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Asymmetric synthesis of 4-amino-γ-butyrolactones via lithium amide conjugate addition

Elin Abraham,[a] Jason W. B. Cooke,[a] Stephen G. Davies,[a,*] Alan Naylor,[b] Rebecca L. Nicholson,[a] Paul. D. Price[a] and Andrew D. Smith[a]

[a]*Department of Organic Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK*
[b]*Department of Medicinal Chemistry, Neurology and Gastrointestinal Diseases Centre of Excellence for Drug Discovery, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK*

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Abstract—Upon treatment with homochiral lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, γ-benzyloxy but-2-enoates undergo competitive conjugate addition and γ-deprotonation, while γ-*tert*-butyldimethylsilyloxy but-2-enoates undergo exclusive conjugate addition. Treatment of γ-benzyloxy or γ-*tert*-butyldimethylsilyloxy but-2-enamides with lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide furnishes exclusively the γ-benzyloxy- or γ-*tert*-butyldimethylsilyloxy-β-amino amide products of conjugate addition in high de. The γ-*tert*-butyldimethylsilyloxy-β-amino butanoate products of conjugate addition readily undergo O-desilylation and concomitant cyclisation to furnish 4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-γ-butyrolactone, which may be stereoselectively functionalised via deprotonation and alkylation to give the corresponding *trans*-3-alkyl-4-amino-γ-butyrolactones. Alternatively, stereoselective alkylation of γ-benzyloxy- or γ-*tert*-butyldimethylsilyloxy-β-amino butanoates and butanamides through enolate formation and alkylation following a tandem (via the (*Z*)-lithium enolate) or stepwise (via the (*E*)-lithium enolate) protocol gives a range of separable *syn*- and *anti*-α-alkyl-β-amino esters and amides. *O*-Silyl deprotection of the *syn*- and *anti*-α-alkyl-β-amino butanoates with TBAF and concomitant cyclisation provide *trans*-3-alkyl-4-amino-γ-butyrolactones, consistent with epimerisation to the thermodynamically favoured *trans*-lactone occurring upon deprotection.

1. Introduction

Enantiomerically pure 4-amino-γ-butyrolactones are widely recognised as valuable synthetic tools within organic synthesis. These versatile intermediates have been used as key synthetic building blocks for the preparation of a wide range of functionality including aziridines,[1] oxazolidinones,[2] β-lactams,[3] tetrahydroindoles[4] and highly functionalized amino acids.[5] The vast majority of routes to this highly desirable class of compound are derived from chiral pool materials, with routes to the parent 4-amino-γ-butyrolactones having been demonstrated from aspartic acid,[6] asparagine[7] and aminocarnitine,[8] while the 4-amino-5-methyl-γ-butyrolactone framework has been synthesised from threonine.[9] Only limited stereoselective routes to the 4-amino-γ-butyrolactone skeleton have been demonstrated, with tandem radical addition–cyclisation reactions of oxime ethers,[10] nucleophilic addition to *tert*-butanesulfinyl α-alkoxyaldimines,[11] the use of chiral auxiliaries,[12] and chemoenzymatic synthesis[13] all having shown promise for the preparation of this valuable motif.

Previous investigations from this laboratory have shown that the conjugate addition of homochiral lithium amides derived from α-methylbenzylamine to α,β-unsaturated esters may be used for the asymmetric synthesis of β-amino acid derivatives.[14] Furthermore, functionalisation of the (*Z*)-β-amino enolate arising from conjugate addition, or the (*E*)-β-amino enolate arising from deprotonation of the corresponding β-amino ester, gives preferentially the corresponding *anti*-stereoisomer with moderate to high stereoselectivity (Fig. 1).[15] This general and versatile methodology has been applied to a number of total syntheses,[16] and as part of our existing research portfolio directed towards the de novo asymmetric synthesis of monosaccharides and amino sugars, we outline herein the scope of this methodology for the asymmetric synthesis of a range of 4-amino-γ-butyrolactones.

It was envisaged that conjugate addition of homochiral lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **1** to a range of γ-benzyloxy and γ-*tert*-butyldimethylsilyloxy but-2-enoates and but-2-enamides **2** would give the corresponding β-amino esters **3** with high stereoselectivity. Subsequent O-deprotection of **3** and concomitant intramolecular cyclisation would generate 4-amino-γ-butyrolactone **4**, which could be readily alkylated at C(2) via enolate formation, to generate **6**.

* Corresponding author. E-mail: steve.davies@chem.ox.ac.uk

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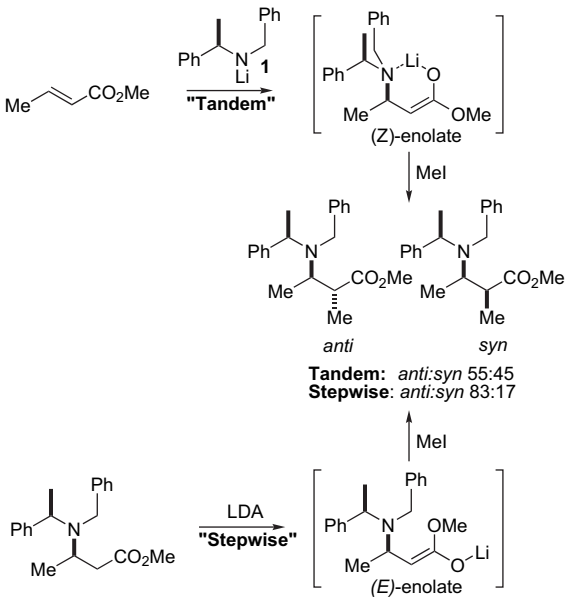


Figure 1. Diastereoselective alkylation of β-amino crotonates.

Alternatively, tandem conjugate addition and enolate alkylation to give **5**, followed by O-deprotection and cyclisation would also generate the 3-substituted-4-amino-γ-butyrolactone **6** (Fig. 2).

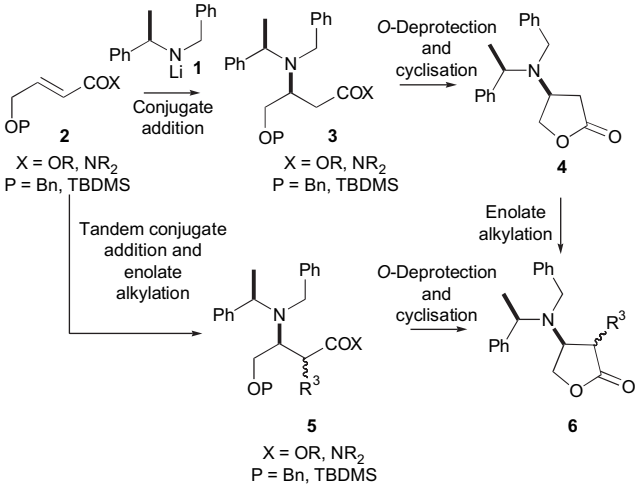
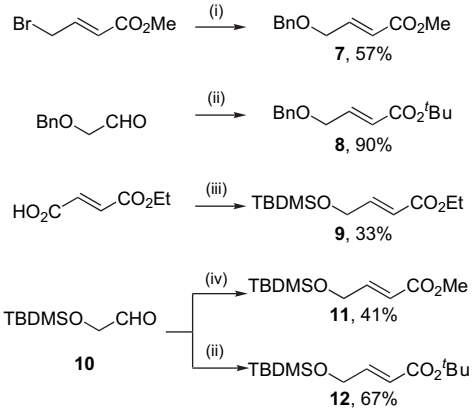


Figure 2. Proposed stereoselective route to 4-amino-γ-butyrolactones.

2. Results and discussion

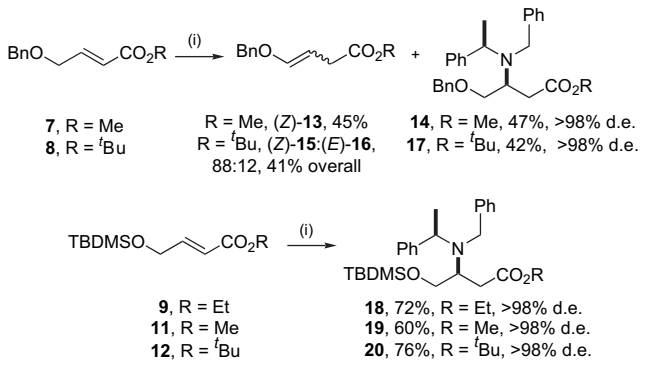
2.1. Lithium amide conjugate addition to γ-benzyloxy and γ-*tert*-butyldimethylsilyloxy but-2-enoates and but-2-enamides

Initial studies concentrated upon the preparation of a range of (*E*)-γ-benzyloxy and (*E*)-γ-*tert*-butyldimethylsilyloxy but-2-enoates. Methyl (*E*)-4-benzyloxybut-2-enoate **7** was prepared in 57% yield via the Ag_2O promoted bromide displacement from commercially available methyl 4-bromocrotonate with benzyl alcohol. The corresponding *tert*-butyl ester was prepared from benzyloxyacetaldehyde via olefination under Masamune–Roush conditions,[17] to afford (*E*)-**8** as the sole product in 90% yield and >98% de after purification. A range of γ-*tert*-butyldimethylsilyloxy but-2-enoates was also prepared, with ethyl 4-(*tert*-butyldimethylsilyloxy)but-2-enoate **9** readily prepared by borane reduction of monoethyl fumarate and subsequent silylation with TBDMSCl, giving (*E*)-**9** in 33% overall yield. Alternatively, treatment of aldehyde **10**[18] with either methyl or *tert*-butyl diethylphosphonoacetate under Masamune–Roush conditions afforded (*E*)-**11** and (*E*)-**12**, respectively, in >98% de in each case and in good yield (Scheme 1).

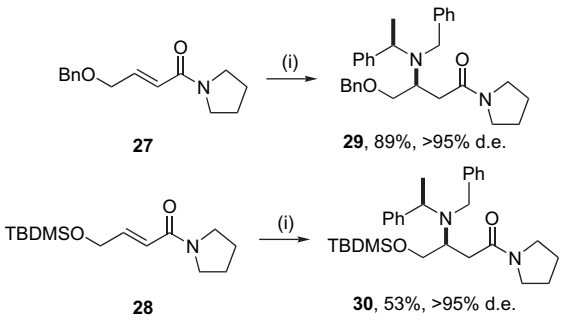


Scheme 1. Reagents and conditions: (i) Ag_2O, BnOH, $CaSO_4$, DCM; (ii) *tert*-butyl diethylphosphonoacetate, LiCl, $^iPr_2NEt$, MeCN, rt, 48 h; (iii) BH_3, THF, −10 °C to rt, then TBDMSCl, Et_3N, DCM, rt; (iv) methyl diethylphosphonoacetate, LiCl, $^iPr_2NEt$, MeCN, rt, 48 h.

The behaviour of γ-benzyloxy butenoates **7** and **8** upon reaction with homochiral lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **1** was evaluated. Addition of lithium amide (*R*)-**1** to γ-benzyloxy methyl ester **7** gave a 44:56 mixture of methyl (*Z*)-4-benzyloxybut-3-enoate (*Z*)-**13** (arising from γ-deprotonation) and β-amino ester **14** in >98% de (arising from conjugate addition). Chromatographic purification gave (*Z*)-**13** in 42% yield and β-amino ester **14** in 47% yield and >98% de. Treatment of γ-benzyloxy *tert*-butyl ester **8** with lithium amide (*R*)-**1** gave a 50:50 mixture of products arising from γ-deprotonation [(*Z*)-**15**/(*E*)-**16**, 88:12] and conjugate addition (**17**, >98% de). Purification gave a partially separable mixture of (*Z*)-**15** and (*E*)-**16** in 41% combined yield, and β-amino ester **15** in 42% yield and >98% de (Scheme 2). These product distributions indicate that γ-deprotonation competes effectively with conjugate addition in the reaction of γ-benzyloxy butenoates **7** and **8** with lithium amide (*R*)-**1**. The predominance of the (*Z*)-olefins **13** and **15** from the γ-deprotonation manifold of **7** and **8** with lithium amide (*R*)-**1** is consistent with previous observations concerning the stereochemical consequence of enoate deprotonation reactions.[19] Addition of lithium amide (*R*)-**1** to γ-*tert*-butyldimethylsilyloxy butenoates **9**, **11** and **12** gave, in each case, a crude reaction product containing exclusively the desired β-amino esters **18**–**20** in >98% de, which were isolated in 60–76% yield. No sign of the β,γ-unsaturated ester products of γ-deprotonation was noted in the crude reaction product in each case. The configuration at the β-centre within β-amino esters (3*S*,α*R*)-**14** and (3*S*,α*R*)-**17**–**20** was assigned by analogy with established models developed to explain the stereoselectivity observed during addition of lithium amide **1** to α,β-unsaturated esters.[20]

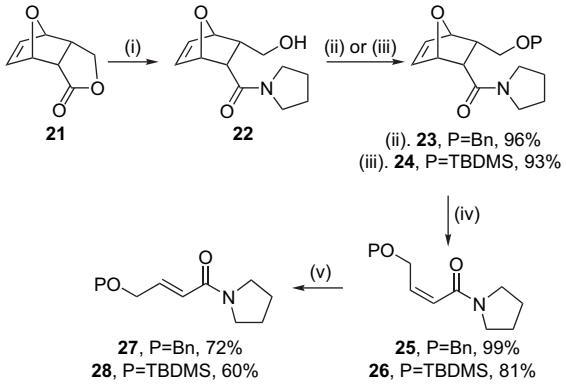


Scheme 2. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **1**, THF, −78 °C, 2 h.



Scheme 4. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **1**, THF, −78 °C, 2 h.

Having demonstrated that γ-*tert*-butyldimethylsilyloxy butenoates **9**, **11** and **12** disfavour γ-deprotonation upon reaction with lithium amide (*R*)-**1**, the product distribution upon conjugate addition to a γ-benzyloxy- and γ-*tert*-butyldimethylsilyloxy butenamide was investigated. The desired γ-benzyloxy and γ-*tert*-butyldimethylsilyloxy amides **27** and **28** were therefore prepared, via a multistep synthetic scheme from the known lactone **21**. Heating lactone **21** with pyrrolidine gave alcohol **22**, which was subsequently *O*-protected, giving the *O*-benzyl and *O*-TBDMS butenamides **23** and **24**, respectively. Heating **23** and **24** in vacuo induced a retro-Diels–Alder reaction and provided (*Z*)-α,β-unsaturated amides **25** and **26** ($J_{2,3}$ 11.7 Hz) in excellent yield, with photolysis in the presence of a catalytic amount of diphenyldisulfide promoting isomerisation to the corresponding (*E*)-α,β-unsaturated amides **27** ($J_{2,3}$ 15.0 Hz) and **28** ($J_{2,3}$ 15.2 Hz) in good yield (Scheme 3).[21]



Scheme 3. Reagents and conditions: (i) pyrrolidine, 65 °C then recrystallisation; (ii) KH, THF, −70 °C then BnBr, −78 °C to rt; (iii) TBDMSCl, NEt_3, DCM, rt; (iv) reflux; (v) diphenyldisulfide, benzene/hexane (1:1), *hv*.

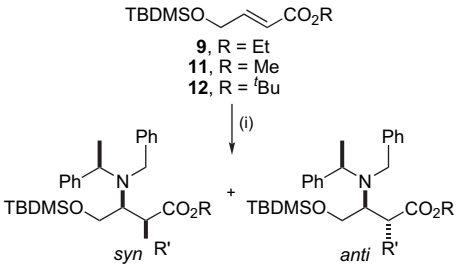
In contrast to the mixture of products observed upon conjugate addition of lithium amide (*R*)-**1** to γ-benzyloxy butenoates **7** and **8**, addition of lithium amide (*R*)-**1** to both the γ-benzyloxy and γ-*tert*-butyldimethylsilyloxy amides **27** and **28** gave exclusively the β-amino amide products from conjugate addition in >95% de in each case. Chromatographic purification gave **29** and **30** in 89 and 53% yield, respectively (Scheme 4).

Analysis of the product distributions arising from these conjugate addition reactions indicates that γ-*tert*-butyldimethylsilyloxy butenoates and butenamides inhibit γ-deprotonation. However, while γ-benzyloxy butenamides promote conjugate addition exclusively, γ-benzyloxy butenoates undergo competitive conjugate addition and γ-deprotonation. A simple model may be used to explain these product distributions. Assuming that lithium amide conjugate addition requires initial binding of the carbonyl functionality of the α,β-unsaturated acceptor via lithium co-ordination, the increased electron donating ability of the amide relative to the ester will result in the amide carbonyl being a far better ligand for the lithium amide than the ester carbonyl, thus promoting the conjugate addition manifold over γ-deprotonation in the butenamide system. Competitive binding by the γ-benzyloxy substituent to the lithium amide favours γ-deprotonation; however, such binding is precluded in both γ-*tert*-butyldimethylsilyloxy butenoates and butenamides.

2.2. Diastereoselective alkylation of lithium (*Z*)- and (*E*)-enolates of γ-*tert*-butyldimethylsilyloxy-β-amino butanoates

β-Amino enolate elaboration following conjugate addition was next investigated, as it was envisaged that subsequent deprotection and cyclisation to the corresponding lactone would offer an attractive route to functionalized 4-amino-γ-butyrolactones. Conjugate addition lithium amide (*R*)-**1** to *tert*-butyl ester **12** and methylation of the resulting (*Z*)-enolate[22] gave a partially separable 50:50 mixture of the *syn*- and *anti*-diastereoisomers **31/32**, which were isolated in 50% combined yield. Conjugate addition of lithium amide (*R*)-**1** to ethyl or methyl esters **9** and **11** and enolate methylation gave a 60:40 mixture of the partially separable *syn*- and *anti*-diastereoisomers **33/34** and **35/36**, respectively, in 53 and 49% yield. The generality of this tandem conjugate addition–alkylation approach was also investigated, with conjugate addition of lithium amide (*R*)-**1** to ethyl ester **9** and alkylation with benzyl bromide and allyl bromide giving a 71:29 and 77:23 mixture of the corresponding *syn*- and *anti*-diastereoisomers, **37/38** and **39/40**, respectively, which were partially separable by chromatography, giving **37/38** and **39/40** in 52 and 55% combined isolated yields (Scheme 5).

