 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_7H_{16}NO^+$ ([M+H]$^+$) requires 130.1226; found 130.1229.

4.14.55. (1R,2′R)-1-Phenyl-2-[N-(1′)methylpyrrolidin-2′-yl]ethanol [(+)-pyrrolsedamine] ***5****.*



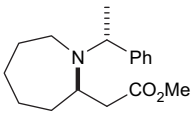
Following General Procedure 13, *syn*-**62** (260 mg, 0.89 mmol), lithium aluminium hydride (165 mg, 4.5 mmol) in THF (13 mL) gave the crude reaction mixture. The crude mixture was dissolved in 1 M aq HCl (10 mL), and washed with CH_2Cl_2 (2×10 mL). The aqueous layer was basified with 1 M aq NaOH and extracted with CH_2Cl_2 (5×10 mL). The combined organics were dried, filtered and concentrated in vacuo. Recrystallisation from CH_2Cl_2/heptane (v:v 1:1) gave **5** as a white solid (102 mg, 56%, >99:1 dr)[1]; mp 88–90 °C; $[\alpha]_D^{23}$ +73.7 (*c* 2.0 in EtOH); ν_{max} (KBr) 3355 (O–H, N–H, br), 3085, 2949 (C–H), 1493; δ_H (400 MHz, $CDCl_3$) 1.39–1.45 (1H, m, C(3′)H_A), 1.62 (1H, ddd, *J* 13.4, 6.0, 2.5, C(2)H_A), 1.75–1.81 (3H, m, C(2)H_B, C(4′)H_2), 1.99–2.04 (1H, m, C(3′)H_B), 2.37–2.42 (4H, m, NCH_3, C(5′)H_A), 2.83–2.87 (1H, m, C(2′)*H*), 3.08–3.12 (1H, m, C(5′)H_B), 4.81 (1H, dd, *J* 13.4, 2.5, C(1)*H*), 7.22–7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.7 (*C*(4′)), 30.4 (*C*(3′)), 40. 0 (*C*(2)), 42.7 (NCH3), 55.5 (*C*(5′)), 65.9 (*C*(2′)), 73.6 (*C*(1)), 125.4, 127.0, 128.2 (*m*-, *p*-, *o*-*Ph*), 145.5 (*i*-*Ph*); *m*/*z* (ESI$^+$) 206 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{20}NO^+$ ([M+H]$^+$) requires 206.1539; found 206.1542.

4.14.56. (2S,2′R)-1-[N(1′)-Methylpyrrolidin-2′-yl]propan-2-ol [(+)-pseudohygroline] ***6****.*



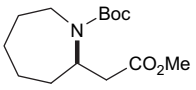
Following General Procedure 13, *syn*-**64** (200 mg, 0.87 mmol), lithium aluminium hydride (165 mg, 4.37 mmol) in THF (13 mL) gave the crude reaction mixture. The crude mixture was dissolved in 1 M aq HCl (10 mL), and washed with CH_2Cl_2 (2×10 mL). The aqueous layer was basified with 1 M aq NaOH and extracted with CH_2Cl_2 (5×10 mL). The combined organics were dried, filtered and concentrated in vacuo to give **6** as a colourless oil (142 mg, 80%, >99:1 dr)[3]; $[\alpha]_D^{22}$ +105.2 (*c* 1.0 in EtOH); {lit.[3] $[\alpha]_D^{20}$ +84.4 (*c* 3.4 in EtOH); lit.[36] $[\alpha]_D^{25}$ +97.0 (*c* 1.0 in EtOH); lit.[37] $[\alpha]_D^{20}$ +78.8 (*c* 0.9 in EtOH)}; ν_{max} (film) 3362 (O–H, N–H, br), 2964 (C–H), 1418; δ_H (400 MHz, $CDCl_3$) 1.14 (2H, d, *J* 6.3, C(3)H_3), 1.32–1.49 (3H, m, C(1)H_2, C(3′)H_A), 1.72–1.78 (2H, m, C(4′)H_2), 1.97–2.03 (1H, m, C(3′)H_B), 2.31–2.36 (4H, m, NCH_3, C(5′)H_A), 2.67–2.69 (1H, m, C(2′)*H*), 3.02 (1H, dt, *J* 10.4, 6.6, C(5′)H_B), 3.88–3.92 (1H, m, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 22.8 (*C*(4′)), 24.3 (*C*H$_3$), 30.5 (*C*(3′)), 42.9 (NCH$_3$), 43.0 (*C*(1)), 55.5 (*C*(5′)), 65.7 (*C*(2′)), 67.4 (*C*(2)); *m*/*z* (ESI$^+$) 144 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_8H_{18}NO^+$ ([M+H]$^+$) requires 144.1383; found 144.1386.

