Parallel kinetic resolution of *tert*-butyl (*RS*)-3-oxy-substituted cyclopent-1-ene-carboxylates for the asymmetric synthesis of 3-oxy-substituted cispentacin and transpentacin derivatives†

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tert-Butyl (*RS*)-3-methoxy- and (*RS*)-3-*tert*-butyldiphenylsilyloxy-cyclopent-1-ene-carboxylates display excellent levels of enantiorecognition in mutual kinetic resolutions with both lithium (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and lithium (*RS*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide. A 50 : 50 pseudoenantiomeric mixture of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide allows for the efficient parallel kinetic resolution of the *tert*-butyl (*RS*)-3-oxy-substituted cyclopent-1-ene-carboxylates, affording differentially protected 3-oxy-substituted cispentacin derivatives in high yield and >98% de. Subsequent *N*-deprotection and hydrolysis provides access to 3-oxy-substituted cispentacin derivatives in good yield, and in >98% de and >98% ee, while stereoselective epimerisation and subsequent deprotection affords the corresponding transpentacin analogues in good yield, and in >98% de and >98% ee.

Introduction

The asymmetric synthesis of vicinal amino alcohols has attracted a great deal of interest in both academic and industrial arenas due to the ubiquitous nature of this functionality in natural products, and the potent biological activity of substrates containing this moiety.[1] In this laboratory the asymmetric synthesis of vicinal amino alcohols has been approached through conjugate addition of a homochiral lithium amide to an α,β-unsaturated ester, either coupled with *in situ* oxidation of the intermediate β-amino enolate,[2] or through addition to acyclic α,β-unsaturated esters bearing a γ-oxy functionality.[3] In the latter category, acyclic α,β-unsaturated esters **2** and **3** (bearing a γ-stereogenic centre) show only low levels of substrate control and, although "matching" and "mismatching" effects have been noted,[4] the additions proceed, in each case, under the dominant stereocontrol of the homochiral lithium amide **1** (reagent control), with high levels of diastereofacial selectivity being observed (Fig. 1).[3b]

In contrast to these acyclic examples, 3- and 5-alkyl-substituted cyclopent-1-ene-carboxylates display high levels of substrate control, and we have demonstrated the efficient kinetic and parallel kinetic resolution of these substrates upon treatment with either homochiral or a pseudoenantiomeric mixture of homochiral lithium amides, respectively.[5] High levels of substrate bias for addition of the homochiral lithium amide **1** *anti* to the 3- or 5-alkyl substituent, coupled with the exceptional diastereofacial preference of **1**, provides highly selective resolutions. High levels of facial selectivity upon kinetic protonation of the intermediate enolates, *anti* to the newly installed nitrogen substituent,[6] allow ready access to single diastereoisomers of homochiral 3- or 5-alkyl-substituted 2-amino-cyclopentane-carboxylic acids.[7] The synthetic utility of these processes is greatly enhanced by the

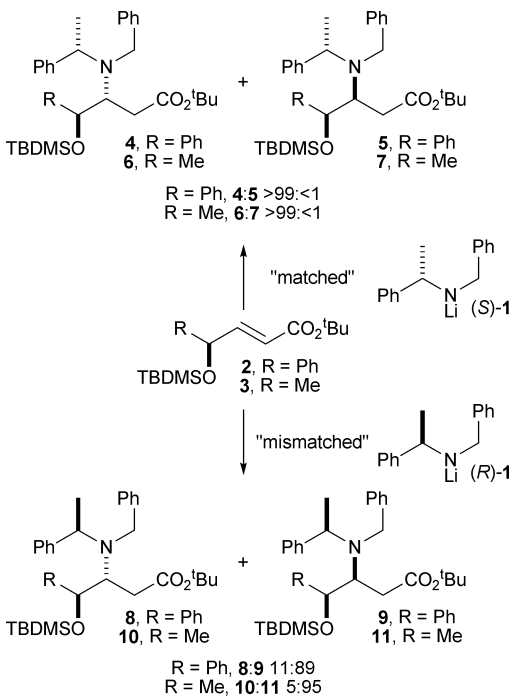

Fig. 1 Addition of homochiral lithium amide **1** to acyclic α,β-unsaturated esters **2** and **3** bearing a γ-oxy functionality.

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utilization of a parallel resolution protocol,[8,9] employing a pseudoenantiomeric mixture of lithium amides, which provides access to both enantiomeric series of addition products. Given the current interest in β-peptide secondary structure,[10,11] cyclic γ-hydroxy-β-amino acids are attractive targets for asymmetric synthesis.[12] The parallel kinetic resolution of racemic, cyclic α,β-unsaturated esters bearing a γ-oxy-substituted stereogenic centre represents an interesting synthetic challenge as the conjugate addition of a lithium amide reagent in the presence of a γ-heteroatom may potentially give rise to either *syn* stereocontrol, due to chelation, or *anti* stereocontrol, due to steric effects or dipolar repulsion (Fig. 2).[13,14] We report herein our full results within this area, and delineate the parallel kinetic resolution of 3-oxy-substituted cyclopent-1-ene-carboxylates.

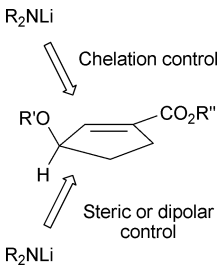


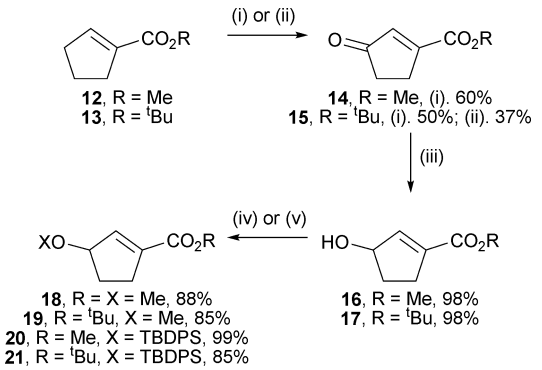
Fig. 2 Substrate control *via* chelation or steric/dipolar factors during conjugate addition of lithium amides.

