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Asymmetric synthesis of (1*R*,2*S*,3*R*)-3-methylcispentacin and (1*S*,2*S*,3*R*)-3-methyltranspentacin by kinetic resolution of *tert*-butyl (±)-3-methylcyclopentene-1-carboxylate †

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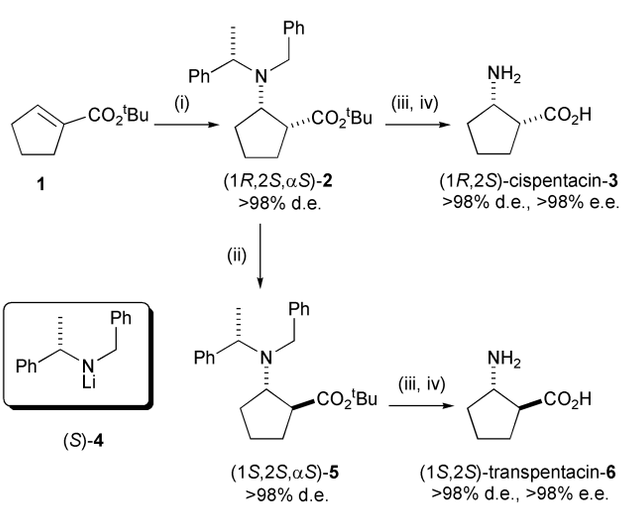
Conjugate addition of lithium dibenzylamide to *tert*-butyl (±)-3-methylcyclopentene-1-carboxylate occurs with high levels of stereocontrol, with preferential addition of lithium dibenzylamide to the face of the cyclic α,β-unsaturated acceptor *anti*- to the 3-methyl substituent. High levels of enantiorecognition are observed between *tert*-butyl (±)-3-methylcyclopentene-1-carboxylate and an excess of lithium (±)-*N*-benzyl-*N*-α-methylbenzylamide (10 eq.) ($E > 140$) in their mutual kinetic resolution, while the kinetic resolution of *tert*-butyl (±)-3-methylcyclopentene-1-carboxylate with lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide proceeds to give, at 51% conversion, *tert*-butyl (1*R*,2*S*,3*R*,α*S*)-3-methyl-2-*N*-benzyl-*N*-α-methylbenzylaminocyclopentane-1-carboxylate consistent with $E > 130$, and in 39% yield and 99 ± 0.5% de after purification. Subsequent deprotection by hydrogenolysis and ester hydrolysis gives (1*R*,2*S*,3*R*)-3-methylcispentacin in >98% de and 98 ± 1% ee. Selective epimerisation of *tert*-butyl (1*R*,2*S*,3*R*,α*S*)-3-methyl-2-*N*-benzyl-*N*-α-methylbenzylaminocyclopentane-1-carboxylate by treatment with KO^{t}Bu in ^{t}BuOH gives *tert*-butyl (1*S*,2*S*,3*R*,α*S*)-3-methyl-2-*N*-benzyl-*N*-α-methylbenzylaminocyclopentane-1-carboxylate in quantitative yield and in >98% de, with subsequent deprotection by hydrogenolysis and ester hydrolysis giving (1*S*,2*S*,3*R*)-3-methyltranspentacin hydrochloride in >98% de and 97 ± 1% ee.

Introduction

The development of new methodology for the asymmetric synthesis of β-amino acid derivatives[1] is of immense current synthetic interest, primarily as β-amino acids occur as fragments within peptidic natural products with potent biological activity,[2] although the β-amino acid structural motif has also been used for the generation of pseudopeptide sequences with highly ordered secondary and tertiary structures.[3] Within this framework, the *cis*-(1*R*,2*S*)- and *trans*-(1*S*,2*S*)-diastereoisomers of 2-aminocyclopentanecarboxylic acid (cispentacin and transpentacin respectively) are particularly worthy of note. The parent *cis*-diastereoisomer shows potent antifungal activity[4] with homo-oligomers forming a sheetlike secondary structure in solution,[5] while homo-oligomers of the *trans*-diastereoisomer show ordered secondary structure in both solution and the solid state.[6] A range of methodologies have been developed for the synthesis of the cispentacin and transpentacin family of β-amino acids in homochiral form,[7] including classical resolution[8] and kinetic resolution,[9] as well as a variety of asymmetric syntheses.[10] We have previously shown that the conjugate addition of homochiral lithium amides derived from α-methylbenzylamine to α,β-unsaturated esters represents efficient and versatile methodology for the asymmetric synthesis of β-amino acid derivatives.[11] This methodology has been applied to the asymmetric synthesis of (1*R*,2*S*)-cispentacin **3** by conjugate addition of homochiral lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **4** to *tert*-butyl cyclopentene-1-carboxylate **1** and subsequent *N*-deprotection and ester hydrolysis, while selective epimerisation of β-amino ester (1*R*,2*S*,α*S*)-**2** to the thermodynamic epimer (1*S*,2*S*,α*S*)-**5** and further deprotection gives (1*S*,2*S*)-transpentacin **6** (Scheme 1).[12]



Scheme 1 *Reagents and conditions*: (i). lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **4**, THF, −95 °C then 2,6-di-*tert*-butylphenol; (ii). KO^{t}Bu, ^{t}BuOH, rt; (iii). Pd–C, MeOH, H_2 (5 atm), rt; (iv). TFA then Dowex 50X8-200.

In order to enhance the structural diversity of monomeric cispentacin and transpentacin derivatives available for both secondary structural and bioactivity studies, an approach to substituted analogues,[13] which maintain the saturated 5-membered ring backbone and (1*R*,2*S*)-absolute configuration essential for biological activity, was desired.[14] It was envisaged that an efficient route to homochiral 3-methyl

† This is one of a number of contributions from the current members of the Dyson Perrins Laboratory to mark the end of almost 90 years of organic chemistry research in that building, as all its current academic staff move across South Parks Road to a new purpose-built laboratory.

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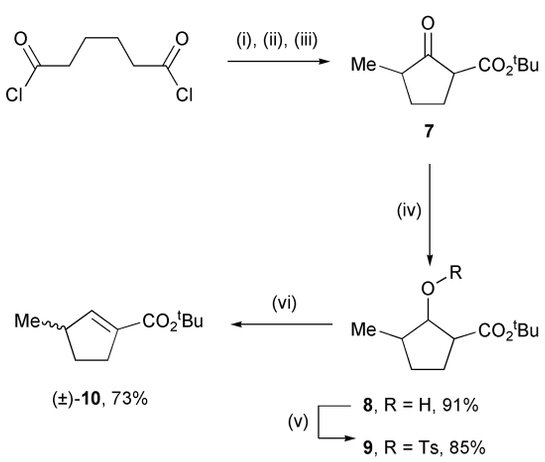
substituted analogues would employ the conjugate addition of homochiral lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide to effect a kinetic resolution of *tert*-butyl (±)-3-methylcyclopentene-1-carboxylate **10**, while simultaneously generating stereoselectively the C(1) and C(2) stereogenic centres of the β-amino ester addition product. Part of this work has been previously communicated.[15]

Results and discussion

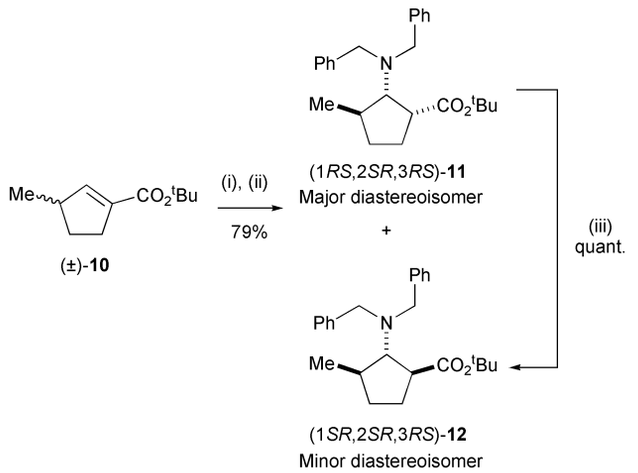
Synthesis and evaluation of the stereodirecting effect of *tert*-butyl (±)-3-methylcyclopentene-1-carboxylate 10

For an efficient kinetic resolution to be achieved, both partners need to exert high stereocontrol over the reaction under study. In the present case, where new stereogenic centres are being formed in the reaction, the matched combination would be expected to show enhanced stereoselectivity over the mismatched combination. The remarkable levels of stereocontrol exerted by lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **4** in the conjugate addition to *tert*-butyl cyclopentene-1-carboxylate **1** has already been established,[12] while the stereodirecting ability of the 3-methyl substituent of *tert*-butyl (±)-3-methylcyclopentene-1-carboxylate **10** has yet to be determined. The desired racemic substrate (±)-**10** required for this analysis was readily prepared from adipoyl chloride by consecutive esterification,[16] Dieckmann cyclisation[17] and regioselective γ-alkylation, furnishing the γ-methyl-β-keto ester **7** as a 71 : 29 mixture of diastereoisomers. Chemoselective $NaBH_4$ reduction of the ketone functionality within the diastereoisomeric mixture of β-keto esters **7** gave alcohol **8**, with formation of tosylate **9** and subsequent elimination furnishing (±)-**10** on a multigram scale and in reasonable yield (Scheme 2).



Scheme 2 *Reagents and conditions*: (i). $PhNMe_2$ (3.15 eq.), ^tBuOH (3.25 eq.), Et_2O, rt; (ii). NaH (1.05 eq.), ^tBuOH (cat.), PhMe, Δ; (iii). NaH (1.05 eq.) then *n*-BuLi (1.0 eq.), then MeI (1.1 eq.), −78 °C to 0 °C; (iv). $NaBH_4$, EtOH, 0 °C; (v). TsCl (1.1 eq.), pyridine, 0 °C to rt; (vi). DBU, DCM, 0 °C.

With the desired (±)-3-methyl α,β-unsaturated acceptor **10** in hand, the level of stereoinduction commanded by the substrate upon conjugate addition of achiral lithium dibenzylamide was evaluated, furnishing the separable C(1) epimeric adducts (1*RS*,2*SR*,3*RS*)-**11** and (1*SR*,2*SR*,3*RS*)-**12** in a 78 : 22 ratio upon protonation with either NH_4Cl or 2,6-di-*tert*-butylphenol (Scheme 3). Purification of the major diastereoisomer to homogeneity *via* fractional crystallisation and subsequent single crystal X-ray analysis allowed the relative (1*RS*,2*SR*,3*RS*) configuration within the major diastereoisomer **11** to be unambiguously established (Fig. 1). Conversion of the major diastereoisomeric product (1*RS*,2*SR*,3*RS*)-**11**, or the 78 : 22 diastereoisomeric mixture arising from the crude reaction mixture, to the thermodynamic epimer (1*SR*,2*SR*,3*RS*)-**12** (>98% de) upon treatment with KO^{t}Bu in ^{t}BuOH, confirmed that the two diastereoisomers (1*RS*,2*SR*,3*RS*)-**11** and (1*SR*,2*SR*,3*RS*)-**12** were epimeric at C(1) (Scheme 3).



Scheme 3 *Reagents and conditions*: (i). lithium dibenzylamide, THF, −78 °C; (ii). $NH_4Cl_{(aq)}$, −78 °C to rt or 2,6-di-*tert*-butylphenol, THF, −78 °C to rt; (iii). KO^{t}Bu, ^{t}BuOH, Δ, 3 hours.