4.14.57. Methyl (2′R,αR)-2-[N-(α-methylbenzyl)azepan-2′-yl]ethanoate ***68****.*



Following General Procedure 3, Wilkinson's catalyst (84.6 mg, 0.091 mmol) and **33** (500 mg, 1.83 mmol) in EtOAc (5 mL) under H_2 (4 atm) at rt gave the crude reaction mixture. Purification via flash column chromatography (eluent pentane/Et_2O, 10:1) gave **68** as a colourless oil (437 mg, 87%, >99:1 dr); $[\alpha]_D^{21}$ −3.3 (*c* 0.8 in $CHCl_3$); ν_{max} (film) 2927 (C–H), 1737 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27–1.72 (7H, m, C(3′)H_A, C(4′)H_2, C(5′)H_2, C(6′)H_2) overlapping 1.38 (3H, d, *J* 6.7, C(α)*Me*), 1.82–1.90 (1H, m, C(3′)H_B), 2.28 (1H, dd, *J* 13.8, 8.0, C(2)H_A), 2.53 (1H, dd, *J* 13.8, 5.8, C(2)H_B), 2.65–2.76 (2H, m, C(7′)H_2), 3.45–3.53 (1H, m, C(2′)*H*), 3.64 (3H, s, O*Me*), 4.01 (1H, q, *J* 6.7, C(α)*H*), 7.20–7.34 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.9 (C(α)*Me*), 24.2, 28.5, 29.4 (*C*(4′), *C*(5′), *C*(6′)), 34.6 (*C*(3′)), 38.4 (*C*(2)), 43.8 (*C*(7′)), 51.3 (O*Me*), 55.1 (*C*(2′)), 59.9 (*C*(α)), 126.6 (*p*-*Ph*), 127.3, 128.2 (*m*-*Ph*, *o*-*Ph*), 145.8 (*i*-*Ph*), 173.4 (*C*(1)); *m*/*z* (ESI$^+$) 276 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{26}NO_2^+$ ([M+H]$^+$) requires 276.1964; found 276.1960.

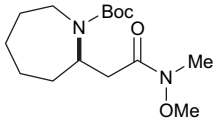
4.14.58. Methyl (R)-2-[N-(tert-butoxycarbonyl)azepan-2′-yl]ethanoate ***69****.*



