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# Parallel kinetic resolution of *tert*-butyl (*RS*)-3-alkyl–cyclopentene-1-carboxylates for the asymmetric synthesis of 3-alkyl–cispentacin derivatives

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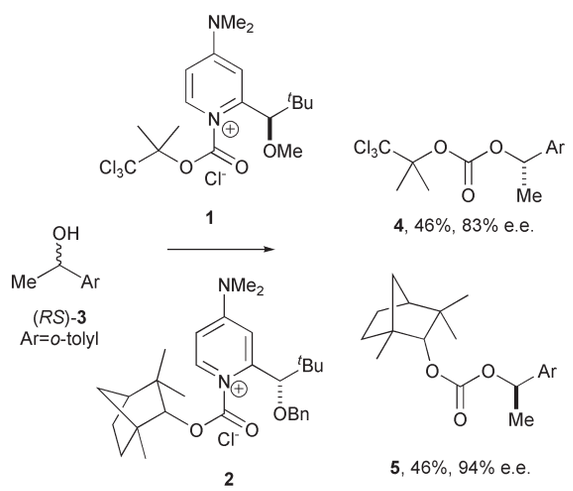
The double mutual kinetic resolution of *tert*-butyl (*RS*)-3-benzyl–cyclopentene-1-carboxylate with a 50 : 50 mixture of lithium (*RS*)-*N*-benzyl-*N*-α-methylbenzylamide and lithium (*RS*)-*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamide gives, after protonation with 2,6-di-*tert*-butylphenol, a 50 : 50 mixture of the readily separable *N*-benzyl-(1*SR*,2*RS*,3*RS*,α*RS*)- and *N*-3,4-dimethoxybenzyl-(1*SR*,2*RS*,3*RS*,α*RS*)-β-amino esters in >98% de in each case. This product distribution indicates that these amides react at very similar rates and with no mutual interference to furnish readily separable products, and are thus ideal for parallel kinetic resolution. The efficient parallel kinetic resolution ($E > 65$) of a range of *tert*-butyl (*RS*)-3-alkyl–cyclopentene-1-carboxylates with a pseudoenantiomeric mixture of homochiral lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide and lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamide gives, after separation and *N*-deprotection, a range of carboxylate protected 3-alkyl–cispentacin derivatives in >98% de and >95% ee.

## Introduction

Kinetic resolution is an underdeveloped procedure for the synthesis of enantiomerically enriched molecules.[1] While the inherent specificity of this process limits its general application within organic synthesis, the most fundamental problem with kinetic resolution is that the maximum product yield is only 50%. Furthermore, since the relative rate of a reaction depends not only upon the rate constants, but also on the relative concentrations of both reactant and substrate, as the faster reacting enantiomer is removed from a kinetic resolution reaction, the relative concentration of the slower reacting enantiomer will be augmented, and so the rate of the mismatched pairing relative to the matched pair will increase. Such concentration effects (known as mass action) influence markedly the efficiency of kinetic resolutions at conversions approaching 50%. A number of procedures have been developed to improve kinetic resolution processes, and to combat the deleterious effects of mass action as a resolution proceeds, by keeping the concentration of the reacting enantiomers identical and constant throughout the process. Dynamic kinetic resolution attempts to address these issues through the *in-situ* racemisation of the substrate undergoing kinetic resolution, and, provided that the rate of racemisation is faster than the rate of the disfavoured reaction, the ee of the product is independent of conversion. The result of this methodology, although rarely achieved, is that complete conversion of a racemic mixture to a single enantiomerically pure product is theoretically possible.[2] Alternatively, a pseudoenantiomeric mixture of two homochiral reagents may react with a racemic substrate with complementary stereoselectivities in a parallel kinetic resolution reaction to give different stereochemical, regiochemical, or differentially protected forms of the products. For parallel kinetic resolution to be viable, the pseudoenantiomeric mixture of reagents must fulfil a number of criteria:[3] they must react independently without mutual interference; the reaction rate of the pseudoenantiomeric components must be similar to ensure that racemic substrate is maintained throughout the reaction; and for ease of isolation, the two diastereoisomeric products of the reaction must be readily separable or amenable to differential deprotection. For example, Vedejs *et al.* have demonstrated that the pseudoenantiomeric chiral DMAP equivalents **1** and **2** can effect enantioselective acyl-transfer for the parallel kinetic resolution of racemic alcohol (*RS*)-**3** (Scheme 1).[4] While kinetic resolution of (*RS*)-**3** proceeds with $E = 42$ using **1**,[5] the parallel kinetic resolution of (*RS*)-**3** with **1** and **2** affords **5** in 46% yield and 94% ee (equivalent to $E > 125$) and **4** in 46% yield and 83% ee. Only recently have further efficient examples of this protocol appeared in the literature,[6] with growing interest in this area demonstrated by a number of recent reviews.[7]




**Scheme 1** Reagents and conditions: **1** (0.56 eq), **2** (0.56 eq), **3** (1 eq), $MgBr_2$ (2.25 eq), $Et_3N$ (3 eq), DCM, rt.

We have previously shown that the conjugate addition of homochiral lithium amides derived from α-methylbenzylamine to α,β-unsaturated esters represents an efficient and versatile approach to the asymmetric synthesis of β-amino acid derivatives.[8] This methodology has been extended recently to the efficient kinetic resolution of a range of *tert*-butyl (*RS*)-3-alkylcyclopentene-1-carboxylates,[9] and we have demonstrated that the maximum level of enantiorecognition between the chiral α,β-unsaturated ester and chiral lithium amide in these systems may be evaluated through their mutual kinetic resolution [addition of the (*RS*)-ester to an excess of the lithium (*RS*)-amide] a protocol initially suggested by Horeau.[10] The effects of mass action are eliminated in this protocol, meaning that the optimal stereoselectivity factor (*E*) for the reaction is identical to the diastereoselectivity observed in the reaction, and may be

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calculated independent of the reaction conversion.[11] In order to improve the efficiency of this kinetic resolution methodology, the investigation of a pseudoenantiomeric mixture of chiral lithium amides to effect the parallel kinetic resolution of *tert*-butyl (*RS*)-3-alkylcyclopentene-1-carboxylates was initiated. In order to evaluate the suitability of a range of homochiral lithium amides to act as pseudoenantiomeric resolving agents for parallel kinetic resolution, the extension of the mutual kinetic resolution strategy to a double mutual kinetic resolution protocol [addition of the (*RS*)-ester to an excess of a 50 : 50 mixture of lithium (*RS*)-amides] and the optimised results of this parallel kinetic resolution methodology are delineated herein (Fig. 1).[12]

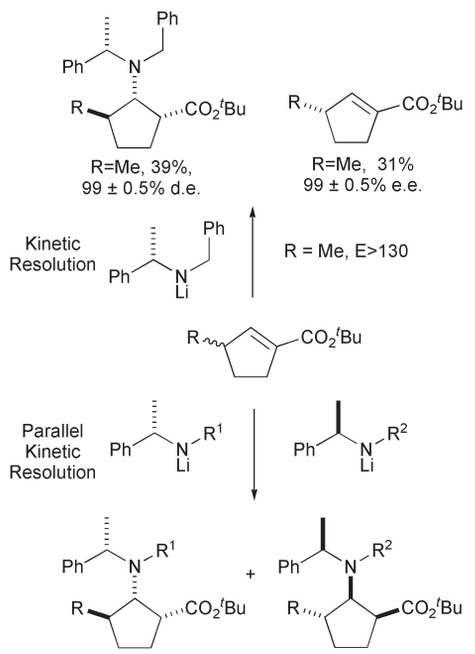
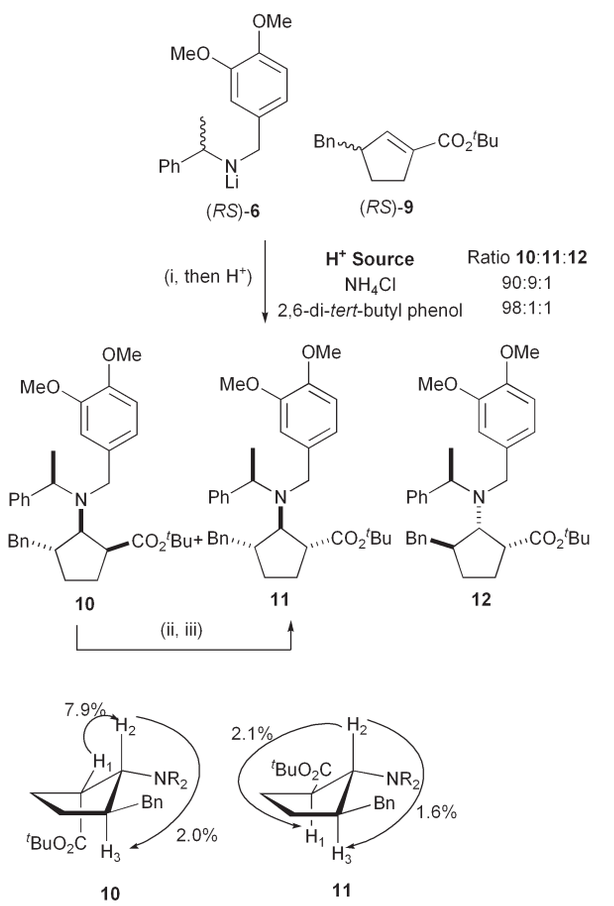



**Fig. 1** Kinetic and parallel kinetic resolution of 3-alkyl cyclopentene-1-carboxylates.

## Results and discussion

### Evaluating the efficiency of chiral lithium amides for parallel kinetic resolution: the development of a double mutual kinetic resolution protocol