Results and discussion

In investigating parallel kinetic resolution it is prudent to follow a strategy[5] of first evaluating the level of substrate control—in this system through the addition of an achiral lithium amide to the racemic α,β-unsaturated ester. In cases where high levels of substrate control are observed, the conjugate addition of a racemic lithium amide to the racemic α,β-unsaturated ester (mutual kinetic resolution) may then be performed, allowing the selectivity factor *E* to be directly determined in the absence of complicating mass action effects.[15] Finally, having established the maximum levels of enantiorecognition with each of the pseudoenantiomeric parallel kinetic resolution components, the parallel kinetic resolution utilizing a 50 : 50 mixture of pseudoenantiomeric lithium amide reagents can be performed.

Preparation of 3-oxy-substituted cyclopent-1-ene-carboxylates

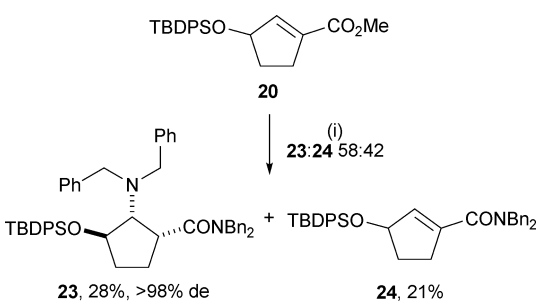
It was envisaged that addition to an unprotected alcohol would be disfavoured for electrostatic reasons and thus two hydroxyl-protecting groups were proposed, *viz.* methyl and *tert*-butyldiphenylsilyl. *O*-*tert*-Butyldiphenylsilyl (TBDPS) protection was expected to preclude chelation of the lithium amide and direct the addition under steric control, while *O*-methyl protection offered potential for either *syn* reagent delivery under chelation control, or *anti* addition due to dipolar repulsion. The desired racemic 3-oxy-substituted cyclopent-1-ene-carboxylates **18–21** were readily prepared from methyl and *tert*-butyl cyclopent-1-ene-carboxylates **12** and **13**.[16] Allylic oxidation[17] of **12** with CrO_3 in acetic anhydride and acetic acid[18] afforded enone **14** in 60% yield after chromatography and analogous oxidation of **13** gave enone **15** in 50% yield. Alternatively, palladium catalysed oxidation of **13** with *tert*-butyl hydroperoxide[19] gave **15** in 37% isolated yield. Subsequent Luche reduction[20] of enones **14** and **15** furnished **16** and **17** in 98% isolated yield in both cases. *O*-Methylation was next investigated and although treatment of **16** and **17** with methyl iodide under strongly basic conditions led to decomposition of the starting material, methylation under neutral conditions, with silver oxide and excess methyl iodide,[21] furnished the corresponding methyl ethers **18** and **19** in 88 and 85% isolated yield respectively. *O*-Silylation of **16** and **17** was readily achieved with TBDPSCl, imidazole and DMAP,[22] yielding **20** and **21** in 99 and 85% yield respectively (Scheme 1).



Scheme 1 *Reagents and conditions*: (i) CrO_3, AcOH, Ac_2O, DCM, 0–5 °C, 30 min, then $NaHCO_3$, H_2O–THF, rt, 12 h; (ii) $Pd(OH)_2/C$, K_2CO_3, ^tBuOOH, DCM, 0 °C, 4 h; (iii) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 10 min; (iv) MeI, Ag_2O, MeCN, 43 °C, 20 h; (v) TBDPSCl, imidazole, DMAP, DMF, 0 °C to rt, 12 h.

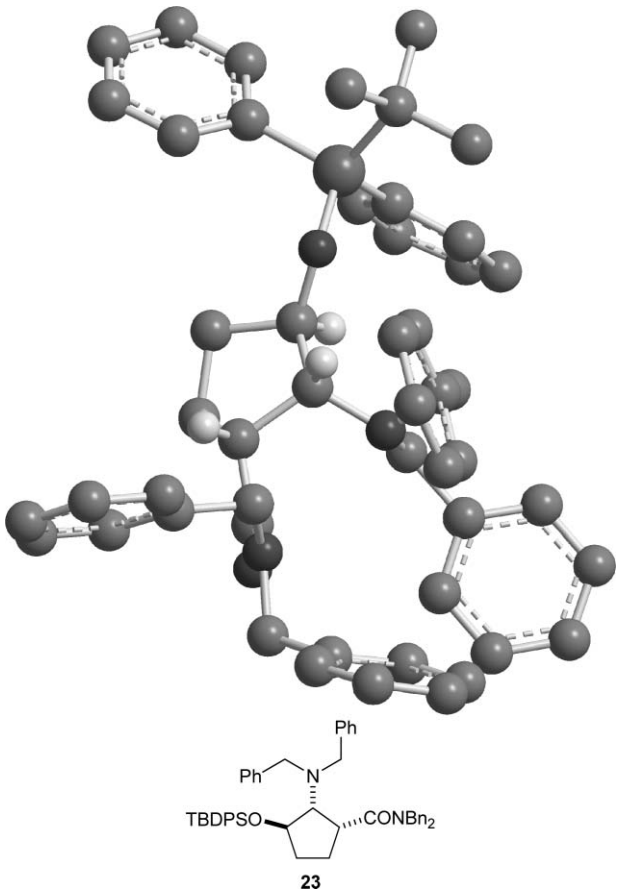
Evaluation of substrate control

Having established a route to 3-oxy-substituted esters **18–21**, the inherent substrate diastereofacial control was evaluated *via* the conjugate addition of lithium dibenzylamide **22**.[23] Preliminary experiments established that the direct treatment of unprotected hydroxy esters **16** and **17** with excess lithium amide **22** did not afford any addition products and extensive decomposition of the starting materials was observed in both cases. Addition of lithium dibenzylamide **22** to 3-*O*-TBDPS methyl ester **20**, meanwhile, afforded a 58 : 42 mixture of β-amino amide (1*RS*,2*RS*,3*RS*)-**23** (the result of sequential 1,2- and 1,4-addition) in >98% de, and α,β-unsaturated amide (*RS*)-**24**, isolated in 28 and 21% yield respectively (Scheme 2). The relative configuration within β-amino amide **23** was unambiguously established by single crystal



Scheme 2 *Reagents and conditions:* (i) lithium dibenzylamide **22** (2 eq.), THF, −78 °C, 4 h, then NH_4Cl (sat., aq.).

