

# Asymmetric synthesis of $\beta$ -amino- $\gamma$ -substituted- $\gamma$ -butyrolactones: double diastereoselective conjugate addition of homochiral lithium amides to homochiral $\alpha,\beta$ -unsaturated esters†‡

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Chiral  $\alpha,\beta$ -unsaturated esters, containing a single,  $\gamma$ -stereogenic centre, show modest levels of substrate control upon conjugate addition of lithium dibenzylamide. Double diastereoselective conjugate additions of homochiral lithium *N*-( $\alpha$ -methylbenzyl)-*N*-( $\alpha$ -methylbenzyl)amide to the homochiral  $\alpha,\beta$ -unsaturated esters display “matching” and “mismatching” effects. In each case, however, these additions proceed under the dominant stereocontrol of the lithium amide to give the corresponding  $\beta$ -amino esters in high de. A remarkable reversal in stereoselectivity is noted by changing the ester functionality to an oxazolidinone. Subsequent *O*-deprotection and cyclisation of the resultant  $\beta$ -amino adducts gives access to the corresponding  $\beta$ -amino- $\gamma$ -substituted- $\gamma$ -butyrolactones in good yield and high de.

## Introduction

The conjugate addition of homochiral secondary lithium amides derived from  $\alpha$ -methylbenzylamine to  $\alpha,\beta$ -unsaturated esters and amides has been widely used for the asymmetric synthesis of  $\beta$ -amino acid derivatives.<sup>1</sup> This methodology has found use in a plethora of applications ranging from total synthesis<sup>2</sup> to kinetic resolution,<sup>3</sup> and has recently been reviewed.<sup>1</sup> As part of our ongoing investigations directed toward the *de novo* asymmetric synthesis of monosaccharides and amino sugars, we have previously demonstrated the extension of this methodology to the conjugate addition to achiral  $\gamma$ -benzyloxy- and  $\gamma$ -silyloxy- $\alpha,\beta$ -unsaturated esters and amides for the asymmetric synthesis of  $\beta$ -amino- $\gamma$ -butyrolactones.<sup>4</sup> In order to extend further the utility of this conjugate addition methodology, its application to the preparation of a range of  $\beta$ -amino- $\gamma$ -substituted- $\gamma$ -butyrolactones was investigated. It was envisaged that an investigation of the double diastereoselectivity<sup>5</sup> observed upon conjugate addition of homochiral lithium amides to chiral  $\alpha,\beta$ -unsaturated esters **1** containing a  $\gamma$ -stereogenic centre, and subsequent cyclisation, would generate a range of  $\beta$ -amino- $\gamma$ -substituted- and  $\alpha,\gamma$ -disubstituted- $\beta$ -amino- $\gamma$ -butyrolactones **4** and **5** with high stereocontrol (Fig. 1).

The conjugate addition of lithium amides to  $\alpha,\beta$ -unsaturated esters containing a  $\gamma$ -alkoxy stereogenic centre has been previously reported in the literature. For example, Yamamoto *et al.* have demonstrated that conjugate addition of lithium *N*-benzyl-

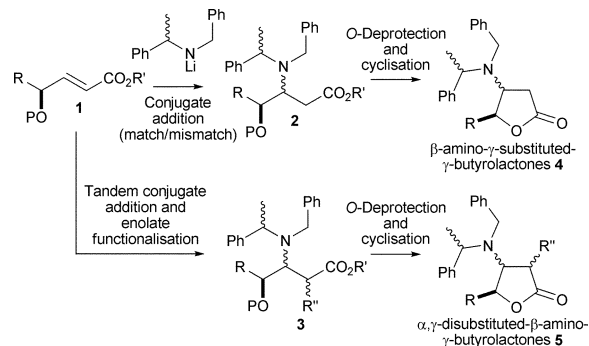


Fig. 1 Proposed route to homochiral  $\beta$ -amino- $\gamma$ -substituted- $\gamma$ -butyrolactones **4** and  $\alpha,\gamma$ -disubstituted- $\beta$ -amino- $\gamma$ -butyrolactones **5**.

*N*-trimethylsilylamide **6** to the mandelate-derived  $\alpha,\beta$ -unsaturated ester **7** proceeds with exclusive *anti* selectivity to furnish  $\beta$ -amino ester *anti*-**8**, whilst conjugate addition of lithium amide **6** to the lactate-derived  $\alpha,\beta$ -unsaturated ester **9** occurs with high *syn* selectivity. Conjugate addition of lithium dibenzylamide **12** to lactate-derived  $\alpha,\beta$ -unsaturated ester **9**, meanwhile, is moderately *anti* selective (Fig. 2).<sup>6</sup>

Furthermore, Sewald *et al.* have shown that conjugate addition of homochiral lithium *N*-( $\alpha$ -methylbenzyl)-*N*-trimethylsilylamide **16** to the homochiral  $\alpha,\beta$ -unsaturated ester (*S,E*)-**17** (derived from glyceraldehyde **15**) in Et<sub>2</sub>O proceeds under the stereocontrol of the chiral acceptor, with high *syn* selectivity noted independent of the absolute configuration of the nucleophile. In THF, however, the additions proceed with no stereocontrol (Fig. 3).<sup>7</sup>

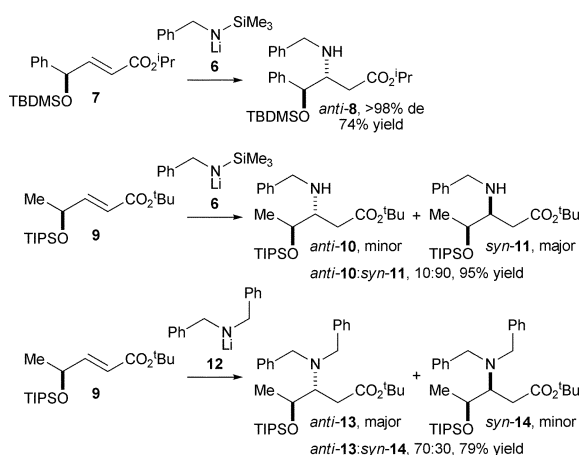
We detail herein our full studies concerning the stereoselectivity observed upon conjugate addition of homochiral lithium amides to a range of homochiral  $\alpha,\beta$ -unsaturated acceptors containing a  $\gamma$ -stereogenic centre. In each case, an evaluation of substrate control through the conjugate addition of an achiral lithium amide

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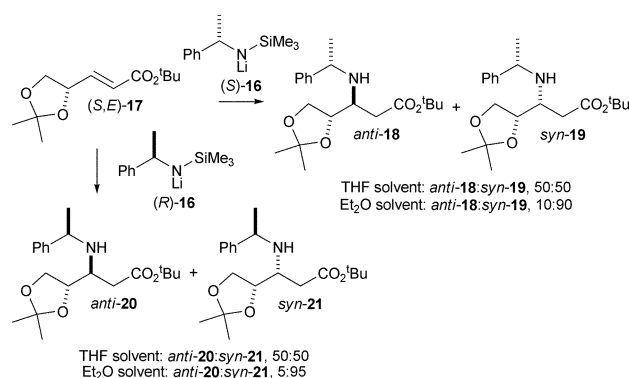
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‡ CCDC reference number 634215. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b712937h



**Fig. 2** Conjugate additions of lithium *N*-benzyl-*N*-trimethylsilylamide **6** and lithium dibenzylamide **12** to mandelate- and lactate-derived homochiral  $\alpha,\beta$ -unsaturated esters **7** and **9**.



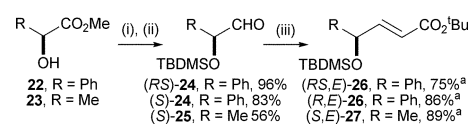
**Fig. 3** Conjugate addition of homochiral lithium *N*-( $\alpha$ -methylbenzyl)-*N*-trimethylsilylamide **16** to glyceraldehyde-derived homochiral  $\alpha,\beta$ -unsaturated ester (*S,E*)-**17**.

to the chiral acceptor is used to predict the configuration of the “matched” reaction pairing.

## Results and discussion

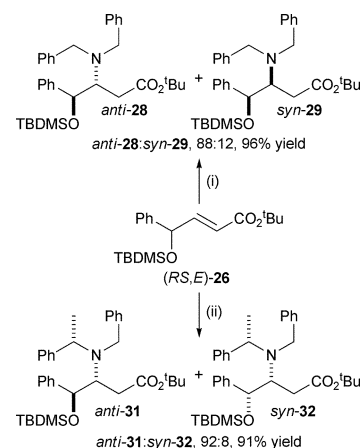
### Double diastereoselective conjugate addition of homochiral lithium amides to homochiral $\gamma$ -silyloxy- $\alpha,\beta$ -unsaturated esters

Initial studies were directed toward the preparation of  $\gamma$ -*tert*-butyldimethylsilyloxy- $\alpha,\beta$ -unsaturated esters derived from methyl mandelate and methyl lactate, containing a single stereogenic centre at the  $\gamma$ -position. Following established experimental procedures<sup>8</sup> methyl (*RS*)-mandelate (*RS*)-**22** was silylated and subsequently reduced with DIBAL-H to give aldehyde (*RS*)-**24** in 96% yield over two steps. Treatment of aldehyde (*RS*)-**24** with the sodium anion of *tert*-butyl diethylphosphonoacetate gave a 92 : 8 (*E*) : (*Z*) mixture of olefins, from which (*RS,E*)-**26** was isolated in 75% yield as a single geometric isomer after chromatography. The corresponding homochiral  $\alpha,\beta$ -unsaturated ester (*R,E*)-**26** (>98% de, 98% ee)<sup>9</sup> was prepared in an analogous fashion from methyl (*S*)-mandelate (*S*)-**22**, and similar elaboration of methyl (*S*)-lactate (*S*)-**23** gave (*S,E*)-**27**<sup>10</sup> (Scheme 1).



