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PAPER

On the origins of diastereoselectivity in the conjugate additions of the antipodes of lithium *N*-benzyl-(*N*-α-methylbenzyl)amide to enantiopure *cis*- and *trans*-dioxolane containing α,β-unsaturated esters†‡

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"Matching" and "mismatching" effects in the doubly diastereoselective conjugate additions of the antipodes of lithium *N*-benzyl-(*N*-α-methylbenzyl)amide to enantiopure *cis*- and *trans*-dioxolane containing α,β-unsaturated esters have been investigated. High levels of substrate control were established first upon conjugate addition of achiral lithium *N*-benzyl-*N*-isopropylamide to both *tert*-butyl (*S*,*S*,*E*)-4,5-*O*-isopropylidene-4,5-dihydroxyhex-2-enoate and *tert*-butyl (4*R*,5*S*,*E*)-4,5-*O*-isopropylidene-4,5-dihydroxyhex-2-enoate. However, upon conjugate addition of lithium (*R*)-*N*-benzyl-(*N*-α-methylbenzyl)-amide and lithium (*S*)-*N*-benzyl-(*N*-α-methylbenzyl)amide to these substrates, neither reaction pairing reinforced the apparent sense of substrate control. These reactions do not, therefore, conform to the classical doubly diastereoselective "matching" or "mismatching" pattern usually exhibited by this class of reaction. A comparison of these reactions with the previously reported doubly diastereoselective conjugate addition reactions of lithium amide reagents to analogous substrates is also discussed.

Introduction

Double asymmetric induction occurs in a reaction when two chiral species are involved. The action of one chiral species upon another will result in diastereoisomeric transition states; the lowest in energy dictating the major stereochemical outcome of the reaction, and the difference in energy between the transition states determining the degree of diastereoselectivity. Masamune *et al.* were the first to define the concept of double asymmetric induction in the context of "matched" and "mismatched" reaction pairings,[1] stating: "*the degree of asymmetric induction is approximated to be (a × b) for a matched pair and (a ÷ b) for a mismatched pair, where a and b are the diastereofacial selectivities of a substrate and a reagent, respectively.*" It is also stipulated, however, that "*the multiplicativity will be valid only in a qualitative sense*", and that "*many secondary interactions which occur in the regions remote from the reaction site are entirely ignored [in this model]*."

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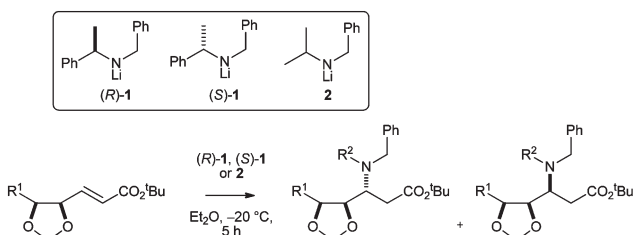
‡ Electronic supplementary information (ESI) available: Full experimental details, copies of ^{1}H and ^{13}C NMR spectra, details of molecular modelling calculations, and crystallographic data (for structures CCDC 846621–846624); see DOI: 10.1039/c2ob25099c

The individual stereochemical preferences of the two chiral species in a doubly diastereoselective reaction can either reinforce or oppose one another. For the "matched" reaction pairing both species favour the same stereochemical outcome and very high levels of diastereoselectivity are often observed.[1] When the two chiral agents favour opposite stereochemical outcomes the pairing is termed "mismatched" and a mixture of diastereoisomeric products is usually observed.[1] In the latter case, the chiral agent with the higher level of directing ability dictates the predominant stereochemical outcome of the reaction, if any. Double asymmetric induction can arise in a reaction as a result of chirality in many forms. For example, the reaction may involve a chiral substrate and a chiral reagent, a chiral substrate and chiral catalyst (with a further achiral reaction partner), rearrangement of a substrate with two stereogenic centres, or the reaction of a chiral substrate in a chiral solvent. Double asymmetric induction has shown increased utility in synthesis in recent years,[2] both as a means of improving reaction diastereoselectivity and also as a tool for mechanistic investigations.[3] The phenomenon has found application in many different classes of reaction, for example dihydroxylations,[4] epoxidations,[5] catalytic hydrogenation,[6] aldol reactions,[7] conjugate additions[8] and pericyclic reactions including Diels–Alder reactions,[9] aza-Claisen rearrangements[10] and 1,3-dipolar cycloadditions.[11] As part of a long-term goal directed towards the *ab initio* asymmetric synthesis of unnatural amino sugars we have previously investigated the effects of double asymmetric induction in the doubly

diastereoselective conjugate additions of lithium amides[12,13] (*R*)-**1** and (*S*)-**1** to enantiopure α,β-unsaturated esters containing *cis*- or *trans*-dioxolane units.[14,15] In the case of α,β-unsaturated ester **3**,[16] conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**1** was found to correspond to the empirically "matched" reaction pairing giving 3,4-*anti*-**6** as the major diastereoisomer (93 : 7 dr). Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**1** to α,β-unsaturated ester **3** represented the empirically "mismatched" reaction pairing, giving a 50 : 50 mixture of C(3)-epimers 3,4-*anti*-**7** and 3,4-*syn*-**13**. Addition of achiral lithium *N*-benzyl-*N*-isopropylamide **2** to **3** gave 3,4-*anti*-**5** as the sole diastereoisomer (>99 : 1 dr), confirming that under purely substrate control attack of the *Si* face at C(3) within **3** is preferred. The effect of having a C(6)-silyloxy substituent within the substrate was then probed by investigating the analogous α,β-unsaturated ester **4**.[17] The doubly diastereoselective conjugate additions of (*R*)-**1** and (*S*)-**1** to **4** were found to follow the same trend: addition of (*S*)-**1** proceeded to give 3,4-*anti*-**9** in >99 : 1 dr and 90% yield, representing the empirically "matched" reaction pairing. Conjugate addition of (*R*)-**1** represented the empirically "mismatched" reaction pairing, and was seen to operate under considerable substrate control as 3,4-*anti*-**10** was isolated as the major diastereoisomer, consistent with **8** being formed exclusively upon conjugate addition of **2** to **4** (Fig. 1).

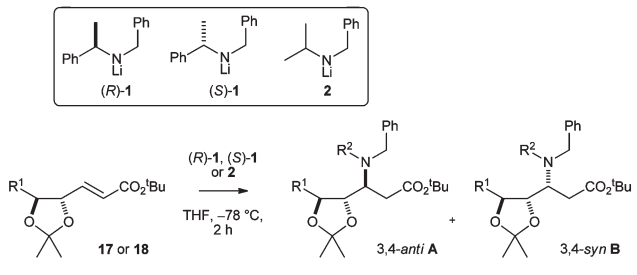
The corresponding conjugate additions of (*R*)-**1**, (*S*)-**1** and **2** to α,β-unsaturated esters **17**[18] and **18**, containing *trans*-dioxolane units, were also investigated. An empirically "matched" reaction pairing was observed upon conjugate addition of (*R*)-**1** to **17**, as 3,4-*anti*-**20** was obtained as the sole product of this reaction (>99 : 1 dr). Reaction of (*S*)-**1** with **17** gave a 35 : 65 mixture of β-amino esters 3,4-*anti*-**21** and 3,4-*syn*-**27**, representing the empirically "mismatched" reaction pairing. As the 3,4-*syn*-product **27** predominated in this system, this indicated that the lithium amide reagent was exerting the dominant stereocontrol. Conjugate addition of the achiral lithium amide **2** confirmed that the 3,4-*anti* product **19** dominated when the reaction was operating under only substrate control. However, the corresponding results for the analogous C(6)-silyloxy substituted α,β-unsaturated ester **18** did not fit this pattern. Unusually, the empirically "matched" reaction pairing was found to be the conjugate addition of (*S*)-**1** to **18**, which gave 3,4-*syn*-**30** in >99 : 1 dr. Conjugate addition of lithium amides (*R*)-**1** and **2** to **18** resulted in formation of 3,4-*anti* products **23** and **22** as the major diastereoisomers in 70 : 30 and 75 : 25 dr, respectively (Fig. 2).

Intrigued by this apparent anomaly we proposed to investigate the effects of double asymmetric induction upon the conjugate addition of lithium amides (*R*)-**1** and (*S*)-**1** to *cis*- and *trans*-dioxolane containing α,β-unsaturated esters **31** and **32** which incorporate a C(6)-methyl group in each case (Fig. 3).



α,β-unsaturated ester	R^1	lithium amide	R^2	A	B	crude dr (A:B)
3	CH_2=CH	**2**	^{i}Pr	**5**	**11**	>99:1
3	CH_2=CH	(*S*)-**1**	(*S*)-α-methylbenzyl	**6**	**12**	93:7
3	CH_2=CH	(*R*)-**1**	(*R*)-α-methylbenzyl	**7**	**13**	50:50
4	TBDMSOCH$_2$	**2**	^{i}Pr	**8**	**14**	>99:1
4	TBDMSOCH$_2$	(*S*)-**1**	(*S*)-α-methylbenzyl	**9**	**15**	>99:1
4	TBDMSOCH$_2$	(*R*)-**1**	(*R*)-α-methylbenzyl	**10**	**16**	82:18

Fig. 1 The doubly diastereoselective conjugate additions of (*R*)-**1**, (*S*)-**1** and **2** to *cis*-dioxolane containing α,β-unsaturated esters **3** and **4**.



α,β-unsaturated ester	R^1	lithium amide	R^2	A	B	crude dr (A:B)
17	CH_2=CH	**2**	^{i}Pr	**19**	**25**	91:9
17	CH_2=CH	(*R*)-**1**	(*R*)-α-methylbenzyl	**20**	**26**	>99:1
17	CH_2=CH	(*S*)-**1**	(*S*)-α-methylbenzyl	**21**	**27**	35:65
18	TBDMSOCH$_2$	**2**	^{i}Pr	**22**	**28**	75:25
18	TBDMSOCH$_2$	(*R*)-**1**	(*R*)-α-methylbenzyl	**23**	**29**	70:30
18	TBDMSOCH$_2$	(*S*)-**1**	(*S*)-α-methylbenzyl	**24**	**30**	1:>99

Fig. 2 The doubly diastereoselective conjugate additions of (*R*)-**1**, (*S*)-**1** and **2** to *trans*-dioxolane containing α,β-unsaturated esters **17** and **18**.

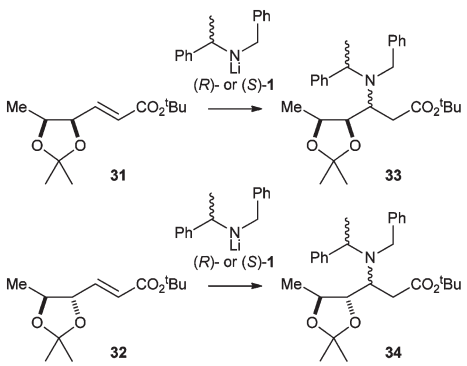


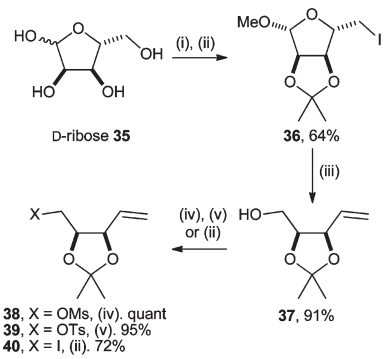
Fig. 3 The doubly diastereoselective conjugate additions of the antipodes of lithium amide **1** to *cis*- and *trans*-dioxolane containing α,β-unsaturated esters **31** and **32**.