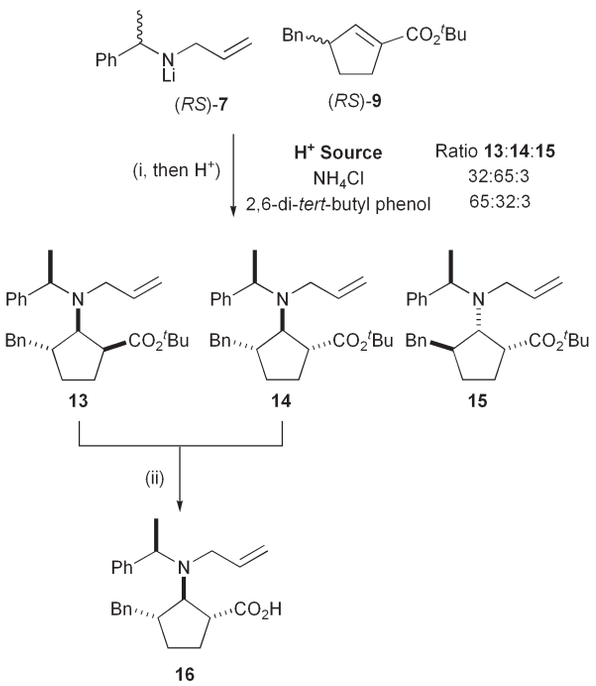
Lithium (*RS*)-*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamide **6**, lithium (*RS*)-*N*-allyl-*N*-α-methylbenzylamide **7** and lithium (*RS*)-*N*-benzyl-*N*-α-methylbenzylamide **8**, all of which show high levels of diastereoselectivity upon conjugate addition to achiral α,β-unsaturated esters, were chosen as potential reagents for parallel kinetic resolution. In the preceding manuscript, we demonstrated that high levels of enantiorecognition are observed in the mutual kinetic resolution of racemic mixtures of lithium (*RS*)-*N*-benzyl-*N*-α-methylbenzylamide **8** with (*RS*)-3-benzylcyclopentene-1-carboxylate **9** ($E$ > 160).[9c] Although lithium (*RS*)-*N*-3,4-dimethoxybenzylamide **6** and lithium (*RS*)-*N*-allylamide **7** may be expected to show similar levels of enantiorecognition upon conjugate addition to acceptor (*RS*)-**9**, the mutual kinetic resolution of these components was evaluated to confirm this hypothesis. In this manner, conjugate addition of lithium (*RS*)-*N*-3,4-dimethoxybenzylamide **6** to (*RS*)-**9**, employing $NH_4Cl_{(aq)}$ as an enolate protonation source, gave a mixture of three β-amino ester diastereoisomers (1*SR*,2*RS*,3*RS*,α*RS*)-**10**, (1*RS*,2*RS*,3*RS*,α*RS*)-**11** and (1*RS*,2*SR*,3*SR*,α*RS*)-**12** in a 90 : 9 : 1 ratio,[13] with chromatographic purification giving the major diastereoisomer **10** in >98% de and in 80% isolated yield. The use of 2,6-di-*tert*-butylphenol as the enolate protonation source after addition of lithium (*RS*)-*N*-3,4-dimethoxybenzylamide **6** to (*RS*)-**9** increased the C(1)-protonation selectivity, furnishing **10** : **11** : **12** in a 98 : 1 : 1 ratio, and giving (1*SR*,2*RS*,3*RS*,α*RS*)-**10** in 80% isolated yield and in >98% de after chromatographic purification. The configuration at C(2) within β-amino esters **10** and **11** was assigned relative to the *N*-α-methylbenzyl stereogenic centre by analogy to previous models rationalising the high stereoselectivity observed upon addition of homochiral lithium amides derived from α-methylbenzylamine to α,β-unsaturated esters,[14] with the relative configuration at C(1) and C(3) assigned from $^1$H NOE difference analysis (Scheme 2). β-Amino ester diastereoisomers **10** and **11** were shown to be epimeric at C(1), since epimerisation of the major diastereoisomer (1*SR*,2*RS*,3*RS*,α*RS*)-**10** gave β-amino ester (1*RS*,2*RS*,3*RS*,α*RS*)-**11** in 89% yield and >98% de over two steps *via* the corresponding acid, consistent with $E$ > 99 in the conjugate addition step of the reaction. These results indicate that high levels of 'matched' *anti*-2,3-selectivity (≥99 : 1) are observed upon addition of lithium (*RS*)-**6** to (*RS*)-3-benzyl **9**, with the two major diastereoisomers **10** and **11** arising from 'matched' lithium amide addition, and **11** only from loss of stereoselectivity upon enolate protonation.[15]




**Scheme 2** Reagents and conditions: (i) (*RS*)-**6** (3 eq), THF, −78 °C then either $NH_4Cl$(aq) or 2,6-di-*tert*-butylphenol, THF, −78 °C to rt; (ii) $^t$BuOH, THF, $^t$BuOK, reflux; (iii) $Cl_3CC{=}NH(O^tBu)$, 1 : 2 DCM : cyclohexane then $BF_3.Et_2O$.

In a similar fashion, addition of lithium (*RS*)-*N*-allylamide **7** to acceptor (*RS*)-**9** and protonation of the resultant enolate with $NH_4Cl$ gave a mixture of three β-amino ester diastereoisomers (1*SR*,2*RS*,3*RS*,α*RS*)-**13**, (1*RS*,2*RS*,3*RS*,α*RS*)-**14** and (1*RS*,2*SR*,3*SR*,α*RS*)-**15** in a 32 : 65 : 3 ratio. Exhaustive chromatographic purification yielded a mixture containing only β-amino esters **13** and **14** in a 33 : 67 ratio and in 85% isolated yield, which were epimerised and hydrolysed quantitatively to a single acid **16** in >98% de, consistent with **13** and **14** being epimeric at C(1). Using 2,6-di-*tert*-butylphenol as the proton source gave a 65 : 32 : 3 ratio of diastereoisomers **13** : **14** : **15**, which was separated with difficulty from 2,6-di-*tert*-butylphenol by chromatography, giving a 65 : 32 : 3 mixture of **13** : **14** : **15** in 40% isolated yield. These results are consistent with high levels of 'matched' *anti*-2,3-selectivity (≥97 : 3) upon addition of lithium

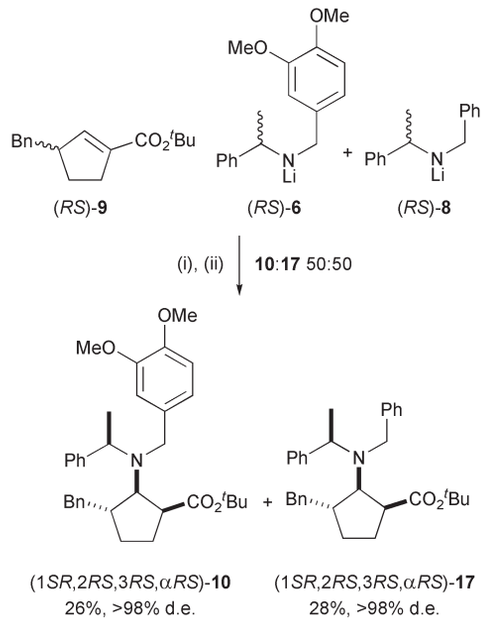
(*RS*)-*N*-allylamide **7** to (*RS*)-3-benzyl **9**, consistent with $E > 32$, although inversion of the sense of selectivity in protonation of the enolate arising from conjugate addition was observed with the use of $NH_4Cl$ and 2,6-di-*tert*-butylphenol. The relative configuration within β-amino esters **13**–**15** was assigned by analogy to those arising from the mutual kinetic resolution of acceptor (*RS*)-**9** with lithium amide **8** (Scheme 3).




**Scheme 3** Reagents and conditions: (i) (*RS*)-**7** (3 eq), THF, −78 °C then either $NH_4Cl$(aq) or 2,6-di-*tert*-butylphenol, THF, −78 °C to rt; (ii) $^t$BuOH, THF, $^t$BuOK, reflux.

These results demonstrate that lithium (*RS*)-amides **6**, **7** and **8** all show high levels of enantiorecognition upon reaction with the chiral acceptor (*RS*)-**9**. However, for an efficient parallel kinetic resolution, a pseudoenantiomeric mixture of these lithium amides must react without mutual interference, at similar rates, and give separable β-amino ester products. To investigate these issues and to find the optimal mixture of lithium amides to use in a parallel kinetic resolution reaction, a double mutual kinetic resolution strategy was explored. In this reaction, acceptor (*RS*)-**9** would be treated with a 50 : 50 mixture of two racemic lithium amides. It was envisaged that this competition experiment would determine the relative rates of addition of each lithium amide, while the levels of diastereoselectivity observed would probe the effects of mutual interference. The differentially protected β-amino ester products from these reactions should also be readily separated. Thus, addition of a 50 : 50 mixture of lithium (*RS*)-*N*-benzylamide **8** and lithium (*RS*)-*N*-3,4-dimethoxybenzylamide **6** to acceptor (*RS*)-**9** and protonation with 2,6-di-*tert*-butylphenol furnished a 50 : 50 mixture of β-amino esters *N*-benzyl-(1*SR*,2*RS*,3*RS*,α*RS*)-**17** in >98% de and *N*-3,4-dimethoxybenzyl-(1*SR*,2*RS*,3*RS*,α*RS*)-**10** in >98% de. The β-amino ester products were easily separable by chromatography, giving **17** in 28% yield and >98% de, and **10** in 26% yield and >98% de (Scheme 4).

Addition of a 50 : 50 mixture of lithium (*RS*)-*N*-allylamide **7** and lithium (*RS*)-*N*-benzylamide **8** to acceptor (*RS*)-**9** gave a 45 : 22 : 33 mixture of *N*-allyl β-amino esters **13** : **14** to *N*-benzyl β-amino ester **17**. This product distribution indicates that although conjugate addition occurs *anti*- to the C(3)-stereodirecting group with each lithium amide, low levels of selectivity are observed upon protonation of the intermediate *N*-allyl-β-amino ester enolate, as observed in the mutual kinetic resolution protocol. Thus, although lithium amides **7** and **8** show no mutual interference in their conjugate addition, the




**Scheme 4** Reagents and conditions: (i) (*RS*)-**6** (1.5 eq), (*RS*)-**8** (1.5 eq), THF, −78 °C to rt; (ii). 2,6-di-*tert*-butylphenol, THF, −78 °C to rt.