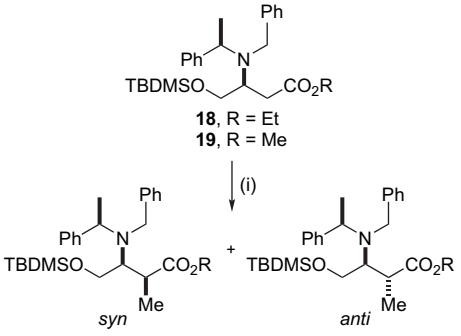
An alternative, stepwise approach to enolate functionalisation was next investigated. Deprotonation of ethyl and methyl β-amino esters **18** and **19**, respectively, with LDA and subsequent alkylation of the in situ formed lithium



R	R'	syn:anti	Yield %[a]
^{t}Bu	Me	**31:32** 50:50	50%
Et	Me	**33:34** 60:40	54%
Me	Me	**35:36** 60:40	49%
Et	Bn	**37:38** 71:29	52%
Et	allyl	**39:40** 77:23	55%

Scheme 5. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **1**, THF, −78 °C, 2 h, then R′X, −78 °C to rt. [[a]Combined yield of both diastereoisomers.]

(*E*)-enolate[22] with methyl iodide gave a 25:75 and 29:71 mixture of the corresponding *syn*- and *anti*-diastereoisomers **33/34** and **35/36**, respectively, and in quantitative yield in each case (Scheme 6).



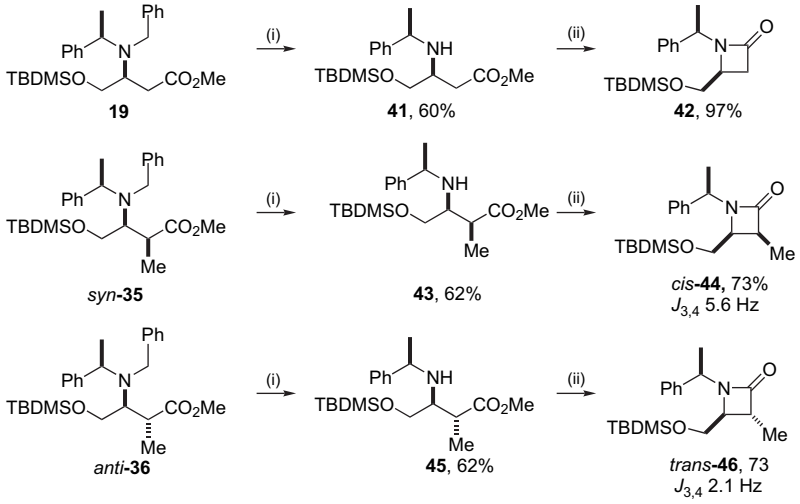
R	syn:anti	Yield %[a]
Et	**33:34** 25:75	quant
Me	**35:36** 29:71	quant

Scheme 6. Reagents and conditions: (i) LDA, THF, −78 °C, then MeI, −78 °C to rt. [[a]Combined yield of both diastereoisomers.]

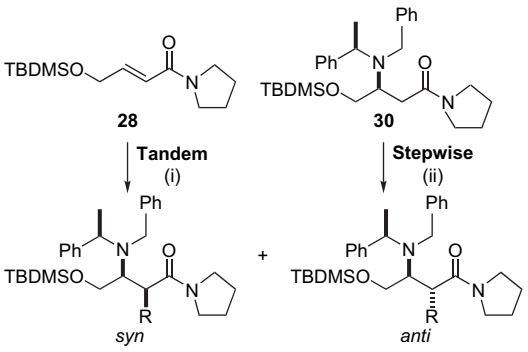
The relative *syn*- and *anti*-configurations within the C(2)-methylated β-amino methyl esters **33** and **34** were next established through conversion to the corresponding β-lactams. As a model system for this transformation, β-amino methyl ester **19** was selectively monodebenzylated with CAN to furnish β-amino ester **41**,[23] with subsequent treatment of **41** with MeMgBr giving the β-lactam **42** in 97% yield. Following this protocol, *syn* diastereoisomer **35** gave the *cis*-β-lactam **44** ($J_{2,3}$ 5.6 Hz), and *anti* diastereoisomer **36** gave the *trans*-β-lactam **46** ($J_{2,3}$ 2.1 Hz) (Scheme 7). The stereodivergent preference for the *syn* stereoisomer in the tandem conjugate addition–methylation protocol and the *anti*-stereoisomer in the stepwise procedure is consistent with alkylation proceeding via the corresponding lithium (*Z*)- and (*E*)-enolates, respectively. However, the preferential *syn* alkylation in the tandem procedure contrasts the known anti preference for the tandem conjugate addition–methylation of methyl crotonate,[15] indicating that the stereoselectivity of tandem β-amino enolate alkylations is highly dependent upon the nature of the substituent at C(4).

In the amide series, tandem conjugate addition of lithium amide (*R*)-**1** to γ-*tert*-butyldimethylsilyloxy butenamide **28** and enolate alkylation with methyl iodide, benzyl bromide or allyl bromide gave a 66:34, 86:14 and 80:20 mixture of the corresponding *syn*- and *anti*-α-methyl-, α-benzyl- and α-allyl-β-amino butanamides **47**–**52** (Scheme 8). Following the stepwise protocol, treatment of β-amino amide (3*R*,α*R*)-**30** with LDA and alkylation of the resultant enolate with MeI gave a 65:35 mixture of *syn*-**47**/*anti*-**48** in quantitative yield. The *syn*-preference for the tandem alkylation within the butanamide series was assigned by analogy to that observed in the corresponding butanoates. The comparable selectivities arising from the tandem (66:34 *syn*/*anti*) and stepwise (65:35 *syn*/*anti*) methylation reactions in this series can be ascribed to the intermediacy of a common lithium (*Z*)-β-amino amide enolate in both protocols, in contrast to the stereodivergent enolate formation in the butanoate series.

Previous investigations from this laboratory have demonstrated that the conjugate addition of lithium amide (*R*)-**1** to a range of α,β-unsaturated esters and subsequent in situ oxidation of the thus formed enolate with the chiral oxidant



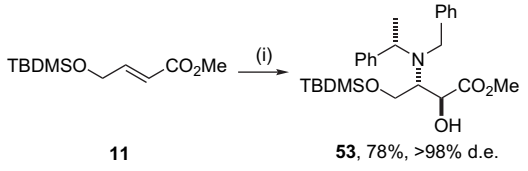
Scheme 7. Reagents and conditions: (i) CAN (2.1 equiv), MeCN/H_2O (5:1), rt; (ii) MeMgBr, Et_2O, 0 °C.



Procedure	R	*syn:anti*	Yield %[a]
Tandem	Me	**47:48** 66:34	72%
Stepwise	Me	**47:48** 65:35	quant
Tandem	Bn	**49:50** 86:14	65%
Tandem	allyl	**51:52** 80:20	54%

Scheme 8. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **1**, THF, −78 °C, 2 h, then RX, −78 °C to rt; (ii) LDA, THF, −78 °C, 30 min, then RX, −78 °C to rt.

(−)-(camphorsulfonyl)oxaziridine (CSO) proceeds with high *anti*-selectivity.[24] Following this procedure, conjugate addition of lithium amide (*S*)-**1** to **11** and subsequent oxidation with (+)-CSO gave *anti*-α-hydroxy-β-amino ester **53** as a single diastereoisomer in 78% isolated yield after chromatography (Scheme 9).

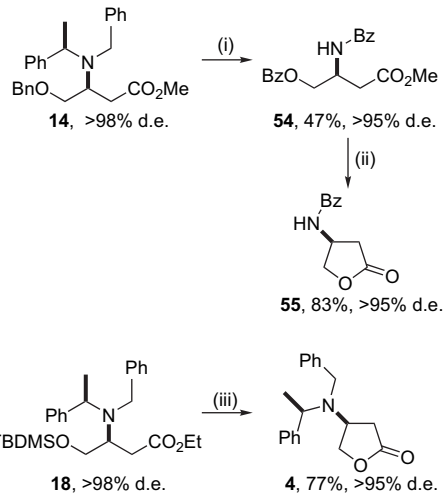


Scheme 9. Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **1**, THF, −78 °C, 2 h, then (+)-CSO, −78 °C to rt, 12 h.

2.3. Synthesis of 3-alkyl-4-amino-γ-butyrolactones

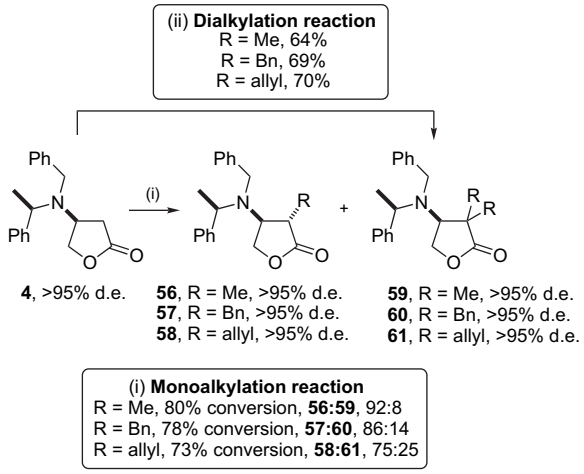
With a range of γ-benzyloxy- and γ-*tert*-butyldimethylsilyloxy-β-amino butanoates and butanamides in hand, their conversion to the corresponding 4-amino-γ-butyrolactones was investigated. The assigned configuration at C(3) arising from conjugate addition within the simple β-amino esters was confirmed unambiguously through the conversion of γ-benzyloxy-β-amino ester **14** into the known *N*-protected-γ-butyrolactone **55**. Hydrogenolysis of β-amino ester **14**, followed by treatment with benzoyl chloride and pyridine gave dibenzoyl β-amino ester **54**, with subsequent selective *O*-benzoyl deprotection giving 4-(*N*-benzoylamino)-γ-butyrolactone **55** in 83% yield after purification, with comparable spectroscopic properties to those reported in the literature {$[\alpha]_D^{21}$ −100.8 (*c* 0.4, $CHCl_3$); lit.[25] $[\alpha]_D^{20}$ −97.0 (*c* 1.4, $CHCl_3$)}. As an alternative route to the 4-amino-γ-butyrolactone framework, treatment of γ-*tert*-butyldimethylsilyloxy-β-amino ester **18** with TBAF gave the lactone **4** in 77% yield (Scheme 10).

The stereoselective functionalisation of the lactone **4** via a deprotonation–alkylation strategy was next examined. Treatment of **4** with KHMDS (1.2 equiv), followed by an excess of methyl iodide gave, at 80% conversion, a 92:8 mixture of *trans* monomethylated lactone **56** (>95% de) and



Scheme 10. Reagents and conditions: (i) Pd/C, AcOH, 50 °C, H_2 (4 atm), then PhCOCl, pyridine, DCM, 0 °C to rt; (ii) LiOH, MeOH, rt, then TFA/DCM (1:5), rt; (iii) TBAF, THF, rt.

dimethylated lactone **59**. The *trans* configuration within monomethyl lactone **56** was subsequently confirmed unambiguously (vide infra), and is consistent with the established *trans* alkylation of 4-amino-γ-butyrolactones derived from aspartic acid.[26] Furthermore, an authentic sample of dimethylated lactone **59** was readily prepared by treatment of lactone **4** with excess KHMDS and methyl iodide, giving **59** in 64% yield (Scheme 11).[27] In an analogous manner, benzylation and allylation of lactone **4** was achieved, with authentic samples of the dibenzylated and diallylated lactones **60** and **61** prepared for spectroscopic comparison. Treatment of **4** with KHMDS and addition of benzyl bromide or allyl bromide gave, at 78 and 73% conversion, respectively, an 86:14 and 75:25 mixture of the corresponding *trans* monoalkylated lactones **57** and **58** in >95% de[28] and the dialkylated lactones **60** and **61**, consistent with high diastereoselectivity being observed for monoalkylation of lactone **4** *trans* to the adjacent C(3)-amino substituent.[29]



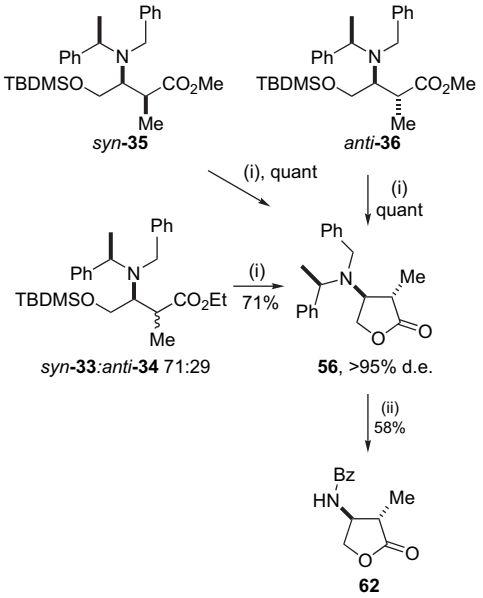
Scheme 11. Reagents and conditions: (i) KHMDS (1.2 equiv), THF, −78 °C then RX (excess); (ii) KHMDS (5.0 equiv), THF, −78 °C then RX (excess).

The relative configurations within α-methyl-β-amino esters **33–36**, and lactone **56**, were next correlated to the known

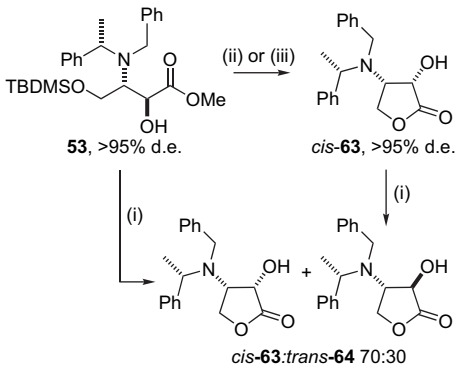
4-(*N*-benzoylamino)-γ-butyrolactone **62**. Treatment of a 29:71 mixture of the *syn*- and *anti*-α-methyl-β-amino ethyl esters **33** and **34**, respectively, or homogeneous *syn*- or *anti*-α-methyl-β-amino methyl esters **35** or **36** (>95% de), with TBAF gave, in all cases, a single diastereoisomeric lactone **56**, identical to that arising from the stereoselective methylation of lactone **4**, in good to excellent yield after chromatographic purification. Hydrogenolysis of **56**, and treatment of the resulting primary amine with benzoyl chloride and pyridine, gave the known *N*-benzoyl lactone **62**, with comparable spectroscopic properties to those reported in the literature (Scheme 12).[25] The isolation of a single lactone **4** from the mixture of *syn*-**33** and *anti*-**34**, and each of the diastereoisomerically pure β-amino butanoates *syn*-**35** and *anti*-**36**, is consistent with a mechanism involving initial desilylation and lactonisation upon treatment with TBAF, with subsequent epimerization occurring under the basic reaction conditions to give the thermodynamically favoured *trans*-lactone **56**.[30]

Lactonisation of the *anti*-2-hydroxy-3-amino ester **53** was next investigated. Treatment of **53** with TBAF gave a 70:30 mixture of the separable lactones *cis*-**63**/*trans*-**64** in 40 and 24% isolated yields, presumably due to lactonisation and partial epimerization under the basic conditions of the reaction. In an attempt to mediate the basicity of TBAF, *anti*-2-hydroxy-3-amino ester **53** was treated with TBAF in AcOH,[31] giving a single lactone **63** in 76% isolated yield and >95% de, while the same transformation could also be achieved by treatment of **53** with I_2 in MeOH.[32] Furthermore, treatment of *cis*-lactone **63** with TBAF gave a 70:30 mixture of **63/64**, consistent with partial epimerization of *cis*-lactone **63** to the *trans*-lactone **64** under the deprotection conditions. The preference for the *cis*-lactone **63** in this case may be due to hydrogen bonding between the amino and alcohol functionalities, which is presumably only significant in the *cis* diastereoisomer **63** (Scheme 13).

This O-deprotection and lactonisation protocol was subsequently investigated in the amide series. Treatment of



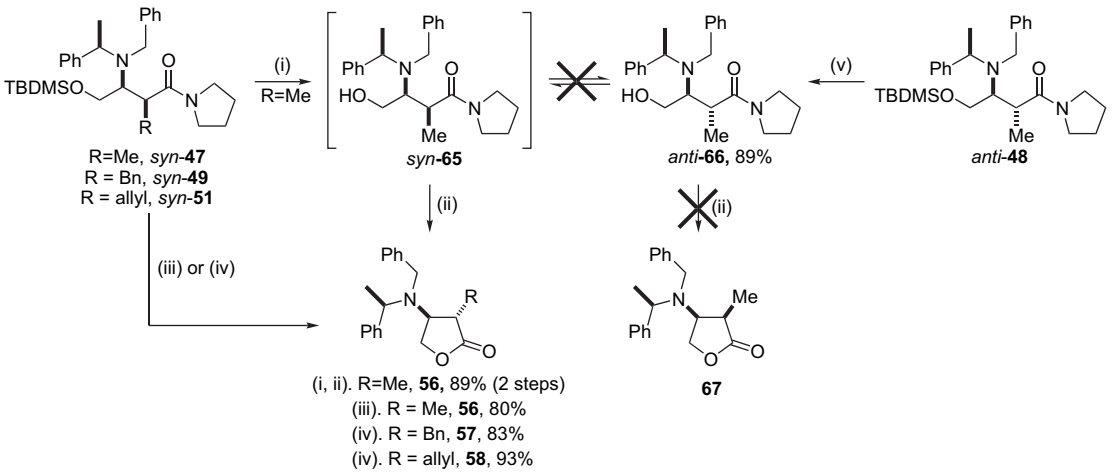
Scheme 12. Reagents and conditions: (i) TBAF, THF, rt; (ii) H_2, Pd/C, AcOH then BzCl, pyridine.



