Doubly diastereoselective conjugate addition of homochiral lithium amides to homochiral α,β-unsaturated esters containing *cis*- and *trans*-dioxolane units†

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As part of a long-term goal directed towards the *ab initio* asymmetric synthesis of unnatural amino sugars, the doubly diastereoselective conjugate addition reactions of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to a range of homochiral α,β-unsaturated esters containing *cis*- and *trans*-dioxolane units was investigated. These reactions resulted in "matching" and "mismatching" effects. In the "matched" cases a single diastereoisomer of the corresponding β-amino ester (containing three contiguous stereocentres) is produced. Upon conjugate addition to a homochiral α,β-unsaturated ester containing a *cis*-dioxolane unit, in the "mismatched" case it is the stereocontrol of the substrate which is dominant over that of the lithium amide, whilst upon addition to homochiral α,β-unsaturated esters containing a *trans*-dioxolane unit the stereocontrol of the homochiral lithium amide is dominant. Hydrogenolytic *N*-deprotection of the β-amino ester products of conjugate addition gives access to polyoxygenated β-amino acid derivatives.

Introduction

Enantioselective molecular recognition phenomena are of extreme importance to the fields of both chemistry and biology. Synthetic chemists can contribute to the understanding of this arena through the development of novel kinetic,[1] dynamic kinetic[2] and parallel kinetic resolution protocols,[3] or through the application of double asymmetric induction.[4] In the latter protocol, the reactions of a homochiral substrate with the enantiomeric forms of a homochiral reagent can proceed under the stereocontrol of either the substrate or the reagent, with the "matched" stereochemical pairing generally leading to very high levels of stereoselectivity. In the "mismatched" stereochemical pairing lower selectivity is observed, with the agent (reagent or substrate) with the higher levels of directing ability dictating the stereochemical outcome of the reaction.

Previous investigations from this laboratory have demonstrated that the conjugate addition of homochiral, secondary lithium amides (derived from α-methylbenzylamine) to α,β-unsaturated esters proceeds with high levels of diastereoselectivity, providing an efficient and general strategy for the synthesis of β-amino acid derivatives.[5,6] This methodology has found use in a plethora of synthetic applications, including molecular recognition phenomena.[6] Chiral 3-alkyl-, 3-alkoxy- and 5-alkyl cyclopent-1-ene-carboxylates, for instance, show high levels of substrate control, facilitating their kinetic and parallel kinetic resolution upon addition of homochiral or a 50:50 pseudoenantiomeric mixture of homochiral lithium amides, respectively.[7] In contrast to these cyclic examples, chiral acyclic α,β-unsaturated esters (containing a single stereogenic centre at the γ-position) generally show lower levels of substrate control in this reaction manifold.[8] Upon conjugate addition of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **1** to the homochiral α,β-unsaturated esters **2** and **3**, "matching" and "mismatching" effects were noted, although the additions proceeded under the dominant stereocontrol of the lithium amide in each case,[8c] consistent with the exceptionally high level of stereofacial bias shown by lithium amide **1** in its conjugate addition reactions[9] (Fig. 1).

As part of our strategy towards the *ab initio* asymmetric synthesis of unnatural amino sugars, and in order to simultaneously probe further double asymmetric induction,[8c] an investigation into the conjugate addition of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **1** to a range homochiral α,β-unsaturated esters **12**, containing *cis*- and *trans*-dioxolane units, was proposed. It was envisaged that these reactions would show "matching" and "mismatching" effects, with the level and sense of stereoinduction in the "mismatched" case giving an indication of the magnitude of stereoinduction exerted by the chiral (multiple stereocentre) α,β-unsaturated ester **12**; this could be further quantified by conjugate additions of achiral lithium amides. *N*-Deprotection of the β-amino ester adducts **13** would give access to polyoxygenated β-amino acid derivatives **15** (Fig. 2). We report herein the conjugate additions of lithium amides to three homochiral α,β-unsaturated esters containing dioxolane units, derived from either D-ribose or dimethyl L-tartrate. Part of this work has been communicated previously.[10]

Results and discussion

Conjugate addition of lithium amides to *tert*-butyl (2*E*,4*S*,5*R*)-4,5-*O*-isopropylidene-hepta-2,6-dienoate

α,β-Unsaturated ester **18** was prepared in 4 steps, in 45% overall yield, from D-ribose. Following literature procedures, D-ribose

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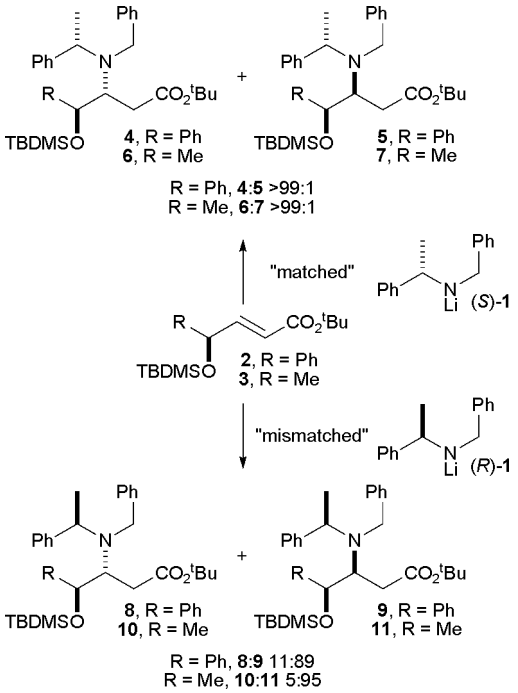
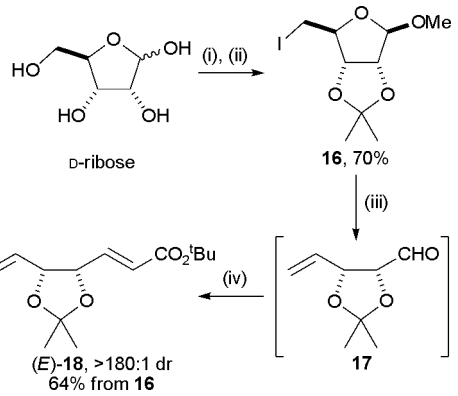


Fig. 1 Double asymmetric induction in the addition of homochiral lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **1** to homochiral α,β-unsaturated esters **2** (R = Ph) and **3** (R = Me).

was converted in two steps to **16**, in 70% yield.[11] Treatment of **16** with activated zinc dust gave aldehyde **17**,[11] which was immediately subjected to olefination with the anion derived from deprotonation of *tert*-butyl diethylphosphonoacetate with MeMgBr.[12] This furnished exclusively (*E*)-**18** [(*E*):(*Z*) >180:1],[13] which was isolated in 64% overall yield from **16** (Scheme 1).

With homochiral α,β-unsaturated ester **18** in hand, the doubly diastereoselective conjugate additions of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **1** were investigated. Conjugate addition of lithium amide (*R*)-**1** to **18** gave a single diastereoisomeric β-amino ester **20** (>98% de) as the major product, along with (*Z*)-β,γ-unsaturated ester **19**, derived from γ-deprotonation of **18** by the lithium amide (the ratio of **19**:**20**



Scheme 1 *Reagents and conditions:* (i) HCl, acetone/MeOH (1:1), reflux, 1 h; (ii) I_2, PPh_3, imidazole, PhMe/MeCN (5:1), 60 °C, 1 h; (iii) Zn, MeOH, reflux, 1 h; (iv) *tert*-butyl diethylphosphonoacetate, MeMgBr, THF, rt, 15 min, then **17**, reflux, 2.5 h.

was 18:82). Purification furnished the desired β-amino ester **20** in 50% yield and >98% de, with **19** being isolated in 11% yield as a single diastereoisomer. As no minor diastereoisomeric β-amino ester product was observed in the ^{1}H NMR spectrum of the crude reaction mixture it was inferred that this pairing of substrate and reagent represented the doubly diastereoselectively "matched" case. On this basis, the configuration of the newly formed stereocentre at C(3) within **20** was assigned by reference to the transition state mnemonic developed to rationalise the high facial bias observed upon conjugate addition of lithium amide (*R*)-**1** to a range of achiral α,β-unsaturated esters,[9] which therefore allowed assignment of the absolute (3*S*,4*S*,5*R*,α*R*)-configuration of **20** (Scheme 2).

Due to the presence of the γ-oxygen atom, the resultant increase in acidity of the γ-hydrogen atom in this system as compared to hydrocarbon analogues presumably evokes the basic nature of the lithium amide, promoting the competing γ-deprotonation pathway.[14] The formation of (*Z*)-β,γ-unsaturated ester **19** as a single diastereoisomer in this reaction is consistent with literature precedent concerning the deprotonation of enones,[15] with the γ-deprotonation of γ-alkoxy substituted enones generally thought to proceed from the enone in a conformation which places

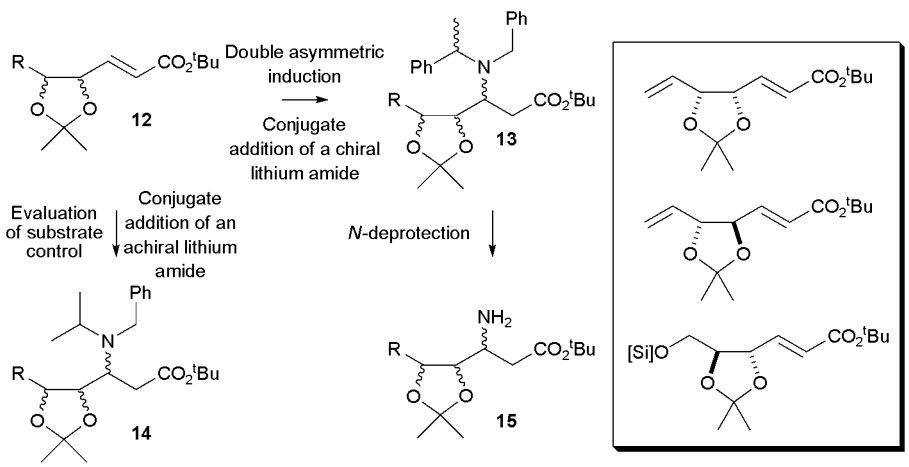
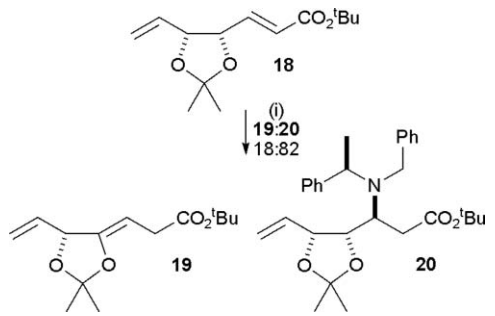


Fig. 2 Double asymmetric induction in the addition of chiral lithium amides to α,β-unsaturated esters **12** containing *cis*- and *trans*-dioxolane units. [Si] = TBDMS.



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

the γ-C–O σ-bond coplanar with the enone system, *via* in this case conformation **18A**.[15l,m] A variety of models have been proposed to explain the selectivity seen in the conjugate addition of nucleophiles to γ-alkoxy-α,β-unsaturated esters, with these proposals either citing modified Felkin-Anh theory[16] or being based on molecular modelling of the preferred conformations of the γ-alkoxy-α,β-unsaturated ester. It is generally assumed that the preferred transition states for such reactions proceed with an allylic σ-bond antiperiplanar to the trajectory of the approaching reagent, although the conformational preference around the vinylic C–C bond 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 α-vinylic hydrogen). Studies by Morokuma,[17] Leonard,[18] Dias[19] and Branchadell[20] concerning conjugate additions in related systems concluded that transition states in which the γ-oxygen is nearly eclipsing the α-hydrogen atom of the alkene may be favoured. This precedent therefore suggests that α,β-unsaturated ester **18** may undergo both conjugate addition and deprotonation in conformation **18A**. In this conformation, approach of the lithium amide reagent to C(3) would be expected to be favoured from the *Si* face, *syn* to the γ-hydrogen atom and opposite the large alkoxyalkyl substituent. Such substrate control, when combined with the known facial selectivity of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (reagent control)[9] would imply that this pairing of substrate and reagent represents the doubly diastereoselectively "matched" case, which is supported by the production of a single diastereoisomeric β-amino ester product **20** (Fig. 3).