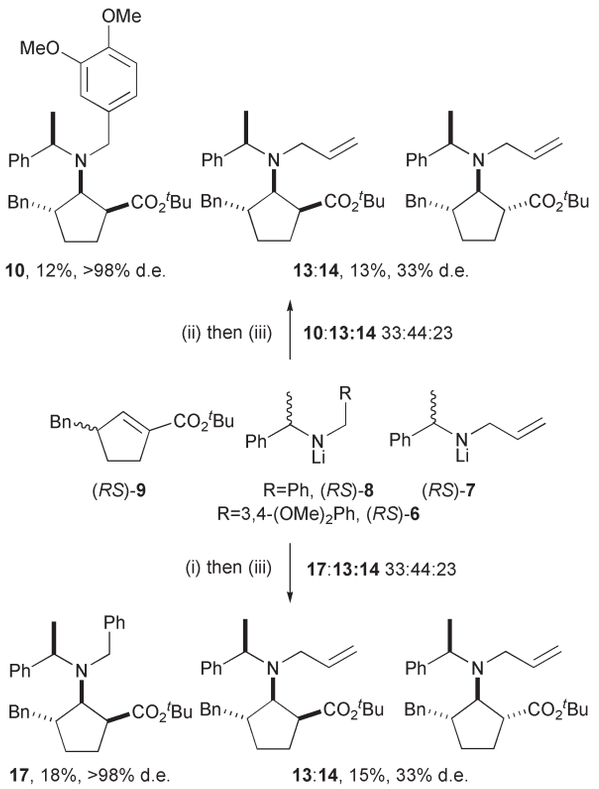
rate of addition of lithium *N*-allylamide **7** is twice the rate of addition of lithium *N*-benzylamide **8**. Chromatography facilitated separation of the *N*-allyl and *N*-benzyl β-amino ester products, giving the inseparable *N*-allyl β-amino esters **13** : **14** in 33% de and 15% yield and *N*-benzyl β-amino ester **17** in >98% de and 18% yield. Consistent with the observed rate difference, the (*RS*)-acceptor was treated with a 67 : 33 mixture of lithium *N*-benzylamide **8** (2 eq) and lithium *N*-allylamide **7** (1 eq), generating a 33.5 : 16.5 : 50 mixture of *N*-allyl β-amino esters **13** : **14** to *N*-benzyl β-amino ester **17**. As expected, addition of a 50 : 50 mixture of lithium (*RS*)-*N*-allylamide **7** and lithium (*RS*)-*N*-3,4-dimethoxybenzylamide **6** to (*RS*)-**9** gave a 45 : 22 : 33 mixture of *N*-allyl β-amino esters **13** : **14** to *N*-3,4-dimethoxybenzyl β-amino ester **10**, with chromatographic purification giving the inseparable *N*-allyl β-amino esters **13** : **14** in 33% de and 13% yield, and *N*-benzyl β-amino ester **10** in >98% de and 12% yield (Scheme 5).

These results are consistent with the mixtures of lithium amides *N*-benzyl-**8**, *N*-3,4-dimethoxybenzyl-**6** and *N*-allyl-**7** showing no mutual interference in their reactions. The rates of the addition of lithium amides *N*-benzyl-**8** and *N*-3,4-dimethoxybenzyl-**6** are essentially identical, and half that of *N*-allyl-**7**. For simplicity, it was decided that the parallel kinetic resolution of 3-alkyl–cyclopentene-1-carboxylates would be undertaken using 50 : 50 mixtures of homochiral lithium (*S*)-*N*-benzylamide **8** and lithium (*R*)-*N*-3,4-dimethoxybenzylamide **6**.

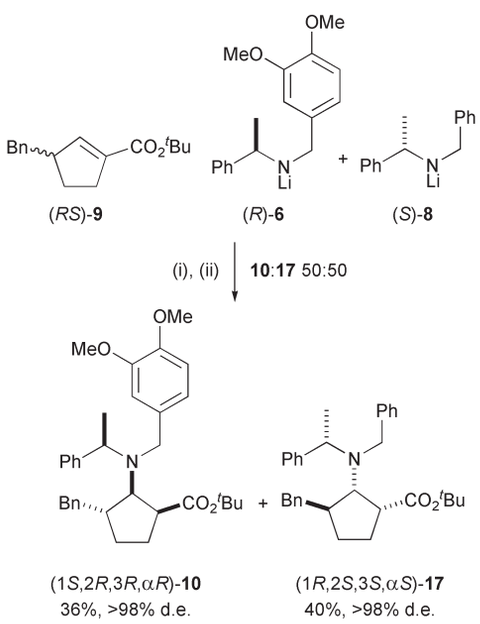
### Parallel kinetic resolution of (*RS*)-3-alkyl–cyclopentene-1-carboxylates with a pseudoenantiomeric mixture of lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamide and lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide

Addition of a 50 : 50 mixture of lithium (*R*)-*N*-3,4-dimethoxybenzylamide **6** (>98% ee)[16] and lithium (*S*)-*N*-benzylamide **8** (>98% ee) to acceptor (*RS*)-**9** gave a 50 : 50 mixture of β-amino esters (1*S*,2*R*,3*R*,α*R*)-**10** and (1*R*,2*S*,3*S*,α*S*)-**17** in >98% de in each case, consistent with $E > 70$. β-Amino esters **10** and **17** were readily separable by chromatography, giving (1*S*,2*R*,3*R*,α*R*)-**10** in 36% yield and >98% de and (1*R*,2*S*,3*S*,α*S*)-**17** in 40% yield and >98% de (Scheme 6).

To demonstrate the efficiency and generality of this methodology, the parallel kinetic resolution of the known (*RS*)-3-methyl and (*RS*)-3-ethyl acceptors **18** and **19** was examined.[17] Addition of a 50 : 50 mixture of lithium (*R*)-*N*-3,4-dimethoxybenzylamide **6** and lithium (*S*)-*N*-benzylamide **8** to (*RS*)-3-methyl **18** gave a 50 : 50 mixture of β-amino esters




**Scheme 5** Reagents and conditions: (i) (*RS*)-**7** (1.5 eq), (*RS*)-**8** (1.5 eq), THF, −78 °C; (ii) (*RS*)-**6** (1.5 eq), (*RS*)-**7** (1.5 eq), THF, −78 °C; (iii) 2,6-di-*tert*-butylphenol, THF, −78 °C to rt.



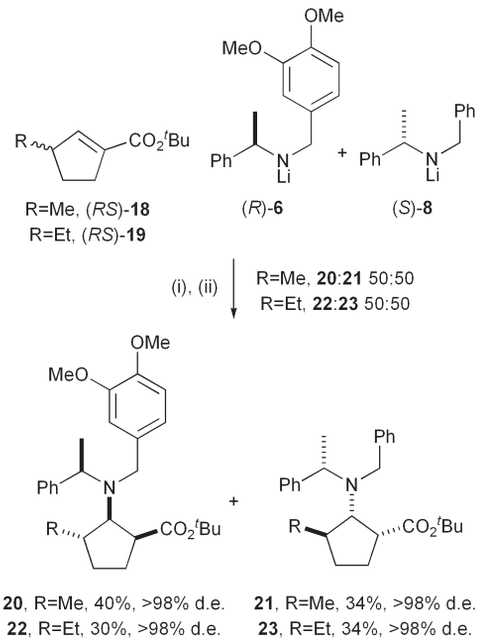

**Scheme 6** Reagents and conditions: (i) (*R*)-**6** (1.5 eq), (*S*)-**8** (1.5 eq), THF, −78 °C; (ii) 2,6-di-*tert*-butylphenol, THF, −78 °C to rt.

*N*-3,4-dimethoxybenzyl **20**:*N*-benzyl **21**, each in 98 ± 1% de, consistent with $E > 65$ in each case. Chromatographic purification gave the *N*-3,4-dimethoxybenzyl-β-amino ester **20** in 40% yield (>98% de), and the *N*-benzyl-β-amino ester **21** in 34% yield (>98% de). Similarly, addition of a 50 : 50 mixture of lithium amides (*R*)-**6**:(*S*)-**8** to (*RS*)-3-ethyl **19** gave a 50 : 50 mixture of β-amino esters *N*-3,4-dimethoxybenzyl **22**:*N*-benzyl **23**, each in 98 ± 1% de ($E > 65$), with purification giving **22** in 30% yield (>98% de) and **23** in 34% yield (Scheme 7).

### Deprotection: Synthesis of the enantiomers of 3-alkyl–cispentacin derivatives

With a range of pseudoenantiomeric β-amino esters prepared by parallel kinetic resolution, *N*-deprotection to the corresponding enantiomeric primary β-amino esters was investigated. Hydrogenolysis of the 3-benzyl, 3-methyl and 3-ethyl-*N*-benzyl-*N*-α-methylbenzyl protected β-amino esters **17**, **21**, and **23** gave the corresponding primary β-amino esters (1*R*,2*S*,3*S*)-**24**, (1*R*,2*S*,3*R*)-**25** and (1*R*,2*S*,3*R*)-**26**, respectively, in good yields and in >98% de. The ee of each β-amino ester was shown to be >95% ee by derivatisation with both racemic and 99% ee Mosher's acid chloride and comparison of the $^{19}F$ and $^{1}H$ NMR spectra of the resulting amides (Scheme 8). In the enantiomeric series, *N*-deprotection of the 3-benzyl, 3-methyl and 3-ethyl-*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzyl β-amino esters **10**, **22**, and **23** to the corresponding primary β-amino esters was effected using a two-step deprotection protocol, as attempted global *N*-deprotection by hydrogenolysis proved problematic. Thus, oxidative removal of the *N*-3,4-dimethoxybenzyl protecting group within **10**, **22** and **23** with DDQ gave the corresponding *N*-α-methylbenzyl protected β-amino esters **27**–**29** in good yield and >98% de, with subsequent hydrogenolysis of *N*-α-methylbenzyl protected β-amino esters **27**–**29** giving the β-amino esters (1*S*,2*R*,3*R*)-**24**, (1*S*,2*R*,3*S*)-**25** and (1*S*,2*R*,3*S*)-**26** in >98% de and >95% ee.

