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Doubly diastereoselective conjugate additions of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to enantiopure ε-*O*-protected α,β-unsaturated esters derived from D-ribose

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ABSTRACT

Enantiopure ε-*O*-silyloxy- and ε-*O*-benzyloxy-α,β-unsaturated esters derived from D-ribose, each containing a *cis*-dioxolane unit, display excellent (⩾95:5 dr) levels of diastereofacial directing ability upon conjugate addition of achiral lithium *N*-benzyl-*N*-isopropylamide. In contrast to the corresponding enantiopure ε-*O*-silyloxy-α,β-unsaturated ester derived from L-tartaric acid, which contains a *trans*-dioxolane unit, the conjugate additions of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to its *cis*-configured counterpart result in doubly diastereoselective 'matched' and 'mismatched' reaction pairings in which the inherent reagent control serves to augment or oppose, respectively, the established substrate diastereocontrol.

1. Introduction

The interaction of any two chiral species (e.g., a reagent and a substrate) results in the phenomenon of double asymmetric induction to form one or more new stereogenic centres. Masamune et al. qualified double asymmetric induction for the interaction of two enantiopure species in terms of 'matched' and 'mismatched' reaction pairings. In these scenarios, the individual stereocontrolling preferences of the reagent and substrate may either promote formation of the same or different diastereoisomers of the product. If the stereocontrolling ability of the two reacting species are able to operate independently of each other, then their use in combination results in either (i) an augmentation of diastereocontrol in the 'matched' reaction pairing, often producing synthetically useful levels of selectivity; or (ii) opposition of diastereocontrol in the 'mismatched' reaction pairing, often resulting in low diastereoselectivity. In the latter case, the element (reagent or substrate) with the dominant stereodirecting ability dictates the identity of the major diastereoisomeric product, although mixtures are often produced.[1] Thus, when planning deployment of double asymmetric induction as a synthetic strategy, it is often therefore desirable to first garner an understanding of the inherent reagent and substrate control independently, before their use in combination. This approach has the benefit of allowing ready identification of systems where the two controlling elements do not act independently, as in these cases it is often possible to extract useful mechanistic information from the results.

As part of an ongoing research programme directed towards the development of de novo asymmetric syntheses of imino[2] and amino[3] sugars, we have investigated double asymmetric induction upon conjugate addition of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **2**[4] to a range of enantiopure α,β-unsaturated esters containing *cis*- and *trans*-dioxolane units.[5–7] We have optimised a strategy to independently evaluate the levels of diastereocontrol offered by the enantiopure α,β-unsaturated ester alone by employing the conjugate addition reaction of an achiral lithium amide that closely mimics the reactivity of **2**, viz. lithium *N*-benzyl-*N*-isopropylamide **1**,[5] before determining the nature of the 'matched' and 'mismatched' reaction pairings of the enantiopure α,β-unsaturated ester with the antipodes of **2**. When this strategy was applied to enantiopure α,β-unsaturated ester **3** (containing a *trans*-dioxolane unit), the (singly) diastereoselective, substrate directed conjugate addition of **1** gave **4** as the major diastereoisomer (75:25 dr), which was isolated in 48% yield and >99:1 dr. From this substrate control, combined with the known diastereofacial preferences of the antipodes of **2**,[4] it was anticipated that the conjugate addition of (*R*)-**2** to **3** would represent the doubly diastereoselective 'matched' case. However, this reaction resulted in the production of a 70:30 mixture of diastereoisomers **6** and **7** which were isolated in 60% and 8% yield, respectively, as single diastereoisomers (>99:1 dr) in each case. Meanwhile, conjugate

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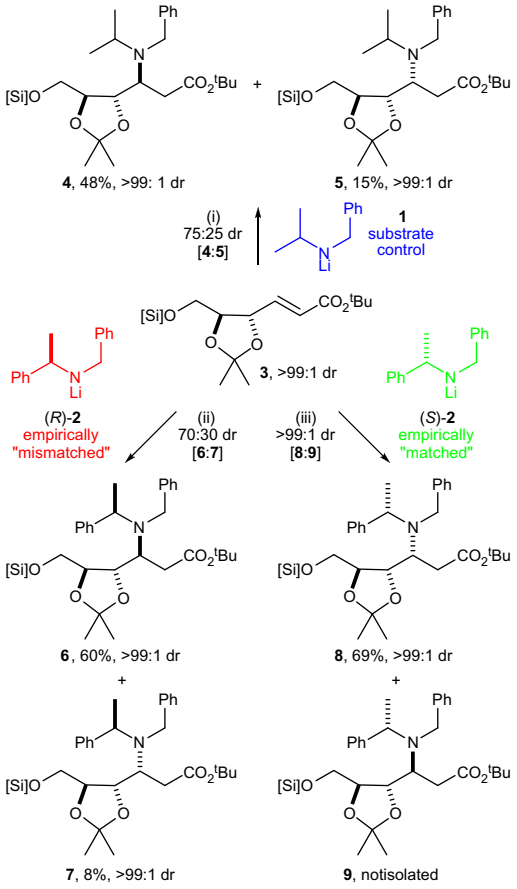
addition of (*S*)-**2** to **3** gave **8** in >99:1 dr, which was isolated in 69% yield. Thus, whilst significant levels of enantiorecognition between the antipodes of **2** and **3** are observed, these empirically 'matched' and 'mismatched' reaction pairings are in contravention to those anticipated from the substrate control elicited upon conjugate addition of **1** to **3**, demonstrating that the established, individual stereocontrolling preferences of the reagent and substrate do not act independently in these cases (Scheme 1).

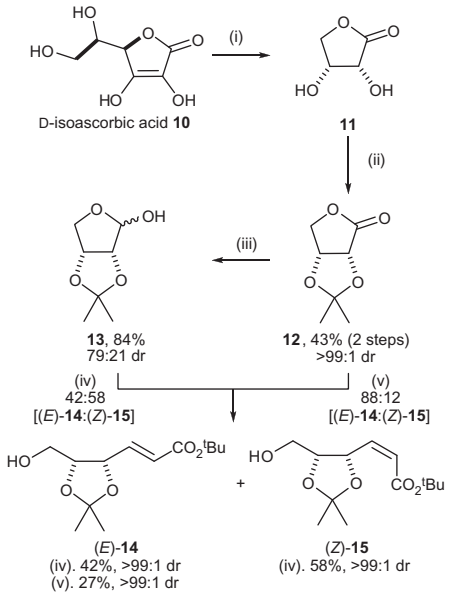


Scheme 1. Reagents and conditions: (i) **1**, THF, −78 °C, 2 h; (ii) (*R*)-**2**, THF, −78 °C, 2 h; (iii) (*S*)-**2**, THF, −78 °C, 2 h. [Si] = TBDMS.

In order to probe this behaviour further, we proposed to evaluate double asymmetric induction upon conjugate addition of the antipodes of **2** to the corresponding enantiopure ε-*O*-silyloxy- and ε-*O*-benzyloxy-α,β-unsaturated esters containing *cis*-dioxolane units, to determine the effects of the ε-*O*-protecting group and configuration of the dioxolane moiety on the diastereoselectivity of this reaction, and report herein the results of our investigations within this area.

2. Results and discussion

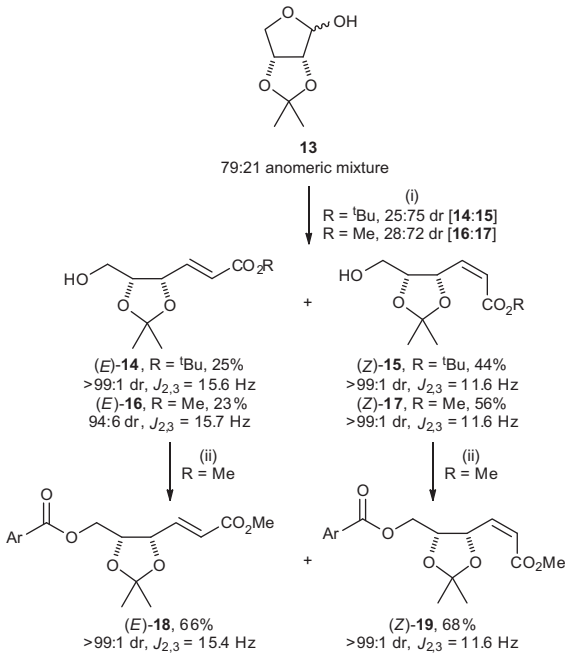
The preparation of the requisite *cis*-dioxolane containing (*E*)-α,β-unsaturated esters from commercially available D-isoascorbic acid **10** was initially evaluated. Treatment of **10** with basic aqueous H_2O_2 gave **11** and subsequent protection gave **12** in 43% isolated yield over the 2 steps.[8] Reduction of lactone **12** with DIBAL-H and in situ reaction of lactol **13** with the lithium anion of *tert*-butyl diethylphosphonoacetate in THF[9] gave an 88:12 mixture of (*E*)-**13** and (*Z*)-**14**, respectively, although the mass return (and hence the isolated yield) was low and unreacted *tert*-butyl diethylphosphonoacetate was present in the crude reaction mixture, indicating that the reaction was not proceeding to full conversion. A stepwise protocol was therefore examined. Reduction of lactone **12** with DIBAL-H gave lactol **13**[10] (79:21 anomeric mixture) in 84% yield. Unfortunately, olefination of lactol **13** under a range of literature conditions[11–15] resulted either in low mass return/isolated yield of the desired olefin product, or in production of a mixture of olefinic products within which the (*E*)-isomer **14** was the minor component. For example, treatment of **13** with $Ph_3P{=}CHCO_2{}^tBu$ in 1,4-dioxane[13] proceeded to full conversion to give a 42:58 mixture of (*E*)-**14** and (*Z*)-**15**, respectively, which were isolated in 42% and 58% yield after chromatography (Scheme 2).



Scheme 2. Reagents and conditions: (i) H_2O_2 (31.3% w/w aq), H_2O, Na_2CO_3, 0 °C, 30 min, then 40 °C, 1 h; (ii) $Me_2C(OMe)_2$, Me_2CO, TsOH, $MgSO_4$, rt, 16 h; (iii) DIBAL-H, CH_2Cl_2, −78 °C, 3 h; (iv) $Ph_3P{=}CHCO_2{}^tBu$, 1,4-dioxane, 90 °C, 6 h, then 50 °C, 12 h; (v) DIBAL-H, THF, −78 °C to rt, 30 min, then −78 °C, then add $(EtO)_2P(O)CH_2CO_2{}^tBu$, BuLi, THF, −78 °C to rt, 16 h.

Independent treatment of lactol **13** (79:21 anomeric mixture) with $Ph_3P{=}CHCO_2{}^tBu$ and $Ph_3P{=}CHCO_2Me$ in CH_2Cl_2 at reflux, according to the procedure of Scharf et al.[11] gave mixtures of chromatographically separable olefin products (*E*)-**14** and (*Z*)-**15** (R = ^{t}Bu) in a 25:75 ratio, and (*E*)-**16** and (*Z*)-**17** (R = Me) in a 28:72 ratio, respectively (Scheme 3). Conversion of both (*E*)-**16** and (*Z*)-**17** to their corresponding *p*-nitrobenzoate esters (*E*)-**18** and (*Z*)-**19** allowed unambiguous determination of the (*E*)-olefin geometry within **18** by single crystal X-ray diffraction analysis (Fig. 1).[16] Hence, the olefin geometries within **16**, **17** and **19** were also unambiguously confirmed. The values of the ^{1}H NMR $^3J_{2,3}$ coupling constants of **14**–**19** were also diagnostic of the olefin geometries (Scheme 3). This stereochemical outcome is, however, in contrast to that of Scharf et al.[11] who report that treatment of lactol **13** with $Ph_3P{=}CHCO_2Me$ under identical conditions gives exclusively (*E*)-**16** (in 60% isolated yield). Comparison of spectroscopic data reveals that the product obtained by Scharf et al. is (*Z*)-**17**, and thus that their stereochemical assignment is in error. This error has previously been corrected by Gallos et al.[17] who reported that treatment of lactol **13** with $Ph_3P{=}CHCO_2Me$ and $PhCO_2H$ in THF at reflux gives a 29:71 mixture of (*E*)-**16** and (*Z*)-**17**.[18]

Given the problems encountered with this approach, an alternative strategy was envisaged. Alcohol **23** was prepared from



Scheme 3. Reagents and conditions: (i) $Ph_3P{=}CHCO_2R$, CH_2Cl_2, reflux, 3 days; (ii) ArCOCl, pyridine, rt, 28 h. [Ar=*p*-$C_6H_4NO_2$].