The detritic formation of β,γ-unsaturated ester **19** *via* a competing γ-deprotonation pathway in this system compromised the yield of the desired β-amino ester product **20**. Sewald observed marked differences in the reactivity of lithium *N*-trimethylsilyl-*N*-(α-methylbenzyl)amide upon addition to a range of chiral γ-alkoxy-α,β-unsaturated esters depending on the solvent employed for the reaction (THF *versus* Et_2O).[8b] However, longer reaction times and increased equivalents of the lithium amide were required for the reaction to proceed efficiently in Et_2O: 2 eq of the lithium amide in Et_2O at −20 °C for 5 hours was necessary for optimal reaction conversion.[8b] The conjugate addition of (*R*)-**1** to α,β-unsaturated ester **18** was performed under these conditions, and gave a 93:7 (86% de) mixture of the β-amino esters **20**:**21** exclusively, with complete suppression of the γ-deprotonation pathway. Although a decrease in the stereoselectivity of the addition was observed

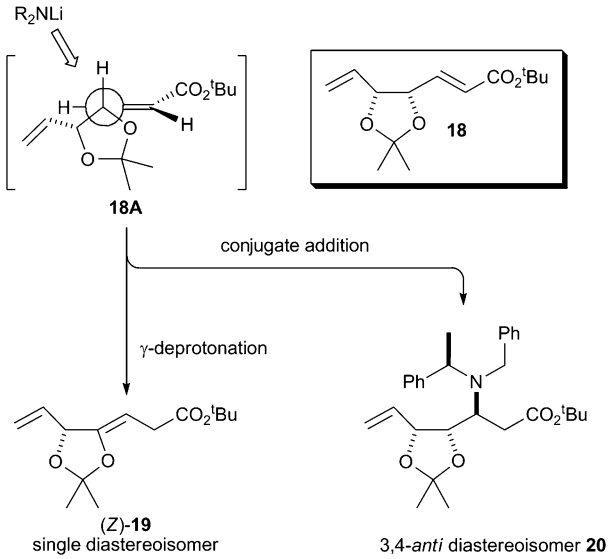
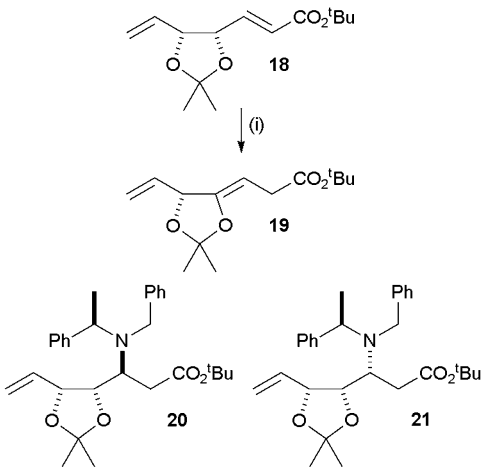


Fig. 3 Proposed transition states for γ-deprotonation of and lithium amide conjugate addition to **18**.

under these reaction conditions (86% de in Et_2O at −20 °C *versus* >98% de in THF at −78 °C) chromatographic purification allowed the isolation of β-amino ester **20** as a single diastereoisomer (>98% de) in a greatly improved 70% yield. Given the marked difference in the reactivity of lithium amide (*R*)-**1** in Et_2O at −20 °C, the effect of changing reaction temperature and solvent upon the product distribution was screened. Addition of lithium amide (*R*)-**1** to α,β-unsaturated ester **18** in Et_2O at −78 °C proceeded to only approximately 40% conversion, consistent with decreased reactivity of lithium amide (*R*)-**1** in Et_2O, and in accordance with the observations of Sewald concerning lithium *N*-trimethylsilyl-*N*-(α-methylbenzyl)amide.[8b] Complete suppression of γ-deprotonation occurs at −20 °C in both THF and Et_2O, although the diastereoselectivity is higher in Et_2O (86% de in Et_2O at −20 °C *versus* 68% de in THF at −20 °C). As lithium amides are widely recognised to form various aggregates in a range of solvents,[21] the observed differences in stereoselectivity and product distribution may be due to a change in amide aggregation with solvent, although the nature of the active species in both the conjugate addition and deprotonation manifolds is currently unknown. Alternatively, a change in the rate of interconversion of the conformers of α,β-unsaturated ester **18** with solvent and temperature may also explain the variations in product distribution in these reactions (Scheme 3).

The minor diastereoisomer **21** resulting from these studies proved crystalline, allowing the relative 3,4-*syn*-configuration to be unambiguously established by single crystal X-ray analysis. The absolute (3*R*,4*S*,5*R*,α*R*)-configuration within **21** was thus assigned relative to the known configurations of the α-methylbenzyl group, and the stereocentres within the dioxolane unit (Fig. 4). This analysis also unambiguously establishes the assigned absolute (3*S*,4*S*,5*R*,α*R*)-configuration within the major β-amino ester diastereoisomer **20**.

Conjugate addition of lithium amide (*S*)-**1** to **18** was next investigated in THF at −78 °C, and gave a 40:36:24 mixture of (*Z*)-β,γ-unsaturated ester **19** and β-amino esters **22** and **23**, respectively. The competing formation of **19** in this reaction again



(*R*)-1 eq	Solvent	T °C	19:20:21[a]	de %	Yield 20 %[b]	Yield 21 %[b]
1.6	THF	−78	18:82:0	>98	50	0
2.0	THF	−78	12:88:0	>98	-	-
2.0	Et_2O	−78	19:60:21	39[c]	-	-
2.0	THF	−40	0:89:11	78	38	3
2.0	Et_2O	−40	4:91:5	86	57	5
1.6	THF	−20	0:84:16	68	40	0
2.0	THF	−20	0:81:19	62	-	-
2.0	Et_2O	−20	0:93:7	86	70	0

Scheme 3 *Reagents and conditions:* (i) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**1**, solvent, temperature. [[a] Crude ratio of products; [b] purified–isolated yield; [c] reaction proceeded to 40% conversion.]

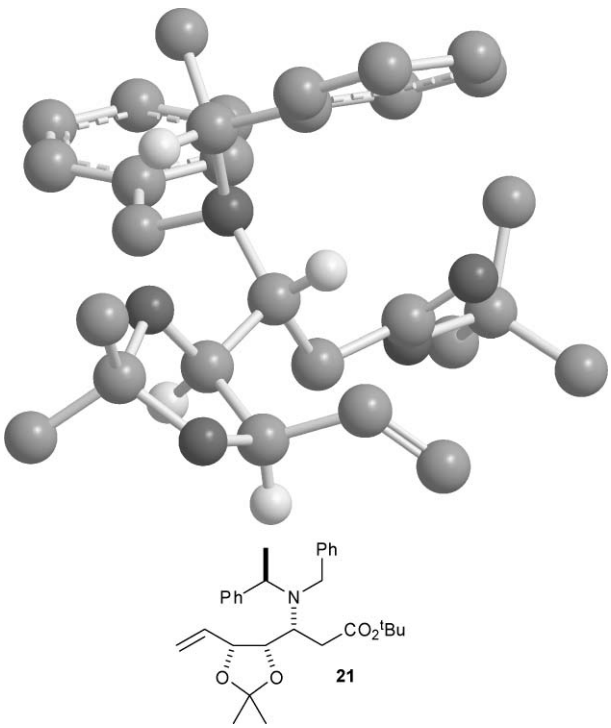
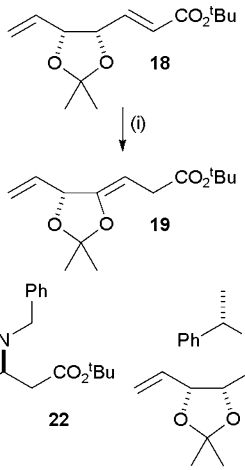


Fig. 4 Chem 3D representation of the X-ray crystal structure of **21** (some H atoms omitted for clarity).

compromised the yields of the desired β-amino ester products of conjugate addition, with chromatographic purification giving **19** in 40% yield, **22** in 14% yield (>98% de) and **23** in 11% yield (>98% de). In light of this result, the conjugate addition reaction of lithium amide (*S*)-**1** in both THF and Et_2O at −20 °C was investigated. Total suppression of the γ-deprotonation pathway was observed irrespective of the solvent although in this case THF offered higher (yet only modest) levels of diastereoselectivity (Scheme 4).

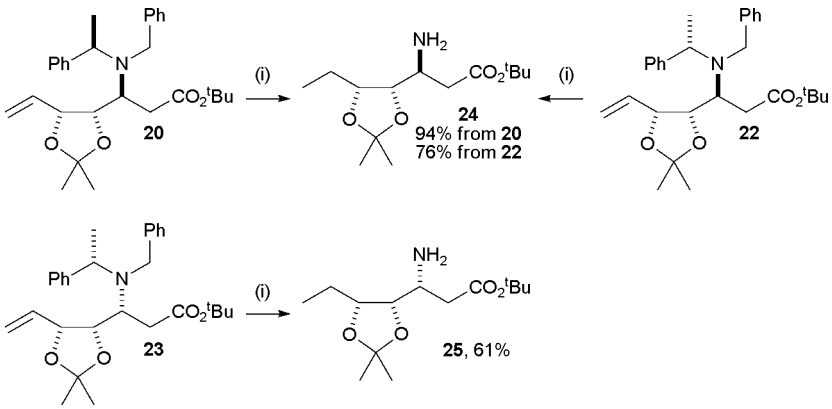
The product distributions observed upon conjugate addition of the antipodes of lithium amide **1** to **18** in THF at −78 °C are consistent with the conjugate addition of lithium amide (*R*)-**1** representing the doubly diastereoselectively "matched" combination of reagent and substrate, with conjugate addition of (*S*)-**1** being "mismatched". In order to determine whether the reagent or substrate exerted the dominant stereocontrol in the doubly diastereoselectively "mismatched" reaction [**18**/(*S*)-**1**], the configurations at C(3) within the β-amino ester products of conjugate addition **20**–**23** were correlated *via* hydrogenolytic removal of the *N*-protecting groups to furnish the corresponding primary β-amino esters. Tandem hydrogenolysis/hydrogenation of **20** gave primary β-amino ester **24** in 94% yield; analogous treatment of **22** (the major diastereoisomer from conjugate addition of lithium amide (*S*)-**1**) also furnished **24**. Meanwhile, tandem hydrogenolysis/hydrogenation of **23** (the minor diastereoisomer from conjugate addition of lithium amide (*S*)-**1**) gave primary β-amino ester **25** in 61% yield (Scheme 5).

In the "mismatched" addition, therefore, it is the stereocontrol of the α,β-unsaturated ester substrate **18** which is dominant over that of lithium amide (*S*)-**1**, resulting in a small preference for formation of the 3,4-*anti*-diastereoisomer **22**. This implies that the chiral α,β-unsaturated ester **18** shows very high levels of substrate control. In order to probe this hypothesis, the levels of substrate control displayed upon conjugate addition of



(*S*)-1 eq	Solvent	T °C	19:22:23	de %	Yield 22 %	Yield 23 %
1.6	THF	−78	40:36:24	20	14	11
2.0	THF	−20	0:62:38	24	24	11
2.0	Et_2O	−20	0:50:50	0	28	29

Scheme 4 *Reagents and conditions:* (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**1**, solvent, temperature.



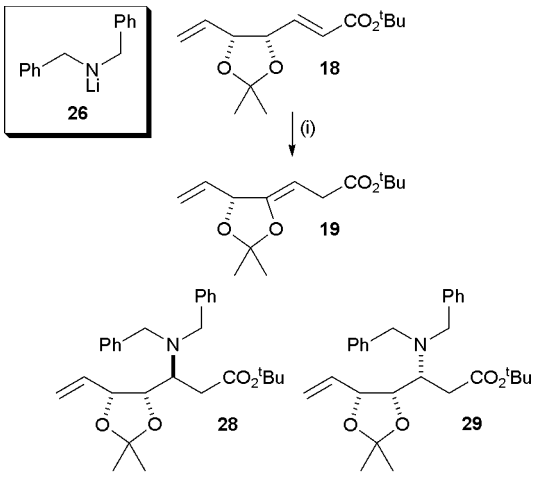
Scheme 5 *Reagents and conditions:* (i) H_2 (5 atm), $Pd(OH)_2/C$, MeOH, rt. [All compounds are single diastereoisomers (>98% de).]

achiral lithium dibenzylamide **26**[7b,c,e,g,h,8c] and lithium *N*-benzyl-*N*-isopropylamide **27**[7g,h] were investigated, the latter being employed as it has been previously shown by us to closely mimic the behaviour of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide. Addition of lithium dibenzylamide **26** to α,β-unsaturated ester **18** in THF at −78 °C gave a 2:65:33 mixture of (*Z*)-β,γ-unsaturated ester **19** and the diastereoisomeric β-amino esters **28** and **29**, respectively. Chromatography allowed the purification of **28** and **29** to homogeneity, giving **28** in 54% yield and **29** in 9% yield. When the reaction was performed in THF at −20 °C, the diastereoselectivity of addition increased, giving an 80:20 mixture of **28**:**29**, with complete suppression of the γ-deprotonation pathway (Scheme 6).