Results and discussion

Syntheses of *cis*- and *trans*-dioxolane containing α,β-unsaturated esters

We have previously reported the synthesis of *cis*-dioxolane containing α,β-unsaturated ester **3** from D-ribose **35**, which proceeds *via* intermediate alcohol **37**.[21] It was anticipated that deoxygenation of alcohol **37** followed by cross metathesis with *tert*-butyl acrylate would give α,β-unsaturated ester **31**. Thus, acetonide protection of D-ribose **35**[19] and subsequent Appel reaction[20] gave iodide **36** in 64% yield, and treatment of **36** with BuLi

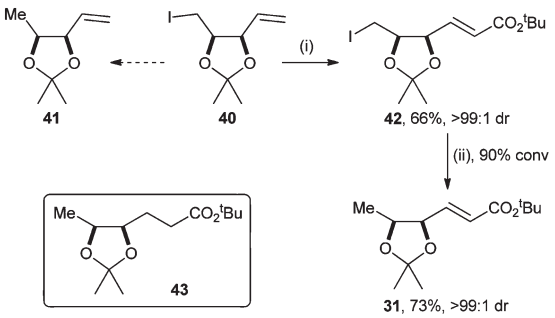
followed by *in situ* reduction of the intermediate aldehyde with DIBAL-H gave alcohol **37** in 91% yield. Alcohol **37** was then derivatised to the corresponding mesylate **38**, tosylate **39** and iodide **40** in quantitative, 95 and 72% yield, respectively, in the hope that displacement of the terminal leaving group with hydride reagents could be achieved (Scheme 1).[21]



Scheme 1 *Reagents and conditions*: (i) conc. HCl, acetone–MeOH (v/v 1 : 1), 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) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 3 h; (v) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 48 h.

Numerous attempts to convert mesylate **38**, tosylate **39** or iodide **40** into **41** were conducted. Unfortunately, reduction with $NaBH_4$, $LiAlH_4$, lithium aminoborohydrides, or Superhydride®, using various procedures,[22] gave either returned starting material or complex mixtures of products from which **41** could not be isolated. Similarly, attempted reduction of iodide **40** *via* radical processes[23] or deoxygenation of alcohol **37** using the Barton–McCombie reaction[24] (*via* the intermediacy of the corresponding xanthate ester) also failed to produce **41**. Moreover, conversion of iodide **40** into the corresponding organometallic reagents (*e.g.* organolithium or Grignard reagent) followed by treatment with a proton source[25] was also unsuccessful. It therefore became clear that an alternative route to access α,β-unsaturated ester **31** would be necessary and it was envisaged that cross-metathesis of iodide **40** with *tert*-butyl acrylate, followed by chemoselective reduction[26] of **42** could lead to α,β-unsaturated ester **31**. Hoveyda-Grubbs II catalysed cross-metathesis of iodide **40** with *tert*-butyl acrylate proceeded to give **42** in 66% yield and >99 : 1 dr. A range of different conditions were then screened for the chemoselective reduction of **42**, which typically gave mixtures of starting material **42** and the desired product **31** which were found to be easily separable. However, ester **43** was also produced *via* over reduction of **31** and it was found that this product could not be separated from **31** chromatographically. After extensive optimisation varying the reaction concentration, time and catalyst loading, a procedure was developed which gave ~90% conversion to **31** exclusively. Purification of this mixture gave **31** in 73% isolated yield, and recovered starting material **42** in 10% yield, which was then recycled. Preparation of enantiopure *cis*-dioxolane containing α,β-unsaturated ester **31** was therefore achieved *via* a six step synthesis in 20% overall yield from D-ribose **35** (Scheme 2).

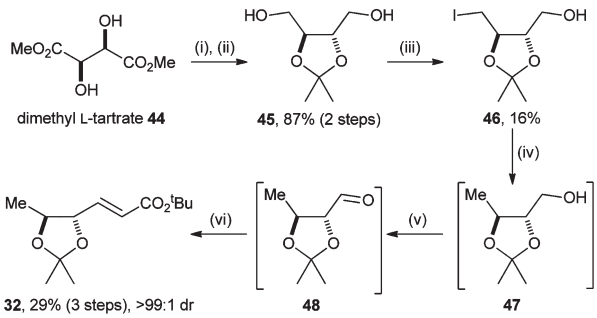
In light of the success of this approach for the synthesis of *cis*-dioxolane containing α,β-unsaturated ester **31**, a strategy



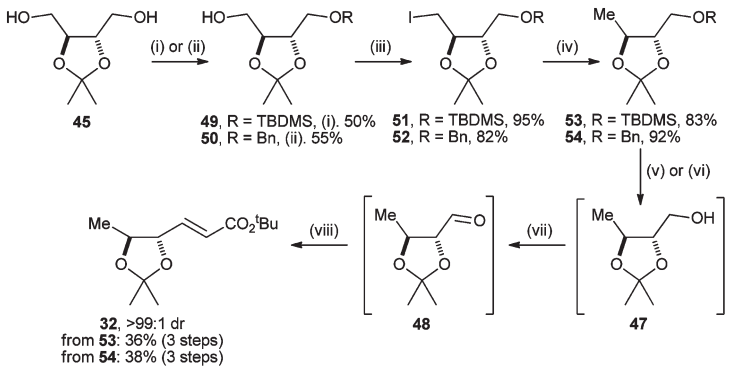
Scheme 2 *Reagents and conditions*: (i) *tert*-butyl acrylate, Hoveyda-Grubbs II, CH_2Cl_2, reflux, 24 h; (ii) H_2 (1 atm), Pd/C, Et_3N, MeOH, rt, 24 h.

involving hydrogenolytic reduction of an iodide intermediate was also adopted for the synthesis of *trans*-dioxolane containing α,β-unsaturated ester **32**. Acetonide protection of dimethyl L-tartrate **44**, followed by reduction with $LiAlH_4$ gave diol **45** in 87% yield over the two steps. Attempted mono-iodination of **45** gave poor mass return and, despite attempted optimisation, **46** was isolated in only 16% yield. Subsequent hydrogenolysis[27] of **46** gave alcohol **47** which was used immediately in a one-pot Swern–Wittig reaction. This approach avoided potential problems associated with the isolation of aldehyde **48**, and gave a 65 : 35 [(*E*) : (*Z*)] mixture of diastereoisomers from which the major product (*E*)-**32** was isolated as a single diastereoisomer (>99 : 1 dr) in 29% overall yield from **46** (Scheme 3).

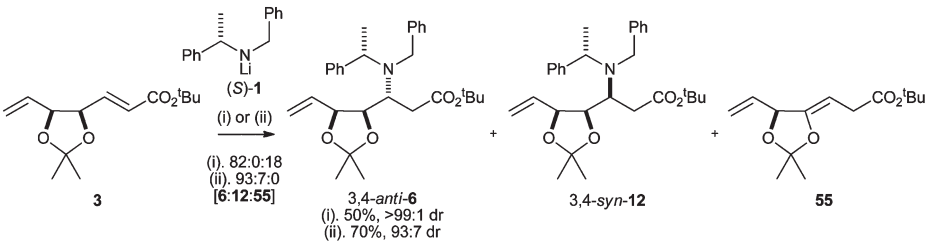
Unfortunately, the mono-iodination of **45** was not scalable as the already poor yield of iodide **46** was observed to decrease further with increasing reaction scale (up to 1.0 g). It was therefore envisaged that the existing route may be improved *via* the introduction of a protecting group strategy. Thus, the mono-*O*-TBDMS and mono-*O*-benzyl protected derivatives of **45** were prepared in 50 and 55% yield, respectively, and in each case an Appel reaction of either **49** or **50** gave the corresponding iodides **51** and **52** in 95 and 82% yield. Hydrogenolysis of *O*-TBDMS protected iodide **51** gave **53** in 83% yield, and subsequent treatment of **53** with TBAF effected *O*-TBDMS deprotection to give alcohol **47**. Treatment of the crude reaction mixture containing **47** under the one-pot Swern–Wittig olefination procedure gave a



Scheme 3 *Reagents and conditions*: (i) DMP, TsOH, PhMe, reflux, 16 h; (ii) $LiAlH_4$, THF, reflux, 16 h; (iii) imidazole, PPh_3, I_2, PhMe–MeCN (v/v 5 : 1), 60 °C, 1 h; (iv) H_2 (1 atm), $Pd(OH)_2/C$, Et_3N, MeOH, rt, 16 h; (v) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h, then Et_3N, rt; (vi) *tert*-butyl (triphenylphosphoranylidene)acetate, CH_2Cl_2, rt, 16 h.



Scheme 4 *Reagents and conditions*: (i) NaH, THF, 0 °C, 45 min, then TBDMSCl, 0 °C to rt, 16 h; (ii) NaH, THF, 0 °C, 45 min, then BnBr, 0 °C to rt, 16 h; (iii) imidazole, PPh_3, I_2, PhMe–MeCN (v/v 5 : 1), 60 °C, 1 h; (iv) H_2 (1 atm), $Pd(OH)_2$/C, Et_3N, MeOH, rt, 24 h; (v) TBAF, THF, rt, 18 h; (vi) H_2 (1 atm), Pd/C, EtOAc–AcOH (v/v 8 : 1), rt, 24 h; (vii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h, then Et_3N; (viii) *tert*-butyl (triphenylphosphoranylidene)acetate, CH_2Cl_2, rt, 16 h.



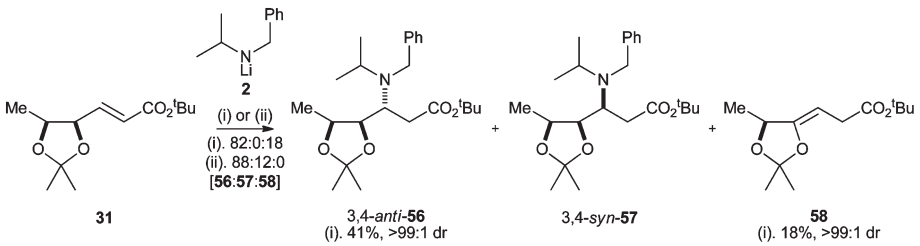
Scheme 5 *Reagents and conditions*: (i) THF, −78 °C, 2 h; (ii) Et_2O, −20 °C, 5 h.

69 : 31 [(*E*) : (*Z*)] mixture of diastereoisomers, from which the major product (*E*)-**32** was isolated in >99 : 1 dr and 36% overall yield from **53**. It was envisaged that the *O*-benzyl protected iodide **52** could be reduced to alcohol **47** in a tandem hydrogenolysis procedure, and upon treatment of a solution of **52** in MeOH with Pearlman's catalyst [$Pd(OH)_2$/C] and Et_3N under an atmosphere of hydrogen, cleavage of the C–I bond was achieved readily. However, it was found that removal of the *O*-benzyl group did not occur under these conditions, even at elevated pressures. It was therefore found to be necessary to purify **54**, which was isolated in 92% yield, before hydrogenolytic removal of the *O*-benzyl group (in the absence of Et_3N) to give **47**. A one-pot Swern–Wittig reaction on this sample of **47** then gave a 68 : 32 [(*E*) : (*Z*)] mixture of diastereoisomers, from which the major product (*E*)-**32** was isolated in >99 : 1 dr and 38% overall yield from **54**.[28] Despite the introduction of additional steps, the yield of α,β-unsaturated ester **32** was greatly improved by employing either a mono-*O*-TBDMS or a mono-*O*-benzyl protecting group strategy (giving **32** in 14 and 16% overall yield from diol **45** respectively), relative to the route in which protecting groups were not used, in which **32** was produced from diol **45** in 5% overall yield.[30] Both procedures employing protecting groups were readily amenable to scale-up and **32** was therefore produced in multigram quantities (Scheme 4).