In conclusion, initial screening has determined that homochiral lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **8** and (*R*)-*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamide **6** constitute an effective pseudoenantiomeric mixture for the parallel kinetic resolution of 3-alkyl cyclopentene-1-carboxylates, giving a 50 : 50 mixture of β-amino ester products in >98% de in each case. The *N*-benzyl and *N*-3,4-dimethoxybenzyl β-amino ester products are readily separated by chromatographic purification, affording differentially protected 3-substituted cispentacin derivatives in high yield and >98% de in all cases examined, which are easily *N*-deprotected to the corresponding primary β-amino esters. The extension of this methodology to the parallel kinetic resolution of 5-alkyl–cyclopentene-1-carboxylates and a range of substituted cyclohexene-1-carboxylates is currently under investigation within our laboratory.

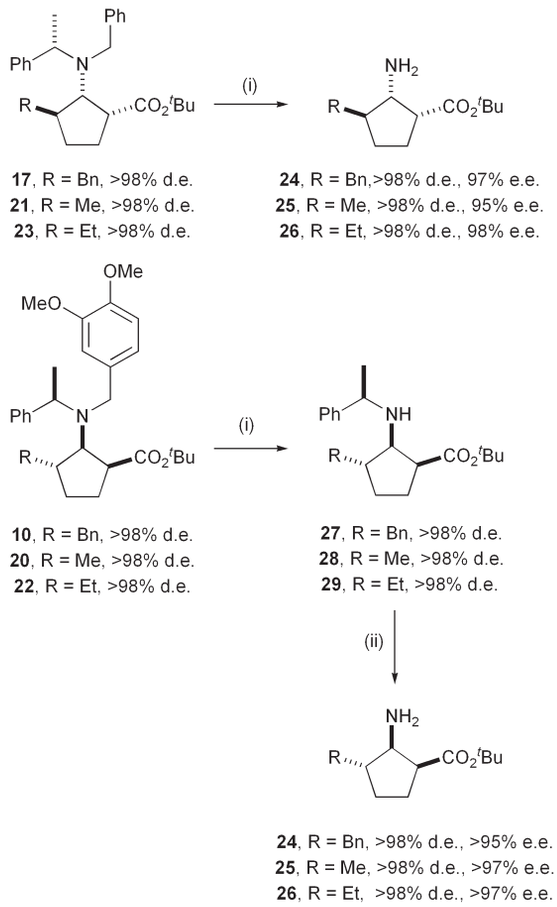



**Scheme 7** Reagents and conditions: (i) (*R*)-**6** (1.5 eq), (*S*)-**8** (1.5 eq), THF, −78 °C; (ii) 2,6-di-*tert*-butylphenol, THF, −78 °C to rt.

## Experimental

### General experimental

All reactions were carried out under nitrogen or argon using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen. THF was distilled from sodium/benzophenone ketyl; *n*-butyllithium was used as a solution in hexanes and was titrated against diphenylacetic




**Scheme 8** Reagents and conditions: (i) $Pd(OH)_2$ on C, MeOH, $H_2$ (5 atm), rt; (ii) DDQ (2.1 eq), DCM : $H_2O$ (3 : 1), rt.

acid prior to use. All other reagents were used as supplied without further purification. Flash column chromatography was performed on silica gel (Kieselgel 60). TLC was performed on Merck aluminium sheets coated with 0.2 mm silica gel 60 $F_{254}$. Plates were visualised either by UV light (254 nm), iodine, ammonium molybdate (7% solution in ethanol), potassium permanganate (1% in 2% aqueous acetic acid, containing 7% potassium carbonate), or Dragendorff's reagent.[18] Infrared spectra were recorded as thin films or KBr discs using a Perkin-Elmer PARAGON 1000 FT-IR spectrometer, with selected peaks reported in $cm^{-1}$. $^1H$ and $^{13}C$ NMR spectra were recorded on Varian Gemini 200 ($^1H$ 200 MHz, $^{13}C$ 50 MHz), Bruker DPX-200 ($^1H$ 200 MHz, $^{13}C$ 50 MHz), Bruker DPX-400 and AVANCE AV-400 ($^1H$ 400 MHz, $^{13}C$ 100 MHz), or Bruker AMX-500 ($^1H$ 500 MHz, $^{13}C$ 125 MHz) spectrometers. Chemical shifts ($\delta_H$) are reported in parts per million (ppm) and are referenced to the residual solvent peak, with coupling constants (*J*) measured in hertz. Low resolution mass spectra (*m*/*z*) were recorded on either a VG Masslab 20–250 instrument (CI, $NH_3$) or Platform instrument (ESI). Major peaks are listed with intensities quoted as percentages of the base peak. Accurate mass measurements were recorded on a VG Autospec and a Waters 2790-Micromass LCT electrospray ionisation mass spectrometer operating at a resolution of 5000 full-width half-height. Positive ion spectra were calibrated relative to PEG with tetraoctylammonium bromide as the internal lock mass. Negative ion spectra were calibrated relative to poly(DL-alanine) with leucine enkephalin as the internal lock mass. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter, using a path length of 10 cm, in spectroscopic grade solvents (Aldrich), with concentrations (*c*) given in g per 100 $cm^3$, solvent and temperature as recorded. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Elemental analyses were performed by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford.

**General procedure 1: Lithium amide additions to α,β-unsaturated esters.** *n*-BuLi was added dropwise to a stirred solution of amine in THF at −78 °C. After 30 min, the ester in THF at −78 °C was added *via* cannula and stirred for 2 h before the addition of either: (method A) aqueous $NH_4Cl$, the resultant mixture extracted with DCM, and the organic layer concentrated *in vacuo*. The residue was redissolved in DCM, washed successively with 10% aqueous citric acid, aqueous $NaHCO_3$, and brine, dried, filtered, and concentrated *in vacuo*; or (method B) addition of 2,6-di-*tert*-butylphenol (DTBP) in THF *via* cannula, stirred for 30 min at −78 °C, and then warmed to 0 °C and stirred for a further 30 min before the solvent was removed *in vacuo*.

**General procedure 2: Epimerization of β-amino acid derivatives.** A catalytic amount of $^t$BuOK was added to the β-amino ester in a 1 : 1 solution of $^t$BuOH and THF. The solution was refluxed for 18 h before addition of excess aqueous $NH_4Cl$, separation and extraction with DCM. The combined organic phases were dried, filtered, and concentrated *in vacuo*.

**General procedure 3: Hydrogenolysis.** $Pd(OH)_2$/C was added to a solution of secondary or tertiary amine in degassed MeOH at room temperature and placed under a hydrogen atmosphere (5 atm). After stirring for 24 h, the reaction mixture was filtered through basic alumina, washed with MeOH and concentrated *in vacuo*.

**General procedure 4: Deprotection of *N*-3,4-dimethoxybenzylamine derivatives.** The adduct was dissolved in 5 : 1 DCM : water, and DDQ was added. The reaction was stirred at rt for 2 days, before addition of aqueous $NaHCO_3$, extraction with DCM, and washing with brine. Combined organic phases were dried, filtered, and concentrated *in vacuo*.

**Preparation of *tert*-butyl (1*SR*,2*RS*,3*RS*,α*RS*)-3-benzyl-2-(*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 10**

Following *General Procedure 1*, *n*-BuLi (0.91 mL, 2.21 mmol), (*RS*)-**6** (617 mg, 2.28 mmol), and (*RS*)-**9** (200 mg, 0.76 mmol) in THF (10 mL), quenching with DTBP (460 mg, 2.21 mmol) gave, after purification by chromatography (3% $Et_2O$ in pentane), **10** (320 mg, 80%) as a colourless oil; $\delta_H$(400 MHz, $CDCl_3$) 1.05–1.15 (1H, m, C(5)$H_A$), 1.25 (3H, d, *J* 7.1, C(α)C$H_3$), 1.49 (9H, s, C(C$H_3$)$_3$), 1.49–1.51 (1H, m, C(5)$H_B$), 1.68–1.82 (2H, m, C(4)$H_2$), 2.08 (1H, dd, *J* 3.0, 1.1, C$H_A$H$_B$Ph), 2.47–2.52 (1H, m, C(3)*H*), 2.56–2.61 (1H, m, C(1)*H*), 3.07–3.11 (1H, m, C(2)*H*), 3.42 (1H, dd, *J* 3.4, 1.5, CH$_A$$H_B$Ph), 3.89 (3H, s, C$_6$H$_3$(OC$H_3$)$_A$), 3.91 (3H, s, C$_6$H$_3$(OC$H_3$)$_B$), 3.99 (1H, d, *J* 15.6, C$H_A$H$_B$Ar), 4.22 (1H, d, *J* 15.6, CH$_A$$H_B$Ar), 4.25 (1H, q, *J* 7.0, C(α)*H*), 6.88–7.74 (13H, m, *Ph*, *Ar*); $\delta_C$(100 MHz, $CDCl_3$) 20.9 (C(α)*C*H$_3$), 27.2 (*C*(4)), 28.1 (*C*(5)), 28.1 (OC(*C*H$_3$)$_3$), 41.0 (*C*H$_2$Ph), 42.2 (*C*(3)), 46.6 (*C*(1)), 50.5 (*C*H$_2$Ar), 55.7, 55.9 (C$_6$H$_3$ (O*C*H$_3$)$_2$), 60.3 (*C*(α)), 69.1 (*C*(2)), 80.0 (O*C*(CH$_3$)$_3$), 110.7, 119.3, 125.6, 126.9, 127.6, 128.1, 128.3, 128.6, 135.9, 145.3, 147.5 (*Ph*, *Ar*), 175.8 (*C*=O); $\nu_{max}$/$cm^{-1}$ (film) 1716 (C=O); *m*/*z* (ESI$^+$) 530 (MH$^+$, 100%); HRMS found 530.3272, $C_{34}H_{44}NO_4$ requires 530.3270.