Scheme 13. Reagents and conditions: (i) TBAF, THF, rt; (ii) TBAF, AcOH, THF, rt; (iii) I_2, MeOH, rt.

syn-β-amino amide **47** with aq HF promoted desilylation to give the alcohol **65**, which cyclised to lactone **56** upon attempted chromatographic purification on silica; treatment of **65** with aq HCl also facilitated cyclisation, giving *trans*-lactone **56** in 89% yield. In a one-pot procedure, treatment of amide **47** with KF and aq HCl gave lactone **56** directly in 80% isolated yield, whilst treatment of amides **49** and **51** with a mixture of aq HF and HCl gave the corresponding *trans*-lactones directly, in good yield (Scheme 14). Meanwhile, treatment of the *anti*-β-amino amide **48** with TBAF gave exclusively the alcohol *anti*-**66**, which was amenable to chromatographic purification upon silica. Attempts to force the cyclisation reaction to **67** by heating in aq HCl resulted in extensive decomposition (Scheme 14). While acid catalysis seems necessary to promote cyclisation of *syn*-**65** to give the *trans*-lactone **56**, it seems that steric hindrance in the formation of the *cis*-lactone **67** from *anti*-**66** precludes lactonisation. Indeed, treatment of a 50:50 mixture of *syn*-**47**/*anti*-**48** with HF and filtration through silica gave a 50:50 mixture of lactone **56**:alcohol **66**. These studies also indicate that epimerisation and interconversion of the *anti*- and *syn*-amides **65** and **66** under the reaction conditions do not occur (Scheme 14).

In conclusion, upon reaction with homochiral lithium amides, γ-benzyloxy butenoates undergo competitive γ-deprotonation and conjugate addition, while γ-*tert*-butyldimethylsilyloxy butenoates undergo exclusive conjugate addition in high de. In contrast, treatment of γ-benzyloxy or γ-*tert*-butyldimethylsilyloxy butenamides with lithium amide **1** yields exclusively the β-amino amide products of conjugate addition in high de. γ-*tert*-Butyldimethylsilyloxy-β-amino butanoates readily undergo O-deprotection upon exposure to TBAF, giving the corresponding 4-amino-γ-butyrolactone, which may be stereoselectively alkylated to give the corresponding *trans*-3-alkyl-4-amino-γ-butyrolactones. Alternatively, stereoselective alkylation of γ-*tert*-butyldimethylsilyloxy-β-amino butanoates and butanamides following a tandem or stepwise protocol furnishes a range of separable *syn*- and *anti*-α-alkyl-β-amino butanoates and butanamides with modest stereoselectivities. *O*-Silyl deprotection of these *syn*- and *anti*-α-alkyl-β-amino butanoates with TBAF and concomitant cyclisation provide *trans*-3-alkyl-4-amino-γ-butyrolactones, consistent with epimerisation occurring upon deprotection. The further application of these protocols to the syntheses of natural products and amino sugars is currently underway in the laboratory.



Scheme 14. Reagents and conditions: (i) HF (aq), rt; (ii) HCl (aq), rt; (iii) KF, HCl (aq), rt; (iv) HF (aq), HCl (aq), rt; (v) TBAF, THF, rt.

3. Experimental

3.1. General experimental

All manipulations of organometallic and air or moisture sensitive reagents were performed under an atmosphere of dry nitrogen with deoxygenated solvents and using standard vacuum line and Schlenk tube techniques.[33] THF was distilled from sodium benzophenone ketyl, and DCM from calcium hydride, under nitrogen. Toluene was dried by standing over sodium wire and hexanes were distilled before use. Benzyl bromide and allyl bromide were distilled from calcium hydride, while methyl iodide was dried over calcium sulfate (Drierite™), prior to use. BuLi was used as a solution in hexanes and KHMDS as a solution in toluene. Photolysis was carried out using a Hanovia 125 W mercury vapour lamp with a Pyrex filter. All organic solutions were dried over $MgSO_4$. Silica gel chromatography was carried out on Kieselgel 60 according to the guidelines of Still.[34] Thin layer chromatography was carried out using Camlab Polygram SIL G/UV254, with a 0.25 mm coating of silica gel containing fluorescent indicator UV254. Plates were visualised using UV light, iodine, or potassium permanganate. Melting points were determined using a Gallenkamp apparatus and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter. Elemental analyses were performed by the analytical department of the Inorganic Chemistry Laboratory, University of Oxford. Infrared spectra were recorded in 0.1 mm solution cells on a Perkin–Elmer 781 spectrophotometer. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker AM 250, WH 300, AV 400 or AM 500 instruments. The field was locked by external referencing to the relevant deuteron resonance. Coupling constants are given in hertz. Materials of sufficient volatility were analysed by GC–MS using a Hewlett Packard 5890A gas chromatograph, fitted with an SGE column (12QC3/BP1-0.5 or 25QC3/BP1-0.5) and coupled to a TRIO 1 mass spectrometer running in CI^+ (NH_3) mode. Other mass spectra were recorded using a VG MASSLAB VG 20-250 CI^+ (NH_3) for low-resolution samples and a VG MICROMASS ZAB-1F with electron impact for high-resolution samples.

3.1.1. Methyl (*E*)-4-(benzyloxy)but-2-enoate 7. To a solution of (*E*)-methyl 4-bromo-2-butenonate (4.0 g, 22.3 mmol) in benzyl alcohol (20 mL) were added silver(I) oxide (6.20 g, 27.0 mmol) and calcium sulfate (13.0 g). The suspension was stirred in the dark, at 60 °C for 48 h before diluting with DCM and filtering through Celite®. Fractional distillation gave **7** as a pale yellow oil (2.6 g, 57%); $C_{12}H_{14}O_3$ requires C, 69.9; H, 6.8%; found C, 69.9; H, 7.1%; bp 112–116 °C (0.3 mmHg); ν_{max} (film) 1719; δ_H (500 MHz, $CDCl_3$) 3.76 (3H, s, O*Me*), 4.20 (2H, dd, *J* 2.0, 4.3, C(4)H_2), 4.58 (2H, s, OCH_2Ph), 6.15 (1H, dt, *J* 15.7, 2.0, C(2)*H*), 7.00 (1H, dt, *J* 15.7, 4.3, C(3)*H*), 7.31–7.39 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 51.5, 68.5, 72.7, 121.0, 127.7, 127.9, 128.6, 137.9, 144.8, 167.0; *m/z* (CI^+) 224 ($[M+NH_4]^+$, 17%), 207 (15), 91 (100).

3.1.2. *tert*-Butyl (*E*)-4-(benzyloxy)but-2-enoate 8. Aqueous H_2SO_4 (2 M, 20 mL) was added dropwise to a stirred solution of benzyloxyacetaldehyde diethyl acetal (1.05 g, 4.7 mmol) in Et_2O (50 mL). The reaction mixture was stirred for a further 12 h, then the mixture was partitioned and the aqueous phase extracted with Et_2O (3×20 mL). The combined organic extracts were dried, filtered and concentrated in vacuo. The residue was redissolved in MeCN (20 mL) and *tert*-butyl diethylphosphonoacetate (1.24 g, 4.90 mmol), LiCl (1.40 g, 31.5 mmol) and $^iPr_2NEt$ (0.59 mL, 3.48 mmol) were added in one portion. The reaction mixture was stirred for a further 48 h and then quenched by the addition of H_2O (5 mL), the organic layer was separated and the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic extracts were dried, filtered and concentrated in vacuo. Purification via column chromatography (eluent 30–40 °C petrol/Et_2O 10:1) gave **8** as a colourless oil (1.06 g, 90%); ν_{max} (film) 1714; δ_H (400 MHz, $CDCl_3$) 1.50 (9H, s, CMe_3), 4.17 (2H, dd, *J* 4.5, 2.0, C(4)H_2), 4.57 (2H, s, OCH_2Ph), 6.05 (1H, dt, *J* 15.9, 2.0, C(2)*H*), 6.89 (1H, dt, *J* 15.9, 4.5, C(3)*H*), 7.29–7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.1, 68.7, 72.7, 80.4, 123.3, 127.6, 127.8, 128.5, 137.8, 142.9, 165.6; *m/z* (CI^+) 249 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{15}H_{21}O_3^+$ ($[M+H]^+$) requires 249.1491; found 249.1479.

3.1.3. Ethyl (*E*)-4-(*tert*-butyldimethylsilyloxy)but-2-enoate 9. Borane (1.0 M in THF, 40.0 mL, 40.0 mmol) was added dropwise to a stirred solution of monoethyl fumarate (5.76 g, 40.0 mmol) in THF (20 mL) at −10 °C. Stirring was continued for a further 10 h during which time the solution was allowed to warm to 20 °C, the reaction was quenched with 50% aq AcOH (30 mL) and concentrated in vacuo. The slurry was poured into satd aq $NaHCO_3$ (100 mL), extracted with EtOAc (2×50 mL), and the combined organic extracts dried and concentrated in vacuo. The residue was redissolved in DCM (100 mL) and treated with TBDMSCl (6.50 g, 43.0 mmol) and Et_3N (6.62 mL, 47.6 mmol). After 55 h at 20 °C the reaction mixture was poured into H_2O (100 mL) and the organic layer washed sequentially with 0.1 M aq HCl (100 mL) and satd aq $NaHCO_3$ (100 mL). The organic layer was dried, filtered through a short plug of silica and the solvent evaporated. Distillation gave the title compound **9** as a colourless oil (3.24 g, 33%); bp 88 °C (0.3 mmHg); ν_{max} (film) 1713, 1662; δ_H (500 MHz, $CDCl_3$) 0.09 (6H, s, Si*Me*$_2$), 0.93 (9H, s, SiC*Me*$_3$), 1.31 (3H, t, *J* 7.2, CO_2CH_2*Me*), 4.21 (2H, q, *J* 7.2, CO_2C*H*$_2$), 4.35 (2H, dd, *J* 3.4, 2.3, C(4)*H*$_2$), 6.10 (1H, dt, *J* 15.4, 2.3, C(2)*H*), 7.01 (1H, dt, *J* 15.4, 3.4, C(3)*H*); δ_C (125 MHz, $CDCl_3$) −5.7, 14.1, 18.2, 25.7, 60.2, 62.1, 119.7, 147.6, 166.9; *m/z* (CI^+) 262 ($[M+NH_4]^+$, 60%), 245 (100), 187 (36); HRMS (CI^+) $C_8H_{15}O_3Si$ ($[M-C_4H_8]^+$) requires 187.0790; found 187.0791.

3.1.4. Methyl (*E*)-4-(*tert*-butyldimethylsilyloxy)butanoate 11. TBDMSCl (6.62 g, 48 mmol) was added in one portion to a stirred solution of but-2-ene-1,4-diol (2.14 g, 24 mmol), imidazole (2.99 g, 24 mmol) and DMAP (50 mg) in DCM (50 mL) at rt. After stirring for 12 h, the reaction mixture was concentrated in vacuo, the residue was dissolved in Et_2O (50 mL) and washed with 1 M aq HCl (50 mL), dried and concentrated in vacuo to give 1,4-di-(*tert*-butyldimethylsilyloxy)but-2-ene as a colourless oil that was used without purification (7.63 g, quant); δ_H (400 MHz, $CDCl_3$) 0.07 (12H, s, 2×Si*Me*$_2$), 0.90 (18H, s, 2×SiC*Me*$_3$), 4.24 (4H, dd, *J* 2.7, 0.7, C(1)*H*$_2$, C(4)*H*$_2$), 5.56 (2H, td, *J* 2.7, 0.7, C(2)*H*, C(3)*H*).

O_3 was bubbled through a stirred solution of 1,4-di-(*tert*-butyldimethylsilyloxy)but-2-ene (7.63 g, 24 mmol) in DCM (50 mL) at −78 °C until the solution turned blue. O_2 was then bubbled through the solution until it turned colourless. DMS (10 mL) was added dropwise via syringe and the reaction mixture stirred for 12 h. The reaction mixture was concentrated in vacuo, the residue was redissolved in Et_2O (50 mL) and washed with H_2O (50 mL), dried and concentrated in vacuo to give **10** as a colourless oil that was used without purification (7.37 g, 88%); δ_H (400 MHz, $CDCl_3$) 0.08 (6H, s, Si*Me*$_2$), 0.90 (6H, s, SiC*Me*$_3$), 4.17–4.21 (2H, m, C(2)*H*$_2$), 9.67–9.69 (1H, m, C(1)*H*).

$(EtO)_2P(O)CH_2CO_2Me$ (10.8 g, 52 mmol), LiCl (10 g, 236 mmol) and $^iPr_2NEt$ (4.43 mL, 34 mmol) were added to a stirred solution of **10** (7.37 g, 42.4 mmol) in MeCN (50 mL). The reaction mixture was stirred for 48 h and then quenched by the addition of H_2O (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (50 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O 60:1) gave **12** as a colourless oil (4.0 g, 41%); ν_{max} (film) 1727, 1664; δ_H (400 MHz, $CDCl_3$) 0.09 (6H, s, Si*Me*$_2$), 0.93 (9H, s, SiC*Me*$_3$), 3.75 (3H, s, O*Me*), 4.34 (2H, dd, *J* 3.4, 2.4, C(4)*H*$_2$), 6.12 (1H, dt, *J* 15.4, 2.4, C(2)*H*), 7.01 (1H, dt, *J* 15.4, 3.4, C(3)*H*); δ_C (100 MHz, $CDCl_3$) −5.5, 18.3, 25.8, 51.5, 62.1, 119.1, 147.7, 167.1; HRMS (CI^+) $C_{11}H_{23}O_3Si^+$ ($[M+H]^+$) requires 231.1416; found 231.1417.

3.1.5. *tert*-Butyl (*E*)-4-(*tert*-butyldimethylsilyloxy)butanoate 12. $(EtO)_2P(O)CH_2CO_2{}^tBu$ (5.74 g, 22.8 mmol), LiCl (5.39 g, 127 mmol) and $^iPr_2NEt$ (2.77 mL, 17.1 mmol) were added to a stirred solution of **10** (3.3 g, 19.0 mmol) in MeCN (40 mL). The reaction mixture was stirred for 48 h and then quenched by the addition of H_2O (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (40 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O 60:1) gave **12** as a colourless oil (2.17 g, 67%); R_f 0.2 (30–40 °C petrol/Et_2O 60:1); ν_{max} (film) 1717, 1661; δ_H (400 MHz, $CDCl_3$) 0.06 (6H, s, Si*Me*$_2$), 0.90 (9H, s, SiC*Me*$_3$), 1.46 (9H, s, OC*Me*$_3$), 4.29 (2H, dd, *J* 3.5, 2.3, C(4)*H*$_2$), 5.97 (1H, dt, *J* 15.4, 2.3, C(2)*H*), 6.86 (1H, dt, *J* 15.4, 3.5, C(3)*H*); δ_C (100 MHz, $CDCl_3$) −5.5, 18.3, 25.8, 28.1, 62.1, 80.1, 121.4, 146.0, 166.0; HRMS (CI^+) $C_{14}H_{28}O_3Si^+$ ($[M]^+$) requires 272.1808; found 272.1808.

3.2. General procedure 1 for lithium amide conjugate addition

BuLi (2.5 M in hexanes, 1.55 equiv) was added dropwise via syringe to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.6 equiv) in THF at −78 °C. After stirring for 30 min a solution of the requisite α,β-unsaturated carbonyl compound (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 and allowed to warm to rt over 15 min. The reaction mixture was concentrated in vacuo and the residue was partitioned between DCM and 10% aq citric acid. The organic layer was separated and the aqueous layer was extracted twice with DCM. The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ and brine, dried and concentrated in vacuo.

3.2.1. Methyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-4-benzyloxybutanoate 14. BuLi (2.5 M in hexanes, 1.51 mL, 3.77 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)-amine (822 mg, 3.89 mmol) in THF (40 mL) and **7** (500 mg, 2.43 mmol) in THF (20 mL) were reacted according to *general procedure 1* and gave a 44:56 mixture of (*Z*)-**13/14**. Chromatography (eluent 30–40 °C petrol/DCM 1:1) gave (*Z*)-**13** as a colourless oil (first to elute, 212 mg, 42%) and **14** (second to elute, 472 mg, 47%) as a pale yellow oil.

Data for (*Z*)-**13**: R_f 0.54 (30–40 °C petrol/DCM 1:1); ν_{max} (film) 1739, 1669; δ_H (400 MHz, $CDCl_3$) 3.20 (2H, dd, *J* 7.1, 1.6, C(2)*H*$_2$), 3.69 (3H, s, O*Me*), 4.60–4.65 (1H, m, C(3)*H*), 4.83 (2H, s, OC*H*$_2$), 6.19 (1H, dt, *J* 6.2, 1.6, C(4)*H*), 7.29–7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 29.7, 51.9, 73.8, 98.6, 127.3, 128.0, 128.5, 137.3, 172.7,

200.0; *m/z* (CI^+) 207 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{12}H_{15}O_3$ ($[M+H]^+$) requires 207.1021; found 207.1024.

Data for **14**: $C_{27}H_{31}NO_3$ requires C, 77.7; H, 7.5; N, 3.35%; found C, 77.6; H, 7.8; N, 3.1%; $[\alpha]_D^{22}$ −14.5 (*c* 1.0, EtOH); ν_{max} (film) 1731; δ_H (500 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.9, C(α)*Me*), 2.26 (1H, dd, *J* 14.7, 5.6, C(2)H_A), 2.39 (1H, dd, *J* 14.7, 7.4, C(2)H_B), 3.49 (3H, s, O*Me*), 3.46–3.85 (5H, m, C(3)*H*, NCH_2), 3.94 (1H, q, *J* 6.9, C(α)*H*), 4.47 (2H, s, OCH_2Ph), 7.20–7.40 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.3, 35.2, 50.6, 51.4, 53.8, 57.7, 72.5, 73.2, 127.0, 127.1, 127.8, 128.1, 128.4, 128.6, 138.7, 141.7, 143.8, 173.2; *m/z* (CI^+) 418 ($[M+H]^+$, 19%), 212 (82), 196 (33), 105 (27), 91 (100).

3.2.2. *tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-4-benzyloxybutanoate 17. BuLi (2.5 M in hexanes, 0.83 mL, 2.08 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)-amine (452 mg, 2.14 mmol) in THF (20 mL) and **8** (330 mg, 1.34 mmol) in THF (10 mL) were reacted according to *general procedure 1* and gave a 44:6:50 mixture of (*Z*)-**15**/(*E*)-**16**/**17**. Chromatography (eluent 30–40 °C petrol/DCM 2:1) gave (*Z*)-**15** as a colourless oil (first to elute, 109 mg, 33%), a 27:73 mixture of (*Z*)-**15**/(*E*)-**16** as a clear colourless oil (second to elute, 27 mg, 8%) and **17** as a pale yellow oil (third to elute, 256 mg, 42%).