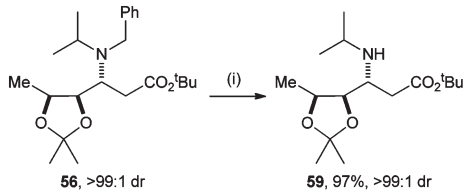
Lithium amide conjugate additions to *cis*-dioxolane containing α,β-unsaturated ester 31

We have previously encountered some problems upon conjugate addition of lithium amides to *cis*-dioxolane containing α,β-unsaturated esters under our standard reaction conditions.[14] In particular, deprotonation at the γ-position of the substrate by the basic lithium amide reagent has been observed as a common side reaction when the reaction is conducted in THF at −78 °C. For example, addition of (*S*)-**1** to **3** gave an 82 : 18 mixture of 3,4-*anti*-**6** (>99 : 1 dr) and β,γ-unsaturated ester (*Z*)-**55** upon reaction in THF at −78 °C. However, suppression of this γ-deprotonation pathway can be achieved if the conjugate addition reaction is carried out in Et_2O at −20 °C.[31] Under these conditions no evidence of **55** was observed upon conjugate addition of (*S*)-**1** to **3**, although the diastereoselectivity of the reaction was slightly compromised giving 3,4-*anti*-**6** in 70% yield and 93 : 7 dr (Scheme 5).

In light of this, the conjugate additions of lithium amides (*R*)-**1**, (*S*)-**1** and **2** to *cis*-dioxolane containing α,β-unsaturated ester **31** were carried out on a small scale in both THF at −78 °C, and Et_2O at −20 °C. This enabled us to examine the product ratios in each case and to identify which solvent may be most amenable to scale up in order to obtain enough material to correlate the stereochemical outcomes of these reactions *via* hydrogenolysis. The level of substrate control elicited by α,β-unsaturated ester **31** was established first upon conjugate addition of achiral lithium *N*-benzyl-*N*-isopropylamide **2**. When the conjugate addition of **2** to **31** was carried out in THF at −78 °C, an 82 : 18 mixture of β-amino ester 3,4-*anti*-**56** (>99 : 1 dr) and β,γ-unsaturated ester **58** was observed in the ^1H NMR spectrum of the crude reaction mixture. Chromatographic purification enabled isolation of **56** in 41% yield and >99 : 1 dr, in addition to **58** which was isolated in 18% yield as a single diastereoisomer (>99 : 1 dr). The (*Z*)-configuration within **58** was then



Scheme 6 *Reagents and conditions*: (i) THF, −78 °C, 2 h; (ii) Et_2O, −20 °C, 5 h.



Scheme 7 *Reagents and conditions*: (i) H_2, $Pd(OH)_2/C$, MeOH, rt, 16 h.

established *via* ^{1}H NMR NOE spectroscopic analysis of the purified sample. When the conjugate addition reaction was carried out in Et_2O at −20 °C, complete suppression of the γ-deprotonation pathway was achieved; however, this was accompanied by a decrease in diastereoselectivity from >99 : 1 dr in THF to 88 : 12 dr in Et_2O (Scheme 6).

The relative configuration within 3,4-*anti*-**56** was unambiguously established *via* hydrogenolysis to give a crystalline derivative. Thus, a solution of 3,4-*anti*-**56** (>99 : 1 dr) in MeOH was treated with $Pd(OH)_2/C$ under an atmosphere of hydrogen to give **59** in 97% yield and >99 : 1 dr (Scheme 7). Subsequent recrystallization and single crystal X-ray diffraction analysis‡ enabled the relative configuration within 3,4-*anti*-**59** to be established unambiguously;[32] in both cases the absolute (3*R*,4*R*,5*S*)-configurations within **56** and **59** were then assigned relative to the known configurations of the (D-ribose **35** derived) C(4) and C(5) stereogenic centres (Fig. 4).

From this established sense of substrate control it was then predicted that the conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**1** to α,β-unsaturated ester **31** would be the "matched" pairing of chiral reagents, and that the conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**1** to α,β-unsaturated ester **31** would be the "mismatched" pairing. Experimentally, however, conjugate addition of (*S*)-**1** to **31** in THF at −78 °C gave 3,4-*anti*-**60** as the major diastereoisomer (in 84 : 16 dr), with 23% conversion to β,γ-unsaturated ester (*Z*)-**58** also being observed. On changing the conditions to

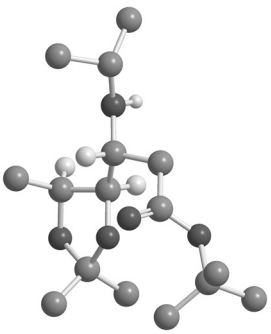
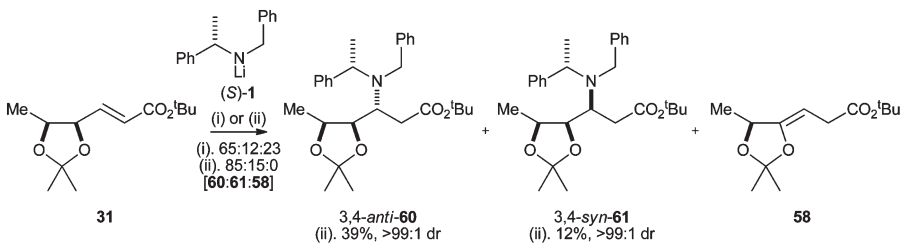


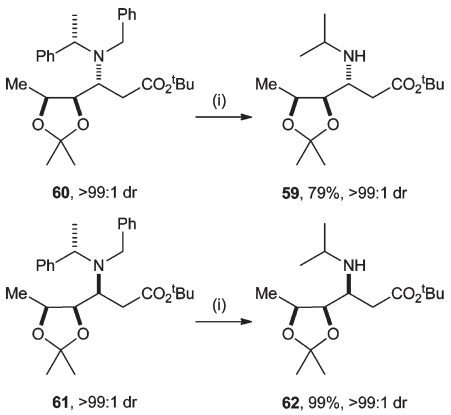
Fig. 4 X-ray crystal structure of 3,4-*anti*-**59** (selected H atoms are omitted for clarity).

Et_2O at −20 °C, the γ-deprotonation pathway was completely suppressed giving an 85 : 15 mixture of β-amino esters 3,4-*anti*-**60** and 3,4-*syn*-**61**, respectively. Upon purification, the major diastereoisomer **60** was isolated in 39% yield and >99 : 1 dr, and the minor diastereoisomer **61** was isolated in 12% yield and >99 : 1 dr (Scheme 8). The diastereoselectivity of the conjugate addition of (*S*)-**1** to **31** (under either set of reaction conditions) was therefore found to be inferior to that observed under substrate control alone.

In order to cross correlate the stereochemical outcome from the conjugate addition of (*S*)-**1** to α,β-unsaturated ester **31** with that observed upon conjugate addition of **2** to **31**, β-amino esters 3,4-*anti*-**60** and 3,4-*syn*-**61** were subjected to a tandem hydrogenolysis–reductive alkylation procedure. Hydrogenolysis of 3,4-*anti*-**60** (>99 : 1 dr) in the presence of acetone gave **59** in 79% yield and >99 : 1 dr and, hydrogenolysis of 3,4-*syn*-**61** (>99 : 1 dr) under identical conditions gave **62** in 99% yield and >99 : 1 dr. The spectroscopic data, including specific rotation, of the sample of **59** so formed were found to be identical to those for the sample obtained by hydrogenolysis of **56**, thus providing unequivocal evidence for the sense of diastereoselectivity observed upon conjugate addition of (*S*)-**1** to α,β-unsaturated ester **31** (Scheme 9).



Scheme 8 *Reagents and conditions*: (i) THF, −78 °C, 2 h; (ii) Et_2O, −20 °C, 5 h.



Scheme 9 *Reagents and conditions*: (i) H_2, $Pd(OH)_2$/C, MeOH–acetone (v/v 9 : 1), rt, 16 h.

Conjugate addition of lithium (*R*)-*N*-benzyl-(*N*-α-methylbenzyl)amide (*R*)-**1** to α,β-unsaturated ester **31** in THF at −78 °C gave an 11 : 29 : 60 mixture of the diastereoisomeric conjugate addition products 3,4-*anti*-**63** and 3,4-*syn*-**64**, and β,γ-unsaturated ester (*Z*)-**58**, respectively. It was found that upon changing the reaction conditions to Et_2O at −20 °C, the γ-deprotonation pathway was again completely suppressed giving 3,4-*anti* **63** as the major diastereoisomer (60 : 40 dr). In this instance, the major diastereoisomer **63** was isolated in 38% yield and >99 : 1 dr and the minor diastereoisomer **64** was isolated in 22% yield and >99 : 1 dr (Scheme 10). The diastereoselectivity of conjugate addition of (*R*)-**1** to **31** (under either set of reaction conditions) was therefore also found to be inferior to that observed under substrate control alone.

Both diastereoisomeric β-amino esters 3,4-*anti*-**63** and 3,4-*syn*-**64** were found to be crystalline and so single crystal X-ray diffraction analyses‡ enabled the relative configurations within both **63** and **64** to be determined (Fig. 5).[32] In both cases the absolute configurations within (3*R*,4*R*,5*S*,α*R*)-**63** and (3*S*,4*R*,5*S*,α*R*)-**64** were assigned unambiguously, relative to the known configurations of the α-methylbenzyl stereogenic centre, and the (D-ribose **35** derived) C(4) and C(5) stereogenic centres.

Tandem hydrogenolysis–reductive alkylation of **63** (>99 : 1 dr) in the presence of acetone gave **59** in 87% yield and >99 : 1 dr, and treatment of **64** (>99 : 1 dr) under identical conditions gave **62** in 84% yield and >99 : 1 dr. This sample of **59** was found to have identical spectroscopic data, including specific rotation, to those obtained for the samples of **59** derived from hydrogenolysis of either 3,4-*anti*-**56** or 3,4-*anti*-**60**, and the sample of **62** was found to have identical spectroscopic data, including specific rotation, to those obtained for the sample derived from hydrogenolysis of 3,4-*syn*-**61** (Scheme 11).