**Preparation of *tert*-butyl (1*RS*,2*RS*,3*RS*,α*RS*)-3-benzyl-2-(*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 11**

Following *General Procedure 2*, **10** (50 mg, 0.11 mmol), $^t$BuOH (10 mL), THF (5 mL) and $^t$BuOK gave a carboxylic acid (44.0 mg, 0.12 mmol, 100%), which was then dissolved in a 2 : 1 cyclohexane : DCM (10 mL) with Cl$_3$CC=NH(O$^t$Bu) (48 mg, 0.24 mmol).[19] The mixture was stirred for 10 h, then $BF_3$–$Et_2O$ (2 μL, 0.08 mmol) was added, followed by saturated aqueous $NaHCO_3$ after 1 h. The aqueous layer was extracted into DCM and the combined organic phases were dried and concentrated *in vacuo*. Purification by chromatography (10% $Et_2O$ in petrol)

gave **11** (45 mg, 89%) as a colourless oil; $\delta_H$(400 MHz, $CDCl_3$) 1.26–1.33 (1H, m, C(5)$H_A$), 1.27 (3H, d, *J* 4.2, C(α)C$H_3$), 1.47 (9H, s, C(C$H_3$)$_3$), 1.48–1.53 (1H, m, C(5)$H_B$), 1.65–1.77 (2H, m, C(4)$H_2$), 1.96–2.23 (1H, m, C(3)*H*), 2.14–2.25 (1H, m, C$H_A$H$_B$Ph), 2.74–2.78 (1H, m, C(1)*H*), 3.22–3.27 (1H, m, CH$_A$$H_B$Ph), 3.45 (1H, dd, *J* 4.2, 1.6, C(2)*H*), 3.64 (1H, d, *J* 15.8, C$H_A$H$_B$Ar), 3.72 (1H, d, *J* 15.8, CH$_A$$H_B$Ar), 3.89 (3H, s, C$_6$H$_3$(OC$H_3$)$_A$), 3.87–3.93 (1H, q, *J* 5.5 C(α)*H*), 3.90 (3H, s, C$_6$H$_3$(OC$H_3$)$_B$), 6.86–7.40 (13H, m, *Ph*, *Ar*); $\delta_C$(100 MHz, $CDCl_3$) 21.3 (C(α)*C*H$_3$), 28.1 (OC(*C*H$_3$)$_3$), 29.7 (*C*(4)), 30.2 (*C*(5)), 40.1 (*C*H$_2$Ph), 45.4 (*C*(1)), 47.0 (*C*(3)), 50.2 (*C*H$_2$Ar), 55.7, 56.0 (C$_6$H$_3$(O*C*H$_3$)$_2$), 61.6 (*C*(α)), 70.0 (*C*(2)), 77.0 (O*C*(CH$_3$)$_3$), 110.8, 111.0, 119.2, 125.6, 126.7, 127.6, 127.8, 128.2, 128.6, 128.8, 135.6, 141.9, 145.2, 148.9 (*Ph*, *Ar*), 176.2 (*C*=O); $\nu_{max}$/cm$^{-1}$ (film) 1720 (C=O, s); *m*/*z* (ESI$^+$) 530 (MH$^+$, 100%); HRMS found 530.3279, $C_{34}H_{44}NO_4$ requires 530.3270.

**Preparation of *tert*-butyl (1*SR*,2*RS*,3*RS*,α*RS*)-3-benzyl-2-(*N*-allyl-*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 13 and *tert*-butyl (1*RS*,2*RS*,3*RS*,α*RS*)-3-benzyl-2-(*N*-allyl-*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 14**

Following *General Procedure 1*, *n*-BuLi (0.91 mL, 2.27 mmol), (*RS*)-**7** (0.38 mg, 2.28 mmol), and (*RS*)-**9** (200 mg, 0.76 mmol) in THF (6 mL), quenching with saturated aqueous $NH_4Cl$, gave after purification by chromatography (1% $Et_2O$ in pentane), a 33 : 67 mixture of **13** : **14** (270 mg, 85%) as a yellow oil. (1*SR*,2*RS*,3*RS*,α*RS*)-**13**: $\delta_H$(400 MHz, $CDCl_3$) 1.37 (3H, d, *J* 7.1, C(α)C$H_3$), 1.42–1.51 (2H, m, C(4)$H_2$), 1.49 (9H, s, OC(C$H_3$)$_3$), 1.70–1.73 (2H, m, C(5)$H_2$), 2.01–2.06 (1H, m, C(3)*H*), 2.15–2.21 (1H, m, C$H_A$H$_B$Ph), 2.63–2.70 (1H, m, C(1)*H*), 3.18 (1H, dd, *J* 9.9, 3.5, CH$_A$$H_B$Ph), 3.28–3.30 (2H, m, NC$H_2$), 3.31–3.34 (1H, m, C(2)*H*), 3.94–3.99 (1H, q, *J* 7.1, C(α)*H*) 5.09–5.13 (1H, m, CH=C$H_A$H$_B$), 5.13–5.36 (1H, m, CH=CH$_A$$H_B$), 5.91–6.00 (1H, m, C*H*=CH$_2$), 7.12–7.50 (10H, m, *Ph*); $\delta_C$(100 MHz, $CDCl_3$) 21.6 (C(α)*C*H$_3$), 28.1 (OC(*C*H$_3$)$_3$), 29.5 (*C*(4)), 30.8 (*C*(5)), 40.0 (*C*H$_2$Ph), 45.9 (*C*(1)), 46.9 (*C*(3)), 49.3 (N*C*H$_2$), 60.8 (*C*(α)), 70.1 (*C*(2)), 77.0 (O*C*(CH$_3$)$_3$), 114.8 (CH=*C*H$_2$), 125.6, 126.6, 127.6, 127.7, 128.2, 128.4, 128.7, 128.8, 142.3 (*Ph*$_{o,m,p}$), 140.0 (*C*H=CH$_2$), 145.2, 145.8 (*Ph*$_{ipso}$), 176.4 (*C*=O); $\nu_{max}$/cm$^{-1}$ (film) 1732 (C=O); *m*/*z* (ESI$^+$) 420 (MH$^+$, 100%); HRMS found 420.2898, $C_{28}H_{37}NO_2$ requires 420.2903. (1*RS*,2*RS*,3*RS*,α*RS*)-**14**: $\delta_H$(400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.8, C(α)C$H_3$), 1.49 (9H, s, C(C$H_3$)$_3$), 1.54–1.79 (4H, m, C(4)$H_2$, C(5)$H_2$), 1.98 (1H, dd, *J* 11.1, 2.3, C$H_A$H$_B$Ph), 2.35–2.55 (2H, m, C(1)*H*, C(3)*H*), 2.92 (1H, dd, *J* 8.3, 2.0, C(2)*H*), 3.19 (1H, d, *J* 9.9, 3.5, CH$_A$$H_B$Ph), 3.50 (1H, ddt, *J* 10.9, 5.3, 1.8, C$H_A$H$_B$CH=CH$_2$), 3.63 (1H, ddt, *J* 10.3, 5.8, 1.5, CH$_A$$H_B$CH=CH$_2$), 4.25 (1H, q, *J* 6.8, C(α)*H*), 5.04–5.14 (1H, m, CH=C$H_A$H$_B$), 5.24–5.35 (1H, m, CH=CH$_A$$H_B$), 5.87–6.04 (1H, m, C*H*=CH$_2$), 7.05–7.50 (10H, m, *Ph*).

**Preparation of (1*RS*,2*RS*,3*RS*,α*RS*)-3-benzyl-2-(*N*-allyl-*N*-α-methylbenzylamino)cyclopentane-1-carboxylic acid 16**

Following *General Procedure 2*, a mixture of **13** : **14** (50 mg, 0.11 mmol), $^t$BuOH (20 mL), THF (20 ml) and $^t$BuOK gave **16** (43.7 mg, 100%) as an off-white solid; $\delta_H$(400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 7.1, C(α)C$H_3$), 1.41–1.53 (2H, m, C(5)$H_2$), 1.49 (9H, s, C(C$H_3$)$_3$), 1.70–1.73 (2H, m, C(4)$H_2$), 2.01–2.06 (1H, m, C(3)*H*), 2.15–2.21 (1H, m, C$H_A$H$_B$Ph), 2.65–2.70 (1H, m, C(1)*H*), 3.18 (1H, dd, *J* 6.0, 2.2, CH$_A$$H_B$Ph), 3.35–3.43 (2H, m, NC$H_2$), 3.31–3.34 (1H, m, C(2)*H*), 4.10 (1H, q, *J* 4.2, C(α)*H*), 5.11 (1H, q, *J* 10.6, 1.8, CH=C$H_A$H$_B$), 5.29 (1H, q, *J* 17.2, 1.8, CH=CH$_A$$H_B$), 5.86–5.96 (1H, m, C*H*=CH$_2$), 7.12–7.56 (10H, m, *Ph*); $\delta_C$(100 MHz, $CDCl_3$) 25.1 (C(α)*C*H$_3$), 32.1 (*C*(4)), 33.0 (*C*(5)), 43.6 (*C*H$_2$Ph), 48.2 (*C*(1)), 50.1 (*C*(3)), 53.1 (N*C*H$_2$), 65.6 (*C*(α)), 74.3 (*C*(2)), 118.5 (CH=*C*H$_2$), 118.5, 129.3, 130.6, 131.4, 131.9, 132.2, 142.9, 145.7 (*Ph*), 146.1 (*C*H=CH$_2$), 180.0 (*C*=O); $\nu_{max}$/cm$^{-1}$ (KBr) 3435 (OH), 1690 (C=O); *m*/*z* (ESI$^-$) 361 (M–H$^-$, 52%); HRMS found 364.2287, $C_{28}H_{32}NO_2$ requires 364.2277; mp 100–104 °C.