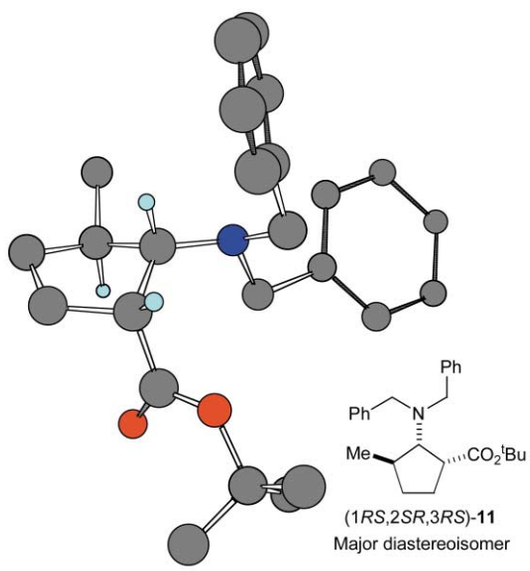


Fig. 1 Chem 3D representation of the X-ray crystal structure of (1*RS*,2*SR*,3*RS*)-**11** (some H atoms are omitted for clarity).

The product distribution arising from addition of lithium dibenzylamide to (±)-acceptor **10** is consistent with the 3-methyl substituent showing complete diastereofacial control at the β-centre during conjugate addition, with preferential addition of lithium dibenzylamide to the face of the acceptor *anti*- to that of the stereocontrolling 3-methyl substituent. The 78 : 22 diastereoisomeric mixture of (1*RS*,2*SR*,3*RS*)-**11** and (1*SR*,2*SR*,3*RS*)-**12** arises only from a lack of selectivity upon protonation of the β-amino enolate, with preferential protonation *anti*- to the C(2)-amino group (Fig. 2).

Mutual kinetic resolution of *tert*-butyl (±)-3-methylcyclopentene-1-carboxylate 10 with lithium (±)-*N*-benzyl-*N*-α-methylbenzylamide 4

Having demonstrated that the (±)-*tert*-butyl 3-methyl acceptor **10** shows high levels of substrate control, the level of chiral recognition between acceptor **10** and lithium (±)-*N*-benzyl-*N*-α-methylbenzylamide **4** was investigated. As first demonstrated by Horeau,[18] the mutual kinetic resolution of the reacting components [addition of (±)-3-methyl acceptor **10** to an excess of lithium (±)-*N*-benzyl-*N*-α-methylbenzylamide **4**] allows the

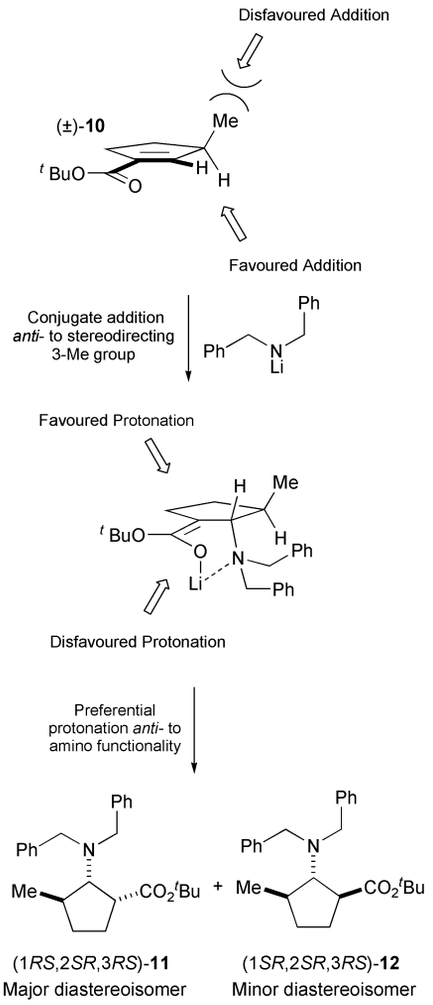


Fig. 2 Schematic to account for diastereoselectivity noted upon conjugate addition of lithium dibenzylamide to (±)-3-methyl acceptor **10**. For clarity, a monomeric lithium amide and β-amino enolate are drawn, although the same argument would apply if other aggregates are involved.

stereoselectivity factor (*E*) for the reaction to be evaluated. The enantiorecognition between the two chiral but racemic components in this strategy is identical to the diastereoselectivity observed in the reaction (since the effects of mass action are eliminated), on the assumption that there are no non-linear effects operating.[19] Four diastereoisomeric products **13**–**16** arising from this reaction are possible [ignoring C(1) protonation selectivity]. Based upon the known excellent stereodirecting capabilities of both the (±)-lithium amide **4** and the (±)-3-methyl acceptor **10**, the major product was predicted to have the C(2)–C(3) *anti*-relative configuration corresponding to **13**, in which synergistic combination of both stereodirecting components of the amide and acceptor are favoured. An evaluation of the stereoselectivity factor (*E*) for the reaction is then simply identical to the ratio of the C(2) diastereoisomeric products observed in the reaction (Figure 3).

Addition of (±)-**10** to an excess (10 eq.) of lithium (±)-*N*-benzyl-*N*-α-methylbenzylamide **4** at −78 °C and quenching of the reaction with $NH_4Cl_{(aq)}$ gave a crude reaction mixture which indicated the presence of three diastereoisomers by ^{1}H NMR spectroscopic analysis. The major products of the reaction were the two C(1) epimeric diastereoisomers (1*RS*,2*SR*,3*RS*,α*SR*)-**17** and (1*SR*,2*SR*,3*RS*,α*SR*)-**18**, the products resulting from the expected "matching" of chiral information from both components of the reaction, in a 90.5 : 9.5 ratio, together with 0.7% (with respect to the sum of the other two) of a third diastereoisomer (1*SR*,2*RS*,3*SR*,α*SR*)-**19** (*vide supra*) (ratio of β-amino ester diastereoisomers **17 : 18 : 19** 90.2 : 9.1 : 0.7). As predicted, (±)-lithium amide **4** adds *anti*- to the C(3) methyl group, with protonation of the resultant enolate *anti*- to the C(2)-amino functionality, resulting in the formation of *tert*-butyl (1*RS*,2*SR*,3*RS*,α*SR*)-3-methyl-2-*N*-benzyl-*N*-α-methylbenzylaminocyclopentane-1-carboxylate **17** as the major diastereoisomer. Measurement of the diastereoisomeric product ratios in this reaction [(1*RS*,2*SR*,3*RS*,α*SR*)-**17** + (1*SR*,2*SR*,3*RS*,α*SR*)-**18** : (1*SR*,2*RS*,3*SR*,α*SR*)-**19** = 99.3 : 0.7] allowed the stereoselectivity factor to be assessed as $E > 140$ in this enantiorecognition protocol. Purification of the major diastereoisomeric product (1*RS*,2*SR*,3*RS*,α*SR*)-**17** to homogeneity and conversion to the thermodynamic epimer (1*SR*,2*SR*,3*RS*,α*SR*)-**18** by treatment with KO^{t}Bu in ^{t}BuOH confirmed that the two major diastereoisomers arising from this mutual resolution protocol (±)-**17** and (±)-**18** were epimeric at C(1). The configuration at C(2) within (±)-**17** and (±)-**18** relative to the *N*-α-methylbenzyl stereocentre was assigned by analogy with previous models developed to explain the stereoselectivity observed during addition of lithium amide **4** to α,β-unsaturated acceptors,[20] with the configuration at C(1) and C(3) confirmed by ^{1}H NOE difference analysis. Both diastereoisomers exhibited a 7.1% NOE enhancement between their C(2)H and C(3)Me protons, but the 8.1% enhancement between C(1)H and C(2)H of the major diastereoisomer (±)-**17** was only 3.1% for the minor diastereoisomer (±)-**18**. Thus, both diastereoisomers (±)-**17** and (±)-**18** have an *anti*-relationship between C(2)H and C(3)Me, but the major diastereoisomer (±)-**17** has a *syn*-relationship between C(1)H and C(2)H, while the minor diastereoisomer (±)-**18** has an *anti*-relationship between C(1)H and C(2)H (Scheme 4).

This configurational analysis is consistent with the expected diastereoisomeric β-amino ester products predicted from Fig. 3, in which a matched combination of the stereodirecting components of both *tert*-butyl (±)-3-methyl acceptor **10** and lithium (±)-*N*-benzyl-*N*-α-methylbenzylamide **4** are favoured.

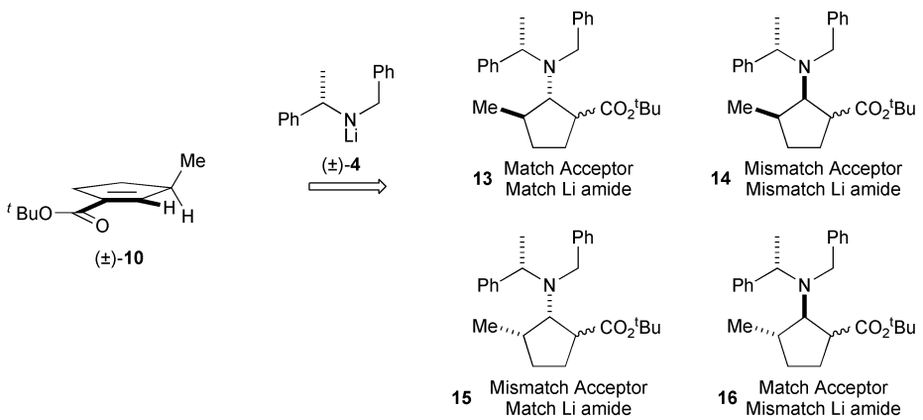
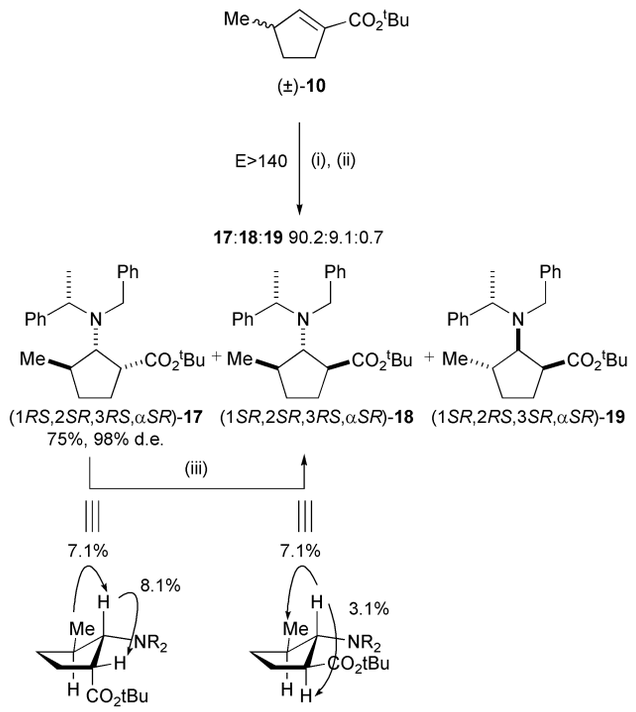


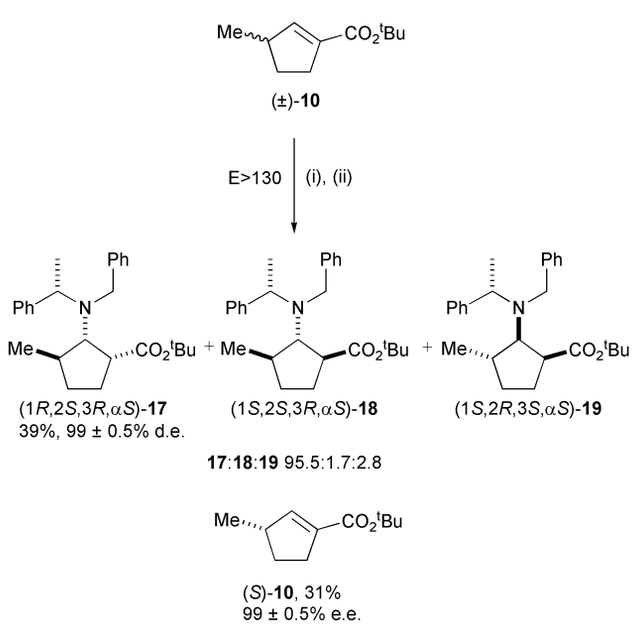
Fig. 3 Possible diastereoisomeric β-amino ester products obtained upon addition of lithium (±)-*N*-benzyl-*N*-α-methylbenzylamide **4** to *tert*-butyl (±)-3-methylcyclopentene-1-carboxylate **10** (ignoring protonation selectivity).