Conjugate addition of lithium *N*-benzyl-*N*-isopropylamide **27** to α,β-unsaturated ester **18** in THF at −78 °C gave a 13:87 mixture of **19** and β-amino ester **30** (>98% de), respectively, with purification furnishing **30** in 55% yield (>98% de). The γ-deprotonation pathway was again suppressed when the reaction was performed at −20 °C in either THF or Et_2O, with the conjugate addition proceeding in >98% de in both solvents (Scheme 7).

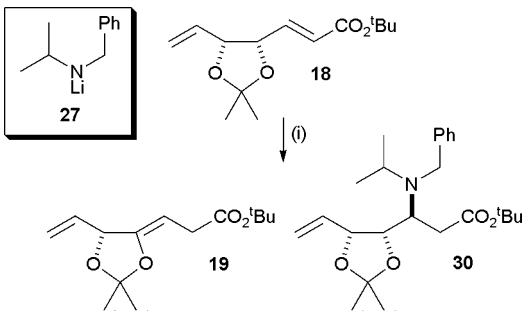
The configuration at C(3) within β-amino esters **28–30** was determined by chemical correlation. Tandem hydrogenolysis/hydrogenation of **28** (the major diastereoisomer from conjugate addition of lithium dibenzylamide **26**) gave primary β-amino ester **24** in 96% yield. Tandem hydrogenolysis/hydrogenation of *N*-benzyl-*N*-isopropyl-β-amino ester **30** gave *N*-isopropyl-β-amino ester **31** in good yield, which was identical to the product of reductive amination of primary β-amino ester **24** with acetone (Scheme 8). Tandem hydrogenolysis/hydrogenation of **29** (the minor diastereoisomer arising from conjugate addition of lithium dibenzylamide **26**) gave primary β-amino ester **25** (Scheme 9).

The preference for formation of the 3,4-*anti*-diastereoisomer and the propensity for competitive γ-deprotonation displayed upon addition of lithium dibenzylamide **26**, lithium *N*-benzyl-*N*-isopropylamide **27** and lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **1** to **18** is consistent with the conjugate addition reaction proceeding with the α,β-unsaturated ester in conformation **18A** (Fig. 3). Partial shielding of the *Re* face of the α,β-unsaturated ester system by the terminal vinyl group in this conformation rationalises the high levels of stereocontrol exerted by the homochiral substrate upon conjugate addition of lithium



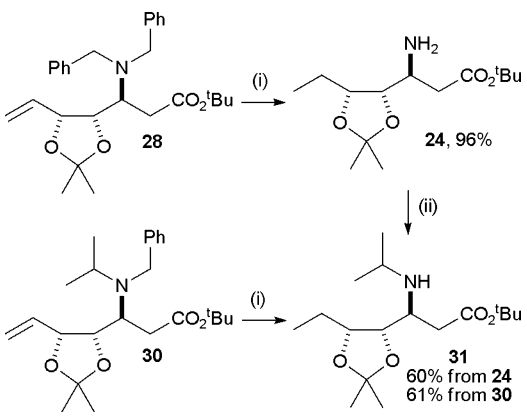
26 eq	Solvent	T °C	19:28:29	de %
1.6	THF	−78	2:65:33	33
2.0	THF	−20	0:80:20	60
2.0	Et_2O	−20	0:68:32	36

Scheme 6 *Reagents and conditions:* (i) lithium dibenzylamide **26**, solvent, temperature.

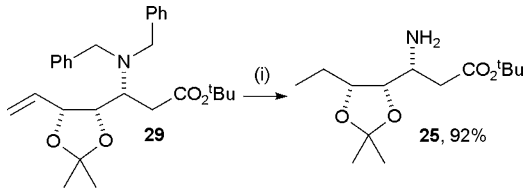


27 eq	Solvent	T °C	19:30	de %
1.6	THF	−78	13:87	>98
2.0	THF	−20	0:100	>98
2.0	Et_2O	−20	0:100	>98

Scheme 7 *Reagents and conditions:* (i) lithium *N*-benzyl-*N*-isopropylamide **27**, solvent, temperature.



Scheme 8 *Reagents and conditions:* (i) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 15 h; (ii) acetone, $NaBH_3CN$, MeOH, rt, 18 h. [All compounds are single diastereoisomers (>98% de).]



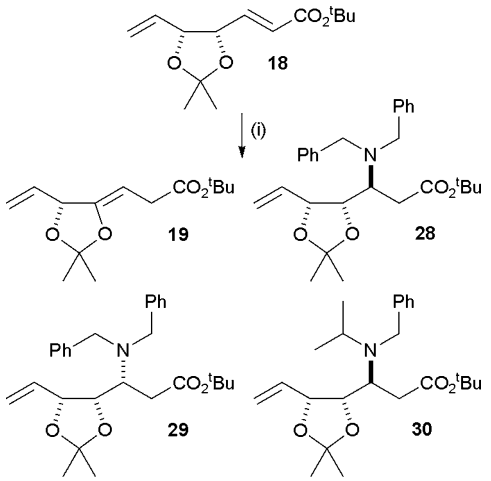
Scheme 9 *Reagents and conditions:* (i) H_2 (5 atm), $Pd(OH)_2/C$, MeOH, rt; (ii) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt. [All compounds are single diastereoisomers (>98% de)].

N-benzyl-*N*-isopropylamide **27**, promoting exclusive formation of the 3,4-*anti*-diastereoisomer **30**. However, upon conjugate addition of lithium dibenzylamide **26** only a modest (~2:1) preference for the formation of the 3,4-*anti* diastereoisomer **28** is observed. Taken with the outcome of the doubly diastereoselective conjugate addition reactions (in which the stereocontrol of the chiral α,β-unsaturated ester **18** overwhelms the exceptionally high facial bias of lithium amide (*S*)-**1** in the "mismatched" reaction pairing), these data indicate that lithium dibenzylamide **26** does not closely mimic the behaviour of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **1** or lithium *N*-benzyl-*N*-isopropylamide **27** within this system. In order to better understand the differences in the diastereoselectivity of addition of lithium amides **1**, **26** and **27** to α,β-unsaturated ester **18**, a series of competition experiments was performed in order to facilitate a qualitative rate comparison. In these experiments, BuLi (2 eq) was added to a 50:50 mixture of amines (2 × 1 eq) in THF at −78 °C to generate the corresponding lithium amides, before addition of α,β-unsaturated ester **18** (1 eq). No marked change in the diastereoselectivity of any of the addition products was observed in the resulting product distributions, indicating that the lithium amides react analogously in both the competitive and individual conjugate addition reactions. Assuming that the conjugate addition is irreversible and that the reaction proceeds under kinetic control, analysis of the product distributions from these reactions was used to qualify the rates of conjugate addition. For instance, addition of a mixture of lithium dibenzylamide **26** and lithium *N*-benzyl-*N*-isopropylamide **27** to α,β-unsaturated ester **18** gave a 4:63:28:5 mixture of **19**:**28**:**29**:**30**. The total amount of β,γ-unsaturated ester **19** was partitioned into the amounts generated by the γ-deprotonation of **18** by lithium amides **26** and **27**: the amount of **19** generated by lithium *N*-benzyl-*N*-isopropylamide **27** was calculated on the basis of the ratio of **19**:**30** being 13:87 (*vide supra*). This corresponds to lithium *N*-benzyl-*N*-isopropylamide **27** being responsible for consumption of approximately 5% of α,β-unsaturated ester **18**, with lithium dibenzylamide **26** being responsible for consumption of the remaining 95%, *i.e.* addition of **26** and **27** in a ratio of approximately 19:1 (Scheme 10).

The product distributions obtained upon competitive addition of lithium dibenzylamide **26** with both antipodes of lithium amide **1**, and those of lithium *N*-benzyl-*N*-isopropylamide **27** with both antipodes of **1**, were determined in an analogous manner (Table 1). From these data, it is concluded that the rates of addition of the four lithium amides to α,β-unsaturated ester **18** are in the order lithium dibenzylamide >> lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide ("matched") ~ lithium *N*-benzyl-*N*-isopropylamide > lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide ("mismatched"). It therefore appears that

Table 1 Consumption of **18** upon competitive addition of lithium amides (*R*)-**1**, (*S*)-**1**, **26** and **27**

Lithium amides	Ratio of addition products
26 *vs* **27**	19:1
26 *vs* (*R*)-**1**	12:1
26 *vs* (*S*)-**1**	52:1
27 *vs* (*R*)-**1**	1:1
27 *vs* (*S*)-**1**	4:1



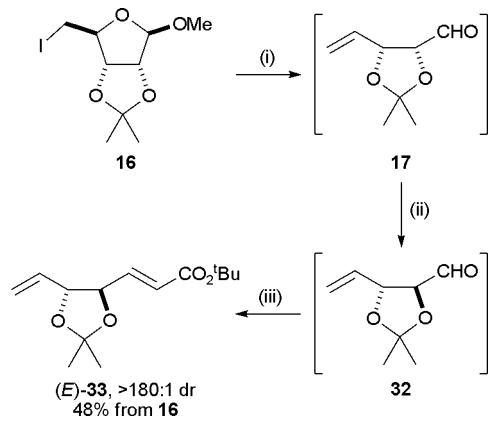
Scheme 10 *Reagents and conditions:* (i) lithium dibenzylamide **26** (1 eq), lithium *N*-benzyl-*N*-isopropylamide **27** (1 eq), THF, −78 °C, 2 h.

lithium *N*-benzyl-*N*-isopropylamide **27** mimics the behaviour of the homochiral lithium amides (*R*)-**1** and (*S*)-**1** in this system due to the similar rates of addition of lithium amides **1** and **27**.

Conjugate addition of lithium amides to *tert*-butyl (2*E*,4*R*,5*R*)-4,5-*O*-isopropylidene-hepta-2,6-dienoate

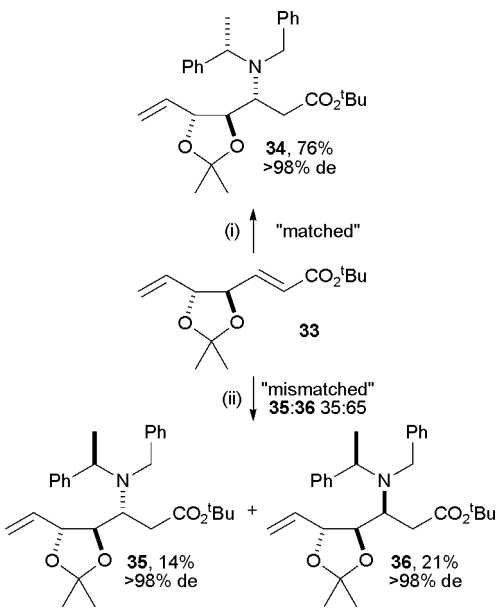
Having demonstrated that α,β-unsaturated ester **18** exerts high levels of substrate control upon conjugate addition of lithium *N*-benzyl-*N*-isopropylamide **27**, and overwhelms the very high stereocontrol of lithium amide (*S*)-**1** in the doubly diastereoselective "mismatched" reaction pairing, subsequent studies were focused upon the conjugate addition of lithium amides to α,β-unsaturated ester **33**, containing a *trans*-dioxolane unit. Sharpless and co-workers have noted the base catalysed epimerisation of *cis*-substituted dioxolane aldehydes to the corresponding *trans*-substituted aldehydes.[22] Following this precedent, under optimised conditions, treatment of **16** with activated zinc dust and immediate addition of K_2CO_3 to the crude reaction mixture was followed by aqueous work-up and olefination with the anion derived from deprotonation of *tert*-butyl diethylphosphonoacetate with MeMgBr.[12] This furnished **33** as the only diastereoisomeric product [(*E*):(*Z*) >180:1],[13] which was isolated in 48% overall yield from **16** (Scheme 11).