**Double mutual kinetic resolution for the preparation of *tert*-butyl (1*SR*,2*RS*,3*RS*,α*RS*)-3-benzyl-2-(*N*-benzyl-*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 17 and *tert*-butyl (1*SR*,2*RS*,3*RS*,α*RS*)-3-benzyl-2-(*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 10**

Following *General Procedure 1*, (*RS*)-**9** (100 mg, 0.39 mmol), (*RS*)-**8** (124 mg, 0.59 mmol), (*RS*)-**6** (159 mg, 0.59 mmol) and *n*-BuLi (0.47 mL, 1.18 mmol) in THF (5 mL), quenching with DTBP (244 mg, 1.18 mmol) gave, after purification by chromatography (0.5% $Et_2O$ in petrol), **17** (51 mg, 28%) and **10** (53 mg, 26%) with identical properties to those reported below and above, respectively.

**Double mutual kinetic resolution for the preparation of *tert*-butyl (1*SR*,2*RS*,3*RS*,α*RS*)-3-benzyl-2-(*N*-benzyl-*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 17, *tert*-butyl (1*SR*,2*RS*,3*RS*,α*RS*)-3-benzyl-2-(*N*-allyl-*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 13 and *tert*-butyl (1*RS*,2*RS*,3*RS*,α*RS*)-3-benzyl-2-(*N*-allyl-*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 14**

Following *General Procedure 1*, (*RS*)-**9** (100 mg, 0.39 mmol), (*RS*)-**8** (124 mg, 0.59 mmol), (*RS*)-**7** (94 mg, 0.59 mmol) and *n*-BuLi (0.47 mL, 1.18 mmol) in THF (5 mL), quenching with DTBP (244 mg, 1.18 mmol) gave, after purification by chromatography (0.5% $Et_2O$ in petrol), **17** (32 mg, 18%) and **13** : **14** (24 mg, 15%) with identical properties to those reported below and above, respectively.

**Double mutual kinetic resolution for the preparation of *tert*-butyl (1*SR*,2*RS*,3*RS*,α*RS*)-3-benzyl-2-(*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 10 and *tert*-butyl (1*SR*,2*RS*,3*RS*,α*RS*)-3-benzyl-2-(*N*-allyl-*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 13 and *tert*-butyl (1*RS*,2*RS*,3*RS*,α*RS*)-3-benzyl-2-(*N*-allyl-*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 14**

Following *General Procedure 1*, (*RS*)-**9** (100 mg, 0.39 mmol), (*RS*)-**6** (159 mg, 0.59 mmol), (*RS*)-**7** (94 mg, 0.59 mmol) and *n*-BuLi (0.47 mL, 1.18 mmol) in THF (5 mL), quenching with DTBP (244 mg, 1.18 mmol) gave, after purification by chromatography (0.5% $Et_2O$ in petrol), **10** (19 mg, 12%) and **13** : **14** (24 mg, 13%) with identical properties to those reported above.

**Parallel kinetic resolution for the preparation of *tert*-butyl (1*R*,2*S*,3*S*,α*S*)-3-benzyl-2-(*N*-benzyl-*N*-α-methylbenzylamino)-cyclopentane-1-carboxylate 17 and *tert*-butyl (1*S*,2*R*,3*R*,α*R*)-3-benzyl-2-(*N*-3,4-dimethoxybenzyl-*N*-α-methyl benzylamino)cyclopentane-1-carboxylate 10**

Following *General Procedure 1*, (*RS*)-**9** (300 mg, 1.16 mmol), (*S*)-**8** (379 mg, 1.80 mmol), (*R*)-**6** (488 mg, 1.80 mmol), and *n*-BuLi (1.39 mL, 3.47 mmol) in THF (5 mL), quenching with DTBP (716 mg, 3.49 mmol) gave, after purification by chromatography (0.5% ether in petrol), **17** (218 mg, 40%) as a colourless solid; $\delta_H$(400 MHz, $CDCl_3$) 1.03–1.12 (1H, m, C(4)$H_A$), 1.25 (3H, d, *J* 6.8, C(α)C$H_3$), 1.41–1.49 (1H, m, C(5)$H_A$), 1.45 (9H, s, C(C$H_3$)$_3$), 1.65–1.79 (2H, m, C(4)$H_B$, C(5)$H_B$), 2.05 (1H, dd *J* 13.7, 11.4, C$H_A$H$_B$Ph), 2.42–2.45 (1H, m, C(3)*H*), 2.56 (1H, ddd, *J* 7.8, 4.6, 3.6, C(1)*H*), 3.06 (1H, dd, *J* 10.3, 7.8, C(2)*H*), 3.31 (1H, dd, *J* 13.4, 3.0, CH$_A$$H_B$Ph), 4.08 (1H, d, *J* 16.2, C$H_A$H$_B$Ph), 4.33 (1H, d, *J* 16.2, CH$_A$$H_B$Ph), 4.27 (1H, q, *J* 6.8, C(α)*H*), 7.14–7.55 (15H, m, *Ph*); $[\alpha]_D^{24}$ −46.3 (*c* 0.73 in $CHCl_3$) (lit.,[9c] $[\alpha]_D^{24}$ −45.1 (*c* 0.49 in $CHCl_3$)); mp 96–98 °C (lit.,[9c] 86–88 °C). Further elution yielded **10** (214 mg, 36%) with identical spectroscopic properties to those reported above and $[\alpha]_D^{24}$ +75.2 (*c* 0.70 in $CHCl_3$).

**Parallel kinetic resolution for the preparation of *tert*-butyl (1*R*,2*S*,3*R*,α*S*)-3-methyl-2-(*N*-benzyl-*N*-α-methylbenzylamino)-cyclopentane-1-carboxylate 21 and *tert*-butyl**

**(1*S*,2*R*,3*S*,α*R*)-3-methyl-2-(*N*-3,4-dimethoxybenzyl-*N*-α-methyl benzylamino)cyclopentane-1-carboxylate 20**

Following *General Procedure 1*, (*RS*)-**18** (300 mg, 1.64 mmol), (*S*)-**8** (519 mg, 2.46 mmol), (*R*)-**6** (664 mg, 2.46 mmol), and *n*-BuLi (2.36 mL, 5.92 mmol) in THF (10 mL), quenching with DTBP (1.21 g, 5.91 mmol) gave, after purification by chromatography (0.5% ether in petrol) **21** (219 mg, 34%) as a colourless oil; $\delta_H$(400 MHz, $CDCl_3$) 0.99–1.04 (1H, m, C(4)$H_A$), 1.02 (3H, d, *J* 6.5, C(3)C$H_3$), 1.19 (3H, d, *J* 6.9, C(α)C$H_3$), 1.51 (9H, s, OC(C$H_3$)$_3$), 1.50–1.54 (1H, m, C(5)$H_A$), 1.68–1.76 (1H, m, C(5)$H_B$), 1.95–1.99 (1H, m, C(4)$H_B$), 2.24–2.32 (1H, m, C(3)*H*), 2.53 (1H, ddd, *J* 7.7, 7.7, 4.0, C(1)*H*), 2.82 (1H, dd, *J* 10.5, 7.7, C(2)*H*), 3.96 (1H, d, *J* 15.9, C$H_A$H$_B$Ph), 4.16 (1H, d, *J* 15.9, CH$_A$$H_B$Ph), 4.15 (1H, q, *J* 6.9, C(α)*H*), 7.21–7.52 (10H, m, *Ph*). Further elution yielded **20** (297 mg, 40%) as a colourless oil; (Found: C, 73.7; H, 8.2; N, 3.1. $C_{28}H_{40}NO_4$ requires C, 74.1; H, 8.7; N, 3.1%); $\delta_H$(400 MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.5, C(3)C$H_3$), 0.96–1.02 (1H, m, C(4)$H_A$), 1.22 (3H, d, *J* 6.7, C(α)C$H_3$), 1.50 (9H, s, OC(C$H_3$)$_3$), 1.54–1.58 (1H, m, C(5)$H_A$), 1.68–1.80 (1H, m, C(5)$H_B$), 1.93–2.06 (1H, m, C(4)$H_B$), 2.21–2.37 (1H, m, C(3)*H*), 2.39–2.58 (1H, m, C(1)*H*), 2.84 (1H, dd, *J* 7.5, 2.9, C(2)*H*), 3.87 (1H, d, *J* 15.1, C$H_A$H$_B$Ar), 3.89 (3H, s, C$_6$H$_3$(OC$H_3$)$_A$), 3.94 (3H, s, C$_6$H$_3$(OC$H_3$)$_B$), 4.09 (1H, d, *J* 15.1, CH$_A$$H_B$Ar), 4.16 (1H, q, *J* 6.8, C(α)*H*), 6.58–7.65 (8H, m, *Ph*, *Ar*); $\delta_C$(100 MHz, $CDCl_3$) 19.7 (C(3)*C*H$_3$), 20.1 (C(α)*C*H$_3$), 27.0 (*C*(4)), 28.1 (OC(*C*H$_3$)$_3$), 30.7 (*C*(5)), 34.6 (*C*(3)), 47.1 (*C*(1)), 50.5 (*C*H$_2$Ar), 55.8, 55.9 (C$_6$H$_3$(O*C*H$_3$)$_2$), 59.6 (*C*(α)), 70.3 (*C*(2)), 79.9 (*C*(CH$_3$)$_3$), 110.8, 111.0, 119.3, 126.7, 127.7, 127.9, 128.0, 128.2, 135.8, 145.3, 147.4, 148.8 (*Ar*, *Ph*), 175.9 (*C*=O); $\nu_{max}$/cm$^{-1}$ (film) 1717 (C=O); [α]$_D^{24}$ +75.3 (*c* 0.70 in $CHCl_3$); *m*/*z* (ESI$^+$) 454 (MH$^+$, 100%).