Scheme 4 *Reagents and conditions*: (i). lithium (±)-*N*-benzyl-*N*-α-methylbenzylamide **4** (10 eq.), THF, −78 °C; (ii). $NH_4Cl_{(aq)}$, −78 °C to rt; (iii). KO^{t}Bu, ^{t}BuOH, Δ, 3 hours.

Kinetic resolution of *tert*-butyl (±)-3-methyl cyclopentene-1-carboxylate 10 with lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide 4

With high levels of enantiorecognition observed between the (±)-3-methyl acceptor **10** and (±)-lithium amide **4**, the kinetic resolution of (±)-**10** was undertaken. After a number of experimental conditions were studied to maximise the isolated yield of both β-amino ester product and the residual 3-methyl acceptor in this protocol, treatment of (±)-*tert*-butyl 3-methyl acceptor **10** with 0.7 eq. of lithium amide (*S*)-**4** and quenching with 2,6-di-*tert*-butylphenol gave, at 51% conversion, a mixture of three β-amino ester diastereoisomers **17 : 18 : 19** in a 95.5 : 1.7 : 2.8 ratio (Scheme 5). Although the relative configurations within **17** and **18** had been determined by ^{1}H NMR spectroscopic analysis in the racemic series, the relative configuration within the major diastereoisomer **17** was unambiguously proven by single crystal X-ray analysis, with the absolute (1*R*,2*S*,3*R*,α*S*) configuration being derived from the known configuration of the (α*S*)-*N*-α-methylbenzyl stereocentre (Figure 4). Purification by column chromatography and subsequent recrystallisation gave (1*R*,2*S*,3*R*,α*S*)-**17** in 39% yield and 99 ± 0.5% de and (*S*)-**10** {$[\alpha]_D^{24}$ −84.7, (*c* 1.1, $CHCl_3$)} in 31% yield and 99 ± 0.5% ee,[21] consistent with $E > 130$.



Scheme 5 *Reagents and conditions*: (i). lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **4** (0.7 eq.), THF, −78 °C; (ii). 2,6-di-*tert*-butylphenol, THF, −78 °C to rt.

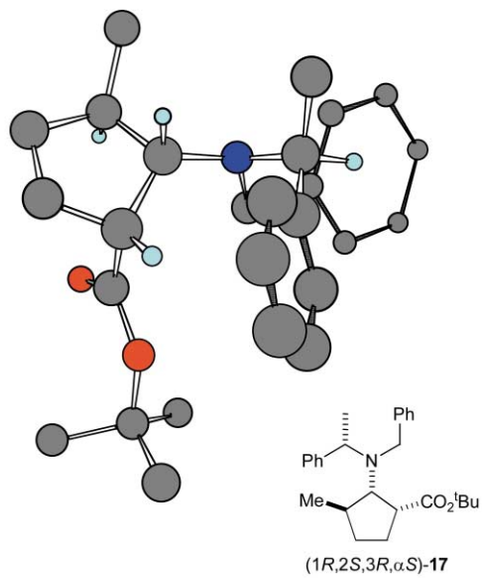
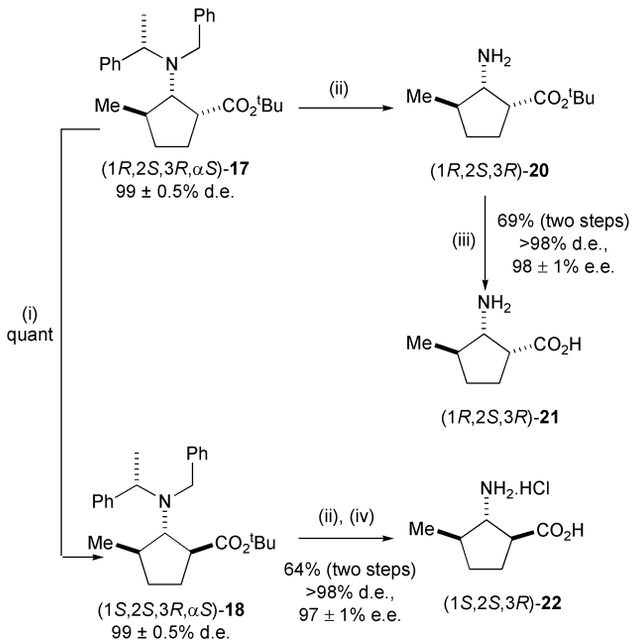


Fig. 4 Chem 3D representation of the X-ray crystal structure of (1*R*,2*S*,3*R*,α*S*)-**17** (some H atoms are omitted for clarity).

The correlation between the observed *E* values in the mutual kinetic resolution ($E > 140$) and kinetic resolution ($E > 130$) protocols validates the concept of screening for high enantiorecognition between two racemic reaction components, being indicative of an efficient kinetic resolution. Given that the effects of mass action act to suppress the final selectivity observed upon kinetic resolution relative to the mutual kinetic resolution protocol, conjugate addition of homochiral lithium amide (*S*)-**4** (1.0 eq.) to an excess (10 eq.) of (±)-3-methyl acceptor **10** and quenching with 2,6-di-*tert*-butylphenol gave, at 94% conversion (relative to amine), a mixture of three β-amino ester diastereoisomers **17 : 18 : 19** in a 97.3 : 1.9 : 0.8 ratio [**17** + **18 : 19** = 99.2 : 0.8], effectively reproducing the level of stereoselectivity noted in the mutual kinetic resolution protocol by reducing the effect of mass action with excess substrate. This is consistent with the third, minor diastereoisomeric β-amino ester (1*S*,2*R*,3*S*,α*S*)-**19** in the kinetic resolution protocol arising from the reaction of a stereochemically mismatched pairing as a consequence of mass action.

With β-amino ester (1*R*,2*S*,3*R*,α*S*)-**17** in hand from the kinetic resolution protocol, deprotection to (1*R*,2*S*,3*R*)-3-methylcispentacin was investigated. Pd mediated *N*-debenzylation of (1*R*,2*S*,3*R*,α*S*)-**17** gave primary β-amino ester (1*R*,2*S*,3*R*)-**20** {$[\alpha]_D^{22}$ −51.8 (*c* 1.02, $CHCl_3$)}, with subsequent treatment with TFA giving (1*R*,2*S*,3*R*)-3-methylcispentacin **21** in 69% yield, >98% de and 98 ± 1% ee[22] after purification by ion exchange chromatography. To prepare selectively the diastereoisomeric (1*S*,2*S*,3*R*)-3-methyltranspentacin, epimerisation of (1*R*,2*S*,3*R*,α*S*)-**17** to the thermodynamic C(1) epimer (1*S*,2*S*,3*R*,α*S*)-**18** was completed by treatment with KO^{t}Bu in ^{t}BuOH, giving (1*S*,2*S*,3*R*,α*S*)-**18** in quantitative yield and 99 ± 0.5% de. Subsequent hydrogenolysis, ester hydrolysis and recrystallisation gave (1*S*,2*S*,3*R*)-3-methyltranspentacin hydrochloride **22** in 64% yield, >98% de and 97 ± 1% ee[22] (Scheme 6).

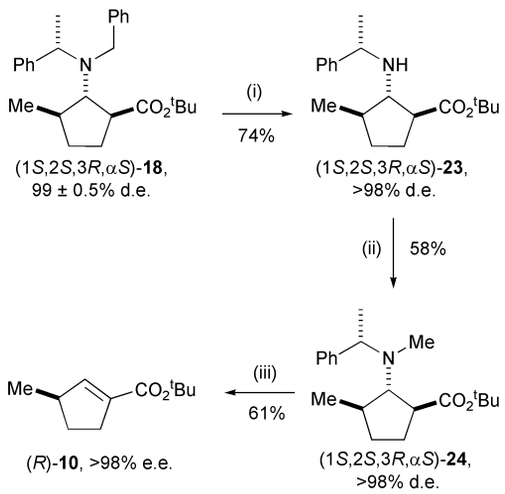


Scheme 6 *Reagents and conditions*: (i). KO^{t}Bu, ^{t}BuOH, Δ, 3 hours; (ii). $Pd(OH)_2$ on C, MeOH, H_2 (5 atm); (iii). TFA then Dowex 50X8-200; (iv). TFA then $HCl_{(aq)}$ and recrystallisation.

Probing enantiorecognition: identification of the mismatched - product

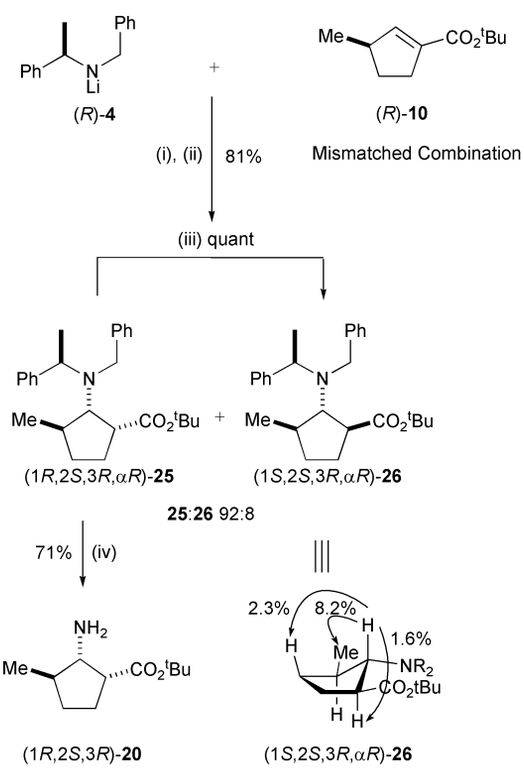
To complete our understanding of the stereochemical course of these resolution reactions, the configuration of the third minor diastereoisomeric product **19** arising from both the mutual kinetic and simple kinetic resolution protocols was investigated by forcing the reaction between the stereochemically mismatched substrate and reagent [homochiral lithium amide (*R*)-**4** and the homochiral acceptor (*R*)-**10**] to completion. Although α,β-unsaturated acceptor (*S*)-**10** is readily available from the kinetic resolution protocol, the relative volatility of resolved acceptor **10** to the β-amino ester components arising from kinetic resolution provided inherent problems in the isolation of sufficient quantities of acceptor for evaluation of the mismatched reaction manifold. An alternative route for the synthesis of an authentic sample of α,β-unsaturated acceptor (*R*)-**10** was therefore employed, using β-amino ester (1*S*,2*S*,3*R*,α*S*)-**18** (99 ± 0.5% de) from the kinetic resolution and epimerisation protocol. Chemoselective *N*-debenzylation of tertiary β-amino ester (1*S*,2*S*,3*R*,α*S*)-**18** with CAN gave secondary β-amino ester (1*S*,2*S*,3*R*,α*S*)-**23** in 74% yield,[23] with *N*-methylation furnishing tertiary β-amino ester (1*S*,2*S*,3*R*,α*S*)-**24** in 58% yield and 99% de. Subsequent *N*-oxidation and Cope elimination[24] upon treatment with *m*CPBA gave the desired acceptor (*R*)-**10** {$[a]_D^{25}$ +83.6 (*c* 0.51, $CHCl_3$)} in 61% yield. The ee of (*R*)-**10** was established to be >98% by ^{1}H NMR chiral shift experiments in the presence of $Eu(hfc)_3$ and by comparison with an authentic racemic sample (Scheme 7).