Following General Procedure 10, Pearlman's catalyst (250 mg), **68** (500 mg, 1.82 mmol) and Boc_2O (515 mg, 2.36 mmol) in EtOAc (5 mL) under H_2 (5 atm) at rt gave the crude reaction mixture. Purification via flash column chromatography (eluent pentane/Et_2O, 20:1; increased to pentane/Et_2O, 10:1) gave **69** as a colourless oil (435 mg, 88%); $[\alpha]_D^{22}$ +33.0 (*c* 1.5 in $CHCl_3$); ν_{max} (film) 2929 (C–H), 1740 (C=O, ester), 1691 (C=O, carbamate); δ_H (400 MHz, $CDCl_3$) [56:44 mixture of rotamers] 1.12–1.73 (m, C(3′)H_A, C(4′)H_2, C(5′)H_2, C(6′)H_2) overlapping 1.38 (s, CMe_3) and 1.39 (s, CMe_3), 1.94–2.05 (m, C(3′)H_B), 2.27 (dd, *J* 14.2, 7.6, C(2)H_A), 2.28 (dd, *J* 13.9, 7.1, C(2)H_A), 2.41 (dd, *J* 13.9, 6.6, C(2)H_B), 2.43 (dd, *J* 14.2, 5.8, C(2)H_B), 2.63–2.73 (m, C(7′)H_A), 3.52–3.62 (m, C(7′)H_B) overlapping 3.57 (s, O*Me*) and 3.59 (s, O*Me*), 3.64–3.71 (m, C(7′)H_B), 4.14–4.22 (m, C(2′)*H*), 4.29–4.37 (m, C(2′)*H*); δ_H (500 MHz, DMSO-d_6, 373 K) 1.15–1.50 (4H, m,

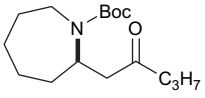
CH_2) overlapping 1.42 (9H, s, CMe_3), 1.59–1.75 (3H, m, CH_2), 1.97–2.02 (1H, m, CH_2), 2.38–2.47 (2H, m, C(2)H_2), 2.87 (1H, ddd, *J* 14.5, 11.0, 2.0, C(7′)H_A), 3.50–3.64 (1H, br m, C(7′)H_B) overlapping 3.60 (3H, s, O*Me*), 4.23 (1H, br s, C(2′)*H*); δ_C (125 MHz, DMSO-d_6, 373 K) 25.4 (*C*H_2), 28.6 (CMe_3), 28.9, 29.0 (*C*H_2), 33.5 (*C*(3′)), 39.6 (*C*(2)), 42.2 (*C*(7′)), 51.5 (O*Me*), 53.0 (*C*(2′)), 78.9 (*C*Me_3), 155.1 (NCO), 171.5 (*C*(1)); *m*/*z* (ESI$^+$) 330 ([M+59]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{26}NO_4^+$ ([M+H]$^+$) requires 272.1862; found 272.1875.

4.14.59. (R)-N-Methoxy-N-methyl-2-[N′-(tert-butoxycarbonyl)azepan-2′-yl]ethanoate ***70****.*



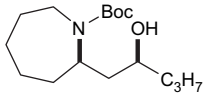
Following General Procedure 8, ^{i}PrMgCl (2.0 M in THF, 1.11 mL, 2.21 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (111 mg, 1.14 mmol) and **69** (200 mg, 0.74 mmol) in THF (5 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent pentane/EtOAc, 5:1) gave **70** as a colourless oil (200 mg, 90%); $[\alpha]_D^{22}$ +35.3 (*c* 3.5 in $CHCl_3$); ν_{max} (film) 2929 (C–H), 1689 (C=O, carbamate, amide); δ_H (400 MHz, $CDCl_3$) [59:41 mixture of rotamers] 1.18–1.78 (m, C(3′)H_A, C(4′)H_2, C(5′)H_2, C(6′)H_2) overlapping 1.42 (s, CMe_3) and 1.44 (s, CMe_3), 2.04–2.11 (m, C(3′)H_B), 2.44 (dd, *J* 14.3, 7.8, C(2)H_A), 2.53 (d, *J* 6.3, C(2)H_2), 2.61 (dd, *J* 14.3, 5.8, C(2)H_B), 2.74–2.85 (m, C(7′)H_A), 3.12 (s, N*Me*), 3.15 (s, N*Me*), 3.54–3.62 (br m, C(7′)H_B), 3.64 (s, O*Me*), 3.66 (s, O*Me*), 3.69–3.75 (m, C(7′)H_B), 4.27–4.35 (m, C(2′)*H*), 4.40 (app br s, C(2′)*H*); δ_H (500 MHz, DMSO-d_6, 373 K) 1.14–1.50 (4H, m, CH_2) overlapping 1.42 (9H, s, CMe_3), 1.60–1.74 (3H, m, CH_2), 1.97–2.04 (1H, m, CH_2), 2.50–2.53 (2H, m, C(2)H_2), 2.91 (1H, ddd, *J* 14.2, 11.0, 1.9, C(7′)H_A), 3.09 (3H, s, N*Me*), 3.51–3.58 (1H, br m, C(7′)H_B), 3.67 (3H, s, O*Me*), 4.26 (1H, app br s, C(2′)*H*); δ_C (125 MHz, DMSO-d_6, 373 K) 25.5 (*C*H_2), 28.7 (CMe_3), 29.0, 29.4 (*C*H_2), 31.0 (N*Me*), 33.6 (*C*(3′)), 37.4 (*C*(2)), 42.6 (*C*(7′)), 53.0 (*C*(2′)), 61.4 (O*Me*), 78.8 (*C*Me_3), 155.1 (N′*C*O), 171.5 (*C*(1)); *m*/*z* (ESI$^+$) 359 ([M+59]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{29}N_2O_4^+$ ([M+H]$^+$) requires 301.2127; found 301.2120.