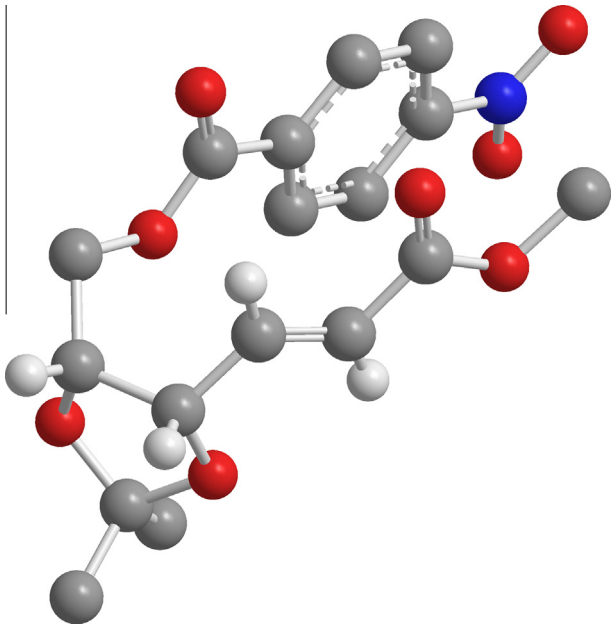
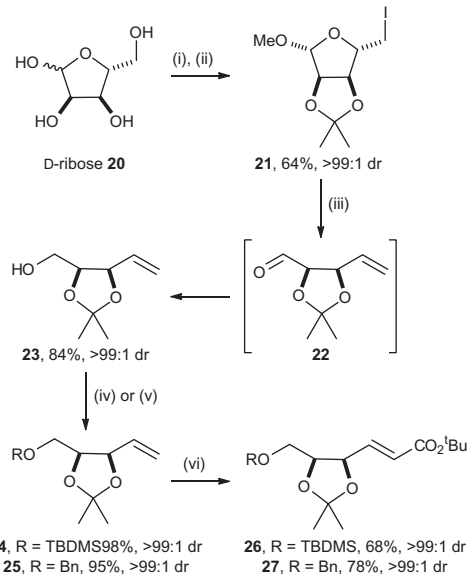


Figure 1. X-ray crystal structure of (4*S*,5*R*,*E*)-**18** (selected H atoms are omitted for clarity).

D-ribose **20** following our previously established route.[6] Treatment of D-ribose **20** with acetone and MeOH in the presence of conc HCl, followed by reaction with I_2 and PPh_3 gave iodide **21** in 64% yield. A one-pot transmetallation/ring-opening/reduction[19] was next performed upon treatment of **21** with BuLi (to give aldehyde **22**), followed by subsequent addition of DIBAL-H to the reaction flask to give alcohol **23** in 84% isolated yield. *O*-Silyl and *O*-benzyl protection of **23** gave **24** and **25**, respectively, with cross-metathesis mediated by Hoveyda–Grubbs II catalyst (optimised conditions) giving the corresponding (*E*)-configured α,β-unsaturated esters **26** ($^3J_{2,3}$ = 15.5 Hz) and **27** ($^3J_{2,3}$ = 15.5 Hz) as single diastereoisomers, in 36% and 40% overall yield from D-ribose **20**, respectively (Scheme 4).



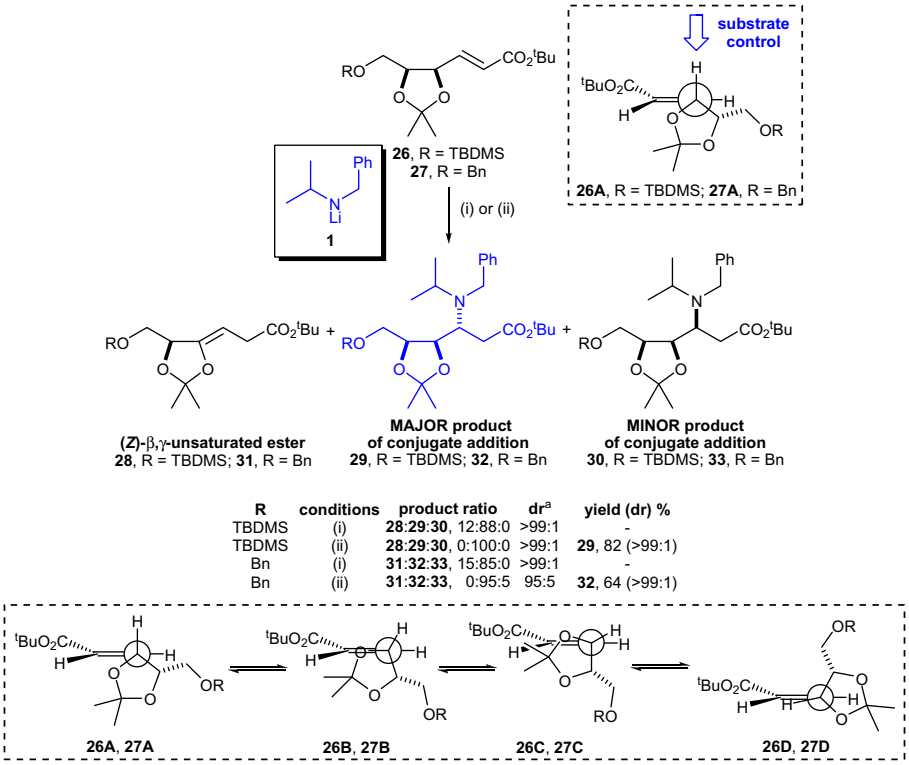
Scheme 4. Reagents and conditions: (i) acetone/MeOH (v/v, 1:1), conc HCl (a few drops), 60 °C, 1 h; (ii) imidazole, PPh_3, I_2, PhMe/MeCN (v/v, 5:1), 60 °C, 1 h; (iii) BuLi, THF, −78 °C, 2 h, then DIBAL-H, −78 °C to rt, 16 h; (iv) TBDMSCl, imidazole, DMAP, CH_2Cl_2, rt, 16 h; (v) NaH, THF, 0 °C, 45 min, then BnBr, rt, 16 h; (vi) Hoveyda–Grubbs II (10 mol%), *tert*-butyl acrylate, CH_2Cl_2, reflux, 24 h.

The inherent levels of substrate control offered by the enantiopure α,β-unsaturated esters **26** and **27** were initially evaluated by reaction with achiral lithium *N*-benzyl-*N*-isopropylamide **1**. When the reactions were run in THF at −78 °C, these (singly) diastereoselective reactions proceeded under the control of the substrate to give the corresponding β-amino esters **29** and **32** as the exclusive products of conjugate addition. However, in these cases the conjugate addition was accompanied by a competing γ-deprotonation reaction, resulting in formation of the corresponding (*Z*)-β,γ-unsaturated esters **28** and **31** after work-up. The configurations of the newly formed C=C double bonds within **28** and **31** were assigned by analogy to other reports concerning the kinetic deprotonation/reprotonation of conjugated enones,[20–25] and to our observations in a very closely related system.[5] Sewald et al. noted a difference in the reactivity of lithium *N*-trimethylsilyl-*N*-(α-methylbenzyl)amide in Et_2O as compared to THF during studies into its conjugate addition to enantiopure γ-alkoxy-α,β-unsaturated esters,[26] and we have noted that competing γ-deprotonation may be effectively suppressed when the reaction solvent is changed from THF to Et_2O.[5] The conjugate additions of **1** to **26** and **27** were conducted in Et_2O at −20 °C and gave β-amino ester **29** in >99:1 dr (isolated in 82% yield, >99:1 dr) in the former case, and β-amino ester **32** in 95:5 dr (isolated in 64% yield, >99:1 dr) in the latter case. The absolute configurations within β-amino esters **29**, **30**, **32** and **33** were subsequently established unambiguously via chemical correlation to a derivative of known absolute configuration (vide infra). The competing production of (*Z*)-configured β,γ-unsaturated esters in this type of reaction[5] is consistent with reactive conformation **A**, with the C(4)-hydrogen atom being well placed to undergo deprotonation; kinetic protonation of the resultant dienolate then gives **28** or **31**.[5,20–25] The substrate control in THF is also consistent with reactive conformation **A** (in which approach of the lithium amide reagent to C(3) from the 2*Re*,3*Re* face[27] would be expected to be favoured) [i.e., approach *syn* to the C(4)-hydrogen atom and opposite the bulky C(4)-alkoxyalkyl substituent, which provides significant shielding of the 2*Si*,3*Si* face[27]]. Although the origin of the difference in reactivity upon switching the reaction solvent to Et_2O is unclear, it could result from either a change of aggregation state of the lithium amide with

solvent,[28–30] or a subtle change in the reactive conformation of the α,β-unsaturated ester, for example to conformations **B** (identical to the preferred solid-state conformation of α,β-unsaturated ester **18**) or **C**,[6] in which the C(4)-alkoxyalkyl substituent is still able to shield the 2*Si*,3*Si* face[27] of the α,β-unsaturated system but the C(4)-hydrogen atom is no longer ideally placed for deprotonation by the lithium amide. It is interesting to note that conformation **D** (an expected, favourable ground-state conformation due to minimisation of allylic 1,3-strain) can be excluded as a reactive conformation by these data, as in this conformation the C(4)-alkoxyalkyl substituent provides shielding of the 2*Re*,3*Re* face[27] (Scheme 5).

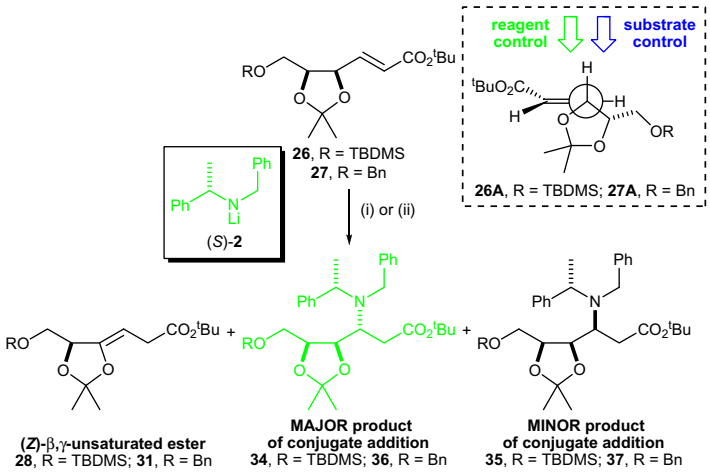
As **26** and **27** both display an inherent facial bias for conjugate addition of **1** to C(3) on the 2*Re*,3*Re* face[27] of the olefin, the conjugate additions of lithium amide (*S*)-**2** to **26** and **27** were anticipated to represent the doubly diastereoselective 'matched' reaction pairings, given the well established facial bias of (*S*)-**2** in its conjugate addition reactions to achiral α,β-unsaturated esters.[4] In accordance with this prediction, reaction of (*S*)-**2** with **26** gave β-amino ester **34** in >99:1 dr, whilst reaction with **27** gave β-amino ester **36** in 93:7 dr. It is noteworthy, however, that the level of diastereoselectivity observed for the addition of lithium amide (*S*)-**2** to **27** (i.e., 93:7 dr) is not as high as would be expected for a doubly diastereoselective 'matched' reaction when considering the very high levels of stereocontrol exerted by (*S*)-**2**.[4] This observation implies that the stereocontrol of the lithium amide **2** does not operate independently of the stereocontrol of the α,β-unsaturated ester **27**, with its normal mode of action being disrupted to some degree in this instance, potentially due to chelation of lithium by the polyoxygenated α,β-unsaturated ester **27**. The conjugate addition reaction was again accompanied by γ-deprotonation in THF at −78 °C, although in Et_2O at −20 °C this reaction was completely suppressed, allowing the isolation of **34** in 90% yield (>99:1 dr) and **36** in 79% yield (93:7 dr). The absolute configurations within **34** and **36** were subsequently established unambiguously by chemical correlation to a derivative of known absolute configuration (vide infra) and are in accord with those predicted by the transition state mnemonic that we have previously developed to rationalise the exceptional inherent diastereofacial bias of this class of lithium amide.[31] This is consistent with reaction of the α,β-unsaturated ester substrate in conformation **A** in THF, with independent substrate control and reagent control[4,31] in the case of **26** resulting in a highly selective reaction (Scheme 6).

We have previously observed very high levels of substrate control in closely related systems: in these cases it is the α,β-unsaturated ester and not the lithium amide reagent **2** which has the dominant stereocontrolling influence in the 'mismatched' reaction.[5–7] When reaction of (*R*)-**2** with **26** was run in THF at −78 °C, this gave (*Z*)-β,γ-unsaturated ester **28** as essentially the only product[32] which was isolated in 72% yield, whilst (*Z*)-β,γ-unsaturated ester **31** was formed as the major product of the reaction of (*R*)-**2** with **27**. These observations are consistent with γ-deprotonation being preferred over conjugate addition. Performing both the reactions in Et_2O at −20 °C led to suppression of the undesired γ-deprotonation pathway and gave an approximate 4:1 mixture of β-amino ester diastereoisomers **38** and **39**, and **40** and **41**, respectively, which proved separable by chromatography in both cases (Scheme 7). The relative configuration within **41** was unambiguously assigned by single crystal X-ray diffraction analysis (Fig. 2),[16] with the absolute (3*S*,4*R*,5*S*,α*R*)-configuration being assigned from the known configurations of the α-methylbenzyl stereocentre, and the C(4) and C(5)-stereogenic centres which were derived from D-ribose **20**. This analysis also allowed the unambiguous assignment of the absolute (3*R*,4*R*,5*S*,α*R*)-configuration within **40**. The absolute configurations within **38** and **39** were subsequently unambiguously established by chemical correlation to those within **40** and **41** (vide infra). With the lithium amide reagent (*R*)-**2** known to exhibit very high diastereocontrol upon conjugate addition to a range of achiral α,β-unsaturated esters (i.e., high reagent control)[4,31] and the enantiopure α,β-unsaturated esters **26** and **27** exhibiting very high diastereocontrol upon



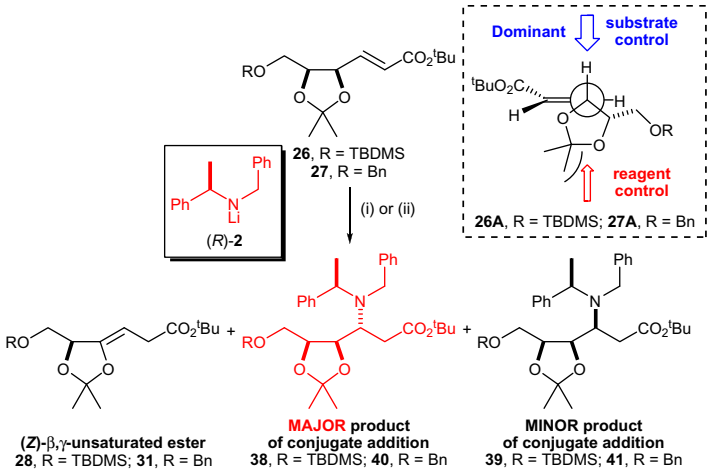
R	conditions	product ratio	dr[a]	yield (dr) %
TBDMS	(i)	**28**:**29**:**30**, 12:88:0	>99:1	-
TBDMS	(ii)	**28**:**29**:**30**, 0:100:0	>99:1	**29**, 82 (>99:1)
Bn	(i)	**31**:**32**:**33**, 15:85:0	>99:1	-
Bn	(ii)	**31**:**32**:**33**, 0:95:5	95:5	**32**, 64 (>99:1)

Scheme 5. Reagents and conditions: (i) **1**, THF, −78 °C, 2 h; (ii) **1**, Et_2O, −20 °C, 5 h. [a]Diastereoisomeric ratio of β-amino ester products.