X-ray analysis (Fig. 3). Despite the undesirable 1,2-addition, β-amino amide **23** was produced as a single diastereoisomer, demonstrating high levels of diastereofacial control both for 1,4-addition *anti* to the 3-*O*-TBDPS substituent[5a,b] and protonation of the intermediate enolate *anti* to the amino group.[6]

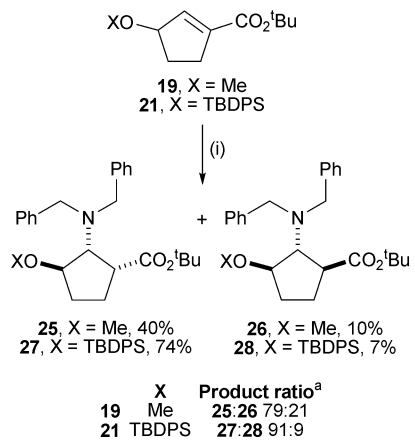


23

Fig. 3 Chem3D representation of the X-ray crystal structure of **23** (some H atoms removed for clarity).

The addition of lithium dibenzylamide **22** to the 3-oxy-substituted *tert*-butyl esters **19** and **21** was next investigated, and afforded only 1,4-addition products. Conjugate addition to 3-*O*-TBDPS *tert*-butyl ester **21**, and protonation with sat. aq. NH_4Cl, gave a 91 : 9 mixture (82% de) of the C(1)-epimeric β-amino esters (1*RS*,2*RS*,3*RS*)-**27** and (1*RS*,2*SR*,3*SR*)-**28**, respectively. Chromatography furnished β-amino esters **27** and **28** in 74 and 7% isolated yield respectively, and in >98% de in each case. Analogous addition of lithium dibenzylamide **22** to 3-*O*-Me *tert*-butyl ester **19** furnished a 79 : 21 mixture (58% de) of β-amino esters (1*RS*,2*RS*,3*RS*)-**25** and (1*RS*,2*SR*,3*SR*)-**26**, which were isolated in 40 and 10% yield respectively, as single diastereoisomers (>98% de) in both cases (Scheme 3).

The high levels of 2,3-*anti* selectivity observed in all the conjugate additions are consistent with the reactions proceeding under steric substrate bias. While this may be expected in the case of the 3-*O*-TBDPS substituent, the 3-*O*-Me ether also acts as an effective polar steric blocking group, directing addition *anti* to itself, and not participating in chelation with the incoming lithium amide. Having demonstrated that 3-oxy-substituted esters **19–21** demonstrate very high levels of substrate control upon

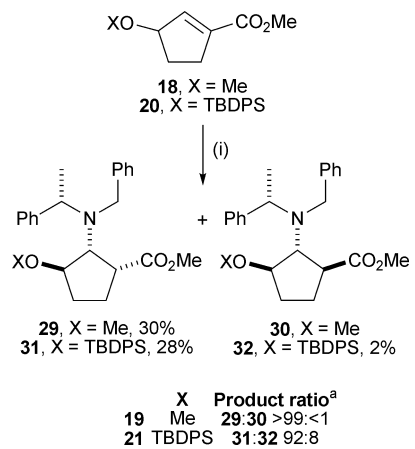


Scheme 3 *Reagents and conditions:* (i) lithium dibenzylamide **22** (5 eq.), THF, −78 °C, 4 h, then NH_4Cl (sat., aq.). [[a] Crude. Isolated yields refer to single diastereoisomers (>98% de).]

conjugate addition of lithium dibenzylamide **22**, the mutual kinetic resolution of **18–21** with lithium (*RS*)-*N*-benzyl-*N*-(α-methybenzyl)amide **1** was investigated in order to determine the maximum value of the stereoselectivity factor *E*.[15]

Mutual kinetic resolution

In mutual kinetic resolutions, mass action effects are negated and the selectivity factor *E* is independent of reaction conversion, and furthermore is equivalent to the ratio of products.[15] The conjugate addition of racemic lithium amide (*RS*)-**1** to the racemic 3-oxy-substituted methyl esters **18** and **20** was initially examined. In both cases high levels of enantiorecognition between the lithium amide reagent and α,β-unsaturated ester substrate were observed, with both additions proceeding with high selectivity (*E* >99 in both cases). The minor diastereoisomeric products were derived from incomplete selectivity in protonation of the intermediate enolates (Scheme 4). The relative configurations of the cyclopentane ring stereogenic centres within of all these addition products were assigned from ^{1}H NMR NOE difference data, while the relative



Scheme 4 *Reagents and conditions:* (i) lithium (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*RS*)-**1** (5 eq.), THF, −78 °C, 4 h, then NH_4Cl (sat., aq.). [[a] Crude. Isolated yields refer to single diastereoisomers (>98% de).]

(1*RS*,2*RS*,3*RS*,α*SR*)-configurations of major diastereoisomers **29** and **31** were unambiguously confirmed by single crystal X-ray structure analysis (Fig. 4 and Fig. 5). These analyses also affirmed that the relative configurations of the C(2) and *N*-α-methylbenzyl stereocentres were consistent with the diastereofacial preference of both the chiral lithium amide (reagent) and the chiral α,β-unsaturated ester (substrate). Notably, no evidence of amide formation was observed in the addition of lithium (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **1** to the methyl esters **18** and **20**, reflecting the sensitivity of 1,2- *versus* 1,4-addition to the steric bulk of the lithium amide reagent.