**Scheme 1** Reagents and conditions: (i) TBDMSO, imidazole, DMF, rt; (ii) DIBAL-H, -78 °C, PhMe; (iii) *tert*-butyl diethylphosphonoacetate, NaH, THF, -78 °C to rt. <sup>a</sup> Isolated as a single alkene stereoisomer (>98% de).

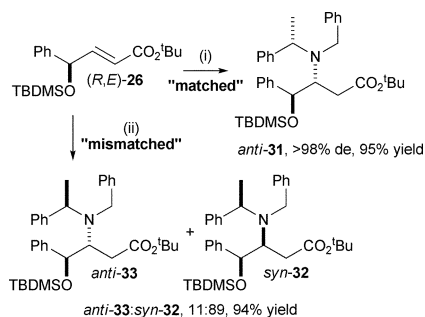
Previous investigations from this laboratory concerning the kinetic resolution of 3- and 5-alkyl-cyclopentene-1-carboxylates have demonstrated that the stereoselectivity in these systems is best evaluated through an initial investigation of the level of substrate control upon conjugate addition of an achiral lithium amide to the chiral acceptor. The level of enantioselectivity between the substrate and the chiral lithium amide is subsequently evaluated through their mutual kinetic resolution (addition of racemic acceptor to an excess of racemic lithium amide).<sup>3</sup> The application of this experimental protocol to acyclic  $\alpha,\beta$ -unsaturated ester (*RS,E*)-**26** was thus examined, with conjugate addition of lithium dibenzylamide **12** to (*RS,E*)-**26** giving an inseparable 88 : 12 mixture of *anti*-**28** : *syn*-**29** in 96% isolated yield. Having demonstrated that the  $\gamma$ -stereocentre within **26** exerts moderate levels of stereocontrol upon addition of lithium dibenzylamide **12**, the extent of enantioselectivity upon reaction of (*RS,E*)-**26** with lithium (*RS*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide (*RS*)-**30** was probed. Conjugate addition of lithium amide (*RS*)-**30** to (*RS,E*)-**26** gave a 92 : 8 mixture (84% de) of *anti*-**31** : *syn*-**32** only, which was isolated in 91% yield, consistent with *E* = 12<sup>11</sup> (Scheme 2). Lithium *N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide **30** is known to add to acyclic  $\alpha,\beta$ -unsaturated esters with extremely high, and predictable, levels of stereocontrol (typically >95% de),<sup>1,12,13</sup> and the *anti* configuration within the major diastereoisomer **31** was therefore assigned on the basis of high levels of enantioselectivity between the chiral  $\alpha,\beta$ -unsaturated ester and chiral lithium amide. The *syn* configuration of the minor diastereoisomer **32** was assumed on the basis that the high stereocontrol of the lithium amide overrides the moderate substrate control of the ester. The configuration at C(3) within both *anti*-**31** and *syn*-**32** relative to the *N*- $\alpha$ -methylbenzyl stereocentre was thus assigned by analogy to the model developed



**Scheme 2** Reagents and conditions: (i) lithium dibenzylamide **12**, THF, -78 °C, 2 h; (ii) lithium (*RS*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide (*RS*)-**30**, THF, -78 to -50 °C, 12 h.

to explain the high stereoselectivity observed during addition of lithium *N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide **30** to  $\alpha,\beta$ -unsaturated acceptors.<sup>12</sup> The preferential *anti* stereoselectivity upon conjugate addition to *tert*-butyl ester (*RS,E*)-**26** is analogous to that described by Yamamoto *et al.* for the conjugate addition of lithium *N*-benzyl-*N*-trimethylsilylamide **6** to the corresponding *iso*-propyl ester **7** (*vide supra*, Fig. 2), and was subsequently confirmed unambiguously by a separate synthesis in the enantiomerically pure series.

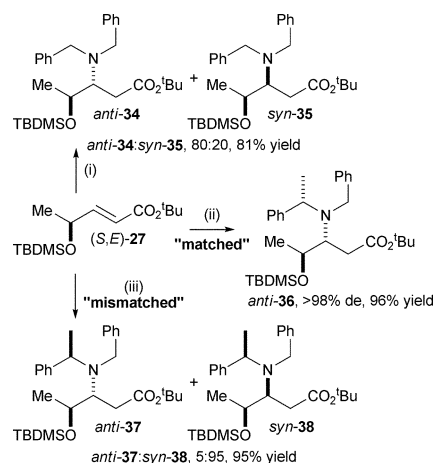
As chiral  $\alpha,\beta$ -unsaturated ester **26** shows reasonable substrate control upon conjugate addition of achiral lithium dibenzylamide **12**, double diastereoselectivity upon conjugate addition of homochiral lithium amides (*S*)-**30** and (*R*)-**30** was anticipated; conjugate addition of lithium amide (*S*)-**30** to homochiral  $\alpha,\beta$ -unsaturated ester (*R,E*)-**26** was expected to represent the doubly diastereoselective “matched” case, with addition of lithium amide (*R*)-**30** to (*R,E*)-**26** the “mismatched” case, although the high stereocontrol of the lithium amide was predicted to override the modest control of the  $\alpha,\beta$ -unsaturated ester. Indeed, conjugate addition of lithium amide (*S*)-**30** to (*R,E*)-**26** gave *anti*-**31** as a single diastereoisomer (>98% de) in 95% yield, whilst conjugate addition of lithium amide (*R*)-**30** to (*R,E*)-**26** gave a chromatographically inseparable 11 : 89 mixture of *anti*-**33** : *syn*-**32** in 94% yield (Scheme 3). The *anti* diastereoisomer **31** from the “matched” addition, and the major *syn* diastereoisomer **32** from the “mismatched” addition were spectroscopically identical to the  $\beta$ -amino ester products **31** and **32** observed from conjugate addition of racemic lithium amide (*RS*)-**30** to racemic  $\alpha,\beta$ -unsaturated ester (*RS,E*)-**26** thus confirming the assigned configurations.



**Scheme 3** Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide (*S*)-**30**, THF,  $-78$  to  $-50$  °C, 12 h; (ii) lithium (*R*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide (*R*)-**30**, THF,  $-78$  to  $-50$  °C, 12 h.

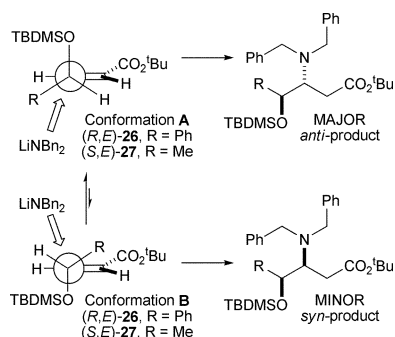
The extension of this protocol to conjugate addition to the lactate-derived  $\alpha,\beta$ -unsaturated ester (*S,E*)-**27** was investigated. In accordance with the observations of Yamamoto *et al.* concerning conjugate addition of lithium dibenzylamide **12** to lactate-derived  $\alpha,\beta$ -unsaturated ester **9** (*vide supra*, Fig. 2)<sup>6</sup> the conjugate addition of lithium dibenzylamide **12** to (*S,E*)-**27** gave a chromatographically separable 80 : 20 mixture of *anti*-**34** : *syn*-**35** in 81% combined yield, consistent with the chiral  $\alpha,\beta$ -unsaturated ester **27** also giving preferentially *anti* substrate control, but to a lower extent than chiral  $\alpha,\beta$ -unsaturated ester **26**. In support of this hypothesis, the “matched” addition of lithium amide (*S*)-**30** gave *anti*-**36** as a single diastereoisomer (>98% de) in 96% yield, whilst “mismatched”

addition of lithium amide (*R*)-**30** gave an inseparable 5 : 95 mixture of *anti*-**37** : *syn*-**38** in 95% isolated yield (Scheme 4).



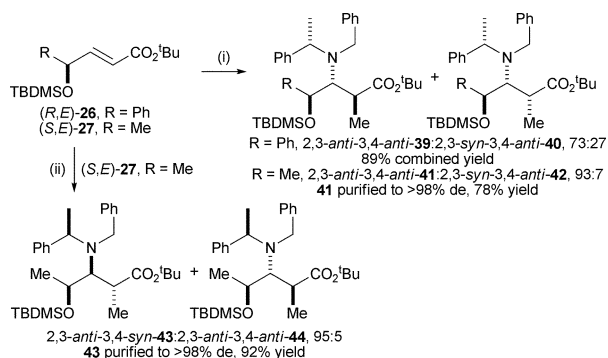
**Scheme 4** Reagents and conditions: (i) lithium dibenzylamide **12**, THF,  $-78$  °C, 2 h; (ii) lithium (*S*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide (*S*)-**30**, THF,  $-78$  °C, 2 h; (iii) lithium (*R*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide (*R*)-**30**, THF,  $-78$  °C, 2 h.