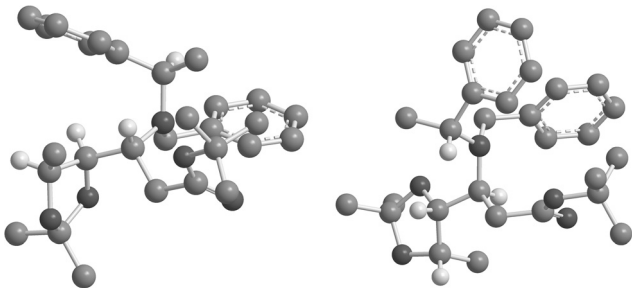
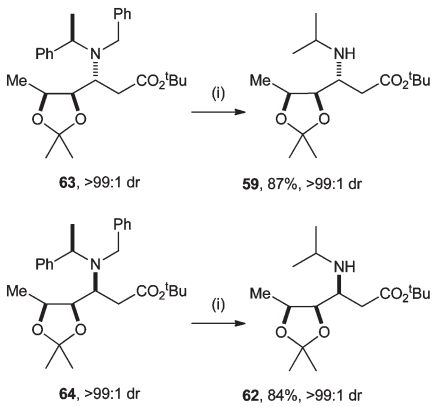
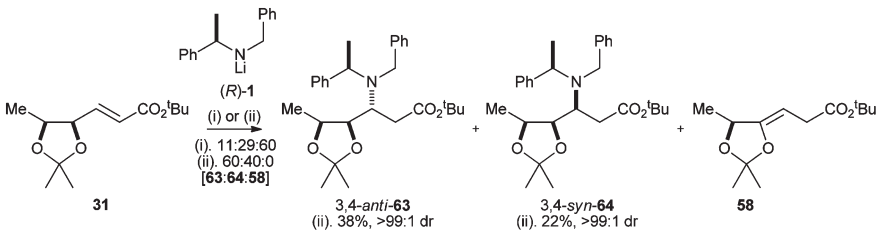


Fig. 5 X-ray crystal structures of 3,4-*anti*-**63** [*left*] and 3,4-*syn*-**64** [*right*] (selected H atoms are omitted for clarity).



Scheme 11 *Reagents and conditions*: (i) H_2, $Pd(OH)_2$/C, MeOH–acetone (v/v 9 : 1), rt, 16 h.

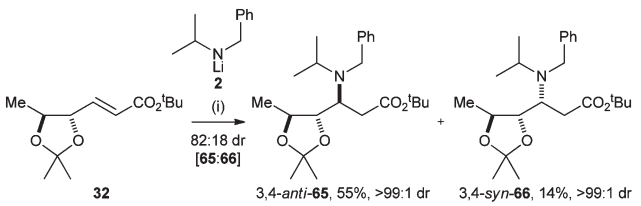
In accordance with our previous observations concerning the conjugate additions of lithium amides to *cis*-dioxolane containing α,β-unsaturated esters,[14] the formation of β,γ-unsaturated ester (*Z*)-**58** was observed in all cases when the reactions were conducted in THF at −78 °C, and this γ-deprotonation pathway was completely suppressed when the reactions were performed in Et_2O at −20 °C. Under the latter set of conditions, conjugate addition of lithium *N*-benzyl-*N*-isopropylamide **2** to *cis*-dioxolane containing α,β-unsaturated ester **31** showed a clear diastereofacial preference for formation of the 3,4-*anti* diastereoisomer, although this apparent sense of substrate control was not reinforced upon conjugate addition of either (*R*)-**1** or (*S*)-**1**.



Scheme 10 *Reagents and conditions*: (i) THF, −78 °C, 2 h; (ii) Et_2O, −20 °C, 5 h.

Lithium amide conjugate additions to *trans*-dioxolane containing α,β-unsaturated ester 32

As we have not previously observed the γ-deprotonation pathway upon conjugate addition to *trans*-dioxolane containing α,β-unsaturated esters, investigations into the conjugate addition of lithium amides (*R*)-**1**, (*S*)-**1** and **2** to *trans*-dioxolane containing α,β-unsaturated ester **32** were undertaken next under our standard conditions (*i.e.*, in THF at −78 °C). The extent of substrate control upon conjugate addition to α,β-unsaturated ester **32** was established *via* reaction of achiral lithium *N*-benzyl-*N*-isopropylamide **2** with **32**, which gave an 82 : 18 mixture of 3,4-*anti*-**65** and 3,4-*syn*-**66**, respectively. Upon purification, the major diastereoisomer **65** was isolated in 55% yield and >99 : 1 dr, whilst the minor diastereoisomer **66** was isolated in 14% yield and >99 : 1 dr (Scheme 12).



Scheme 12 *Reagents and conditions*: (i) THF, −78 °C, 2 h.

The relative configurations within 3,4-*anti*-**65** and 3,4-*syn*-**66** were unambiguously established *via* hydrogenolysis which gave a crystalline derivative: hydrogenolysis of 3,4-*anti*-**65** (>99 : 1 dr) gave **67** which was isolated in 92% yield and >99 : 1 dr. Similarly, hydrogenolysis of 3,4-*syn*-**66** (>99 : 1 dr) under identical conditions gave **68** in 66% isolated yield and >99 : 1 dr (Scheme 13). Subsequent single crystal X-ray diffraction analysis‡ established the relative configuration within **67** unambiguously,[32] with the absolute (*S*,*S*,*S*)-configuration within **67** being assigned relative to the known configurations of the (dimethyl L-tartrate **44** derived) C(4) and C(5) stereogenic centres (Fig. 6). This analysis therefore allowed the absolute (*S*,*S*,*S*)-configuration within **65** [and the absolute (3*R*,4*S*,5*S*)-configurations within **66** and **68**] to also be assigned unambiguously.

From this established sense of substrate control it was then predicted that the conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**1** to α,β-unsaturated ester **32** would be the "matched" pairing of chiral reagents, and that the conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**1** to α,β-unsaturated ester **32** would be the "mismatched" pairing. Experimentally, however, conjugate addition of (*R*)-**1** to **32** gave a 76 : 24 mixture of 3,4-*anti*-**69** and 3,4-*syn*-**70**, respectively, with chromatographic purification of the crude reaction mixture giving **69** in 98 : 2 dr and 47% isolated yield, and **70** in 13% yield and >99 : 1 dr (Scheme 14).

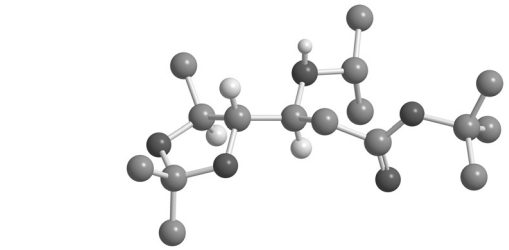
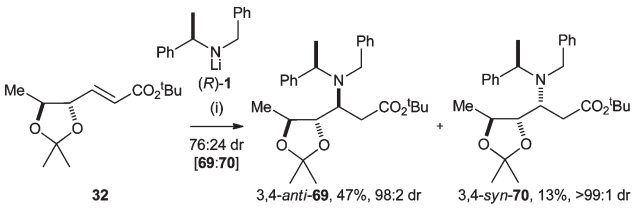
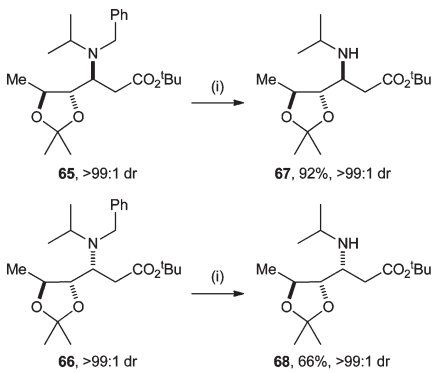


Fig. 6 X-ray crystal structure of 3,4-*anti*-**67** (selected H atoms are omitted for clarity).

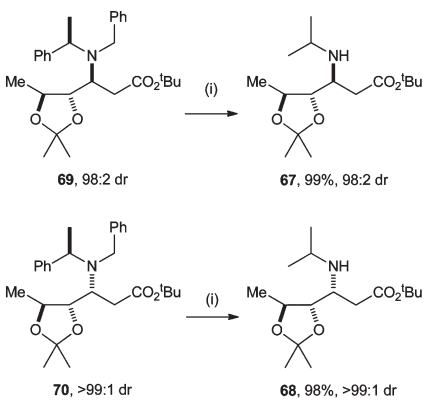


Scheme 14 *Reagents and conditions*: (i) THF, −78 °C, 2 h.

The stereochemical outcome of this reaction was then established by hydrogenolytic chemical correlation to *N*-isopropyl substituted β-amino esters **67** and **68**. Hydrogenolysis of 3,4-*anti*-**69** (98 : 2 dr) in the presence of acetone gave **67** in 99% yield and 98 : 2 dr, and hydrogenolysis of 3,4-*syn*-**70** (>99 : 1 dr) under identical conditions gave **68** in 98% yield and >99 : 1 dr (Scheme 15). These samples of **67** and **68** were found to have identical spectroscopic data, including specific rotations, to those obtained previously, providing unequivocal evidence of the



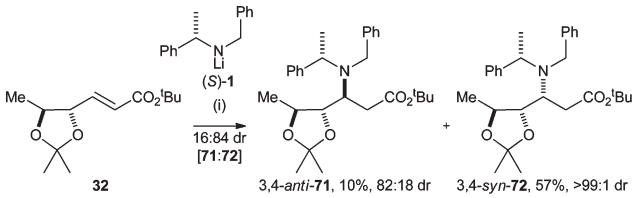
Scheme 13 *Reagents and conditions*: (i) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 16 h.



Scheme 15 *Reagents and conditions*: (i) H_2, $Pd(OH)_2/C$, MeOH–acetone (v/v 9 : 1), rt, 16 h.

sense of stereoinduction upon conjugate addition of (*R*)-**1** to α,β-unsaturated ester **32**.

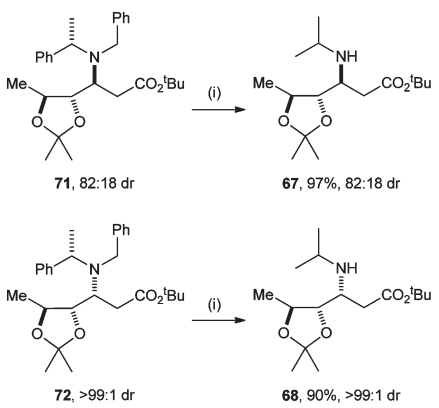
Upon conjugate addition of (*S*)-**1** to **32** the apparent sense of substrate control was found to be overwhelmed by the lithium amide reagent, giving a predominance of the 3,4-*syn*-diastereoisomer **72** (84 : 16 dr). After chromatographic purification of the crude reaction mixture, the major diastereoisomeric product **72** was isolated in 57% yield and >99 : 1 dr, and the minor diastereoisomer **71** was isolated in 10% yield and 82 : 18 dr (Scheme 16).



Scheme 16 *Reagents and conditions*: (i) THF, −78 °C, 2 h.

In each case the configurations within 3,4-*anti*-**71** and 3,4-*syn*-**72**[33] were again established by hydrogenolytic chemical correlation to the corresponding *N*-isopropyl substituted β-amino esters **67** and **68**. Hydrogenolysis of 3,4-*anti*-**71** (82 : 18 dr) in the presence of acetone effected reductive alkylation of **71** to give **67** in 97% yield and 82 : 18 dr, whereas hydrogenolysis of the sample of 3,4-*syn*-**72** (>99 : 1 dr) under the same conditions gave **68** in 90% yield and >99 : 1 dr (Scheme 17). In both cases the ^{1}H and ^{13}C NMR spectroscopic data for these samples of **67** and **68** were identical to those for the authentic samples prepared from either **65** or **69**, and either **66** or **70**, respectively, providing unequivocal evidence of the sense of stereoinduction upon conjugate addition of (*S*)-**1** to α,β-unsaturated ester **32**.

