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Kinetic resolution of *tert*-butyl (*RS*)-3-alkylcyclopentene-1-carboxylates for the synthesis of homochiral 3-alkyl-cispentacin and 3-alkyl-transpentacin derivatives

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High levels of stereocontrol are observed in the conjugate addition of lithium dibenzylamide to *tert*-butyl (*RS*)-3-alkylcyclopentene-1-carboxylates (alkyl = Et, Bn), with addition occurring exclusively *anti*- to the 3-alkyl substituent. Treatment of a range of *tert*-butyl (*RS*)-3-alkylcyclopentene-1-carboxylates (alkyl = Et, Bn, ^{i}Pr, ^{t}Bu) with lithium (*RS*)-*N*-benzyl-*N*-α-methylbenzylamide indicates that good enantiorecognition is observed ($E > 80$) in their mutual kinetic resolution. In these reactions, conjugate addition of the lithium amide occurs exclusively *anti*- to the 3-alkyl substituent, with subsequent C(1)-protonation occurring preferably *anti*- to the 2-amino group in the 3-Et, 3-Bn and 3-^{i}Pr cases, giving predominantly the corresponding 1,2-*syn*-2,3-*anti*-diastereoisomers. Conjugate addition to (*RS*)-3-*tert*-butyl cyclopentene-1-carboxylate results in exclusive 2,3-*anti* -addition and a reversal in C(1)-protonation selectivity, giving predominantly the 1,2-*anti*-2,3-*anti*-diastereoisomer. Furthermore, the kinetic resolution of the *tert*-butyl (*RS*)-3-alkylcyclopentene-1-carboxylates (alkyl = Et, Bn, ^{i}Pr, ^{t}Bu) with lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide proceeds efficiently, giving, at between 47 and 51% conversion, the resolved 3-alkylcyclopentene-1-carboxylates in >85 to >98% ee and the β-amino ester products of conjugate addition in high de, consistent with $E > 80$ in each case. Subsequent deprotection of the 1,2-*syn*-2,3-*anti*-3-alkyl-β-amino esters (alkyl = Et, Bn, ^{i}Pr) by hydrogenolysis and ester hydrolysis gives the corresponding 1,2-*syn*-2,3-*anti*-3-alkylcispentacins in >98% de and 98 ± 1% ee. Selective epimerisation of the 1,2-*syn*-2,3-*anti*-3-alkyl-β-amino esters (alkyl = Et, Bn, ^{i}Pr, ^{t}Bu) by treatment with KO^{t}Bu in ^{t}BuOH gives the corresponding 1,2-*anti*-2,3-*anti*-3-alkyl-β-amino esters in quantitative yield and in >98% de, with subsequent deprotection by hydrogenolysis and ester hydrolysis giving the corresponding 1,2-*anti*-2,3-*anti*-3-alkylcispentacin hydrochlorides in >98% de.

Introduction

The generation of bespoke pseudopeptide sequences that exhibit highly ordered secondary and tertiary structures in both solution and solid phase has developed into a highly competitive field of research in recent years, with the ability to predict the conformation of a given peptide sequence from knowledge of its primary structure an elusive goal. While much effort has been directed towards understanding the factors that control the secondary structure of α-peptides, the utility of peptides incorporating the β-amino acid structural motif has recently been investigated widely, most notably by Seebach[1] and Gellman.[2] For instance, Gellman *et al.* have shown that β-peptides derived from *trans*-2-aminocyclopentanecarboxylic acid (transpentacin) **1** adopt a helical stucture in both the solid state and in solution,[3] while Fülop *et al.* have shown that homo-oligomers of *cis*-2-aminocyclopentanecarboxylic acid (cispentacin) **2** form a sheetlike secondary structure in solution (Fig. 1).[4] The ability of mixed α,β-peptides containing both α-amino and β-amino acid derivatives to adopt a preferred conformation in solution has also been reported recently.[5]

We have shown extensively that the conjugate addition of lithiumamides derived from α-methylbenzylamine to α,β-unsaturated acceptors may be used for the asymmetric synthesis of β-amino acid derivatives.[6] This methodology has recently been utilised for the synthesis of (1*R*,2*S*,3*R*)-3-methylcispentacin **5** in >98% de and 98 ± 1% ee and (1*S*,2*S*,3*R*)-3-methyltranspentacin **7** in >98% de and 97 ± 1% ee by the kinetic resolution of *tert*-butyl (*RS*)-3-methylcyclopentene-1-carboxylate **3** with lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (Scheme 1).[7]

The protocol that we use to understand fully the stereoselectivity observed in these kinetic resolution reactions requires an initial evaluation of the level of stereocontrol offered by the chiral α,β-unsaturated ester undergoing conjugate addition, which is achieved through the addition of an achiral lithium amide to the ester. If the α,β-unsaturated ester shows high facial selectivity upon conjugate addition, the level of enantiorecognition between the chiral α,β-unsaturated ester and a chiral lithium amide is evaluated through their mutual kinetic resolution [addition of (*RS*)-ester to an excess of an (*RS*)-lithium amide]. In this approach,[8] the effects of mass action are eliminated, allowing the maximum stereoselectivity factor (E) for the reaction to be calculated independent of the reaction conversion, as it is identical to the diastereoselectivity observed in the reaction.[9] If high enantiorecognition is seen between the reacting partners in a mutual kinetic resolution, then efficient kinetic resolution may be expected upon the

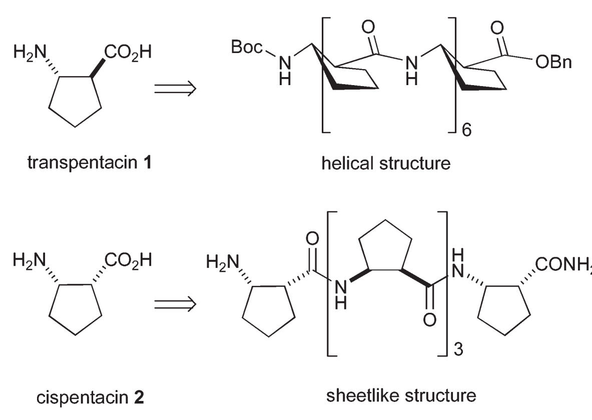

Fig. 1 Secondary structure of poly homo-pentacins.

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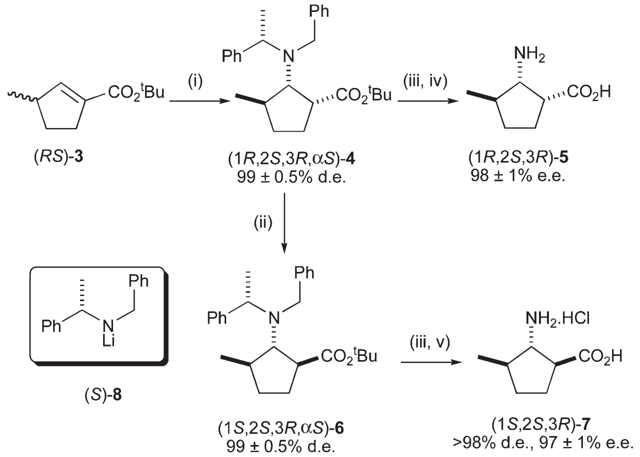


Scheme 1 Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **8**, THF, −78 °C then 2,6-di-*tert*-butylphenol, THF, −78 °C to rt; (ii) KO^{t}Bu, ^{t}BuOH, Δ, 3 h; (iii) $Pd(OH)_2$ on C, MeOH, H_2 (5 atm); (iv) TFA then Dowex 50WX8-200; (v) TFA then $HCl_{(aq)}$ and recrystallisation.

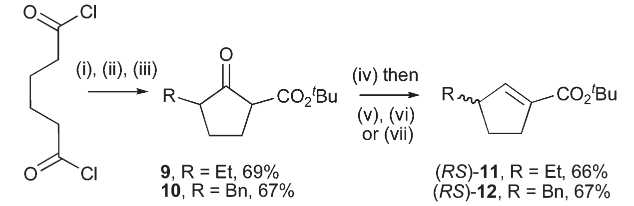
addition of homochiral lithium amide to the (*RS*)-ester. To understand fully the reactivity and stereoselectivity observed in these kinetic resolution reactions, the forced reaction of the 'mismatched' pairing allows the preparation of the minor diastereoisomers of the kinetic resolution reaction, while an evaluation of the evolution of the ee of the substrate with conversion allows the theoretical and experimentally observed values for the kinetic resolution reaction to be compared. As part of our ongoing studies concerning the application of kinetic resolution strategies in asymmetric synthesis,[10,11] and to provide a general route to the synthesis of stereodefined 3-alkyl-cispentacin and 3-alkyl-transpentacin analogues to facilitate an understanding of the secondary structure of peptides derived thereof, we report herein the generality of this strategy through the investigation of the kinetic resolution of a range of *tert*-butyl (*RS*)-3-alkylcyclopentene-1-carboxylates with homochiral lithium amides.