The levels of 1,2-asymmetric induction exerted upon conjugate additions of a range of nucleophiles to acyclic  $\alpha,\beta$ -unsaturated carbonyl systems with an adjacent stereocentre have been reported widely.<sup>14</sup> The sense of stereoselectivity in these transformations is generally rationalised by invoking a modified Felkin–Anh model.<sup>15,16</sup> It is generally assumed that the preferred transition states for such reactions proceed with an allylic  $\sigma$ -bond antiperiplanar to the trajectory of the approaching reagent, although the conformational preference of the allylic stereocentre may be biased by steric effects (approach *anti* to the largest allylic substituent), stereoelectronic effects (approach *anti* to the best electron acceptor), and minimisation of 1,3-allylic strain (preferred orientation of an allylic C–H in the same plane or the same sector as the  $\alpha$ -vinylic hydrogen). In the case of conjugate addition of lithium dibenzylamide **12** to mandelate- and lactate-derived  $\alpha,\beta$ -unsaturated esters (*R,E*)-**26** and (*S,E*)-**27**, the following transition states may be invoked. Assuming that any possible chelation-controlled delivery of the lithium amide by the  $\gamma$ -oxygen substituent can be discounted due to the low propensity of silyl ethers to coordinate lithium,<sup>17</sup> and placing the  $\gamma$ -*tert*-butyldimethylsilyloxy group perpendicular to the plane of the  $\alpha,\beta$ -unsaturated carbonyl system on stereoelectronic grounds, then conjugate addition of lithium dibenzylamide **12** to (*R,E*)-**26** or (*S,E*)-**27** in conformation **A** leads to the observed *anti* products. Conformation **B** (leading to the corresponding *syn* products) is presumably disfavoured due to increased 1,3-allylic strain. The increased substrate control observed upon conjugate addition to the mandelate-derived  $\alpha,\beta$ -unsaturated ester (*R,E*)-**26** (with a  $\gamma$ -phenyl substituent) as compared to the lactate-derived  $\alpha,\beta$ -unsaturated ester (*S,E*)-**27** (with a  $\gamma$ -methyl substituent) is potentially due to the increased steric demand in the former case, making reaction through conformation **B** much less favourable (Fig. 4).<sup>18</sup> This substrate control, combined with the known facial preference observed upon conjugate addition of the antipodes of lithium *N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide **30**<sup>12,13</sup> is also successful in rationalising the “matched” and “mismatched” reaction pairings.

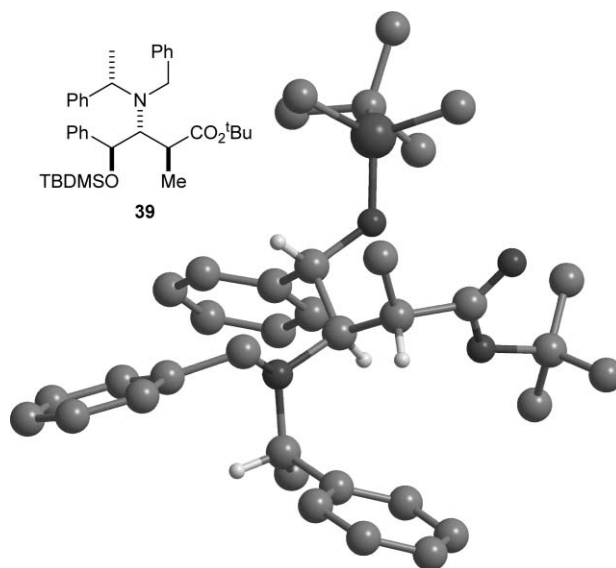


**Fig. 4** Proposed transition states for the conjugate addition of lithium dibenzylamide **12** to mandelate- and lactate-derived  $\alpha,\beta$ -unsaturated esters (*R,E*)-**26** and (*S,E*)-**27**.

Having shown that conjugate addition of lithium amide (*S*)-**30** to both homochiral  $\alpha,\beta$ -unsaturated esters (*R,E*)-**26** and (*S,E*)-**27** represents the “matched” combination, methylation of the  $\beta$ -amino enolates arising from these “matched” pairs was investigated. Conjugate addition of lithium amide (*S*)-**30** to the mandelate-derived  $\alpha,\beta$ -unsaturated ester (*R,E*)-**26** and subsequent addition of methyl iodide gave a 73 : 27 mixture of 2,3-*anti*-3,4-*anti*-**39** : 2,3-*syn*-3,4-*anti*-**40**,<sup>19</sup> from which the major diastereoisomer **39** was isolated in >98% de (Scheme 5). The relative 2,3-*anti*-3,4-*anti*-configuration within **39** was unambiguously established by single crystal X-ray analysis,<sup>20†</sup> with the absolute (2*S*,3*R*,4*S*, $\alpha$ *S*)-configuration determined from the known (*S*)-configuration of the  $\alpha$ -methylbenzyl stereocentre (Fig. 5). Conjugate addition of lithium amide (*S*)-**30** to the lactate-derived  $\alpha,\beta$ -unsaturated ester (*S,E*)-**27** and subsequent addition of methyl iodide gave a 93 : 7 mixture of 2,3-*anti*-3,4-*anti*-**41** : 2,3-*syn*-3,4-*anti*-**42** from which the major diastereoisomer **41** was isolated in 78% yield and >98% de. Furthermore, conjugate addition of lithium amide (*R*)-**30** to (*S,E*)-**27** and *in situ* methylation gave a 95 : 5 mixture of 2,3-*anti*-3,4-*syn*-**43** : 2,3-*anti*-3,4-*anti*-**44**, with the major diastereoisomer **43** purified to homogeneity. The configuration at C(2) within both **43** and **44** was assigned on the basis of preferential alkylation *anti* to the C(3)-amino functionality<sup>19</sup> as shown for “matched” reagent pairings (Scheme 5). It is apparent from this study that the configurations of both the *N*- $\alpha$ -methylbenzyl and  $\gamma$ -stereocentres seem to have a pronounced bearing upon the selectivity of enolate alkylation, as alkylations of



**Scheme 5** Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide (*S*)-**30**, THF,  $-78^\circ\text{C}$  then MeI,  $-78^\circ\text{C}$  to rt, 12 h; (ii) lithium (*R*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide (*R*)-**30**, THF,  $-78^\circ\text{C}$  then MeI,  $-78^\circ\text{C}$  to rt, 12 h.



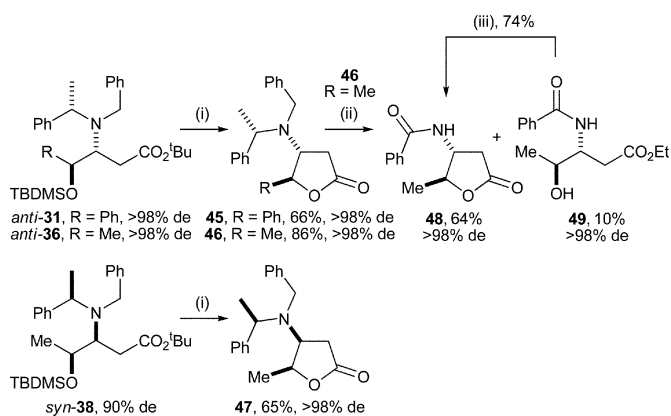
**Fig. 5** Chem 3D representation of the X-ray crystal structure of **39** (some H atoms removed for clarity). There are two molecules of **39** in the asymmetric unit; only one of these is shown, the other suffers from disorder of the TBDMS group.

simple  $\gamma$ -silyloxy- $\beta$ -amino enolates lacking a  $\gamma$ -stereogenic centre proceed with a modest *syn* preference.<sup>4</sup>

With a range of polyfunctionalised  $\beta$ -amino esters prepared stereoselectively following these double diastereoselective conjugate addition reactions, their conversion to the corresponding  $\beta$ -amino- $\gamma$ -substituted- and  $\alpha,\gamma$ -disubstituted- $\beta$ -amino- $\gamma$ -butyrolactones was carried out.  $\beta$ -Amino esters *anti*-**31** (>98% de) and *anti*-**36** (>98% de), derived from the “matched” pairings [(*S*)-**30**/(*R,E*)-**26** and (*S*)-**30**/(*S,E*)-**27**], and *syn*-**38** (90% de), derived from the “mismatched” pairing in the lactate series [(*R*)-**30**/(*S,E*)-**27**], were therefore treated with tetrabutylammonium fluoride (TBAF) and then trifluoroacetic acid (TFA) to promote intramolecular cyclisation, to give the corresponding lactones **45**, **46** and **47** in 66, 86 and 65% yield respectively, and in >98% de in each case after purification. *N*-Deprotection of **46** by hydrogenolysis with Pd/C in ethanol followed by treatment with benzoyl chloride gave a chromatographically separable mixture of  $\beta$ -amino- $\gamma$ -methyl- $\gamma$ -butyrolactone **48** and  $\beta$ -amino ethyl ester **49**, which were isolated in 64 and 10% yield, respectively. However, treatment of ethyl ester **49** with TFA promoted cyclisation to lactone **48** (Scheme 6).