These data demonstrate that neither (*R*)-**1** nor (*S*)-**1** underwent conjugate addition to *trans*-dioxolane containing α,β-unsaturated



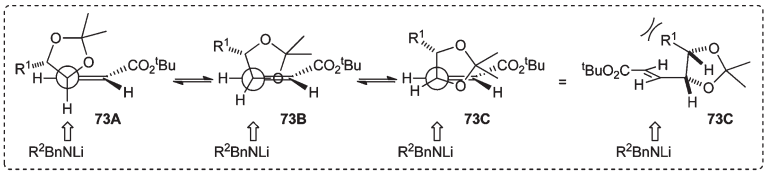
Scheme 17 *Reagents and conditions*: (i) H_2, $Pd(OH)_2$/C, MeOH–acetone (v/v 9 : 1), rt, 16 h.

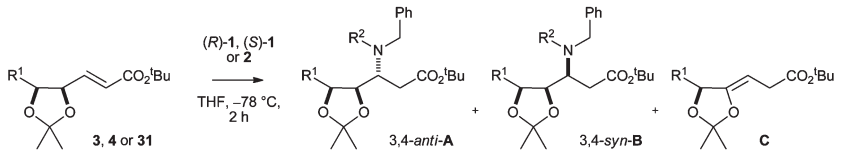
ester **32** with the very high degree of diastereoselectivity that would usually be expected from conjugate addition reactions of these lithium amide reagents. In both cases the lithium amide reagent was the dominant stereocontrolling factor. However, neither conjugate addition reaction appeared to reinforce the apparent sense of substrate control.

The origins of diastereoselectivity observed upon conjugate addition

The conjugate addition of enantiopure lithium amides [such as (*R*)-**1** and (*S*)-**1**] to achiral α,β-unsaturated esters has been shown, by us and others, to be highly diastereoselective (>95 : 5 dr) for many substrates,[13] with a highly predictable sense of diastereoselectivity. We have previously reported a transition state mnemonic which correctly and reliably rationalises the diastereoselectivity of this class of conjugate addition reactions.[34] However, given the known tendency of lithium amides to exist as a variety of aggregates in a range of solvents,[35] the true origin of diastereoselectivity within these reactions is unclear and our investigations in this area are ongoing. Our preliminary studies have shown that (i) the Michael acceptor is required to adopt an *s-cis* conformation upon conjugate addition;[3,36] (ii) only secondary lithium amides undergo highly diastereoselective transformations;[3a] and (iii) two-fold stoichiometries of the lithium amide reagent are required in a few cases.[37] Considering the conjugate additions of (*R*)-**1**, (*S*)-**1** and **2** to *cis*-dioxolane containing α,β-unsaturated esters **3**,[16] **4**[17] and **31**, the formation of the corresponding (*Z*)-β,γ-unsaturated esters **55**, **58** and **74** was observed in all cases when the reactions were conducted in THF at −78 °C.[14] We have previously postulated that formation of (*Z*)-β,γ-unsaturated esters is consistent with γ-deprotonation in reactive conformation **73A**, and it may be assumed that conjugate addition also proceeds *via* a similar reactive conformation of the α,β-unsaturated ester.[14,38] Upon inspection of the full set of data for these three substrates we determined that the "facial selectivity" of *both* conjugate addition and γ-deprotonation (*i.e.*, the [**A** + **C**] : **B** ratio) should be considered. From these data it is clear that *cis*-dioxolane containing α,β-unsaturated esters **3**, **4** and **31** all exhibit exceptionally high levels of substrate control, showing a clear diastereofacial preference for either γ-deprotonation or conjugate addition to give the corresponding 3,4-*anti* diastereoisomer. These experimentally determined reaction outcomes are consistent with approach of the lithium amide reagent on the lower face (as drawn) of the α,β-unsaturated ester in either conformations **73A**, **73B** or **73C** where the upper face is sterically blocked in all accessible conformations by the C(5)-substituent (as illustrated for **73C**, for example) and it is not possible for the expected "mismatched" lithium amide reagent to overwhelm this inherent substrate control; this trend was also observed upon reaction in Et_2O at −20 °C (Fig. 7).

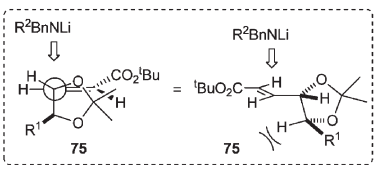
The conjugate additions of achiral lithium *N*-benzyl-*N*-isopropylamide **2** to *trans*-dioxolane containing α,β-unsaturated esters **17**,[18] **18** and **32** also displayed a clear diastereofacial preference for formation of the 3,4-*anti* diastereoisomers as the major products, although the levels of "facial selectivity" (which in this case is equivalent to the dr of crude reaction mixture as γ-deprotonation was not observed for these substrates) under substrate control alone were not as great as those observed for *cis*-dioxolane containing α,β-unsaturated esters **3**, **4** and **31**. We have previously postulated a model for conjugate addition to *trans*-dioxolane containing α,β-unsaturated esters which is consistent with this stereochemical outcome [*i.e.*, conjugate addition on the upper face (as drawn) of **75** gives rise to the corresponding 3,4-*anti*-diastereoisomeric product],[14] although other possible reactive conformations of the α,β-unsaturated ester should not be

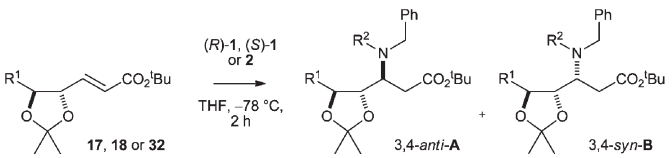




α,β-unsaturated ester	R^1	lithium amide	R^2	expected result	A	B	C	crude ratio (A:B:C)	facial selectivity [(A+C):B]	combined yield (%)[a]
31	Me	**2**	^{i}Pr	substrate control	**56**	**57**	**58**	82:0:18	>99:1	59
31	Me	(*S*)-**1**	(*S*)-α-methylbenzyl	"matched"	**60**	**61**	**58**	65:12:23	88:12	(51)[b]
31	Me	(*R*)-**1**	(*R*)-α-methylbenzyl	"mismatched"	**63**	**64**	**58**	11:29:60	71:29	(60)[b]
3	CH_2=CH	**2**	^{i}Pr	substrate control	**5**	**11**	**55**	87:0:13	>99:1	55
3	CH_2=CH	(*S*)-**1**	(*S*)-α-methylbenzyl	"matched"	**6**	**12**	**55**	82:0:18	>99:1	50
3	CH_2=CH	(*R*)-**1**	(*R*)-α-methylbenzyl	"mismatched"	**7**	**13**	**55**	36:24:40	76:24	25
4	$TBDMSOCH_2$	**2**	^{i}Pr	substrate control	**8**	**14**	**74**	88:0:12	>99:1	(82)[b]
4	$TBDMSOCH_2$	(*S*)-**1**	(*S*)-α-methylbenzyl	"matched"	**9**	**15**	**74**	75:0:25	>99:1	(90)[b]
4	$TBDMSOCH_2$	(*R*)-**1**	(*R*)-α-methylbenzyl	"mismatched"	**10**	**16**	**74**	0:0:100	>99:1	0

Fig. 7 The doubly diastereoselective conjugate additions of (*R*)-**1**, (*S*)-**1** and **2** to *cis*-dioxolane containing α,β-unsaturated esters **3**, **4** and **31**. [[a]Combined yield of both diastereoisomeric conjugate addition products, each isolated in >99 : 1 dr; [b]The combined yields in parentheses correspond to the analogous reactions in Et_2O].





α,β-unsaturated ester	R^1	lithium amide	R^2	expected result	A	B	crude ratio (A:B)	combined yield (%)[a]
32	Me	**2**	^{i}Pr	substrate control	**65**	**66**	82:18	69
32	Me	(*R*)-**1**	(*R*)-α-methylbenzyl	"matched"	**69**	**70**	76:24	60
32	Me	(*S*)-**1**	(*S*)-α-methylbenzyl	"mismatched"	**71**	**72**	16:84	67
17	CH_2=CH	**2**	^{i}Pr	substrate control	**19**	**25**	91:9	72
17	CH_2=CH	(*R*)-**1**	(*R*)-α-methylbenzyl	"matched"	**20**	**26**	>99:1	76
17	CH_2=CH	(*S*)-**1**	(*S*)-α-methylbenzyl	"mismatched"	**21**	**27**	35:65	35
18	$TBDMSOCH_2$	**2**	^{i}Pr	substrate control	**22**	**28**	75:25	63
18	$TBDMSOCH_2$	(*R*)-**1**	(*R*)-α-methylbenzyl	"matched"	**23**	**29**	70:30	66
18	$TBDMSOCH_2$	(*S*)-**1**	(*S*)-α-methylbenzyl	"mismatched"	**24**	**30**	1:>99	69

Fig. 8 The doubly diastereoselective conjugate additions of (*R*)-**1**, (*S*)-**1** and **2** to *trans*-dioxolane containing α,β-unsaturated esters **17**, **18** and **32**. [[a]Combined yield of both diastereoisomeric conjugate addition products, each isolated in >99 : 1 dr].

discounted.[38] In each case, the sense of diastereoselectivity observed upon conjugate addition of either antipode of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **1** to *trans*-dioxolane containing α,β-unsaturated esters **17**, **18** and **32** was found to correlate with reagent control, a finding which is also consistent with a decreased level of substrate control for **17**, **18** and **32** with respect to *cis*-dioxolane containing α,β-unsaturated esters **3**, **4** and **31**. Since conjugate addition to the lower face of **75** is not blocked by the C(5)-substituent, in this case the reagent control is able to overwhelm the inherent substrate control in the "mismatched" reaction. The C(5)-vinyl substituted α,β-unsaturated ester **17** was the only one of these substrates for which an enhancement in diastereoselectivity was observed upon reaction of the expected "matched" pairing of chiral reagents (Fig. 8). In both cases, molecular modelling calculations (MM2 force field) of α,β-unsaturated esters **31** and **32** produced minimum energy conformations consistent with these proposed models to rationalise the diastereoselectivity observed upon the conjugate additions of the antipodes of lithium *N*-benzyl-(*N*-α-methylbenzyl)amide **1** to α,β-unsaturated esters such as **31** and **32**.‡

As the high diastereoselectivity usually synonymous with conjugate addition of either antipode of lithium amide **1** was not observed upon conjugate addition to some of these enantiopure dioxolane containing α,β-unsaturated esters, it seems that the

lithium amide reagent may be prevented from partaking in its normal mode of reactivity. In addition, the fact that the sense of substrate control in some of these reactions is not augmented upon the conjugate addition of either chiral lithium amide (*R*)-**1** or (*S*)-**1** suggests that the factors which influence the substrate and reagent control in each case are not independent and thus the reaction pairings cannot be simply classified according to the classical "matched" and "mismatched" definitions of Masamune and co-workers.[1] These effects may be due to chelation between the lithium amide reagent and any of the pendant oxygen atoms within the α,β-unsaturated esters, giving rise to alternative reaction pathways that compete with the normal mode of reactivity.