Conjugate addition of lithium amide (*R*)-**4** to the mismatched acceptor (*R*)-**10** gave a 92 : 8 mixture of the partially separable C(1) epimers (1*R*,2*S*,3*R*,α*R*)-**25** and (1*S*,2*S*,3*R*,α*R*)-**26** in 81% combined yield. Epimerisation of a mixture of (1*R*,2*S*,3*R*,α*R*)-**25** and (1*S*,2*S*,3*R*,α*R*)-**26** gave (1*S*,2*S*,3*R*,α*R*)-**26** as a single diastereoisomer (>98% de by ^{1}H NMR) and in quantitative yield, with the relative configuration of the C(1), C(2) and C(3) stereocentres within (1*S*,2*S*,3*R*,α*R*)-**26** verified by ^{1}H NMR NOE difference experiments. The absolute configurations within this series were verified by hydrogenolysis of (1*R*,2*S*,3*R*,α*R*)-**25** (>98% de) to the tertiary β-amino ester (1*R*,2*S*,3*R*)-**20**, which was spectroscopically identical to that arising from the kinetic resolution experiments {$[a]_D^{22}$ −50.7 (*c* 0.8, $CHCl_3$)}. The (1*R*,2*S*,3*R*,α*R*)- and (1*S*,2*S*,



Scheme 7 *Reagents and conditions*: (i). CAN (2.1 eq.), MeCN : H_2O (5 : 1), rt; (ii). MeI, rt; (iii). *m*CPBA, $CHCl_3$, rt.

3*R*,α*R*)-configurations within β-amino esters **25** and **26** are consistent with conjugate addition of lithium amide (*R*)-**4** occurring *anti* to the 3-methyl group of the acceptor (*R*)-**10**, contrary to the expected facial selectivity of lithium amide (*R*)-**4**. This indicates that while both the α-methylbenzyl of the amide and the 3-methyl substituent on the substrate are both powerful stereochemical directing groups, the 3-methyl substituent, not the lithium amide, is the dominating factor affecting the stereoselectivity observed in these reactions (Scheme 8).



Scheme 8 *Reagents and conditions*: (i). lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **4** (3 eq.), THF, −78 °C; (ii). 2,6-di-*tert*-butylphenol, THF, −78 °C to rt; (iii). KO^{t}Bu, ^{t}BuOH, Δ, 3 hours; (iv). $Pd(OH)_2$ on C, MeOH, H_2 (5 atm).

In conclusion, this protocol verifies that mutual kinetic resolution allows the identification of efficient kinetic resolution procedures. The conjugate addition of homochiral lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **4** has been used to effect the kinetic resolution of *tert*-butyl (±)-3-methylcyclopentene-1-carboxylate **10**, while simultaneously generating stereoselectively the C(1) and C(2) stereogenic centres within β-amino

ester (1*R*,2*S*,3*R*,α*S*)-**17**, which allows for the synthesis of (1*R*,2*S*,3*R*)-3-methylcispentacin **21** by *N*-deprotection and ester hydrolysis, and (1*S*,2*S*,3*R*)-3-methyltranspentacin **22** by selective C(1) epimerisation, followed by *N*-deprotection and ester hydrolysis. The application of this protocol to the kinetic resolution of a range of (±)-3-alkyl-, (±)-4-alkyl and (±)-5-alkylcyclopentene-1-carboxylic acid esters is currently underway within this laboratory.

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 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) or potassium permanganate (1% in 2% aqueous acetic acid, containing 7% potassium carbonate). Infra red 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 (^1H 400 MHz, ^{13}C 100 MHz), or Bruker AM-500 (^1H 500 MHz, ^{13}C 125 MHz) spectrometers. Chemical shifts (δ_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 (APCI). MALDI spectra were recorded on a Micromass MALDI TOF SPEC 2E spectrometer. 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, and the solvent and temperature as recorded; [*a*] values are given in units of 10^{-1} deg cm^2 g^{-1}. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Di-*tert*-butyl adipate[16] and *tert*-butyl 2-oxocyclopentane-1-carboxylate[17] were prepared in accordance with literature procedures.

General procedure A

A solution of the amine in anhydrous THF under an inert atmosphere was cooled to −78 °C prior to the slow addition of *n*-butyllithium (titrated before use, 1 eq.). The resultant pink solution was stirred for 1 h at this temperature before *tert*-butyl (±)-3-methylcyclopentene-1-carboxylate **10** as a solution in anhydrous THF was added dropwise *via* syringe. The resulting mixture was stirred for 3 h at −78 °C after which time the reaction was quenched by addition of either (a) a precooled solution of 2,6-di-*tert*-butylphenol in anhydrous THF or (b) saturated aqueous NH_4Cl solution. The resultant mixture was kept at −78 °C for 0.5 h, then allowed to warm to rt over 1 h. A saturated aqueous NH_4Cl solution was added and the mixture diluted with Et_2O. The organic layer was separated and the aqueous layer extracted with Et_2O (2×). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude products. The individual products were purified as described.

General procedure B

To a solution of the substrate in *tert*-butanol was added a catalytic quantity of potassium *tert*-butoxide (≅20 mg). The resultant mixture was heated at reflux for 3 h then allowed to cool. The reaction was quenched by addition of saturated aqueous NH_4Cl and the mixture diluted with Et_2O. The organic layer was separated and the aqueous layer extracted with Et_2O (2×). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. The individual products were purified as described.

General procedure C

A solution of the substrate in methanol was placed in a Fischer–Porter bottle. The vessel was pump-filled five times with nitrogen prior to charging with $Pd(OH)_2$ (20 wt% on carbon, 20% by mass of substrate used). The reaction was stirred rapidly at rt overnight, after which time the mixture was filtered through a pad of Celite, washed through with methanol and concentrated *in vacuo* to give the crude product.

Preparation of *tert*-butyl 3-methyl-2-oxocyclopentane-1-carboxylate 7

tert-Butyl-2-oxocyclopentane-1-carboxylate (20.0 g, 0.11 mol) was added dropwise to a stirred solution of NaH (4.6 g, 0.11 mol) in THF (200 ml) at 0 °C. After 0.5 h, *n*-BuLi (1.5 M, 73.1 ml, 0.11 mol) was added at 0 °C, and the mixture cooled to −78 °C before the addition of methyl iodide (7.4 ml, 0.12 mol). After 0.5 h the reaction was warmed to rt before the sequential addition of MeOH (2 ml), H_2O (5 ml) and saturated aqueous NH_4Cl (10 ml). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (5% Et_2O–*n*-pentane) to give **7** (19.5 g, 91%) as a colourless oil; ν_{max} (film) 1751 (C=O), 1720 (C=O), 1142 (C–O); data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.7, C(3)*Me*), 1.41 (1H, m, C(4)H_A), 1.47 (9H, s, OC(CH_3)$_3$), 2.09–2.32 (4H, m, C(3)*H*, C(4)H_B and C(5)H_2), 3.04 (1H, dd, *J* 8.5, 10.9, C(1)*H*); δ_C (50 MHz, $CDCl_3$) 13.8 (C(3)*Me*), 24.9 (*C*(5)), 27.8 (OC(CH_3)$_3$), 29.3 (*C*(4)), 44.1 (*C*(3)), 55.4 (*C*(1)), 81.6 (O*C*(CH_3)$_3$), 169.2 (*C*O$_2^t$Bu), 215.1 (*C*(2)O); minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.14 (3H, d, *J* 6.1, C(3)*Me*), 1.46 (9H, s, OC(CH_3)$_3$), 1.79 (1H, m, C(4)H_A), 2.09–2.32 (4H, m, C(3)*H*, C(4)H_B and C(5)H_2), 3.16 (1H, dd, *J* 4.7, 8.8, C(1)*H*); δ_C (50 MHz, $CDCl_3$) 14.5 (C(3)*Me*), 25.0 (*C*(5)), 27.8 (OC(CH_3)$_3$), 29.7 (*C*(4)), 43.5 (*C*(3)), 54.8 (*C*(1)), 81.6 (O*C*(CH_3)$_3$), 169.2 (*C*O$_2^t$Bu), 215.1 (*C*(2)O); *m*/*z* (CI^+, NH_3) 216 (MNH_4^+, 5%), 199 (MH^+, 5), 188 (MNH_4^+ − 28, 81), 171 (MH^+ − 28, 100), 160 (MNH_4^+ − 56, 60), 143 (MH^+ − 56, 25); HRMS, found 199.1332; $C_{11}H_{19}O_3$ (MH^+) requires 199.1334.

Preparation of *tert*-butyl 2-hydroxy-3-methylcyclopentane-1-carboxylate 8

$NaBH_4$ (3.55 g, 93.9 mmol) was added portionwise to a stirred solution of β-keto ester **7** (18.6 g, 93.9 mmol) in EtOH (50 ml) at 0 °C. After 0.75 h, H_2O (5 ml) and saturated aqueous NH_4Cl (30 ml) were added, the mixture diluted with Et_2O (150 ml), and the organic layer separated, dried ($MgSO_4$) and concentrated *in vacuo* to give **8** as a complex mixture of diastereoisomers (17.1 g, 91%). This material was routinely used without purification, although a small quantity was purified by flash chromatography on silica gel (20% Et_2O : hexane) for the purposes of analysis; ν_{max} (film) 3437 (br, O–H), 1701 (C=O), 1150 (C–O); major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.8,

C(3)*Me*), 1.14–1.31 (1H, m, C(4)H_A), 1.47 (9H, s, OC(CH_3)$_3$), 1.55–2.10 (4H, m, C(3)*H*, C(4)H_B and C(5)H_2), 2.78 (1H, app td, *J* 5.6, *J* 4.5, C(1)*H*), 3.88 (1H, dd, *J* 5.6, *J* 3.7, C(2)*H*); δ_C (50 MHz, $CDCl_3$) 19.0 (C(3)*Me*), 26.5 (*C*(5)), 28.3 (OC(*C*H_3)$_3$), 30.8 (*C*(4)), 41.4 (*C*(3)), 48.3 (*C*(1)), 80.2 (*C*(2)), 82.1 (O*C*(CH_3)$_3$), 174.7 (*C*O_2^{t}Bu); *m*/*z* (CI^+, NH_3) 218 (MNH_4^+, 2%), 162 (MNH_4^+ − C_4H_8, 100); HRMS, found 201.1493; $C_{11}H_{21}O_3$ (MH^+) requires 201.1491.