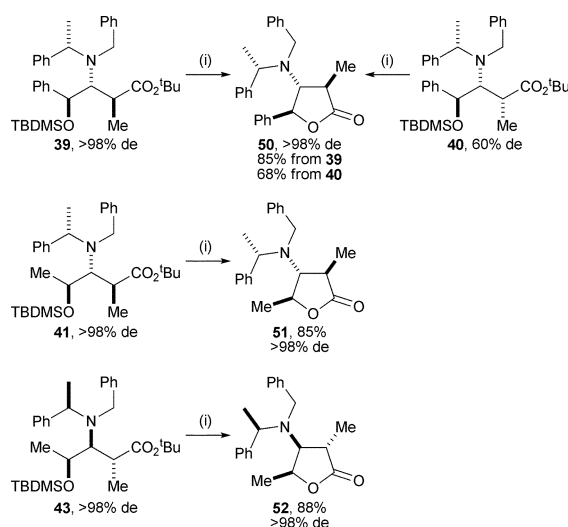
In a similar fashion, deprotection of the polyfunctionalised  $\alpha$ -methyl- $\beta$ -amino esters **39–41** and **43** to the corresponding lactones was investigated. In the mandelate-derived series, treatment of both 2,3-*anti*-3,4-*anti*-**39** (>98% de) and 2,3-*syn*-3,4-*anti*-**40** (60% de) with TBAF gave a single diastereoisomeric lactone **50** in 85 and 68% yield, respectively. The production of only a single diastereoisomeric lactone from the C(2)-epimeric  $\beta$ -amino esters **39** and **40** is consistent with epimerisation taking place under the reaction conditions to give the thermodynamic lactone **50**.<sup>4,21</sup> In the lactate-derived series, treatment of  $\alpha$ -methyl- $\beta$ -amino esters **41** and **43** under identical conditions gave lactones **51** and **52**, respectively, as single diastereoisomers. The configurations of **51** and **52** were assigned by analogy to **50**, assuming that, in each case, epimerisation of the  $\alpha$ -stereocentre of the lactone to give the





**Scheme 6** Reagents and conditions: (i) TBAF, THF, 50 °C, then TFA, rt; (ii) Pd/C, H<sub>2</sub> (6 bar), EtOH, 60 °C, then PhCOCl, pyridine, DCM, rt; (iii) TFA, PhMe, rt.

thermodynamically more stable product occurs under the reaction conditions (Scheme 7).

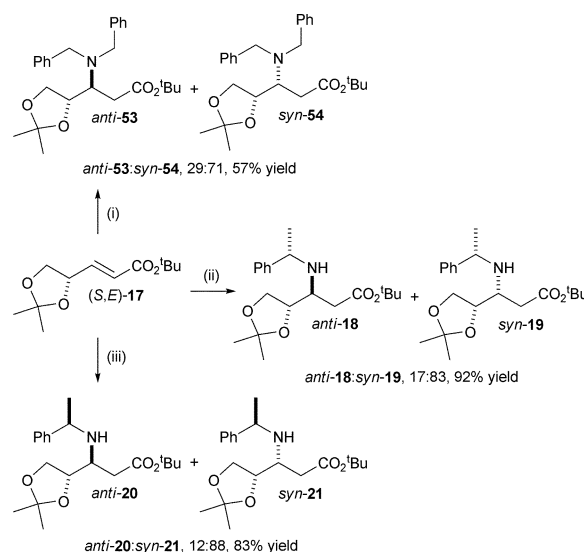


**Scheme 7** Reagents and conditions: (i) TBAF, THF, 50 °C, then TFA, rt.

### Double diastereoselective conjugate addition of homochiral lithium amides to a homochiral $\alpha,\beta$ -unsaturated ester and oxazolidinone derived from glyceraldehyde

Having demonstrated that conjugate addition of homochiral lithium amide **30** to the chiral  $\gamma$ -silyloxy- $\alpha,\beta$ -unsaturated esters **26** and **27** proceed predominantly under the stereocontrol of the lithium amide, the stereoselectivity upon conjugate addition to the chiral  $\alpha,\beta$ -unsaturated ester **17**, derived from glyceraldehyde, was investigated. Homochiral ester (*S,E*)-**17** was readily prepared from D-mannitol through conversion to (*R*)-isopropylidene glyceraldehyde according to literature procedures,<sup>22</sup> followed by Horner–Wadsworth–Emmons reaction with the sodium anion of *tert*-butyl diethylphosphonoacetate. To evaluate the levels of substrate control offered by (*S,E*)-**17** upon lithium amide conjugate addition in THF, the stereoselectivity upon reaction with lithium dibenzylamide **12** was probed, giving a separable 29 : 71 mixture of *anti*-**53** : *syn*-**54** in 57% combined yield. Conjugate addition of the enantiomers of lithium *N*-( $\alpha$ -methylbenzyl)amide

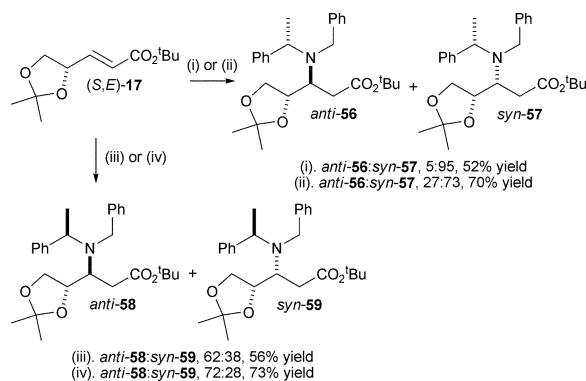
**55**, which shows only low stereoselectivity upon conjugate addition to achiral  $\alpha,\beta$ -unsaturated esters,<sup>1,13</sup> was next evaluated, with addition of lithium amide (*S*)-**55** to (*S,E*)-**17** giving a separable 17 : 83 mixture of *anti*-**18** : *syn*-**19** in 92% combined yield {*syn*-**19** [ $\alpha$ ]<sub>D</sub><sup>21</sup> –35.8 (*c* 1.1 in CHCl<sub>3</sub>); lit.<sup>7</sup> [ $\alpha$ ]<sub>D</sub><sup>21</sup> –32.0 (*c* 1.1 in CHCl<sub>3</sub>)}, while addition of lithium amide (*R*)-**55** to (*S,E*)-**17** gave a partially separable 12 : 88 mixture of *anti*-**20** : *syn*-**21** in 83% combined yield {*syn*-**21** [ $\alpha$ ]<sub>D</sub><sup>21</sup> +22.7 (*c* 1.0 in CHCl<sub>3</sub>); lit.<sup>7</sup> [ $\alpha$ ]<sub>D</sub><sup>21</sup> +24.0 (*c* 1.0 in CHCl<sub>3</sub>)} (Scheme 8). The preferential *syn* selectivity observed upon conjugate addition of lithium dibenzylamide **12** and the antipodes of lithium *N*-( $\alpha$ -methylbenzyl)amide **55** to (*S,E*)-**17** is consistent with the preferential *syn* addition noted by Sewald *et al.* upon conjugate addition of lithium *N*-( $\alpha$ -methylbenzyl)-*N*-trimethylsilylamide **16** (*vide supra*, Fig. 3).<sup>7</sup>



**Scheme 8** Reagents and conditions: (i) lithium dibenzylamide **12**, THF, –78 °C, 2 h; (ii) lithium (*S*)-*N*-( $\alpha$ -methylbenzyl)amide (*S*)-**55**, THF, –78 °C, 2 h; (iii) lithium (*R*)-*N*-( $\alpha$ -methylbenzyl)amide (*R*)-**55**, THF, –78 °C, 2 h.

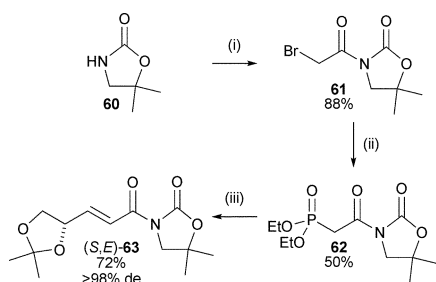
Consistent with this *syn* substrate control, the conjugate addition of lithium (*S*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide (*S*)-**30** to (*S,E*)-**17** was predicted to be the “matched” reaction pairing. Thus, conjugate addition of lithium amide (*S*)-**30** to (*S,E*)-**17** gave a 5 : 95 mixture of *anti*-**56** : *syn*-**57**, giving *syn*-**57** as a single diastereoisomer (>98% de) in 52% yield after purification, while in the “mismatched” series conjugate addition of lithium amide (*R*)-**30** to (*S,E*)-**17** gave an inseparable 62 : 38 mixture of *anti*-**58** : *syn*-**59** in 57% isolated yield. While the additions of the antipodes of lithium amide **30** to (*S,E*)-**17** in THF proceed predominantly under the stereocontrol of the lithium amide, the effect of changing the solvent to Et<sub>2</sub>O, previously noted by Sewald *et al.* to have a dramatic effect upon the stereoselectivity of conjugate addition of lithium *N*-trimethylsilyl-*N*-( $\alpha$ -methylbenzyl)amide **16**, was investigated. Preliminary investigations showed that lithium *N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide **30** in Et<sub>2</sub>O at –78 °C showed decreased reactivity relative to that in THF, although in Et<sub>2</sub>O at –20 °C conjugate addition of lithium amide (*R*)-**30** to (*S,E*)-**17** gave a 72 : 28 mixture of *anti*-**58** : *syn*-**59**, representing an increase in stereoselectivity as compared to addition in THF at –78 °C (*anti*-**58** : *syn*-**59**, 62 : 38). However, conjugate addition of lithium

amide (*S*)-**30** in Et<sub>2</sub>O at −20 °C gave a 27 : 73 mixture of *anti*-**56** : *syn*-**57**, a decrease in stereoselectivity compared to the analogous addition in THF at −78 °C (*anti*-**56** : *syn*-**57**, 5 : 95) (Scheme 9).