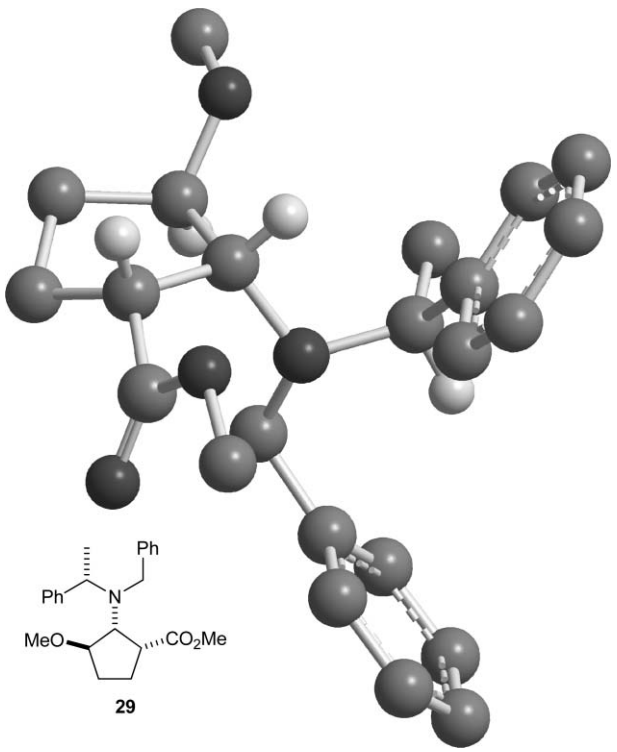


Fig. 4 Chem3D representation of the X-ray crystal structure **29** (some H atoms removed for clarity).

The addition of lithium amide (*RS*)-**1** to *tert*-butyl esters **19** and **21** was next investigated (Scheme 5). Addition of (*RS*)-**1** to 3-*O*-Me **19**, and quenching with sat. aq. NH_4Cl, gave a >99 : <1 mixture of **33** : **34**, from which **33** was isolated in 86% yield and >98% de. Addition to 3-*O*-TBDPS **21** and quenching with sat. aq. NH_4Cl gave a 90 : 10 mixture of β-amino esters **35** : **36**; however the enolate protonation selectivity could be improved by changing the proton source to 2,6-di-*tert*-butylphenol,[5a,b] giving a 97 : 3 mixture of **35** : **36**. The 2,3-*anti* arrangement, and the correlation of the C(2) and *N*-α-methylbenzyl stereogenic centres observed within β-amino esters **33–36** is indicative of excellent enantiorecognition in this system, consistent with E >99.[15] The observation of C(1)-epimeric products **35** and **36** in the case of the 3-*O*-TBDPS substituent is consistent with the steric bulk of the 3-substituent competing with the 2-amino functionality in controlling protonation selectivity, as previously observed in the kinetic resolution of 3-alkyl-substituted cyclopent-1-ene-carboxylates.[5a,b] The relative configurations of the stereogenic centres of the cyclopentane ring within addition products **33–36**

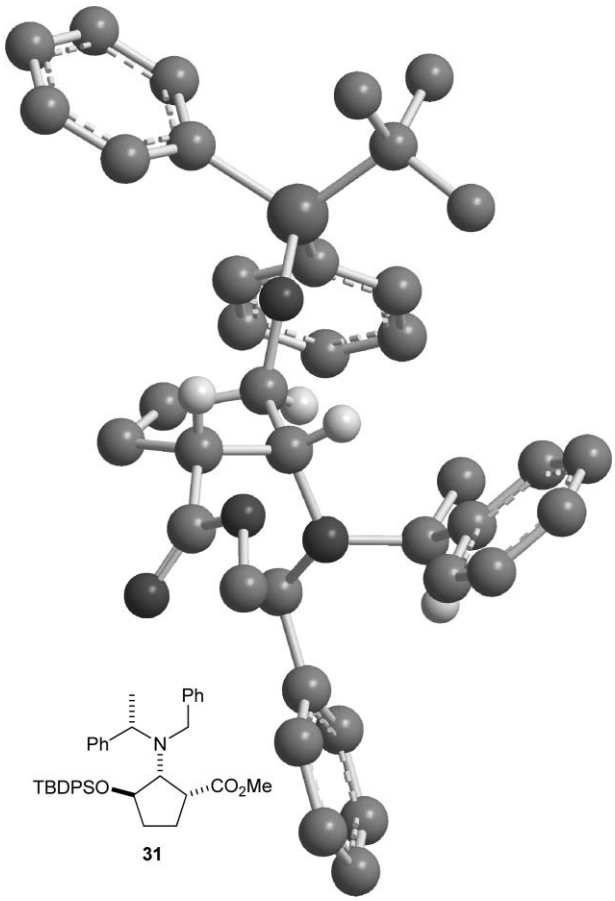
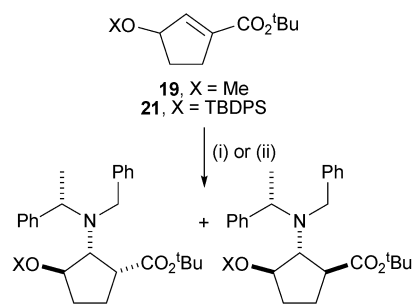


Fig. 5 Chem3D representation of the X-ray crystal structure **31** (some H atoms removed for clarity).

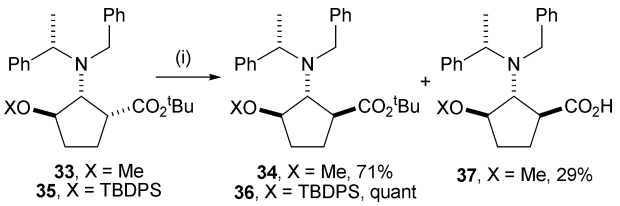


	X	Conditions	Product ratio[a]
19	Me	(i)	**33**:**34** >99:<1
21	TBDPS	(i)	**35**:**36** 90:10
21	TBDPS	(ii)	**35**:**36** 97:3

Scheme 5 *Reagents and conditions*: (i) lithium (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*RS*)-**1** (5 eq.), THF, −78 °C, 4 h, then NH_4Cl (sat., aq.); (ii) lithium (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*RS*)-**1**, THF, −78 °C, 4 h, then 2,6-di-*tert*-butylphenol. [[a] Crude. Isolated yields refer to single diastereoisomers (>98% de).]