R	conditions	product ratio	dr[a]	yield (dr) %
TBDMS	(i)	**28**:**34**:**35**, 25:75:0	>99:1	-
TBDMS	(ii)	**28**:**34**:**35**, 0:100:0	>99:1	**34**, 90 (>99:1)
Bn	(i)	**31**:**36**:**37**, 14:80:6	93:7	-
Bn	(ii)	**31**:**36**:**37**, 0:93:7	93:7	**36**, 79 (93:7)

Scheme 6. Reagents and conditions: (i) (*S*)-**2**, THF, −78 °C, 2 h; (ii) (*S*)-**2**, Et_2O, −20 °C, 5 h. [a]Diastereoisomeric ratio of β-amino ester products.



R	conditions	product ratio	dr[a]	yield (dr) %
TBDMS	(i)	**28**:**38**:**39**, 100:0:0	-	**28**, 72 (>99:1)
TBDMS	(ii)	**28**:**38**:**39**, 0:82:18	82:18	**38**, 58 (>99:1), **39**, 12 (>99:1)
Bn	(i)	**31**:**40**:**41**, 46:37:17	69:31	**40**, 29 (>99:1)
Bn	(ii)	**31**:**40**:**41**, 0:83:17	83:17	**40**, 44 (>99:1), **41**, 7 (>99:1)

Scheme 7. Reagents and conditions: (i) (*R*)-**2**, THF, −78 °C, 2 h; (ii) (*R*)-**2**, Et_2O, −20 °C, 5 h. [a]Diastereoisomeric ratio of β-amino ester products.

conjugate addition of achiral lithium amide **1** (i.e., high substrate control), it is impossible to predict *a priori* which will exert the dominant controlling influence in the 'mismatched' reaction pairings. However, the stereochemical outcomes from these conjugate addition reactions have shown that the stereocontrol of substrates **26** and **27** is dominant over the stereocontrol of the reagent (*R*)-**2**, consistent with our previous observations.[5–7]

In order to unambiguously establish the configurations within β-amino esters **29**, **30** and **32**–**39**, a series of hydrogenolytic *N*-debenzylation and reductive *N*-alkylation chemical correlation experiments was performed. For the ε-*O*-benzyl protected series, initial hydrogenolytic *N*-debenzylation of **40** [of known absolute (3*R*,4*R*,5*S*,α*R*)-configuration] gave an authentic sample of primary β-amino ester **42** in 42% yield and >99:1 dr. Similar treatment of **36** (93:7 dr) gave a sample of **42** in 81% yield and 93:7 dr (the major diastereoisomer being identical by ^1H and ^{13}C NMR spectroscopic analysis to the authentic sample). Next, reductive alkylation of **42** (>99:1 dr) using $NaBH_3CN$ and acetone gave an authentic sample of **43** in 61% yield and >99:1 dr. Finally, hydrogenolysis of **32** gave a sample of **43** in quantitative yield and >99:1 dr, identical by ^1H and ^{13}C NMR spectroscopic analysis to the authentic sample. Thus, from the known absolute (3*R*,4*R*,5*S*,α*R*)-configuration of **40**, the known absolute configurations of the C(4) and C(5) stereogenic centres (derived from D-ribose **20**) within **32** and **36**, and the known absolute configuration of the (*S*)-α-methylbenzyl stereocentre within **36**, the absolute configurations (3*R*,4*R*,5*S*)-**32** and (3*R*,4*R*,5*S*,α*S*)-**36** were unambiguously assigned, as well as the absolute configurations (3*S*,4*R*,5*S*)-**33** and (3*S*,4*R*,5*S*,α*S*)-**37** for the C(3)-epimers of **32** and **36**, respectively (Scheme 8).

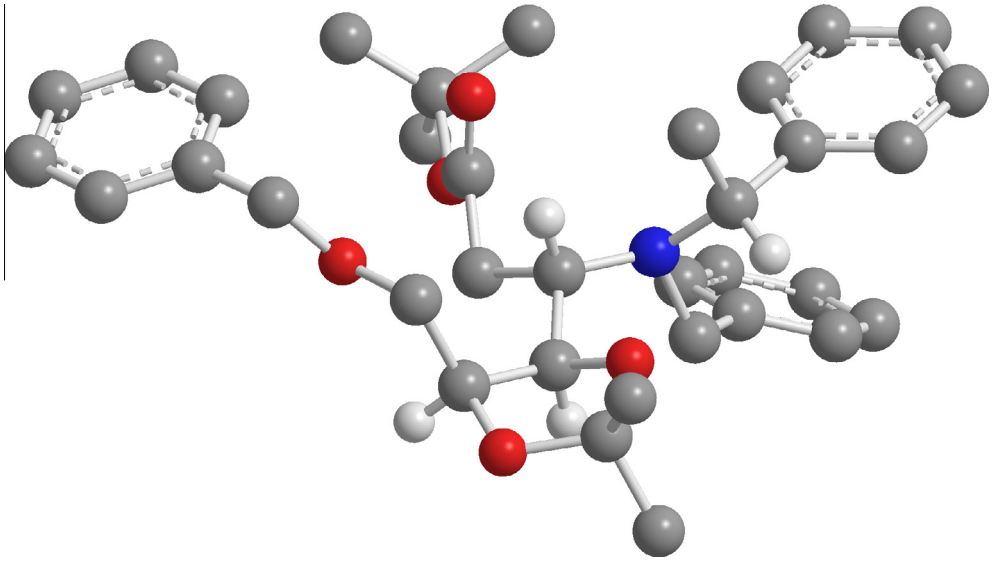
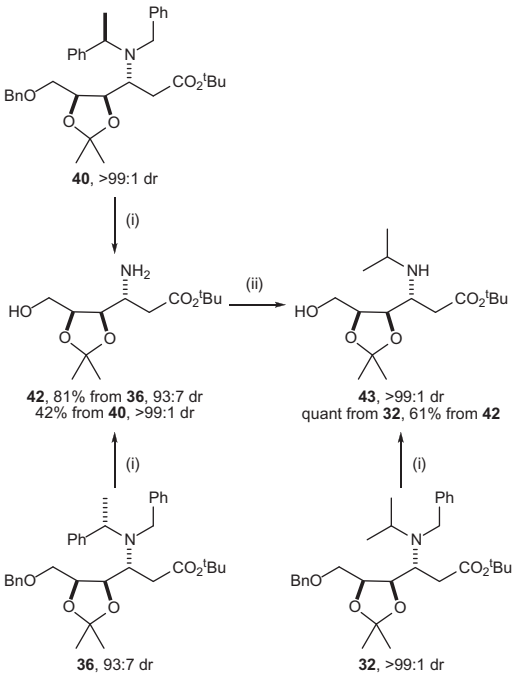
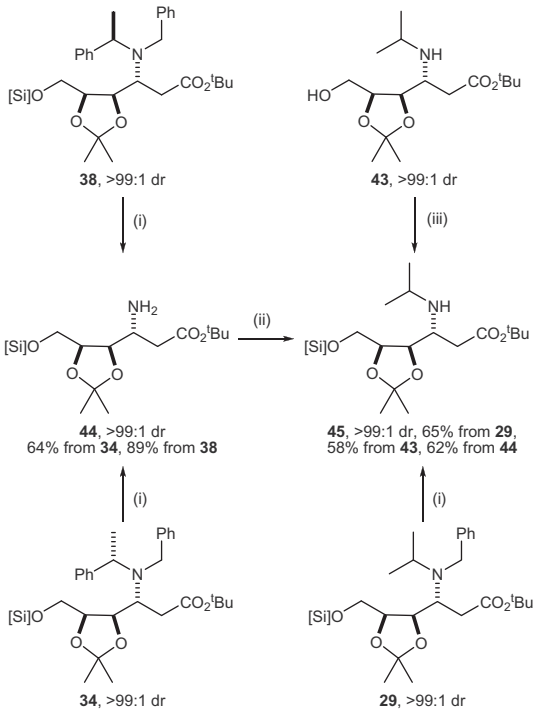


Figure 2. Chem 3D representation of the single crystal X-ray diffraction structure of (3*S*,4*R*,5*S*,α*R*)-**41** (selected H atoms are omitted for clarity).



Scheme 8. Reagents and conditions: (i) $Pd(OH)_2/C$, H_2 (1 atm), EtOAc, 18 h, rt; (ii) $NaBH_3CN$, acetone, MeOH, rt, 18 h.



Scheme 9. Reagents and conditions: (i) $Pd(OH)_2/C$, H_2 (1 atm), EtOAc, 18 h, rt. (ii) $NaBH_3CN$, acetone, MeOH, rt, 18 h; (iii) TBDMSCl, DMAP, imidazole, CH_2Cl_2, rt, 16 h. [Si] = TBDMS.

In order to unambiguously establish the absolute configurations within the ε-*O*-*tert*-butyldimethylsilyl protected series of β-amino esters, initial preparation of an authentic sample of **45** was achieved via treatment of **43** [of known absolute (3*R*,4*R*,5*S*)-configuration] with TBDMSCl, imidazole and catalytic DMAP. Subsequently, *N*-debenzylation of **29** gave a sample of **45** which was identical by ^1H and ^{13}C NMR spectroscopic analysis to the authentic sample. Meanwhile, hydrogenolysis of **34** and **38** gave the same primary β-amino ester **44** in 64 and 89% yield, respectively, and reductive alkylation of **44** using $NaBH_3CN$ and acetone gave a sample of **45**, which was again identical by ^1H and ^{13}C NMR spectroscopic analysis to the authentic sample. Thus, the absolute configurations (3*R*,4*R*,5*S*)-**29**, (3*R*,4*R*,5*S*,α*S*)-**34** and (3*R*,4*R*,5*S*,α*R*)-**38** were unambiguously assigned, as well as the absolute configurations (3*S*,4*R*,5*S*)-**30**, (3*S*,4*R*,5*S*,α*S*)-**35** and (3*S*,4*R*,5*S*,α*R*)-**39** within the C(3)-epimeric series (Scheme 9).

3. Conclusion

In conclusion, the singly diastereoselective conjugate additions of achiral lithium *N*-benzyl-*N*-isopropylamide and the doubly diastereoselective conjugate additions of both antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to enantiopure ε-silyloxy- and ε-benzyloxy-α,β-unsaturated ester substrates containing *cis*-dioxolane units (derived from D-ribose) have been evaluated. Both of these substrates display excellent (⩾95:5 dr) levels of

diastereofacial directing ability (substrate control) for attack at C(3) on the 2*Re*,3*Re* face upon conjugate addition of lithium *N*-benzyl-*N*-isopropylamide. Conjugate additions of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to the ε-silyloxy-α,β-unsaturated ester result in classical, doubly diastereoselective 'matched' and 'mismatched' reaction pairings in which the inherent reagent control serves to augment (favour attack on the 2*Re*,3*Re* face) or oppose (favour attack on the 2*Si*,3*Si* face), respectively, the established substrate diastereocontrol, in contrast to the corresponding enantiopure ε-silyloxy-α,β-unsaturated ester derived from L-tartaric acid, which contains a *trans*-dioxolane unit. The application of this methodology to the synthesis of a range of 1-deoxyimino and 1-deoxyamino sugars will be reported in due course.

4. Experimental section

4.1. General experimental details

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.[33] Water was purified by an Elix® UV-10 system. 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 or on an automated flash column chromatography platform.

Melting points are uncorrected. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded as a thin film on NaCl plates (film), as a KBr disc (KBr), or using an ATR module (ATR), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. ^{1}H–^{1}H COSY and ^{1}H–^{13}C HMQC analyses were used to establish atom connectivity.

4.2. General procedure for lithium amide conjugate addition

BuLi was added dropwise to a stirred solution of the requisite amine in either THF or Et_2O (as stated) at −78 °C or −20 °C, respectively, and stirring was continued for 30 min. A solution of the requisite α,β-unsaturated ester in either THF or Et_2O (as stated) was then added *via* cannula and the reaction mixture was stirred for 2 h (for THF) or 5 h (for Et_2O). The reaction mixture was quenched with satd aq NH_4Cl and then diluted with Et_2O and H_2O. The layers were separated and the aqueous layer was extracted three times with Et_2O. The combined organic extracts were washed sequentially with 10% aq citric acid, satd aq $NaHCO_3$ and brine, then dried and concentrated in vacuo.