**Parallel kinetic resolution for the preparation of *tert*-butyl (1*R*,2*S*,3*R*,α*S*)-3-ethyl-2-(*N*-benzyl-*N*-α-methylbenzylamino)-cyclopentane-1-carboxylate 23 and *tert*-butyl (1*S*,2*R*,3*S*,α*R*)-3-ethyl-2-(*N*-3,4-dimethoxybenzyl-*N*-α-methyl-benzylamino)cyclopentane-1-carboxylate 22**

Following *General Procedure 1*, (*RS*)-**19** (300 mg, 1.53 mmol), (*S*)-**8** (484 mg, 2.30 mmol), (*R*)-**6** (626 mg, 2.30 mmol), and *n*-BuLi (3.6 mL, 4.60 mmol) in THF (10 mL), quenching with DTBP (923 mg, 4.60 mmol) gave, after purification by chromatography (0.5% ether in petrol), **23** (219 mg, 34%) as a colourless oil; $\delta_H$(400 MHz, $CDCl_3$) 0.82 (3H, t, *J* 7.3, C(3)CH$_2$C$H_3$), 0.94–0.99 (1H, m, C(3)C$H_A$H$_B$CH$_3$), 1.00–1.07 (1H, m, C(4)$H_A$), 1.19 (3H, d, *J* 6.8, C(α)C$H_3$), 1.49–1.51 (1H, m, C(5)$H_A$), 1.52 (9H, s, OC(C$H_3$)$_3$), 1.70–1.75 (1H, m, C(5)$H_B$), 1.88–1.90 (1H, m, C(3)CH$_A$$H_B$CH$_3$), 1.95–2.03 (1H, m, C(4)$H_B$), 2.04–2.07 (1H, m, C(3)*H*), 2.54 (1H, ddd, *J* 7.6, 7.6, 4.0, C(1)*H*), 2.92 (1H, dd, *J* 10.0, 7.6, C(2)*H*), 3.94 (1H, d, *J* 15.9, C$H_A$H$_B$Ph), 4.17 (1H, d, *J* 15.9, CH$_A$$H_B$Ph), 4.16 (1H, q, *J* 6.8, C(α)*H*), 7.21–7.48 (10H, m, *Ph*); [α]$_D^{24}$ −126.3 (*c* 0.70 in $CHCl_3$) (lit.,[9c] [α]$_D^{24}$ −125.3 (*c* 1.11 in $CHCl_3$)). Further elution yielded **22** (214 mg, 30%) as a colourless oil; $\delta_H$(400 MHz, $CDCl_3$) 0.85 (3H, t, *J* 7.3, C(3)CH$_2$C$H_3$), 0.92–1.00 (1H, m, C(3)C$H_A$H$_B$CH$_3$), 1.02–1.11 (1H, m, C(4)$H_A$), 1.21 (3H, d, *J* 7.2, C(α)C$H_3$), 1.51 (9H, s, C(C$H_3$)$_3$), 1.52–1.55 (1H, m, C(5)$H_A$), 1.70–1.74 (1H, m, C(5)$H_B$), 1.81–1.92 (1H, m, C(3)CH$_A$$H_B$CH$_3$), 1.98–2.15 (2H, m, C(3)*H*, C(4)$H_B$), 2.49–2.54 (1H, m, C(1)*H*), 2.91–2.95 (1H, dd, *J* 7.8, 2.3, C(2)*H*), 3.80 (1H, d, *J* 15.5, C$H_A$H$_B$Ar), 3.89 (3H, s, C$_6$H$_3$(OC$H_3$)$_A$), 3.93 (3H, s, C$_6$H$_3$(OC$H_3$)$_B$), 4.08 (1H, d, *J* 15.5, CH$_A$$H_B$Ar), 4.12 (1H, q, *J* 3.2, C(α)*H*), 6.79–7.44 (8H, m, *Ph*, *Ar*); $\delta_C$(100 MHz, $CDCl_3$) 12.6 (CH$_2$*C*H$_3$), 22.0 (C(α)*C*H$_3$), 27.5 (*C*H$_2$CH$_3$), 28.1 (OC(*C*H$_3$)$_3$) 29.3 (*C*(4)), 30.4 (*C*(5)), 45.8 (*C*(1)), 46.6 (*C*(3)), 50.3 (*C*H$_2$DMP), 55.8, 55.9 (C$_6$H$_3$ (O*C*H$_3$)$_2$), 61.6 (*C*(α)), 68.4 (*C*(2)), 77.6 (O*C*(CH$_3$)$_3$), 110.8, 119.1, 126.7, 127.6, 128.2, 136.1, 145.4, 147.4, 148.8 (*Ph*, *Ar*), 176.4 (*C*=O); $\nu_{max}$/cm$^{-1}$ (film) 1717 (C=O); [α]$_D^{24}$ +30.1 (*c* 0.70 in $CHCl_3$); *m*/*z* (ESI$^+$) 468 (MH$^+$, 100%); HRMS found 468.3114, $C_{29}H_{42}NO_4$ requires 468.3115.

**Preparation of *tert*-butyl (1*R*,2*S*,3*S*)-3-benzyl-2-aminocyclopentane-1-carboxylate 24**

Following *General Procedure 3*, **17** (200 mg, 0.43 mmol) and Pd(OH)$_2$/C (30 mg) under $H_2$ (5 atm) in MeOH (4 mL) gave (1*R*,2*S*,3*S*)-**24** (88 mg, 75%) as a colourless oil; $\delta_H$(400 MHz, $CDCl_3$) 1.19–1.24 (1H, m, C(4)$H_A$), 1.48 (9H, s, OC(C$H_3$)$_3$), 1.60 (2H, br s, N$H_2$), 1.82–1.95 (3H, m, C(4)$H_B$, C(5)$H_2$), 2.06 (1H, m, C(3)*H*), 2.48 (1H, dd, *J* 13.5, 8.8, C$H_A$H$_B$Ph), 2.84–2.91 (2H, m, CH$_A$$H_B$Ph, C(1)*H*), 3.13 (1H, dd, *J* 7.4, 7.3, C(2)*H*), 7.12–7.45 (5H, m, *Ph*); [α]$_D^{24}$ −34.0 (*c* 1.20 in $CHCl_3$), (lit.,[9c] [α]$_D^{23}$ −32.5 (*c* 1.00 in $CHCl_3$)).

**Preparation of *tert*-butyl (1*R*,2*S*,3*R*)-3-methyl-2-aminocyclopentane-1-carboxylate 25**

Following *General Procedure 3*, **21** (53 mg, 0.13 mmol) and Pd(OH)$_2$/C (10 mg) under $H_2$ (5 atm) in MeOH (10 mL) gave, after purification by chromatography (20% ether in petrol), (1*R*,2*S*,3*R*)-**25** (12 mg, 45%) as a colourless oil; $\delta_H$(400 MHz, $CDCl_3$) 1.01 (3H, d, *J* 6.4, C(3)C$H_3$), 1.12–1.15 (1H, m, C(4)$H_A$), 1.40 (9H, s, OC(C$H_3$)$_3$), 1.80 (2H, br s, N$H_2$), 1.83–1.97 (4H, m, C(3)*H*, C(4)$H_B$, C(5)$H_2$), 2.82–2.88 (1H, m, C(1)*H*), 2.94 (1H, dd, *J* 7.4, 7.4, C(2)*H*); [α]$_D^{24}$ −55.1 (*c* 0.70 in $CHCl_3$) (lit.,[9b] [α]$_D^{24}$ −51.8 (*c* 1.02 in $CHCl_3$)).

**Preparation of (1*R*,2*S*,3*R*)-*tert*-butyl 3-ethyl-2-aminocyclopentane-1-carboxylate 26**

Following *General Procedure 3*, **23** (200 mg, 0.5 mmol) and Pd(OH)$_2$/C (20 mg) under $H_2$ in MeOH (10 mL) gave (1*R*,2*S*,3*R*)-**26** (62 mg, 60%) as a yellow oil; $\delta_H$(400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.2, CH$_2$C$H_3$), 1.09–1.23 (2H, m, (C(4)$H_A$, C(3)C$H_A$H$_B$CH$_3$), 1.45 (9H, s, OC(C$H_3$)$_3$), 1.59–169 (2H, m, C(3)*H*, C(4)$H_B$), 1.80–1.97 (5H, m, C(5)$H_2$, C(3)CH$_A$$H_B$CH$_3$, N$H_2$), 2.76 (1H, ddd, *J* 7.5, 7.5 and 7.9, C(1)*H*), 3.05–3.11 (1H, m, C(2)*H*); [α]$_D^{24}$ −46.5 (*c* 0.70 in $CHCl_3$) (lit.,[9c] [α]$_D^{23}$ −44.7 (*c* 1.00 in $CHCl_3$)).