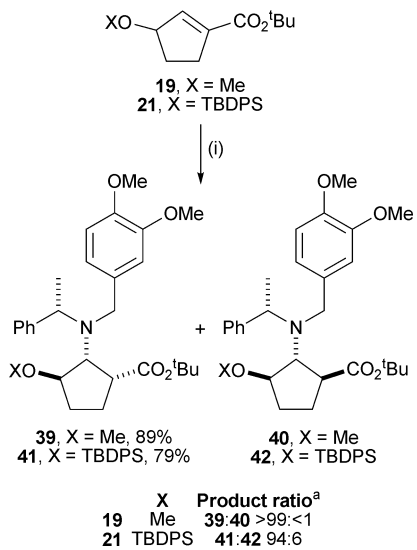
were assigned from ^{1}H NMR NOE difference data. Furthermore, the C(1)-epimeric nature of the diastereoisomers was confirmed by epimerisation of the major 1,2-*syn*-diastereoisomers **33** (>98% de) and **35** (>98% de) to the thermodynamically more stable 1,2-*anti*-diastereoisomers **34** (>98% de) and **36** (>98% de) upon treatment

with KO^{t}Bu. The epimerisation of **33** was accompanied by partial ester hydrolysis, however, yielding a separable 71 : 29 mixture of ester **34** and carboxylic acid **37**, in quantitative combined yield (Scheme 6).



Scheme 6 *Reagents and conditions*: (i) KO^{t}Bu, ^{t}BuOH–THF (1 : 1), 80 °C, 12 h.

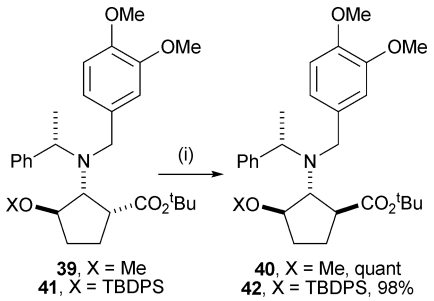
The mutual kinetic resolution of the racemic 3-*O*-Me and 3-*O*-TBDPS *tert*-butyl esters **19** and **21** and lithium (*RS*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide (*RS*)-**38** was next examined, employing the optimized reaction conditions (Scheme 7). These additions showed near identical selectivities (E >99) to the mutual kinetic resolutions with lithium amide (*RS*)-**1**, with authentic samples of the minor diastereoisomers in these reactions isolated by epimerisation of the major addition products (Scheme 8).



Scheme 7 *Reagents and conditions*: (i) lithium (*RS*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide (*RS*)-**38** (5 eq.), THF, −78 °C, 4 h, then NH_4Cl (sat., aq.). [[a] Crude. Isolated yields refer to single diastereoisomers (>98% de).]

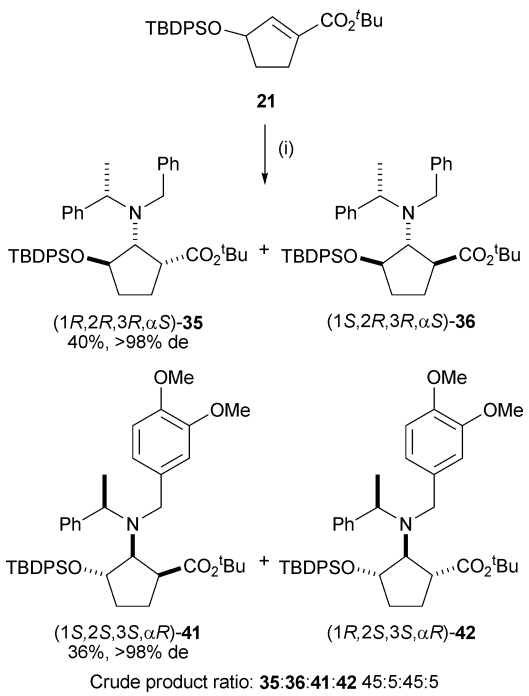
Parallel kinetic resolution

Having successfully established separately the mutual kinetic resolutions of *tert*-butyl esters **19** and **21** with lithium amides (*RS*)-**1** and (*RS*)-**38**, the parallel kinetic resolution of **19** and **21** with a pseudoenantiomeric mixture of (*S*)-**1** and (*R*)-**38** was investigated, to facilitate the asymmetric synthesis of each enantiomer of 3-oxy-substituted cispentacin. Furthermore, it was anticipated that the corresponding 3-oxy-substituted transpentacin derivatives would be available from the epimerisation of the β-amino ester



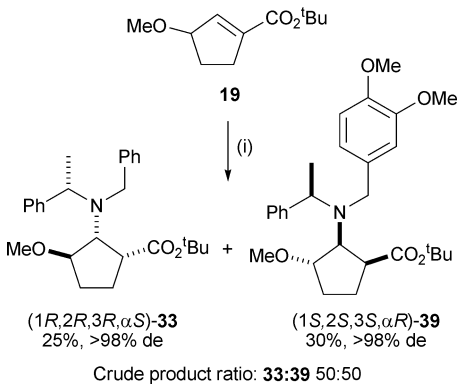
Scheme 8 *Reagents and conditions*: (i) KO^{t}Bu, ^{t}BuOH–THF (1 : 1), 80 °C, 12 h.

intermediates. The conjugate addition of a 50 : 50 mixture of lithium amides (*S*)-**1** and (*R*)-**38** to *tert*-butyl 3-*O*-TBDPS **21**, followed by protonation with 2,6-di-*tert*-butylphenol afforded a 45 : 5 : 45 : 5 mixture of β-amino esters (1*R*,2*R*,3*R*,α*S*)-**35**, (1*S*,2*R*,3*R*,α*S*)-**36**, (1*S*,2*S*,3*S*,α*R*)-**41** and (1*R*,2*S*,3*S*,α*R*)-**42**. This selectivity is consistent with identical reactivity and complementary stereoselectivities in the initial conjugate addition of the pseudoenantiomeric mixture of lithium amides (*S*)-**1** and (*R*)-**38** (E >99 in each case) to give a 50 : 50 mixture of addition products derived from each lithium amide. The minor diastereoisomers (1*S*,2*R*,3*R*,α*S*)-**36** and (1*R*,2*S*,3*S*,α*R*)-**42** derive from incomplete protonation selectivity, consistent with that previously observed in the mutual kinetic resolutions of this substrate. Facile chromatographic separation, due to the disparate polarities of the *N*-benzyl and *N*-3,4-dimethoxybenzyl protecting groups, gave **35** in 40% yield and >98% de, and **41** in 36% yield and >98% de (Scheme 9).