4.14.60. (R)-1-[N-(tert-butoxycarbonyl)azepan-2′-yl]pentan-2-one ***71****.*



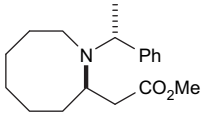
Following General Procedure 9, C_3H_7MgCl (2.0 M in Et_2O, 0.33 mL, 0.67 mmol) **70** (100 mg, 0.33 mmol) in Et_2O (2 mL) gave the crude reaction mixture. Purification of the residue via flash column chromatography on silica gel (eluent pentane/Et_2O 10:1) gave **71** as a colourless oil, a 59:41 mixture of rotamers (59:41, 68.6 mg, 73%); $[\alpha]_D^{23}$ +28.2 (*c* 2.1 in $CHCl_3$); ν_{max} (film) 2930 (C–H), 1712 (C=O, ketone), 1689 (C=O, carbamate); δ_H (500 MHz, DMSO-d_6, 373 K) 0.87 (3H, t, *J* 7.3, C(5)H_3), 1.15–1.73 (9H, m, C(4)H_2, C(3′)H_A, C(4′)H_2, C(5′)H_2, C(6′)H_2) overlapping 1.42 (9H, s, C(CH_3)$_3$), 1.93–2.01 (1H, m, C(3′)H_B), 2.34–2.45 (2H, m, C(3)H_2), 2.53 (2H, br d, *J* 6.6, C(1)H_2), 2.89 (1H, ddd, *J* 14.5, 10.7, 2.2, C(7′)H_A), 3.48–3.58 (1H, br m, C(7′)H_B), 4.25 (1H, app br s, C(2′)*H*); δ_C (125 MHz, DMSO-d_6, 373 K) 13.9 (*C*(5)), 17.1 (*C*(4)), 25.4 (*C*H_2), 28.7 (C(CH_3)$_3$), 28.9 (*C*H_2), 29.2 (*C*H_2), 33.9 (*C*(3′)), 42.4 (*C*(7′)), 44.8 (*C*(3)), 47.9 (*C*(1)), 52.6 (*C*(2′)), 78.9 (*C*(CH_3)$_3$), 155.1 (NCO), 208.8 (*C*(2)); *m*/*z* (ESI$^+$) 306 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{30}NO_3^+$ ([M+H]$^+$) requires 284.2226; found 284.2233.