**Scheme 9** Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide (*S*)-**30**, THF, −78 °C, 2 h; (ii) lithium (*S*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide (*S*)-**30**, Et<sub>2</sub>O, −20 °C, 6 h; (iii) lithium (*R*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide (*R*)-**30**, THF, −78 °C, 2 h; (iv) lithium (*R*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide (*R*)-**30**, Et<sub>2</sub>O, −20 °C, 6 h.

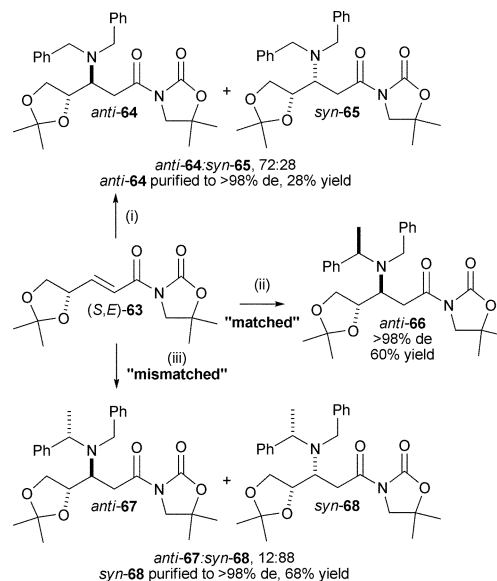
The effect of changing the ester functionality within the acceptor to an oxazolidinone was next investigated. The desired  $\alpha,\beta$ -unsaturated oxazolidinone (*S,E*)-**63** was prepared from oxazolidinone **60**<sup>23</sup> by a simple three-step procedure. Acylation of the lithium anion of **60** with bromoacetyl bromide<sup>24</sup> gave **61** in 88% yield, with subsequent reaction with triethylphosphite generating the phosphonate **62** in 50% yield. Reaction of phosphonate **62** with (*R*)-isopropylidene glyceraldehyde<sup>22</sup> under Masamune–Roush conditions<sup>25</sup> gave a 95.5 : 4.5 (*E*) : (*Z*) mixture of the corresponding  $\alpha,\beta$ -unsaturated oxazolidinones, with purification giving (*S,E*)-**63** in 72% yield and >98% de (Scheme 10).



**Scheme 10** Reagents and conditions: (i) BuLi, THF, −78 °C then BrCH<sub>2</sub>COBr; (ii) P(OEt)<sub>3</sub>, PhMe, reflux; (iii) (*R*)-isopropylidene glyceraldehyde, <sup>i</sup>Pr<sub>2</sub>NEt, LiCl, MeCN, rt.

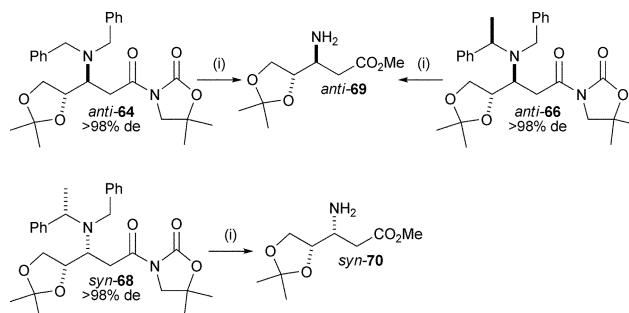
Upon conjugate addition of lithium dibenzylamide **12** to (*S,E*)-**63**, a complex mixture of reaction products, containing a 72 : 28 mixture of  $\beta$ -amino oxazolidinones *anti*-**64** : *syn*-**65**, was formed. Extensive purification allowed the isolation of the major diastereoisomer *anti*-**64** in 28% yield and >98% de, consistent with  $\alpha,\beta$ -unsaturated oxazolidinone (*S,E*)-**63** showing approximately the same magnitude but the *opposite sense* of stereoinduction as the corresponding *tert*-butyl ester (*S,E*)-**17** upon addition of lithium dibenzylamide **12**. Furthermore, conjugate addition of the antipodes of lithium *N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide (*S*)-**30** and (*R*)-**30** to (*S,E*)-**63** resulted in a reversal in the sense

of the “matched” and “mismatched” reaction pairings. In the “mismatched” case, conjugate addition of lithium amide (*S*)-**30** gave a 12 : 88 mixture of *anti*-**67** : *syn*-**68**, giving *syn*-**68** in >98% de and in 68% yield after purification, while “matched” conjugate addition of lithium amide (*R*)-**30** gave *anti*-**66** as a single diastereoisomer, isolated in 60% isolated yield and >98% de (Scheme 11).



**Scheme 11** Reagents and conditions: (i) lithium dibenzylamide **12**, THF, −78 °C, 2 h; (ii) lithium (*R*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide (*R*)-**30**, THF, −78 °C, 2 h; (iii) lithium (*S*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amide (*S*)-**30**, THF, −78 °C, 2 h.

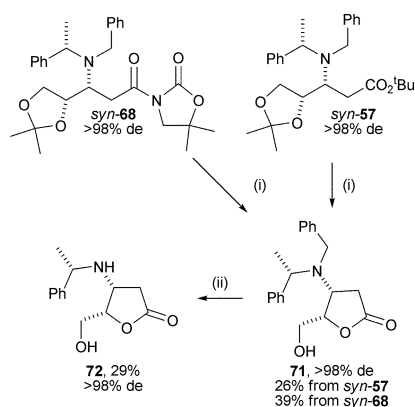
The assigned relative configurations within  $\beta$ -amino oxazolidinones **64**–**68** were next established by chemical correlation. The major diastereoisomer *anti*-**64**, from the conjugate addition of lithium dibenzylamide **12**, and *anti*-**66**, resulting from the “matched” addition of lithium amide (*R*)-**30**, were treated with Pearlman’s catalyst in MeOH under hydrogen (5 atm), promoting hydrogenolysis and methanolysis, giving the known *anti*- $\beta$ -amino ester **69**.<sup>26</sup> Under identical conditions the major diastereoisomer *syn*-**68** resulting from the “mismatched” addition of lithium amide (*S*)-**30** gave the known *syn*- $\beta$ -amino ester **70**<sup>26</sup> (Scheme 12).



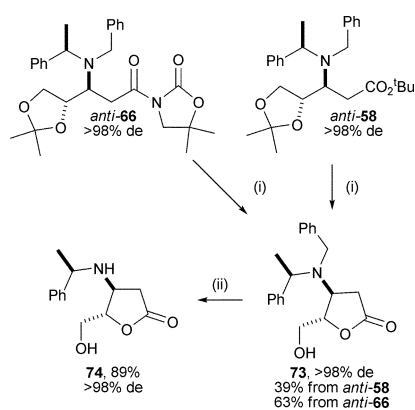
**Scheme 12** Reagents and conditions: (i) Pd(OH)<sub>2</sub>/C, H<sub>2</sub> (5 atm), MeOH, rt.

The conversion of  $\beta$ -amino esters *syn*-**57** and *anti*-**58**, and oxazolidinones *syn*-**68** and *anti*-**66** to the corresponding  $\beta$ -amino- $\gamma$ -substituted- $\gamma$ -butyrolactones was next attempted.  $\beta$ -Amino ester

*syn*-**57** (>98% de) and oxazolidinone *syn*-**68** (>98% de), derived from conjugate addition of lithium amide (*S*)-**30**, were therefore treated with 60% aqueous TFA, giving lactone **71** in both cases, with subsequent oxidative debenzoylation of **71** with CAN giving the known lactone **72** {[ $\alpha$ ]<sub>D</sub><sup>21</sup> –67.8 (*c* 0.35 in CHCl<sub>3</sub>); lit.<sup>7</sup> [ $\alpha$ ]<sub>D</sub><sup>21</sup> –78.6 (*c* 1.85 in CHCl<sub>3</sub>)} (Scheme 13). Similarly, under identical conditions,  $\beta$ -amino ester *anti*-**58** (>98% de) and oxazolidinone *anti*-**66** (>98% de), derived from conjugate addition of lithium amide (*R*)-**30**, gave lactone **73**.<sup>27</sup> Subsequent oxidative debenzoylation of **73** gave lactone **74** in good yield (Scheme 14).



**Scheme 13** Reagents and conditions: (i) TFA (60% aq.), rt; (ii) CAN, MeCN/H<sub>2</sub>O (5:1), rt.



**Scheme 14** Reagents and conditions: (i) TFA (60% aq.), rt; (ii) CAN, MeCN/H<sub>2</sub>O (5:1), rt.

## Conclusion

In conclusion, chiral  $\alpha,\beta$ -unsaturated esters containing a single,  $\gamma$ -stereogenic centre, derived from methyl lactate, methyl mandelate and isopropylidene glyceraldehyde, show reasonable levels of substrate control upon conjugate addition of lithium dibenzylamide. In each case, the *anti* or *syn* stereoselectivity observed upon conjugate addition of lithium dibenzylamide to the chiral acceptors (substrate control), combined with the known facial selectivity of lithium *N*-benzyl-*N*-( $\alpha$ -methylbenzyl)-amide, allows a prediction of the doubly diastereoselective “matched” reaction pairing. Double diastereoselective conjugate addition of homochiral lithium *N*-benzyl-*N*-( $\alpha$ -methylbenzyl)-

amide to the homochiral  $\alpha,\beta$ -unsaturated esters proceeds in high de under the dominant stereocontrol of the lithium amide. The resultant  $\beta$ -amino esters can be deprotected and cyclised to give the corresponding  $\beta$ -amino- $\gamma$ -substituted- $\gamma$ -butyrolactones. The application of this methodology to the synthesis of a range of natural products is currently underway in this laboratory.