Results and discussion

Synthesis of a range of *tert*-butyl (*RS*)-3-alkyl–cyclopentene-1-carboxylates (alkyl = Et, Bn, ^{i}Pr, ^{t}Bu)

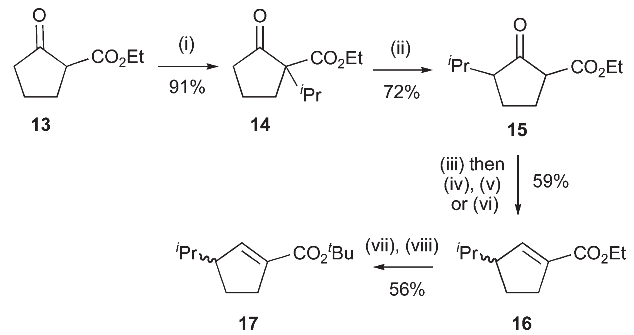
To investigate the generality of this kinetic resolution protocol, the effects of increasing size and branching in the 3-alkyl group upon the level of stereocontrol and enantiorecognition in these reactions was proposed, which necessitated the synthesis of *tert*-butyl (*RS*)-3-ethyl, (*RS*)-3-benzyl, (*RS*)-3-*iso*-propyl and (*RS*)-3-*tert*-butyl cyclopentene-1-carboxylates. The (*RS*)-3-ethyl and (*RS*)-3-benzyl derivatives **11** and **12**, respectively, were readily prepared on a multigram scale from adipoyl chloride *via* consecutive esterification,[12] Dieckmann cyclisation[13] and regioselective γ-alkylation with either ethyl iodide or benzyl bromide, furnishing the γ-alkyl β-keto esters **9** and **10** as a 70 : 30 mixture of diastereoisomers in each case. Chemoselective $NaBH_4$ reduction to the alcohol, followed by either tosylation and subsequent elimination, or treatment with PPh_3/diisopropyl azodicarboxylate (DIAD)[14] gave the desired (*RS*)-3-ethyl and (*RS*)-3-benzyl derivatives **11** and **12**, respectively, in reasonable yield (Scheme 2).

Attempted application of this protocol to the synthesis of the 3-*iso*-propyl cyclopentene-1-carboxylate proved unsuccessful, with attempted alkylation of the dianion of β-keto ester **13** with 2-iodopropane returning only starting material. However, alkylation of the mono enolate of ethyl β-keto ester **13** with 2-iodopropane proceeded smoothly, giving α,α′-dialkyl β-keto ester **14** in 91% yield,[15] with subsequent rearrangement upon treatment with NaOEt giving the 3-*iso*-propyl β-keto ester **15** as a 65 : 35 mixture of diastereoisomers in 72% yield.[16] Subsequent reduction, followed by either tosylation and elimination or treatment with PPh_3/diisopropyl azodicarboxylate, furnished



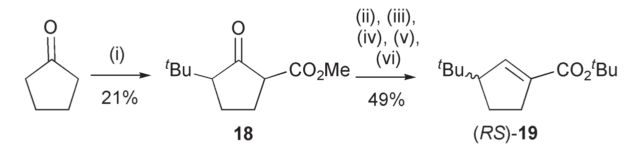
Scheme 2 Reagents and conditions: (i) $PhNMe_2$ (3.15 eq), ^{t}BuOH (3.25 eq), Et_2O, rt; (ii) NaH (1.05 eq), ^{t}BuOH (cat), PhMe, Δ; (iii) NaH (1.05 eq) then n-BuLi (1.0 eq), then RX (1.1 eq), −78 to 0 °C; (iv) $NaBH_4$, EtOH, 0 °C; (v) TsCl (1.1 eq), pyridine, 0 °C to rt; (vi) DBU, DCM, 0 °C; (vii) PPh_3 (1.5 eq), DIAD (1.3 eq), THF, 0 °C to rt.

ethyl (*RS*)-3-*iso*-propyl cyclopentene-1-carboxylate **16**, with transesterification giving the *tert*-butyl (*RS*)-3-*iso*-propyl cyclopentene-1-carboxylate **17** (Scheme 3).[17]



Scheme 3 Reagents and conditions: (i) NaH (1.05 eq), then 2-iodopropane (1.1 eq), −78 to 0 °C; (ii) NaOEt, EtOH, Δ; (iii) $NaBH_4$, EtOH, 0 °C; (iv) TsCl (1.1 eq), pyridine, 0 °C to rt; (v) DBU, DCM, 0 °C; (vi) PPh_3 (1.5 eq), DIAD (1.3 eq), THF, 0 °C to rt; (vii) KOH, Δ; (viii). isobutylene, H_2SO_4 (cat).

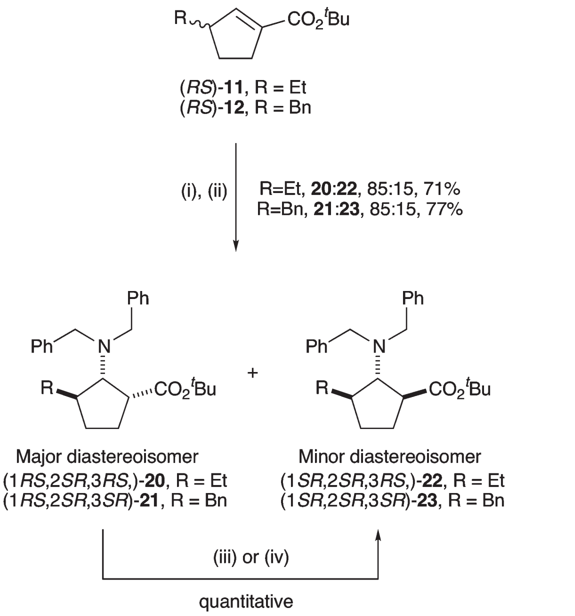
The synthesis of the (*RS*)-3-*tert*-butyl derivative **19** necessitated an alternative synthetic strategy, *via* alkylation of the trimethylsilyl enol ether of cyclopentanone[18] with $TiCl_4$ and *tert*-butyl chloride and subsequent acylation with NaH and dimethyl carbonate generating β-keto ester **18** as a 65 : 35 mixture of diastereoisomers. Further manipulation generated the desired (*RS*)-3-*tert*-butyl acceptor **19** (Scheme 4).[19]



Scheme 4 Reagents and conditions: (i) TMSCl, NEt_3, Δ; then ^{t}BuCl, $TiCl_4$; (ii) NaH, dimethyl dicarbonate; (iii) $NaBH_4$, ^{i}PrOH, 0 °C to rt; (iv) PPh_3 (1.5 eq), DIAD (1.3 eq), THF, 0 °C to rt; (v) KOH, Δ; (vi) isobutylene, H_2SO_4 (cat).

Evaluating substrate control: Conjugate addition of lithium dibenzylamide to *tert*-butyl (*RS*)-3-ethyl- and (*RS*)-3-benzyl-cyclopentene-1-carboxylates