Preparation of *tert*-butyl 3-methyl-2-(4-methylbenzenesulfonyloxy)cyclopentane-1-carboxylate 9

p-Toluenesulfonyl chloride (17.1 g, 89.5 mmol) was added to a solution of alcohol **8** (17.1 g, 85.2 mmol) in pyridine (25 ml) at 0 °C and stirred overnight. Distilled H_2O (10 ml) was added slowly and the mixture was diluted with Et_2O (100 ml), washed with 2 M HCl (3 × 20 ml) and neutralised with excess aqueous $NaHCO_3$. The organic layer was washed with aqueous $CuSO_4$ (20 ml) and brine (30 ml), and then dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude tosylate **9** as a yellow oil (25.75 g, 85%). This material was routinely used without purification, although a small quantity was purified by flash chromatography on silica gel (10% Et_2O : hexane) for the purposes of analysis; ν_{max} (film) 1726 (C=O), 1367 (SO_2), 1178 (SO_2), 1156 (C–O); major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 0.84 (3H, d, *J* 7.0, C(3)*Me*), 1.16 (1H, m, C(4)H_A), 1.44 (9H, s, OC(*C*H_3)$_3$), 1.52–2.10 (4H, m, C(5)H_2, C(4)H_B and C(3)*H*), 2.45 (3H, s, Ar-*Me*), 2.95 (1H, m, C(1)*H*), 4.67 (1H, dd, *J* 6.2, *J* 4.5, C(2)*H*), 7.33 and 7.80 (4H, AB, J_{AB} 8.3, *Ar*–H); δ_C (50 MHz, $CDCl_3$) 17.9 (C(3)*Me*), 21.5 (Ar-*Me*), 24.7 (*C*(5)), 27.8 (OC(*C*H_3)$_3$), 29.8 (*C*(4)), 38.8 (*C*(3)), 48.4 (*C*(1)), 81.2 (O*C*(CH_3)$_3$), 89.6 (*C*(2)), 128.0 (*m*-Ar), 129.8 (*o*-Ar), 144.8 (*ipso*-Ar and *p*-Ar), 170.7 (*C*O_2^{t}Bu); *m*/*z* (CI^+, NH_3) 372 (MNH_4^+, 36%), 316 (MNH_4^+ − C_4H_8, 100) and 298 (MH^+ − C_4H_8, 19); HRMS, found 372.1849; $C_{18}H_{30}NO_5S$ (MNH_4^+) requires 372.1845.

Preparation of *tert*-butyl (±)-3-methylcyclopentene-1-carboxylate 10

A solution of DBU (21.79 g, 0.143 mol) in DCM (25 ml) was added dropwise to a stirred solution of tosylate **9** (25.37 g, 71.57 mmol) in DCM (200 ml) at 0 °C. After 4 h, the reaction mixture was concentrated *in vacuo* and the residue passed through a plug of silica (2% Et_2O : *n*-pentane) to give (±)-**10** as a volatile oil (9.54 g, 73%); ν_{max} (film) 1709 (C=O), 1631 (C=C), 1167 (C–O); δ_H (400 MHz, $CDCl_3$) 1.08 (3H, d, *J* 7.1, C(3)*Me*), 1.46 (1H, m, C(4)*H*), 1.49 (9H, s, OC(CH_3)$_3$), 2.16 (1H, dddd, *J* 12.9, 8.6, 8.4, 4.5, C(4)H_A), 2.49 (1H, m, C(5)H_A), 2.56 (1H, m, C(5)H_B), 2.88 (1H, m, C(3)*H*), 6.54 (1H, m, C(2)*H*); δ_C (50 MHz, $CDCl_3$) 19.9 (C(3)*Me*), 28.3 (OC(*C*H_3)$_3$), 31.1 (*C*(5)), 32.0 (*C*(4)), 40.6 (*C*(3)), 79.9 (O*C*(CH_3)$_3$), 137.0 (*C*(1)), 147.5 (*C*(2)), 165.3 (*C*O_2^{t}Bu); *m*/*z* (CI^+, NH_3) 200 (MNH_4^+, 32%), 183 (MH^+, 83), 144 (MNH_4^+ − C_4H_8, 100), 127 (MH^+ − C_4H_8, 18); HRMS, found 183.1388; $C_{11}H_{19}O_2$ (MH^+) requires 183.1385.

Preparation of *tert*-butyl (1*RS*,2*SR*,3*RS*)-3-methyl-2-(*N*,*N*-dibenzylamino)cyclopentane-1-carboxylate 11

Following *general procedure A*, *n*-BuLi (2.25 M, 1.46 ml, 3.29 mmol), dibenzylamine (650 mg, 3.29 mmol) in THF (20 ml) and (±)-**10** (200 mg, 1.10 mmol) in THF (5 ml) gave, after quenching with 2,6-di-*tert*-butylphenol (747 mg, 3.62 mmol) in THF (10 ml) and purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane), the diastereoisomeric products (1*RS*,2*SR*,3*RS*)-**11** and (1*SR*,2*SR*,3*RS*)-**12** as a 78 : 22 mixture (328 mg, 79%). Successive recrystallisation (2% Et_2O : *n*-pentane) gave (1*RS*,2*SR*,3*RS*)-**11**; found: C, 78.8; H, 8.7; N, 3.7%; $C_{25}H_{33}NO_2$ requires: C, 79.1; H, 8.8; N, 3.7%; mp 72–73 °C; ν_{max} (film) 1718 (C=O), 1141 (C–O); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, d, *J* 6.5, C(3)*Me*), 0.97 (1H, m, C(4)*H*), 1.44 (9H, s, OC(CH_3)$_3$), 1.57 (1H, m, C(5)H_A), 1.76 (1H, m, C(5)H_B), 1.92 (1H, m, C(4)H_B), 2.39 (1H, m, C(3)*H*), 2.74–2.82 (2H, m, C(1)*H* and C(2)*H*), 3.68 and 3.75 (2 × 2H, AB, J_{AB} 14.0, N(CH_2Ph)$_2$), 7.09–7.30 (10H, m, Ar*H*); δ_C (50 MHz, $CDCl_3$) 19.3 (C(3)*Me*), 27.0 (*C*(5)), 28.1 (OC(*C*H_3)$_3$), 31.1 (*C*(4)), 33.3 (*C*(3)), 45.9 (*C*(1)), 54.4 (N(*C*H_2Ph)$_2$), 69.8 (*C*(2)), 80.2 (O*C*(CH_3)$_3$), 126.9 (*p*-Ar), 128.3 and 128.7 (*o*-, *m*-Ar), 140.7 (*ipso*-Ar), 176.1 (*C*O_2^{t}Bu); *m*/*z* (APCI$^+$) 380 (MH^+, 100%), 324 (MH^+ − C_4H_8, 53); HRMS, found 380.2593; $C_{25}H_{34}NO_2$ (MH^+) requires 380.2590.

X-Ray crystal structure data for (1*RS*,2*SR*,3*RS*)-11

Data were collected using an Enraf–Nonius CAD4 diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at room temperature. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The model was refined using CRYSTALS.[25] The crystal faded at high θ values, with reflections after [1 0 15] omitted from the data set accounting for low completeness. The asymmetric unit contains two moieties of formula $C_{25}H_{33}NO_2$. Crystal data for **11** [$C_{25}H_{33}NO_2$]: colourless plate, M = 379.54, triclinic, space group $P\bar{1}$, a = 11.289 (1) Å, b = 11.4013 (8) Å, c = 19.344 (4) Å, α = 96.03 (1)°, β = 95.87 (1)°, γ = 112.820 (7)°, U = 2254.06 Å^3, Z = 4, μ = 0.541 mm^{-1}, crystal dimensions 0.18 × 0.54 × 0.60 mm. A total of 7981 unique reflections were measured for $0 < \theta < 72$ and 4360 reflections were used in the refinement. The final parameters were R_1 = 0.0596 [$I > 3\sigma(I)$] and wR_2 = 0.0669.

CCDC reference number 213043.

See http://www.rsc.org/suppdata/ob/b3/b306935b/ for crystallographic files in CIF or other electronic format.

Preparation of *tert*-butyl (1*SR*,2*SR*,3*RS*)-3-methyl-2-(*N*,*N*-dibenzylamino)cyclopentane-1-carboxylate 12

Following *general procedure B*, a 78 : 22 mixture of (1*RS*,2*SR*,3*RS*)-**11** and (1*SR*,2*SR*,3*RS*)-**12** (100 mg, 0.26 mmol) in ^{t}BuOH (5 ml) was treated with KO^{t}Bu and heated at reflux for three hours. Purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane) gave (1*SR*,2*SR*,3*RS*)-**12** (97 mg, quantitative) as a white solid in >98% de; mp 103–104 °C; ν_{max} (film) 1718 (C=O), 1139 (C–O); δ_H (400 MHz, $CDCl_3$) 1.02 (3H, d, *J* 7.5, C(3)*Me*), 1.24–1.38 (1H, m, C(4)H_A), 1.48 (9H, s, OC(CH_3)$_3$), 1.55–1.63 (1H, m, C(5)H_B), 1.69–1.83 (2H, m, C(4)H_B and C(5)H_B), 1.99 (1H, m, C(3)*H*), 2.86 (1H, m, C(1)*H*), 3.04 (1H, app t, C(2)*H*), 3.55 and 3.76 (2 × 2H, AB, J_{AB} 13.8, N(CH_2Ph)$_2$), 7.19–7.38 (10H, m, Ar*H*); δ_C (50 MHz, $CDCl_3$) 18.7 (C(3)*Me*), 28.1 (OC(*C*H_3)$_3$), 28.8 (*C*(5)), 32.1 (*C*(4)), 37.3 (*C*(3)), 44.5 (*C*(1)), 54.8 (N(*C*H_2Ph)$_2$), 71.4 (*C*(2)), 79.8 (O*C*(CH_3)$_3$), 126.7 (*p*-Ar), 128.0 and 128.7 (*o*-, *m*-Ar), 140.2 (*ipso*-Ar), 176.5 (*C*O_2^{t}Bu); *m*/*z* (APCI$^+$) 380 (MH^+, 100%), 324 (MH^+ − C_4H_8, 22); HRMS, found 380.2580; $C_{25}H_{34}NO_2$ (MH^+) requires 380.2590.