Conjugate addition of lithium amide (*S*)-**1** to **33** gave a single β-amino ester product **34** (>98% de), which was isolated in 76% yield and >98% de. As in the series of conjugate additions to α,β-unsaturated ester **18**, the absence of a minor diastereoisomeric product in the ^{1}H NMR spectrum of the crude reaction mixture suggested that this pairing of substrate and reagent



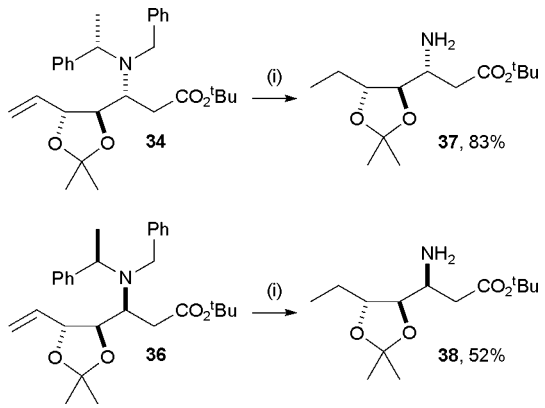
Scheme 11 *Reagents and conditions:* (i) Zn, MeOH, reflux, 1 h; (ii) K_2CO_3, MeOH, rt, 2.5 h; (iii) *tert*-butyl diethylphosphonoacetate, MeMgBr, THF, rt, 15 min, then **32**, reflux, 2 h.

represented the doubly diastereoselectively "matched" case. The (3*R*)-configuration within β-amino ester (3*R*,4*R*,5*R*,α*S*)-**34** was thus assigned by reference to the transition state mnemonic developed to rationalise the stereoselectivity observed during addition of lithium amide **1** to achiral α,β-unsaturated esters.[9] Addition of lithium amide (*R*)-**1** gave a 35:65 mixture (30% de) of the β-amino esters **35**:**36**, suggesting that this represented the "mismatched" reaction pairing. Purification enabled partial separation of the mixture, with **35** isolated in 14% yield and >98% de, and **36** in 21% yield and >98% de, and a mixed fraction (**35**:**36**, 42:58) in 19% yield. It is notable that even at −78 °C in THF the γ-deprotonation pathway forming **19**, which competed with lithium amide conjugate addition upon reaction with the α,β-unsaturated ester **18**, is not observed upon addition to α,β-unsaturated ester **33** (Scheme 12).



Scheme 12 *Reagents and conditions:* (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**1**, THF, −78 °C, 2 h; (ii) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**1**, THF, −78 °C, 2 h.

In order to determine the configuration of the major diastereoisomer in the "mismatched" reaction pairing, the C(3) configurations within the β-amino ester products of conjugate addition **34**–**36** were correlated *via* hydrogenolytic removal of the *N*-protecting groups. Tandem hydrogenolysis/hydrogenation of β-amino ester **34** furnished primary β-amino ester **37** in 83% yield as a single diastereoisomer; similar treatment of β-amino ester **36** (the major diastereoisomer from conjugate addition of (*R*)-**1**) gave primary β-amino ester **38** in 52% yield as a single diastereoisomer (Scheme 13).

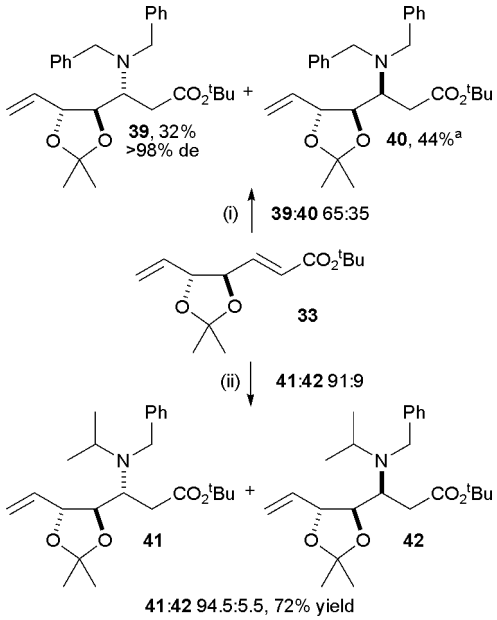


Scheme 13 *Reagents and conditions:* (i) H_2 (5 atm), $Pd(OH)_2/C$, MeOH, rt, 15 h. [All compounds are single diastereoisomers (>98% de).]

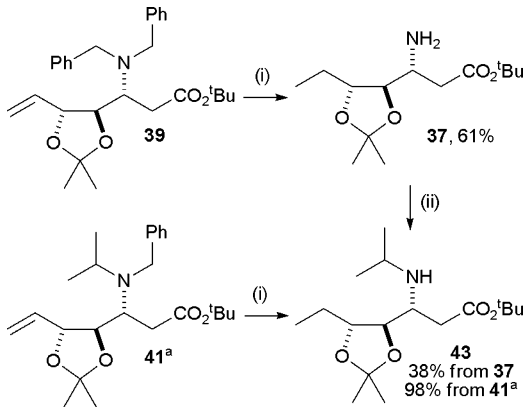
The formation of the C(3)-epimeric β-amino esters **37** and **38** in these reactions suggest that in the "mismatched" conjugate addition of lithium amide (*R*)-**1** to α,β-unsaturated ester **33**, it is the stereocontrol of the lithium amide which is dominant. This is in contrast to the outcome of the studies into conjugate addition of the antipodes of **1** to α,β-unsaturated ester **18**. In order to further investigate this result, the level of substrate control exerted by α,β-unsaturated ester **33** was evaluated by conjugate addition of achiral lithium amides **26** and **27**. Addition of lithium dibenzylamide **26** gave exclusively the β-amino ester products of conjugate addition **39** and **40** in a 65:35 ratio, respectively, with chromatographic purification giving the major diastereoisomer **39** in 32% yield (>98% de), and a 45:55 mixture of **39**:**40** in 44% yield. Conjugate addition of lithium *N*-benzyl-*N*-isopropylamide **27** also gave exclusively the β-amino ester products of conjugate addition, **41** and **42**, in a 91:9 ratio (82% de) respectively. Purification gave a 94.5:5.5 (89% de) mixture of **41**:**42** in 72% yield (Scheme 14).

The configuration at C(3) within β-amino esters **39**–**42** was determined by chemical correlation. Tandem hydrogenolysis/hydrogenation of β-amino ester **39** (the major diastereoisomer from conjugate addition of lithium dibenzylamide **26**) furnished primary β-amino ester **37** in 61% yield. Tandem hydrogenolysis/hydrogenation of *N*-benzyl-*N*-isopropyl-protected β-amino ester **41** (89% de) gave *N*-isopropyl-β-amino ester **43** in 98% yield and 89% de, which was identical to the product of reductive amination of primary β-amino ester **37** with acetone (Scheme 15).

Additionally, tandem hydrogenolysis/hydrogenation of the 45:55 mixture of diastereoisomers **39**:**40** (from addition of lithium dibenzylamide **26**) gave a 45:55 mixture of diastereoisomers **37**:**38** in 74% yield, and treatment of **36** with Pearlman's catalyst in MeOH/acetone under hydrogen gave **44**, which was identical by



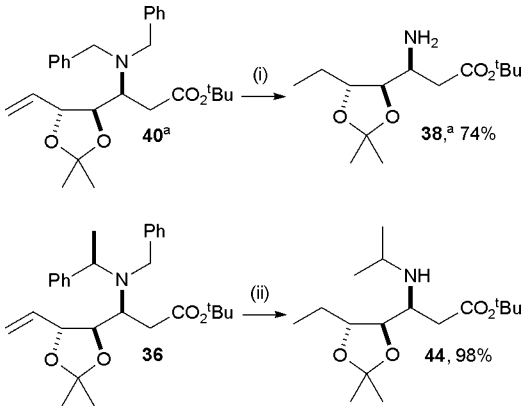
Scheme 14 *Reagents and conditions:* (i) lithium dibenzylamide **26**, THF, −78 °C, 2 h; (ii) lithium *N*-benzyl-*N*-isopropylamide **27**, THF, −78 °C, 2 h. [[a] 45:55 mixture of diastereoisomers **39**:**40**.]



Scheme 15 *Reagents and conditions:* (i) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 15 h; (ii) acetone, $NaBH_3CN$, MeOH, rt, 18 h. [All compounds are single diastereoisomers (>98% de) unless stated; [a] 94.5:5.5 (89% de) mixture of diastereoisomers **41**:**42** or **43**:**44**.]

^{1}H NMR to the *minor* product observed upon hydrogenolysis of **41** (89% de) (Scheme 16).

The product distributions arising from conjugate addition of the achiral lithium amides **26** and **27** to α,β-unsaturated ester **33** indicate reasonable substrate control, resulting in preference for the 3,4-*anti*-diastereoisomer in both cases. The stereocontrol using lithium *N*-benzyl-*N*-isopropylamide **27** is again markedly higher than that with lithium dibenzylamide **26**, although the magnitude of the stereoinduction (82% de) is not as great as that observed upon the addition to α,β-unsaturated ester **18** (>98% de). Consistent with the lower levels of substrate control shown by **33** (*versus* **18**) upon conjugate addition of lithium *N*-benzyl-*N*-isopropylamide **27**, in the doubly diastereoselective "mismatched" reaction it is the lithium amide (*R*)-**1** that has the dominant stereocontrol. Addition to the α,β-unsaturated ester system **33** in conformation **33A**, with the large alkoxyalkyl group *anti* to the



Scheme 16 *Reagents and conditions:* (i) H_2 (5 atm), $Pd(OH)_2/C$, MeOH, rt, 15 h; (ii) H_2 (5 atm), Pd/C, MeOH/acetone (9:1), rt, 16 h. [All compounds are single diastereoisomers (>98% de) unless stated; [a] 45:55 mixture of diastereoisomers **37**:**38** or **39**:**40**.]

incoming nucleophile, is able to rationalise the observed 3,4-*anti* preference for conjugate addition of the achiral lithium amides **26** and **27** to α,β-unsaturated ester **33**, as well as the "matched" and "mismatched" pairings of **33** with the antipodes of lithium amide **1**. The propensity for competing γ-deprotonation of **33** in this conformation would be expected to be diminished due to poor overlap of the σ_{C-H} bond with the π-system of the α,β-unsaturated ester. Furthermore, in comparison to α,β-unsaturated ester **18**, the configurational change at C(4) within **33** results in the terminal vinyl group being orientated away from the α,β-unsaturated system, resulting in less effective shielding of one face of the enone, and therefore potentially rationalising the lower levels of diastereofacial control shown by **33** (Fig. 5).

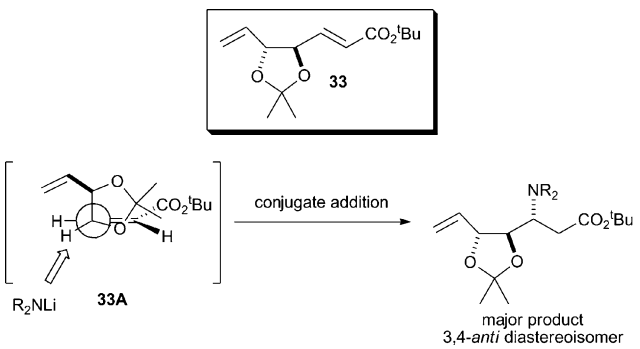
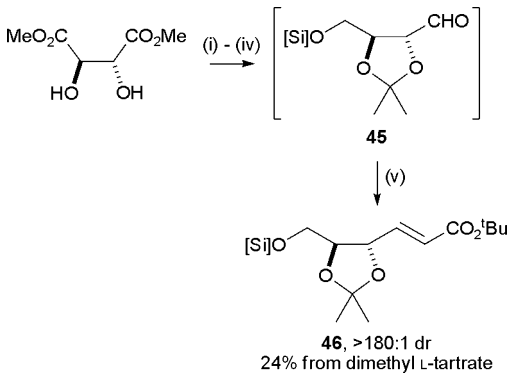


Fig. 5 Postulated transition state for lithium amide conjugate addition to **33**.

Conjugate addition of lithium amides to *tert*-butyl (2*E*,4*S*,5*R*)-4,5-*O*-isopropylidene-6-(*tert*-butyldimethylsilyloxy)hex-2-enoate

Having demonstrated that lithium amide addition to α,β-unsaturated ester **33** is preferentially *anti*-selective, and that the doubly diastereoselective conjugate additions of lithium amide **1** proceed under the predominant stereocontrol of the lithium amide, the stereoselectivity observed upon addition to an alternative α,β-unsaturated ester **46** containing a *trans*-dioxolane unit derived from dimethyl L-tartrate was investigated. Following literature procedures, dimethyl L-tartrate was heated to reflux in dimethoxypropane with catalytic TsOH to afford the corresponding 1,3-dioxolane, with subsequent reduction with an excess of $NaBH_4$ and mono-silylation of the resultant diol allowing Swern oxidation of the free alcohol to give aldehyde **45**.[23] Olefination of aldehyde **45** with *tert*-butyl diethylphosphonoacetate and MeMgBr[12] furnished (*E*)-**46** as the only diastereoisomeric product [(*E*):(*Z*) >180:1],[13] which was isolated in 24% overall yield from dimethyl L-tartrate (Scheme 17).