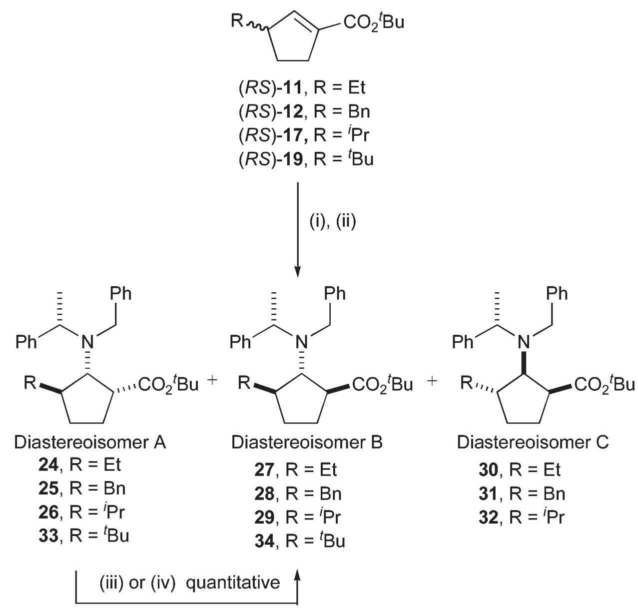
With a range of (*RS*)-3-alkyl-cyclopentene-1-carboxylates in hand, the level of stereoinduction commanded by (*RS*)-3-ethyl **11** and (*RS*)-3-benzyl **12** upon conjugate addition of lithium dibenzylamide was evaluated. In each case, only the C(1)-epimeric β-amino esters were observed in an 85 : 15 ratio, with the major diastereoisomers **20** and **21** having the *syn*-1,2-*anti*-2,3-arrangement, and the minor diastereoisomers **22** and **23** the *anti*-1,2-*anti*-2,3-arrangement.[20] Chromatographic purification yielded an inseparable mixture of diastereoisomers without enhancement of diastereoisomeric purity, giving **20** : **22** (85 : 15) in 71% yield and **21** : **23** (85 : 15) in 77% yield. In both cases, treatment of the diastereoisomeric mixture with KO^{t}Bu in ^{t}BuOH allowed quantitative conversion to the thermodynamic *anti*-1,2-*anti*-2,3 diastereoisomers **22** and **23** in >98% de in each case (Scheme 5). This study indicates that complete diastereofacial control at the C(2)-centre during conjugate addition of lithium dibenzylamide to the face of the acceptor *anti*- to that of the stereocontrolling 3-alkyl substituent is observed in these reactions, with the mixture of diastereoisomers arising only as a consequence of low diastereoselectivity upon enolate protonation. Although the conjugate addition of lithium dibenzylamide to (*RS*)-3-*iso*-propyl **17** and (*RS*)-3-*tert*-butyl **19** was not evaluated, these substrates were expected to show similar high levels of *anti*-2,3 facial control.



Scheme 5 Reagents and conditions: (i) Lithium dibenzylamide, THF, −78 °C; (ii) $NH_4Cl_{(aq)}$; (iii) KO*ᵗ*Bu, *ᵗ*BuOH, Δ, 3 h (R = Et); (iv) KO*ᵗ*Bu, *ᵗ*BuOH, rt, 7 d (R = Bn).

Mutual kinetic resolution of *tert*-butyl (*RS*)-3-alkyl–cyclopentene-1-carboxylates with lithium (*RS*)-*N*-benzyl-*N*-α-methylbenzylamide

Having shown that high levels of substrate control operate in the conjugate addition of lithium dibenzylamide to (*RS*)-**11** and (*RS*)-**12**, the mutual kinetic resolution of the full range of (*RS*)-α,β-unsaturated esters **11**, **12**, **17** and **19** with lithium (*RS*)-*N*-benzyl-*N*-α-methylbenzylamide **8** was investigated to evaluate the maximum value of the stereoselectivity factors (*E*) for their respective reactions.[8] Addition of (*RS*)-amide **8** to the (*RS*)-3-ethyl, (*RS*)-3-benzyl and (*RS*)-3-*iso*-propyl esters indicated the presence of three diastereoisomers by ^{1}H NMR spectroscopic analysis, with the two C(1) epimeric diastereoisomers **24**–**26** and **27**–**29** predominating in each case, with *ca.* 1% of the third diastereoisomer **30**–**32** noted. In each case, the sum of the two C(1) epimeric diastereoisomers to the third diastereoisomer (A + B:C, Scheme 6) allowed *E* to be evaluated as >80, >160 and >140, respectively, with the major diastereoisomeric products **24**–**26** assigned the expected 1,2-*syn*-2,3-*anti*- configuration on the assumption that conjugate addition proceeds predominantly *anti*- to the 3-alkyl group, with protonation of the resultant enolate *anti*- to the 2-amino functionality (Scheme 6).[7] Application of this protocol for addition of lithium (*RS*)-*N*-benzyl-*N*-α-methylbenzylamide to the (*RS*)-3-*tert*-butyl acceptor **19** resulted in a 23.1 : 76.9 mixture of the 1,2-*syn*-2,3-*anti*- and 1,2-*anti*-2,3-*anti* diastereoisomers **33** and **34**. Although exclusive *anti*- addition of the lithium amide relative to the 3-alkyl substituent is observed in all cases, the incorporation of branched substituents in the 3-position of the cyclopentene-1-carboxylate has a notable effect upon the selectivity of enolate protonation at C(1). Protonation occurs predominantly *anti*- to the 2-amino group in the 3-ethyl, 3-benzyl and 3-*iso*-propyl cases, giving preferentially the 1,2-*syn*-2,3-*anti*-diastereoisomers **24**–**26**, but the steric bulk of the 3-*tert*-butyl group results in a reversal of selectivity, giving preferably the 1,2-*anti*-2,3-*anti*-diastereoisomer **34**. Chromatographic purification and/or recrystallisation allowed the isolation and characterisation of the major diastereoisomeric 3-ethyl-, 3-benzyl- and 3-*iso*-propyl-1,2-*syn*-2,3-*anti*-β-amino esters **24**–**26** in >98% de, with subsequent conversion to the corresponding thermodynamically favoured 1,2-*anti*-2,3-*anti*-diastereoisomers **27**–**29** (>98% de) achieved in quantitative yield by treatment with KO*ᵗ*Bu in *ᵗ*BuOH. In the 3-*tert*-butyl case, exposure of the 23.1 : 76.9 mixture of 1,2-*syn*-2,3-*anti*- and 1,2-*anti*-2,3-*anti*-diastereoisomers **33** : **34** to equilibrating conditions allowed complete and quantitative conversion to the 1,2-*anti*-2,3-*anti*-diastereoisomer **34**. These experiments confirm that, in each case, the two major diastereoisomers from the mutual resolution protocol of the range of (*RS*)-3-alkyl-cyclopentene-1-carboxylates **11**, **12**, **17** and **19** are epimeric at C(1), with complete 2,3-*anti*- stereocontrol being achieved upon conjugate addition.[21]



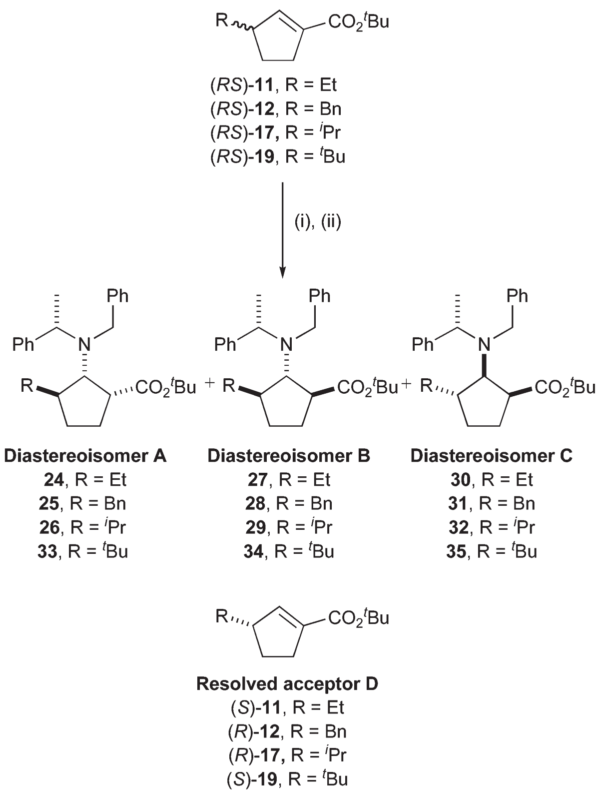
R	Ratio A:B:C		Ratio A+B:C	Yield	E
Et	**24**:**27**:**30**	96.9:1.9:1.2	98.8:1.2	68	>80
Bn	**25**:**28**:**31**	97.6:1.8:0.6	99.4:0.6	74	>160
*ⁱ*Pr	**26**:**29**:**32**	94.1:5.2:0.7	99.3:0.7	72	>140
*ᵗ*Bu	**33**:**34**	23.1:76.9:0	100:0	66	>200

Scheme 6 Reagents and conditions: (i) lithium (*RS*)-*N*-benzyl-*N*-α-methylbenzylamide (2 eq), THF, −78 °C; (ii) 2,6-di-*tert*-butylphenol, THF, −78 °C to rt; (iii) KO*ᵗ*Bu, *ᵗ*BuOH, Δ, 3 h (R = Et, *ⁱ*Pr, *ᵗ*Bu); (iv) KO*ᵗ*Bu, *ᵗ*BuOH, rt, 7 days (R = Bn).