## Experimental

### General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.<sup>28</sup> Water was purified by an Elix<sup>®</sup> UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over MgSO<sub>4</sub>. Thin layer chromatography was performed on aluminium plates coated with 60 F<sub>254</sub> silica. Plates were visualised using UV light (254 nm), iodine, 1% aq. KMnO<sub>4</sub>, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, UK. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10<sup>–1</sup> deg cm<sup>2</sup> g<sup>–1</sup> and concentrations in g per 100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film), as a KBr disc (KBr), or as chloroform solutions in 0.1 mm cells (CHCl<sub>3</sub>), as stated. Selected characteristic peaks are reported in cm<sup>–1</sup>. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuterium resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20–250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF and were internally calibrated with polyaniline in positive and negative modes, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m  $\times$  0.25 mm) using amyl acetate as a lock mass.

### General procedure 1a for lithium amide conjugate addition

BuLi (as a solution in hexanes) was added dropwise *via* syringe to a stirred solution of the requisite amine in THF at –78 °C. After stirring for 30 min, a solution of the requisite  $\alpha,\beta$ -unsaturated carbonyl compound 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 sat. aq. NH<sub>4</sub>Cl 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 sat. aq.  $\text{NaHCO}_3$  and brine, dried and concentrated *in vacuo*.

#### General procedure 1b for lithium amide conjugate addition

BuLi (as a solution in hexanes) was added dropwise *via* syringe to a stirred solution of the requisite amine in THF at  $-78^\circ\text{C}$ . After stirring for 30 min, a solution of the requisite  $\alpha,\beta$ -unsaturated carbonyl compound in THF at  $-78^\circ\text{C}$  was added dropwise *via* cannula. The reaction mixture was allowed to warm to  $-50^\circ\text{C}$  over 12 h, quenched with sat. aq.  $\text{NH}_4\text{Cl}$  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 sat. aq.  $\text{NaHCO}_3$  and brine, dried and concentrated *in vacuo*.

#### General procedure 2 for lithium amide conjugate addition and MeI quench

BuLi (as a solution in hexanes) was added dropwise *via* syringe to a stirred solution of the requisite amine in THF at  $-78^\circ\text{C}$ . After stirring for 30 min, a solution of  $\alpha,\beta$ -unsaturated carbonyl compound in THF at  $-78^\circ\text{C}$  was added dropwise *via* cannula. After stirring for a further 2 h at  $-78^\circ\text{C}$ , the reaction mixture was quenched with MeI and allowed to warm to rt over 12 h, then quenched with sat. aq.  $\text{NaHCO}_3$ . 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 sat. aq.  $\text{NaHCO}_3$  and brine, dried and concentrated *in vacuo*.

#### General procedure 3 for desilylation and concomitant lactonisation

TBAF was added to a solution of the requisite  $\gamma$ -silyloxy- $\beta$ -amino ester in THF and heated at  $50^\circ\text{C}$  for 24 h. The reaction mixture was then allowed to cool to rt and poured into brine. The resultant mixture was extracted with EtOAc ( $3 \times 25\text{ mL}$ ) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was then dissolved in PhMe and TFA was added. The resultant suspension was stirred at rt for 24 h before being concentrated *in vacuo*. The residue was then partitioned between sat. aq.  $\text{NaHCO}_3$  (50 mL) and EtOAc (25 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc ( $2 \times 25\text{ mL}$ ). The combined organic extracts were dried and concentrated *in vacuo*.

***tert*-Butyl (3*RS*,4*SR*)- and (3*RS*,4*RS*)-3-[*N,N*-dibenzylamino]-4-(*tert*-butyldimethylsilyloxy)-4-phenylbutanoate (3*RS*,4*SR*)-*anti*-28 and (3*RS*,4*RS*)-*syn*-29.** Following *general procedure 1a*, BuLi (1.60 mL, 1.00 mmol), dibenzylamine (394 mg, 2.00 mmol) in THF (5 mL), and (*RS,E*)-26 (348 mg, 1.00 mmol) in THF (5 mL) gave an 88 : 12 mixture of *anti*-28 : *syn*-29. Purification *via* flash column chromatography (eluent hexane–EtOAc, 20 : 1) gave an 88 : 12 mixture of *anti*-28 : *syn*-29 as a pale yellow oil (524 mg, 96%);  $\text{C}_{34}\text{H}_{47}\text{NO}_3\text{Si} \cdot \text{HCl}$  requires C, 70.1; H, 8.3; N, 2.4%; found C, 70.1; H, 8.4; N, 2.3%;  $\nu_{\text{max}}$  (film) 1718 (C=O);  $m/z$  ( $\text{CI}^+$ ) 546 ( $[\text{M} + \text{H}]^+$ , 12%), 324 (36), 91 (100).

Data for *anti*-28:  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ )  $-0.33$  (3H, s,  $\text{SiMe}_A$ ),  $0.04$  (3H, s,  $\text{SiMe}_B$ ),  $0.85$  (9H, s,  $\text{SiCMe}_3$ ),  $1.44$  (9H, s,  $\text{OCMe}_3$ ),  $2.58$  (1H, dd,  $J$  15.4, 5.2 Hz,  $\text{C}(2)H_A$ ),  $2.70$  (1H, dd,  $J$  15.4, 7.4 Hz,  $\text{C}(2)H_B$ ),  $3.43$ – $3.49$  (1H, m,  $\text{C}(3)H$ ),  $3.70$  (4H, app s,  $\text{N}(\text{CH}_2\text{Ph})_2$ ),  $4.84$  (1H, d,  $J$  6.0 Hz,  $\text{C}(4)H$ ),  $7.10$ – $7.27$  (15H, m, *Ph*);  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ )  $-4.8$  ( $\text{SiMe}_A$ ),  $-4.2$  ( $\text{SiMe}_B$ ),  $18.1$  ( $\text{SiCMe}_3$ ),  $26.0$  ( $\text{SiCMe}_3$ ),  $28.2$  ( $\text{OCMe}_3$ ),  $32.8$  ( $\text{C}(2)$ ),  $54.8$  ( $\text{N}(\text{CH}_2\text{Ph})_2$ ),  $62.5$  ( $\text{C}(3)$ ),  $75.2$  ( $\text{C}(4)$ ),  $80.1$  ( $\text{OCMe}_3$ ),  $127.0$ ,  $127.4$ ,  $127.5$ ,  $127.9$ ,  $128.1$ ,  $128.3$ ,  $129.0$ ,  $129.1$  (*o-Ph*, *m-Ph*, *p-Ph*),  $139.9$ ,  $144.3$  (*i-Ph*),  $172.6$  ( $\text{C}(1)$ ).

***tert*-Butyl (3*RS*,4*SR*, $\alpha$ *SR*)- and (3*RS*,4*RS*, $\alpha$ *SR*)-3-[*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amino]-4-(*tert*-butyldimethylsilyloxy)-4-phenylbutanoate (3*RS*,4*SR*, $\alpha$ *SR*)-*anti*-31 and (3*RS*,4*SR*, $\alpha$ *SR*)-*syn*-32.** Following *general procedure 1b*, BuLi (3.20 mL, 2.00 mmol), (*RS*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amine (633 mg, 3.00 mmol) in THF (10 mL), and (*RS,E*)-26 (696 mg, 2.00 mmol) in THF (10 mL) gave a 92 : 8 mixture of *anti*-31 : *syn*-32. Purification *via* flash column chromatography (eluent hexane–EtOAc, 20 : 1) gave a 92 : 8 mixture of *anti*-31 : *syn*-32 as a pale yellow oil (1.01 g, 91%);  $\text{C}_{35}\text{H}_{49}\text{NO}_3\text{Si}$  requires C, 75.1; H, 8.8; N, 2.5%; found C, 75.3; H, 9.1; N, 2.3%;  $\nu_{\text{max}}$  (film) 1718 (C=O);  $m/z$  ( $\text{CI}^+$ ) 560 ( $[\text{M} + \text{H}]^+$ , 35%), 338 (100), 282 (37), 178 (47), 105 (88), 91 (74).