Scheme 9 *Reagents and conditions:* (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**1** (2.5 eq.), lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide (*R*)-**38** (2.5 eq.), THF, −78 °C, 4 h, then 2,6-di-*tert*-butylphenol.

Similar treatment of 3-*O*-Me *tert*-butyl ester **19** with a 50 : 50 mixture of (*S*)-**1** and (*R*)-**38** gave equally excellent stereoselectivity, affording a 50 : 50 mixture of β-amino esters (1*R*,2*R*,3*R*,α*S*)-**33** and (1*S*,2*S*,3*S*,α*R*)-**39** only (*E* >99). Chromatographic separation gave **33** in 25% yield and **39** in 30% yield (Scheme 10).

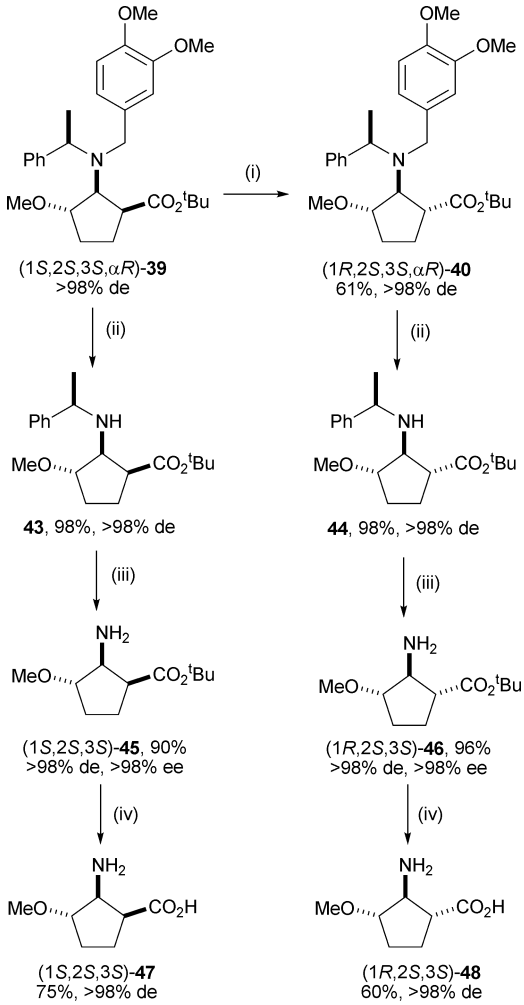


Scheme 10 *Reagents and conditions:* (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**1** (2.5 eq), lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide (*R*)-**38** (2.5 eq.), THF, −78 °C, 4 h, then NH_4Cl (sat., aq.).

Preparation of 3-methoxy-substituted cispentacin and transpentacin

Subsequent investigations focused upon deprotection and epimerisation of the 3-*O*-Me substituted derivatives to the parent 3-*O*-Me substituted cispentacin and transpentacin. *N*-3,4-Dimethoxybenzyl β-amino ester (1*S*,2*S*,3*S*,α*R*)-**39** was epimerised to give (1*R*,2*S*,3*S*,α*R*)-**40** in 61% yield and in >98% de. A three-step deprotection procedure of **39** and **40** was then implemented. Oxidative removal of the *N*-3,4-dimethoxybenzyl protecting group from **39** and **40** with DDQ gave the corresponding *N*-α-methylbenzyl protected amines **43** and **44** in 98% isolated yield in each case. Subsequent hydrogenolysis furnished the primary β-amino esters (1*S*,2*S*,3*S*)-**45** and (1*R*,2*S*,3*S*)-**46** in 90 and 96% yield respectively, and in >98% de and >98% ee[24] in each case. Acid catalysed ester hydrolysis and purification by ion-exchange chromatography gave the enantiomers of 3-*O*-Me cispentacin and transpentacin (1*S*,2*S*,3*S*)-**47** and (1*R*,2*S*,3*S*)-**48**, respectively, in good yield and >98% de in each case (Scheme 11).

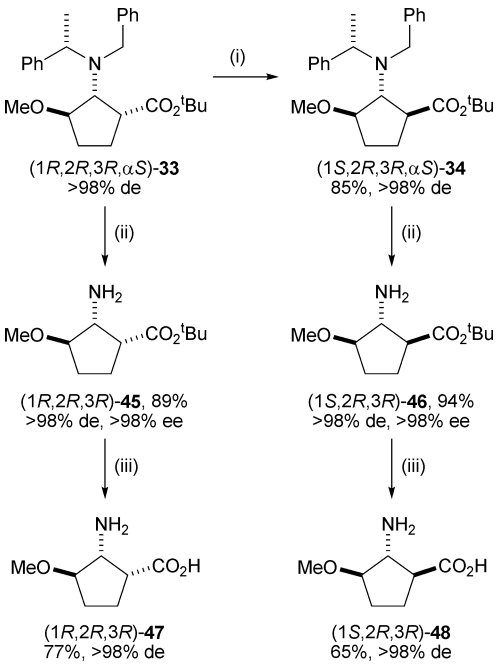
In a related strategy, epimerisation of *N*-benzyl β-amino ester (1*R*,2*R*,3*R*,α*S*)-**33** gave a 85 : 15 mixture of the C(1)-epimeric β-amino ester (1*S*,2*R*,3*R*,α*S*)-**34** and the corresponding acid derivative (1*S*,2*R*,3*R*,α*S*)-**37** only, from which **34** was isolated in 85% yield and >98% de after chromatography. *N*-Debenzylation of β-amino esters **33** and **34** with Pearlman's catalyst under H_2 (5 atm), gave the corresponding primary β-amino esters (1*R*,2*R*,3*R*)-**45** and (1*S*,2*R*,3*R*)-**46** in 89 and 94% yield, and in >98% de and >98% ee in each case.[24] The β-amino esters (1*R*,2*R*,3*R*)-**45** and (1*S*,2*R*,3*R*)-**46** were then hydrolysed by treatment with TFA, with subsequent purification by ion-exchange chromatography affording 3-*O*-Me cispentacin and transpentacin analogues (1*R*,2*R*,3*R*)-**47** and (1*S*,2*R*,3*R*)-**48** in 77 and 65% yield respectively, and in >98% de in each case (Scheme 12).