Preparation of *tert*-butyl (1*RS*,2*SR*,3*RS*,α*SR*)-3-methyl-2-(*N*-benzyl-*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 17

Following *general procedure A*, *n*-BuLi (2.5 M, 1.10 ml, 2.74 mmol), (±)-*N*-benzyl-*N*-α-methylbenzylamine (581 mg, 2.74 mmol) in THF (20 ml) and (±)-**10** (50 mg, 0.28 mmol) in THF (2 ml) gave, after quenching with saturated aqueous NH_4Cl (10 ml), (1*RS*,2*SR*,3*RS*,α*SR*)-**17**, (1*SR*,2*SR*,3*RS*,α*SR*)-**18** and (1*SR*,2*RS*,3*SR*,α*SR*)-**19** in a 90.2 : 9.1 : 0.7 ratio. Purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane) gave (1*RS*,2*SR*,3*RS*,α*SR*)-**17** (83 mg, 75%) as a clear oil; found: C, 79.0; H, 9.3; N, 3.6%; $C_{26}H_{35}NO_2$ requires: C, 79.3; H, 9.0; N, 3.6%; ν_{max} (film) 1712 (C=O), 1149 (C–O); δ_H (400 MHz, $CDCl_3$) 0.99–1.04 (1H, m, C(4)H_A), 1.02 (3H, d, *J* 6.5, C(3)*Me*),

1.19 (3H, d, *J* 6.9, C(α)*Me*), 1.51 (9H, s, OC(CH_3)$_3$), 1.58 (1H, m, C(5)H_A), 1.72 (1H, m, C(5)H_B), 1.97 (1H, m, C(4)H_B), 2.28 (1H, m, C(3)*H*), 2.53 (1H, ddd, *J* 4.0, 7.7, 7.7, C(1)*H*), 2.82 (1H, dd, *J* 7.7, 10.5, C(2)*H*), 3.96 and 4.16 (2H, AB, J_{AB} 15.9, NCH_2Ph), 4.15 (1H, q, *J* 6.9, C(α)*H*), 7.21–7.52 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 19.5 (C(3)*Me*), 20.5 (C(α)*Me*), 26.9 (*C*(5)), 28.1 (OC(*C*H_3)$_3$), 30.7 (*C*(4)), 34.6 (*C*(3)), 46.7 (*C*(1)), 50.9 (N*C*H_2Ph), 60.1 (*C*(2)), 70.4 (*C*(α)H), 80.0 (O*C*(CH$_3$)$_3$), 126.4 and 127.0 (*p*-Ar), 127.8, 127.9, 128.1 and 128.3 (*o*-, *m*-Ar), 143.6 and 145.6 (*ipso*-Ar), 176.5 (*C*O_2^{t}Bu); *m*/*z* (CI^+) 394 (MH^+, 100%); HRMS, found 394.2741; $C_{26}H_{36}NO_2$ (MH^+) requires 394.2746.

Preparation of *tert*-butyl (1*S*,2*S*,3*R*,α*S*)-3-methyl-2-(*N*-benzyl-*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 17 by kinetic resolution

Following *general procedure A*, *n*-BuLi (1.5 M, 0.96 mmol, 0.64 ml), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (204 mg, 0.96 mmol) in THF (20 ml) and (±)-**10** (250 mg, 1.37 mmol) in THF (5 ml) gave, after quenching with 2,6-di-*tert*-butylphenol (435 mg, 2.11 mmol) in THF (10 ml), (1*R*,2*S*,3*R*,α*S*)-**17**, (1*S*,2*S*,3*R*,α*S*)-**18** and (1*S*,2*R*,3*S*,α*S*)-**19** in a 95.5 : 1.7 : 2.8 ratio. The amines were separated from the unused acrylate by dissolving the crude mixture in pentane (25 ml) and passing HCl (g) through the mixture. The pentane was decanted from the solid, neutralised ($NaHCO_3$) and concentrated *in vacuo* to give the crude acrylate, which was purified by flash chromatography on silica gel (2% Et_2O : *n*-pentane) furnishing (*S*)-**10** (77 mg, 31%) {$[\alpha]_D^{24}$ −84.7 (*c* 1.1, $CHCl_3$)} with spectroscopic data identical to the racemate. The adducts (1*R*,2*S*,3*R*,α*S*)-**17**, (1*S*,2*S*,3*R*,α*S*)-**18** and (1*S*,2*R*,3*S*,α*S*)-**19** were neutralised (KOH) and purified by flash chromatography in the same manner as the racemate, but with subsequent recrystallisation from 2% Et_2O : *n*-pentane, to give the diastereoisomerically pure product (1*R*,2*S*,3*R*,α*S*)-**17** as a white crystalline solid (210 mg, 39%); mp 60–62 °C; $[\alpha]_D^{23}$ −151.3 (*c* 1.0, $CHCl_3$) with spectroscopic data identical to the racemate.

X-Ray crystal structure data for (1*S*,2*S*,3*R*,α*S*)-17

Data were collected using an Enraf–Nonius CAD4 diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at room temperature. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The model was refined using CRYSTALS.[25] Crystal data for **17** [$C_{26}H_{35}NO_2$]: colourless plate, M = 393.55, orthorhombic, space group $P2_122_1$, a = 9.9698 (8) Å, b = 10.8697 (9) Å, c = 21.974 (4) Å, U = 2381.28 Å^3, Z = 4, μ = 0.528 mm^{-1}, crystal dimensions 0.17 × 0.80 × 1.00 mm. A total of 6749 unique reflections were measured for $0 < \theta < 72$ and 4273 reflections were used in the refinement. The final parameters were R_1 = 0.0408 [$I > 3\sigma(I)$] and wR_2 = 0.0508.

CCDC reference number 213044.

See http://www.rsc.org/suppdata/ob/b3/b306935b/ for crystallographic files in CIF or other electronic format.

Preparation of *tert*-butyl (1*S*,2*S*,3*R*,α*S*)-3-methyl-2-(*N*-benzyl-*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 18 by epimerisation

Following *general procedure B*, a solution of (1*R*,2*S*,3*R*,α*S*)-**17** (150 mg, 0.38 mmol) in ^{t}BuOH (10 ml) was treated with KO^{t}Bu and heated at reflux for three hours. Purification by flash chromatography on silica (2% Et_2O : *n*-pentane) gave **18** in >98% de as a colourless oil which slowly crystallised on standing (148 mg, quantitative); found C, 79.4; H, 9.1; N, 3.6%; $C_{26}H_{35}NO_2$ requires: C, 79.3; H, 9.0; N, 3.6%; mp 47–49 °C; $[\alpha]_D^{22}$ +18.8 (*c* 1.00, $CHCl_3$); ν_{max} (film) 1724 (C=O), 1132 (C–O); δ_H (400 MHz, $CDCl_3$) 1.06 (3H, d, *J* 6.5, 3-*Me*), 1.21 (1H, m, C(4)H_A), 1.22 (3H, d, *J* 6.8, C(α)*Me*), 1.43 (9H, s, OC(CH_3)$_3$), 1.67 (1H, m, C(5)H_A), 1.74 (2H, m, C(4)H_B and C(5)H_B), 1.86 (1H, m, C(3)*H*), 2.86 (1H, m, C(1)*H*), 3.19 (1H, dd, *J* 6.0, 8.7, C(2)*H*), 3.73 and 3.83 (2H, AB, J_{AB} 15.7, NCH_2Ph), 3.89 (1H, q, *J* 6.9, C(α)*H*), 7.19–7.45 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 18.6 (C(3)*Me*), 21.7 (C(α)*Me*), 28.0 (OC(*C*H_3)$_3$), 30.1 (*C*(5)), 32.4 (*C*(4)), 39.1 (*C*(3)), 45.9 (*C*(1)), 51.0 (N*C*H_2Ph), 61.5 (*C*(2)), 71.1 (*C*(α)H), 79.7 (O*C*(CH$_3$)$_3$), 126.5 and 126.8 (*p*-Ar), 127.8, 127.9, 128.2 and 128.3 (*o*, *m*-Ar), 143.4 and 145.7 (*ipso*-Ar), 176.5 (*C*O_2^{t}Bu); *m*/*z* ($APCI^+$) 394 (MH^+, 100%); HRMS, found 394.2747; $C_{26}H_{36}NO_2$ (MH^+) requires 394.2746.

Preparation of *tert*-butyl (1*R*,2*S*,3*R*)-3-methyl-2-aminocyclopentane-1-carboxylate 20

Following *general procedure C*, $Pd(OH)_2$ on C (11 mg) was added to a stirred degassed solution of (1*R*,2*S*,3*R*,α*S*)-**17** (53 mg, 0.13 mmol) in MeOH (5 ml) and stirred under H_2 (5 atm) overnight. Filtration through Celite and concentration *in vacuo* gave the crude β-amino ester. Purification by flash chromatography on silica (Et_2O) gave an analytical sample of **20** as a colourless oil (23 mg, 66%); $[\alpha]_D^{22}$ −51.8 (*c* 1.02, $CHCl_3$); ν_{max} (film) 3388 (N–H, br), 1721 (C=O), 1153 (C–O); δ_H (400 MHz, $CDCl_3$) 1.03 (3H, d, *J* 6.7, C(3)*Me*), 1.16 (1H, m, C(4)H_A), 1.40 (9H, s, OC(CH_3)$_3$), 1.80 (2H, br s, NH_2), 1.80–1.98 (4H, m, C(3)*H*, C(4)H_B and C(5)H_2), 2.86 (1H, m, C(1)*H*), 2.94 (1H, app t, C(2)*H*); δ_C (50 MHz, $CDCl_3$) 18.4 (C(3)*Me*), 25.9 (*C*(5)), 28.1 (OC(*C*H_3)$_3$), 31.6 (*C*(4)), 41.8 (*C*(3)), 49.8 (*C*(1)), 62.0 (*C*(2)), 80.3 (O*C*(CH$_3$)$_3$), 174.5 (*C*O_2^{t}Bu); *m*/*z* (CI^+, NH_3) 200 (MH^+, 7%), 144 ($MH^+ - C_4H_8$, 100); HRMS, found 200.1652; $C_{11}H_{22}NO_2$ (MH^+) requires 200.1651.

Preparation of (1*R*,2*S*,3*R*)-3-methyl-2-aminocyclopentane-1-carboxylate 21

TFA (5 ml) was added to a solution of crude β-amino ester **20** (86 mg, 0.43 mmol) at rt and stirred for 16 h. Concentration *in vacuo* gave an oil which was dissolved in methanol (2 ml) and sat. HCl in Et_2O (2 ml). Concentration *in vacuo* gave a pale brown solid which was partitioned between Et_2O (4 ml) and water (4 ml). The aqueous phase was concentrated to a quarter of its volume and chromatographed using Dowex 50X8-200 resin to give **21** (48 mg, 69% from **17**) as a white solid; found: C, 58.65; H, 9.22; N, 9.93; O, 22.6%; $C_7H_{13}NO_2$ requires: C, 58.72; H, 9.25; N, 9.78; O, 22.35%; mp 218–220 °C (decomposes); $[\alpha]_D^{24}$ −38.5 (*c* 2.0, H_2O); ν_{max} (KBr) 2953 (NH_3^+, br), 2101, 1645 (amino acid I), 1570 (amino acid II), 1513 (CO_2^-, NH_3^+), 1403; δ_H (400 MHz, D_2O) 0.92 (3H, d, *J* 6.8, C(3)*Me*), 1.15 (1H, m, C(4)H_A), 1.67 (1H, m, C(5)H_A), 1.82–2.06 (3H, m, C(3)*H*, C(4)H_B and C(5)H_B), 2.82 (1H, ddd, *J* 8.2, 8.2, 7.1, C(1)*H*), 3.09 (1H, app t, *J* 6.7, C(2)*H*); δ_C (100.6 MHz, D_2O) 18.3 (C(3)*Me*), 28.1 (*C*(5)), 30.9 (*C*(4)), 38.0 (*C*(3)), 46.9 (*C*(1)), 59.1 (*C*(2)), 181.3 (*C*O_2H); *m*/*z* ($APCI^+$) 144 (MH^+, 80%), 126 ($MH^+ - NH_3$, 100); HRMS, found 144.1027; $C_7H_{14}NO_2$ (MH^+) requires 144.1026.