Data for *anti*-31:  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ )  $-0.28$  (3H, s,  $\text{SiMe}_A$ ),  $-0.10$  (3H, s,  $\text{SiMe}_B$ ),  $0.77$  (9H, s,  $\text{SiCMe}_3$ ),  $0.89$  (3H, d,  $J$  7.1 Hz,  $\text{C}(\alpha)\text{Me}$ ),  $1.46$  (9H, s,  $\text{OCMe}_3$ ),  $1.76$  (1H, dd,  $J$  16.6, 2.3 Hz,  $\text{C}(2)H_A$ ),  $2.28$  (1H, dd,  $J$  16.6, 8.9 Hz,  $\text{C}(2)H_B$ ),  $3.60$  (1H, q,  $J$  7.1 Hz,  $\text{C}(\alpha)H$ ),  $3.63$  (1H, d,  $J$  15.2 Hz,  $\text{NCH}_A$ ),  $3.80$  (1H, d,  $J$  15.2 Hz,  $\text{NCH}_B$ ),  $4.00$ – $4.06$  (1H, m,  $\text{C}(3)H$ ),  $4.41$  (1H, d,  $J$  8.1 Hz,  $\text{C}(4)H$ ),  $7.08$ – $7.45$  (15H, m, *Ph*);  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ )  $-4.9$  ( $\text{SiMe}_A$ ),  $-4.6$  ( $\text{SiMe}_B$ ),  $18.2$  ( $\text{SiCMe}_3$ ),  $18.5$  ( $\text{C}(\alpha)\text{Me}$ ),  $25.9$  ( $\text{SiCMe}_3$ ),  $28.2$  ( $\text{OCMe}_3$ ),  $34.6$  ( $\text{C}(2)$ ),  $51.2$  ( $\text{NCH}_2$ ),  $57.5$ ,  $59.3$  ( $\text{C}(3)$ ,  $\text{C}(\alpha)$ ),  $77.8$  ( $\text{C}(4)$ ),  $79.8$  ( $\text{OCMe}_3$ ),  $127.0$ ,  $127.1$ ,  $127.4$ ,  $127.9$ ,  $128.1$ ,  $128.3$ ,  $128.6$  (*o-Ph*, *m-Ph*, *p-Ph*),  $141.1$ ,  $141.4$ ,  $145.4$  (*i-Ph*),  $172.1$  ( $\text{C}(1)$ ).

Data for *syn*-32:  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ )  $-0.26$  (3H, s,  $\text{SiMe}_A$ ),  $-0.01$  (3H, s,  $\text{SiMe}_B$ ),  $0.65$  (3H, d,  $J$  7.1 Hz,  $\text{C}(\alpha)\text{Me}$ ),  $0.81$  (9H, s,  $\text{SiCMe}_3$ ),  $1.45$  (9H, s,  $\text{OCMe}_3$ ),  $1.50$  (1H, dd,  $J$  16.7, 2.2 Hz,  $\text{C}(2)H_A$ ),  $2.43$  (1H, dd,  $J$  16.7, 10.6 Hz,  $\text{C}(2)H_B$ ),  $3.54$ – $3.63$  (3H, m,  $\text{C}(3)H$ ,  $\text{C}(\alpha)H$ ,  $\text{NCH}_A$ ),  $4.39$  (1H, d,  $J$  14.7 Hz,  $\text{NCH}_B$ ),  $4.84$  (1H, d,  $J$  2.5 Hz,  $\text{C}(4)H$ ),  $7.09$ – $7.49$  (15H, m, *Ph*).

***tert*-Butyl (3*R*,4*S*, $\alpha$ *S*)-3-[*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amino]-4-(*tert*-butyldimethylsilyloxy)-4-phenylbutanoate *anti*-31.** Following *general procedure 1b*, BuLi (0.91 mL, 0.57 mmol), (*S*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amine (250 mg, 1.18 mmol) in THF (2.5 mL), and (*R,E*)-26 (200 mg, 0.57 mmol) in THF (2.5 mL) gave *anti*-31 in >98% de. Purification *via* flash column chromatography (eluent hexane–EtOAc, 20 : 1) gave *anti*-31 as a colourless oil (306 mg, 95%, >98% de);  $\text{C}_{35}\text{H}_{49}\text{NO}_3\text{Si}$  requires C, 75.1; H, 8.8; N, 2.5%; found C, 74.9; H, 9.1; N, 2.2%;  $[\alpha]_{\text{D}}^{25} +50.3$  (*c* 1.1 in  $\text{CHCl}_3$ ).

***tert*-Butyl (3*S*,4*S*, $\alpha$ *R*)- and (3*R*,4*S*, $\alpha$ *R*)-3-[*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amino]-4-(*tert*-butyldimethylsilyloxy)-4-phenylbutanoate (3*S*,4*S*, $\alpha$ *R*)-*anti*-33 and (3*R*,4*S*, $\alpha$ *R*)-*syn*-32.** Following *general procedure 1b*, BuLi (0.91 mL, 0.57 mmol), (*R*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amine (250 mg, 1.18 mmol) in THF (2.5 mL), and (*R,E*)-26 (200 mg, 0.57 mmol) in THF (2.5 mL) gave an 11 : 89 mixture of *anti*-33 : *syn*-32. Purification *via* flash column



chromatography (eluent hexane–EtOAc, 20 : 1) gave an 11 : 89 mixture of *anti*-**33** : *syn*-**32** as a colourless oil (301 mg, 94%); C<sub>35</sub>H<sub>49</sub>NO<sub>3</sub>Si requires C, 75.1; H, 8.8; N, 2.5%; found C, 75.05; H, 8.9; N, 2.3%;  $\nu_{\max}$  (film) 1714 (C=O);  $m/z$  (CI<sup>+</sup>) 560 ([M + H]<sup>+</sup>, 48%), 338 (100), 282 (30), 178 (37), 105 (56), 91 (45).

Data for *anti*-**33**:  $\delta_{\text{H}}$  (400 MHz, C<sub>6</sub>D<sub>6</sub>) –0.17 (3H, s, SiMe<sub>A</sub>), 0.07 (3H, s, SiMe<sub>B</sub>), 0.79 (3H, d,  $J$  7.1 Hz, C( $\alpha$ )Me), 0.88 (9H, s, SiCMe<sub>3</sub>), 1.41 (9H, s, OCM<sub>3</sub>), 1.70 (1H, dd,  $J$  16.8, 2.1 Hz, C(2)*H<sub>A</sub>*), 2.62 (1H, dd,  $J$  16.8, 10.7 Hz, C(2)*H<sub>B</sub>*), 3.63 (1H, d,  $J$  15.2 Hz, NCH<sub>A</sub>), 4.58 (1H, d,  $J$  15.2 Hz, NCH<sub>B</sub>), 3.72 (1H, q,  $J$  7.1 Hz, C( $\alpha$ )H), 3.90 (1H, app dt,  $J$  10.7, 2.3 Hz, C(3)H), 5.14 (1H, d,  $J$  2.3 Hz, C(4)H), 7.06–7.72 (15H, m, *Ph*);  $\delta_{\text{C}}$  (100 MHz, C<sub>6</sub>D<sub>6</sub>) –5.5 (SiMe<sub>A</sub>), –4.6 (SiMe<sub>B</sub>), 18.0 (SiCMe<sub>3</sub>), 18.5 (C( $\alpha$ )Me), 25.8 (SiCMe<sub>3</sub>), 28.1 (OCMe<sub>3</sub>), 33.7 (C(2)), 53.2 (NCH<sub>2</sub>), 57.0, 57.1 (C(3), C( $\alpha$ )), 78.3 (C(4)), 80.1 (OCMe<sub>3</sub>), 126.5, 127.0, 127.1, 127.4, 127.6, 128.1, 128.2, 128.4, 128.5 (*o-Ph*, *m-Ph*, *p-Ph*), 141.4, 141.6, 144.4 (*i-Ph*), 172.5 (C(1)).

**tert-Butyl (2*S*,3*R*,4*S*, $\alpha$ *S*)- and (2*R*,3*R*,4*S*, $\alpha$ *S*)-2-methyl-3-[*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amino]-4-(*tert*-butyldimethylsilyloxy)-4-phenylbutanoate (2*S*,3*R*,4*S*, $\alpha$ *S*)-**39** and (2*R*,3*R*,4*S*, $\alpha$ *S*)-**40**.** Following *general procedure* 2, BuLi (4.80 mL, 3.00 mmol), (*S*)-*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amine (1.27 g, 6.00 mmol) in THF (15 mL), (*R,E*)-**26** (1.04 g, 3.00 mmol) in THF (15 mL) and MeI (5.82 mL, 18.0 mmol) gave a 73 : 27 mixture of **39** : **40**. Purification *via* flash column chromatography (eluent hexane–EtOAc, 25 : 1) gave a 73 : 27 mixture of **39** : **40** as a white solid (1.53 g, 89%). Fractional crystallisation from MeCN at 20 °C gave **39** as a colourless solid (>98% de). Concentration of the mother liquors gave a 20 : 80 mixture of **39** : **40** as a colourless oil.