Scheme 11 *Reagents and conditions*: (i) KO^{t}Bu, ^{t}BuOH–THF (1 : 1), 80 °C, 12 h; (ii) DDQ, DCM–H_2O (5 : 1), rt, 48 h; (iii) H_2 (5 atm.), $Pd(OH)_2/C$, MeOH, rt, 24 h; (iv) TFA, DCM, rt, 16 h, then HCl, Et_2O, then Dowex 50WX8-200.

Conclusion

In conclusion, racemic *tert*-butyl 3-oxy-substituted cyclopent-1-ene-carboxylates display excellent levels of selectivity in mutual kinetic resolution with lithium (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and lithium (*RS*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide, with *E* >99 in both cases. Homochiral lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide were then employed as pseudoenantiomeric resolving agents in the parallel kinetic resolution of *tert*-butyl 3-methoxy- and 3-*tert*-butyldiphenylsilyloxy-cyclopent-1-ene-carboxylate. These reactions afforded differentially protected 3-oxy-substituted cispentacin analogues in high yield and >98% de. Subsequent *N*-deprotection and hydrolysis provides access to 3-oxy-substituted cispentacin derivatives in good yield, >98% de and >98% ee, while highly stereoselective epimerisation and deprotection affords 3-oxy-substituted transpentacin analogues in good yield, >98% de and >98% ee. The application of these substrates as



Scheme 12 *Reagents and conditions*: (i) KO^{t}Bu, ^{t}BuOH–THF (1 : 1), 80 °C, 12 h; (ii) H_2 (5 atm), $Pd(OH)_2/C$, MeOH, rt, 24 h; (iii) TFA, DCM, rt, 16 h, then HCl, Et_2O, then Dowex 50WX8-200.

organocatalysts, and as monomers for the construction of β-peptides is currently ongoing within our laboratory.

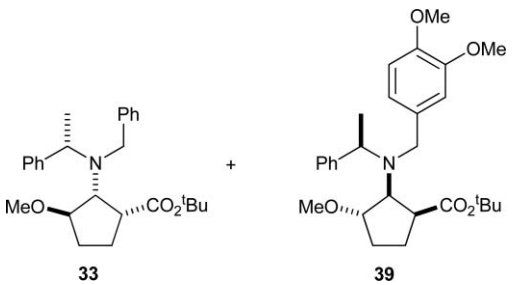
Experimental

General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[25] Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq. $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

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

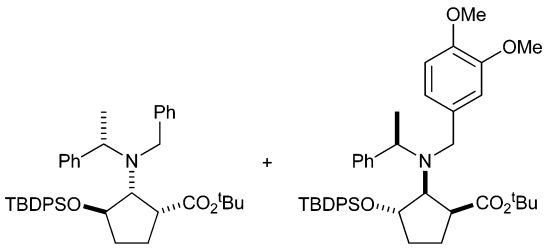
Parallel kinetic resolution of 19: *tert*-butyl (1*R*,2*R*,3*R*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-methoxy-cyclopentane-carboxylate 33 and *tert*-butyl (1*S*,2*S*,3*S*,α*R*)-2-[*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amino]-3-methoxy-cyclopentane-carboxylate 39



BuLi (2.5 M in hexanes, 0.75 mL, 1.87 mmol) was added dropwise *via* syringe to a stirred solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (200 mg, 0.95 mmol) and (*R*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amine (257 mg, 0.95 mmol) in THF (52 mL) at −78 °C. After stirring for 30 min a solution of **19** (75 mg, 0.38 mmol) in THF (3.2 mL) at −78 °C was added dropwise *via* a cannula. After stirring for a further 4 h at −78 °C the reaction mixture was quenched with a solution of 2,6-di-*tert*-butylphenol in THF and allowed to warm to rt over 1 h before being concentrated *in vacuo.* The residue was partitioned between DCM (50 mL) and 10% aq. citric acid (10 mL). The organic layer was separated and the aqueous layer was extracted with DCM (2 × 50 mL). The combined organic extracts were washed sequentially with sat aq. $NaHCO_3$ (50 mL) and brine (50 mL), dried and concentrated *in vacuo* to give a 50 : 50 mixture of **33** : **39**. Purification by chromatography (3% Et_2O in pentane) gave (1*R*,2*R*,3*R*,α*S*)-**33** as a colourless oil (39 mg, 25%, >98% de); $[\alpha]_D^{24}$ −91.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.37 [3H, d, *J* 6.9, C(α)*Me*], 1.52 (9H, s, CMe_3), 1.72–1.80 [2H, m, C(5)H_2], 2.18–2.29 [2H, m, C(4)H_2], 2.78–2.83 [1H, m, C(1)*H*], 3.10 (3H, s, O*Me*), 3.19 [1H, app t, *J* 7.6, C(2)*H*], 3.95–4.00 [1H, m, C(3)*H*], 3.99 (2H, app d, *J* 15.7, NCH_2), 4.24 [1H, q, *J* 6.9, C(α)*H*], 7.21–7.49 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.3, 25.0, 28.2, 28.3, 48.4, 50.9, 56.6, 57.9, 68.8, 79.9, 82.2, 126.1, 126.7, 127.9, 128.0, 128.6, 128.7, 129.7, 142.8, 143.1, 174.9; *m/z* (ESI$^+$) 410 ([M + H]$^+$, 100%); HRMS (ESI$^+$) found 410.2704; $C_{26}H_{36}NO_3$ ([M + H]$^+$) requires 410.2695. Further elution gave (1*S*,2*S*,3*S*,α*R*)-**39** as a pale yellow oil (53 mg, 30%, >98% de); $[\alpha]_D^{24}$ +67.4 (*c* 1.2 in $CHCl_3$); ν_{max} (film) 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 1.37 [3H, d, *J* 6.8, C(α)*Me*], 1.48 (9H, s, CMe_3), 1.67–1.77 [2H, m, C(5)H_2], 2.17–2.26 [2H, m, C(4)H_2], 2.74–2.78 [1H, m, C(1)*H*], 3.14 [3H, s, C(3)O*Me*], 3.16–3.20 [1H, m, C(2)*H*], 3.83–3.98 (2H, m, NCH_2), 3.87 (3H, s, ArO*Me*), 3.91 (3H, s, ArO*Me*), 4.01–4.06 [1H, m, C(3)*H*], 4.21 [1H, q, *J* 6.8, C(α)*H*], 6.80–7.42 (8H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.7, 24.9, 28.0, 28.1, 48.2, 50.7, 55.7, 55.8, 57.6, 68.7, 79.9, 82.0, 110.6, 111.3, 119.5, 126.5,