4.14.61. (2S,2′R)-1-[N-(tert-Butoxycarbonyl)azepan-2′-yl]pentan-2-ol syn- ***72****.*



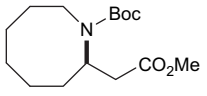
Following General Procedure 7, LiAl(O^{t}Bu)$_3$H (224 mg, 0.88 mmol) and **71** (100 mg, 0.35 mmol) in THF (5 mL) at 0 °C for 6 h gave the crude reaction mixture. Analysis by 400 MHz ^{1}H NMR spectroscopy revealed the presence of *syn*-**72** in >99:1 dr. Purification of the residue via flash column chromatography on silica gel (eluent pentane/EtOAc 10:1) gave *syn*-**72** as a colourless oil (95 mg, 95%, >99:1 dr); $[\alpha]_D^{22}$ +87.2 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 3418 (O–H), 2929 (C–H), 1690, 1662 (carbamate); δ_H (500 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.0, C(5)H_3), 1.23–1.90 (13H, m, C(1)H_2, C(3)H_2, C(4)H_2, C(3′)H_A, C(4′)H_2, C(5′)H_2, C(6′)H_2) overlapping 1.52 (9H, s, C(CH_3)$_3$), 2.09–2.14 (1H, m, C(3′)H_B), 2.75 (1H, t, *J* 13.2, C(7′)H_A), 3.62–3.68 (1H, m, C(7′)H_B), 3.70–3.76 (1H, m, C(2)*H*), 4.13–4.19 (1H, m, C(2′)*H*); δ_C (125 MHz, CDCl3) 14.1 (*C*(5)), 19.2 (*C*H_2), 25.0 (*C*H_2), 28.5 (C(CH_3)$_3$), 28.9 (*C*H_2), 29.7 (*C*H_2), 35.8 (*C*H_2), 39.6 (*C*H_2), 41.9 (*C*(7′)), 42.9 (*C*(1)), 53.4 (*C*(2′)), 70.2 (*C*(2)), 79.7 (*C*(CH_3)$_3$), 157.0 (NCO); *m*/*z* (ESI$^+$) 344 ([M+59]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{32}NO_3^+$ ([M+H]$^+$) requires 286.2382; found 286.2381.

4.14.62. Methyl (2′R,αR)-2-[N-(α-methylbenzyl)azocan-2′-yl]ethanoate ***73****.*



Following General Procedure 3, Wilkinson's catalyst (80.5 mg, 0.087 mmol) and **39** (500 mg, 1.74 mmol) in EtOAc (5 mL) under H_2 (4 atm) at rt gave the crude reaction mixture. Purification via flash column chromatography (eluent pentane/Et_2O, 10:1) gave **73** as a colourless oil (474 mg, 94%, >99:1 dr); $[\alpha]_D^{22}$ +7.3 (*c* 0.8 in $CHCl_3$); ν_{max} (film) 2923 (C–H), 1735 (C=O); δ_H (400 MHz, $CDCl_3$) 1.28–1.66 (8H, m, CH_2) overlapping 1.37 (3H, d, *J* 6.6, C(α)*Me*), 1.82–1.91 (1H, m, CH_2), 2.03–2.09 (2H, m, C(2)H_A, CH_2), 2.46 (1H, dd, *J* 13.4, 3.7, C(2)H_B), 2.56–2.62 (1H, m, C(8′)H_A), 2.70–2.78 (1H, m, C(8′)H_B), 2.93–3.00 (1H, m, C(2′)*H*), 3.53 (3H, s, O*Me*), 3.74 (1H, q, *J* 6.6, C(α)*H*), 7.21–7.36 (5H, m *Ph*); δ_C (100 MHz, $CDCl_3$) 23.6 (C(α)*Me*), 25.8, 26.4, 28.7, 31.3, 33.0 (*C*(3′), *C*(4′), *C*(5′), *C*(6′), *C*(7′)), 33.6 (*C*(2)), 43.2 (*C*(8′)), 51.3 (O*Me*), 56.2 (*C*(2′)), 61.8 (*C*(α)), 126.8 (*p*-*Ph*), 127.4, 128.3 (*m*-*Ph*, *o*-*Ph*), 145.9 (*i*-*Ph*), 173.1 (*C*(1)); *m*/*z* (ESI$^+$) 290 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{28}NO_2^+$ ([M+H]$^+$) requires 290.2120; found 290.2118.