Data for **39**: C<sub>36</sub>H<sub>51</sub>NO<sub>3</sub>Si requires C, 75.3; H, 9.0; N, 2.7%; found C, 75.4; H, 9.2; N, 2.7%; mp 95–97 °C;  $[\alpha]_{\text{D}}^{25} +66.5$  ( $c$  1.0 in CHCl<sub>3</sub>);  $\nu_{\max}$  (film) 1718 (C=O);  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) –0.33 (3H, s, SiMe<sub>A</sub>), –0.04 (3H, s, SiMe<sub>B</sub>), 0.68 (9H, s, SiCMe<sub>3</sub>), 0.86 (3H, d,  $J$  7.1 Hz, C(2)Me), 1.26 (3H, d,  $J$  7.1 Hz, C( $\alpha$ )Me), 1.55 (9H, s, OCM<sub>3</sub>), 2.79 (1H, qd,  $J$  7.1, 1.8 Hz, C(2)H), 3.64 (1H, q,  $J$  7.1 Hz, C( $\alpha$ )H), 3.75 (1H, d,  $J$  14.8 Hz, NCH<sub>A</sub>), 4.16 (1H, d,  $J$  14.8 Hz, NCH<sub>B</sub>), 4.43 (1H, dd,  $J$  9.5, 1.8 Hz, C(3)H), 4.65 (1H, d,  $J$  9.5 Hz, C(4)H), 7.07–7.44 (15H, m, *Ph*);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) –4.7 (SiMe<sub>A</sub>), –4.6 (SiMe<sub>B</sub>), 12.6, 18.4 (C(2)Me, C( $\alpha$ )Me), 18.2 (SiCMe<sub>3</sub>), 25.9 (SiCMe<sub>3</sub>), 28.4 (OCMe<sub>3</sub>), 40.1 (C(2)), 52.3 (NCH<sub>2</sub>), 57.0, 61.7 (C(3), C( $\alpha$ )), 75.0 (C(4)), 79.8 (OCMe<sub>3</sub>), 126.8, 127.0, 127.7, 127.8, 128.0, 128.3, 128.5, 129.2 (*o-Ph*, *m-Ph*, *p-Ph*), 141.1, 141.7, 145.3 (*i-Ph*), 174.5 (C(1));  $m/z$  (CI<sup>+</sup>) 574 ([M + H]<sup>+</sup>, 32%), 352 (100), 296 (39), 192 (55), 105 (87), 91 (96).

Data for **40**:  $\nu_{\max}$  (film) 1714 (C=O);  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) –0.33 (3H, s, SiMe<sub>A</sub>), –0.02 (3H, s, SiMe<sub>B</sub>), 0.79 (9H, s, SiCMe<sub>3</sub>), 1.11 (3H, d,  $J$  7.3 Hz, C(2)Me), 1.17 (3H, d,  $J$  6.9 Hz, C( $\alpha$ )Me), 1.38 (9H, s, OCM<sub>3</sub>), 2.79 (1H, app quintet,  $J$  7.2 Hz, C(2)H), 3.63 (1H, app t,  $J$  6.5 Hz, C(3)H), 3.89 (1H, q,  $J$  6.9 Hz, C( $\alpha$ )H), 3.96 (1H, d,  $J$  15.6 Hz, NCH<sub>A</sub>), 4.09 (1H, d,  $J$  15.6 Hz, NCH<sub>B</sub>), 4.90 (1H, d,  $J$  6.2 Hz, C(4)H), 7.02–7.37 (15H, m, *Ph*);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) –4.8 (SiMe<sub>A</sub>), –4.4 (SiMe<sub>B</sub>), 16.5, 20.4 (C(2)Me, C( $\alpha$ )Me), 18.2 (SiCMe<sub>3</sub>), 26.0 (SiCMe<sub>3</sub>), 28.0 (OCMe<sub>3</sub>), 42.0 (C(2)), 52.4 (NCH<sub>2</sub>), 60.0, 65.6 (C(3), C( $\alpha$ )), 77.8 (C(4)), 79.5 (OCMe<sub>3</sub>), 126.5, 126.9, 127.3, 127.9, 128.1, 128.4, 128.7 (*o-Ph*, *m-Ph*, *p-Ph*), 142.4, 144.2, 144.9 (*i-Ph*), 175.5 (C(1));  $m/z$  (CI<sup>+</sup>) 574 ([M + H]<sup>+</sup>, 63%), 352 (100), 296 (44), 192 (83), 105 (46), 91 (84).

## X-Ray crystal structure determination for **39**

Data were collected using an Enraf–Nonius  $\kappa$ -CCD diffractometer with graphite monochromated MoK $\alpha$  radiation using standard procedures at 190 K. The structure was solved by direct methods (SIR92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.<sup>29</sup>

**X-Ray crystal structure data for **39**.** [C<sub>36</sub>H<sub>51</sub>NO<sub>3</sub>Si]:  $M$  = 1147.78, triclinic, space group  $P1$ ,  $a$  = 11.4449(2),  $b$  = 11.8000(2),  $c$  = 14.6478(2) Å,  $V$  = 1722.68(5) Å<sup>3</sup>,  $Z$  = 2,  $\mu$  = 0.10 mm<sup>–1</sup>, colourless block, crystal dimensions = 0.1 × 0.1 × 0.1 mm. A total of 7805 unique reflections were measured for  $5 < \theta < 27$  and 6098 reflections were used in the refinement. The final parameters were  $wR_2$  = 0.082 and  $R_1$  = 0.066 [ $I > 3.0\sigma(I)$ ].

**(4*R*,5*S*, $\alpha$ *S*)-4-[*N*-Benzyl-*N*-( $\alpha$ -methylbenzyl)amino]-5-phenyl-tetrahydro-2-furanone **45**.** Following *general procedure* 3, TBAF (868 mg, 2.75 mmol) and *anti*-**31** (280 mg, 0.50 mmol) in THF (10 mL) gave the crude reaction product. Purification *via* sequential flash column chromatography (eluent hexane–EtOAc, 6 : 1) and recrystallisation from hexane–DCM (1 : 1) at –30 °C gave **45** as a white crystalline solid (123 mg, 66%, >98% de); C<sub>25</sub>H<sub>25</sub>NO<sub>2</sub> requires C, 80.8; H, 6.8; N, 3.8; found: C, 80.45; H, 6.8; N, 3.5%; mp 122–124 °C;  $[\alpha]_{\text{D}}^{25} -124.0$  ( $c$  0.6 in CHCl<sub>3</sub>);  $\nu_{\max}$  (KBr) 1780 (C=O);  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 1.15 (3H, d,  $J$  7.0 Hz, C( $\alpha$ )Me), 2.05 (2H, dd,  $J$  18.1, 8.6 Hz, C(2)*H<sub>A</sub>*), 2.29 (2H, dd,  $J$  18.1, 8.2 Hz, C(2)*H<sub>B</sub>*), 3.73–3.93 (4H, m, C(4)H, C( $\alpha$ )H, NCH<sub>2</sub>), 5.25 (1H, d,  $J$  6.9 Hz, C(5)H), 7.15–7.49 (15H, m, *Ph*);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 18.2 (C( $\alpha$ )Me), 29.6 (C(3)), 50.6 (NCH<sub>2</sub>), 57.4, 62.0 (C(4), C( $\alpha$ )), 84.1 (C(5)), 126.1, 127.6, 127.8, 128.5, 128.8, 129.0 (*o-Ph*, *m-Ph*, *p-Ph*), 139.0, 139.7, 141.4 (*i-Ph*), 176.0 (C(2));  $m/z$  (CI<sup>+</sup>) 372 ([M + H]<sup>+</sup>, 89%), 268 (97), 237 (54), 146 (84), 105 (77), 91 (100).

**(3*R*,4*R*,5*S*, $\alpha$ *S*)-3-Methyl-4-[*N*-benzyl-*N*-( $\alpha$ -methylbenzyl)amino]-5-phenyl-tetrahydro-2-furanone **50**.** From **39**. Following *general procedure* 3, TBAF (678 mg, 2.15 mmol) and **39** (410 mg, 0.72 mmol) in THF (10 mL) gave the crude reaction product. Purification *via* flash column chromatography (eluent hexane–EtOAc, 6 : 1) gave **50** as a colourless oil (235 mg, 85%, >98% de).

From **40**. Following *general procedure* 3, TBAF (678 mg, 2.15 mmol) and **40** (283 mg, 0.49 mmol) in THF (10 mL) gave the crude reaction product. Purification *via* flash column chromatography (eluent hexane–EtOAc, 6 : 1) gave **50** as a yellow oil (129 mg, 68%, >98% de).

Data for **50**:  $[\alpha]_{\text{D}}^{25} -42.5$  ( $c$  0.55 in CHCl<sub>3</sub>); C<sub>26</sub>H<sub>27</sub>NO<sub>2</sub> requires C, 81.0; H, 7.1; N, 3.6; found: C, 81.05; H, 7.2; N, 3.5%; mp 109–110 °C,  $\nu_{\max}$  (KBr) 1767 (C=O);  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 1.00 (3H, d,  $J$  7.1 Hz, C(3)Me), 1.08 (3H, d,  $J$  6.9 Hz, C( $\alpha$ )Me), 2.77 (1H, dq,  $J$  10.2, 7.1 Hz, C(3)H), 3.45 (1H, dd,  $J$  10.2, 8.4 Hz, C(4)H), 3.86 (1H, d,  $J$  14.6 Hz, NCH<sub>A</sub>), 3.94 (1H, d,  $J$  14.6 Hz, NCH<sub>B</sub>), 3.98 (1H, q,  $J$  6.9 Hz, C( $\alpha$ )H), 5.07 (1H, d,  $J$  8.4 Hz, C(5)H), 7.15–7.49 (15H, m, *Ph*);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 14.0, 18.3 (C(3)Me, C( $\alpha$ )Me), 37.8 (C(3)), 50.6 (NCH<sub>2</sub>), 58.2, 69.9 (C(4), C( $\alpha$ )), 81.9 (C(5)H), 127.3, 127.4, 127.9, 128.3, 128.5, 128.7 (*o-Ph*, *m-Ph*, *p-Ph*), 138.2, 140.2, 143.3 (*i-Ph*), 177.8 (C(2));  $m/z$  (CI<sup>+</sup>) 386 ([M + H]<sup>+</sup>, 100%), 282 (61), 251 (31), 105 (37), 91 (42).

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