Conclusion

Classical "matching" and "mismatching" effects in the doubly diastereoselective conjugate additions of the antipodes of lithium *N*-benzyl-(*N*-α-methylbenzyl)amide to *tert*-butyl (*S*,*S*,*E*)-4,5-*O*-isopropylidene-4,5-dihydroxyhex-2-enoate and *tert*-butyl (4*R*,5*S*,*E*)-4,5-*O*-isopropylidene-4,5-dihydroxyhex-2-enoate were not observed. The levels of substrate control were established in each case upon conjugate addition of achiral lithium *N*-benzyl-*N*-isopropylamide. However, upon conjugate addition of lithium (*R*)-*N*-benzyl-(*N*-α-methylbenzyl)amide and lithium (*S*)-*N*-benzyl-(*N*-α-methylbenzyl)amide to these substrates, neither reaction pairing reinforced the apparent sense of substrate control. These reactions do not, therefore, conform to the doubly diastereoselective "matching" or "mismatching" pattern usually exhibited by this class of reaction. Further investigations into the origin of diastereoselectivity observed upon conjugate addition of enantiopure lithium amides to dioxolane containing α,β-unsaturated esters are ongoing within our laboratories. The implication of the above finding is however clear: cyclic dioxolane protection should be avoided in favour of acyclic protection.[8a,c]

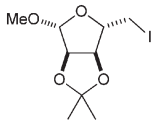
Experimental

General experimental details

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. BuLi was purchased from Sigma-Aldrich (as a solution in hexanes) and titrated against diphenylacetic acid before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[39] Water was purified by an Elix® UV-10 system. All other reagents were used as supplied 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.

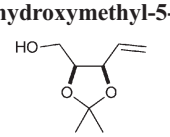
Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer on an ATR module. 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. The field was locked by external referencing to the relevant deuteron resonance. When the diastereotopic methyl groups of acetonide and isopropyl functionalities could not be unambiguously assigned, the descriptors *Me*CMe and *Me*CHMe were employed. 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.

(2*R*,3*R*,4*S*,5*S*)-2-Methoxy-3,4-*O*-isopropylidene-3,4-dihydroxy-5-iodomethyltetrahydrofuran 36



Conc aq HCl (2.0 mL) was added to a solution of D-ribose **35** (50.0 g, 0.333 mol) in acetone–MeOH (v/v 1 : 1, 700 mL). The resultant solution was heated at 60 °C for 1 h then allowed to cool to rt and neutralised by the addition of Na_2CO_3 (~10 g). The resultant suspension was filtered through Celite® (eluent EtOAc) and the filtrate was concentrated *in vacuo*. The residue was dissolved in EtOAc (250 mL) and the resultant solution was washed with H_2O (250 mL). The aqueous layer was extracted with EtOAc (2 × 250 mL) and the combined organic extracts were dried and concentrated *in vacuo*. PPh_3 (105 g, 0.40 mol) and imidazole (34.0 g, 0.500 mol) were added to the residue and the resultant mixture was dissolved in PhMe–MeCN (v/v 5 : 1, 1 L). I_2 (101 g, 0.399 mol) was then added and the reaction mixture was heated at 60 °C for 1 h, then allowed to cool to rt and diluted with Et_2O (250 mL). 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, 20 : 1) gave **36** as an orange oil (66.4 g, 64%, >99 : 1 dr);[19,40] $[\alpha]_D^{24}$ − 72.3 (*c* 1.0 in $CHCl_3$); {lit.[41] $[\alpha]_D^{24}$ − 79.8 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, s, *Me*CMe), 1.49 (3H, s, *Me*CMe), 3.17 (1H, app t, *J* 10.1, CH_AH_BI), 3.30 (1H, dd, *J* 10.1, 5.8, CH_AH_BI), 3.38 (3H, s, O*Me*), 4.45 (1H, app dd, *J* 10.1, 5.8, C(5)*H*), 4.64 (1H, app d, *J* 5.8, C(4)*H*), 4.78 (1H, app d, *J* 5.8, C(3)*H*), 5.06 (1H, app s, C(2)*H*).

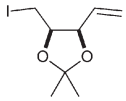
(4*S*,5*R*)-2,2-Dimethyl-4-hydroxymethyl-5-vinyl-1,3-dioxolane 37



BuLi (2.1 M in hexanes, 31.7 mL, 66.7 mmol) was added to a solution of **36** (20.9 g, 66.7 mmol, >99 : 1 dr) in THF (340 mL) at −78 °C and the resultant solution was stirred at −78 °C for 2 h. DIBAL-H (1.0 M in THF, 100 mL, 100 mmol) was then added *via* cannula and the resultant mixture was allowed to warm to rt over 16 h. Acetone (500 mL) and satd aq sodium

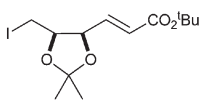
potassium tartrate (500 mL) were added sequentially and stirring was continued for 1 h at rt. The reaction mixture was then partitioned between brine (300 mL) and EtOAc (300 mL), and the aqueous layer was extracted with EtOAc (300 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–EtOAc, 2 : 1) gave **37** as a pale yellow oil (9.60 g, 91%, >99 : 1 dr);[42] $[\alpha]_D^{24}$ − 45.7 (*c* 1.0 in $CHCl_3$); {lit.[43] $[\alpha]_D^{24}$ − 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), 1.94 (1H, s, O*H*), 3.58 (2H, app t, *J* 5.5, CH_2OH), 4.24–4.30 (1H, m, C(4)*H*), 4.65 (1H, app t, *J* 7.0, C(5)*H*), 5.29 (1H, dd, *J* 10.4, 1.0, CH=CH_AH$_B$), 5.40 (1H, dd, *J* 17.4, 1.0, CH=CH$_A$*H*$_B$), 5.87 (1H, ddd, *J* 17.4, 10.4, 7.0, C*H*=CH$_2$).

(*R*,*R*)-2,2-Dimethyl-4-iodomethyl-5-vinyl-1,3-dioxolane 40



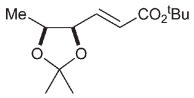
PPh_3 (396 mg, 1.51 mmol) and imidazole (129 mg, 1.89 mmol) were added to a solution of **37** (200 mg, 1.26 mmol, >99 : 1 dr) in PhMe–MeCN (v/v 5 : 1, 4 mL). I_2 (384 mg, 1.51 mmol) was then added and the resultant mixture was heated at 60 °C for 1 h. The reaction mixture was allowed to cool to rt, diluted with Et_2O (5 mL) and washed sequentially with 10% aq $Na_2S_2O_3$ (5 mL), H_2O (5 mL) and brine (5 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 2 : 1) gave **40** as a pale yellow oil (244 mg, 72%, >99 : 1 dr); $[\alpha]_D^{24}$ − 13.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2986, 2935 (C–H); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, s, *Me*CMe), 1.47 (3H, s, *Me*CMe), 3.02 (1H, dd, *J* 10.2, 6.3, CH_AH$_B$I), 3.10 (1H, dd, *J* 10.2, 7.5, CH$_A$*H*$_B$I), 4.40 (1H, app dt, *J* 7.5, 6.3, C(4)*H*), 4.59 (1H, app t, *J* 6.3, C(5)*H*), 5.29 (1H, d, *J* 10.6, CH=CH_AH$_B$), 5.39 (1H, d, *J* 17.4, CH=CH$_A$*H*$_B$), 5.81 (1H, ddd, *J* 17.4, 10.6, 6.3, C*H*=CH$_2$); δ_C (100 MHz, $CDCl_3$) 4.0 (*C*H$_2$I), 25.6, 28.2 (C*Me*$_2$), 78.4 (*C*(4)), 79.1 (*C*(5)), 109.0 (*C*Me$_2$), 119.3 (CH=*C*H$_2$), 132.4 (*C*H=CH$_2$); *m*/*z* (FI^+) 268 ($[M]^+$, 100%); HRMS (FI^+) $C_8H_{13}IO_2^+$ ($[M]^+$) requires 267.9955; found 267.9966.

***tert*-Butyl (*R*,*R*,*E*)-4,5-*O*-isopropylidene-4,5-dihydroxy-6-iodohex-2-enoate 42**



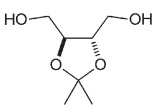
Hoveyda-Grubbs II (1.55 g, 1.82 mmol) was added to a degassed solution of **40** (4.89 g, 18.2 mmol, >99 : 1 dr) and *tert*-butyl acrylate (7.01 mL, 54.7 mmol) in CH_2Cl_2 (94 mL) and the resultant mixture was heated at reflux for 24 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–EtOAc, 20 : 1) gave **42** as a pale yellow solid (4.45 g, 66%, >99 : 1 dr); mp 39–43 °C; $[\alpha]_D^{24}$ − 0.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3031, 2978, 2934, 2903, 2852, 2361, 2342 (C–H), 1696 (C=O), 1645 (C=C); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, s, *Me*CMe), 1.50 (9H, s, C*Me*$_3$), 1.53 (3H, s, *Me*CMe), 3.02 (1H, dd, *J* 10.4, 6.5, C(6)*H*$_A$), 3.13 (1H, dd, *J* 10.4, 7.5, C(6)*H*$_B$), 4.52 (1H, app q, *J* 6.5, C(5)*H*), 4.79 (1H, app dt, *J* 6.5, 1.3, C(4)*H*), 6.09 (1H, dd, *J* 15.5, 1.3, C(2)*H*), 6.81 (1H, dd, *J* 15.5, 6.5, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 3.1 (*C*(6)), 25.5, 28.0 (C*Me*$_2$), 28.1 (C*Me*$_3$), 76.9 (*C*(4)), 78.5 (*C*(5)), 80.8 (*C*Me$_3$), 109.6 (*C*Me$_2$), 125.8 (*C*(2)), 139.8 (*C*(3)), 165.0 (*C*(1)); *m*/*z* (ESI^+) 759 ($[2M + Na]^+$, 100%), 391 ($[M + Na]^+$, 53%); HRMS (ESI^+) $C_{13}H_{21}INaO_4^+$ ($[M + Na]^+$) requires 391.0377; found 391.0365.

***tert*-Butyl (4*R*,5*S*)-4,5-*O*-isopropylidene-4,5-dihydroxyhex-2-enoate 31**



Pd/C (2.27% w/w of substrate, 23 mg) and Et_3N (5.20 mL, 27.2 mmol) were added to a solution of **42** (1.00 g, 2.72 mmol, >99 : 1 dr) in MeOH (179 mL) at rt. The resultant mixture was degassed and saturated with H_2, then left to stir under an atmosphere of H_2 (1 atm) for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo* to give a 90 : 10 mixture of **31** and **42**. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 5 : 1) gave **42** as a yellow solid (110 mg, 10%, >99 : 1 dr) and **31** as a pale yellow oil (480 mg, 73%, >99 : 1 dr); $[\alpha]_D^{24}$ + 3.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2982, 2937, 2905 (C–H), 1714 (C=O), 1659 (C=C); δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.3, C(6)*H*$_3$), 1.38 (3H, s, *Me*CMe), 1.49 (9H, s, C*Me*$_3$), 1.53 (3H, s, *Me*CMe), 4.42 (1H, app quintet, *J* 6.3, C(5)*H*), 4.64 (1H, app t, *J* 6.3, C(4)*H*), 6.00 (1H, app d, *J* 15.7, C(2)*H*), 6.73 (1H, dd, *J* 15.7, 6.3, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 16.2 (*C*(6)), 25.4, 28.0 (C*Me*$_2$), 28.1 (C*Me*$_3$), 74.0 (*C*(5)), 77.7 (*C*(4)), 80.6 (*C*Me$_3$), 108.6 (*C*Me$_2$), 124.9 (*C*(2)), 142.3 (*C*(3)), 165.3 (*C*(1)); *m*/*z* (ESI^+) 265 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{13}H_{22}NaO_4^+$ ($[M + Na]^+$) requires 265.1410; found 265.1403.