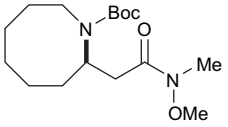
4.14.63. Methyl (R)-2-[N-(tert-butoxycarbonyl)azocan-2′-yl]ethanoate ***74****.*



Following General Procedure 10, Pearlman's catalyst (250 mg), **73** (500 mg, 1.73 mmol) and Boc_2O (490 mg, 2.25 mmol) in EtOAc

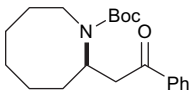
(5 mL) under H_2 (5 atm) rt gave the crude reaction mixture. Purification via flash column chromatography (eluent pentane/Et_2O, 20:1; increased to pentane/Et_2O, 10:1) gave **74** as a colourless oil (418 mg, 85%); $[\alpha]_D^{22}$ −5.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2928 (C–H), 1741 (C=O, ester), 1692 (C=O, carbamate); δ_H (400 MHz, $CDCl_3$) [57:43 mixture of rotamers] 1.38–1.93 (m, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2, C(7′)H_2) overlapping 1.46 (s, CMe_3) and 1.47 (s, CMe_3), 2.32–2.39 (m, C(2)H_A), 2.49 (dd, *J* 14.0, 7.6, C(2)H_B), 2.53–2.65 (m, C(2)H_B), 2.92–3.01 (m, C(8′)H_A), 3.18–3.39 (m, C(8′)H_2), 3.64 (s, O*Me*), 3.66 (s, O*Me*), 4.08–4.20 (m, C(2′)*H*), 4.31–4.41 (m, C(2′)*H*); δ_H (500 MHz, DMSO-d_6, 373 K) 1.32–1.81 (10H, m, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2, C(7′)H_2) overlapping 1.39 (9H, s, CMe_3), 2.31–2.53 (2H, m, C(2)H_2), 2.96–3.35 (2H, m, C(8′)H_2), 3.56 (3H, s, O*Me*), 3.95–4.23 (1H, m, C(2′)*H*); δ_C (125 MHz, DMSO-d_6, 373 K) 24.9, 25.8, 26.2, 26.7 (CH_2), 28.6 (CMe_3), 30.8 (CH_2), 41.2 (*C*(8′)), 51.6 (*C*(2′)), 53.4 (O*Me*), 79.2 (*C*Me_3), 155.3 (NCO), 172.0 (*C*(1)); *m*/*z* (ESI^+) 344 ($[M+59]^+$, 100%); HRMS (ESI^+) $C_{15}H_{28}NO_4^+$ ($[M+H]^+$) requires 286.2018; found 286.2007.