4.3. (*R*,*R*)-3,4-Dihydroxy-*O*-isopropylidenedihydrofuran-2(3*H*)-one 12

Na_2CO_3 (42.4 g, 0.400 mol) was added portionwise to a solution of D-isoascorbic acid **10** (35.2 g, 0.200 mol) in H_2O (500 mL) at 0 °C. H_2O_2 (31.3% w/w, 44.0 mL, 0.450 mol) was then added dropwise over 30 min. The resultant solution was stirred at 0 °C for 30 min then heated at 40 °C for 1 h. Decolourising carbon (Norit A®, 8.0 g) was then added to decompose any excess peroxide and the reaction mixture was stirred until a negative starch-iodide test was observed (ca. 30 min). The reaction mixture was filtered through Celite® (eluent H_2O). The filtrate was acidified to pH 1 by the addition of 6 M aq. HCl and then concentrated in vacuo. Acetone (175 mL) and $MgSO_4$ (50 g) were added to the residue and the resultant mixture was stirred as 2,2-dimethoxypropane (350 mL, 2.85 mol) and $TsOH{\cdot}H_2O$ (420 mg, 2.21 mmol) were added sequentially at rt. The reaction mixture was stirred at rt for 16 h then concd aq NH_4OH (20 mL) was added. The resultant mixture was stirred for a further 10 min then diluted with Et_2O (500 mL) and filtered. The filter cake was washed with Et_2O (300 mL) and the filtrate was concentrated in vacuo. The residue was dissolved in Et_2O, then $MgSO_4$ (10 g) was added. The mixture was filtered through Celite® (eluent Et_2O) and the filtrate was concentrated in vacuo. Purification via recrystallisation (Et_2O/30–40 °C petrol) gave **12** as a pale yellow solid (13.5 g, 43%, >99:1 dr); [8] $[\alpha]_D^{25} = -113$ (*c* 1.0 in H_2O); {lit.[8] $[\alpha]_D^{25} = -120$ (*c* 1.0 in H_2O)}; mp 55–58 °C; {lit.[8] mp 64–65 °C}; δ_H (400 MHz, $CDCl_3$) 1.41 (3H, s, *Me*CMe), 1.49 (3H, s, *Me*CMe), 4.39–4.50 (2H, m, C(5)H_2), 4.76 (1H, d, *J* 5.7, C(3)*H*), 4.89 (1H, dd, *J* 5.7, 3.8, C(4)*H*).

4.4. (*R*,*R*)-3,4-Dihydroxy-3,4-*O*-isopropylidenetetrahydrofuran-2-ol 13

DIBAL-H (1.0 M in CH_2Cl_2, 10 mL, 10 mmol) was added dropwise to a solution of **12** (1.00 g, 6.32 mmol) in CH_2Cl_2 (20 mL) at −78 °C and stirring was continued at −78 °C for 3 h. MeOH (3.2 mL) was then slowly added and the reaction mixture was allowed to warm to rt over 1 h. The resultant mixture was poured into a mixture of EtOAc/H_2O (v/v, 1:1, 100 mL). The resultant mixture was then acidified to pH 3 with 1 M aq H_2SO_4 and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were then dried and concentrated in vacuo to give **13** as a yellow oil (851 mg, 84%, 79:21 dr);[10] δ_H (400 MHz, $CDCl_3$) 1.33 (3H, s, *Me*CMe), 1.48 (3H, s, *Me*CMe), 2.45 (1H, br s, O*H*), 4.04 (1H, d, *J* 10.2, C(5)H_A), 4.09 (1H, dd, *J* 10.2, 3.4, C(5)H_B), 4.59 (1H, d, *J* 5.8, C(3)*H*), 4.85 (1H, dd, *J* 5.8, 3.4, C(4)*H*), 5.44 (1H, br s, C(2)*H*).

4.5. *tert*-Butyl (4*S*,5*R*,*E*)- and (4*S*,5*R*,*Z*)-4,5,6-trihydroxy-4,5-*O*-isopropylidenehex-2-enoate (*E*)-14 and (*Z*)-15

Method A: *tert*-Butyl (triphenylphosphoranylidene)acetate (3.04 g, 8.08 mmol) was added to a stirred solution of **13** (851 mg, 5.31 mmol) in CH_2Cl_2 (17 mL) at rt. The resultant mixture was heated at reflux for 3 days then concentrated in vacuo to give a 25:75 mixture of (*E*)-**14**:(*Z*)-**15**. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 3:1) gave (*Z*)-**15** as a pale yellow oil (602 mg, 44%, >99:1 dr); $C_{13}H_{22}O_5$ requires C, 60.45; H, 8.6%; found C, 60.4; H, 8.4%; $[\alpha]_D^{25} = +127.6$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3483 (O–H), 2982, 2936, 2877 (C–H), 1710 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (3H, s, *Me*CMe), 1.48 (9H, s, C*Me*$_3$), 1.53 (3H, s, *Me*CMe), 2.14 (1H, br s, O*H*), 3.44–3.53 (1H, m, C(6)H_A), 3.56–3.64 (1H, m, C(6)H_B), 4.54–4.59 (1H, m, C(5)*H*), 5.55–5.61 (1H, m, C(4)*H*), 5.85 (1H, dd, *J* 11.6, 1.7, C(2)*H*), 6.27 (1H, dd, *J* 11.6, 6.8, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 24.7, 27.4 (C*Me*$_2$), 28.0 (C*Me*$_3$), 61.45 (*C*(6)), 74.55 (*C*(4)), 78.8 (*C*(5)), 81.0. (*C*Me$_3$), 108.7 (*C*Me$_2$), 122.9 (*C*(2)), 145.6 (*C*(3)), 165.3 (*C*(1)); *m*/*z* (ESI$^+$) 281 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{22}NaO_5^+$ ([M+Na]$^+$) requires 281.1359; found 281.1357. Further elution gave (*E*)-**14** as a pale yellow oil (343 mg, 25%, >99:1 dr); $[\alpha]_D^{25} = +30.6$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3462 (O–H), 2983, 2936, 2888 (C–H), 1715 (C=O); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, s, *Me*CMe), 1.47 (9H, s, C*Me*$_3$), 1.51 (3H, s, *Me*CMe), 2.25 (1H, br s, O*H*), 3.55 (2H, app d, *J* 6.1, C(6)H_2), 4.31–4.37 (1H, m, C(5)*H*), 4.74–4.79 (1H, m, C(4)*H*), 6.03 (1H, dd, *J* 15.6, 1.0, C(2)*H*), 6.76 (1H, dd, *J* 15.6, 5.8, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 25.2, 27.7 (C*Me*$_2$), 28.1 (C*Me*$_3$), 61.9 (*C*(6)), 76.0 (*C*(4)), 78.3 (*C*(5)), 80.8 (*C*Me$_3$), 109.4 (*C*Me$_2$), 125.0 (*C*(2)), 140.7 (*C*(3)), 165.2 (*C*(1)); *m*/*z* (ESI$^+$) 281 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{22}NaO_5^+$ ([M+Na]$^+$) requires 281.1359; found 281.1359.

Method B: Dioxane (1.31 mL) was added to a mixture of **13** (84 mg, 0.52 mmol) and *tert*-butyl (triphenylphosphoranylidene)acetate (237 mg, 0.63 mmol) and the resultant solution was stirred at 90 °C for 6 h. The reaction mixture was allowed to cool to 50 °C and stirring was continued at this temperature for a further 12 h. The reaction mixture was then concentrated in vacuo to give a 42:58 mixture of (*E*)-**14**:(*Z*)-**15**. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc, 3:2) gave (*Z*)-**15** as a pale yellow oil (80 mg, 58%, >99:1 dr). Further elution gave (*E*)-**14** as a pale yellow oil (56 mg, 42%, >99:1 dr).

Method C: BuLi (2.35 M in hexanes, 0.30 mL, 0.70 mmol) was added dropwise to a stirred solution of *tert*-butyl diethylphosphonoacetate (175 mg, 0.70 mmol) in THF (0.5 mL) at −78 °C and stirring was continued at this temperature for 30 min. A solution of **12** (100 mg, 0.63 mmol) in THF (0.5 mL) at −78 °C was then added via cannula. DIBAL-H (1.0 M in THF, 0.63 mL, 0.63 mmol) was then added dropwise and the reaction mixture was allowed to warm to rt over 16 h. Satd aq sodium potassium tartrate was then added and the reaction mixture was partitioned between EtOAc (10 mL) and 0.5 M aq HCl (10 mL). The organic layer was washed with 1 M aq K_2CO_3 (20 mL) and brine (20 mL), then dried and concentrated in vacuo to give an 88:12 mixture of (*E*)-**14**:(*Z*)-**15**; unreacted *tert*-butyl diethylphosphonoacetate was also present in the crude reaction mixture. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 3:1) gave (*E*)-**14** as a pale yellow oil (44 mg, 27%, >99:1 dr).

4.6. Methyl (4*S*,5*R*,*E*)- and (4*S*,5*R*,*Z*)-4,5,6-trihydroxy-4,5-*O*-isopropylidenehex-2-enoate (*E*)-16 and (*Z*)-17

Methyl (triphenylphosphoranylidene)acetate (933 mg, 2.79 mmol) was added to a solution of **13** (294 mg, 1.84 mmol, 79:21 anomeric mixture) in CH_2Cl_2 (6 mL) at rt. The resultant mixture was heated at reflux for 3 days then concentrated in vacuo to give a 28:72 mixture of (*E*)-**16**:(*Z*)-**17**. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 3:2) gave (*Z*)-**17** as a pale yellow oil (223 mg, 56%, >99:1 dr); $C_{10}H_{16}O_5$ requires C, 55.55; H, 7.5%; found C, 55.4; H, 7.4%; $[\alpha]_D^{25} = +144.6$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3475 (O–H), 2988, 2953, 2978 (C–H), 1719 (C=O), 1647 (C=C); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, s, *Me*CMe), 1.53 (3H, s, *Me*CMe), 2.10 (1H, br s, O*H*), 3.40–3.50 (1H, m, C(6)H_A), 3.55–3.64 (1H, m, C(6)H_B), 3.73 (3H, s, O*Me*), 4.54–4.60 (1H, m, C(5)*H*), 5.60 (1H, td, *J* 7.0, 1.6, C(4)*H*), 5.93 (1H, dd, *J* 11.6, 1.6, C(2)*H*), 6.40 (1H, dd, *J* 11.6, 7.0, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 24.6, 27.4 (C*Me*$_2$), 51.7 (O*Me*), 61.5 (*C*(6)), 74.8 (*C*(4)), 78.8 (*C*(5)), 108.9 (*C*Me$_2$), 120.5 (*C*(2)), 147.6 (*C*(3)), 166.4 (*C*(1)); *m*/*z* (ESI$^+$) 239 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{16}NaO_5^+$ ([M+Na]$^+$) requires 239.0890; found 239.0891. Further elution gave (*E*)-**16** as a pale yellow oil (92 mg, 23%, 94:6 dr); $C_{10}H_{16}O_5$ requires C, 55.55; H, 7.5%; found C, 55.7; H, 7.2%; $[\alpha]_D^{21} = +17.1$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3472 (O–H), 2989, 2952, 2938, 2890 (C–H), 1725 (C=O), 1662 (C=C); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, s, *Me*CMe), 1.50 (3H, s, *Me*CMe), 2.37 (1H, br s, O*H*), 3.54 (2H, d, *J* 5.6, C(6)H_2), 3.72 (3H, s, O*Me*), 4.31–4.38 (1H, m, C(5)*H*), 4.75–4.81 (1H, m, C(4)*H*), 6.11 (1H, dd, *J* 15.7, 1.5, C(2)*H*), 6.88 (1H, dd, *J* 15.7, 5.3, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 25.2, 27.6 (C*Me*$_2$), 51.7 (O*Me*), 61.7 (*C*(6)), 75.9 (*C*(4)), 78.2 (*C*(5)), 109.5 (*C*Me$_2$), 122.5 (*C*(2)), 142.65 (*C*(3)), 166.3 (*C*(1)); *m*/*z* (ESI$^+$) 239 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{16}NaO_5^+$ ([M+Na]$^+$) requires 239.0890; found 239.0890.