Kinetic resolution of *tert*-butyl (*RS*)-3-alkyl-cyclopentene-1-carboxylates with lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide

With high levels of enantiorecognition noted between acceptors (*RS*)-**11**, **12**, **17** and **19** and lithium (*RS*)-*N*-benzyl-*N*-α-methylbenzylamide, the kinetic resolutions of (*RS*)-**11**, **12**, **17** and **19** were attempted with homochiral lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **8**. Treatment of (*RS*)-3-ethyl, (*RS*)-3-benzyl and (*RS*)-3-*iso*-propyl esters **11**, **12** and **17** with between 0.6 and 0.9 eq of lithium amide (*S*)-**8** gave, at 47 to 51% conversion, a mixture of three β-amino ester diastereoisomers, the configurations within which (**A** : **B** : **C**) were identified as shown in Scheme 7. As expected, conjugate addition *anti*- to the 3-alkyl substituent was noted in each case, with high levels of *syn*-1,2-selectivity upon protonation. However, addition of (*S*)-**8** (0.7 eq) to the (*RS*)-3-*tert*-butyl ester **19** gave, at 51% conversion, a 31.9 : 66.9 : 1.2 mixture of diastereoisomers,[22] with only moderate *anti*-1,2-selectivity upon protonation. Chromatographic purification gave the major 3-ethyl, 3-benzyl and 3-*iso*-propyl-β-amino ester diastereoisomers **24**–**26** in >98% de and an inseparable 32.2 : 67.8 mixture of 3-*tert*-butyl diastereoisomers **33** : **34** in 32–41% isolated yield. The resolved acceptors

(*S*)-**11**, (*R*)-**12**, (*R*)-**17** and (*S*)-**19** were also isolated in 36–43% yield, and in >86 to >99 ± 1% ee,[23] consistent with an *E* value of >80 in each case. The relative configurations within the three diastereoisomers were identical to those observed in the mutual recognition protocol, and in the 3-*iso*-propyl series, analytical samples of all three diastereoisomers **26**, **29** and **32** were isolated after exhaustive chromatographic purification and fractional crystallisation. The relative configurations within diastereoisomers **26**, **29** and **32** were proven independently by ^{1}H NMR NOE difference analysis, with the configuration within the third diastereoisomer consistent with the 'mismatched' addition of the lithium amide to the substrate (Fig. 2).



R	(*S*)-8	Ratio A:B:C	Ratio A+B:C	Conv
Et	0.9eq	93.3:2.5:4.2	95.8:4.2	51%
Bn	0.6eq	96.9:1.4:1.7	98.3:1.7	48%
^{i}Pr	0.7eq	93.8:4.7:1.5	98.5:1.5	47%
^{t}Bu	0.7eq	31.9:66.9:1.2	98.8:1.2	51%

Yield (A)	Yield (D)	e.e. (D, %)	E
32	36	96±1	>80
41	39	89±1	>120
35	43	86±1	>120
37	40	99±1	>150

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

These results indicate good correlation between the levels of enantiorecognition observed in the mutual and kinetic resolution reactions, and verify that mutual kinetic resolution allows the identification of efficient kinetic resolution procedures.

Investigation of the enantiorecognition in the kinetic resolution of *tert*-butyl (*RS*)-3-alkyl-cyclopentene-1-carboxylates with lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide

a. Minor diastereoisomer identification: evaluation of the mismatched reaction product. Having demonstrated the viability of this lithium amide mediated kinetic resolution methodology, studies were directed towards understanding further the stereochemical course of these reactions. In the resolution reactions, four possible diastereoisomeric products **36**–**39** may arise [ignoring C(1) protonation selectivity]. The two major

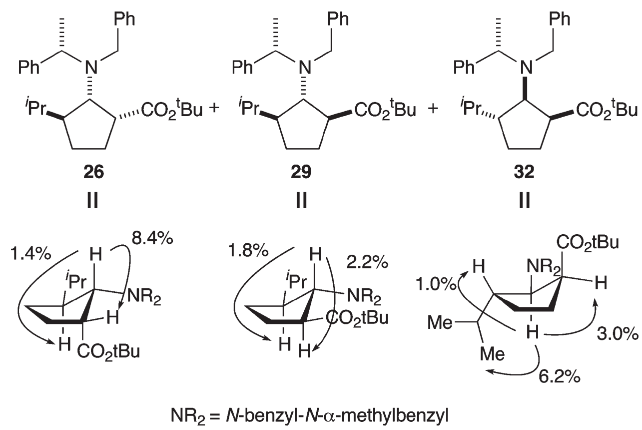


Fig. 2 Selected NOE difference enhancements for diastereoisomers **26**, **29** and **32**; other NOE enhancements omitted for clarity.

diastereoisomeric products arising from kinetic resolution have the 2,3-*anti*- relative configuration in which the known stereodirecting properties of the chiral lithium amide and (*RS*)-acceptor combine in a "matched" fashion, with the ratio of these diastereoisomers reflecting the selectivity upon protonation of a common β-amino enolate. However, the 2,3-*anti*- configuration contained within the minor third diastereoisomer **39** (consistent with **32**, R = ^{i}Pr) indicates preferential conjugate addition of lithium amide (*S*)-**8** *anti*- to the 3-alkyl substituent, contrary to the expected diastereofacial preference of lithium amide (*S*)-**8**, consistent with the 3-alkyl substituent being the dominant stereocontrolling feature in this reaction (Fig. 3).

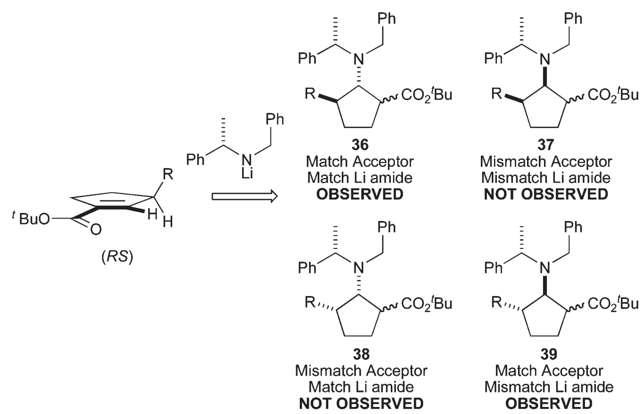
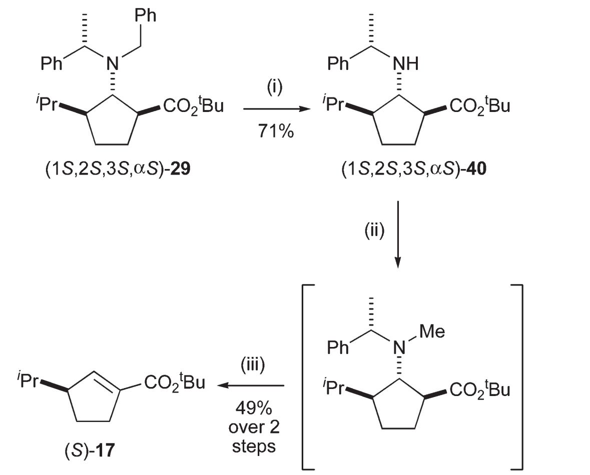


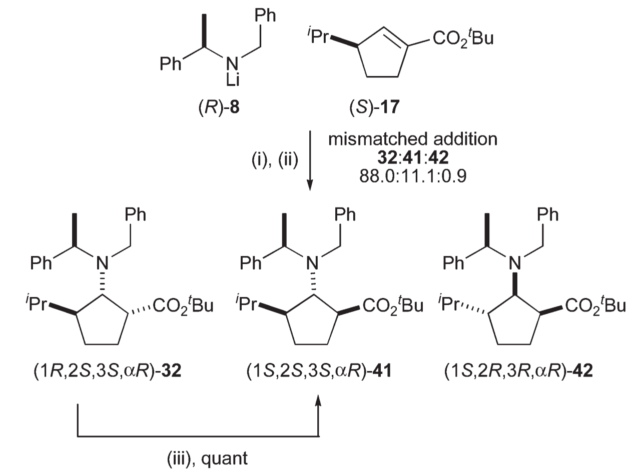
Fig. 3 Possible diastereoisomeric β-amino ester products obtained upon addition of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **8** to *tert*-butyl (*RS*)-3-alkylcyclopentene-1-carboxylates (ignoring protonation selectivity).

To investigate this theory, the ability of the 3-*iso*-propyl substituent to overcome the usual diastereofacial bias shown by homochiral lithium *N*-benzyl-*N*-α-methylbenzylamide was investigated through reaction of the mismatched combination of (*S*)-3-*iso*-propyl acceptor **17** and lithium amide (*R*)-**8**. The desired (*S*)-3-*iso*-propyl acceptor **17** was prepared from β-amino ester (1*S*,2*S*,3*S*,α*S*)-**29** (>98% de)[24] in 35% overall yield, by chemoselective *N*-debenzylation to afford β-amino ester **40**,[25] and subsequent *N*-methylation and *N*-oxidation/Cope elimination.[26] The ee of (*S*)-**17** was established to be >98% by ^{1}H NMR chiral shift experiments in the presence of Eu(hfc)$_3$ and comparison with an authentic racemic sample (Scheme 8).