Data for (*Z*)-**15**: R_f 0.2 (30–40 °C petrol/DCM 2:1); ν_{max} (film) 1732, 1669; δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, CMe_3), 3.11 (2H, dd, *J* 7.1, 1.6, C(2)H_2), 4.59–4.64 (1H, m, C(3)*H*), 4.82 (2H, s, OCH_2Ph), 6.16 (1H, dt, *J* 6.3, 1.6, C(4)*H*), 7.29–7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.1, 31.1, 73.7, 80.3, 99.4, 127.9, 127.9, 128.5, 137.4, 146.3, 171.6; *m/z* (CI^+) 249 ($[M+H]^+$, 25%), 193 (100); HRMS (CI^+) $C_{15}H_{21}O_3$ ($[M+H]^+$) requires 249.1491; found 249.1486.

Data for (*E*)-**16**: R_f 0.14 (30–40 °C petrol/DCM 2:1); δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, CMe_3), 2.87 (2H, dd, *J* 7.5, 1.2, C(2)H_2), 4.77 (2H, s, OCH_2Ph), 4.97 (1H, dt, *J* 12.7, 7.5, C(3)*H*), 6.45 (1H, dt, *J* 12.7, 1.2, C(4)*H*), 7.29–7.41 (5H, m, *Ph*).

Data for **17**: R_f 0.06 (30–40 °C petrol/DCM 2:1); $[\alpha]_D^{24}$ −72.9 (*c* 0.8, $CHCl_3$); ν_{max} (film) 1727; δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, *J* 7.1, C(α)*Me*), 1.39 (9H, s, CMe_3), 2.11 (1H, dd, *J* 15.0, 4.6, C(2)H_A), 2.25 (1H, dd, *J* 15.0, 8.5, C(2)H_B), 3.46 (1H, dd, *J* 9.6, 6.0, C(4)H_A), 3.60 (1H, dd, *J* 9.6, 6.0, C(4)H_B), 3.65 (1H, d, *J* 15.0, NCH_A), 3.68–3.74 (1H, m, C(3)*H*), 3.83 (1H, d, *J* 15.0, NCH_B), 3.90–3.95 (1H, m, C(α)*H*), 4.47 (2H, OCH_2Ph), 7.21–7.39 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.3, 28.0, 36.1, 50.7, 53.7, 58.4, 72.4, 73.0, 80.0, 126.5, 126.8, 127.4, 127.5, 127.8, 128.0, 128.1, 128.2, 128.3, 138.6, 141.8, 143.6, 171.7; *m/z* (ESI^+) 460 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{30}H_{38}NO_3$ ($[M+H]^+$) requires 460.2852; found 460.2848.

3.2.3. Ethyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-4-(*tert*-butyldimethylsilyloxy)butanoate 18. BuLi (2.5 M in hexanes, 0.51 mL, 1.27 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (277 mg, 1.31 mmol) in THF (20 mL) and **9** (200 mg, 0.82 mmol) in THF (10 mL) were reacted according to *general procedure 1*. Chromatography (eluent 30–40 °C petrol/DCM 2:1) gave **18** as a colourless oil (268 mg, 72%); $C_{27}H_{41}NO_3Si$ requires C, 71.2; H, 9.1; N, 3.1%; found C, 71.0; H, 9.35; N, 3.0%; $[\alpha]_D^{23}$ −7.9 (*c* 2.0, $CHCl_3$); ν_{max} (film) 1729; δ_H (500 MHz, $CDCl_3$) 0.02 (6H, s, SiMe_2), 0.88 (9H, s, SiCMe_3), 1.19 (3H, t, *J* 7.2, CO_2CH_2Me), 1.38 (3H, d, *J* 6.9, C(α)*Me*), 2.19 (2H, dd, *J* 15.0, 5.5, C(2)H_A), 2.36 (1H, dd, *J* 15.0, 7.7, C(2)H_B), 3.49–4.09 (8H, m, C(3)*H*, C(4)H_2, C(α)*H*, CO_2CH_2Me, NCH_2), 7.19–7.42 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) −5.7, 14.0, 18.2, 18.7, 25.8, 34.4, 50.8, 55.5, 57.8, 60.1, 65.1, 126.8, 127.0, 128.1, 128.3, 128.4, 128.5, 142.0, 144.0, 173.0; *m/z* (CI^+) 456 ($[M+H]^+$, 100%), 310 (60), 206 (38).

3.2.4. Methyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-4-(*tert*-butyldimethylsilyloxy)butanoate 19. BuLi (2.5 M in hexanes, 0.96 mL, 2.02 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (0.44 g, 2.08 mmol) in THF (20 mL) and **11** (0.30 g, 1.30 mmol) in THF (10 mL) were reacted according to *general procedure 1*. Chromatography (eluent 30–40 °C petrol/DCM 2:1) gave **19** as a colourless oil (344 mg, 60%); R_f 0.21 (30–40 °C petrol/Et_2O 20:1); $[\alpha]_D^{18}$ −10.6 (*c* 1.0, $CHCl_3$); ν_{max} (film) 1739; δ_H (400 MHz, $CDCl_3$) 0.02 (3H, s, SiMe_A), 0.03 (3H, s, SiMe_B), 0.88 (9H, s, SiCMe_3), 1.38 (3H, d, *J* 6.8, C(α)*Me*), 2.22 (1H, dd, *J* 15.0, 5.8, C(2)H_A), 2.38 (1H, dd, *J* 15.0, 7.9, C(2)H_B), 3.48–3.56 (1H, m, C(4)H_A), 3.55 (3H, s, O*Me*), 3.58–3.79 (3H, m, C(3)*H*, C(4)H_B, NCH_A), 3.84 (1H, d, *J* 14.7, NCH_B), 3.94 (1H, q, *J* 6.8, C(α)*H*), 7.18–7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) −5.6, 18.2, 18.5, 25.9, 34.4, 50.7, 51.3, 55.4, 57.6, 65.0, 126.6, 126.7, 127.8, 128.0, 128.1, 128.3, 141.5, 143.7, 173.0; *m/z* (ESI^+) 442 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{40}NO_3Si$ ($[M+H]^+$) requires 442.2776; found 442.2777.

3.2.5. *tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-4-(*tert*-butyldimethylsilyloxy)butanoate 20. BuLi (2.5 M in hexanes, 0.46 mL, 1.14 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (248 mg, 1.17 mmol) in THF (20 mL) and **12** (200 mg, 0.73 mmol) in THF (10 mL) were reacted according to *general procedure 1*. Chromatography (eluent 30–40 °C petrol/Et_2O 100:1) gave **20** as a colourless oil (269 mg, 76%); $[\alpha]_D^{23}$ −13.7 (*c* 1.0, $CHCl_3$); ν_{max} (film) 1728; δ_H (400 MHz, $CDCl_3$) 0.02 (3H, s, SiMe_A), 0.03 (3H, s, SiMe_B), 0.89 (9H, s, SiCMe_3), 1.37 (3H, d, *J* 7.0, C(α)*Me*), 1.42 (9H, s, CMe_3), 2.06 (1H, dd, *J* 15.3, 4.5, C(2)H_A), 2.27 (1H, dd, *J* 15.1, 8.3, C(2)H_B), 3.47–3.52 (1H, m, C(3)*H*), 3.59–3.72 (3H, m, C(4)H_2, NCH_A), 3.88 (1H, d, *J* 14.9, NCH_B), 3.93 (1H, q, *J* 7.0, C(α)*H*), 7.20–7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) −5.6 −5.5, 18.3, 19.5, 25.8, 25.9, 35.1, 50.8, 55.5, 58.3, 64.8, 79.9, 126.4, 126.7, 127.8, 128.0, 128.1, 128.2, 142.1, 143.9, 171.9; *m/z* (ESI^+) 484 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{45}NO_3Si$ ($[M+H]^+$) requires 484.3247; found 484.3229.

3.2.6. (1*S*,2*S*,3*S*,4*R*)-{3-(Hydroxymethyl)-7-oxabicyclo[2.2.1]hept-5-en-2-yl}(pyrrolidin-1′-yl)methanone 22. A solution of **21** (7.48 g, 49.2 mmol) in pyrrolidine (10 mL, 120 mmol) was heated at 65 °C (6 h) before cooling and evaporation of excess pyrrolidine. The resulting oil was crystallised by the addition of acetone, and the resultant solid recrystallised from acetone to give **22** as pale brown crystals (4.99 g, 45%) that were used without further purification. Filtration of an EtOAc/EtOH (1:1) solution through a short

plug of silica (R_f 0.50), followed by recrystallisation from acetone gave an analytically pure sample of **22** as colourless crystals; mp 130–131 °C (dec); $C_{12}H_{17}NO_3$ requires C, 64.5; H, 7.7; N, 6.3%; found C, 64.4; H, 7.7; N, 6.3%; ν_{max} (KBr) 3625, 1628; δ_H (500 MHz, $CDCl_3$) 1.73–2.07 (4H, m, $N(CH_2CH_2)_2$), 2.14 (1H, dt, *J* 8.5, 5.9, C*H*CH_2OH), 2.56 (1H, d, *J* 8.5, C*H*CON), 3.37–3.70 (6H, m, CH_2OH, $N(CH_2CH_2)_2$), 5.03 (1H, s, OC*H*), 5.12 (1H, s, OC*H*), 6.44 (2H, AB system, J_{AB} 6.1, C*H*=C*H*); δ_C (125 MHz, $CDCl_3$) 24.1, 25.8, 42.1, 44.5, 45.7, 46.6, 61.8, 79.2, 80.1, 136.5, 136.6, 171.4; *m/z* (CI^+) 224 ($[M+H]^+$, 10%), 156 (100).

3.2.7. (1*S*,2*S*,3*S*,4*R*)-{3-(Benzyloxymethyl)-7-oxabicyclo[2.2.1]hept-5-en-2-yl}(pyrrolidin-1′-yl)methanone 23. Potassium hydride (1.26 g of a 35% dispersion in mineral oil, 11.0 mmol) was washed with hexane (2×5 mL) and suspended in THF (40 mL) at −70 °C. To this was added a solution of the alcohol **22** (1.96 g, 8.80 mmol) in THF (50 mL), followed by BnBr (1.15 mL, 9.70 mmol) and the mixture stirred for 2 h at −70 °C and overnight (18 h) at 20 °C. The reaction mixture was filtered through a plug of silica, eluting with EtOAc and evaporation of the solvent gave **23** as a pale yellow oil, which crystallised on standing (2.64 g, 96%). Chromatography (eluent EtOAc) and recrystallisation from PhMe/hexane (1:2) gave an analytically pure sample; mp 106–108 °C; $C_{19}H_{23}NO_3$ requires C, 72.8; H, 7.4; N, 4.5%; found C, 72.9; H, 7.6; N, 4.3%; ν_{max} (KBr) 1631; δ_H (500 MHz, $CDCl_3$) 1.64–1.88 (4H, m, $N(CH_2CH_2)_2$), 2.23 (1H, td, *J* 8.7, 5.8, C*H*CH_2OBn), 2.50 (1H, d, *J* 8.7, C*H*CON), 3.27–3.51 (6H, m, CH_2OBn, $N(CH_2CH_2)_2$), 4.43, 4.54 (2H, AB system, J_{AB} 11.6, OCH_2Ph), 4.96 (1H, s, OC*H*), 5.15 (1H, s, OC*H*), 6.42 (2H, AB system, J_{AB} 5.8, C*H*=C*H*), 7.28–7.35 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 24.0, 25.6, 40.4, 44.3, 45.6, 46.4, 70.4, 73.2, 79.6, 80.3, 127.7, 127.9, 128.4, 136.2, 136.8, 138.3, 170.7; *m/z* (CI^+) 314 ($[M+H]^+$, 2%), 246 (100), 154 (25), 91 (16).

3.2.8. (1*S*,2*S*,3*S*,4*R*)-{3-(*tert*-Butyldimethylsilyloxymethyl)-7-oxabicyclo[2.2.1]hept-5-en-2-yl}(pyrrolidin-1′-yl)methanone 24. To a solution of the alcohol **22** (3.70 g, 16.6 mmol) in DCM (60 mL) were added TBDMSCl (2.76 g, 18.3 mmol) and Et_3N (2.77 mL, 19.9 mmol) and the mixture stirred at 20 °C for 48 h. The reaction mixture was extracted sequentially with H_2O (100 mL), 0.1 M aq HCl (100 mL) and satd aq $NaHCO_3$ (100 mL), dried and concentrated in vacuo to give **24** as a yellow oil (5.19 g, 93%) that was used without further purification. Chromatography (eluent Et_2O) gave an analytically pure sample; R_f 0.12 (Et_2O); $C_{18}H_{31}NO_3Si$ requires C, 64.05; H, 9.3; N, 4.15%; found C, 63.8; H, 9.5; N, 4.1%; ν_{max} (film) 1632; δ_H (500 MHz, $CDCl_3$) 0.04 (3H, s, $SiMe_A$), 0.06 (3H, s, $SiMe_B$), 0.89 (9H, s, $SiCMe_3$), 1.81–2.11 (5H, m, $N(CH_2CH_2)_2$, C*H*CH_2OSi), 2.46 (1H, d, *J* 8.6, C*H*CON), 3.33–3.58 (6H, m, CH_2OSi, $N(CH_2CH_2)_2$), 4.96 (1H, s, OC*H*), 5.14 (1H, s, OC*H*), 6.41 (2H, s, C*H*=C*H*); δ_C (125 MHz, $CDCl_3$) −5.6, 18.0, 24.1, 25.8, 25.7, 42.4, 44.2, 45.5, 46.4, 62.8, 78.9, 80.0, 136.2, 136.7, 170.5; *m/z* (CI^+) 338 ($[M+H]^+$, 3%), 270 (100), 212 (60), 138 (20).

3.2.9. (*Z*)-1-(Pyrrolidin-1′-yl)-4-(benzyloxy)but-2-ene-1-one 25. Compound **23** (1.78 g, 5.69 mmol) was pyrolysed under vacuum with a hot air gun for 5 min and the residue distilled (bp 190 °C/0.5 mmHg) to give **25** as an oil, which crystallised on standing (1.37 g, 98%); mp 39–41 °C; $C_{15}H_{19}NO_2$ requires C, 73.4; H, 7.8; N, 5.7%; found C, 73.4; H, 7.8; N, 5.4%; ν_{max} (KBr) 1656, 1610; δ_H (500 MHz, $CDCl_3$) 1.82–2.01 (4H, m, $N(CH_2CH_2)_2$), 3.45–3.51 (4H, m, $N(CH_2CH_2)_2$), 4.55 (2H, s, OCH_2Ph), 4.68 (2H, dd, *J* 4.9, 2.2, C(4)H_2), 6.04 (1H, dt, *J* 11.7, 2.2, C(2)*H*), 6.23 (1H, dt, *J* 11.7, 4.9, C(3)*H*), 7.28–7.37 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 24.1, 25.9, 45.3, 46.7, 68.8, 72.7, 120.9, 127.6, 127.9, 128.4, 138.3, 143.2, 165.0; *m/z* (CI^+) 246 ($[M+H]^+$, 100%), 140 (65), 91 (28).

3.2.10. (*Z*)-1-(Pyrrolidin-1′-yl)-4-(*tert*-butyldimethylsilyloxy)but-2-en-1-one 26. Compound **24** (5.00 g, 14.8 mmol) was pyrolysed under vacuum with a hot air gun for 5 min and the residue distilled to give **26** as a pale yellow oil (3.25 g, 81%); $C_{14}H_{27}NO_2Si$ requires C, 62.4; H, 10.1; N, 5.2%; found C, 62.5; H, 10.2; N, 5.0%; bp 140 °C (0.3 mmHg); ν_{max} (film) 1651, 1608; δ_H (400 MHz, $CDCl_3$) 0.04 (6H, s, $SiMe_2$), 0.87 (9H, s, $SiCMe_3$), 1.79–1.98 (4H, m, $N(CH_2CH_2)_2$), 3.42–3.48 (4H, m, $N(CH_2CH_2)_2$), 4.75 (2H, dd, *J* 4.7, 2.3, C(4)H_2), 5.92 (1H, dt, *J* 11.7, 2.3, C(2)*H*), 6.13 (1H, dt, *J* 11.7, 4.7, C(3)*H*); δ_C (125 MHz, $CDCl_3$) −5.5, 18.1, 24.2, 26.0, 25.8, 45.3, 46.7, 61.9, 119.2, 147.5, 165.2; *m/z* (CI^+) 269 ($[M]^+$, 8%), 212 (100), 73 (25).

3.2.11. (*E*)-1-(Pyrrolidin-1′-yl)-4-benzyloxybut-2-en-1-one 27. A solution of **25** (1.13 g, 4.63 mmol) and diphenyldisulfide (50 mg, 0.23 mmol) in benzene/hexane (1:1, 100 mL) was photolysed at 25 °C for 5 h. Filtration of the solution through Celite® and evaporation of the solvent gave a yellow oil. Chromatography (eluent EtOAc/hexane 2:1) and recrystallisation (Et_2O/pentane) gave **27** as a white solid (820 mg, 72%); R_f 0.16 (EtOAc/hexane 2:1); $C_{15}H_{19}NO_2$ requires C, 73.4; H, 7.8; N, 5.7%; found C, 73.7; H, 8.05; N, 5.65%; mp 34 °C; ν_{max} (KBr) 1667, 1607; δ_H (500 MHz, $CDCl_3$) 1.84–2.02 (4H, m, $N(CH_2CH_2)_2$), 3.55 (4H, t, *J* 6.8, $N(CH_2CH_2)_2$), 4.21 (2H, dd, *J* 2.0, 4.2, C(4)H_2), 4.59 (2H, s, OCH_2Ph), 6.44 (1H, dt, *J* 15.2, 2.0, C(2)*H*), 6.96 (1H, dt, *J* 15.2, 4.2, C(3)*H*), 7.29–7.38 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 24.3, 26.1, 45.9, 46.6, 69.2, 72.7, 121.7, 127.7, 127.8, 128.5, 138.1, 140.8, 164.4; *m/z* (CI^+) 246 ($[M+H]^+$, 100%).