4.7. Methyl (4*S*,5*R*,*E*)-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(*p*-nitrobenzoyloxy)hex-2-enoate 18

p-Nitrobenzoyl chloride (82 mg, 0.44 mmol) was added to a solution of **16** (87 mg, 0.40 mmol) in pyridine (5 mL) at rt and the resultant mixture was stirred at rt for 28 h. 1 M aq HCl (20 mL) was then added and the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed sequentially with 1 M aq HCl (20 mL), H_2O (20 mL) and satd aq $NaHCO_3$ (20 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 4:1) gave **18** as a pale yellow solid (96 mg, 66%, >99:1 dr); $C_{17}H_{19}NO_8$ requires C, 55.9; H, 5.2; N, 3.8%; found C, 56.0; H, 5.1; N, 3.75%; mp 90–94 °C; $[\alpha]_D^{25} = +3.6$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2990, 2953 (C–H), 1728, 1663 (C=O), 1530 (N=O); δ_H (400 MHz, $CDCl_3$) 1.42 (3H, s, *Me*CMe), 1.53 (3H, s, *Me*CMe), 3.70 (3H, s, O*Me*), 4.30 (1H, dd, *J* 11.7, 6.4, C(6)H_A), 4.35 (1H, dd, *J* 11.7, 5.7, C(6)H_B), 4.56–4.62 (1H, m, C(5)*H*), 4.88–4.95 (1H, m, C(4)*H*), 6.21 (1H, d, *J* 15.4, C(2)*H*), 6.94 (1H, dd, *J* 15.4, 5.3, C(3)*H*), 8.17–8.22 (2H, m, *Ar*), 8.26–8.31 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 25.3, 27.7 (C*Me*$_2$), 51.8 (O*Me*), 63.9 (*C*(6)), 75.5 (*C*(5)), 75.9 (*C*(4)), 110.1 (*C*Me$_2$), 123.0 (*C*(2)), 123.6, 130.9, 135.0 (*Ar*), 141.3 (*C*(3)), 150.7 (*Ar*), 164.2 (OCOAr), 166.0 (*C*(1)); *m*/*z* (ESI$^+$) 388 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{19}NNaO_8^+$ ([M+Na]$^+$) requires 388.1003; found 388.1002.

4.8. Methyl (4*S*,5*R*,*Z*)-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(*p*-nitrobenzoyloxy)hex-2-enoate 19

p-Nitrobenzoyl chloride (76 mg, 0.41 mmol) was added to a solution of **17** (80 mg, 0.37 mmol) in pyridine (4 mL) at rt and the resultant mixture was stirred at rt for 28 h. 1 M aq HCl (20 mL) was then added and the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed sequentially with 1 M aq HCl (20 mL), H_2O (20 mL) and satd aq $NaHCO_3$ (20 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 7:1) gave **19** as a pale yellow oil (92 mg, 68%, >99:1 dr); $[\alpha]_D^{25} = +176.5$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2990, 2954 (C–H), 1727, 1650 (C=O), 1530 (N=O); δ_H (400 MHz, $CDCl_3$) 1.42 (3H, s, *Me*CMe), 1.52 (3H, s, *Me*CMe), 3.72 (3H, s, O*Me*), 4.18 (1H, dd, *J* 11.7, 5.4, C(6)H_A), 4.39 (1H, dd, *J* 11.7, 3.2, C(6)H_B), 4.83–4.89 (1H, m, C(5)*H*), 5.66–5.71 (1H, m, C(4)*H*), 5.95 (1H, dd, *J* 11.6, 1.3, C(2)*H*), 6.39 (1H, dd, *J* 11.6, 6.6, C(3)*H*), 8.18–8.23 (2H, m, *Ar*), 8.26–8.31 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 24.8, 27.4 (C*Me*$_2$), 51.7 (O*Me*), 64.6 (*C*(6)), 74.8 (*C*(4)), 75.8 (*C*(5)), 109.4 (*C*Me$_2$), 121.5 (*C*(2)), 123.6, 130.8, 135.3 (*Ar*), 146.2 (*C*(3)), 150.6 (*Ar*), 164.3 (OCOAr), 166.0 (*C*(1)); *m*/*z* (ESI$^+$) 388 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{19}NNaO_8^+$ ([M+Na]$^+$) requires 388.1003; found 388.1003.

4.9. (2*R*,3*R*,4*S*,5*S*)-2-Methoxy-3,4-dihydroxy-3,4-*O*-isopropylidene-5-iodomethyltetrahydrofuran 21

Concd aq HCl (2.0 mL) was added to a solution of D-ribose **20** (50.0 g, 333 mmol) in acetone (350 mL) and MeOH (350 mL) and the resultant solution was heated at 60 °C for 1 h. The reaction mixture was allowed to cool to rt and was then neutralised by addition of solid Na_2CO_3 (~10 g). The resultant mixture was then filtered through Celite® (eluent EtOAc) and the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc (300 mL) and was washed with H_2O (300 mL). The aqueous layer was extracted with EtOAc (2 × 300 mL) and the combined organic extracts were dried and concentrated in vacuo. Imidazole (34.0 g, 500 mmol) and PPh_3 (105 g, 400 mmol) were added to the residue, and the mixture was dissolved in PhMe/MeCN (v/v, 5:1, 1.05 L). I_2 (101 g, 400 mmol) was then added and the resultant mixture was heated at 60 °C for 1 h. The reaction mixture was then allowed to cool to rt, diluted with Et_2O (500 mL) and the resultant mixture was washed sequentially with 10% aq $Na_2S_2O_3$ (1 L), H_2O (1 L) and brine (1 L), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1) gave

21 as a pale yellow oil (67.2 g, 64%, >99:1 dr); [34] $[\alpha]_D^{25} = -65.3$ (*c* 1.0 in $CHCl_3$); {lit.[34] $[\alpha]_D = -67.8$ (*c* 3.2 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, s, *Me*CMe), 1.49 (3H, s, *Me*CMe), 3.17 (1H, app t, *J* 9.9, CH_AH_BI), 3.29 (1H, dd, *J* 9.9, 6.1, CH_AH_BI), 3.38 (3H, s, O*Me*), 4.45 (1H, app dd, *J* 9.9, 6.1, C(5)*H*), 4.63 (1H, app d, *J* 6.1, C(4)*H*), 4.77 (1H, app d, *J* 6.1, C(3)*H*), 5.06 (1H, app s, C(2)*H*).

4.10. (4*S*,5*R*)-2,2-Dimethyl-4-hydroxymethyl-5-vinyl-1,3-dioxolane 23

BuLi (2.5 M in hexanes, 23.4 mL, 58.4 mmol) was added to a solution of **21** (18.35 g, 58.4 mmol) in THF (300 mL) at −78 °C and the resultant solution was stirred at −78 °C for 2 h. DIBAL-H (1.0 M in THF, 87.6 mL, 87.6 mmol) was then added and the reaction mixture was allowed to warm to rt over 16 h. Acetone (100 mL) and satd aq sodium potassium tartrate (150 mL) were then added sequentially and stirring was continued at rt for 30 min. The reaction mixture was partitioned between brine (300 mL) and EtOAc (300 mL) and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 3:1) gave **23** as a yellow oil (7.74 g, 84%, >99:1 dr);[35,36] $[\alpha]_D^{25} = -40.0$ (*c* 1.0 in $CHCl_3$); {lit.[35] $[\alpha]_D^{25} = -44.0$ (*c* 4.9 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.40 (3H, s, *Me*CMe), 1.52 (3H, s, *Me*CMe), 1.86 (1H, br s, O*H*), 3.59 (2H, d, *J* 5.5, C(4)CH_2OH), 4.25–4.31 (1H, m, C(4)*H*), 4.66 (1H, app t, *J* 7.2, C(5)*H*), 5.29 (1H, dd, *J* 10.5, 2.6, C(5)CH=CH_AH_B), 5.41 (1H, dd, *J* 17.1, 2.6, C(5)CH=CH_AH_B), 5.88 (1H, ddd, *J* 17.1, 10.5, 7.2, C(5)CH=CH_2).

4.11. (4*S*,5*R*)-2,2-Dimethyl-4-(*tert*-butyldimethylsilyloxymethyl)-5-vinyl-1,3-dioxolane 24

Imidazole (3.87 g, 56.9 mmol), DMAP (93 mg, 0.76 mmol) and TBDMSCl (3.43 g, 19.0 mmol) were sequentially added to a solution of **23** (3.00 g, 19.0 mmol) in CH_2Cl_2 (135 mL) at rt and the resultant solution was stirred at rt for 16 h. The reaction mixture was then concentrated in vacuo. The residue was dissolved in Et_2O (20 mL) and the resultant solution was washed with 1 M aq HCl (20 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 20:1) gave **24** as a pale yellow oil (5.06 g, 98%, >99:1 dr); $[\alpha]_D^{25} = +1.6$(*c* 1.0 in $CHCl_3$); ν_{max} (film) 2988, 2956, 2931, 2858 (C–H), 1645 (C=C); δ_H (400 MHz, $CDCl_3$) 0.03 (3H, s, *Me*SiMe), 0.04 (3H, s, *Me*SiMe), 0.87 (9H, s, C*Me*$_3$), 1.35 (3H, s, *Me*CMe), 1.45 (3H, s, *Me*CMe), 3.58 (1H, dd, *J* 10.7, 6.1, C(4)CH_AH_BOSi), 3.61 (1H, dd, *J* 10.7, 6.1, C(4)CH_AH_BOSi), 4.18 (1H, app q, *J* 6.1, C(4)*H*), 4.60 (1H, app t, *J* 6.8, C(5)*H*), 5.19 (1H, d, *J* 10.4, C(5)CH=CH_AH_B), 5.33 (1H, d, *J* 17.2, C(5)CH=CH_AH_B), 5.87 (1H, ddd, *J* 17.2, 10.4, 6.8, C(5)CH=CH_2); δ_C (100 MHz, $CDCl_3$) −5.5, −5.4 (Si*Me*$_2$), 18.2 (*C*Me$_3$), 25.3 (*Me*CMe), 25.9 (C*Me*$_3$), 27.8 (*Me*CMe), 62.3 (C(4)CH_2OSi), 78.5, 78.6 (*C*(4), *C*(5)), 108.5 (*C*Me$_2$), 117.6 (C(5)CH=*C*H_2), 133.7 (C(5)CH=CH_2); *m*/*z* (ESI$^+$) 295 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{28}NaO_3Si^+$ ([M+Na]$^+$) requires 295.1700; found 295.1699.

4.12. (4*S*,5*R*)-2,2-Dimethyl-4-(benzyloxymethyl)-5-vinyl-1,3-dioxolane 25

NaH (60% dispersion in mineral oil, 1.89 g, 47.4 mmol) was stirred vigorously in 30–40 °C petrol (20 mL) at rt for 10 min and then the solvent was decanted via cannula. THF (30 mL) was then added and the suspension was cooled to 0 °C. A solution of **23** (3.00 g, 19.0 mmol) in THF (30 mL) was then added dropwise via cannula and the reaction mixture was stirred at rt for 45 min. BnBr (3.38 mL, 28.4 mmol) was then added at rt and stirring was continued at rt for 16 h. The solution was diluted with Et_2O (50 mL) and washed with satd aq $NaHCO_3$ (2 × 50 mL). The aqueous layer was extracted with Et_2O (2 × 50 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 20:1) gave **25** as a pale yellow oil (4.49 g, 95%, >99:1 dr); $[\alpha]_D^{25} = +1.7$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3030, 2987, 2934, 2865 (C–H), 1644 (C=C); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, s, *Me*CMe), 1.52 (3H, s, *Me*CMe), 3.46 (1H, dd, *J* 9.9, 5.4, C(4)CH_AH_BOBn), 3.48 (1H, dd, *J* 9.9, 6.3, C(4)CH_AH_BOBn), 4.37–4.43 (1H, m, C(4)*H*), 4.52 (1H, d, *J* 12.0, OCH_AH_BPh), 4.60 (1H, d, *J* 12.0, OCH_AH_BPh), 4.60–4.65 (1H, m, C(5)*H*), 5.23 (1H, d, *J* 10.4, C(5)CH=CH_AH_B), 5.36 (1H, d, *J* 17.4, C(5)CH=CH_AH_B), 5.82 (1H, ddd, *J* 17.4, 10.4, 7.3, C(5)CH=CH_2), 7.27–7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.4, 27.9 (*C*Me$_2$), 69.5 (C(4)CH_2OBn), 73.5 (OCH_2Ph), 76.9 (*C*(4)), 78.5 (*C*(5)), 108.9 (*C*Me$_2$), 118.2 (C(5)CH=*C*H_2), 127.7 (*p*-*Ph*), 127.8, 128.4 (*o*,*m*-*Ph*), 133.5 (C(5)CH=CH_2), 138.0 (*i*-*Ph*); *m*/*z* (ESI$^+$) 271 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{20}NaO_3^+$ ([M+Na]$^+$) requires 271.1305; found 271.1305.

4.13. *tert*-Butyl (4*R*,5*S*,*E*)-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(*tert*-butyldimethylsilyloxy)hex-2-enoate 26

Hoveyda-Grubbs II (23 mg, 36.7 μmol) was added to a degassed solution of **24** (100 mg, 0.367 mmol) and *tert*-butyl acrylate (0.16 mL, 1.10 mmol) in CH_2Cl_2 (2 mL) and the resultant mixture was heated at reflux for 22 h. The reaction mixture was then concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **26** as a colourless oil (93 mg, 68%, >99:1 dr); $[\alpha]_D^{25} = +9.4$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2981, 2956, 2932, 2859 (C–H), 1717 (C=O), 1660 (C=C); δ_H (400 MHz, $CDCl_3$) 0.04 (6H, s, Si*Me*$_2$), 0.87 (9H, s, SiC*Me*$_3$), 1.37 (3H, s, *Me*CMe), 1.48 (12H, s, *Me*CMe, OC*Me*$_3$), 3.54 (1H, dd, *J* 10.1, 8.1, C(6)H_A), 3.62 (1H, dd, *J* 10.1, 4.6, C(6)H_B), 4.24–4.30 (1H, m, C(5)*H*), 4.78 (1H, app dt, *J* 5.4, 1.3, C(4)*H*), 6.02 (1H, dd, *J* 15.5, 1.3, C(2)*H*), 6.85 (1H, dd, *J* 15.5, 5.4, C(3)*H*); δ_C (100 MHz, $CDCl_3$) −5.6, −5.5 (Si*Me*$_2$), 18.2 (SiCMe$_3$), 25.2 (*Me*CMe), 25.9 (SiC*Me*$_3$), 27.7 (*Me*CMe), 28.1 (OC*Me*$_3$), 61.8 (*C*(6)), 76.7 (*C*(4)), 78.3 (*C*(5)), 80.4 (OCMe$_3$), 109.6 (*C*Me$_2$), 124.3 (*C*(2)), 141.6 (*C*(3)), 165.3 (*C*(1)); *m*/*z* (ESI$^+$) 395 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{36}NaO_5Si^+$ ([M+Na]$^+$) requires 395.2224; found 295.2221.