(*S*,*S*)-2,2-Dimethyl-4,5-bis(hydroxymethyl)-1,3-dioxolane 45

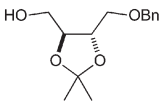


Step 1: DMP (12.0 mL, 96.9 mmol) and TsOH (128 mg, 0.65 mmol) were added to a solution of dimethyl L-tartrate **44** (11.5 g, 64.6 mmol) in PhMe (75 mL). The resultant mixture was fitted with a Dean–Stark apparatus and heated at reflux for 16 h. The reaction mixture was then cooled to rt and satd aq $NaHCO_3$ (50 mL) was added. The resultant mixture was stirred at rt for 15 min then the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic extracts were sequentially washed with H_2O (40 mL) and brine (40 mL), then dried and concentrated *in vacuo* to give dimethyl (*R*,*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate as a yellow oil (13.5 g, 96%, >99 : 1 dr);[44] $[\alpha]_D^{24}$ − 56.1 (*c* 1.0 in MeOH); {lit.[45] $[\alpha]_D^{24}$ − 49.1 (*c* 1.0 in

MeOH)}; δ_H (400 MHz, $CDCl_3$) 1.50 (6H, s, C*Me*$_2$), 3.83 (6H, s, CO_2*Me*), 4.82 (2H, s, C(4)*H*, C(5)*H*).

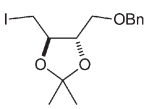
Step 2: $LiAlH_4$ (1.0 M in THF, 100 mL, 100 mmol) was added dropwise to a stirred solution of dimethyl (*R*,*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (9.32 g, 42.7 mmol, >99 : 1 dr) in THF (160 mL) at 0 °C. The resultant mixture was heated at reflux for 16 h then allowed to cool to rt. 10% aq NaOH (150 mL), H_2O (70 mL) and EtOAc (150 mL) were added and the resultant mixture was stirred at rt for 1 h. The reaction mixture was then filtered through Celite® (eluent EtOAc) and the filtrate was dried and concentrated *in vacuo* to give **45** as a pale yellow oil (6.55 g, 91%, >99 : 1 dr);[46] δ_H (400 MHz, $CDCl_3$) 1.44 (6H, s, C*Me*$_2$), 2.52 (2H, br s, O*H*), 3.67–3.74 (2H, m, CH_AH$_B$OH), 3.81–3.87 (2H, m, CH$_A$$H_B$OH), 4.02–4.05 (2H, m, C(4)*H*, C(5)*H*).

(*S*,*S*)-2,2-Dimethyl-4-benzyloxymethyl-5-hydroxymethyl-1,3-dioxolane 50



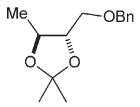
NaH (60% dispersion in mineral oil, 50 mg, 1.23 mmol) was stirred in 30–40 °C petrol (2 mL) for 10 min. The petrol was removed *via* cannula, then THF (2 mL) was added and the resultant suspension was cooled to 0 °C. A solution of **45** (200 mg, 1.23 mmol, >99 : 1 dr) in THF (2 mL) was added *via* cannula and the resultant mixture was allowed to warm to rt then stirred for 45 min. BnBr (0.15 mL, 1.23 mmol) was then added and the resultant solution was stirred at rt for 16 h. The reaction mixture was diluted with Et_2O (5 mL) and washed with satd aq $NaHCO_3$ (2 × 10 mL). The aqueous layer was separated and extracted with Et_2O (2 × 6 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 7 : 3) gave **50** as a pale yellow oil (170 mg, 55%, >99 : 1 dr);[47] $[\alpha]_D^{24}$ + 8.6 (*c* 1.0 in $CHCl_3$); {lit.[48] $[\alpha]_D^{20}$ + 8.7 (*c* 1.2 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.47 (3H, s, *Me*CMe), 1.48 (3H, s, *Me*CMe), 2.23 (1H, app q, *J* 4.3, O*H*), 3.61 (1H, dd, *J* 9.9, 5.8, CH_AH$_B$OBn), 3.70–3.77 (2H, m, CH_AH$_B$OH, CH$_A$$H_B$OBn), 3.83 (1H, dt, *J* 11.6, 4.4, CH$_A$$H_B$OH), 3.97–4.02 (1H, m, C(4)*H*), 4.09–4.14 (1H, m, C(5)*H*), 4.64 (2H, app s, CH_2Ph), 7.33–7.44 (5H, m, *Ph*).

(4*R*,5*S*)-2,2-Dimethyl-4-iodomethyl-5-benzyloxymethyl-1,3-dioxolane 52



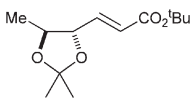
PPh_3 (1.00 g, 3.81 mmol) and imidazole (324 mg, 4.76 mmol) were added to a solution of **50** (800 mg, 3.17 mmol, >99 : 1 dr) in PhMe–MeCN (v/v 5 : 1, 10 mL). I_2 (966 mg, 3.81 mmol) was then added and the resultant solution was heated at 60 °C for 1 h. Et_2O (6 mL) was added and the resultant mixture was washed sequentially with satd aq $Na_2S_2O_3$ (10 mL), H_2O (10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 2 : 1) gave **52** as a pale yellow oil (939 mg, 82%, >99 : 1 dr);[49] $[\alpha]_D^{24}$ − 9.6 (*c* 1.0 in $CHCl_3$); {lit. [49] $[\alpha]_D^{23}$ − 10.1 (*c* 2.1 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.43 (3H, s, *Me*CMe), 1.48 (3H, s, *Me*CMe), 3.29 (1H, dd, *J* 10.6, 5.5, CH_AH$_B$I), 3.36 (1H, dd, *J* 10.6, 5.1, CH$_A$$H_B$I), 3.64 (1H, dd, *J* 10.2, 5.1, CH_AH$_B$OBn), 3.68 (1H, dd, *J* 10.2, 5.1, CH$_A$$H_B$OBn), 3.87 (1H, app dt, *J* 7.5, 5.1, C(4)*H*), 3.98 (1H, app dt, *J* 7.5, 5.1, C(5)*H*), 4.60 (2H, app s, CH_2Ph), 7.28–7.40 (5H, m, *Ph*).

(*S*,*S*)-2,2-Dimethyl-4-benzyloxymethyl-5-methyl-1,3-dioxolane 54



Pd(OH)$_2$/C (50% w/w of substrate, 100 mg) and Et_3N (0.20 mL, 1.66 mmol) were added to a solution of **52** (200 mg, 0.55 mmol, >99 : 1 dr) in MeOH (5 mL) at rt. The resultant solution was degassed and saturated with H_2, then left to stir under an atmosphere of H_2 (1 atm) for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 10 : 1) gave **54** as a yellow oil (117 mg, 92%, >99 : 1 dr);[50] $[\alpha]_D^{24}$ + 10.4 (*c* 1.0 in $CHCl_3$); {lit.[50] $[\alpha]_D^{24}$ + 10.1 (*c* 1.4 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.1, C(5)*Me*), 1.41 (3H, s, *Me*CMe), 1.44 (3H, s, *Me*CMe), 3.56 (1H, dd, *J* 10.2, 4.4, CH_AH$_B$OBn), 3.61 (1H, dd, *J* 10.2, 5.5, CH$_A$$H_B$OBn), 3.74–3.79 (1H, m, C(4)*H*), 3.94 (1H, dq, *J* 8.2, 6.1, C(5)*H*), 4.58 (1H, d, *J* 12.2, CH_AH$_B$Ph), 4.62 (1H, d, *J* 12.2, CH$_A$$H_B$Ph), 7.28–7.38 (5H, m, *Ph*).

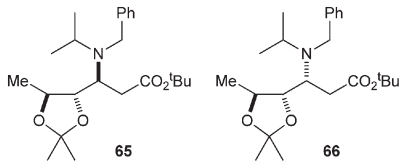
***tert*-Butyl (*S*,*S*,*E*)-4,5-*O*-isopropylidene-4,5-dihydroxyhex-2-enoate 32**



10% Pd/C (60% w/w of substrate, 4.20 g) was added to a solution of **54** (7.00 g, 29.6 mmol) in EtOAc–AcOH (v/v 8 : 1, 144 mL) at rt. The resultant mixture was degassed and saturated with H_2, then left to stir under an atmosphere of H_2 (1 atm) for 24 h. The reaction mixture was then filtered through Celite® (eluent EtOAc) and the filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (100 mL) and washed with H_2O (100 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 50 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **47** as a brown oil (4.33 g); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 5.8, C(5)*Me*), 1.40 (3H, s, *Me*CMe), 1.43 (3H, s, *Me*CMe), 3.58–3.67 (2H, m, CH_2OH), 3.78–3.83 (1H, m, C(4)*H*), 3.98–4.05 (1H, m, C(5)*H*). DMSO (2.74 mL, 38.5 mmol) was added dropwise to a solution of $(COCl)_2$ (3.00 mL, 35.5 mmol) in CH_2Cl_2 (260 mL) at −78 °C and the resultant mixture was left to stir for 10 min. A solution of **47** (4.33 g) in CH_2Cl_2 (20 mL) was added dropwise and the resultant mixture was left to stir at −78 °C for 1 h. Et_3N (11.5 mL, 59.2 mmol) was added and the reaction mixture

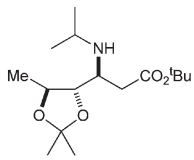
was allowed to warm to rt over 2 h. *tert*-Butyl (triphenylphosphoranylidene)acetate (11.1 g, 29.6 mmol) was added and the resultant mixture was left to stir at rt for 16 h. Satd aq Na_2CO_3 (150 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a 68 : 32 [(*E*) : (*Z*)] mixture of diastereoisomers. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 20 : 1) gave **32** as pale yellow oil (2.69 g, 38% from **54**, >99 : 1 dr); $[\alpha]_D^{24}$ + 11.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2982, 2934, 2875 (C–H), 1715 (C═O), 1661 (C═C); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.1, C(6)H_3), 1.42 (3H, s, *Me*CMe), 1.44 (3H, s, *Me*CMe), 1.49 (9H, s, CMe_3), 3.84 (1H, dq, *J* 8.5, 6.1, C(5)*H*), 4.05 (1H, ddd, *J* 8.5, 6.1, 1.3, C(4)*H*), 6.04 (1H, dd, *J*, 15.7, 1.3, C(2)*H*), 6.75 (1H, dd, *J* 15.7, 6.1, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 16.6 (*C*(6)), 26.7, 27.3 (CMe_2), 28.0 (CMe_3), 76.4 (*C*(5)), 80.7 (*C*Me_3), 81.7 (*C*(4)), 109.1 (*C*Me_2), 124.8 (*C*(2)), 142.1 (*C*(3)), 165.2 (*C*(1)); *m*/*z* (ESI$^+$) 265 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{22}NaO_4^+$ ([M + Na]$^+$) requires 265.1410; found 265.1419.