3.2.12. (*E*)-1-(Pyrrolidin-1′-yl)-4-(*tert*-butyldimethylsilyloxy)but-2-en-1-one 28. A solution of **26** (2.32 g, 8.59 mmol) and diphenyldisulfide (94 mg, 0.43 mmol) in hexane (100 mL) was photolysed at 25 °C for 4 h. Filtration of the solution through Celite® and evaporation of the solvent gave a yellow oil. Chromatography (eluent EtOAc/hexane 2:1) and distillation gave **28** as a low-melting solid (1.39 g, 60%); R_f 0.37 (EtOAc/hexane 2:1); $C_{14}H_{27}NO_2Si$ requires C, 62.4; H, 10.1; N, 5.2%; found C, 62.3; H, 10.0; N, 5.05%; bp 170 °C (0.5 mmHg); ν_{max} (film) 1667, 1605; δ_H (500 MHz, $CDCl_3$) 0.09 (6H, s, $SiMe_2$), 0.94 (9H, s, $SiCMe_3$), 1.84–2.03 (4H, m, $N(CH_2CH_2)_2$), 3.54 (4H, t, *J* 6.8, $N(CH_2CH_2)_2$), 4.36 (2H, dd, *J* 3.1, 2.4, $SiOCH_2$), 6.42 (1H, dt, *J* 15.0, 2.2, C(2)*H*), 6.97 (1H, dt, *J* 15.0, 3.3, C(3)*H*); δ_C (125 MHz, $CDCl_3$) −5.6, 18.1, 24.1, 25.9, 25.7, 45.7, 46.4, 62.4, 119.8, 144.1, 164.9; *m/z* (CI^+) 269 ($[M]^+$, 1%), 212 (100).

3.2.13. (3*S*,α*R*)-1-(Pyrrolidin-1′-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-benzyloxybutan-1-one 29. BuLi (2.5 M in hexanes, 0.38 mL, 0.95 mmol), (*R*)-*N*-benzyl-*N*-

(α-methylbenzyl)amine (206 mg, 0.98 mmol) in THF (20 mL) and **27** (150 mg, 0.61 mmol) in THF (10 mL) were reacted according to *general procedure 1*. Chromatography (eluent EtOAc/hexane 3:2) gave **27** as a colourless oil (248 mg, 89%); R_f 0.29 (EtOAc/hexane 3:2); $C_{30}H_{36}N_2O_2 \cdot HCl$ requires C, 73.1; H, 7.6; N, 5.7%; found C, 73.1; H, 7.7; N, 5.6%; $[\alpha]_D^{21}$ −0.2 (*c* 1.2, $CHCl_3$); ν_{max} (film) 1621; δ_H (500 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.9, C(α)*Me*), 1.69–1.77 (4H, m, $N(CH_2CH_2)_2$), 2.12 (1H, dd, *J* 14.8, 5.1, C(2)H_A), 2.39 (1H, dd, *J* 14.8, 8.2, C(2)H_B), 2.91–3.40 (4H, m, $N(CH_2CH_2)_2$), 3.60 (1H, dd, *J* 9.6, 5.4, C(4)H_A), 3.71 (1H, dd, *J* 9.6, 5.6, C(4)H_B), 3.76–3.81 (1H, m, C(3)*H*), 3.79 (1H, d, *J* 15.0, NCH_A), 3.96 (1H, d, *J* 15.0, NCH_B), 3.99 (1H, q, *J* 6.9, C(α)*H*), 4.49 (2H, AB system, J_{AB} 11.9, OCH_2Ph), 7.20–7.46 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.6, 24.1, 25.8, 34.9, 45.4, 46.3, 50.8, 53.1, 57.9, 73.0, 126.7, 126.8, 127.5, 127.6, 128.2, 128.4, 138.9, 142.2, 144.3, 170.4; *m/z* (CI^+) 457 ($[M+H]^+$, 100%).

3.2.14. (3*S*,α*R*)-1-(Pyrrolidin-1′-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*tert*-butyldimethylsilyloxy)-butan-1-one 30. BuLi (2.5 M in hexanes, 0.43 mL, 1.07 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (233 mg, 1.10 mmol) in THF (20 mL) and **28** (187 mg, 0.69 mmol) in THF (10 mL) were reacted according to *general procedure 1*. Chromatography (eluent EtOAc/hexane 2:1) gave **30** as a colourless oil (177 mg, 54%); R_f 0.29 (EtOAc/hexane 2:1); $C_{29}H_{44}N_2O_2Si$ requires C, 72.45; H, 9.2; N, 5.8%; found C, 72.5; H, 9.5; N, 5.6%; $[\alpha]_D^{21}$ +8.4 (*c* 2.0, $CHCl_3$); ν_{max} (film) 1641; δ_H (500 MHz, $CDCl_3$) 0.01 (3H, s, SiMe_A), 0.03 (3H, s, SiMe_B), 0.87 (9H, s, SiCMe_3), 1.39 (3H, d, *J* 6.9, C(α)*Me*), 1.74–1.78 (4H, m, $N(CH_2CH_2)_2$), 2.07 (1H, dd, *J* 15.0, 5.5, C(2)H_A), 2.38 (1H, dd, *J* 15.0, 7.6, C(2)H_B), 2.93–3.41 (4H, m, $N(CH_2CH_2)_2$), 3.52–3.58 (1H, m, C(3)*H*), 3.68 (2H, dd, *J* 10.0, 5.1, C(4)H_2), 3.77 (1H, dd, *J* 10.0, 5.6, C(4)H_2), 3.79 (1H, d, *J* 14.9, NCH_A), 3.94 (1H, d, *J* 14.9, NCH_B), 3.98 (1H, q, *J* 7.0, C(α)*H*), 7.17–7.47 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) −5.7, 18.0, 18.7, 24.1, 25.8, 25.8, 34.3, 45.4, 46.2, 50.8, 54.7, 57.8, 65.3, 126.6, 126.7, 128.0, 128.1, 128.2, 128.4, 142.4, 144.5, 170.6; *m/z* (CI^+) 481 ($[M+H]^+$, 100%), 375 (48), 335 (35), 231 (36), 105 (23), 91 (25).

3.3. General procedure 2 for tandem lithium amide conjugate addition and enolate alkylation

BuLi (2.5 M in hexanes, 1.55 equiv) was added dropwise via syringe to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.6 equiv) in THF at −78 °C. After stirring for 30 min a solution of the requisite α,β-unsaturated carbonyl compound (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 the requisite electrophile and allowed to warm to rt over 12 h. The reaction mixture was concentrated in vacuo and the residue was partitioned between DCM and 10% aq citric acid. The organic layer was separated and the aqueous layer was extracted twice with DCM. The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ and brine, dried and concentrated in vacuo.

3.3.1. *tert*-Butyl (2*R*,3*S*,α*R*)- and *tert*-butyl (2*S*,3*S*,α*R*)-2-methyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*tert*-butyldimethylsilyloxy)butanoate 31 and 32. BuLi (2.5 M in hexanes, 0.46 mL, 1.14 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (248 mg, 1.17 mmol) in THF (20 mL), **12** (200 mg, 0.73 mmol) in THF (10 mL) and MeI (0.23 mL, 3.67 mmol) were reacted according to *general procedure 2* and gave a 50:50 mixture of **31**:**32**. Chromatography (eluent 30–40 °C petrol/Et_2O 100:1) gave **31** as a colourless oil (first to elute, 56.8 mg, 16%), a mixed fraction containing **31** and **32** as a colourless oil (second to elute, 88 mg, 24%), and **32** as a colourless oil (third to elute, contaminated with ~12% **20**, 34.8 mg).

Data for **31**: $[\alpha]_D^{27}$ +0.3 (*c* 1.0, $CHCl_3$); ν_{max} (film) 1725; δ_H (400 MHz, $CDCl_3$) 0.09 (3H, s, SiMe_A), 0.12 (3H, s, SiMe_B), 0.92 (3H, d, *J* 7.0, C(2)*Me*), 0.97 (9H, s, SiCMe_3), 1.41 (OCMe_3), 1.44 (3H, d, *J* 7.0, C(α)*Me*), 2.51–2.58 (1H, m, C(2)*H*), 3.01–3.05 (1H, m, C(3)*H*), 3.82–3.87 (2H, m, C(4)H_2), 3.91 (1H, d, *J* 14.1, NCH_A), 4.05 (1H, d, *J* 14.1, NCH_B), 4.13 (1H, q, *J* 6.8, C(α)*H*), 7.19–7.36 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) −5.6, −5.5, 16.6, 16.7, 18.2, 26.0, 28.0, 41.2, 51.6, 56.9, 59.7, 62.7, 79.7, 126.5, 127.9, 128.0, 128.9, 129.0, 141.6, 145.0, 175.8; *m/z* (ESI^+) 498 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{30}H_{48}NO_3Si$ ($[M+H]^+$) requires 498.3403; found 498.3414.

Data for **32**: ν_{max} (film) 1727; δ_H (400 MHz, $CDCl_3$) 0.06 (3H, s, SiMe_A), 0.07 (3H, s, SiMe_B), 0.92 (9H, s, SiCMe_3), 1.01 (3H, d, *J* 6.9, C(2)*Me*), 1.37 (3H, d, *J* 7.0, C(α)*Me*), 1.46 (OCMe_3), 2.65–2.73 (1H, m, C(2)*H*), 3.22–3.26 (1H, m, C(3)*H*), 3.72–3.80 (3H, m, C(4)H_2, NCH_A), 4.03 (1H, d, *J* 14.6, NCH_B), 4.13 (1H, q, *J* 6.7, C(α)*H*), 7.17–7.34 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) −5.8, −5.6, 14.9, 18.0, 18.1, 25.9, 28.1, 42.5, 51.2, 59.2, 61.0, 62.2, 79.6, 126.3, 126.4, 127.7, 128.0, 128.8, 142.0, 144.7, 175.5; *m/z* (ESI^+) 498 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{30}H_{48}NO_3Si$ ($[M+H]^+$) requires 498.3403; found 498.3399.

3.3.2. Ethyl (2*S*,3*S*,α*R*)- and ethyl-(2*R*,3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*tert*-butyldimethylsilyloxy)-2-methylbutanoate 33 and 34. *Tandem procedure*: BuLi (2.5 M in hexanes, 0.94 mL, 2.34 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (511 mg, 2.42 mmol) in THF (20 mL), **9** (368 mg, 1.51 mmol) in THF (10 mL) and MeI (0.14 mL, 2.17 mmol) were reacted according to *general procedure 2* and gave a 60:40 mixture of **33**:**34**. Chromatography (eluent hexane/EtOAc 20:1) gave **33** as a colourless oil (first to elute, 207 mg, 30%) and **36** as a colourless oil (second to elute, 138 mg, 19%).

Data for **33**: R_f 0.34 (hexane/EtOAc 20:1); $[\alpha]_D^{23}$ −6.5 (*c* 1.7, $CHCl_3$); $C_{28}H_{43}NO_3Si$ requires C, 71.6; H, 9.2; N, 3.0%; found C, 71.95; H, 9.4; N, 2.9%; ν_{max} (film) 1722; δ_H (500 MHz, $CDCl_3$) 0.04 (3H, s, SiMe_A), 0.08 (3H, s, SiMe_B), 0.92 (9H, s, SiCMe_3), 0.93 (3H, obsc d, C(2)*Me*), 1.20 (3H, t, *J* 7.2, OCH_2Me), 1.41 (3H, d, *J* 6.8, C(α)*Me*), 2.66 (1H, dq, *J* 9.5, 7.0, C(2)*H*), 2.98–3.04 (1H, m, C(3)*H*), 3.79–4.13 (7H, m, C(4)H_2, C(α), OCH_2Me), 7.17–7.34 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) −5.9, −5.8, 14.0, 15.8, 16.2, 18.1, 25.8, 40.2, 51.4, 56.8, 59.7, 60.0, 62.5, 126.8, 126.9, 128.0, 128.2, 128.3, 129.2, 141.6, 144.9, 176.6; *m/z* (ESI^+) 470 ($[M+H]^+$, 46%), 324 (100), 220 (38), 105 (46), 91 (70).

Data for **34**: R_f 0.29 (hexane/EtOAc 20:1); $[\alpha]_D^{20}$ −16.8 (*c* 1.3, $CHCl_3$); $C_{28}H_{43}NO_3Si$ requires C, 71.6; H, 9.2; N, 3.0%; found C, 71.7; H, 9.5; N, 2.9%; ν_{max} (film) 1723; δ_H (500 MHz, $CDCl_3$) 0.07 (3H, s, Si*Me*$_A$), 0.09 (3H, s, Si*Me*$_B$), 0.92 (9H, s, SiC*Me*$_3$), 1.03 (3H, d, *J* 6.9, C(2)*Me*), 1.14 (3H, t, *J* 7.1, OCH_2*Me*), 1.38 (3H, d, *J* 6.9, C(α)*Me*), 2.85 (1H, dq, *J* 9.4, 6.9, C(2)*H*), 3.12–3.20 (1H, m, C(3)*H*), 3.73–4.11 (7H, m, C(4)H_2, C(α)*H*, OCH_2Me), 7.17–7.36 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) −5.9, −5.8, 13.9, 14.7, 16.5, 18.1, 25.8, 41.2, 51.3, 57.5, 60.0, 60.6, 61.3, 126.6, 126.8, 128.0, 128.2, 128.3, 129.2, 141.6, 144.9, 176.2; *m/z* (ESI^+) 470 ($[M+H]^+$, 52%), 324 (100), 220 (38), 105 (43), 91 (71).

Stepwise procedure: BuLi (0.79 mL, 1.0 mmol) was added dropwise to a solution of di-*iso*-propylamine (106 mg, 1.05 mmol) in THF (5 mL) at 0 °C. After 1 h the LDA solution was added to a solution of **18** (228 mg, 0.50 mmol) in THF (5 mL) at −78 °C. The reaction mixture was stirred for 2 h before being quenched with MeI (156 μL, 2.50 mmol), then after 3 h at −78 °C the reaction was allowed to warm slowly to rt overnight (18 h). The resultant solution was poured into brine (25 mL), extracted with Et_2O (3×25 mL), dried and concentrated in vacuo to give a 25:75 mixture of **35/36** as a pale yellow oil (245 mg, quant).

3.3.3. Methyl (2*S*,3*S*,α*R*)- and methyl (2*R*,3*S*,α*R*)-2-methyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*tert*-butyldimethylsilyloxy)butanoate 35 and 36. *Tandem procedure*: BuLi (2.5 M in hexanes, 0.27 mL, 0.67 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (147 mg, 0.70 mmol) in THF (20 mL), **11** (100 mg, 0.43 mmol) in THF (10 mL) and MeI (0.14 mL, 2.17 mmol) were reacted according to *general procedure 2* and gave a 16:53:31 mixture of **19/35/36**. Chromatography (eluent 30–40 °C petrol/Et_2O 200:1) gave **35** as a colourless oil (first to elute, 58.4 mg, 30%), and **36** as a colourless oil (second to elute, contaminated with ~23% **19**, 61.4 mg).

Data for **35**: $[\alpha]_D^{21}$ −10.5 (*c* 1.2, $CHCl_3$); ν_{max} (film) 1736, 1603; δ_H (400 MHz, $CDCl_3$) 0.05 (3H, s, Si*Me*$_A$), 0.09 (3H, s, Si*Me*$_B$), 0.93 (9H, s, SiC*Me*$_3$), 0.94 (3H, obsc d, C(2)*Me*), 1.42 (3H, d, *J* 6.9, C(α)*Me*), 2.63–2.73 (1H, m, C(2)*H*), 3.00–3.04 (1H, m, C(3)*H*), 3.57 (3H, s, O*Me*), 3.81 (1H, d, *J* 14.2, NCH_A), 3.82–3.90 (2H, m, C(4)H_2), 4.04 (1H, d, *J* 14.1, NCH_B), 4.10 (1H, q, *J* 6.8, C(α)*H*), 7.19–7.35 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) −5.9, −5.8, 15.7, 16.0, 18.1, 25.7, 40.1, 51.1, 51.2, 56.7, 59.6, 62.3, 126.5, 126.6, 127.8, 127.9, 128.0, 128.8, 141.2, 144.5, 176.5; *m/z* (ESI^+) 456 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{42}NO_3Si$ ($[M+H]^+$) requires 456.2934; found 456.2934.

Data for **36**: ν_{max} (film) 1738; δ_H (500 MHz, $CDCl_3$) 0.08 (3H, s, Si*Me*$_A$), 0.10 (3H, s, Si*Me*$_B$), 0.92 (9H, s, SiC*Me*$_3$), 1.03 (3H, d, *J* 7.0, C(2)*Me*), 1.39 (3H, d, *J* 7.0, C(α)*Me*), 2.89–2.95 (1H, m, C(2)*H*), 3.13 (1H, ddd, *J* 9.5, 4.3, 3.3, C(3)*H*), 3.45 (3H, s, O*Me*), 3.77 (1H, d, *J* 14.5, NCH_A), 3.77–3.81 (1H, obsc dd, C(4)H_A), 3.90 (1H, dd, *J* 10.8, 3.0, C(4)H_B), 4.06 (1H, d, *J* 14.5, NCH_B), 4.10 (1H, q, *J* 7.0, C(α)*H*), 7.17–7.36 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) −5.4, −5.2, 15.2, 16.6, 18.6, 26.3, 41.6, 51.6, 51.7, 57.6, 61.0, 61.7, 126.8, 127.0, 128.2, 128.4, 128.5, 129.4, 141.6, 145.0, 176.6; *m/z* (ESI^+) 456 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{42}NO_3Si$ ($[M+H]^+$) requires 456.2934; found 456.2917.

Stepwise procedure: BuLi (0.14 mL, 0.34 mmol) was added dropwise to a solution of di-*iso*-propylamine (36.1 mg, 0.36 mmol) in THF (5 mL) at 0 °C. After 1 h the LDA solution was added to a solution of **19** (75.0 mg, 0.17 mmol) in THF (5 mL) at −78 °C. The reaction mixture was stirred for 2 h before being quenched with MeI (0.06 mL, 0.85 mmol), then after 3 h at −78 °C the reaction was allowed to warm slowly to rt overnight. The resultant solution was poured into brine (25 mL), extracted with Et_2O (3× 25 mL), dried and concentrated in vacuo to give a 25:75 mixture of **35/36** as a pale yellow oil (80 mg, quant).

3.3.4. Ethyl (2*S*,3*S*,α*R*)-2-benzyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*tert*-butyldimethylsilyloxy)butanoate 37. BuLi (2.5 M in hexanes, 0.84 mL, 2.09 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (456 mg, 2.16 mmol) in THF (20 mL), **9** (329 mg, 1.35 mmol) in THF (10 mL) and BnBr (0.64 mL, 5.4 mmol) were reacted according to *general procedure 2* and gave a 71:29 mixture of **37/38**. Chromatography (eluent hexane/EtOAc 20:1) gave **37** as a colourless oil (first to elute, 60 mg, 8%), and a mixture of **37** and **38** as a colourless oil (second to elute, 332 mg, 44%).