4.14. *tert*-Butyl (4*R*,5*S*,*E*)-4,5-dihydroxy-4,5-*O*-isopropylidene-6-benzyloxyhex-2-enoate 27

Hoveyda–Grubbs II (25 mg, 39.9 μmol) was added to a degassed solution of **25** (100 mg, 0.40 mmol) and *tert*-butyl acrylate (0.18 mL, 1.21 mmol) in CH_2Cl_2 (2 mL) and the resultant mixture was heated at reflux for 22 h. The reaction mixture was then concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 10:1) gave **27** as a colourless oil (109 mg, 78%, >99:1 dr); $[\alpha]_D^{25} = +19.7$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2982, 2934, 2867 (C–H), 1714 (C=O), 1658 (C=C); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, s, *Me*CMe), 1.48 (9H, s, C*Me*$_3$), 1.51 (3H, s, *Me*CMe), 3.40 (1H, dd, *J* 9.6, 6.3, C(6)H_A), 3.49 (1H, dd, *J* 9.6, 6.8, C(6)H_B), 4.41–4.48 (1H, m, C(5)*H*), 4.48 (1H, d, *J* 12.0, OCH_AH_BPh), 4.52 (1H, d, *J* 12.0, OCH_AH_BPh), 4.77 (1H, dt, *J* 5.6, 1.4, C(4)*H*), 6.05 (1H, dd, *J* 15.5, 1.5, C(2)*H*), 6.82 (1H, dd, *J* 15.5, 5.6, C(3)*H*), 7.25–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.3, 27.7 (*C*Me$_2$), 28.1 (C*Me*$_3$), 69.1 (*C*(6)), 73.5 (OCH_2Ph), 76.3 (*C*(4)), 76.8 (*C*(5)), 80.6 (*C*Me$_3$), 109.4 (*C*Me$_2$), 124.6 (*C*(2)), 127.8 (*p*-*Ph*), 127.8, 128.4 (*o*,*m*-*Ph*), 137.7 (*i*-*Ph*), 141.3 (*C*(3)), 165.3 (*C*(1)); *m*/*z* (ESI$^+$) 371 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{28}NaO_5^+$ ([M+Na]$^+$) requires 371.1829; found 371.1828.

4.15. *tert*-Butyl (*S*,*Z*)-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(*tert*-butyldimethylsilyloxy)hex-3-enoate 28

Following the general procedure, (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (114 mg, 0.540 mmol) in THF (4 mL), BuLi (2.50 M in hexanes, 0.21 mL, 0.521 mmol) and **26** (100 mg, 0.268 mmol) in THF (4 mL) at −78 °C gave a mixture of products, of which the major component was **28**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave **28** as a colourless oil (72 mg, 72%, >99:1 dr); $[\alpha]_D^{25} = -24.4$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2980, 2956, 2931, 2859 (C–H), 1735 (C=O); δ_H (400 MHz, $CDCl_3$) 0.08 (6H, s, Si*Me*$_2$), 0.91 (9H, s, Si*CMe*$_3$), 1.40 (3H, s, *Me*CMe), 1.45 (9H, s, OC*Me*$_3$), 1.50 (3H, s, *Me*CMe), 2.99 (1H, ddd, *J* 17.7, 6.4, 1.4, C(2)H_A), 3.10 (1H, ddd, *J* 17.7, 7.3, 1.3, C(2)H_B), 3.70 (1H, dd, *J* 10.9, 5.6, C(6)H_A), 3.74 (1H, dd, *J* 10.9, 4.6, C(6)H_B), 4.40–4.45 (1H, m, C(3)*H*), 4.60–4.65 (1H, m, C(5)*H*); δ_C (100 MHz, $CDCl_3$) −5.3 (Si*Me*$_2$), 18.4 (Si*C*Me$_3$), 25.6 (*Me*CMe), 25.9 (SiC*Me*$_3$), 26.8 (*Me*CMe), 28.1 (OC*Me*$_3$), 32.1 (*C*(2)), 66.0 (*C*(6)), 78.1 (*C*(5)), 80.3 (OCMe$_3$), 87.8 (*C*(3)), 111.1 (*C*Me$_2$), 151.8 (*C*(4)), 171.7 (*C*(1)); *m*/*z* (ESI$^+$) 395 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{36}O_5Si^+$ requires 395.2224; found 395.2222.

4.16. *tert*-Butyl (3*R*,4*R*,5*S*)-3-(*N*-benzyl-*N*-isopropylamino)-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(*tert*-butyldimethylsilyloxy)-hexanoate 29

Method A: Following the general procedure, *N*-benzyl-*N*-isopropylamine (481 mg, 3.22 mmol) in Et_2O (24 mL), BuLi (2.50 M in hexanes, 1.25 mL, 3.13 mmol) and **26** (600 mg, 1.61 mmol) in Et_2O (24 mL) at −20 °C gave **29** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave **29** as a colourless oil (687 mg, 82%, >99:1 dr); $C_{29}H_{51}NO_5Si$ requires C, 66.75; H, 9.85; N, 2.7%; found C, 66.9; H, 9.8; N, 2.6%; $[\alpha]_D^{25} = +36.0$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2960, 2932, 2884, 2858 (C–H), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 0.13 (6H, s, Si*Me*$_2$), 0.95 (9H, s, SiC*Me*$_3$), 1.03 (6H, d, *J* 6.8, NCH*Me*$_2$), 1.34 (3H, s, *Me*CMe), 1.42 (3H, s, *Me*CMe), 1.52 (9H, s, OC*Me*$_3$), 2.22 (1H, dd, *J* 15.1, 3.8, C(2)H_A), 2.60 (1H, dd, *J* 15.1, 8.8, C(2)H_B) 2.88–3.00 (1H, m, C*H*Me$_2$), 3.67 (1H, d, *J* 14.9, NCH_AH_BPh), 3.74 (1H, app td, *J* 8.8, 3.5, C(3)*H*), 3.78 (1H, dd, *J* 10.6, 6.3, C(6)H_A), 3.91 (1H, dd, *J* 10.6, 6.1, C(6)H_B), 3.99 (1H, d, *J* 14.9, NCH$_A$$H_B$Ph), 4.20–4.27 (1H, m, C(5)*H*), 4.35 (1H, dd, *J* 7.0, 3.2, C(4)*H*), 7.18–7.43 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) −5.2, −5.1 (Si*Me*$_2$), 18.5 (Si*C*Me$_3$), 18.6, 21.7 (NCH*Me*$_2$), 24.9 (*Me*CMe), 26.1 (SiC*Me*$_3$), 26.9 (*Me*CMe), 28.2 (OC*Me*$_3$), 37.6 (*C*(2)), 49.8 (NCH$_2$Ph), 50.1 (NCHMe$_2$), 53.2 (*C*(3)), 62.0 (*C*(6)), 78.2, 78.3 (*C*(4), *C*(5)), 79.8 (*C*Me$_3$), 107.8 (*C*Me$_2$), 126.4 (*p*-*Ph*), 128.0, 128.3 (*o*,*m*-*Ph*), 142.0 (*i*-*Ph*), 172.0 (*C*(1)); *m*/*z* (ESI$^+$) 522 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{52}NO_5Si^+$ ([M+H]$^+$) requires 522.3609; found 522.3602.

Method B: Following the general procedure, *N*-benzyl-*N*-isopropylamine (80 mg, 0.54 mmol) in THF (4 mL), BuLi (2.50 M in hexanes, 0.21 mL, 0.52 mmol) and **26** (100 mg, 0.268 mmol) in THF (4 mL) at −78 °C gave a 12:88 mixture of **28**:**29**.

4.17. *tert*-Butyl (3*R*,4*R*,5*S*)-3-(*N*-benzyl-*N*-isopropylamino)-4,5-dihydroxy-4,5-*O*-isopropylidene-6-benzyloxyhexanoate 32

Method A: Following the general procedure, *N*-benzyl-*N*-isopropylamine (290 mg, 1.94 mmol) in Et_2O (15 mL), BuLi (2.50 M in hexanes, 0.75 mL, 1.88 mmol) and **27** (338 mg, 0.970 mmol) in Et_2O (15 mL) at −20 °C gave a 95:5 mixture of **32**:**33** respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **32** as a colourless oil (309 mg, 64%, >99:1 dr); $[\alpha]_D^{25} = +10.6$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3029, 2978, 2934, 2873 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.01 (6H, d, *J* 6.6, NCH*Me*$_2$), 1.33 (3H, s, *Me*CMe), 1.42 (3H, s, *Me*CMe), 1.52 (9H, s, C*Me*$_3$), 2.33 (1H, dd, *J* 15.1, 5.1, C(2)H_A), 2.64 (1H, dd, *J* 15.1, 7.3, C(2)H_B), 2.96 (1H, septet, *J* 6.6, NC*H*Me$_2$), 3.53 (1H, dd, *J* 9.6, 7.1, C(6)H_A), 3.58–3.65 (2H, m, C(3)*H*, C(6)H_B), 3.67 (1H, d, *J* 14.9, NCH_AH_BPh), 3.85 (1H, d, *J* 14.9, NCH$_A$$H_B$Ph), 4.29 (1H, dd, *J* 7.1, 5.1, C(4)*H*), 4.36 (1H, td, *J* 7.1, 4.8, C(5)*H*), 4.57 (1H, d, *J* 12.4, OCH_AH_BPh), 4.60 (1H, d, *J* 12.4, OCH$_A$$H_B$Ph), 7.21–7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.7, 21.3 (NCH*Me*$_2$), 25.1, 27.2 (*Me*CMe), 28.3 (C*Me*$_3$), 37.2 (*C*(2)), 49.6 (NCH$_2$Ph), 50.1 (NCHMe$_2$), 53.9 (*C*(3)), 68.7 (*C*(6)), 73.5 (OCH$_2$Ph), 76.5 (*C*Me$_3$), 78.2 (*C*(5)), 80.0 (*C*(4)), 108.1 (*C*Me$_2$), 126.6, 127.6 (*p*-*Ph*), 127.9, 128.1, 128.3, 128.5 (*o*,*m*-*Ph*), 138.2, 141.6 (*i*-*Ph*), 172.1 (*C*(1)); *m*/*z* (ESI$^+$) 498 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{44}NO_5^+$ ([M+H]$^+$) requires 498.3214; found 498.3213.

Method B: Following the general procedure, *N*-benzyl-*N*-isopropylamine (86 mg, 0.58 mmol) in THF (4 mL), BuLi (2.50 M in hexanes, 0.21 mL, 0.56 mmol) and **27** (100 mg, 0.287 mmol) in THF (4 mL) at −78 °C gave an 15:85 mixture of **31**:**32**.

4.18. *tert*-Butyl (3*R*,4*R*,5*S*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(*tert*-butyldimethylsilyloxy)hexanoate 34

Method A: Following the general procedure, (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (657 mg, 3.11 mmol) in Et_2O (23 mL), BuLi (2.50 M in hexanes, 1.21 mL, 3.02 mmol) and **26** (579 mg, 1.56 mmol) in Et_2O (23 mL) at −20 °C gave **34** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave **34** as a colourless oil (821 mg, 90%, >99:1 dr); $[\alpha]_D^{25} = +13.8$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3063, 3028, 2932, 2857 (C–H), 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 0.14 (6H, s, Si*Me*$_2$), 0.98 (9H, s, SiC*Me*$_3$), 1.30 (3H, s, *Me*CMe), 1.41 (3H, s, *Me*CMe), 1.43 (3H, d, *J* 6.8, C(α)*Me*), 1.48 (9H, s, OC*Me*$_3$), 2.25 (1H, dd, *J* 15.7, 5.1, C(2)H_A), 2.43 (1H, dd, *J* 15.7, 7.3, C(2)H_B), 3.69 (1H, dd, *J* 10.9, 6.6, C(6)H_A), 3.78 (1H, d, *J* 15.2, NCH_AH_BPh), 3.80–3.84 (2H, m, C(3)*H*, C(6)H_B), 3.86 (1H, d, *J* 15.2, NCH$_A$$H_B$Ph), 4.07 (1H, q, *J* 6.8, C(α)*H*), 4.18–4.26 (2H, m, C(4)*H*, C(5)*H*), 7.20–7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) −5.1, −5.0 (Si*Me*$_2$), 18.6 (Si*C*Me$_3$), 18.9 (C(α)*Me*), 25.0 (*Me*CMe), 26.1 (SiC*Me*$_3$), 27.3 (*Me*CMe), 28.2 (OC*Me*$_3$), 36.7 (*C*(2)), 45.8 (*C*(3)), 50.1 (NCH$_2$Ph), 60.0 (*C*(α)), 62.5 (*C*(6)), 77.5, 78.5 (*C*(4), *C*(5)), 79.8 (OCMe$_3$), 107.7 (*C*Me$_2$), 126.5, 127.0 (*p*-*Ph*), 128.0, 128.1, 128.3 (*o*,*m*-*Ph*), 141.8, 143.5 (*i*-*Ph*), 171.5 (*C*(1)); *m*/*z* (ESI$^+$) 584 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{54}NO_5Si^+$ ([M+H]$^+$) requires 584.3766; found 584.3763.