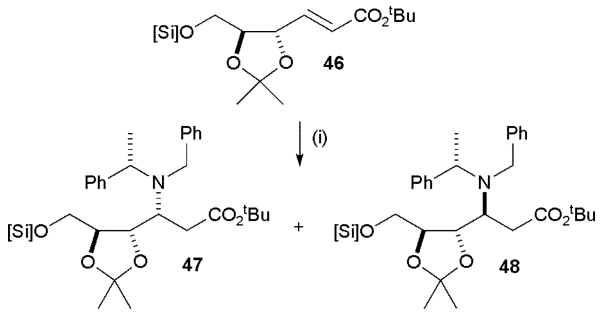


Scheme 17 *Reagents and conditions:* (i) 2,2-dimethoxypropane, TsOH, reflux, 16 h; (ii) $NaBH_4$, MeOH, rt, 16 h; (iii) NaH (1 eq), TBDMSCl (1 eq), THF, rt, 16 h; (iv) DMSO, $(COCl)_2$, DCM, −78 °C, then Et_3N, −78 °C to rt; (v) *tert*-butyl diethylphosphonoacetate, MeMgBr, THF, rt, 15 min, then **45**, reflux, 2.5 h. [Si] = TBDMS.

Conjugate addition of lithium amide (*S*)-**1** to α,β-unsaturated ester **46** gave a single diastereoisomeric product **47**, which was isolated in 69% yield after chromatography. On the basis that this represented the "matched" reaction pairing, β-amino ester **47** was assigned the absolute (3*R*,4*S*,5*R*,α*S*)-configuration by reference to the transition state mnemonic developed to rationalise the selectivity observed during addition of lithium amide **1** to achiral α,β-unsaturated esters.[9] The effect of solvent and temperature on the product distribution was also investigated, and although addition in THF at −20 °C proceeded to give **47** as a single product, the diastereoselectivity was eroded in Et_2O at −20 °C, giving a 63:37 mixture of **47**:**48**. Purification allowed isolation of **47** in 60% yield and **48** in 11% yield, as single diastereoisomers in each case. No trace of competing γ-deprotonation of the α,β-unsaturated ester by the lithium amide was observed in any of these addition reactions (Scheme 18).

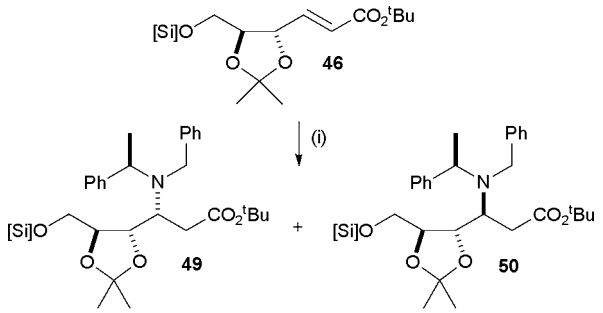
Conjugate addition of lithium amide (*R*)-**1** to **46** gave a separable 30:70 mixture of β-amino esters **49**:**50**, respectively, with **49** isolated in 24% yield and >98% de, and **50** in 42% yield and >98% de. This suggests that the pairing of (*R*)-**1** and **46** is doubly diastereoselectively "mismatched". When the reaction was performed in Et_2O at −20 °C, the diastereoselectivity of addition increased, giving a 15:85 mixture of diastereoisomers **49**:**50** from which **49** was isolated in 8% yield, and **50** in 60% yield, as single diastereoisomers in both cases (Scheme 19).

In order to determine the sense of stereoinduction in the "mismatched" case, the configurations at C(3) within β-amino esters **47**–**50** were correlated *via* hydrogenolysis. Treatment of **47** with $Pd(OH)_2/C$ under hydrogen gave primary β-amino ester **51** as a single diastereoisomer, whilst analogous treatment of **50** (the major diastereoisomer resulting from addition of lithium amide (*R*)-**1**) and **48** (the minor diastereoisomer resulting from addition



(*S*)-1 eq	Solvent	T °C	47:48	de %
1.6	THF	−78	>99:1	>98
2.0	THF	−20	>99:1	>98
2.0	Et_2O	−20	63:37	26

Scheme 18 *Reagents and conditions:* (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**1**, solvent, temperature. [Si] = TBDMS.

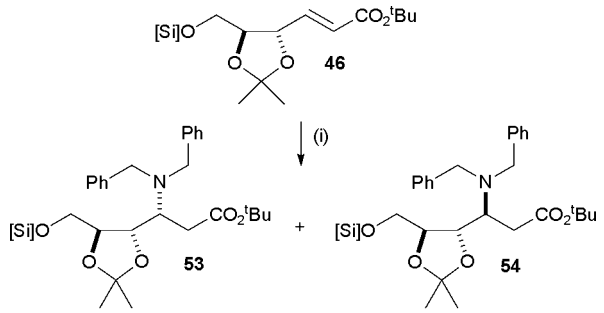


(*R*)-1 eq	Solvent	T °C	49:50	de %
1.6	THF	−78	30:70	40
2.0	THF	−20	43:57	14
2.0	Et_2O	−20	15:85	70

Scheme 19 *Reagents and conditions:* (i) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**1**, solvent, temperature. [Si] = TBDMS.

of lithium amide (*S*)-**1**) furnished primary β-amino ester **52** in both cases (Scheme 20).

The product distributions arising from the conjugate addition of the antipodes of chiral lithium amide **1** to **46** indicate that the lithium amide has the dominant stereocontrol in each of these reactions, giving a single 3,4-*syn*-diastereoisomeric product in the "matched" case, and preferentially the 3,4-*anti*-diastereoisomeric product in the "mismatched" case. This is in contrast to the results pertaining to α,β-unsaturated esters **18** and **33**, in which the "matched" case gave the corresponding 3,4-*anti*-diastereoisomer. In order to further probe the levels of substrate control offered in this system, the conjugate addition of lithium dibenzylamide **26** and lithium *N*-benzyl-*N*-isopropylamide **27** to α,β-unsaturated ester **46** was next investigated. Conjugate addition of lithium dibenzylamide **26** gave an approximate 50:50 mixture of **53**:**54**, from which **53** and **54** were isolated in 50 and 40% yield respectively. When the addition was performed in Et_2O at −20 °C a complex mixture of products was formed, although reaction in THF at −20 °C gave a 64:36 mixture of **53**:**54** (Scheme 21).

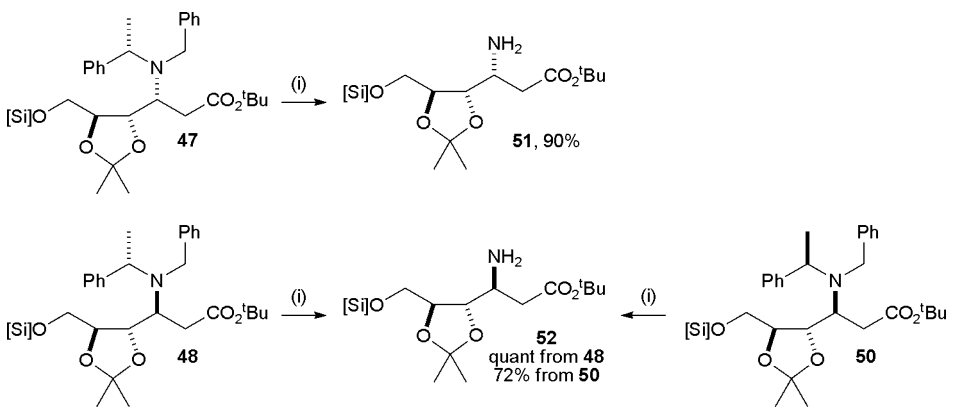


26 eq	Solvent	T °C	53:54	de %
1.6	THF	−78	50:50	0
2.0	THF	−20	64:36	28

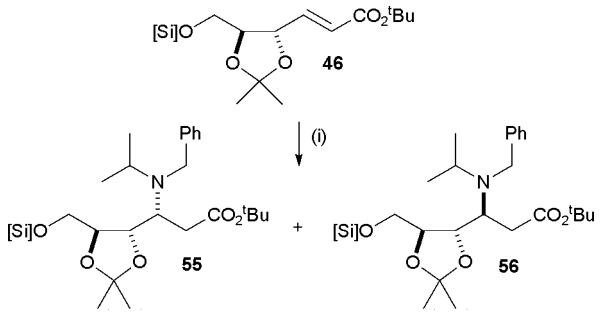
Scheme 21 *Reagents and conditions:* (i) lithium dibenzylamide **26**, solvent, temperature. [Si] = TBDMS.

The conjugate addition of lithium *N*-benzyl-*N*-isopropylamide **27** gave a 25:75 mixture (50% de) of **55**:**56**, with chromatographic separation giving **55** in 15% yield and **56** in 48% yield, in >98% de in each case. The sensitivity of this product distribution to changes in solvent and temperature was also investigated, although **56** was produced as the major diastereoisomer in all cases and the highest selectivity was offered by reaction in THF at −78 °C (Scheme 22).

The absolute configurations at C(3) within β-amino esters **53**–**56** were next assigned by chemical correlation. Tandem hydrogenolysis/reductive amination of **47**, **49** and **53** furnished, in each case, primary β-amino ester **57**, which was identical to the product of hydrogenolysis of **55** (Scheme 23). In an analogous fashion,

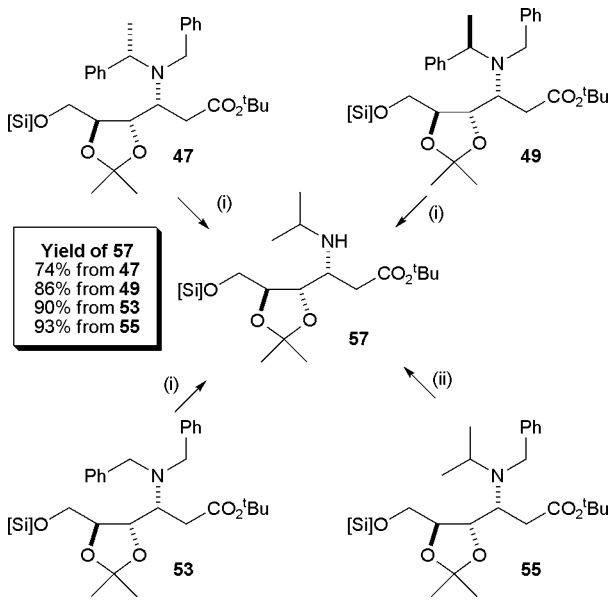


Scheme 20 *Reagents and conditions:* (i) H_2 (1 atm), $Pd(OH)_2/C$, EtOAc, rt, 16 h. [Si] = TBDMS.



27 eq	Solvent	T °C	55:56	de %
1.6	THF	−78	25:75	50
2.0	THF	−20	38:62	24
2.0	Et_2O	−20	27:73	48

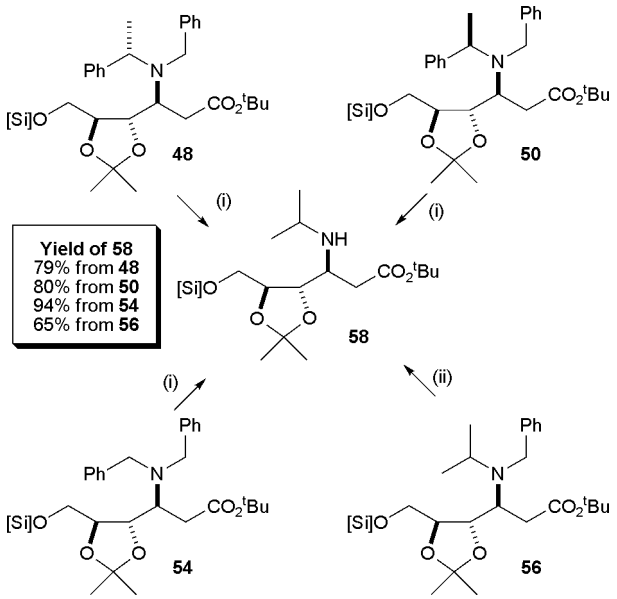
Scheme 22 *Reagents and conditions:* (i) lithium *N*-benzyl-*N*-isopropylamide **27**, solvent, temperature. [Si] = TBDMS.