Data for **37**: R_f 0.36 (hexane/EtOAc 20:1); $[\alpha]_D^{21}$ +32.6 (*c* 1.4, $CHCl_3$); $C_{34}H_{47}NO_3Si$ requires C, 74.8; H, 8.7; N, 2.6%; found C, 74.7; H, 8.3; N, 3.0%; ν_{max} (film) 1720; δ_H (500 MHz, $CDCl_3$) 0.06 (3H, s, Si*Me*$_A$), 0.09 (3H, s, Si*Me*$_B$), 0.87 (3H, t, *J* 7.1, OCH_2*Me*), 0.94 (9H, s, SiC*Me*$_3$), 1.47 (3H, d, *J* 6.8, C(α)*Me*), 2.13 (1H, dd, *J* 13.5, 11.9, C(2)CH_A), 2.76 (1H, ddd, *J* 13.5, 9.4, 4.0, C(2)*H*), 3.10–3.20 (2H, m, C(3)*H*, C(2)CH_B), 3.45–4.19 (7H, m, C(4)H_2, C(α)*H*, OCH_2Me), 6.87–7.42 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) −5.8, −5.7, 13.8, 16.6, 18.2, 26.0, 37.4, 49.3, 51.7, 57.5, 59.8, 59.9, 62.7, 126.1, 127.0, 128.3, 128.4, 128.5, 129.1, 129.3, 140.3, 141.6, 145.2, 175.1; *m/z* (ESI^+) 546 ($[M+H]^+$, 100%), 400 (56), 302 (75), 181 (87), 91 (65).

3.3.5. Ethyl (2*S*,3*S*,α*R*)-2-allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*tert*-butyldimethylsilyloxy)butanoate 39. BuLi (2.5 M in hexanes, 0.82 mL, 2.06 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (450 mg, 2.13 mmol) in THF (20 mL), **9** (325 mg, 1.33 mmol) in THF (10 mL) and allyl bromide (0.23 mL, 2.66 mmol) were reacted according to *general procedure 2* and gave a 77:23 mixture of **39/40**. Chromatography (eluent hexane/EtOAc 25:1) gave **39** as a colourless oil (first to elute, 194 mg, 30%), and a mixture of **39** and **40** as a colourless oil (second to elute, 165 mg, 25%).

Data for **39**: R_f 0.28 (hexane/EtOAc 25:1); $[\alpha]_D^{20}$ +11.0 (*c* 1.1, $CHCl_3$); $C_{30}H_{45}NO_3Si$ requires C, 72.7; H, 9.15; N, 2.9%; found C, 72.4; H, 9.2; N, 2.6%; ν_{max} (film) 1721; δ_H (500 MHz, $CDCl_3$) 0.06 (3H, s, Si*Me*$_A$), 0.08 (3H, s, Si*Me*$_B$), 0.93 (9H, s, SiC*Me*$_3$), 1.18 (3H, t, *J* 7.1, OCH_2*Me*), 1.43 (3H, d, *J* 6.9, C(α)*Me*), 1.75–1.86 (1H, m, C(2)CH_A), 2.45–2.61 (2H, m, C(2)*H*, C(2)CH_B), 3.03–3.09 (1H, m, C(3)*H*), 3.78–4.13 (7H, m, C(4)H_2, C(α)*H*, OCH_2Me), 4.80–4.86 (2H, m, CH=CH_2), 5.37–5.50 (1H, m, C*H*=CH_2), 7.19–7.33 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) −5.9, 14.2, 16.3,

18.1, 25.9, 35.1, 46.5, 51.4, 57.3, 58.9, 59.9, 62.5, 116.1, 127.0, 128.3, 129.2, 136.0, 141.5, 145.0, 175.1; *m/z* (ESI^+) 496 ($[M+H]^+$, 88%), 350 (100), 246 (55), 105 (59), 91 (53).

3.3.6. Methyl (3*S*,α*R*)-3-(*N*-α-methylbenzylamino)-4-(*tert*-butyldimethylsilyloxy)butanoate 41. CAN (394 mg, 0.72 mmol) was added to a solution of **19** (151 mg, 0.34 mmol) in MeCN/H_2O (v/v 5:1; 6 mL) and the resultant solution allowed to stir at rt for 2 h. Satd aq $NaHCO_3$ and Et_2O were added, the organic layer separated and the aqueous layer extracted with Et_2O. The combined organic extracts were dried, filtered and concentrated in vacuo to furnish the crude product. Chromatography (eluent 30–40 °C petrol/Et_2O 10:1) gave **41** as a colourless oil (71.8 mg, 60%); $[\alpha]_D^{21}$ −22.3 (*c* 1.3, $CHCl_3$); ν_{max} (film) 3343, 1739, 1603; δ_H (500 MHz, $CDCl_3$) −0.01 (3H, s, SiMe_A), 0.00 (3H, s, SiMe_B), 0.87 (9H, s, SiCMe_3), 1.34 (3H, d, *J* 6.5, C(α)*Me*), 1.89 (1H, br s, N*H*), 2.43–2.50 (2H, m, C(2)H_2), 2.95 (1H, app quintet, *J* 5.3, C(3)*H*), 3.47–3.53 (2H, m, C(4)H_2), 3.66 (3H, s, O*Me*), 3.88 (1H, q, *J* 6.7, C(α)*H*), 7.21–7.25 (1H, m, *Ph*), 7.30–7.33 (4H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) −5.7, −5.6, 18.1, 24.6, 25.7, 36.0, 51.2, 53.5, 55.1, 64.9, 126.7, 126.5, 128.3, 145.7, 172.7; *m/z* (ESI^+) 352 ($[M+H]^+$, 100%), 248 (50); HRMS (ESI^+) $C_{19}H_{34}NO_3Si$ ($[M+H]^+$) requires 352.2308; found 352.2305.

3.3.7. (4*S*,α*R*)-*N*(1)-α-Methylbenzyl-4-(*tert*-butyldimethylsilyloxymethyl)azetidin-2-one 42. Compound **41** (35 mg, 0.100 mmol) was dissolved in Et_2O (2 mL) and the solution cooled to 0 °C. MeMgBr (3 M in Et_2O, 0.04 mL, 0.110 mmol) was added dropwise and the resultant solution stirred for 30 min at 0 °C before the addition of satd aq NH_4Cl. The organic layer was separated and the aqueous layer extracted with Et_2O. The combined organic extracts were dried and concentrated in vacuo. Chromatography (eluent 30–40 °C petrol/Et_2O/Et_3N 50:50:1) gave **42** as a colourless oil (30.9 mg, 97%); $[\alpha]_D^{21}$ −23.0 (*c* 0.9, $CHCl_3$); ν_{max} (film) 1751; δ_H (500 MHz, $CDCl_3$) 0.01 (3H, s, SiMe_A), 0.02 (3H, s, SiMe_B), 0.88 (9H, s, SiCMe_3), 1.63 (3H, d, *J* 7.5, C(α)*Me*), 2.64 (1H, dd, *J* 14.7, 2.3, C(3)H_A), 2.83 (1H, dd, *J* 14.4, 4.8, C(3)H_B), 3.47–3.51 (1H, m, C(4)*H*), 3.62 (2H, app qd, *J* 11.0, 4.9, C(4)CH_2), 4.96 (1H, q, *J* 6.8, C(α)*H*), 7.26–7.29 (1H, m, *Ph*), 7.33–7.38 (4H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) −5.8, −5.7, 18.1, 19.2, 25.6, 38.4, 51.6, 52.3, 127.4, 127.0, 128.4, 140.3, 166.7; *m/z* (ESI^+) 352 ($[M+MeOH+H]^+$, 100%), 320 (20); HRMS (ESI^+) $C_{18}H_{30}NO_2Si$ ($[M+H]^+$) requires 320.2046; found 320.2043.

3.3.8. Methyl (2*S*,3*S*,α*R*)-2-methyl-3-(*N*-α-methylbenzylamino)-4-(*tert*-butyldimethylsilyloxy)butanoate 43. CAN (147 mg, 0.267 mmol) was added to a solution of **35** (58.0 mg, 0.127 mmol) in MeCN/H_2O (v/v 5:1; 3 mL) and the resultant solution allowed to stir at rt for 2 h. Satd aq $NaHCO_3$ and Et_2O were added, the organic layer separated and the aqueous layer extracted with Et_2O. The combined organic extracts were dried, filtered and concentrated in vacuo. Chromatography (eluent 30–40 °C petrol/Et_2O 10:1) gave **43** as a colourless oil (28.7 mg, 62%); $[\alpha]_D^{22}$ +34.7 (*c* 0.7, $CHCl_3$); ν_{max} (film) 3447, 3345, 1737, 1602; δ_H (500 MHz, $CDCl_3$) −0.03 (3H, s, SiMe_A), −0.01 (3H, s, SiMe_B), 0.85 (9H, s, SiCMe_3), 1.15 (3H, d, *J* 6.9, C(2)*Me*), 1.29 (3H, d, *J* 6.5, C(α)*Me*), 1.75 (1H, br s, N*H*), 2.72 (1H, app quintet, *J* 7.1, C(2)*H*), 2.79–2.83 (1H, m, C(3)*H*), 3.46–3.51 (2H, m, C(4)H_2), 3.68 (3H, s, O*Me*), 3.81 (1H, q, *J* 6.5, C(α)*H*), 7.21–7.25 (1H, m, *Ph*), 7.29–7.32 (4H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) −5.7, −5.6, 11.9, 18.1, 24.4, 25.7, 39.9, 51.2, 55.6, 58.1, 63.0, 126.7, 126.5, 128.2, 146.1, 176.3; *m/z* (ESI^+) 366 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{36}NO_3Si$ ($[M+H]^+$) requires 366.2464; found 366.2461.

3.3.9. (3*S*,4*S*,α*R*)-*N*(1)-α-Methylbenzyl-3-methyl-4-(*tert*-butyldimethylsilyloxymethyl)azetidin-2-one 44. Compound **43** (28.7 mg, 0.079 mmol) was dissolved in Et_2O (2 mL) and the solution cooled to 0 °C. MeMgBr (3 M in Et_2O, 0.03 mL, 0.086 mmol) was added dropwise and the resultant solution stirred for 30 min at 0 °C before the addition of satd aq NH_4Cl. The organic layer was separated and the aqueous layer extracted with Et_2O. The combined organic extracts were dried and concentrated in vacuo. Chromatography (eluent 30–40 °C petrol/Et_2O/Et_3N 50:50:1) gave a clear, colourless oil **44** (19.0 mg, 73%); $[\alpha]_D^{23}$ +6.9 (*c* 0.5, $CHCl_3$); ν_{max} (film) 1749; δ_H (500 MHz, $CDCl_3$) 0.00 (3H, s, SiMe_A), 0.01 (3H, s, SiMe_B), 0.87 (9H, s, SiCMe_3), 1.21 (3H, d, *J* 7.4, C(3)*Me*), 1.62 (3H, d, *J* 7.1, C(α)*Me*), 3.17 (1H, qd, *J* 7.5, 5.6, C(3)*H*), 3.49 (1H, app q, *J* 5.8, C(4)*H*), 3.65 (1H, app d, *J* 0.7, C(4)CH_A), 3.66 (1H, app d, *J* 1.3, C(4)CH_B), 4.94 (1H, q, *J* 7.1, C(α)*H*), 7.23–7.37 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) −5.7, 8.7, 18.0, 19.4, 25.7, 45.6, 51.5, 55.8, 62.4, 127.3, 127.0, 128.4, 140.5, 170.9; *m/z* (ESI^+) 334 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{32}NO_2Si$ ($[M+H]^+$) requires 334.2202; found 334.2199.

3.3.10. Methyl (2*R*,3*S*,α*R*)-2-methyl-3-(*N*-α-methylbenzylamino)-4-(*tert*-butyldimethylsilyloxy)butanoate 45. CAN (162 mg, 0.295 mmol) was added to a solution of **36** (64 mg, contaminated with ~23% **19**) in MeCN/H_2O (v/v 5:1; 3 mL) and the resultant solution allowed to stir at rt for 2 h. Satd aq $NaHCO_3$ and Et_2O were added, the organic layer separated and the aqueous layer reextracted with Et_2O. The combined organic extracts were dried, filtered and concentrated in vacuo. Chromatography (eluent 30–40 °C petrol/Et_2O 10:1) furnished **45** as a colourless oil (20.6 mg, 62%); $[\alpha]_D^{22}$ −18.5 (*c* 0.8, $CHCl_3$); ν_{max} (film) 3448, 3346, 1739, 1602; δ_H (500 MHz, $CDCl_3$) 0.03 (3H, s, SiMe_A), 0.01 (3H, s, SiMe_B), 0.85 (9H, s, SiCMe_3), 1.15 (3H, d, *J* 6.9, C(2)*Me*), 1.29 (3H, d, *J* 6.5, C(α)*Me*), 1.75 (1H, br s, N*H*), 2.72 (1H, app quintet, *J* 7.1, C(2)*H*), 2.79–2.83 (1H, m, C(3)*H*), 3.47–3.50 (2H, m, C(4)H_2), 3.68 (3H, s, O*Me*), 3.81 (1H, q, *J* 6.5, C(α)*H*), 7.21–7.25 (1H, m, *Ph*), 7.29–7.32 (4H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) −5.8, −5.7, 13.3, 18.1, 23.9, 25.7, 41.4, 51.2, 55.7, 58.5, 61.3, 126.7, 126.4, 128.2, 146.3, 176.2; *m/z* (ESI^+) 366 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{36}NO_3Si$ ($[M+H]^+$) requires 366.2464; found 366.2461.

3.3.11. (3*R*,4*S*,α*R*)-*N*(1)-α-Methylbenzyl-3-methyl-4-(*tert*-butyldimethylsilyloxymethyl)azetidin-2-one 46. Compound **45** (20.6 mg, 0.056 mmol) was dissolved in Et_2O (2 mL) and the solution cooled to 0 °C. MeMgBr (3 M in Et_2O, 0.03 mL, 0.086 mmol) was added dropwise and the resultant solution stirred for 30 min at 0 °C before the addition of satd aq NH_4Cl. The organic layer was separated and the aqueous layer extracted with Et_2O. The combined organic extracts were dried and concentrated in vacuo. Chromatography (eluent 30–40 °C petrol/Et_2O/Et_3N 50:50:1) furnished **46** as a colourless oil (13.7 mg, 73%);

$[\alpha]_D^{23}$ +48.7 (*c* 0.4, $CHCl_3$); ν_{max} (film) 1750; δ_H (500 MHz, $CDCl_3$) 0.01 (3H, s, SiMe_A), 0.02 (3H, s, SiMe_B), 0.88 (9H, s, SiCMe_3), 1.20 (3H, d, *J* 7.4, C(3)*Me*), 1.61 (3H, d, *J* 7.1, C(α)*Me*), 2.84 (1H, qd, *J* 7.3, 2.1, C(3)*H*), 3.04 (1H, app td, *J* 4.8, 2.0, C(4)*H*), 3.58–3.65 (2H, m, C(4)CH_2), 4.99 (1H, q, *J* 7.1, C(α)*H*), 7.26–7.35 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) −5.6, 12.6, 18.2, 19.2, 25.8, 46.4, 51.0, 60.7, 63.9, 127.5, 127.1, 128.6, 140.3, 170.6; *m*/*z* (ESI^+) 334 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{32}NO_2Si$ ($[M+H]^+$) requires 334.2202; found 334.2208.

3.3.12. (2*S*,3*S*,α*R*)- and (2*R*,3*S*,α*R*)-1-(Pyrrolidin-1′-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*tert*-butyldimethylsilyloxy)-2-methylbutan-1-one 47 and 48. *Tandem procedure*: BuLi (2.5 M in hexanes, 0.66 mL, 1.66 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (362 mg, 1.71 mmol) in THF (20 mL), **28** (289 mg, 1.07 mmol) in THF (10 mL) and MeI (0.65 mL, 10.4 mmol) were reacted according to *general procedure 2* and gave a 66:34 mixture of **47/48**. Chromatography (eluent hexane/EtOAc 4:1) gave **47** as a colourless oil (first to elute, 223 mg, 42%), a mixture of **47** and **48** as a colourless oil (second to elute, 60 mg, 11%) and **48** as a colourless oil (third to elute, 97 mg, 19%).

Data for **47**: R_f 0.12 (hexane/EtOAc 4:1); $C_{30}H_{46}N_2O_2Si$ requires C, 72.8; H, 9.4; N, 5.7%; found C, 72.9; H, 9.6; N, 5.4%; $[\alpha]_D^{20}$ +21.3 (*c* 1.3, $CHCl_3$); ν_{max} (film) 1641; δ_H (500 MHz, $CDCl_3$) 0.03 (3H, s, SiMe_A), 0.07 (3H, s, SiMe_B), 0.88 (3H, d, *J* 7.0, C(2)*Me*), 0.91 (9H, s, SiCMe_3), 1.41 (3H, d, *J* 6.9, C(α)*Me*), 1.73–1.91 (4H, m, N(CH_2CH_2)$_2$), 2.69 (1H, dq, *J* 9.7, 6.9, C(2)*H*), 3.14–3.42 (5H, m, C(3)*H*, N(CH_2CH_2)$_2$), 3.80–4.13 (5H, m, C(4)H_2, C(α)*H*, NCH_2Ph), 7.15–7.39 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) −5.8, 15.6, 16.0, 18.2, 24.2, 25.8, 26.0, 37.7, 45.4, 46.1, 51.9, 57.8, 59.6, 62.7, 126.7, 127.1, 128.1, 128.2, 129.1, 142.0, 145.0, 174.9; *m*/*z* (ESI^+) 495 ($[M+H]^+$, 100%), 403 (26), 389 (49), 368 (23), 349 (63), 245 (40), 105 (23), 91 (19).