Method B: Following the general procedure, (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (114 mg, 0.540 mmol) in THF (4 mL), BuLi (2.50 M in hexanes, 0.21 mL, 0.52 mmol) and **26** (100 mg, 0.268 mmol) in THF (4 mL) at −78 °C gave a 25:75 mixture of **28**:**34**.

4.19. *tert*-Butyl (3*R*,4*R*,5*S*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-4,5-dihydroxy-4,5-*O*-isopropylidene-6-benzyloxyhexanoate 36

Method A: Following the general procedure, (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (784 mg, 3.71 mmol) in Et_2O (28 mL), BuLi (2.50 M in hexanes, 1.44 mL, 3.60 mmol) and **27** (646 mg, 1.86 mmol) in Et_2O (28 mL) at −20 °C gave a 93:7 mixture of **36**:**37** respectively. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 10:1) gave a **36** as a pale yellow oil (820 mg, 79%, 93:7 dr); $[\alpha]_D^{25} = +3.3$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3062, 3029, 2979, 2933, 2877 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, s, *Me*CMe), 1.36 (3H, d, *J* 7.0, C(α)*Me*), 1.42 (3H, s, *Me*CMe), 1.47 (9H, s, C*Me*$_3$), 2.25 (1H, dd, *J* 15.5, 5.9, C(2)H_A), 2.42 (1H, dd, *J* 15.5, 5.9, C(2)H_B), 3.48 (1H, dd, *J* 9.9, 8.1, C(6)H_A), 3.56 (1H, dd, *J* 9.9, 4.3, C(6)H_B), 3.69 (1H, app q, *J* 5.9, C(3)*H*), 3.77 (1H, d, *J* 15.4, NCH_AH_BPh), 3.82 (1H, d, *J* 15.4, NCH$_A$$H_B$Ph), 4.00 (1H, q, *J* 7.0, C(α)*H*), 4.27 (1H, dd, *J* 6.3, 5.9, C(4)*H*),

4.38–4.44 (1H, m, C(5)*H*), 4.56 (1H, d, *J* 12.6, OC*H*$_A$H$_B$Ph), 4.60 (1H, d, *J* 12.6, OCH$_A$*H*$_B$Ph), 7.22–7.44 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.8 (C(α)*Me*), 25.1, 27.4 (C*Me*$_2$), 28.2 (C*Me*$_3$), 36.4 (*C*(2)), 50.4 (NCH$_2$Ph), 54.6 (*C*(3)), 59.4 (*C*(α)), 68.7 (*C*(6)), 73.3 (OCH$_2$Ph), 76.6 (*C*(5)), 77.7 (*C*(4)), 79.9 (*C*Me$_3$), 108.0 (*C*Me$_2$), 126.7, 127.1 (*p-Ph*), 127.9, 128.1, 128.2, 128.3, 128.4 (*o*,*m-Ph*), 138.3, 141.5, 143.4 (*i-Ph*), 171.5 (*C*(1)); *m*/*z* (ESI$^+$) 560 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{46}NO_5^+$ ([M+H]$^+$) requires 560.3371; found 560.3370.

Method B: Following the general procedure, (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (121 mg, 0.573 mmol) in THF (4 mL), BuLi (2.50 M in hexanes, 0.21 mL, 0.56 mmol) and **27** (100 mg, 0.287 mmol) in THF (4 mL) at −78 °C gave a 14:80:6 mixture of **31**:**36**:**37**.

4.20. *tert*-Butyl (3*R*,4*R*,5*S*,α*R*)- and (3*S*,4*R*,5*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(*tert*-butyldimethylsilyloxy)hexanoate 38 and 39

Following the general procedure, (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (641 mg, 3.04 mmol) in Et_2O (23 mL), BuLi (2.50 M in hexanes, 1.18 mL, 2.94 mmol) and **26** (565 mg, 1.52 mmol) in Et_2O (23 mL) at −20 °C gave an 82:18 mixture of **38**:**39**. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 30:1) gave **38** as a colourless oil (513 mg, 58%, >99:1 dr); $[\alpha]_D^{25} = +34.7$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2978, 2955, 2932, 2884, 2857 (C–H), 1729 (C=O); δ_H (400 MHz, $CDCl_3$) 0.16 (6H, s, Si*Me*$_2$), 0.98 (9H, s, SiC*Me*$_3$), 1.12 (3H, s, *Me*CMe), 1.34 (3H, s, *Me*CMe), 1.39 (3H, d, *J* 7.1, C(α)*Me*), 1.56 (9H, s, OC*Me*$_3$), 2.27 (1H, dd, *J* 15.4, 3.8, C(2)*H*$_A$), 2.55 (1H, dd, *J* 15.4, 9.1, C(2)*H*$_B$), 3.54 (1H, dd, *J* 6.7, 2.7, C(4)*H*), 3.56 (1H, d, *J* 15.2, NC*H*$_A$H$_B$Ph), 3.68 (1H, dd, *J* 10.7, 6.7, C(6)*H*$_A$), 3.74 (1H, dd, *J* 10.7, 5.3, C(6)*H*$_B$), 3.82 (1H, q, *J* 7.1, C(α)*H*), 3.82–3.88 (1H, m, C(5)*H*), 3.95 (1H, m, C(3)*H*), 4.05 (1H, d, *J* 15.2, NCH$_A$*H*$_B$Ph), 7.23–7.50 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) −5.1 (Si*Me*$_2$), 18.7 (SiCMe$_3$), 19.4 (C(α)*Me*), 24.5 (*Me*CMe), 26.2 (SiC*Me*$_3$), 27.0 (*Me*CMe), 28.3 (OC*Me*$_3$), 37.2 (*C*(2)), 50.3 (NCH$_2$Ph), 52.5 (*C*(3)), 58.0 (*C*(α)), 62.5 (*C*(6)), 76.9 (*C*(4)), 78.2 (*C*(5)), 79.9 (OCMe$_3$), 107.5 (*C*Me$_2$), 126.6, 127.2 (*p-Ph*), 128.1, 128.6 (*o*,*m-Ph*), 141.5, 141.9 (*i-Ph*), 171.8 (*C*(1)); *m*/*z* (ESI$^+$) 584 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{54}NO_5Si^+$ ([M+H]$^+$) requires 584.3766; found 584.3769. Further elution gave **39** as a colourless oil (109 mg, 12%, >99:1 dr); $[\alpha]_D^{25} = -10.0$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2980, 2955, 2931, 2858 (C–H), 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 0.04 (3H, s, *Me*SiMe), 0.05 (3H, s, *Me*SiMe), 0.87 (9H, s, SiC*Me*$_3$), 1.42 (3H, s, *Me*CMe), 1.48 (3H, s, *Me*CMe), 1.49 (9H, s, OC*Me*$_3$), 1.51 (3H, d, *J* 6.8, C(α)*Me*), 2.19 (1H, dd, *J* 15.4, 9.85, C(2)*H*$_A$), 2.28 (1H, dd, *J* 15.4, 3.5, C(2)*H*$_B$), 3.50 (1H, dd, *J* 10.6, 4.8, C(6)*H*$_A$), 3.75 (1H, dd, *J* 10.6, 7.3, C(6)*H*$_B$), 3.81 (1H, d, *J* 14.4, NC*H*$_A$H$_B$Ph), 3.84–3.89 (1H, m, C(3)*H*), 3.88 (1H, d, *J* 14.4, NCH$_A$*H*$_B$Ph), 3.95–4.01 (1H, m, C(5)*H*), 4.19 (1H, q, *J* 6.8, C(α)*H*), 4.37 (1H, dd, *J* 10.6, 5.1, C(4)*H*), 7.10–7.47 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) −5.5, −5.4 (Si*Me*$_2$), 18.4 (SiCMe$_3$), 20.5 (C(α)*Me*), 25.5 (*Me*CMe), 26.1 (SiC*Me*$_3$), 28.2 (OC*Me*$_3$), 28.5 (*Me*CMe), 37.7 (*C*(2)), 51.4 (NCH$_2$Ph), 52.6 (*C*(3)), 60.9 (*C*(α)), 62.7 (*C*(6)), 78.5 (*C*(5)), 78.9 (*C*(4)), 79.9 (OCMe$_3$), 107.7 (*C*Me$_2$), 126.3 (*p-Ph*), 127.7, 127.8, 128.0, 129.0 (*o*,*m-Ph*), 141.9, 146.7 (*i-Ph*), 170.7 (*C*(1)); *m*/*z* (ESI$^+$) 584 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{54}NO_5Si^+$ ([M+H]$^+$) requires 584.3766; found 584.3766.

4.21. *tert*-Butyl (3*R*,4*R*,5*S*,α*R*)- and (3*S*,4*R*,5*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-dihydroxy-4,5-*O*-isopropylidene-6-benzyloxyhexanoate 40 and 41

Method A: Following the general procedure, (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (437 mg, 2.07 mmol) in Et_2O (15 mL), BuLi (2.50 M in hexanes, 0.80 mL, 2.01 mmol) and **27** (360 mg, 1.03 mmol) in Et_2O (15 mL) at −20 °C gave an 83:17 mixture of **40**:**41**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **40** as a colourless oil (257 mg, 44%, >99:1 dr); $[\alpha]_D^{25} = +25.8$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3062, 3028, 2978, 2933, 2872 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, s, *Me*CMe), 1.34 (3H, d, *J* 7.1, C(α)*Me*), 1.38 (3H, s, *Me*CMe), 1.57 (9H, s, C*Me*$_3$), 2.29 (1H, dd, *J* 15.2, 4.6, C(2)*H*$_A$), 2.57 (1H, dd, *J* 15.2, 7.6, C(2)*H*$_B$), 3.44–3.54 (2H, m, C(6)*H*$_2$), 3.61 (1H, d, *J* 15.0, NC*H*$_A$H$_B$Ph), 3.62 (1H, dd, *J* 7.3, 4.0, C(4)*H*), 3.78–3.86 (1H, m, C(3)*H*) overlapping 3.81 (1H, q, *J* 7.1, C(α)*H*), 4.00 (1H, d, *J* 15.0, NCH$_A$*H*$_B$Ph), 4.06 (1H, app dt, *J* 7.2, 5.1, C(5)*H*), 4.59 (1H, d, *J* 12.3, OC*H*$_A$H$_B$Ph), 4.63 (1H, d, *J* 12.3, OCH$_A$*H*$_B$Ph), 7.22–7.49 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.8 (C(α)*Me*), 24.7, 27.0 (C*Me*$_2$), 28.3 (C*Me*$_3$), 37.3 (*C*(2)), 50.5 (NCH$_2$Ph), 53.2 (*C*(3)), 58.2 (*C*(α)), 68.7 (*C*(6)), 73.4 (OCH$_2$Ph), 76.4 (*C*(5)), 77.1 (*C*(4)), 80.1 (*C*Me$_3$), 107.9 (*C*Me$_2$), 126.8, 127.2, 127.7 (*p-Ph*), 128.0, 128.1, 128.2, 128.4, 128.6 (*o*,*m-Ph*), 138.3, 141.4, 142.2 (*i-Ph*), 172.1 (*C*(1)); *m*/*z* (ESI$^+$) 560 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{46}NO_5^+$ ([M+H]$^+$) requires 560.3371; found 560.3367. Further elution gave **41** as a pale yellow oil (41 mg, 7%, >99:1 dr); $[\alpha]_D^{25} = -26.5$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3062, 3028, 2980, 2933, 2864 (C–H), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 1.43 (3H, s, *Me*CMe), 1.46 (9H, s, C*Me*$_3$), 1.49 (3H, s, *Me*CMe), 1.51 (3H, d, *J* 6.8, C(α)*Me*), 2.14 (1H, dd, *J* 15.3, 2.9, C(2)*H*$_A$), 2.26 (1H, dd, *J* 15.3, 10.1, C(2)*H*$_B$), 3.43 (1H, dd, *J* 9.9, 5.6, C(6)*H*$_A$), 3.52 (1H, dd, *J* 9.9, 6.1, C(6)*H*$_B$), 3.72–3.80 (1H, m, C(3)*H*), 3.78 (1H, d, *J* 14.2, NC*H*$_A$H$_B$Ph), 3.93 (1H, d, *J* 14.2, NCH$_A$*H*$_B$Ph), 4.12–4.17 (1H, m, C(5)*H*), 4.21 (1H, q, *J* 6.8, C(α)*H*), 4.35 (1H, dd, *J* 10.4, 5.1, C(4)*H*), 4.39 (1H, d, *J* 12.1, OC*H*$_A$H$_B$Ph), 4.53 (1H, d, *J* 12.1, OCH$_A$*H*$_B$Ph), 7.13–7.47 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.0 (C(α)*Me*), 25.6 (*Me*CMe), 28.1 (C*Me*$_3$), 28.4 (*Me*CMe), 37.6 (*C*(2)), 51.3 (NCH$_2$Ph), 52.9 (*C*(3)), 59.6 (*C*(α)), 69.4 (*C*(6)), 73.5 (OCH$_2$Ph), 76.7 (*C*(5)), 79.0 (*C*(4)), 80.2 (*C*Me$_3$), 108.2 (*C*Me$_2$), 126.4, 127.6, 127.7 (*p-Ph*), 127.8, 128.0, 128.3, 129.1 (*o*,*m-Ph*), 138.0, 141.6, 146.3 (*i-Ph*), 170.7 (*C*(1)); *m*/*z* (ESI$^+$) 560 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{46}NO_5^+$ ([M+H]$^+$) requires 560.3371; found 560.3373.