Scheme 23 *Reagents and conditions:* (i) H_2 (5 atm), Pd/C, MeOH/acetone (9:1), rt, 16 h; (ii) H_2 (5 atm), Pd/C, EtOAc, rt, 15 h. [Si] = TBDMS.

the C(3)-configurations within **48**, **50**, **54** and **56** were similarly correlated (Scheme 24).

The results obtained upon conjugate addition of lithium amides **1** and **27** to α,β-unsaturated ester **46** therefore present an intriguing mechanistic paradox, *viz*. the doubly diastereoselective "matched" addition of lithium amide (*S*)-**1** in THF at −78 °C occurs to the *Re* face of the α,β-unsaturated system to give 3,4-*syn*-β-amino ester **47** whereas the substrate directed addition of lithium *N*-benzyl-*N*-isopropylbenzylamide **27** occurs with modest levels of selectivity to the *Si* face, furnishing 3,4-*anti*-β-amino ester **56** as the major diastereoisomeric product. The stereocontrol exerted by homochiral α,β-unsaturated ester **46** upon addition of lithium *N*-benzyl-*N*-isopropylamide **27** is consistent with the reaction proceeding with the α,β-unsaturated ester in conformation **46A**, which is analogous to conformation **33A**, proposed to rationalise the product distributions upon conjugate addition of the range of lithium amides to α,β-unsaturated ester **33**. In the case of



Scheme 24 *Reagents and conditions:* (i) H_2 (5 atm), Pd/C, MeOH/acetone (9:1), rt, 16 h; (ii) H_2 (5 atm), Pd/C, EtOAc, rt, 15 h. [Si] = TBDMS.

α,β-unsaturated ester **46**, however, the doubly diastereoselective "matched" and "mismatched" pairings with homochiral lithium *N*-benzyl-*N*-(α-methylbenzyl)amide cannot be accounted for by reaction through conformation **46A**. This suggests that the origin of the reversal in selectivity may be due to the presence of an alternative reactive conformation of **46**, although the mechanistic origin for this observed stereoselectivity cannot be fully explained (Fig. 6).

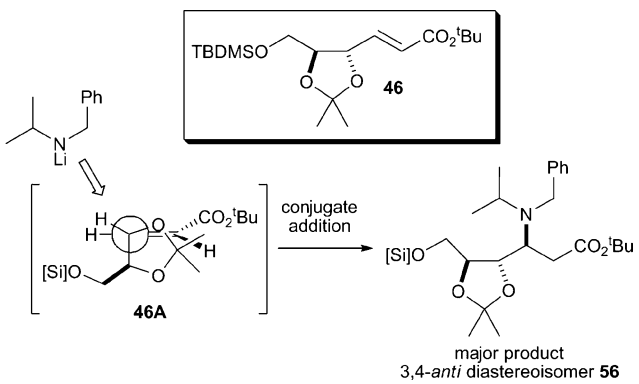


Fig. 6 Proposed transition state for conjugate addition of lithium *N*-benzyl-*N*-isopropylamide **27** to **46**. [Si] = TBDMS.

Conclusion

In conclusion, doubly diastereoselective conjugate addition reactions of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to a range of homochiral α,β-unsaturated esters containing *cis*- and *trans*-dioxolane units result in "matching" and "mismatching" effects. In the "matched" cases a single diastereoisomer of the corresponding β-amino ester is produced. Upon conjugate addition to an α,β-unsaturated ester containing a *cis*-dioxolane unit in the "mismatched" case it is the stereocontrol

of the substrate which is dominant over that of the lithium amide, whilst upon addition to α,β-unsaturated esters containing a *trans*-dioxolane unit the stereocontrol of the homochiral lithium amide is dominant. Consistent with these observations, upon conjugate addition of lithium *N*-benzyl-*N*-isopropylamide to homochiral α,β-unsaturated esters, modest to high levels of substrate control leading to the corresponding 3,4-*anti*-diastereoisomeric β-amino ester product are observed in each case, which can be rationalised by invoking a modified Felkin-Anh transition state. In one case, however, an unprecedented *reversal* in the sense of substrate control upon addition of lithium *N*-benzyl-*N*-isopropylamide than that suggested by the doubly diastereoselectively "matched" and "mismatched" reaction pairings is potentially indicative of alternative transition states for the conjugate addition reaction, reflecting the sensitivity of this system to changes in both the structure of the chiral α,β-unsaturated ester and the nature of the lithium amide reagent. Further investigations toward both bettering our understanding of these phenomena, and the application of this double induction strategy for the asymmetric synthesis of unnatural amino sugars and other polyfunctionalised products are currently underway within our 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.[24] Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

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

General Procedure 1: Lithium amide conjugate addition

BuLi was added dropwise to a stirred solution of the requisite amine in the solvent stated (THF or Et_2O), at the temperature stated (–78, –40 or –20 °C), and the resulting solution was stirred for 30 min. A solution of the requisite α,β-unsaturated ester in the solvent stated (THF or Et_2O), at the temperature stated (–78, –40 or –20 °C) was added dropwise *via* cannula. The reaction mixture was stirred for either 2 h (for reactions at –78 °C) or 5 h (for reactions at –40 or –20 °C) before addition of sat aq NH_4Cl. The reaction mixture was warmed to rt and concentrated *in vacuo*. The residue was dissolved in DCM and washed sequentially with 10% aq. citric acid, sat aq $NaHCO_3$ and brine, dried, and concentrated *in vacuo*.

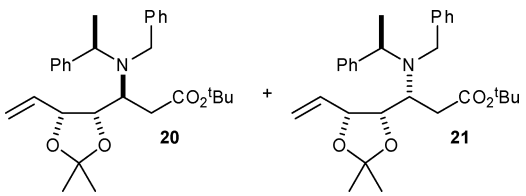
General Procedure 2: Hydrogenolysis with Pearlman's catalyst

$Pd(OH)_2/C$ (20% w/w of substrate) was added to a vigorously stirred, degassed solution of the requisite substrate in either EtOAc or MeOH, and placed under a hydrogen atmosphere (either 1 or 5 atm). Stirring was continued for 15 h at rt, after which time the reaction mixture was filtered through Celite (eluent EtOAc or MeOH) and concentrated *in vacuo*.

General Procedure 3: Tandem hydrogenolysis/reductive amination with Pearlman's catalyst

$Pd(OH)_2/C$ (50% w/w of substrate) was added to a vigorously stirred, degassed solution of the requisite substrate in EtOAc/acetone (v:v 9:1), and placed under a hydrogen atmosphere (1 atm). Stirring was continued for 16 h at rt, after which time the reaction mixture was filtered through Celite (eluent EtOAc) and concentrated *in vacuo*.

tert-Butyl (3*S*,4*S*,5*R*,α*R*)- and (3*R*,4*S*,5*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-*O*-isopropylidene-hepta-6-enoate (3*S*,4*S*,5*R*,α*R*)-20 and (3*R*,4*S*,5*R*,α*R*)-21



Method A. Following *General Procedure 1*, BuLi (2.5 M in hexanes, 0.61 mL, 1.53 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (332 mg, 1.57 mmol) in THF (4 mL) at –78 °C, and **18** (200 mg, 0.79 mmol) in THF (4 mL) at –78 °C gave a 18:82 mixture of **19**:**20**. Purification *via* flash column chromatography (eluent pentane/Et_2O, 25:1) gave **19** as a colourless oil (22 mg, 11%, >98% de); R_f 0.26 (pentane/Et_2O, 20:1); $[\alpha]^{24}_D$ –35.8 (*c* 1.15 in $CHCl_3$); ν_{max} (film) 1733 (C=O); δ_H (400 MHz, $CDCl_3$) 1.43 (3H, s, *Me*CMe), 1.45 (9H, s, C*Me*$_3$), 1.52 (3H, s, MeC*Me*), 2.98–3.12 (2H, m, C(2)H_2), 4.32 (1H, app td, *J* 7.0, 1.8, C(3)*H*), 4.94–4.97 (1H, m, C(5)*H*), 5.29 (1H, dd, *J* 10.1, 0.4, C(7)H_A), 5.38 (1H, app d, *J* 17.0, C(7)H_B), 5.74–5.83 (1H, m, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 25.2, 26.8 (C*Me*$_2$), 28.1 (C*Me*$_3$), 32.0 (*C*(2)), 78.8 (*C*(5)), 80.3 (*C*Me$_3$), 88.2 (*C*(3)), 111.0 (*C*Me$_2$), 119.3 (*C*(7)), 135.3 (*C*(6)), 152.9 (*C*(4)), 171.7 (*C*(1)); *m*/*z* (CI$^+$) 272 ([M + NH_4]$^+$, 13%), 255 (16), 199 (100). Further

elution gave **20** as a colourless oil (184 mg, 50%, >98% de); R_f 0.07 (pentane/Et_2O, 25:1); $[\alpha]^{22}_D$ +1.7 (*c* 0.3 in $CHCl_3$); ν_{max} (film) 1729 (C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, s, *Me*CMe), 1.36 (3H, d, *J* 7.0, C(α)*Me*), 1.40 (3H, s, MeC*Me*), 1.44 (9H, s, CMe_3), 2.12–2.22 (2H, m, C(2)H_2), 3.75 (2H, app d, *J* 4.2, NCH_2), 3.79 (1H, app q, *J* 6.0, C(3)*H*), 3.92 (1H, q, *J* 7.0, C(α)*H*), 4.18 (1H, app t, *J* 6.0, C(4)*H*), 4.59 (1H, app t, *J* 7.6, C(5)*H*), 5.30 (1H, app d, *J* 10.0, C(7)H_A), 5.37 (1H, app d, *J* 17.1, C(7)H_B), 5.95 (1H, ddd, *J* 17.1, 10.0, 7.6, C(6)*H*), 7.22–7.34 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 15.3 (C(α)*Me*), 25.1, 27.5 (CMe_2), 28.1 (CMe_3), 36.0 (*C*(2)), 50.2 (NCH_2), 54.3 (*C*(3)), 59.1 (*C*(α)), 78.8 (*C*(4)), 79.7 (*C*(5)), 79.8 (*C*Me$_3$), 107.9 (*C*Me$_2$), 119.1 (*C*(7)), 126.6, 127.0 (*p-Ph*), 128.0, 128.1, 128.2 (*o-*, *m-Ph*), 134.7 (*C*(6)), 141.4, 142.8 (*i-Ph*), 171.5 (*C*(1)); *m/z* (APCI$^+$) 466 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{40}NO_4$ ([M + H]$^+$) requires 466.2957; found 466.2951.

Method B. Following *General Procedure 1*, BuLi (2.5 M in hexanes, 0.31 mL, 0.77 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (166 mg, 0.79 mmol) in THF (2 mL) at –40 °C, and **18** (100 mg, 0.39 mmol) in THF (2 mL) at –40 °C gave an 89:11 mixture of **20**:**21**. Purification *via* flash column chromatography (eluent pentane/Et_2O, 25:1) gave **20** as a colourless oil (69 mg, 38%, >98% de). Further elution gave **21** as a colourless oil (5 mg, 3%, >98% de); R_f 0.03 (pentane/Et_2O, 25:1); $[\alpha]^{26}_D$ +22.7 (*c* 1.05 in $CHCl_3$); ν_{max} (film) 1731 (C=O), 1602 (C=C); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 7.0, C(α)*Me*), 1.34 (3H, s, *Me*CMe), 1.50 (9H, s, CMe_3), 1.53 (3H, s, MeC*Me*), 1.95 (1H, dd, *J* 14.9, 2.8, C(2)H_A), 2.23 (1H, dd, *J* 15.0, 10.0, C(2)H_B), 3.49 (1H, app td, *J* 10.0, 2.8, C(3)*H*), 3.84 (1H, d, *J* 15.4, NCH_A), 4.05 (1H, d, *J* 15.4, NCH_B), 4.18 (1H, dd, *J* 10.0, 5.4, C(4)*H*), 4.25 (1H, dd, *J* 8.8, 5.4, C(5)*H*), 4.31 (1H, q, *J* 7.0, C(α)*H*), 5.11–5.19 (2H, m, C(7)H_2), 5.67 (1H, ddd, *J* 17.0, 9.3, 8.8, C(6)*H*), 7.20–7.33 (7H, m, *Ph*), 7.44–7.47 (3H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.4 (C(α)*Me*), 25.5 (*Me*CMe), 28.2 (CMe_3), 28.3 (MeC*Me*), 37.6 (*C*(2)), 50.1 (NCH_2), 55.3 (*C*(3)), 61.8 (*C*(α)), 78.8 (*C*(4)), 79.7 (*C*(5)), 80.3 (*C*Me$_3$), 108.4 (*C*Me$_2$), 119.0 (*C*(7)), 126.4, 126.7 (*p-Ph*), 127.8, 127.9, 128.0, 128.5 (*o-*, *m-Ph*), 134.2 (*C*(6)), 142.8, 145.0 (*i-Ph*), 170.7 (*C*(1)); *m/z* (ESI$^+$) 466 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{40}NO_4$ ([M + H]$^+$) requires 466.2957; found 466.2951.