Data for **48**: R_f 0.06 (hexane/EtOAc 4:1); $C_{30}H_{46}N_2O_2Si$ requires C, 72.8; H, 9.4; N, 5.7%; found C, 72.7; H, 9.5; N, 5.6%; $[\alpha]_D^{23}$ −16.4 (*c* 1.4, $CHCl_3$); ν_{max} (film) 1630; δ_H (500 MHz, $CDCl_3$) 0.05 (3H, s, SiMe_A), 0.07 (3H, s, SiMe_B), 0.92 (9H, s, SiCMe_3), 1.02 (3H, d, *J* 6.9, C(2)*Me*), 1.42 (3H, d, *J* 6.9, C(α)*Me*), 1.58–1.78 (4H, m, N(CH_2CH_2)$_2$), 2.67–3.49 (5H, m, C(3)*H*, N(CH_2CH_2)$_2$), 2.85 (1H, dq, *J* 9.2, 6.9, C(2)*H*), 3.69 (1H, dd, *J* 10.9, 4.8, C(4)H_A), 3.80 (1H, dd, *J* 10.9, 2.4, C(4)H_B), 3.88 (1H, d, *J* 15.4, NCH_AH_BPh), 4.09 (1H, d, *J* 15.4, NCH_AH_BPh), 4.22 (1H, q, *J* 6.9, C(α)*H*), 7.13–7.37 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) −6.0, −5.8, 14.6, 19.2, 18.0, 24.1, 25.8, 25.8, 39.0, 45.6, 45.8, 50.8, 59.3, 60.9, 61.0, 126.3, 126.4, 127.9, 128.4, 142.3, 145.7, 174.4; *m*/*z* (ESI^+) 495 ($[M+H]^+$, 87%), 389 (38), 245 (38), 105 (63), 91 (100).

Stepwise procedure: BuLi (0.22 mL, 0.34 mmol) was added dropwise to a solution of di-*iso*-propylamine (36.1 mg, 0.36 mmol) in THF (5 mL) at 0 °C. After 1 h the LDA solution was added to a solution of **30** (55 mg, 0.11 mmol) in THF (5 mL) at −78 °C. The reaction mixture was stirred for 2 h before being quenched with MeI (36 μL, 0.57 mmol), then after 3 h at −78 °C the reaction was allowed to warm slowly to rt overnight. The resultant solution was poured into brine (25 mL), extracted with Et_2O (3×25 mL), dried and concentrated in vacuo to give a 65:35 mixture of **35/36** as a pale yellow oil (63 mg, quant).

3.3.13. (2*S*,3*S*,α*R*)-1-(Pyrrolidin-1′-yl)-2-benzyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*tert*-butyldimethylsilyloxy)butan-1-one 49. BuLi (2.5 M in hexanes, 0.69 mL, 1.72 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)-amine (375 mg, 1.78 mmol) in THF (20 mL), **28** (300 mg, 1.11 mmol) in THF (10 mL) and BnBr (0.90 mL, 7.57 mmol) were reacted according to *general procedure 2* and gave a 86:14 mixture of **49/50**. Chromatography (eluent hexane/EtOAc 4:1) gave **49** as a colourless oil (first to elute, 57 mg, 9%) and a mixture of **49** and **50** as a colourless oil (second to elute, 355 mg, 56%).

Data for **49**: R_f 0.12 (hexane/EtOAc 6:1); $C_{36}H_{50}N_2O_2Si$ requires C, 75.7; H, 8.8; N, 4.9%; found C, 75.4; H, 8.9; N, 4.7%; $[\alpha]_D^{21}$ +29.4 (*c* 1.6, $CHCl_3$); ν_{max} (film) 1622; δ_H (500 MHz, $CDCl_3$) 0.04 (3H, s, SiMe_A), 0.07 (3H, s, SiMe_B), 0.91 (9H, s, SiCMe_3), 1.21–1.63 (4H, m, N(CH_2CH_2)$_2$), 1.46 (3H, d, *J* 6.9, C(α)*Me*), 1.90–1.98, 2.93–3.01, 3.12–3.22 (5H, m, C(2)CH_A, N(CH_2CH_2)$_2$), 2.18 (1H, t, *J* 12.3, C(2)CH_A), 2.77 (1H, ddd, *J* 12.3, 9.6, 3.4, C(2)*H*), 3.29 (1H, ddd, *J* 9.6, 4.0, 3.0, C(3)*H*), 3.87–3.94 (3H, m, C(4)H_2, NCH_AH_BPh), 4.17 (1H, q, *J* 6.9, C(α)*H*), 4.24 (1H, d, *J* 14.4, NCH_AH_BPh), 6.90–7.50 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) −5.6, 16.7, 18.3, 23.9, 25.4, 26.0, 37.8, 45.1, 45.8, 47.1, 52.1, 58.5, 60.0, 62.9, 126.0, 126.9, 128.0, 128.2, 128.5, 129.1, 129.3, 140.8, 142.1, 145.1, 173.1; *m*/*z* (ESI^+) 571 ($[M+H]^+$, 100%), 465 (17), 425 (21).

3.3.14. (2*S*,3*S*,α*R*)-1-(Pyrrolidin-1′-yl)-2-allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*tert*-butyldimethylsilyloxy)butan-1-one 51. BuLi (2.5 M in hexanes, 0.40 mL, 1.01 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)-amine (220 mg, 1.04 mmol) in THF (20 mL), **28** (175 mg, 0.65 mmol) in THF (10 mL) and allyl bromide (0.11 mL, 1.3 mmol) were reacted according to *general procedure 2* and gave a 80:20 mixture of **51/52**. Chromatography (eluent hexane/EtOAc 4:1) gave **51** as a colourless oil (first to elute, 114 mg, 34%) and a mixture of **51** and **52** as a colourless oil (second to elute, 68 mg, 20%).

Data for **51**: R_f 0.31 (hexane/EtOAc 3:1); $C_{32}H_{48}N_2O_2Si$ requires C, 73.8; H, 9.3; N, 5.4%; found C, 73.8; H, 9.5; N, 5.3%; $[\alpha]_D^{20}$ +20.7 (*c* 2.6, $CHCl_3$); ν_{max} (film) 1625; δ_H (500 MHz, $CDCl_3$) 0.07 (3H, s, SiMe_A), 0.08 (3H, s, SiMe_B), 0.93 (9H, s, SiCMe_3), 1.43 (3H, d, *J* 6.9, C(α)*Me*), 1.65–1.93 (5H, m, C(2)CH_A N(CH_2CH_2)$_2$), 2.53–2.61 (2H, m, C(2)*H*, C(2)CH_B), 3.13–3.42 (5H, m, C(3)*H*, N(CH_2CH_2)$_2$), 3.81–3.91, 4.08–4.14 (5H, m, C(4)H_2, C(α)*H*, NCH_2Ph), 4.83 (1H, dd, *J* 9.9, 2.3, CH=CH_AH_B), 4.89 (1H, dd, *J* 17.0, 2.2, CH=CH_AH_B), 5.41–5.50 (1H, m, C*H*=CH_2), 7.18–7.37 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) −5.6, 17.4, 18.2, 24.3, 25.8, 26.0, 35.7, 44.3, 45.3, 46.4, 51.9, 59.1, 59.8, 62.8, 116.2, 126.8, 126.9, 128.2, 128.3, 128.7, 128.9, 129.1, 136.7, 142.1, 145.3, 173.5; *m*/*z* (ESI^+) 521 ($[M+H]^+$, 87%), 415 (41), 375 (78), 271 (43), 105 (100), 91 (72).

3.3.15. Methyl (2*S*,3*S*,α*S*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*tert*-butyldimethylsilyloxy)butanoate 53. BuLi (2.5 M in hexanes, 2.7 mL, 6.74 mmol),

(*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.47 g, 6.96 mmol) in THF (20 mL), **11** (1.0 g, 4.35 mmol) in THF (10 mL) and (+)-CSO (4.20 g, 18.4 mmol) were reacted according to *general procedure 2*. Chromatography (eluent 30–40 °C petrol/Et_2O 20:1) gave **53** as a colourless oil (1.55 g, 78%); R_f 0.25 (30–40 °C petrol/Et_2O 20:1); $[\alpha]_D^{21}$ +25.0 (*c* 1.2, $CHCl_3$); ν_{max} (film) 3512, 1736; δ_H (400 MHz, $CDCl_3$) 0.02 (3H, s, Si*Me*$_A$), 0.03 (3H, s, Si*Me*$_B$), 0.88 (SiC*Me*$_3$), 1.37 (3H, d, *J* 6.8, C(α)*Me*), 2.98 (1H, d, *J* 6.5, O*H*), 3.55–3.62 (1H, m, C(3)*H*), 3.68 (3H, s, O*Me*), 3.70–3.76 (1H, m, C(4)H_A), 3.83 (1H, d, *J* 15.2, NCH_B), 3.87–4.02 (3H, m, C(2)*H*, C(4)H_B, C(α)*H*), 4.14 (1H, d, *J* 15.2, NCH_B), 7.16–7.48 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) −5.6, 18.0, 18.4, 25.9, 51.5, 52.2, 57.7, 59.6, 61.8, 71.2, 126.6, 127.0, 127.9, 128.1, 128.2, 128.3, 141.6, 142.8, 174.8; *m*/*z* (ESI^+) 458 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{40}NO_4Si$ ($[M+H]^+$) requires 458.2727; found 458.2708.

3.3.16. Methyl (*S*)-3-(benzoylamino)-4-benzoyloxybutanoate 54. The hydrochloride salt of **14** (204 mg, 0.45 mmol), as a solution in acetic acid (3 mL), was treated with palladium on charcoal (10%, 55 mg) and heated at 50 °C for 24 h under an atmosphere of H_2 (4 bar). The mixture was filtered through Celite® and the solvent evaporated. The residue was suspended in DCM (5 mL) at 0 °C and treated with pyridine (182 μL, 2.25 mmol) and benzoyl chloride (157 μL, 1.35 mmol). The solution was allowed to warm to rt and stirred for 72 h before the solvent was evaporated. Chromatography (eluent Et_2O) and recrystallisation (EtOAc/hexane) gave **54** as fine, colourless needles (72 mg, 47%); R_f 0.53 (Et_2O); $C_{19}H_{19}NO_5$ requires C, 66.85; H, 5.6; N, 4.1%; found C, 66.7; H, 5.3; N, 4.0%; mp 145–146 °C; $[\alpha]_D^{20}$ +7.3 (*c* 0.5, $CHCl_3$); ν_{max} (film) 1725, 1665, 1516; δ_H (500 MHz, $CDCl_3$) 2.80 (2H, dd, *J* 16.4, 5.8, C(2)H_A), 2.87 (1H, dd, *J* 16.4, 4.8, C(2)H_B), 3.70 (3H, s, O*Me*), 4.52 (1H, dd, *J* 11.4, 5.3, C(4)H_A), 4.62 (1H, dd, *J* 11.4, 5.7, C(4)H_B), 4.84–4.94 (1H, m, C(3)*H*), 7.35 (1H, d, *J* 7.7, N*H*), 7.42–8.06 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 35.2, 46.0, 51.9, 65.5, 127.0, 128.4, 128.6, 129.7, 131.6, 133.2, 134.2, 166.6, 166.9, 173.3; *m*/*z* (ESI^+) 342 ($[M+H]^+$, 63%), 220 (100), 105 (45).

3.3.17. (*S*)-4-(*N*-Benzoylamino)dihydrofuran-2(3*H*)-one 55. Compound **54** (18 mg, 0.053 mmol) was suspended in MeOH (2 mL) and H_2O (0.1 mL), treated with lithium hydroxide (45 mg, 1.06 mmol) and stirred at 20 °C (18 h). After evaporation of the solvent the residue was suspended in DCM (5 mL) and treated with TFA (1 mL), the suspension was stirred at 20 °C (48 h) and the solvents evaporated. The residue was treated with satd aq $NaHCO_3$ (25 mL), extracted with EtOAc (3×15 mL), the combined extracts dried and the solvent evaporated to give **55** as a white solid (11.5 mg). The material was further purified by filtration of an EtOAc solution through a plug of silica and crystallisation by the addition of hexane to give **55** as fine white needles (9 mg, 83%); $[\alpha]_D^{21}$ −100.8 (*c* 0.4, $CHCl_3$); mp 129 °C; δ_H (500 MHz, $CDCl_3$) 2.63 (1H, dd, *J* 18.1, 2.4, C(3)H_A), 2.99 (1H, dd, *J* 18.1, 8.0, C(3)H_B), 4.39 (1H, dd, *J* 9.9, 1.8, C(5)H_A), 4.63 (1H, dd, *J* 9.9, 5.9, C(5)H_B), 4.94–4.97 (1H, m, C(4)*H*), 6.24 (1H, br s, N*H*), 7.42–7.47 (2H, m, *Ph*), 7.52–7.57 (1H, m, *Ph*), 7.79–7.82 (2H, m, *Ph*); *m*/*z* 206 ($[M+H]^+$, 100%).

3.3.18. (4*S*,α*R*)-4-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-dihydrofuran-2(3*H*)-one 4. Compound **18** (910 mg, 2.00 mmol) in THF (5 mL) was treated with TBAF (948 mg, 3.00 mmol) and the solution stirred at 20 °C (6 h). The mixture was poured into satd aq $NaHCO_3$ (50 mL), extracted with Et_2O (3×25 mL), dried and the solvent evaporated. Chromatography (eluent hexane/EtOAc 4:1) gave **4** as a colourless oil (456 mg, 77%); R_f 0.33 (hexane/EtOAc 4:1); $C_{19}H_{21}NO_2 \cdot HCl$ requires C, 68.8; H, 6.7; N, 4.2%; found C, 68.7; H, 7.0; N, 4.35%; mp (HCl salt) 90–110 °C (dec); $[\alpha]_D^{22}$ +74.7 (*c* 2.3, $CHCl_3$); ν_{max} (film) 1775; δ_H (500 MHz, $CDCl_3$) 1.41 (3H, d, *J* 7.0, C(α)*Me*), 2.21 (1H, dd, *J* 18.0, 7.8, C(3)H_A), 2.28 (1H, dd, *J* 18.0, 8.2, C(3)H_B), 3.72 (2H, AB system, J_{AB} 14.7, NCH_2Ph), 3.86–3.97 (2H, m, C(3)*H*, C(α)*H*), 4.17 (1H, dd, *J* 9.4, 7.6, C(5)H_A), 4.37 (1H, dd, *J* 9.4, 6.6, C(5)H_B), 7.24–7.41 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 16.3, 31.8, 50.5, 54.3, 57.5, 71.7, 127.5, 127.6, 127.9, 128.3, 128.7, 128.8, 140.2, 142.3, 176.6; *m*/*z* (ESI^+) 296 ($[M+H]^+$, 53%), 192 (100), 105 (22), 91 (25).

3.3.19. Methylation of (4*S*,α*R*)-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]dihydrofuran-2(3*H*)-one 4. To a solution of **4** (100 mg, 0.34 mmol) at −70 °C was added KHMDS (0.75 M in PhMe, 0.54 mL, 0.41 mmol) and the yellow solution stirred for 90 min before it was treated with MeI (64 μL, 1.02 mmol). The mixture was stirred at −70 °C for 2.5 h and then quenched with pH 7 phosphate buffer before being allowed to warm to rt. The biphasic solution was extracted with Et_2O (3×5 mL), the combined extracts dried and the solution filtered through a plug of silica gel. The solvent was evaporated to give a pale yellow oil (105 mg), which was analysed by ^1H NMR spectroscopy and GC–MS, and found to contain a mixture of **4**,**56** and **59** in the ratio 23:71:6.

3.3.20. (3*S*,4*S*,α*R*)-4-[*N*-Benzyl-*N*-(α-methylbenzyl)-amino]-3-methyldihydrofuran-2(3*H*)-one 56. A mixture of **33** and **34** (1:2.5 mixture, 235 mg, 0.50 mmol) in THF (5 mL) was treated with TBAF (948 mg, 3.00 mmol) and the solution stirred at 20 °C (6 h). The mixture was poured into satd aq $NaHCO_3$ (50 mL), extracted with Et_2O (3× 25 mL), dried and the solvent evaporated. Chromatography (eluent hexane/EtOAc 4:1) gave **56** as a colourless oil (110 mg, 71%); R_f 0.53 (hexane/EtOAc 4:1); $C_{20}H_{23}NO_2 \cdot HCl$ requires C, 69.45; H, 7.0; N, 4.05%; found C, 69.7; H, 6.7; N, 3.8%; mp (HCl salt) 170–173 °C (dec); $[\alpha]_D^{21}$ −38.7 (*c* 0.9, $CHCl_3$); ν_{max} (film) 1772; δ_H (500 MHz, $CDCl_3$) 1.01 (3H, d, *J* 7.1, C(3)*Me*), 1.38 (3H, d, *J* 6.9, C(α)*Me*), 2.50 (1H, dq, *J* 9.7, 7.1, C(3)*H*), 3.35 (1H, ddd, *J* 9.7, 8.2, 8.0, C(4)*H*), 3.81 (1H, d, *J* 14.4, NCH_A), 3.94 (1H, d, *J* 14.4, NCH_B), 3.99 (1H, q, *J* 6.9, C(α)*H*), 4.18 (1H, dd, *J* 9.2, 7.8, C(5)H_A), 4.25 (1H, dd, *J* 9.2, 8.4, C(5)H_B), 7.24–7.43 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.5, 15.6, 37.0, 49.8, 57.1, 61.1, 67.7, 127.1, 127.6, 128.1, 128.4, 139.8, 142.9, 177.9; *m*/*z* (ESI^+) 310 ($[M+H]^+$, 100%), 206 (38), 105 (33), 91 (28).

3.3.21. Benzylation of (4*S*,α*R*)-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]dihydrofuran-2(3*H*)-one 4. To a solution of **4** (100 mg, 0.34 mmol) at −70 °C was added KHMDS (0.75 M in PhMe, 0.54 mL, 0.41 mmol) and the yellow solution stirred for 90 min before it was treated with BnBr

(121 μL, 1.02 mmol). The mixture was stirred at −70 °C for 5 h and then treated as before to give a pale yellow oil (134 mg), which was analysed by ^{1}H NMR spectroscopy and GC–MS, and found to contain a mixture of **4**, **57** and **60** in the ratio 22:67:11.