Conjugate addition of lithium amide (*R*)-**8** to acceptor (*S*)-**17** gave an 88 : 11.1 : 0.9 mixture of diastereoisomers (1*R*,2*S*,3*S*,α*R*)-**32**:(1*S*,2*S*,3*S*,α*R*)-**41** : (1*S*,2*R*,3*R*,α*R*)-**42** in 64% yield, with ^{1}H NMR spectroscopic analysis of the major product (1*R*,2*S*,3*S*,α*R*)-**32** indicating that this was identical to the minor third diastereoisomer arising from the kinetic resolution protocol. Purification by chromatography and subsequent recrystallisation gave (1*R*,2*S*,3*S*,α*R*)-**32** as a single diastereoisomer in 29% yield, the relative configuration within which



Scheme 8 Reagents and conditions: (i) CAN (2.1 eq), MeCN : H_2O (5 : 1), rt; (ii) MeI; (iii) mCPBA, $CHCl_3$, rt.



Scheme 9 Reagents and conditions: (i) (*R*)-**8**, THF, −78 °C; (ii) 2,6-di-*tert*-butylphenol, THF, −78 °C to rt; (iii) KO^{t}Bu, ^{t}BuOH, Δ, 3 h.

was established by single crystal X-ray diffraction, with the absolute configuration known relative to the (*R*)-α-methylbenzyl stereogenic centre (Fig. 4). As expected, epimerisation of a mixed fraction of (1*R*,2*S*,3*S*,α*R*)-**32** : (1*S*,2*S*,3*S*,α*R*)-**41** gave (1*S*,2*S*,3*S*,α*R*)-**41** as a single diastereoisomer in quantitative yield, establishing them as epimeric at C(1) (Scheme 9).

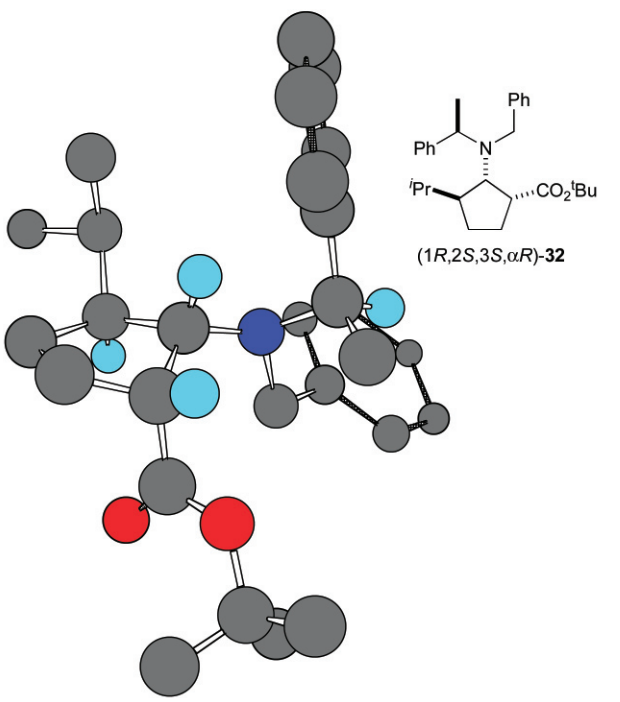
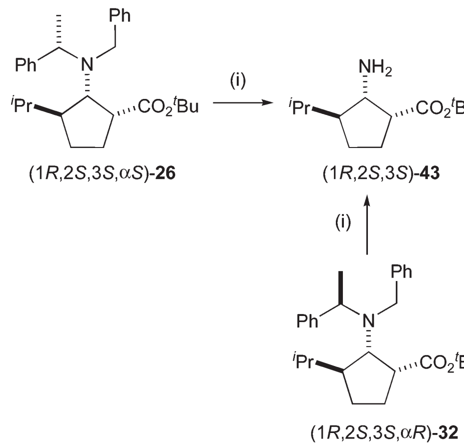


Fig. 4 Chem 3D representation of the X-ray crystal structure of (1*R*,2*S*,3*S*,α*R*)-**32** (some H omitted for clarity).

The assigned configurations within the 3-*iso*-propyl series of diastereoisomers were verified further by hydrogenolysis of (1*R*,2*S*,3*S*,α*S*)-**26** (the major product from kinetic resolution) and (1*R*,2*S*,3*S*,α*R*)-**32** (the major product from the mismatched addition), which both gave the primary β-amino ester (1*R*,2*S*,3*S*)-**43**. This verifies the hypothesis that the 3-alkyl substituent, not the lithium amide, is the dominating factor affecting the stereoselectivity in these reactions (Scheme 10).

b. Effects of mass action in the resolution reaction. With the diastereoisomeric configurations formed in the kinetic resolution protocol unambiguously assigned, attention turned to a full analysis of the product distributions arising from these reactions. Close examination indicated a reasonable correlation between the levels of *syn*-1,2-protonation selectivity noted in the mutual kinetic resolution and kinetic resolution experiments,

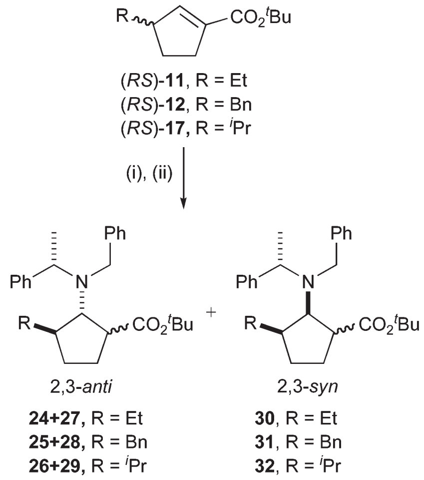


Scheme 10 Reagents and conditions: (i) $Pd(OH)_2$ on C, MeOH, H_2 (5 atm).

although markedly lower levels of selectivity for the 'matched' *anti*-2,3-diastereoisomers upon conjugate addition were noted in the kinetic resolution experiments. As these resolution reactions were run close to 50% conversion in each case, this difference in selectivity arises as a consequence of mass action due to the accumulation of the slower reacting enantiomer of the 3-alkyl acceptor under the reaction conditions. To confirm this hypothesis by drowning out the mass action effect, addition of a large excess (10 eq) of (*RS*)-3-alkyl-acceptors **11**, **12** and **17** to the homochiral lithium amide (*S*)-**8** was performed, which at 87–97% conversion (with respect to the lithium amide) was found to reproduce essentially the diastereoselectivities noted in the mutual kinetic resolution experiments. Less than 1.5% of a third diasteroisomer was noted in each of these reactions, corresponding to 2,3-*anti*-selectivity in the range of >98.5 : 1.5. This is consistent with the third, minor diastereoisomeric product in the kinetic resolution protocol arising from the stereochemically mismatched pairing reaction as a consequence of mass action (Scheme 11).

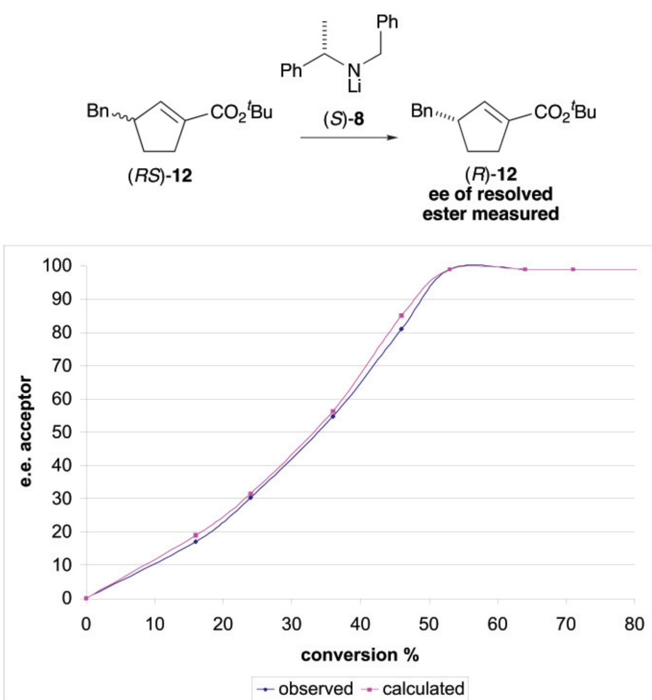
c. Evolution of ee in kinetic resolution. To further our understanding of the kinetic resolution reaction, the evolution of ee in the substrate with increasing conversion during the resolution of (*RS*)-3-benzyl-**12** was monitored (Fig. 5). Evaluation of the stereoselectivity factor by linear regression allows quantification of $E = 164$, in agreement with the values of >160 and >120 from the mutual and kinetic resolution protocols, respectively, and with excellent agreement between the experimentally determined and theoretical values. As expected, at a conversion of approximately 51%, the acceptor (*R*)-**12** is recovered in essentially homochiral form.