127.9, 135.2, 143.4, 147.3, 148.6, 174.6; *m/z* (ESI$^+$) 470 ([M + H]$^+$, 100%); HRMS (ESI$^+$) found 470.2903; $C_{43}H_{56}NO_5Si$ ([M + H]$^+$) requires 470.2906.

Parallel kinetic resolution of 21: *tert*-butyl (1*R*,2*R*,3*R*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-*tert*-butyldiphenylsilyloxy-cyclopentane-carboxylate 35 and *tert*-butyl (1*S*,2*S*,3*S*,α*R*)-2-[*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amino]-3-*tert*-butyldiphenylsilyloxy-cyclopentane-carboxylate 41



35 41

BuLi (2.5 M in hexanes, 469 μL, 1.17 mmol) was added dropwise *via* syringe to a stirred solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (125 mg, 0.59 mmol), (*R*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amine (161 mg, 0.59 mmol) in THF (16 mL) at −78 °C. After stirring for 30 min a solution of **21** (100 mg, 0.24 mmol) in THF (2 mL) at −78 °C was added dropwise *via* a cannula. After stirring for a further 4 h at −78 °C the reaction mixture was quenched with a solution of 2,6-di-*tert*-butylphenol in THF and allowed to warm to rt over 1 h before being concentrated *in vacuo.* The residue was partitioned between DCM (50 mL) and 10% aq. citric acid (10 mL). The organic layer was separated and the aqueous layer was extracted with DCM (2 × 50 mL). The combined organic extracts were washed sequentially with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL), dried and concentrated *in vacuo* to give a 45 : 5 : 45 : 5 mixture of **35** : **36** : **41** : **42**. Purification by chromatography (1% Et_2O in pentane) gave (1*R*,2*R*,3*R*,α*S*)-**35** as a colourless oil (60 mg, 40%, >98% de); $[\alpha]_D^{24}$ −22.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.09 (9H, s, SiC*Me*$_3$), 1.33–1.34 [1H, m, C(4)H_A], 1.35 [3H, d, *J* 6.6, C(α)*Me*], 1.41 (9H, s, OC*Me*$_3$), 1.52–1.28 [3H, m, C(4)H_B, C(5)H_2], 2.48–2.49 [1H, m, C(1)*H*], 3.41 [1H, app t, *J* 7.7, C(2)*H*], 4.04–4.07 [3H, m, C(α)*H*, NCH_2], 4.65–4.70 [1H, m, C(3)*H*], 7.24–7.72 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.5, 19.2, 25.0, 27.0, 28.1, 31.5, 47.3, 51.6, 57.2, 69.6, 76.0, 80.0, 126.4, 126.6, 127.4, 127.6, 128.0, 128.2, 128.3, 129.4, 129.5, 134.0, 134.9, 135.8, 135.9, 142.0, 144.1, 174.8; *m/z* (ESI$^+$) 634 ([M + H]$^+$, 100%); HRMS (ESI$^+$) found 634.3759; $C_{41}H_{52}NO_3Si$ ([M + H]$^+$) requires 634.3787. Further elution gave (1*S*,2*S*,3*S*,α*R*)-**41** as a colourless oil (59 mg, 36%, >98% de); $[\alpha]_D^{24}$ +13.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 1.07 (9H, s, SiC*Me*$_3$), 1.21–1.47 [13H, m, C(4)H_A, C(α)*Me*, OC*Me*$_3$], 1.52–1.60 [2H, m, C(5)H_2], 1.61–1.68 [2H, m, C(4)H_B], 2.46–2.49 [1H, m, C(1)*H*], 3.38–3.41 [1H, m, C(2)*H*], 3.86 (3H, s, ArO*Me*), 3.88 (3H, s, ArO*Me*), 3.95 (2H, AB system, J_{AB} 14.3, NCH_2), 4.05 [1H, q, *J* 6.7, C(α)*H*], 4.66–4.70 [1H, m, C(3)*H*], 6.76–7.71 (18H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.5, 19.1, 24.8, 26.9, 28.0, 31.5, 47.7, 51.1, 55.5, 55.6, 56.4, 69.3, 75.9, 79.7, 110.6, 111.4, 119.9, 126.4, 129.4, 133.9, 135.8, 143.9, 147.5, 148.7, 174.9; *m/z* (ESI$^+$) 694 ([M + H]$^+$, 100%); HRMS (ESI$^+$) found 694.3920; $C_{43}H_{56}NO_5Si$ ([M + H]$^+$) requires 694.3928.

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