Preparation of (1*S*,2*S*,3*R*)-3-methyl-2-aminocyclopentane-1-carboxylate hydrochloride 22

Following *general procedure C*, $Pd(OH)_2$ on C (35 mg) was added to a stirred degassed solution of (1*S*,2*S*,3*R*,α*S*)-**18** (160 mg, 0.40 mmol) in MeOH (5 ml) and stirred under H_2 (5 atm) overnight. Filtration through Celite and concentration *in vacuo* gave the crude β-amino ester, from which an analytical sample was purified by flash chromatography on silica (Et_2O), giving *tert*-butyl (1*S*,2*S*,3*R*)-3-methyl-2-aminocyclopentane-1-carboxylate as a colourless oil (32 mg); $[\alpha]_D^{22}$ +31.2 (*c* 0.44, $CHCl_3$); ν_{max} (film) 3380 (N–H, br), 1724 (C=O), 1152 (C–O); δ_H (500 MHz, $CDCl_3$) 1.06 (3H, d, *J* 6.5, C(3)*Me*), 1.31 (1H, m, C(4)H_A), 1.48 (9H, s, OC(CH_3)$_3$), 1.59 (1H, m, C(3)*H*), 1.64 (2H, br s, NH_2), 1.83–1.95 (3H, m, C(4)H_B and C(5)H_2), 2.40 (1H, m, C(1)*H*), 2.79 (1H, br m, C(2)*H*); δ_C (125 MHz, $CDCl_3$) 18.0 (C(3)*Me*), 25.8 (*C*(5)), 28.6 (OC(*C*H_3)$_3$), 31.6 (*C*(4)), 43.2

(*C*(3)), 54.5 (*C*(1)), 63.9 (*C*(2)), 80.6 (O*C*(CH_3)$_3$), 175.3 (*C*O_2^{t}Bu); *m*/*z* (APCI$^+$) 200 (MH^+, 9%), 144 ($MH^+ - C_4H_8$, 100); HRMS, found 200.1642; $C_{11}H_{22}NO_2$ (MH^+) requires 200.1651.

TFA (4 ml) was added to a solution of the crude β-amino ester (86 mg, 0.43 mmol) at rt and stirred for 16 h. Concentration *in vacuo* gave an oil which was dissolved in methanol (2 ml) and sat. HCl in Et_2O (2 ml). Concentration *in vacuo* gave a pale brown solid which was partitioned between Et_2O (4 ml) and water (4 ml). The aqueous phase was concentrated to afford the crude α-amino acid as its hydrochloride salt. Recrystallisation from water gave **22** as a white solid (48 mg, 64% from **18**); mp 162–164 °C; $[\alpha]_D^{25}$ +29.9 (*c* 0.75, H_2O); ν_{max} (KBr) 2946 (NH_3^+, br), 1649 (amino acid I), 1573 (amino acid II), 1509 (CO_2^-, NH_3^+), 1397; δ_H (400 MHz, D_2O) 1.02 (3H, d, *J* 6.0, C(3)*Me*), 1.32 (1H, m, C(4)H_A), 1.80–2.64 (4H, m, C(3)*H*, C(4)H_B and C(5)H_2), 2.80 (1H, m, C(1)*H*), 3.09 (1H, app t, *J* 8.6, C(2)*H*); δ_C (100.6 MHz, D_2O) 16.8 (C(3)*Me*), 26.6 (*C*(5)), 31.3 (*C*(4)), 39.2 (*C*(3)), 48.3 (*C*(1)), 60.4 (*C*(2)), 176.1 (*C*O_2H); *m*/*z* (APCI+) 144 (MH^+, 90%), 126 ($MH^+ - NH_3$, 100); HRMS, found 144.1020; $C_7H_{14}NO_2$ (MH^+) requires 144.1026.

Preparation of *tert*-butyl (1*S*,2*S*,3*R*,α*S*)-3-methyl-2-(*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 23

In accordance with the literature procedure,[23] CAN (1.15 g, 2.09 mmol), (1*S*,2*S*,3*R*,α*S*)-**18** (392 mg, 1.00 mmol) in 5 : 1 MeCN : water (6 ml) at rt overnight gave, after purification by flash chromatography on silica gel (30% Et_2O : hexane), **23** as a colourless oil (225 mg, 74%); $[\alpha]_D^{23}$ −42.9 (*c* 0.45, $CHCl_3$); ν_{max} (film) 3331 (N–H, br), 1722 (C=O), 1147 (C–O); δ_H (400 MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.6, C(3)*Me*), 1.30 (1H, m, C(4)H_A), 1.33 (3H, d, *J* 6.6, C(α)*Me*), 1.42 (9H, s, OC(CH_3)$_3$), 1.62 (1 H, m, C(5)H_A), 1.72–1.80 (2H, m, C(4)H_B and C(5)H_B), 1.88 (1H, m, C(3)*H*), 2.49 (1H, m, C(1)*H*), 2.66 (1H, m, C(2)*H*), 3.88 (1H, q, *J* 6.6, C(α)*H*), 7.20–7.34 (5H, m, Ar*H*); δ_C (50 MHz, $CDCl_3$) 17.9 (C(3)*Me*), 25.3 (C(α)*Me*), 27.9 (OC(*C*H_3)$_3$), 28.3 (*C*(5)), 32.4 (*C*(4)), 42.3 (*C*(3)), 53.3 (*C*(1)), 56.2 (*C*(2)), 67.6 (*C*(α)H), 79.9 (O*C*(CH$_3$)$_3$), 126.9, 126.9 and 128.3 (*o*-, *m*-, *p*-Ar), 146.1 (*ipso*-Ar), 176.4 (*C*O_2^{t}Bu); *m*/*z* (APCI$^+$) 304 (MH^+, 91%), 248 (MH^+– − C_4H_8, 100); HRMS, found 304.2276; $C_{19}H_{30}NO_2$ (MH^+) requires 304.2277.

Preparation of *tert*-butyl (1*S*,2*S*,3*R*,α*S*)-3-methyl-2-(*N*-methyl-*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 24

MeI (5 ml) was added neat, dropwise, to (1*S*,2*S*,3*R*,α*S*)-**23** (146 mg, 0.48 mmol) and the reaction mixture stirred for 2 days at rt. After the addition of saturated aqueous $NaHCO_3$ solution (5 ml), the mixture was extracted with Et_2O (3 × 10 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (20% Et_2O : hexane) gave **24** (88 mg, 58%) as a clear oil; $[\alpha]_D^{23}$ +7.3 (*c* 1.01, $CHCl_3$); ν_{max} (film) 1723 (C=O), 1145 (C–O); δ_H (500 MHz, $CDCl_3$) 0.88 (3H, d, *J* 6.6, C(3)*Me*), 1.16 (1H, m, C(4)H_A), 1.26 (3H, d, *J* 6.7, C(α)*Me*), 1.37 (9H, s, OC(CH_3)$_3$), 1.61–1.70 (3H, m, C(4)H_B and C(5)H_2), 1.85 (1H, m, C(3)*H*), 2.15 (3H, s, N*Me*), 2.70 (1H, m, C(1)*H*), 2.99 (1H, dd, *J* 8.7, 7.6, C(2)*H*), 3.64 (1H, q, *J* 6.7, C(α)*H*), 7.11–7.27 (5H, m, Ar*H*); δ_C (50 MHz, $CDCl_3$) 19.2 (C(3)*Me*), 21.3 (C(α)*Me*), 28.5 (OC(*C*H_3)$_3$), 29.6 (*C*(5)), 32.5 (*C*(4)), 32.7 (N*Me*), 38.0 (*C*(3)), 44.6 (*C*(1)), 62.8 (*C*(α)H), 72.9 (*C*(2)), 80.1 (O*C*(CH$_3$)$_3$), 126.9 (*p*-Ar), 127.9 and 128.4 (*o*-, *m*-Ar), 146.8 (*ipso*-Ar), 177.0 (*C*O_2^{t}Bu); *m*/*z* (APCI$^+$) 318 (MH^+, 100%), 262 ($MH^+ - C_4H_8$, 57); HRMS, found 318.2444; $C_{20}H_{32}NO_2$ (MH^+) requires 318.2433.

Preparation of *tert*-butyl (*R*)-3-methylcyclopentene-1-carboxylate 10

A solution of *m*CPBA (50% by mass, 130 mg) in $CHCl_3$ (2 ml) was added dropwise to a stirred solution of **24** (111 mg, 0.35 mmol) in $CHCl_3$ (3 ml) and stirred at rt overnight. After 16 h, aqueous $NaHCO_3$ (5 ml) was added and the aqueous layer was extracted with $CHCl_3$ (3 × 10 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane) gave (*R*)-**10** as a volatile oil (39 mg, 61%); $[\alpha]_D^{25}$ +83.6 (*c* 0.51, $CHCl_3$). The material was judged to be in >98% ee by chiral shift NMR spectroscopy with 4 eq. to Eu(hfc)$_3$ by mass, with spectroscopic data consistent with that obtained for the racemate.

Preparation of *tert*-butyl (1*R*,2*S*,3*R*,α*R*)-3-methyl-2-(*N*-benzyl-*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 25 and *tert*-butyl (1*S*,2*S*,3*R*,α*R*)-3-methyl-2-(*N*-benzyl-*N*-α-methylbenzylamino)cyclopentane-1-carboxylate 26