Although not included in the graphical representation of Fig. 5, the use of more than one equivalent of homochiral lithium



R	2,3-anti : 2,3-syn	Conversion
Et	98.6:1.4	87%
Bn	99.6:0.4	95%
^{i}Pr	99.3:0.7	97%

Scheme 11 Reagents and conditions: (i) Lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (0.1 eq), THF, −78 °C; (ii) 2,6-di-*tert*-butylphenol, THF, −78 °C to rt.



(*S*)-8 (eq)	Conversion(%)	Observed e.e. %	Theoretical e.e. %
0.2	16	17	19.0
0.3	24	30	31.6
0.4	36	55	56.3
0.5	46	81	85.1
0.6	53	>98	100
0.7	64	>98	100
0.8	71	>98	100
0.9	81	>98	100
1.2	87	96	100
1.5	97	61	100
2.0	98	36	100

Fig. 5 Evolution of ee of recovered acceptor in the kinetic resolution of (*RS*)-3-benzyl–**12**.

amide gives anomalous results, with the ee of the recovered substrate decreasing from the >98% ee measured at 81% conversion with 0.9 eq of lithium amide to 36% ee at 98% conversion with 2.0 eq of lithium amide. This decrease in ee at high conversion is consistent with epimerisation of the chiral α,β-unsaturated ester under the reaction conditions, presumably *via* a γ-deprotonation and subsequent *in situ* reprotonation mechanism. As this phenomenon is seen only with >1 eq of lithium amide, these results are consistent with a simple model in which initial binding and activation of the α,β-unsaturated ester by lithium co-ordination to a lithium amide leads to subsequent conjugate addition or, in the presence of excess lithium amide, to competitive γ-deprotonation by lithium amide. Further evidence for this mechanism may be derived from analysis of the diastereoselectivity of the isolated β-amino ester products from the kinetic resolution reactions, with excellent correlation between experimentally observed and theoretical values observed with less than 1 eq of lithium amide, with anomalous results only obtained with a molar excess of lithium amide (*S*)-**8**. For example, at 97% conversion, ^{1}H NMR analysis indicates an 8% de in favour of the matched 2,3-*anti*-diastereoisomers. At this conversion, this level of stereoselectivity cannot ordinarily be obtained, as the theoretical diastereoisomer ratio (matched 2,3-*anti*-diastereoisomers : mismatched 2,3-*anti*-diastereoisomers) should be 50 : 47 (3% de) in which all of the faster reacting (*S*)-ester substrate enantiomer is consumed, leaving the slower reacting mismatched (*R*)-substrate. This discrepancy may be ascribed to a process in which the ester substrate enantiomers are racemised under the reaction conditions by a γ-deprotonation mechanism.

Deprotection: Asymmetric synthesis of 3-alkylcispentacin and 3-alkyltranspentacin analogues

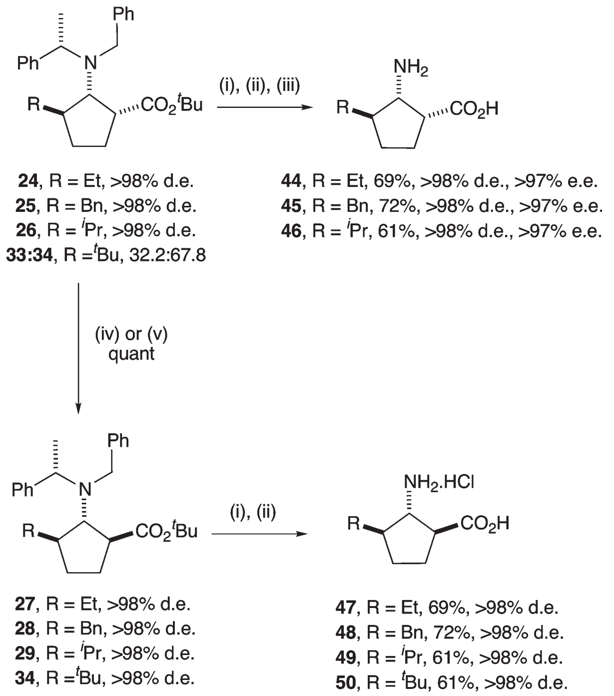
With the homogenous 3-ethyl, 3-benzyl and 3-*iso*-propyl-*syn*-1,2-*anti*-2,3-β-amino esters **24**–**26** (>98% de) in hand from the kinetic resolution protocol, deprotection to their respective 3-alkylcispentacin derivatives was investigated. Pd mediated *N*-debenzylation of **24**–**26** gave the corresponding primary β-amino esters, with subsequent treatment with TFA giving the desired 3-alkylcispentacins **44**–**46** in good yield (61–72%) and in >98% de and 98 ± 1% ee[27] after purification by ion exchange chromatography. The 3-ethyl, 3-benzyl and 3-*iso*-propyl-*syn*-1,2-*anti*-2,3-β-amino esters **24**–**26** and the 32.2 : 67.8 mixture of *syn*-1,2-*anti*-2,3- : *anti*-1,2-*anti*-2,3- 3-*tert*-butyl β-amino ester diastereoisomers **33** : **34** were subsequently converted quantitatively to their thermodynamic *anti*-1,2-*anti*-2,3-diastereoisomers **27**–**29** and **34** in >98% de, with subsequent hydrogenolysis and ester hydrolysis giving the 3-alkyltranspentacin hydrochlorides **47**–**50** in good yield (61–72%) and in >98% de (Scheme 12).

In conclusion, we have demonstrated the generality of the kinetic resolution of (*RS*)-3-alkyl-cyclopentene-1-carboxylates with homochiral lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide and have used this protocol for the synthesis of 3-alkylcispentacin and 3-alkyltranspentacin analogues in high de and high ee. The further applications of this protocol to the parallel kinetic resolution of (*RS*)-3-alkylcyclopentene-1-carboxylates and the kinetic and parallel kinetic resolution of a range of (*RS*)-5-alkylcyclopentene-1-carboxylates are reported in the following papers, while bioactivity studies and the secondary structural studies of oligomers of these building blocks are in progress.

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 hexane 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), potassium permanganate (1% in 2% aqueous acetic acid, containing 7% potassium carbonate) or Draggendorf's



Scheme 12 Reagents and conditions: (i) $Pd(OH)_2$ on C, MeOH, H_2 (5 atm); (ii) TFA : DCM (1 : 1) then HCl, Et_2O; (iii) Dowex 50WX8-200; (iv) KO^{t}Bu, ^{t}BuOH, Δ, 3 h (R = Et, ^{i}Pr, ^{t}Bu); (v) KO^{t}Bu, ^{t}BuOH, rt, 7 d (R = Bn).

reagent.[28] 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}. ^{1}H and ^{13}C NMR spectra were recorded on Varian Gemini 200 (^{1}H 200 MHz, ^{13}C 50 MHz), Bruker DPX-200 (^{1}H 200 MHz, ^{13}C 50 MHz), Bruker DPX-400 or AVANCE AV-400 (^{1}H 400 MHz, ^{13}C100 MHz), or Bruker AM-500 (^{1}H500 MHz, ^{13}C125 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). 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.

General procedure 1: Double enolate formation. Sodium hydride (60 wt% in mineral oil) was first prepared for use by careful washing with *n*-pentane (3×) and discarding the supernatant. The liberated sodium hydride (1.05 eq) was suspended in anhydrous THF and cooled to 0 °C. A solution of the β-keto ester in anhydrous THF was added dropwise and stirring continued for 20 min after the evolution of H_2(g) had ceased. *n*-Butyllithium (titrated before use, 1.05 eq) was added dropwise and the reaction mixture stirred for an additional 0.5 h, prior to cooling to −78 °C. The dianion was used immediately and the individual products purified as described.