Method C. Following *General Procedure 1*, BuLi (2.5 M in hexanes, 0.31 mL, 0.77 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (166 mg, 0.79 mmol) in Et_2O (2 mL) at –40 °C and **18** (100 mg, 0.39 mmol) in Et_2O (2 mL) at –40 °C gave a 4:91:5 mixture of **19**:**20**:**21**. Purification *via* flash column chromatography (eluent pentane/Et_2O, 25:1) gave **20** as a colourless oil (105 mg, 57%, >98% de). Further elution gave **21** as a colourless oil (9 mg, 5%, >98% de).

Method D. Following *General Procedure 1*, BuLi (2.5 M in hexanes, 0.24 mL, 0.61 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (133 mg, 0.63 mmol) in THF (2 mL) at –20 °C and **18** (100 mg, 0.39 mmol) in THF (2 mL) at –20 °C gave an 84:16 mixture of **20**:**21**. Purification *via* flash column chromatography (eluent pentane/Et_2O, 25:1) gave **20** as a colourless oil (71 mg, 40%, >98% de). Further elution gave a mixture of **20**:**21** (32 mg, 18%).

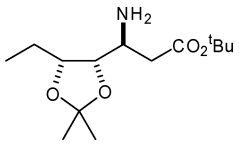
Method E. Following *General Procedure 1*, BuLi (2.2 M in hexanes, 0.35 mL, 0.77 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (166 mg, 0.79 mmol) in Et_2O (2 mL) at –20 °C and **18** (100 mg, 0.39 mmol) in Et_2O (2 mL) at –20 °C gave a 93:7 mixture of **20**:**21**. Purification *via* flash column chromatography (eluent pentane/Et_2O, 25:1) gave **20** as a colourless oil (128 mg, 70%, >98% de).

X-ray crystal structure determination for 21

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-*Kα* 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.[25]

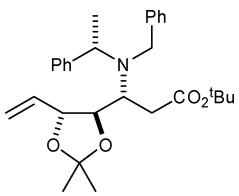
X-ray crystal structure data for **21** [$C_{29}H_{39}NO_4$]: M = 465.63, orthorhombic, space group $P\,2_1\,2_1\,2_1$, a = 11.5712(2) Å, b = 13.9737(2) Å, c = 17.0380(2) Å, V = 2754.92(7) Å^3, Z = 4, μ = 0.074 mm^{-1}, colourless block, crystal dimensions = 0.2 × 0.2 × 0.2 mm^3. A total of 3491 unique reflections were measured for 5 < θ < 27 and 2932 reflections were used in the refinement. The final parameters were wR_2 = 0.040 and R_1 = 0.032 [I>3σ(I)]. CCDC 668996.†

tert-Butyl (3*S*,4*S*,5*R*)-3-amino-4,5-*O*-isopropylidene-heptanoate 24



Following *General Procedure 2*, **20** (200 mg, 0.43 mmol), $Pd(OH)_2$/C (50 mg) and H_2 (5 atm) in MeOH (5 mL) gave **24** as a colourless oil (110 mg, 94%, >98% de); $[\alpha]^{25}_D$ +19.4 (*c* 1.2 in $CHCl_3$); ν_{max} (film) 3390, 3322 (N–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.01 (3H, t, *J* 7.5, C(7)H_3), 1.31 (3H, s, *Me*CMe), 1.40 (3H, s, MeC*Me*), 1.44 (9H, s, CMe_3), 1.48–1.65 (2H, m, C(6)H_2), 2.20 (1H, dd, *J* 16.2, 9.0, C(2)H_A), 2.71 (1H, dd, *J* 16.2, 2.7, C(2)H_B), 3.20 (1H, app td, *J* 9.0, 2.7, C(3)*H*), 3.80 (1H, dd, *J* 9.0, 5.6, C(4)*H*), 4.03–4.08 (1H, m, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 10.6 (*C*(7)), 22.7 (*C*(6)), 25.8 (*Me*CMe), 28.1 (CMe_3, MeC*Me*), 41.6 (*C*(2)), 47.9 (*C*(3)), 79.3 (*C*(5)), 80.6 (*C*(4)), 80.9 (*C*Me$_3$), 107.7 (*C*Me$_2$), 171.9 (*C*(1)); *m/z* (ESI$^+$) 274 ([M + H]$^+$, 100%), 218 (18); HRMS (ESI$^+$) $C_{14}H_{28}NO_4$ ([M + H]$^+$) requires 274.2018; found 274.2013.

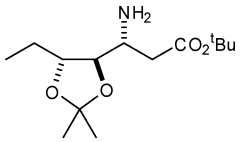
tert-Butyl (3*R*,4*R*,5*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-*O*-isopropylidene-hepta-6-enoate 34



Following *General Procedure 1*, BuLi (2.5 M in hexanes, 0.24 mL, 0.60 mmol), (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (131 mg, 0.62 mmol) in THF (2 mL) at –78 °C, and **33** (99 mg, 0.39 mmol) in THF (2 mL) at –78 °C, gave **34** in >98% de. Purification *via*

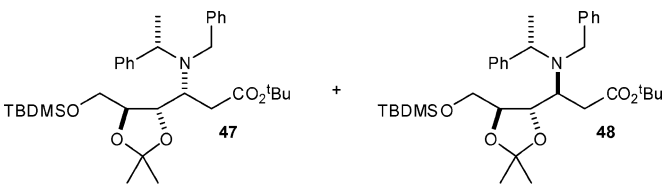
flash column chromatography (eluent pentane/Et_2O, 25:1) gave **34** as a colourless oil (138 mg, 76%, >98% de); $[\alpha]^{20}_D$ +9.4 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 1728 (C=O), 1602 (C=C); δ_H (500 MHz, $CDCl_3$) 1.39 (3H, s, *Me*CMe), 1.40 (3H, s, MeC*Me*), 1.41 (3H, obsc d, C(α)*Me*), 1.44 (9H, s, CMe_3), 2.15 (1H, dd, *J* 15.9, 4.7, C(2)H_A), 2.36 (1H, dd, *J* 15.9, 6.9, C(2)H_B), 3.66 (1H, d, *J* 14.5, NCH_A), 3.68–3.72 (1H, m, C(3)*H*), 3.82 (1H, d, *J* 14.5, NCH_B), 3.94 (1H, q, *J* 6.9, C(α)*H*), 3.97 (1H, dd, *J* 8.3, 3.9, C(4)*H*), 4.14 (1H, app t, *J* 6.9, C(5)*H*), 5.29 (1H, app d, *J* 10.3, C(7)H_A), 5.39–5.43 (1H, m, C(7)H_B), 5.88–5.95 (1H, m, C(6)*H*), 7.23–7.39 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.8 (C(α)*Me*), 26.8, 26.9 (CMe_2), 28.0 (CMe_3), 33.9 (*C*(2)), 51.0 (NCH_2), 54.0 (*C*(3)), 57.6 (*C*(α)), 79.9 (*C*(5)), 80.8 (*C*(4)), 82.5 (*C*Me_3), 108.9 (*C*Me_2), 118.4 (*C*(7)), 126.6, 126.8 (*p-Ph*), 127.9, 128.0, 128.4, 128.5 (*o-*, *m-Ph*), 135.9 (*C*(6)), 140.8, 142.8 (*i-Ph*), 171.7 (*C*(1)); *m/z* (ESI$^+$) 466 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{40}NO_4$ ([M + H]$^+$) requires 466.2957; found 466.2953.

tert-Butyl (3*R*,4*R*,5*R*)-3-amino-4,5-*O*-isopropylidene-heptanoate 37



Following *General Procedure 2*, **34** (75 mg, 0.16 mmol), $Pd(OH)_2/C$ (35 mg) and H_2 (5 atm) in MeOH (5 mL) gave **37** as a colourless oil (36 mg, 83%, >98% de); $[\alpha]^{23}_D$ +27.7 (*c* 0.8 in $CHCl_3$); ν_{max} (film) 3389 (N – H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.01 (3H, t, *J* 7.5, C(7)H_3), 1.37 (6H, app s, CMe_2), 1.45 (9H, s, CMe_3), 1.48–1.61 (1H, m, C(6)H_A), 1.64–1.73 (1H, m, C(6)H_B), 2.23 (1H, dd, *J* 15.8, 9.7, C(2)H_A), 2.55 (1H, app d, *J* 15.8, C(2)H_B), 3.26 (1H, br s, C(3)*H*), 3.57 (1H, app t, *J* 5.5, C(4)*H*), 3.83 (1H, app td, *J* 7.7, 3.6, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 10.3 (*C*(7)), 27.2 (*C*(6)), 27.3, 27.4 (CMe_2), 28.1 (CMe_3), 40.0 (*C*(2)), 50.3 (*C*(3)), 79.7 (*C*(5)), 80.8 (*C*(4)), 83.5 (*C*Me_3), 108.3 (*C*Me_2), 171.7 (*C*(1)); *m/z* (ESI$^+$) 274 ([M + H]$^+$, 100%), 218 (75); HRMS (ESI$^+$) $C_{14}H_{28}NO_4$ ([M + H]$^+$) requires 274.2018; found 274.2013.

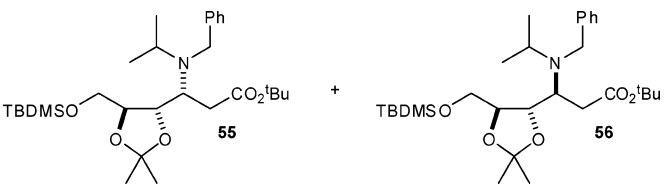
tert-Butyl (3*R*,4*S*,5*R*,α*S*)- and (3*S*,4*S*,5*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-*O*-isopropylidene-6-(*tert*-butyldimethylsilyloxy)hexanoate (3*R*,4*S*,5*R*,α*S*)-47 and (3*S*,4*S*,5*R*,α*S*)-48



Method A. Following *General Procedure 1*, BuLi (1.6 M in hexanes, 0.56 mL, 0.41 mmol), (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (89 μL, 0.43 mmol) in THF (10 mL) at –78 °C, and **46** (100 mg, 0.27 mmol) in THF (5 mL) at –78 °C gave **47** in >98% de. Purification *via* flash column chromatography (eluent 30–40°C petrol, increased to 30–40 °C petrol/Et_2O, 50:1) gave **47** as a colourless oil that solidified on standing (107 mg, 69%, >98% de); mp 44–45 °C; $[\alpha]^{21}_D$ –1.5 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 1728 (C=O); δ_H (400 MHz, $CDCl_3$), 0.10 (6H, s, SiMe_2), 0.94 (9H, s, SiCMe_3), 1.25–1.39 (9H, m, CMe_2, C(α)*Me*), 1.45 (9H, s, OCMe_3), 1.70 (1H, dd, *J* 15.2, 2.8, C(2)H_A), 2.44 (1H, dd, *J* 15.2, 10.6, C(2)H_B), 3.50–3.58 (2H, m, C(3)*H*, NCH_A), 3.63 (1H, dd, *J* 10.9, 2.1, C(6)H_A), 3.81–3.85 (2H, m, C(6)H_B, C(α)*H*), 4.07 (1H, dd, *J* 7.9, 2.8 C(4)*H*), 4.34 (1H, d, *J* 14.7, NCH_B), 4.53–4.55 (1H, m, C(5)*H*), 7.22–7.40 (8H, m, *Ph*), 7.51 (2H, d, *J* 7.5, *Ph*); δ_C (100 MHz, $CDCl_3$) –5.5, –5.3 (SiMe_2), 18.5 (SiCMe$_3$), 19.9 (C(α)*Me*), 25.9 (SiCMe_3), 26.3, 27.1 (CMe_2), 28.1 (OCMe_3), 34.2 (*C*(2)), 50.8 (*C*(α)), 53.0 (NCH_2), 57.6 (*C*(3)), 63.2 (*C*(6)), 77.7, 80.0 (*C*(4), *C*(5)), 80.2 (O*C*Me$_3$), 108.2 (*C*Me$_2$), 126.5, 127.1 (*p-Ph*), 128.0, 128.1, 128.2, 128.2 (*o-*, *m-Ph*), 141.5, 141.3 (*i-Ph*), 171.5 (*C*(1)); *m/z* (ESI$^+$) 584 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{54}NO_5Si$ ([M + H]$^+$) requires 584.3771; found 584.3776.