Following *general procedure A*, *n*-BuLi (1.6 M, 0.63 mmol, 0.39 ml), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (134 mg, 0.63 mmol) in THF (5 ml) and (±)-**10** (38 mg, 0.21 mmol) in THF (1 ml) gave, after quenching with 2,6-di-*tert*-butylphenol (286 mg, 1.39 mmol) in THF (4 ml), (1*R*,2*S*,3*R*,α*R*)-**25** and (1*S*,2*S*,3*R*,α*R*)-**26** in a 92 : 8 ratio. Purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane) gave a sample of pure (1*R*,2*S*,3*R*,α*R*)-**25** as a colourless oil (30 mg, 36%); $[\alpha]_D^{24}$ −25.2 (*c* 1.50, $CHCl_3$); found C, 79.0; H, 9.4; N, 3.7%; $C_{26}H_{35}NO_2$ requires: C, 79.3; H, 9.0; N, 3.6%; ν_{max} (film) 1695 (C=O), 1131 (C–O); δ_H (400 MHz, $CDCl_3$) 0.74 (3H, dd, *J* 6.6, 2.0, C(3)*Me*), 0.95–1.04 (1H, m, C(4)H_A), 1.51 (3H, d, *J* 6.7, C(α)*Me*), 1.53 (9H, s, OC(CH_3)$_3$), 1.65–1.81 (2H, m, C(5)H_A and C(5)H_B), 1.98 (1H, m, C(4)H_B), 2.33 (1H, m, C(3)*H*), 2.77 (1H, dd, *J* 9.7, 7.3, C(2)*H*), 2.86 (1H, app td, *J* 7.3, 3.5, C(1)*H*), 3.90 and 4.09 (2 × 1H, AB, J_{AB} 14.2, NCH_2Ph), 3.99 (1H, q, *J* 6.7, C(α)*H*), 7.23–7.45 (10H, m, *Ph*); δ_C (100.6 MHz, $CDCl_3$) 15.3 (C(3)*Me*), 19.3 (C(α)*Me*), 27.1 (*C*(5)), 28.1 (OC(*C*H_3)$_3$), 30.0 (*C*(4)), 35.5 (*C*(3)), 49.3 (*C*(1)), 50.9 (N*C*H_2Ph), 55.9 (*C*(α)H), 67.9 (*C*(2)), 79.9 (O*C*(CH$_3$)$_3$), 126.5 and 126.6 (*p*-Ar), 127.5, 127.7, 128.5 and 128.7 (*o*, *m*-Ar), 141.3 and 143.5 (*ipso*-Ar), 175.9 (*C*O_2^{t}Bu); *m*/*z* (APCI$^+$) 394 (MH^+, 100%); HRMS, found 394.2749; $C_{26}H_{36}NO_2$ (MH^+) requires 394.2746. A mixed fraction of (1*R*,2*S*,3*R*,α*R*)-**25** and (1*S*,2*S*,3*R*,α*R*)-**26** (37 mg, 45%) as a colourless oil, was also obtained. This material was subsequently re-dissolved in *tert*-butanol and epimerised under thermodynamic conditions in accordance with *general procedure B*. Purification by flash chromatography on silica (2% Et_2O : *n*-pentane) gave **26** in >98% de as a colourless oil (35 mg, quantitative); $[\alpha]_D^{25}$ −5.3 (*c* 2.00, MeOH); ν_{max} (film) 1670 (C=O), 1127 (C–O); δ_H (500 MHz, $CDCl_3$) 0.77 (3H, d, *J* 6.2, C(3)*Me*), 1.08–1.27 (1H, m, C(4)H_A), 1.36 (3H, d, *J* 6.9, C(α)*Me*), 1.55 (9H, s, OC(CH_3)$_3$), 1.67 (1 H, m, C(5)H_A), 1.78–1.90 (3H, m, C(3)*H*, C(4)H_B and C(5)H_B), 2.84 (1H, m, C(1)*H*), 3.13 (1H, dd, *J* 9.2, 6.2, C(2)*H*), 3.75 and 3.79 (2H, AB, J_{AB} 14.2, PhCH_2N), 3.94 (1H, q, *J* 6.9, C(α)*H*), 7.20–7.42 (10H, m, Ar*H*); δ_C (50 MHz, $CDCl_3$) 14.8 (C(3)*Me*), 18.1 (C(α)*Me*), 28.0 (OC(*C*H_3)$_3$), 30.1 (*C*(5)), 32.0 (*C*(4)), 38.9 (*C*(3)), 46.5 (*C*(1)), 50.8 (Ph*C*H_2N), 56.9 (*C*(2)), 68.6 (C(α)*H*), 80.0 (O*C*(CH$_3$)$_3$), 126.7 and 126.8 (*p*-Ar), 127.9, 128.3, 128.4 and 128.7 (*o*-, *m*-Ar), 141.9 and 144.8 (*ipso*-Ar), 176.9 (*C*O_2^{t}Bu); *m*/*z* (APCI$^+$) 394 (MH^+, 100%); HRMS, found 394.2739; $C_{26}H_{36}NO_2$ (MH^+) requires 394.2746.

Preparation of *tert*-butyl (1*R*,2*S*,3*R*)-3-methyl-2-aminocyclopentane-1-carboxylate 20 by hydrogenolysis of (1*R*,2*S*,3*R*,α*R*)-25

Following *general procedure C*, $Pd(OH)_2$ on C (8 mg) was added to a degassed solution of (1*S*,2*S*,3*R*,α*S*)-**25** (28 mg, 0.071 mmol) in MeOH (3 ml) and stirred under H_2 (5 atm) overnight. Filtration through Celite, concentration *in vacuo* and purification by flash chromatography on silica (Et_2O) gave **20** as a colourless oil (10 mg, 71%); $[\alpha]_D^{22}$ −50.7 (*c* 0.8, $CHCl_3$). All other spectroscopic data were consistent with that obtained for the same compound reported above.

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Notes and references

1 For reviews see: G. Cardillo and C. Tomasini, *Chem. Soc. Rev.*, 1996, 117; D. C. Cole, *Tetrahedron*, 1994, **50**, 9517; M. Liu and M. P. Sibi, *Tetrahedron*, 2002, **58**, 7991.
2 For instance see: P. A. Grieco, Y. S. Hon and A. Perez-Madrano, *J. Am. Chem. Soc.*, 1988, **110**, 1630; K.-I. Yoshida, Y. Minami, R. Azuma, M. Saeki and T. Otani, *Tetrahedron Lett.*, 1993, **43**, 2637.
3 For reviews see: D. Seebach and J. L. Matthews, *Chem. Commun.*, 1997, 2015; S. H. Gellman, *Acc. Chem. Res.*, 1998, **31**, 173.
4 For instance see: M. Konishi, M. Nishio, K. Saitoh, T. Miyaki, T. Oki and H. Kawaguchi, *J. Antibiot.*, 1989, **42**, 1749; T. Oki, M. Hirano, K. Tomatsu, K. Numata and H. Kamei, *J. Antibiot.*, 1989, **42**, 1756.
5 T. A. Martinek, G. K. Táth, E. Vass, M. Hollósi and F. Fülop, *Angew. Chem., Int. Ed.*, 2002, **41**, 1718.
6 D. H. Appella, L. A. Christianson, D. A. Klein, D. R. Powell, X. Huang, J. J. Barchi and S. H. Gellman, *Nature*, 1997, **387**, 381; D. H. Appella, L. A. Christianson, D. A. Klein, M. R. Richards, D. R. Powell and S. H. Gellman, *J. Am. Chem. Soc.*, 1999, **121**, 7574; J. J. Barchi, Jr, X. Huang, D. H. Appella, L. A. Christianson, S. R. Durell and S. H. Gellman, *J. Am. Chem. Soc.*, 2000, **122**, 2711.
7 For a review see: F. Fülöp, *Chem. Rev.*, 2001, 2181.
8 M. Konishi, M. Nishio, K. Saitoh, T. Miyaki, T. Oki and H. Kawaguchi, *J. Antiobiot.*, 1989, **42**, 1749; K. Kuwabata, Y. Inamoto and K. Sakane, *J. Antiobiot.*, 1990, **43**, 513.
9 T. Konosu and S. Oida, *Chem. Pharm. Bull.*, 1993, **43**, 1012; C. Evans, R. McCague, S. M. Roberts, A. G. Sutherland and R. Wisdom, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2276.
10 V. K. Aggarwal, S. J. Roseblade, J. K. Barrell and R. Alexander, *Org. Lett.*, 2002, **4**, 1227; P. R. LePlae, N. Umezawa, H-S. Lee and S. H. Gellman, *J. Org. Chem.*, 2001, **66**, 5629; F. Theil and S. Ballschuh, *Tetrahedron: Asymmetry*, 1996, **7**, 3565; C. Cimarelli, G. Palmieri and G. Bartoli, *Tetrahedron: Asymmetry*, 1994, **5**, 1455; C. Cimarelli, G. Palmieri and E. Volpini, *Synth. Commun.*, 2001, **31**, 2943; D. Enders, J. Wiedemann and W. Bettray, *Synlett*, 1995, 369; P. Perlmutter, M. Patrick and F. Vounatsos, *Eur. J. Org. Chem.*, 2003, 756; A. M. Chippindale, S. G. Davies, K. Iwamoto, R. M. Parkin, C. A. P. Smethurst, A. D. Smith and H. Rodriguez-Solla, *Tetrahedron*, 2003, **59**, 3253.
11 S. G. Davies and O. Ichihara, *Tetrahedron: Asymmetry*, 1991, **2**, 183; S. G. Davies, O. Ichihara and I. A. S. Walters, *Synlett*, 1993, 461; S. G. Davies, N. M. Garrido, O. Ichihara and I. A. S. Walters, *J. Chem. Soc., Chem. Commun.*, 1993, 1153; S. G. Davies, M. E. Bunnage and C. J. Goodwin, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1375; S. G. Davies, M. E. Bunnage and C. J. Goodwin, *Synlett*, 1993, 731; S. G. Davies, O. Ichihara and I. A. S. Walters, *Synlett*, 1994, 117; S. G. Davies and O. Ichihara, *Tetrahedron: Asymmetry*, 1996, **7**, 1919; S. G. Davies and O. Ichihara, *Tetrahedron Lett.*, 1999, **40**, 9313; S. G. Davies and D. Dixon, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2629; S. D. Bull, S. G. Davies and A. D. Smith, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2931; S. D. Bull, S. G. Davies and A. D. Smith, *Tetrahedron: Asymmetry*, 2001, **12**, 2191; S. D. Bull, S. G. Davies, P. M. Roberts, E. D. Savory and A. D. Smith, *Tetrahedron*, 2002, **58**, 4629.
12 S. G. Davies, O. Ichihara, I. Lenoir and I. A. S. Walters, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1411.
13 For an alternative synthesis of 3-substituted 2-aminocyclopentane-carboxylic acid derivatives see: M. G. Woll, J. D. Fisk, P. R. LePlae and S. H. Gellman, *J. Am. Chem. Soc.*, 2002, **124**, 12447.
14 H. Ohki, Y. Inamoto, K. Kawabata, T. Kamimura and K. Sakane, *J. Antibiot.*, 1991, **44**, 546 and references contained therein.
15 S. Bailey, S. G. Davies, A. D. Smith and J. M. Withey, *Chem. Commun.*, 2002, 2910.
16 J. H. Babler and S. J. Sarussi, *J. Org. Chem.*, 1987, **52**, 3462.
17 D. Henderson, K. A. Richardson, R. J. K Taylor and J. Saunders, *Synthesis*, 1983, **12**, 996.
18 A. C. R. Horeau, *Tetrahedron*, 1975, **31**, 1307.
19 For a mini review on non-linear effects in asymmetric synthesis see: H. B. Kagan, *Adv. Synth. Catal.*, 2001, 343. For manuscripts describing non-linear effects and related topics in kinetic resolution reactions see: D. W. Johnson, Jr and D. A. Singleton, *J. Am. Chem. Soc.*, 1999, **121**, 9307; R. F. Ismagilov, *J. Org. Chem.*, 1998, **63**, 3772.
20 J. F. Costello, S. G. Davies and O. Ichihara, *Tetrahedron: Asymmetry*, 1994, **5**, 3919.
21 As shown by ^{1}H NMR chiral shift experiments with commercially available Eu(hfc)$_3$ (Aldrich) and with reference to an authentic racemic sample.
22 As shown by ^{19}F and ^{1}H NMR spectroscopic analysis of the derived methyl esters and subsequent derivatisation with both racemic and 99% ee Mosher's acid chloride.
23 S. D. Bull, S. G. Davies, G. Fenton, A. W. Mulvaney, R. S. Prasad and A. D. Smith, *Chem. Commun.*, 2000, 337; S. D. Bull, S. G. Davies, G. Fenton, A. W. Mulvaney, R. S. Prasad and A. D. Smith, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3765.
24 For leading references see: D. J. Cram, M. R. V. Sahyun and G. R. Knox, *J. Am. Chem. Soc.*, 1962, **84**, 1734; D. J. Cram and J. E. McCarthy, *J. Am. Chem. Soc.*, 1954, **76**, 5740; A. C. Cope and E. M. Acton, *J. Am. Chem. Soc.*, 1958, **80**, 355 . For previous applications of this methodology from this laboratory see: S. G. Davies and G. D. Smyth, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2467; S. G. Davies and G. D. Smyth, *Tetrahedron: Asymmetry*, 1996, **7**, 1005; S. G. Davies and G. D. Smyth, *Tetrahedron: Asymmetry*, 1996, **7**, 1001; A. N. Chernega, S. G. Davies, C. A. P. Smethurst, A. D. Smith and G. D. Smyth, *Tetrahedron: Asymmetry*, 2000, 10.
25 D. J. Watkin, C. K. Prout, J. R. Carruthers and P. W. Betteridge, *CRYSTALS*, 1996, Issue 10, Chemical Crystallography.