General procedure 2: $NaBH_4$ reduction of β-keto esters. To a stirred solution of the β-keto ester in EtOH at 0 °C was added portionwise $NaBH_4$ (1 eq). The reaction mixture was stirred for an additional 1 h, after which distilled water was added dropwise, followed by NH_4Cl (aq, sat) solution to excess. The solution was diluted with Et_2O and the aqueous phase separated and extracted with Et_2O (2×). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude β-hydroxy ester. The individual products were purified as described.

General procedure 3: PPh_3/DIAD mediated elimination to furnish α,β-unsaturated acceptors. A solution of the β-hydroxy ester and PPh_3 (1.5 eq) in anhydrous THF was cooled to 0 °C prior to the dropwise addition of DIAD (1.3 eq). The reaction mixture was warmed to rt, whereat it was stirred overnight. The solvent was removed *in vacuo* and *n*-pentane (50 ml) added. After stirring at rt for 0.5 h, the precipitate was removed by filtration and the filtrate concentrated *in vacuo*. Additional *n*-pentane was added and the process repeated a further two times. Concentration *in vacuo* of the resultant filtrate furnished a yellow oil, which was passed through a silica gel plug (eluting 2% Et_2O/*n*-pentane) to give the requisite α,β-unsaturated acceptor.

General procedure 4: Lithium amide conjugate additions. 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 the requisite α,β-unsaturated acceptor 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) NH_4Cl (aq, sat) solution. The resultant mixture was kept at −78 °C for 0.5 h and then allowed to warm to rt over 1 h. NH_4Cl (aq, sat) solution was added and the mixture diluted with Et_2O. The organic layer was separated and the aqueous layer extracted with Et_2O (3×). 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 5: Lithium amide kinetic resolutions. 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 being added, *via* cannula, to the requisite *tert*-butyl (*RS*)-3-alkylcyclopentene-1-carboxylate as a solution in anhydrous THF at −78 °C. The resulting mixture was stirred for 3 h at −78 °C after which time the reaction was quenched by addition of a precooled solution of 2,6-di-*tert*-butylphenol in anhydrous THF. The resultant mixture was kept at −78 °C for 0.5 h, then allowed to warm to rt over 1 h. 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 (3×). 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 6: Epimerisation of β-amino esters. To a solution of the substrate in *tert*-butanol was added a catalytic quantity of potassium *tert*-butoxide (*ca.* 20 mg). The resultant mixture was heated at reflux for 3 h then allowed to cool (*n.b.* in the case of adducts of *tert*-butyl (*RS*)-3-benzylcyclopentene-1-carboxylate, the epimerisation was carried out at rt over 7 d to prevent ester cleavage). The reaction was quenched by addition of NH_4Cl (aq, sat) and the mixture diluted with Et_2O. The organic layer was separated and the aqueous layer extracted with Et_2O (3×). 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 7: Hydrogenolysis of β-amino esters using Pearlman's catalyst. A solution of the substrate in MeOH 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 mixture was stirred rapidly at rt overnight, after which time the solution was filtered through a pad of Celite®, washed through with MeOH and concentrated *in vacuo* to give the crude product. The individual products were purified as described.

General procedure 8: TFA cleavage furnishing free amino acids. TFA was added to a solution of the crude β-amino ester at rt and stirred for 16 h. Concentration *in vacuo* gave an oil, which was dissolved in MeOH (2 ml) and HCl in Et_2O (sat, 2 ml). Concentration *in vacuo* gave a pale brown solid, which was partitioned between Et_2O (4 ml) and H_2O (4 ml). The aqueous phase was separated and concentrated to a quarter of its volume and chromatographed using Dowex 50WX8-200 resin to give the free amino acid.

General procedure 9: TFA cleavage furnishing amino acid hydrochloride salts. TFA was added to a solution of the crude β-amino ester at rt and stirred for 16 h. Concentration *in vacuo* gave an oil, which was dissolved in MeOH (2 ml) and HCl in Et_2O (sat, 2 ml). Concentration *in vacuo* gave a pale brown solid, which was partitioned between Et_2O (4 ml) and H_2O (4 ml). The aqueous phase was concentrated to afford the crude β-amino acid as its hydrochloride salt. The individual products were purified as described.

Preparation of di-*tert*-butyl adipate

To a rapidly stirred solution of *tert*-butanol (77.7 ml, 0.81 mol) and *N*,*N*-dimethylaniline (99.7 ml, 0.79 mol) in diethyl ether (200 ml) at 0 °C was added dropwise a solution of adipoyl chloride (36.3 ml, 0.25 mol) in diethyl ether (100 ml). The mixture was stirred for 20 h at rt, after which time the mixture was diluted with H_2O (100 ml) and the ethereal layer separated. The organic layer was washed with HCl (aq, 2 M, 5 × 50 ml), $NaHCO_3$ (aq, sat, 2 × 50 ml) and brine (aq, sat, 100 ml), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The title compound (57.3 g, 89%) was obtained as a colourless oil, which slowly crystallised on standing; mp 28–29 °C (lit.[3] 29–31 °C); δ_H (200 MHz, $CDCl_3$) 1.45 (18H, s, OC(CH_3)$_3$), 1.56–1.73 (4H, m, C(3)H_2 and C(4)H_2), 2.15–2.32 (4H, m, C(2)H_2 and C(5)H_2), with all other spectroscopic data consistent with that previously reported.[12]

Preparation of *tert*-butyl 2-oxocyclopentane-1-carboxylate

Sodium hydride (60% suspension in mineral oil, 8.0 g, 0.20 mol) was first prepared for use by careful washing with *n*-pentane (3 × 50 ml) and discarding the supernatant. The liberated sodium hydride was then suspended in anhydrous toluene (400 ml) and the mixture heated to 60 °C. A solution of di-*tert*-butyladipate (2.0 g) in *tert*-butanol (2 mL) was added in one portion followed by, after an additional 30 min, the dropwise addition of the remaining di-*tert*-butyl adipate (50.0 g, 0.19 mol) in toluene (50 ml). Once addition was complete the reaction mixture was heated at 100 °C for 3 h, then allowed to cool in an ice bath. The reaction was quenched by cautious, sequential addition of MeOH (10 ml), H_2O (10 ml) and NH_4Cl (aq, sat, 100 ml). The organic layer was separated and the aqueous layer extracted with toluene (3 × 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product as a yellow oil. Subsequent purification by vacuum distillation (bp 110–112 °C, 10 mm Hg; lit.[4] 80–85 °C, 2 mm Hg) gave the title compound (32.1 g, 84%) as a colourless oil; δ_H (200 MHz, $CDCl_3$) 1.45 (9H, s, OC(CH_3)$_3$), 1.74–1.97 (1H, m, C(4)H_A), 2.05–2.33 (5H, m, C(3)H_2, C(4)H_B and C(5)H_2), 3.05 (1H, app t, *J* 8.7, C(1)*H*), with all other spectroscopic data consistent with that previously reported.[13]

Preparation of *tert*-butyl 3-ethyl-2-oxocyclopentane-1-carboxylate 9

A solution of *tert*-butyl 2-oxocyclopentane-1-carboxylate (5.0 g, 27.3 mmol) in anhydrous THF (100 ml) at −78 °C was deprotonated with sodium hydride (1.14 g, 28.6 mmol) then *n*-butyllithium (1.6 M, 17.9 ml, 28.6 mmol) in accordance with *general procedure 1*. Ethyl iodide (2.40 ml, 29.8 mmol) was added neat, dropwise, and the mixture stirred for 0.5 h at −78 °C before being allowed to slowly warm to 0 °C. The reaction was quenched by sequential addition of MeOH (2 ml), H_2O (5 ml) and NH_4Cl (aq, sat, 50 ml). The organic layer was separated and the aqueous layer extracted with Et_2O (3 × 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product as a yellow oil. The residue was purified by flash chromatography on silica gel (5% Et_2O/*n*-pentane) to give **9** (5.32 g, 92%) as a colourless oil; ν_{max} (film) 1749s, 1721s, 1161m; major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.5, CH$_2$CH_3), 1.22–1.42 (2H, m, C(4)H_A and CH_AH$_B$CH$_3$), 1.47 (9H, s, OC(CH_3)$_3$), 1.83 (1H, m, CH$_A$$H_BCH_3$), 2.02–2.50 (4H, m, C(3)*H*, C(4)H_B and C(5)H_2), 3.03 (1H, dd, *J* 11.1, 8.3, C(1)*H*); δ_C (100 MHz, $CDCl_3$) 11.7 (CH$_2$CH$_3$), 22.6 (*C*H$_2$CH$_3$), 25.0 (*C*(5)), 26.7 (*C*(4)), 28.0 (OC(*C*H$_3$)$_3$), 50.7 (*C*(3)), 56.2 (*C*(1)), 81.6 (O*C*(CH$_3$)$_3$), 168.9 (*C*O$_2$^{t}Bu), 214.3 (*C*(2)); minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.4, CH$_2$CH_3), 1.22–1.42 (2H, m, C(4)H_A and CH_AH$_B$CH$_3$), 1.46 (9H, s, OC(CH_3)$_3$), 1.83 (1H, m, CH$_A$$H_BCH_3$), 2.02–2.50 (4H, m, C(3)*H*, C(4)H_B and C(5)H_2), 3.15 (1H, m, C(1)*H*); δ_C (100 MHz, $CDCl_3$) 10.7 (CH$_2$CH$_3$), 22.6 (*C*H$_2$CH$_3$), 25.2 (*C*(5)), 27.0 (*C*(4)), 28.0 (OC(*C*H$_3$)$_3$), 50.3 (*C*(3)), 55.4 (*C*(1)), 81.6 (O*C*(CH$_3$)$_3$), 168.9 (*C*O$_2$^{t}Bu), 215.3 (*C*(2)); *m*/*z* (CI$^+$, NH$_3$) 230 (MNH$_4$$^+$, 5), 213 (MH$^+$, 5), 175 (MNH$_4$$^+$–C$_4H_8$, 100), 157 (MH$^+$–C$_4H_8$, 10%); HRMS, found 213.1492; $C_{12}H_{21}O_3$ (MH$^+$) requires 213.1491.