Method B. Following *General Procedure 1*, BuLi (1.6 M in hexanes, 0.52 mL, 0.83 mmol), (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (0.18 mL, 0.86 mmol) in Et_2O (5 mL) at –20 °C, and **46** (200 mg, 0.54 mmol) in Et_2O (5 mL) at –20 °C gave a 63:37 mixture of **47**:**48**. Purification *via* flash column chromatography (eluent 30–40 °C petrol, increased to 30–40 °C petrol/Et_2O, 50:1) gave **47** as a colourless oil (187 mg, 60%, >98% de). Further elution gave **48** as a colourless oil (64 mg, 11%, >98% de); $[\alpha]^{22}_D$ –51.0 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 0.08 (3H, s, *Me*SiMe), 0.12 (3H, s, MeSi*Me*), 0.94 (9H, s, SiCMe_3), 1.24 (3H, s, *Me*CMe), 1.29 (3H, s, MeC*Me*), 1.37 (3H, d, *J* 7.07, C(α)*Me*), 1.51 (9H, s, OCMe_3), 2.47 (1H, dd, *J* 15.7, 6.1, C(2)H_A), 2.64 (1H, dd, *J* 15.7, 5.4, C(2)H_B), 3.11–3.18 (1H, m, C(5)*H*), 3.41–3.57 (3H, m, C(3)*H*, C(6)H_2), 3.75 (1H, d, *J* 14.2, NCH_A), 3.88 (1H, d, *J* 14.2, NCH_B), 3.92–4.00 (2H, m, C(4)*H*, C(α)*H*), 7.19–7.37 (8H, m, *Ph*), 7.44–7.47 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) –5.2, –5.1 (SiMe_2), 15.5 (SiCMe$_3$), 18.5 (C(α)*Me*), 26.1 (SiCMe_3), 26.9, 27.1 (CMe_2), 29.2 (OCMe_3), 35.5 (*C*(2)), 51.3 (NCH_2), 54.9 (*C*(3)), 57.3 (*C*(α)), 63.0 (*C*(6)), 77.7 (*C*(4)), 80.2 (*C*(5)), 80.4 (O*C*Me$_3$), 108.5 (*C*Me$_2$), 126.8, 127.0 (*p-Ph*), 128.0, 128.2, 129.0 (*o-*, *m-Ph*), 141.2, 143.7 (*i-Ph*), 172.2 (*C*(1)); *m/z* (ESI$^+$) 548 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{54}NO_5Si$ ([M + H]$^+$) requires 584.3771; found 584.3776.

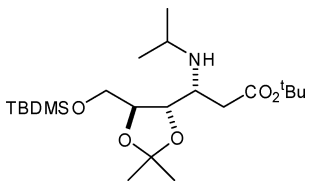
tert-Butyl (3*R*,4*S*,5*R*)- and (3*S*,4*S*,5*R*)-3-(*N*-benzyl-*N*-isopropylamino)-4,5-*O*-isopropylidene-6-(*tert*-butyldimethylsilyloxy)hexanoate (3*R*,4*S*,5*R*)-55 and (3*S*,4*S*,5*R*)-56



Following *General Procedure 1*, BuLi (1.6 M in hexanes, 1.3 mL, 2.08 mmol), *N*-benzyl-*N*-isopropylamine (3.53 mL, 2.14 mmol) in THF (10 mL) at –78 °C, and **46** (500 mg, 1.34 mmol) in THF (10 mL) at –78 °C gave a 25:75 mixture of **55**:**56**. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 100:1, increased to 50:1) gave **55** as a colourless oil (102 mg, 15%, >98% de); $[\alpha]^{18}_D$ +4.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 0.03 (6H, s, SiMe_2), 0.88 (9H, s, SiCMe_3), 1.01 (3H, d, *J* 6.6, *Me*CHMe), 1.08 (3H, d, *J* 6.6, MeCH*Me*), 1.32

(6H, s, CMe_2), 1.48 (9H, s, OCMe_3), 2.62–2.74 (2H, m, C(2)H_2), 3.07–3.18 (1H, m, CHMe$_2$), 3.22–3.32 (2H, m, C(3)H, C(6)H_A), 3.65 (1H, d, J 13.9, NCH_A), 3.64 (1H, dd, J 11.4, 3.8, C(6)H_B), 4.01 (1H, dd, J 8.1, 3.3, C(4)H), 4.09 (1H, d, J 13.9, NCH_B), 4.21–4.29 (1H, m, C(5)H), 7.17–7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) −5.5, −5.4 (SiMe_2), 17.3 (SiCMe$_3$), 18.5, 22.5 (CHMe_2), 26.0 (SiCMe_3), 26.3, 27.2 (CMe_2), 28.1 (OCMe_3), 36.0 (C(2)), 49.0 (CHMe$_2$), 52.0 (NCH_2), 52.0 (C(3)), 62.5 (C(6)), 77.8 (C(5)), 79.7 (OCMe$_3$), 80.3 (C(4)), 107.9 (CMe$_2$), 126.5 (*p-Ph*), 128.0, 128.7 (*o-*, *m-Ph*), 141.5 (*i-Ph*), 172.0 (C(1)); m/z (ESI$^+$) 522 ([M + H]$^+$, 100%), 466 (98); HRMS (ESI$^+$) $C_{33}H_{52}NO_5Si$ ([M + H]$^+$) requires 522.3615; found 522.3609. Further elution gave **56** as a colourless oil (331 mg, 48%, >98% de); $[\alpha]^{18}_D$ −124 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 0.10 (6H, s, SiMe_2), 0.93 (9H, s, SiCMe_3), 1.02–1.09 (6H, m, CHMe_2), 1.34 (3H, s, *Me*CMe), 1.37 (3H, s, MeC*Me*), 1.50 (9H, s, OCMe_3), 2.41 (1H, dd, J 15.4, 5.3, C(2)H_A), 2.63 (1H, dd, J 15.4, 7.2, C(2)H_B), 2.98–2.99 (1H, m, CHMe$_2$), 3.46–3.48 (1H, m, C(3)H), 3.63–3.71 (2H, m, C(5)H, NCH_A), 3.73–3.86 (3H, m, C(6)H_2, NCH_B), 4.22 (1H, dd, J 8.1, 4.1, C(4)H), 7.19–7.24 (1H, m, *Ph*), 7.29 (2H, t, J 7.5 *Ph*), 7.34–7.39 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) −5.3, −5.2 (SiMe_2), 18.5 (SiCMe$_3$), 19.8, 20.2 (CHMe_2), 26.0 (SiCMe_3), 27.1, 27.2 (CMe_2), 28.2 (OCMe_3), 35.5 (C(2)), 48.4 (CHMe$_2$), 50.1 (NCH_2), 55.0 (C(3)), 63.2 (C(6)), 78.1 ((C(4)), 80.0 (OCMe$_3$), 80.7 (C(5)), 108.7 (CMe$_2$), 126.6 (*p-Ph*), 128, 128.7 (*o-*, *m-Ph*), 141.2 (*i-Ph*), 172.4 (C(1)); m/z (ESI$^+$) 522 ([M + H]$^+$, 100%), 466 (92); HRMS (ESI$^+$) $C_{33}H_{52}NO_5Si$ ([M + H]$^+$) requires 522.3615; found 522.3609.

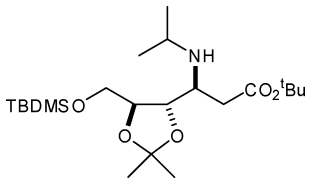
tert-Butyl (3*R*,4*S*,5*R*)-3-(*N*-isopropylamino)-4,5-*O*-isopropylidene-6-(*tert*-butyldimethylsilyloxy)hexanoate 57



From 47. Following *General Procedure 3*, Pd(OH)$_2$/C (40 mg) and **47** (78 mg, 0.12 mmol) in MeOH/acetone (v:v 9:1, 2 mL) under H_2 (1 atm) gave **57** as a colourless oil (42 mg, 74%, >98% de); $[\alpha]^{19}_D$ −20.5 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 1729 (C=O); δ_H (500 MHz, $CDCl_3$) 0.08 (6H, s, SiMe_2), 0.91 (9H, s, SiCMe_3), 1.00 (3H, d, J 6.0, *Me*CHMe), 1.05 (3H, d, J 6.3, MeCH*Me*), 1.38 (3H, s, *Me*CMe), 1.41 (3H, s, MeC*Me*), 1.46 (9H, s, OCMe_3), 2.35 (1H, dd, J 14.8, 6.6, C(2)H_A), 2.48–2.51 (1H, m, C(2)H_B), 2.87–2.94 (1H, m, CHMe$_2$), 3.19–3.22 (1H, m, C(3)H), 3.75 (2H, app t, J 4.4, C(6)H_2), 3.96 (1H, dd, J 7.7, 3.3, C(4)H), 4.07–4.10 (1H, m, C(5)H); δ_C (125 MHz, $CDCl_3$) −5.4, −5.3 (SiMe_2), 18.4 (SiCMe$_3$), 22.8, 24.0 (CHMe_2), 26.0 (SiCMe_3), 27.2 (CMe_2), 28.1 (OCMe_3), 38.8 (C(2)), 45.6 (CHMe$_2$), 52.2 (C(3)), 64.1 (C(6)), 77.8 (C(4)), 80.3 (OCMe$_3$), 80.4 (C(5)), 108.7 (CMe$_2$), 171.1 (C(1)); m/z (ESI$^+$) 432 ([M + H]$^+$, 26%), 376 (82), 318 (100); HRMS (ESI$^+$) $C_{26}H_{45}NO_5Si$ ([M + H]$^+$) requires 432.3145; found 432.3141.

From 55. Following *General Procedure 2*, Pd(OH)$_2$/C (42 mg) and **55** (83 mg, 0.16 mmol) in EtOAc (5 mL) under H_2 (1 atm) gave **57** as a colourless oil (64 mg, 93%, >98% de).

tert-Butyl (3*S*,4*S*,5*R*)-3-(*N*-isopropylamino)-4,5-*O*-isopropylidene-6-(*tert*-butyldimethylsilyloxy)hexanoate 58



From 48. Following *General Procedure 3*, Pd(OH)$_2$/C (40 mg) and **48** (26 mg, 0.12 mmol) in MeOH/acetone (v:v 9:1, 2 mL) under H_2 (1 atm) gave **58** as a colourless oil (15 mg, 79%, >98% de); $[\alpha]^{19}_D$ −3.8 (*c* 3.2 in $CHCl_3$); ν_{max} (film) 1729 (C=O); δ_H (500 MHz, $CDCl_3$) 0.08 (6H, s, SiMe_2), 0.90 (9H, s, SiCMe_3), 1.03 (6H, app t, J 6.3, CHMe_2), 1.38 (3H, s, *Me*CMe), 1.39 (3H, s, MeC*Me*), 1.46 (9H, s, OCMe_3), 2.38 (1H, dd, J 15.1, 6.6, C(2)H_A), 2.53 (1H, dd, J 15.1, 4.4, C(2)H_B), 2.89–3.98 (1H, m, CHMe$_2$), 3.11–3.16 (1H, m, C(3)H), 3.76–3.86 (3H, m, C(4)H, C(6)H_2), 3.91–3.96 (1H, m, C(5)H); δ_C (125 MHz, $CDCl_3$) −5.4, −5.3 (SiMe_2), 18.5 (SiCMe$_3$), 22.9, 23.7 (CHMe_2), 26.0 (SiCMe_3), 27.1, 27.2 (CMe_2), 28.2 (OCMe_3), 36.6 (C(2)), 45.6 (CHMe$_2$), 54.3 (C(3)), 64.5 (C(6)), 79.4 (C(4)), 80.1 (C(5)), 80.1 (OCMe$_3$), 108.9 (CMe$_2$), 171.9 (C(1)); m/z (ESI$^+$) 432 ([M + H]$^+$, 10%), 376 (58), 318 (100); HRMS (ESI$^+$) $C_{26}H_{45}NO_5Si$ ([M + H]$^+$) requires 432.3145; found 432.3142.

From 56. Following *General Procedure 2*, Pd(OH)$_2$/C (77 mg) and **56** (153 mg, 0.29 mmol) in EtOAc (5 mL) under H_2 (1 atm) gave **58** as a colourless oil (82 mg, 65%, >98% de).

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