Representative procedure for lithium amide conjugate addition: *tert*-butyl (*S*,*S*,*S*)-3-(*N*-benzyl-*N*-isopropylamino)-4,5-*O*-isopropylidene-4,5-dihydroxyhexanoate 65 and *tert*-butyl (3*R*,4*S*,5*S*)-3-(*N*-benzyl-*N*-isopropylamino)-4,5-*O*-isopropylidene-4,5-dihydroxyhexanoate 66



BuLi (2.5 M in hexanes, 1.60 mL, 4.00 mmol) was added dropwise to a stirred solution of *N*-benzyl-*N*-isopropylamine (0.68 mL, 4.13 mmol) in THF (15 mL) at −78 °C and stirring was continued for 30 min. A solution of **32** (500 mg, 2.06 mmol, >99 : 1 dr) in THF (25 mL) was then added *via* cannula and the reaction mixture was stirred for 2 h. Satd aq NH_4Cl (2 mL) was then added and the reaction mixture was partitioned between Et_2O (75 mL) and H_2O (75 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic extracts were washed sequentially with 10% aq citric acid (200 mL), satd aq $NaHCO_3$ (200 mL) and brine (200 mL), then dried and concentrated *in vacuo* to give an 82 : 18 mixture of **65** and **66**. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 20 : 1) gave **66** as a yellow oil (114 mg, 14%, >99 : 1 dr); $[\alpha]_D^{24}$ − 15.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977, 2935, 2872, 2720 (C–H), 1725 (C═O); δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.4, *Me*CHMe), 1.01 (3H, d, *J* 6.4, *Me*CHMe), 1.09 (3H, d, *J* 6.5, C(6)H_3), 1.30 (3H, s, *Me*CMe), 1.32 (3H, s, *Me*CMe), 1.48 (9H, s, CMe_3), 2.67 (1H, dd, *J* 14.8, 8.0, C(2)H_A), 2.70 (1H, dd, *J* 14.8, 5.9, C(2)H_B), 3.18 (1H, septet, *J* 6.4, *CH*Me_2), 3.18–3.23 (1H, m, C(3)*H*), 3.48 (1H, dd, *J* 8.3, 2.8, C(4)*H*), 3.54 (1H, d, *J* 14.0, NC$H_A$$H_B$Ph), 4.06 (1H, d, *J* 14.0, NCH$_A$$H_B$Ph), 4.22 (1H, dq, *J* 8.3, 6.5, C(5)*H*), 7.17–7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.1, 17.3 (CH*Me*$_2$), 22.7 (*C*(6)), 26.9, 27.2 (CMe_2), 28.1 (CMe_3), 35.8 (*C*(2)), 48.7 (*C*HMe$_2$), 51.1 (*C*(3)), 51.3 (*C*H_2Ph), 73.1 (*C*(5)), 80.5 (*C*Me$_3$), 85.3 (*C*(4)), 107.3 (*C*Me$_2$), 126.5 (*p*-*Ph*), 128.1, 128.6 (*o*,*m*-*Ph*), 141.3 (*i*-*Ph*), 172.1 (*C*(1)); *m*/*z* (ESI$^+$) 392 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{38}NO_4^+$ ([M + H]$^+$) requires 392.2795; found 392.2805. Further elution gave **65** as a colourless oil (440 mg, 55%, >99 : 1 dr); $[\alpha]_D^{24}$ − 24.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977, 2933, 2875, 2718 (C–H), 1727 (C═O); δ_H (400 MHz, $CDCl_3$) 1.05 (3H, d, *J* 6.7, *Me*CHMe), 1.08 (3H, d, *J* 6.7, *Me*CHMe), 1.31 (3H, s, *Me*CMe), 1.32 (3H, d, *J* 5.6, C(6)H_3), 1.38 (3H, s, *Me*CMe), 1.49 (9H, s, CMe_3), 2.43 (1H, dd, *J* 15.5, 5.7, C(2)H_A), 2.61 (1H, dd, *J* 15.5, 6.6, C(2)H_B), 3.01 (1H, septet, *J* 6.7, C*H*Me$_2$), 3.41 (1H, app dt, *J* 6.1, 4.1, C(3)*H*), 3.69 (1H, d, *J* 14.7, NC$H_A$$H_B$Ph), 3.78 (1H, d, *J* 14.7, NCH$_A$$H_B$Ph), 3.68–3.77 (2H, m, C(4)*H*, C(5)*H*), 7.19–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.7 (*C*(6)), 19.7, 20.5 (CH*Me*$_2$), 26.9, 27.4 (CMe_2), 28.1 (CMe_3), 35.4 (*C*(2)), 48.4 (*C*HMe$_2$), 50.1 (*C*H_2Ph), 54.4 (*C*(3)), 75.7, 83.9 (*C*(4), *C*(5)), 80.0 (*C*Me$_3$), 108.0 (*C*Me$_2$), 126.6 (*p*-*Ph*), 128.0, 128.6 (*o*,*m*-*Ph*), 141.0 (*i*-*Ph*), 172.3 (*C*(1)); *m*/*z* (ESI$^+$) 392 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{38}NO_4^+$ ([M + H]$^+$) requires 392.2795; found 392.2790.

Representative procedure for hydrogenolytic chemical correlation: *tert*-butyl (*S*,*S*,*S*)-3-*N*-isopropylamino-4,5-*O*-isopropylidene-4,5-dihydroxyhexanoate 67



$Pd(OH)_2$/C (50% w/w of substrate, 125 mg) was added to a solution of **65** (250 mg, 0.64 mmol, >99 : 1 dr) in MeOH (12.9 mL) at rt. The resultant mixture was degassed and saturated with H_2, then left to stir under an atmosphere of H_2 (1 atm) for 16 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo* to give **67** as a pale yellow solid (176 mg, 92%, >99 : 1 dr);[32] mp 38–42 °C; $[\alpha]_D^{24}$ + 2.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3345, 3325 (N–H), 2975, 2932, 2873 (C–H), 1707 (C═O); δ_H (400 MHz, $CDCl_3$) 1.01 (3H, d, *J* 6.1, *Me*CHMe), 1.03 (3H, d, *J* 6.1, *Me*CHMe), 1.34 (3H, d, *J* 5.9, C(6)H_3), 1.37 (3H, s, *Me*CMe), 1.39 (3H, s, *Me*CMe), 1.46 (9H, s, CMe_3), 2.37 (1H, dd, *J* 15.3, 6.1, C(2)H_A), 2.50 (1H, dd, *J* 15.3, 5.1, C(2)H_B), 2.91 (1H, septet, *J* 6.1, C*H*Me$_2$), 3.06 (1H, app q, *J* 5.6, C(3)*H*), 3.57 (1H, dd, *J* 8.1, 5.6, C(4)*H*), 3.89 (1H, dq, *J* 8.1, 5.9, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 19.2 (*C*(6)), 22.9, 23.8 (CH*Me*$_2$), 27.0, 27.3 (CMe_2), 28.1 (CMe_3), 37.2 (*C*(2)), 45.5 (*C*HMe$_2$), 53.4 (*C*(3)), 75.2 (*C*(5)), 80.5 (*C*Me$_3$), 84.1 (*C*(4)), 107.9 (*C*Me$_2$), 171.8 (*C*(1)); *m*/*z* (ESI$^+$) 302 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{32}NO_4^+$ ([M + H]$^+$) requires 302.2326; found 302.2331.

X-ray crystal structure determination for 59, 63, 64 and 67‡

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structures were 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.[51]

X-ray crystal structure data for **59** $[C_{16}H_{31}NO_4]$:[32] M = 301.43, monoclinic, space group $P2_1$, a = 5.7565(2) Å, b = 19.4300(8) Å, c = 8.1386(3) Å, β = 96.168(2)°, V = 905.02(6) Å^3, Z = 2, μ = 0.078 mm^{-1}, colourless prism, crystal dimensions = 0.07 × 0.08 × 0.26 mm. A total of 2122 unique reflections were measured for $5 < \theta < 27$ and 1907 reflections were used in the refinement. The final parameters were wR_2 = 0.094 and R_1 = 0.043 [$I > -3.0\sigma(I)$].

X-ray crystal structure data for **63** $[C_{28}H_{39}NO_4]$:[32] M = 453.62, monoclinic, space group $P2_1$, a = 7.9717(2) Å, b = 12.5518(3) Å, c = 13.0678(3) Å, β = 95.5854(9)°, V = 1301.35 (5) Å^3, Z = 2, μ = 0.076 mm^{-1}, colourless block, crystal dimensions = 0.18 × 0.23 × 0.27 mm. A total of 3107 unique reflections were measured for $5 < \theta < 27$ and 2549 reflections were used in the refinement. The final parameters were wR_2 = 0.117 and R_1 = 0.046 [$I > -3.0\sigma(I)$].

X-ray crystal structure data for **64** $[C_{28}H_{39}NO_4]$:[32] M = 453.62, orthorhombic, space group $P2_12_12_1$, a = 9.3260(2) Å, b = 13.7383(3) Å, c = 20.3169(6) Å, V = 2603.07(11) Å^3, Z = 4, μ = 0.076 mm^{-1}, colourless block, crystal dimensions = 0.12 × 0.15 × 0.16 mm. A total of 3316 unique reflections were measured for $5 < \theta < 27$ and 2639 reflections were used in the refinement. The final parameters were wR_2 = 0.098 and R_1 = 0.045 [$I > -3.0(I)$].

X-ray crystal structure data for **67** $[C_{16}H_{31}NO_4]$:[32] M = 301.43, monoclinic, space group $C\,2$, a = 22.1832(6) Å, b = 5.8375(2) Å, c = 14.5119(4) Å, β = 105.8953(12)°, V = 1807.36 (9) Å^3, Z = 4, μ = 0.078 mm^{-1}, colourless prism, crystal dimensions = 0.14 × 0.17 × 0.90 mm. A total of 2239 unique reflections were measured for $5 < \theta < 27$ and 2239 reflections were used in the refinement. The final parameters were wR_2 = 0.121 and R_1 = 0.049 [$I > -3.0(I)$].

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16 The conjugate additions to α,β-unsaturated ester **3** were conducted in the enantiomeric series but are represented here as the antipodes for ease of comparison.
17 S. G. Davies and E. M. Foster, unpublished results; these data will be reported in full in a forthcoming publication from this laboratory.
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33 The absolute (3*R*,4*S*,5*S*,α*S*)-configuration within 3,4-*syn*-**72** was also independently verified by chemical correlation: an authentic sample of (3*S*,4*R*,5*R*,α*R*)-**72** was prepared via acetonide protection of *tert*-butyl

(3*S*,4*R*,5*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-dihydroxyhexanoate; this sample was found to have identical ^{1}H and ^{13}C NMR spectroscopic data (and an equal and opposite specific rotation) to those of (3*R*,4*S*,5*S*,α*S*)-**72**. For the preparation of *tert*-butyl (3*S*,4*R*,5*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-dihydroxyhexanoate, see: K. Csatayová, S. G. Davies, J. A. Lee, P. M. Roberts, A. J. Russell, J. E. Thomson and D. L. Wilson, *Org. Lett.*, 2011, **13**, 2606.

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