4.14.64. N-Methoxy-N-methyl (R)-2-[N′-(tert-butoxycarbonyl)azocan-2′-yl]ethanoamide ***75****.*



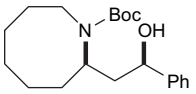
Following General Procedure 8, ^{i}PrMgCl (2.0 M in THF, 2.63 mL, 5.26 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (265 mg, 2.72 mmol) and **74** (500 mg, 1.75 mmol) in THF (10 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent pentane/EtOAc, 5:1) gave **75** as a colourless oil (112 mg, 93%); $[\alpha]_D^{22}$ −11.0 (*c* 2.5 in $CHCl_3$); ν_{max} (film) 2929 (C–H), 1689 (C=O, carbamate, amide); δ_H (400 MHz, $CDCl_3$) [54:46 mixture of rotamers] 1.32–1.82 (m, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2, C(7′)H_2) overlapping 1.42 (s, CMe_3) and 1.44 (s, CMe_3), 2.42–2.79 (m, C(2)H_2), 3.00–3.18 (m, C(8′)H_A) overlapping 3.11 (s, N*Me*) and 3.14 (s, N*Me*), 3.20–3.36 (m, C(8′)H_B), 3.64 (s, O*Me*), 3.66 (s, O*Me*), 4.11–4.23 (m, C(2′)*H*), 4.24–4.38 (m, C(2′)*H*); δ_H (500 MHz, DMSO-d_6, 373 K) 1.35–1.84 (m, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2, C(7′)H_2) overlapping 1.43 (s, CMe_3), 2.47–2.65 (2H, m, C(2)H_2), 3.07–3.18 (1H, m, C(8′)H_A) overlapping 3.09 (3H, s, N*Me*), 3.19–3.30 (1H, m, C(8′)H_B), 3.67 (3H, s, O*Me*), 4.08–4.27 (1H, m, C(2′)*H*); δ_C (125 MHz, DMSO-d_6, 373 K) 25.3, 26.5, 26.8, 26.7 (CH_2), 28.7 (CMe_3), 30.0 (CH_2), 32.7 (N*Me*), 37.1 (*C*(2)), 43.2 (*C*(8′)), 53.5 (*C*(2′)), 61.4 (O*Me*), 78.7 (*C*Me_3), 155.0 (N′*C*O), 171.7 (*C*(1)); *m*/*z* (ESI^+) 373 ($[M+59]^+$, 100%); HRMS (ESI^+) $C_{16}H_{31}N_2O_4^+$ ($[M+H]^+$) requires 315.2284; found 315.2278.

4.14.65. (R)-1-Phenyl-2-[N-(tert-butoxycarbonyl)azocan-2′-yl]ethanone ***76****.*



Following General Procedure 9, PhMgBr (3.0 M in Et_2O, 0.21 mL, 0.64 mmol) and **75** (100 mg, 0.32 mmol) in Et_2O (2 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent pentane/Et_2O, 10:1) gave **76** as a colourless oil (80.2 mg, 76%); $[\alpha]_D^{23}$ −32.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2928 (C–H), 1688 (C=O, carbamate), 1652 (C=O, ketone); δ_H (400 MHz, $CDCl_3$) 1.38–1.93 (10H, m, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2, C(7′)H_2) overlapping 1.43 (9H, s, CMe_3), 2.93–3.01 (1H, m, C(2)H_A), 3.11–3.43 (3H, m, C(2)H_B, C(8′)H_2), 4.30–4.47 (1H, m, C(2′)*H*), 7.32–7.59 (3H, m, *Ph*), 7.94–8.00 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) [rotameric] 25.3, 26.4, 26.8, 27.7 (CH_2), 28.4, 28.5 (CMe_3), 30.0 (CH_2), 43.7, 44.1 (*C*(2), *C*(8)), 53.8 (*C*(2′)), 79.1, 79.5 (*C*Me_3), 128.2, 128.4, 128.5, 128.6, 128.7 (*p-Ph*, *m-Ph*, *o-Ph*), 133.0, 133.2 (*i-Ph*), 155.0, 155.4 (NCO), 198.5, 199.2 (*C*(1)); *m*/*z* (ESI^+) 390 ($[M+59]^+$, 100%); HRMS (ESI^+) $C_{20}H_{30}NO_3^+$ ($[M+H]^+$) requires 332.2226; found 332.2214.

4.14.66. (1R,2′R)-1-Phenyl-2-[N-(tert-butoxycarbonyl)azocan-2′-yl]ethanol syn- ***77****.*