3.3.22. (3*S*,4*S*,α*R*)-3-Benzyl-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]dihydrofuran-2(3*H*)-one 57. Compound **49** (160 mg, 0.28 mmol) in acetonitrile (3 mL) was treated with 48% aq HF (0.5 mL) and 6 M aq HCl (0.5 mL) and the solution stirred at 20 °C for 10 days. The mixture was basified to pH>10 with satd aq $NaHCO_3$, the solution extracted with Et_2O (4×4 mL) and the combined extracts dried. Chromatography (eluent DCM) gave **57** as a colourless oil (90 mg, 83%); R_f 0.56 (DCM); $C_{26}H_{27}NO_2$ requires C, 81.0; H, 7.1; N, 3.6%; found C, 81.1; H, 7.0; N, 3.75%; $[\alpha]_D^{22}$ −64.3 (*c* 0.7, $CHCl_3$); ν_{max} (film) 1769; δ_H (500 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.9, C(α)*Me*), 2.66 (1H, dd, *J* 13.4, 5.4, C(3)CH_A), 2.93 (1H, dd, *J* 13.4, 4.8, C(3)CH_B), 2.84 (1H, ddd, *J* 6.9, 5.4, 4.9, C(3)*H*), 3.54 (1H, ddd, *J* 7.8, 6.9, 6.0, C(4)*H*), 3.78–3.84 (3H, m, NCH_2Ph, C(5)H_A), 3.91 (1H, q, *J* 6.9, C(α)*H*), 4.19 (1H, dd, *J* 9.7, 6.0, C(5)H_B), 6.72–7.40 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.1, 34.0, 44.7, 49.9, 57.1, 68.3, 126.9, 127.4, 127.6, 128.2, 128.6, 128.7, 128.8, 129.7, 137.6, 140.1, 143.4, 178.2; *m/z* (ESI$^+$) 386 ([M+H]$^+$, 100%), 282 (63), 105 (46), 91 (64).

3.3.23. Allylation of (4*S*,α*R*)-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]dihydrofuran-2(3*H*)-one 4. To a cooled (−70 °C) solution of **4** (100 mg, 0.34 mmol) was added KHMDS (0.75 M in PhMe, 0.55 mL, 0.41 mmol) and the yellow solution stirred for 90 min before it was treated with allyl bromide (88 μL, 1.02 mmol). The mixture was treated as before to give a pale yellow oil (103 mg), which was analysed by ^{1}H NMR spectroscopy and GC–MS, and found to contain a mixture of **4**, **58** and **61** in the ratio 30:60:20.

3.3.24. (3*S*,4*S*,α*R*)-3-Allyl-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]dihydrofuran-2(3*H*)-one 58. Compound **51** (40 mg, 0.08 mmol) in acetonitrile (3 mL) was treated with 48% aq HF (0.5 mL) and 6 M aq HCl (0.5 mL) and the solution stood at 20 °C for 10 days. The mixture was basified to pH>10 with satd aq $NaHCO_3$, the solution extracted with Et_2O (4×4 mL) and the combined extracts dried. Purification by filtration through silica (Et_2O) gave **58** as a colourless oil (24 mg, 93%); $C_{22}H_{25}NO_2$ requires C, 78.8; H, 7.5; N, 4.2%; found C, 78.5; H, 7.55; N, 4.3%; $[\alpha]_D^{22}$ −41.3 (*c* 1.2, $CHCl_3$); ν_{max} (film) 1772; δ_H (500 MHz, $CDCl_3$) 1.35 (3H, d, *J* 6.9, C(α)*Me*), 2.09–2.18 (1H, m, C(3)CH_A), 2.29–2.38 (2H, m, C(3)CH_B), 2.61 (1H, dt, *J* 7.9, 5.5, C(3)*H*), 3.50–3.57 (1H, m, C(4)*H*), 3.81 (1H, d, *J* 14.3, NCH_A), 3.90 (1H, d, *J* 14.3, NCH_B), 3.95 (1H, q, *J* 6.9, C(α)*H*), 4.19–4.31 (2H, m, C(5)H_2), 4.64 (1H, dd, *J* 17.0, 1.3, CH=CH_AH$_B$), 4.85 (1H, d, *J* 10.1, CH=CH$_A$$H_B$), 5.34–5.47 (1H, m, C*H*=CH$_2$), 7.24–7.44 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.2, 32.3, 42.8, 50.0, 57.1, 57.4, 68.1, 118.4, 127.2, 127.3, 127.8, 128.3, 128.4, 128.5, 133.2, 139.8, 143.1, 177.2; *m/z* (ESI$^+$) 335 ([M+H]$^+$, 30%), 232 (100), 212 (58), 105 (46), 91 (61).

3.3.25. (4*S*,α*R*)-3,3-Dimethyl-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]dihydrofuran-2(3*H*)-one 59. Compound **4** (97 mg, 0.33 mmol) in THF (5 mL) was cooled to −70 °C and treated with KHMDS (0.75 M in PhMe, 2.19 mL, 1.64 mmol), and after 1 h the enolate was quenched with MeI (205 μL, 3.30 mmol) and the reaction allowed to warm slowly to 20 °C over 19 h. The white suspension was poured into satd aq $NaHCO_3$ (25 mL), the solution extracted with Et_2O (3×15 mL) and the combined extracts dried. Evaporation of the solvent and purification by filtration through silica (Et_2O) and recrystallisation from EtOAc/hexane (−30 °C) gave **59** as large colourless needles (67 mg, 64%); $C_{21}H_{25}NO_2$ requires C, 78.0; H, 7.8; N, 4.3%; found C, 78.0; H, 7.9; N, 4.2%; mp 140–143 °C; $[\alpha]_D^{21}$ −35.4 (*c* 0.7, $CHCl_3$); ν_{max} (KBr) 1768; δ_H (500 MHz, $CDCl_3$) 0.93 (3H, s, C(2)*Me*$_A$), 1.29 (3H, s, C(2)*Me*$_B$), 1.32 (3H, d, *J* 6.9, C(α)*Me*), 3.21 (1H, dd, *J* 6.4, 3.2, C(4)*H*), 3.79 (2H, AB system, J_{AB} 13.8, NCH_2), 3.96 (1H, q, *J* 6.9, C(α)*H*), 4.37 (1H, dd, *J* 10.2, 3.2, C(5)H_A), 4.51 (1H, dd, *J* 10.2, 6.4, C(5)H_B), 7.24–7.52 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 11.7, 18.9, 25.3, 41.7, 50.6, 54.9, 61.4, 66.9, 127.3, 127.7, 128.1, 128.3, 128.9, 138.9, 143.4, 182.6; *m/z* (ESI$^+$) 324 ([M+H]$^+$, 20%), 280 (34), 220 (100), 105 (29), 91 (38).

3.3.26. (4*S*,α*R*)-3,3-Dibenzyl-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]dihydrofuran-2(3*H*)-one 60. Compound **4** (137 mg, 0.46 mmol) in THF (5 mL) was cooled to −70 °C and treated with KHMDS (0.75 M in PhMe, 3.72 mL, 2.79 mmol), and after 1 h the enolate was quenched with BnBr (547 μL, 4.60 mmol) and the reaction allowed to warm slowly to 20 °C over 19 h. The white suspension was poured into satd aq $NaHCO_3$ (25 mL), the solution extracted with Et_2O (3×15 mL) and the combined extracts dried. Evaporation of the solvent and purification by chromatography (eluent hexane/EtOAc 8:1), followed by crystallisation from Et_2O/pentane (−30 °C) gave **60** as a micro-crystalline white solid (150 mg, 69%); R_f 0.27 (hexane/EtOAc 8:1); $C_{33}H_{33}NO_2$ requires C, 83.3; H, 7.0; N, 2.95%; found C, 83.55; H, 7.3; N, 2.8%; $[\alpha]_D^{20}$ −113.5 (*c* 1.0, $CHCl_3$); mp 125–127 °C; ν_{max} (KBr) 1760; δ_H (500 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.9, C(α)*Me*), 1.99 (1H, d, *J* 13.3, C(3)CH_AH$_B$Ph), 2.57 (1H, d, *J* 13.3, C(3)CH$_A$$H_B$Ph), 2.70 (1H, dd, *J* 10.3, 7.2, C(4)*H*), 3.20 (1H, d, *J* 14.3, C(3)CH_AH$_B$Ph), 3.37 (1H, d, *J* 14.3, C(3)CH$_A$$H_B$Ph), 3.65 (1H, d, *J* 6.5, C(5)H_A), 3.77 (1H, d, *J* 14.1, NCH_A), 3.87 (1H, d, *J* 14.1, NCH_B), 4.05 (1H, q, *J* 6.9, C(α)*H*), 4.14 (1H, d, *J* 11.5, C(5)H_B), 6.75–7.55 (20H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 11.8, 37.9, 43.9, 49.5, 51.3, 55.9, 59.6, 66.4, 126.7, 127.5, 127.9, 128.2, 128.6, 128.9, 129.0, 129.8, 131.8, 136.5, 137.6, 138.7, 143.2, 182.0; *m/z* (ESI$^+$) 476 ([M+H]$^+$, 67%), 372 (75), 212 (38), 108 (59), 91 (100).

3.3.27. (4*S*,α*R*)-3,3-Diallyl-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]dihydrofuran-2(3*H*)-one 61. Compound **4** (129 mg, 0.44 mmol) in THF (5 mL) was cooled to −70 °C and treated with KHMDS (0.75 M in PhMe, 3.50 mL, 2.62 mmol), and after 1 h the enolate was quenched with allyl bromide (381 μL, 4.40 mmol) and the reaction allowed to warm slowly to 20 °C over 19 h. The white suspension was poured into satd aq $NaHCO_3$ (25 mL), the solution extracted with Et_2O (3×15 mL) and the combined extracts dried. Evaporation of the solvent and purification by chromatography (eluent hexane/EtOAc 8:1), followed by

crystallisation from Et_2O/pentane (−30 °C) gave **61** as a micro-crystalline white solid (115 mg, 70%); R_f 0.22 (hexane/EtOAc 8:1); $C_{25}H_{29}NO_2$ requires C, 80.0; H, 7.8; N, 3.7%; found C, 80.1; H, 7.95; N, 3.55%; mp 94–95 °C; $[\alpha]_D^{20}$ −38.1 (*c* 0.9, $CHCl_3$); ν_{max} (KBr) 1765; δ_H (500 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.9, C(α)*Me*), 2.06 (2H, d, *J* 7.3, C(3)CH_2CH=CH_2), 2.40 (1H, dd, *J* 14.6, 6.6, C(3)CH_A), 2.50 (1H, dd, *J* 14.6, 7.7, C(3)CH_B), 3.47 (1H, dd, *J* 6.4, 1.8, C(4)*H*), 3.73 (1H, d, *J* 13.9, NC$H_A$$H_B$Ph), 3.85 (1H, d, *J* 13.9, NC$H_A$$H_B$Ph), 3.98 (1H, q, *J* 6.9, C(α)*H*), 4.36 (1H, dd, *J* 10.4, 1.8, C(5)H_A), 4.54 (1H, dd, *J* 10.4, 6.4, C(5)H_B), 4.83–5.08 (4H, m, 2×CH=CH_2), 5.23–5.37 (1H, m, C*H*=CH_2), 5.59–5.73 (1H, m, C*H*=CH_2), 7.25–7.50 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 11.4, 33.9, 39.1, 47.3, 51.2, 55.4, 58.7, 66.8, 118.4, 119.6, 127.5, 127.8, 128.3, 128.7, 128.9, 131.8, 134.1, 138.7, 142.6, 180.7; *m/z* (ESI^+) 375 ($[M+H]^+$, 85%), 272 (100), 105 (53), 91 (78).

3.3.28. (3*S*,4*S*)-3-Methyl-4-(*N*-benzoylamino)dihydrofuran-2(3*H*)-one 62. Compound **56** (100 mg, 0.32 mmol), as a solution in acetic acid (3 mL), was stirred vigorously with palladium on charcoal (10%, 25 mg) while being heated at 60 °C for 24 h under an atmosphere of H_2 (6 bar). The mixture was filtered through Celite and the solvent evaporated. The residue was dissolved in EtOH/hexane and the hydrochloride salt precipitated by the addition of ethereal HCl. The resultant salt was azeotroped with PhMe (10 mL), then suspended in DCM (2 mL) and treated with pyridine (78 μL, 0.97 mmol) and benzoyl chloride (75 μL, 0.65 mmol). The solution was stirred at 20 °C for 7 days before the solvent was evaporated. Chromatography (eluent hexane/EtOAc 1:1) gave **62** as a white solid (41 mg, 58%); R_f 0.33 (hexane/EtOAc 1:1); $C_{12}H_{13}NO_3$ requires C, 65.7; H, 6.0; N, 6.4%; found C, 66.0; H, 5.6; N, 6.1%; mp 177–178 °C; $[\alpha]_D^{20}$ −98.8 (*c* 0.3, $CHCl_3$); ν_{max} (KBr) 1780, 1669, 1519; δ_H (500 MHz, $CDCl_3$) 1.43 (3H, d, *J* 7.3, C(3)*Me*), 2.68 (1H, quintet, *J* 7.4, C(3)*H*), 4.11 (1H, dd, *J* 9.3, 6.5, C(5)H_A), 4.72 (1H, dd, *J* 9.3, 7.0, C(5)H_B), 4.54–4.64 (1H, m, C(4)*H*), 6.31 (1H, br s, N*H*), 7.45–7.59 (3H, m, *Ph*), 7.76–7.79 (2H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.7, 40.8, 53.8, 70.7, 127.0, 128.8, 132.2, 133.3, 167.8, 177.4; *m/z* (ESI^+) 220 ($[M+H]^+$, 100%).

3.3.29. (3*S*,4*S*,α*S*)- and (3*R*,4*S*,α*S*)-3-Hydroxy-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]dihydrofuran-2(3*H*)-one *syn*-(3*S*,4*S*,α*S*)-63 and *anti*-(3*S*,4*S*,α*S*)-64. *Desilylation of **53** with TBAF*: TBAF (1.39 mL, 1.39 mmol) was added to a stirred solution of **53** (430 mg, 0.93 mmol) in THF (20 mL) at 0 °C and allowed to warm to rt. After stirring for 6 h, the reaction mixture was diluted with DCM, washed with H_2O, dried and concentrated in vacuo. Chromatography (eluent 30–40 °C petrol/Et_2O 2:1) gave *anti*-**64** as a colourless oil (first to elute, 70 mg, 24%) and *syn*-**63** as a white crystalline solid (second to elute, 150 mg, 40%).

Data for *anti*-**64**: R_f 0.27 (30–40 °C petrol/Et_2O 2:1); $[\alpha]_D^{22}$ +6.3 (*c* 2.1, $CHCl_3$); ν_{max} (film) 3441, 1776; δ_H (400 MHz, $CDCl_3$) 1.43 (3H, d, *J* 6.8, C(α)*Me*), 3.66 (1H, d, *J* 13.3, NCH_A), 3.70–3.77 (2H, m, C(3)*H*, O*H*), 3.81 (1H, d, *J* 13.3, NCH_B), 4.01 (1H, d, *J* 8.2, C(2)*H*), 4.07 (1H, q, *J* 6.8, C(α)*H*), 4.36–4.42 (1H, m, C(4)H_A), 4.53–4.59 (1H, m, C(4)H_B), 7.19–7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.4, 50.5, 55.2, 65.1, 67.3, 127.6, 127.6, 127.9, 128.6, 128.9, 129.0, 137.6, 141.7, 176.0; *m/z* (ESI^+) 312 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{21}NO_3Na$ ($[M+Na]^+$) requires 334.1419; found 334.1418.

Data for *syn*-**63**: R_f 0.11 (30–40 °C petrol/Et_2O 2:1); mp 77–78 °C; $[\alpha]_D^{22}$ −19.4 (*c* 0.7, $CHCl_3$); ν_{max} (KBr) 3415, 1770; δ_H (400 MHz, $CDCl_3$) 1.46 (3H, d, *J* 7.2, C(α)*Me*), 3.73 (1H, d, *J* 15.5, NCH_A), 3.76 (1H, m, C(3)*H*), 3.89 (1H, d, *J* 15.5, NCH_B), 3.95 (1H, d, *J* 8.6, C(4)H_A), 4.18 (1H, m, C(α)*H*), 4.22 (1H, d, *J* 8.6, C(4)H_B), 4.34 (1H, d, *J* 9.9, C(2)*H*), 7.25–7.49 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.3, 50.4, 58.8, 63.3, 67.6, 69.7, 127.1, 127.3, 127.7, 128.0, 128.3, 128.5, 140.7, 142.4, 176.1; *m/z* (ESI^+) 312 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{21}NO_3Na$ ($[M+H]^+$) requires 334.1419; found 334.1426.

*Desilylation of **53** with TBAF/AcOH*: A solution of TBAF/AcOH (1.5:1, 0.16 mL, 0.16 mmol) was added to a stirred solution of **53** (50 mg, 0.11 mmol) in THF (5 mL) at 0 °C and allowed to cool to rt. After stirring for 18 h, the reaction mixture was diluted with DCM, washed with H_2O and dried. The solvents were removed in vacuo. Chromatography (eluent 30–40 °C petrol/Et_2O 2:1) gave *syn*-**63** (30 mg, 76%).

3.3.30. (2*R*,3*S*,α*R*)-1-(Pyrrolidin-1′-yl)-2-methyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-hydroxybutan-1-one *anti*-66. To a THF (2 mL) solution of **48** (194 mg, 0.39 mmol) was added TBAF (186 mg, 0.60 mmol) and the solution allowed to stand at rt for 3 days before concentration in vacuo. Chromatography (eluent Et_2O/EtOAc 1:1) gave *anti*-**66** as a viscous oil (132 mg, 89%); R_f 0.31 (Et_2O/EtOAc 1:1); $C_{24}H_{32}N_2O_2$ requires C, 75.75; H, 8.5; N, 7.4%; found C, 75.6; H, 8.7; N, 7.1%; $[\alpha]_D^{20}$ −62.2 (*c* 1.9, EtOH) for **66**·HCl; ν_{max} (film) 3250, 1603; δ_H (500 MHz, $CDCl_3$) 1.16 (3H, d, *J* 7.3, C(2)*Me*), 1.38 (3H, d, *J* 7.0, C(α)*Me*), 1.71–1.82 (4H, m, N($CH_2C\mathit{H}_2$)$_2$), 2.22–3.38 (4H, m, N($C\mathit{H}_2CH_2$)$_2$), 2.38 (1H, qd, *J* 7.3, 2.8, C(2)*H*), 3.52 (1H, td, *J* 5.8, 2.8, C(3)*H*), 3.71 (1H, dd, *J* 10.5, 6.0, C(4)H_A), 3.82–3.95 (4H, m, C(4)H_B, C(α)*H*), 4.35 (1H, br s, O*H*), 7.21–7.47 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 12.8, 16.9, 24.1, 25.7, 40.4, 45.8, 45.9, 51.3, 56.0, 56.9, 60.8, 126.9, 127.2, 128.3, 128.4, 128.7, 141.0, 143.3, 175.9; *m/z* (ESI^+) 310 ([M−70], 49%), 212 (45), 206 (100).

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