Method B: Following the general procedure, (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (121 mg, 0.573 mmol) in THF (4 mL), BuLi (2.50 M in hexanes, 0.21 mL, 0.56 mmol) and **27** (100 mg, 0.287 mmol) in THF (4 mL) at −78 °C gave a 46:37:17 mixture of **31**:**40**:**41**. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 10:1) gave **40** as a colourless oil (46 mg, 29%, >99:1 dr). Further elution gave a 70:30 mixture of **31**:**41** as a pale yellow oil (38 mg). Data for **31**: δ_H (400 MHz, $CDCl_3$) 1.43 (3H, s, *Me*CMe), 1.45 (9H, s, C*Me*$_3$), 1.54 (3H, s, *Me*CMe), 3.01 (1H, ddd, *J* 17.8, 6.7, 1.3, C(2)*H*$_A$), 3.09 (1H, ddd, *J* 17.8, 7.2, 1.0, C(2)*H*$_B$), 3.56 (1H, dd, *J* 10.4, 7.3, C(6)*H*$_A$), 3.62 (1H, dd, *J* 10.4, 3.5, C(6)*H*$_B$), 4.35–4.40 (1H, m, C(3)*H*), 4.59 (1H, d, *J* 12.3, OC*H*$_A$H$_B$Ph), 4.67 (1H, d, *J* 12.3, OCH$_A$*H*$_B$Ph), 4.82 (1H, ddd, *J* 7.3, 3.5, 1.5, C(5)*H*), 7.12–7.46 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.4, 26.8 (C*Me*$_2$), 28.1 (C*Me*$_3$), 32.0 (*C*(2)), 72.4 (*C*(6)), 73.5 (OCH$_2$Ph), 76.5 (*C*(5)), 80.3 (*C*Me$_3$), 87.8 (*C*(3)), 111.4 (*C*Me$_2$), 126.4 (*p-Ph*), 127.8, 128.4 (*o*,*m-Ph*), 137.9 (*i-Ph*), 151.2 (*C*(4)), 171.6 (*C*(1)).

4.22. *tert*-Butyl (3*R*,4*R*,5*S*)-3-amino-4,5,6-trihydroxy-4,5-*O*-isopropylidenehexanoate 42

*Method A (From **36**):* Pd(OH)$_2$/C (50% w/w of substrate, 155 mg) was added to a stirred solution of **36** (310 mg, 0.55 mmol, 93:7 dr) in EtOAc (5 mL) at rt. The solution was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) for 18 h. The reaction mixture was then filtered through a short plug of Celite® (eluent EtOAc) and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:2) gave **42** as a pale yellow oil (124 mg, 81%, 93:7 dr).

*Method B (From **40**):* Pd(OH)$_2$/C (50% w/w of substrate, 63 mg) was added to a stirred solution of **40** (126 mg, 0.23 mmol) EtOAc

(5 mL) at rt. The solution was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) for 18 h. The reaction mixture was then filtered through a short plug of Celite® (eluent EtOAc) and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:2) gave **42** as a pale yellow oil (26 mg, 42%, >99:1 dr); $[\alpha]_D^{25} = +20.7$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3367, 3288 (N–H, O–H), 2983, 2935 (C–H), 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, s, *Me*CMe), 1.35 (3H, s, *Me*CMe), 1.43 (9H, s, C*Me*$_3$), 2.29 (1H, dd, *J* 16.8, 9.4, C(2)H_A), 2.75 (1H, dd, *J* 16.8, 2.8, C(2)H_B), 3.36 (1H, app td, *J* 9.4, 2.8, C(3)*H*), 3.53 (3H, br s, NH_2, O*H*), 3.63 (1H, dd, *J* 11.5, 3.9, C(6)H_A), 3.73 (1H, dd, *J* 11.5, 9.9, C(6)H_B), 3.97 (1H, dd, *J* 9.4, 5.8, C(4)*H*), 4.32–4.39 (1H, m, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 25.1, 27.7 (C*Me*$_2$), 28.1 (C*Me*$_3$), 41.0 (*C*(2)), 48.1 (*C*(3)), 60.3 (*C*(6)), 77.6 (*C*(5)), 79.3 (*C*(4)), 81.2 (*C*Me$_3$), 108.2 (*C*Me$_2$), 171.5 (*C*(1)); *m*/*z* (ESI$^+$) 276 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{26}NO_5^+$ ([M+H]$^+$) requires 276.1805; found 276.1799.

4.23. *tert*-Butyl (3*R*,4*R*,5*S*)-3-*N*-isopropylamino-4,5,6-trihydroxy-4,5-*O*-isopropylidenehexanoate 43

Method A (From ***32****)*: $Pd(OH)_2$/C (50% w/w of substrate, 93 mg) was added to a stirred solution of **32** (185 mg, 0.37 mmol) EtOAc (5 mL) at rt. The solution was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) for 18 h. The reaction mixture was then filtered through a short plug of Celite® (eluent EtOAc) and the filtrate was concentrated in vacuo to give **43** as a pale yellow oil (118 mg, quant, >99:1 dr); $[\alpha]_D^{25} = -4.5$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3261 (N–H, O–H), 2978, 2935, 2876 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.10 (6H, d, *J* 6.1, CH*Me*$_2$), 1.30 (3H, s, *Me*CMe), 1.35 (3H, s, *Me*CMe), 1.43 (9H, s, C*Me*$_3$), 2.56 (1H, dd, *J* 16.5, 3.9, C(2)H_A), 2.69 (1H, dd, *J* 16.5, 4.6, C(2)H_B), 2.99–3.09 (1H, m, C*H*Me$_2$), 3.33 (1H, app dt, *J* 9.9, 4.4, C(3)*H*), 3.66 (1H, dd, *J* 11.6, 9.1, C(6)H_A), 3.69 (1H, dd, *J* 11.6, 5.1, C(6)H_B), 4.18 (1H, dd, *J* 9.9, 5.7, C(4)*H*), 4.40 (1H, app dt, *J* 9.1, 5.7, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 20.0, 23.9 (CH*Me*$_2$), 25.1, 27.7 (C*Me*$_2$), 28.1 (C*Me*$_3$), 34.1 (*C*(2)), 44.9 (*C*HMe$_2$), 50.9 (*C*(3)), 60.0 (*C*(6)), 77.4 (*C*(5)), 78.1 (*C*(4)), 81.0 (*C*Me$_3$), 108.1 (*C*Me$_2$), 171.1 (*C*(1)); *m*/*z* (ESI$^+$) 318 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{32}NO_5^+$ ([M+H]$^+$) requires 318.2275; found 318.2270.

Method B (From ***42****):* Acetone (51 μL, 0.69 mmol) and $NaBH_3CN$ (87 mg, 1.4 mmol) were added sequentially to a solution of **42** (95 mg, 0.35 mmol) in MeOH (3 mL) at rt. The resultant solution was stirred at rt for 18 h and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (5 mL) and H_2O (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 3:1) gave **43** as a pale yellow oil (67 mg, 61%, >99:1 dr).

4.24. *tert*-Butyl (3*R*,4*R*,5*S*)-3-amino-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(*tert*-butyldimethylsilyloxy)hexanoate 44

Method A (From ***34****)*: $Pd(OH)_2$/C (50% w/w of substrate, 45 mg) was added to a stirred solution of **34** (89 mg, 0.15 mmol) in EtOAc (5 mL) at rt. The solution was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) for 18 h. The reaction mixture was then filtered through a short plug of Celite® (eluent EtOAc) and the filtrate was concentrated in vacuo to give **44** as a pale yellow oil (38 mg, 64%, >99:1 dr); $[\alpha]_D^{25} = -6.7$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3320 (N–H), 2982, 2956, 2933, 2859 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 0.08 (6H, app s, Si*Me*$_2$), 0.89 (9H, s, SiC*Me*$_3$), 1.29 (3H, s, *Me*CMe), 1.34 (3H, s, *Me*CMe), 1.45 (9H, s, OC*Me*$_3$), 1.81 (2H, br s, NH_2), 2.27 (1H, dd, *J* 15.9, 9.1, C(2)H_A), 2.72 (1H, dd, *J* 15.9, 3.3, C(2)H_B), 3.40 (1H, app td, *J* 9.1, 3.3, C(3)*H*), 3.53 (1H, dd, *J* 10.2, 3.4, C(6)H_A), 3.75–3.82 (1H, m, C(6)H_B), 3.92 (1H, dd, *J* 9.1, 5.1, C(4)*H*), 4.14–4.20 (1H, m, C(5)*H*); δ_C (100 MHz, $CDCl_3$) −5.6 (Si*Me*$_2$), 18.2 (SiCMe$_3$), 25.5 (*Me*CMe), 25.9 (SiC*Me*$_3$), 28.1 (*Me*CMe), 28.2 (OC*Me*$_3$), 40.8 (*C*(2)), 47.4 (*C*(3)), 62.0 (*C*(6)), 77.6 (*C*(5)), 80.4 (OCMe$_3$), 81.3 (*C*(4)), 107.8 (*C*Me$_2$), 171.7 (*C*(1)); *m*/*z* (ESI$^+$) 390 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{40}NO_5Si^+$ ([M+H]$^+$) requires 390.2670; found 390.2665.

Method B (From ***38****):* $Pd(OH)_2$/C (50% w/w of substrate, 70 mg) was added to a stirred solution of **38** (140 mg, 0.24 mmol) in EtOAc (5 mL) at rt. The solution was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) for 18 h. The reaction mixture was then filtered through a short plug of Celite® (eluent EtOAc) and the filtrate was concentrated in vacuo to give **44** as a pale yellow oil (83 mg, 89%, >99:1 dr).

4.25. *tert*-Butyl (3*R*,4*R*,5*S*)-3-*N*-isopropylamino-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(*tert*-butyldimethylsilyloxy)hexanoate 45

Method A (From ***29****)*: $Pd(OH)_2$/C (50% w/w of substrate, 67 mg) was added to a stirred solution of **29** (133 mg, 0.26 mmol) in EtOAc (5 mL) at rt. The solution was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) for 18 h. The reaction mixture was then filtered through a short plug of Celite® (eluent EtOAc) and the filtrate was concentrated in vacuo to give **45** as a pale yellow oil (72 mg, 65%, >99:1 dr); $[\alpha]_D^{25} = -8.1$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3330 (N–H), 2960, 2932, 2858 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 0.07 (6H, app s, Si*Me*$_2$), 0.89 (9H, s, SiC*Me*$_3$), 0.99 (3H, d, *J* 5.8, *Me*CHMe), 1.01 (3H, d, *J* 6.1, *Me*CHMe), 1.31 (3H, s, *Me*CMe), 1.41 (3H, s, *Me*CMe), 1.44 (9H, s, OC*Me*$_3$), 2.38 (1H, dd, *J* 15.4, 5.6, C(2)H_A), 2.53 (1H, dd, *J* 15.4, 4.0, C(2)H_B), 2.86–2.97 (1H, m, C*H*Me$_2$), 3.18–3.25 (1H, m, C(3)*H*), 3.72 (1H, dd, *J* 10.7, 6.4, C(6)H_A), 3.95 (1H, dd, *J* 10.7, 4.9, C(6)H_B), 4.05–4.11 (1H, m, C(4)*H*), 4.15–4.22 (1H, m, C(5)*H*); δ_C (100 MHz, $CDCl_3$) −5.3, −5.2 (Si*Me*$_2$), 18.5 (SiCMe$_3$), 22.3, 24.2 (CH*Me*$_2$), 25.3 (*Me*CMe), 26.0 (SiC*Me*$_3$), 27.5 (*Me*CMe), 28.1 (OC*Me*$_3$), 37.2 (*C*(2)), 44.9 (*C*HMe$_2$), 51.2 (*C*(3)), 62.3 (*C*(6)), 78.4, 78.5 (*C*(4), *C*(5)), 80.2 (OCMe$_3$), 107.8 (*C*Me$_2$), 171.7 (*C*(1)); *m*/*z* (ESI$^+$) 432 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{46}NO_5Si^+$ ([M+H]$^+$) requires 432.3140; found 432.3134.

Method B (From ***43****):* Imidazole (37 mg, 0.54 mmol), DMAP (1 mg, cat.) and TBDMSCl (27 mg, 0.18 mmol) were sequentially added to a solution of **43** (57 mg, 0.18 mmol) in CH_2Cl_2 (1.5 mL) at rt and the resultant solution was stirred at rt for 16 h. The reaction mixture was then concentrated in vacuo. The residue was dissolved in Et_2O (10 mL) and the resultant solution was washed with 1.0 M aq HCl (10 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **45** as a pale yellow oil (45 mg, 58%, >99:1 dr).

Method C (From ***44****)*: Acetone (25 μL, 0.33 mmol) and $NaBH_3CN$ (42 mg, 0.67 mmol) were added sequentially to a solution of **44** (65 mg, 0.17 mmol) in MeOH (3 mL) at rt. The resultant solution was stirred at rt for 18 h and then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (5 mL) and H_2O (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O) gave **45** as a pale yellow oil (45 mg, 62%, >99:1 dr).

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