Following General Procedure 7, $LiAl(O^tBu)_3H$ (192 mg, 0.75 mmol) and **76** (100 mg, 0.30 mmol) in THF (2 mL) at 0 °C for 6 h gave *syn*-**77** in >99:1 dr. Purification via flash column chromatography (eluent pentane/EtOAc, 10:1) gave *syn*-**77** as a colourless oil (92 mg, 91%, >99:1 dr); $[\alpha]_D^{23}$ +77.4 (*c* 0.8, in $CHCl_3$); ν_{max} (film) 3411 (O–H), 2927 (C–H), 1687, 1662 (carbamate); δ_H (400 MHz, $CDCl_3$) 1.32–1.92 (12H, m, C(2)H_2, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2, C(7′)H_2) overlapping 1.46 (9H, s, CMe_3), 2.72–2.80 (1H, m, C(8′)H_A), 3.00–3.06 (1H, m, C(8′)H_B), 4.15–4.22 (1H, m, C(2′)*H*), 4.74–4.79 (1H, m, C(1)*H*), 7.20–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.5, 26.1, 27.0, 27.7 (CH_2), 28.6 (CMe_3), 30.5 (CH_2), 41.4 (*C*(8′)), 44.3 (*C*(2)), 53.1 (*C*(2′)), 71.8 (*C*(1)), 79.7 (*C*Me_3), 125.4, 126.8, 128.2 (*p-Ph*, *m-Ph*, *o-Ph*), 144.9 (*i-Ph*), 156.8 (NCO); *m*/*z* (ESI^+) 356 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{20}H_{31}NNaO_3^+$ ($[M+Na]^+$) requires 356.2196; found 356.2195.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.09.104.

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40. Repetition of this experiment led, on occasion, to isolation of a small amount (<1%) of (*RS*)-*tert*-butyl 3-butylhex-5-enoate as a colourless oil (first to elute); ν_{max} (film) 2928 (C–H), 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 0.86–0.90 (3H, m, C(4′) H_3), 1.15–1.37 (6H, m, C(1′) H_2, C(2′) H_2, C(3′) H_2), 1.43 (9H, s, C Me_3), 1.65 (1H, dd, *J* 6.5, 1.4, C(6) H_3), 2.11 (1H, dd, *J* 14.3, 8.6, C(2) H_A), 2.24 (1H, dd, *J* 14.3, 6.1, C(2) H_B), 2.32–2.49 (1H, m, C(3) H), 5.21 (1H, ddd, *J* 15.0, 8.5, 1.4, C(4) H), 5.43 (1H, dq, *J* 15.0, 6.5, C(5) H); δ_C (100 MHz, $CDCl_3$) 14.1 (C(4′)), 17.8 (C(6)), 22.7 (CH_2), 28.1 (C Me_3), 29.3, 34.7 (CH_2), 39.8 (C(3)), 41.9 (C(2)), 79.3 (CMe_3), 125.2, 134.0 (C(4), C(5)); *m*/*z* (CI^+) 227 ($[M+H]^+$, 32%), 171(100); HRMS (CI^+) $C_{14}H_{27}O_2^+$ ($[M+H]^+$) requires 227.2011; found 227.2003.
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44. Repetition of this experiment led, on occasion, to isolation of a small amount (<1% conversion of starting material) of (*RS*)- *tert*-butyl 3-butylhept-6-enoate as a colourless oil (first to elute); ν_{max} (film) 2929 (C–H), 1731 (C=O), 1641 (C=C); δ_H (400 MHz, $CDCl_3$) 0.88–0.91 (3H, m, C(4′) H_3), 1.26–1.49 (8H, m, C(4) H_2, C(1′) H_2, C(2′) H_2, C(3′) H_2) overlapping 1.45 (9H, s, C Me_3), 1.82–1.86 (1H, m, C(3) H), 2.06 (2H, app q, *J* 7.9, C(5) H_2), 2.16 (2H, app d, *J* 6.8, C(2) H_2), 4.93–5.04 (2H, m, C(7) H_2), 5.76–5.86 (1H, m, C(6) H); δ_C (100 MHz, $CDCl_3$) 14.1 (C(4′)), 22.9 (CH_2), 28.1 (C Me_3), 28.7, 30.8, 33.1, 33.4 (CH_2), 34.6 (C(3)), 40.3 (C(2)), 80.0 (CMe_3), 114.3 (C(7)), 138.9 (C(6)), 172.9 (C(1)); *m*/*z* (CI^+) 241 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{15}H_{29}O_2^+$ ($[M+H]^+$) requires 241.2168; found 241.2173.