**Preparation of *tert*-butyl (1*S*,2*R*,3*R*,α*R*)-3-benzyl-2-(*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 27**

Following *General Procedure 4*, **10** (70 mg, 0.13 mmol) and DDQ (41 mg, 0.26 mmol) in 5:1 DCM:water (20 mL) gave, after purification by chromatography (30% ether in petrol), **27** (33 mg, 70%) as a yellow oil; (Found: C, 79.4; H, 8.7; N, 3.7. $C_{25}H_{34}NO_2$ requires C, 79.1; H, 8.9; N, 3.7%); $\delta_H$(400 MHz, $CDCl_3$) 0.98–1.13 (1H, m, C(4)$H_A$), 1.15–1.20 (1H, m, C(5)$H_A$), 1.30 (3H, d, *J* 20.3, C(α)C$H_3$), 1.53 (9H, s, OC(C$H_3$)$_3$), 1.61 (1H, br s, N*H*), 1.63–1.83 (2H, m, C(4)$H_B$, C(5)$H_B$), 2.07–2.19 (2H, m, C$H_A$H$_B$Ph, C(3)*H*), 2.60 (1H, dd, *J* 6.9, 2.0, C(2)*H*), 2.89–3.00 (1H, m, C(1)*H*), 3.10 (1H, q, *J* 8.6, CH$_A$$H_B$Ph), 3.88 (1H, q, *J* 6.4, C(α)*H*), 7.05–7.45 (10H, m, *Ph*); $\delta_C$(100 MHz, $CDCl_3$) 26.7 (*C*(5)), 28.2 (OC(*C*H$_3$)$_3$), 28.7 (*C*(4)), 25.4 (C(α)*C*H$_3$), 39.6 (*C*H$_2$Ph), 46.4 (*C*(3)), 46.7 (*C*(1)), 56.4 (*C*(α)), 64.3 (*C*(2)), 80.1 (*C*(CH$_3$)$_3$), 125.5, 126.9, 127.0, 128.1, 128.3, 128.9 (*Ph*$_{o,m,p}$), 141.6 (*Ph*$_{ipso}$), 176.2 (*C*=O); $\nu_{max}$/cm$^{-1}$ (film) 1717 (C=O); [α]$_D^{24}$ +115.1 (*c* 0.70 in $CHCl_3$); *m*/*z* (ESI$^+$) 380 (MH$^+$, 100%); HRMS found 380.2590, $C_{25}H_{34}NO_2$ requires 380.2590.

**Preparation of *tert*-butyl (1*S*,2*R*,3*S*,α*R*)-3-methyl-2-(*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 28**

Following *General Procedure 4*, **20** (200 mg, 0.44 mmol) and DDQ (160 mg, 0.88 mmol) in 5:1 DCM:water mixture (20 mL) gave, after purification by chromatography (20% Et$_2$O in petrol), **28** (100 mg, 75%) as a colourless oil; $\delta_H$(400 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.1, C(3)C$H_3$), 0.97–1.08 (1H, m, C(5)$H_A$), 1.29 (3H, d, *J* 6.8, C(α)C$H_3$), 1.53 (9H, s, OC(C$H_3$)$_3$), 1.66 (1H, br s, N*H*), 1.67–1.93 (4H, m, C(3)*H*, C(4)$H_2$, C(5)$H_B$), 2.40 (1H, dd, *J* 7.9, 1.7, C(1)*H*), 2.84–2.95 (1H, m, C(2)*H*), 3.91 (1H, q, *J* 4.2, C(α)*H*), 7.15–7.44 (5H, m, *Ph*); $\delta_C$(100 MHz, $CDCl_3$) 18.1 (C(3)*C*H$_3$), 25.5 (C(α)*C*H$_3$), 26.7 (*C*(4)), 28.2 (OC(*C*H$_3$)$_3$), 31.3

(*C*(5)), 39.2 (*C*(3)), 48.8 (*C*(1)), 56.3 (*C*(α)), 66.1 (*C*(2)), 80.0 (O*C*(CH$_3$)$_3$), 126.8, 126.8, 128.3 (*Ph$_{o,m,p}$*), 146.0 (*Ph$_{ipso}$*), 175.1 (*C*=O). $\nu_{max}$/cm$^{-1}$ (film) 3333 (NH), 1718 (C=O); $[\alpha]_D^{24}$ +172.2 (*c* 0.70 in $CHCl_3$); *m*/*z* (ESI$^+$) 304 (MH$^+$, 100%); HRMS found 304.2271, $C_{19}H_{30}NO_2$ requires 304.2277.

**Preparation of *tert*-butyl (1*S*,2*R*,3*S*,α*R*)-3-ethyl-2-(*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 29**

Following *General Procedure 4*, **22** (200 mg, 0.42 mmol) and DDQ (190 mg, 0.84 mmol) in 5:1 DCM:water (10 mL) gave, after purification by chromatography (20% ether in petrol), **29** (94 mg, 70%) as a colourless oil; $\delta_H$(400 MHz, $CDCl_3$) 0.85 (3H, t, *J* 7.1, $CH_2CH_3$), 0.88–1.10 (2H, m, C(3)$H_AH_BCH_3$, C(4)$H_A$), 1.28 (3H, d, *J* 6.3, C(α)C$H_3$), 1.53 (9H, s, OC(C$H_3$)$_3$), 1.53 (1H, br s, N*H*), 1.63–1.77 (3H, m, C(4)$H_B$, C(5)$H_A$, C(3)$CH_AH_BCH_3$), 1.76–1.98 (2H, m, C(3)*H*, C(5)$H_B$), 2.50 (1H, dd, *J* 7.7, 1.8, C(1)*H*), 2.86–2.92 (1H, m, C(2)*H*), 3.89 (1H, q, *J* 5.5, C(α)*H*), 7.19–7.70 (5H, m, *Ph*); $\delta_C$(100 MHz, $CDCl_3$) 12.4 ($CH_2CH_3$), 25.5 (C(α)*C*H$_3$), 26.4 (C(3)*C*H$_2$CH$_3$), 26.7 (*C*(5)), 28.5 (C(*C*H$_3$)$_3$), 29.4 (*C*(4)), 46.3 (*C*(3), 47.1 (*C*(1)), 56.3 (*C*(α)), 64.4 (*C*(2)), 80.0 (*C*(CH$_3$)), 126.7, 126.8, 128.0, 128.3 (*Ph$_{o,m,p}$*), 146.0 (*Ph$_{ipso}$*), 175.0 (*C*=O); $\nu_{max}$/cm$^{-1}$ (film) 1718 (C=O); $[\alpha]_D^{24}$ +124.0 (*c* 0.70 in $CHCl_3$); *m*/*z* (ESI$^+$) 318 (MH$^+$, 100%); HRMS found 318.2432, $C_{20}H_{32}NO_2$ requires 318.2433.

**Preparation of *tert*-butyl (1*S*,2*R*,3*R*)-3-benzyl-2-aminocyclopentane-1-carboxylate 24**

Following *General Procedure 3*, **27** (200 mg, 0.53 mmol) and $Pd(OH)_2$/C (30 mg) under $H_2$ (5 atm) in MeOH (4 mL) gave (1*S*,2*R*,3*R*)-**24** (65 mg, 45%) with $^1$H NMR data identical to those reported above; $[\alpha]_D^{24}$ +36.0 (*c* 1.10 in $CHCl_3$).

**Preparation of *tert*-butyl (1*S*,2*R*,3*S*)-3-methyl-2-aminocyclopentane-1-carboxylate 25**

Following *General Procedure 3*, **28** (50.0 mg, 0.17 mmol) and $Pd(OH)_2$/C (10 mg) under $H_2$ (5 atm) in MeOH (10 mL) gave (1*S*,2*R*,3*S*)-**25** (11.8 mg, 35%) as a colourless oil with $^1$H NMR data identical to those reported above; $[\alpha]_D^{24}$ +54.1 (*c* 0.50 in $CHCl_3$).

**Preparation of *tert*-butyl (1*S*,2*R*,3*S*)-3-ethyl-2-aminocyclopentane-1-carboxylate 26**

Following *General Procedure 3*, **29** (150 mg, 0.47 mmol) and $Pd(OH)_2$/C (70 mg) under $H_2$ (5 atm) in MeOH (5 mL) gave (1*S*,2*R*,3*S*)-**26** (70 mg, 70%) as a yellow oil with $^1$H NMR data identical to those reported above; $[\alpha]_D^{24}$ +40.3 (*c* 0.7 in $CHCl_3$).

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12 We have previously demonstrated that a pseudoenantiomeric mixture of lithium amides can be used for the parallel kinetic resolution of methyl (*RS*)-5-*tert*-butylcyclopentene-1-carboxylate; see S. G. Davies, D. Díez, M. M. El Hammouni, N. M. Garrido, A. C. Garner, M. J. C. Long, R. M. Morrison, A. D. Smith, M. J. Sweet and J. M. Withey, *Chem. Commun.*, 2003, 2410.

13 As determined by $^1$H NMR spectroscopic analysis of the crude reaction mixture.

14 J. F. Costello, S. G. Davies and O. Ichihara, *Tetrahedron: Asymmetry*, 1994, **5**, 3919.

15 The configuration of the third minor diastereoisomer **12** arising from mutual kinetic resolution was assigned as arising from the 'mismatched' addition of the lithium amide to the chiral ester by analogy to that observed in the mutual kinetic resolution of (*RS*)-3-benzyl **9** with lithium (*RS*)-*N*-benzyl-*N*-α-methylbenzylamide **8**.

16 In these parallel kinetic resolution reactions the ee of (*S*)-*N*-benzyl-*N*-α-methylbenzylamine and (*R*)-*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamine was established as 98% by $^1$H NMR chiral shift experiments with (*R*)-*O*-acetyl mandelic acid and comparison with an authentic racemic standard in each case.

17 The mutual kinetic resolution of chiral (*RS*)-3-methyl **18** and (*RS*)-3-ethyl **19** with lithium (*RS*)-*N*-3,4-dimethoxybenzyl-*N*-α-methylbenzylamide was evaluated, giving, as expected, high 1,2-*syn*-2,3-*anti*- selectivity, with *E* > 75 in each case.

18 E. Stahl,*Thin Layer Chromatography*, Springer-Verlag, Berlin, 1969, p. 873.

19 A. Armstrong, I. Brackenridge, R. F. W. Jackson and J. M. Kirk, *Tetrahedron Lett.*, 1988, **29**, 2483.