Preparation of *tert*-butyl 3-benzyl-2-oxocyclopentane-1-carboxylate 10

A solution of *tert*-butyl 2-oxocyclopentane-1-carboxylate (5.0 g, 27.3 mmol) in anhydrous THF (100 ml) at −78 °C was deprotonated with sodium hydride (1.14 g, 28.6 mmol) then *n*-butyllithium (1.6 M, 17.9 ml, 28.6 mmol) in accordance with *general procedure 1*. Benzyl bromide (3.56 ml, 29.8 mmol) was added neat, dropwise, and the mixture stirred for 0.5 h at −78 °C before being allowed to slowly warm to 0 °C. The reaction was quenched by sequential addition of MeOH (2 ml), H_2O (5 ml) and NH_4Cl (aq, sat, 50 ml). The organic layer was separated and the aqueous layer extracted with Et_2O (3 × 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product as a yellow oil. The residue was purified by flash chromatography on silica gel (5% Et_2O/*n*-pentane) to give **10** (6.66 g, 89%) as a colourless oil; ν_{max} (film) 1716s, 1146m; major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, OC(CH_3)$_3$), 1.49 (1H, m, C(4)H_A), 1.99–2.40 (3H, m, C(4)H_B and C(5)H_2), 2.54 (1H, m, C(3)*H*), 2.60 (1H, m, CH_AH$_B$Ph), 3.02 (1H, dd, *J* 10.6, 8.5, C(1)*H*), 2.17 (1H, m, CH$_A$$H_B$Ph), 7.16–7.31 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.8 (*C*(5)), 26.8 (*C*(4)), 27.9 (OC(*C*H$_3$)$_3$), 35.4 (*C*H$_2$Ph), 51.1 (*C*(3)), 56.1 (*C*(1)), 81.7 (O*C*(CH$_3$)$_3$), 126.5 (*p*-Ar), 128.7 and 129.1 (*o*-, *m*-Ar), 139.9 (*ipso*-Ar), 169.0 (*C*O$_2$^{t}Bu), 215.7 (*C*(2)); minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, OC(CH_3)$_3$), 1.49 (1H, m, C(4)H_A), 1.86 (1H, m, C(5)H_A), 1.99–2.40 (3H, m, C(3)*H*, C(4)H_B and C(5)H_B), 2.60 (1H, m, CH_AH$_B$Ph), 3.17 (1H, m, CH$_A$$H_B$Ph), 3.20 (1H, m, C(1)*H*), 7.16–7.31 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.0 (*C*(5)), 27.2 (*C*(4)), 27.9 (OC(*C*H$_3$)$_3$), 35.8 (*C*H$_2$Ph), 50.8 (*C*(3)), 55.2 (*C*(1)), 81.7 (O*C*(CH$_3$)$_3$), 126.5 (*p*-Ar), 128.7 and 129.1 (*o*, *m*-Ar), 139.7 (*ipso*-Ar), 169.0 (*C*O$_2$^{t}Bu), 215.7 (*C*(2)); *m*/*z* (CI$^+$, NH$_3$) 292 (MNH$_4$$^+$, 85), 275 (MH$^+$, 10), 236 (MNH$_4$$^+$–C$_4H_8$, 100), 219 (MH$^+$−56, 24%); HRMS, found 275.1649; $C_{17}H_{23}O_3$ (MH$^+$) requires 275.1647.

Preparation of ethyl 2-oxo-1-(1′-methylethyl)-cyclopentane-1-carboxylate 14

A mixture of β-keto ester **13** (15.0 g, 96.0 mmol), anhydrous K_2CO_3 (53.1 g, 0.384 mol) and isopropyl iodide (38.4 ml, 0.38 mol) in acetone (300 ml) was heated at reflux for 6 h.

Following cooling to rt the mixture was filtered, the residue washed with acetone (3 × 20 ml) and the filtrate concentrated *in vacuo* to afford the crude product as a yellow oil. Purification by flash chromatography on silica gel (10% Et_2O/*n*-pentane) gave **14** (17.3 g, 91%) as a colourless oil; δ_H (200 MHz, $CDCl_3$) 0.84 (3H, d, *J* 6.8, CH(CH_{3A}CH$_{3B}$)), 0.89 (3H, d, *J* 6.8, CH(CH$_{3A}$CH_{3B})), 1.26 (3H, t, *J* 6.9, OCH$_2$CH_3), 1.80–2.70 (7H, m, C(3)H_2, C(4)H_2, C(5)H_2 and C*H*(CH$_3$)$_2$), 4.18 (2H, m, OCH_2CH$_3$), with all other spectroscopic data consistent with that previously reported.[15]

Preparation of ethyl 3-(1′-methylethyl)-2-oxo-cyclopentane-1-carboxylate 15

To a freshly prepared solution of sodium ethoxide in EtOH (1.37 g, 60.4 mmol Na in 50 ml absolute EtOH) was added neat, dropwise, ethyl-2-oxo-1-(1-methylethyl)-cyclopentane-1-carboxylate **14** (10.0 g, 50.4 mmol). The solution was heated at reflux for 3 h, after which time half the solvent was removed by distillation. Toluene (100 ml) was added and the remaining EtOH removed by azeotropic distillation. The reaction mixture was heated at reflux for a further 3 h, cooled to 0 °C and then quenched by addition of NH_4Cl (aq, sat, 50 ml). The aqueous layer was separated and extracted with toluene (2 × 50 ml) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (10% Et_2O/*n*-pentane) gave **15** (7.20 g, 72%) as a colourless oil; major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 0.90 (3H, d, *J* 6.8, CH(CH_{3A}CH$_{3B}$)), 1.07 (3H, d, *J* 6.8, CH(CH$_{3A}$CH_{3B})), 1.29 (3H, m, OCH$_2$CH_3), 1.64 (1H, m, C(4)H_A), 2.01–2.40 (5H, m, C(3)*H*, C(4)H_B, C(5)H_2 and C*H*(CH$_3$)$_2$), 3.06 (1H, dd, *J* 11.4, 8.4, C(1)*H*), 4.20 (2H, m, OCH_2CH$_3$); minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) 0.92 (3H, d, *J* 6.8, CH(CH_{3A}CH$_{3B}$)), 1.05 (3H, d, *J* 6.8, CH(CH$_{3A}$CH_{3B})), 1.28 (3H, m, OCH$_2$CH_3), 1.64 (1H, m, C(4)H_A), 2.01–2.40 (5H, m, C(3)*H*, C(4)H_B, C(5)H_2 and C*H*(CH$_3$)$_2$), 3.26 (1H, m, C(1)*H*), 4.20 (2H, m, OCH_2CH$_3$), with all other spectroscopic data consistent with that previously reported.[16]

Preparation of methyl 2-oxo-3-(1′,1′-dimethylethyl)-1-cyclopentanecarboxylate 18

(i) Preparation of 1-trimethylsilyloxycylopentene. To a rapidly stirred solution of cyclopentanone (20.0 g, 0.24 mol) and trimethylsilylchloride (30.2 ml, 0.24 mol) in DMF (100 ml) was added dropwise triethylamine (33.2 ml, 0.24 mol). The resulting mixture was heated at 100 °C for 12 h, cooled to rt and then diluted with *n*-pentane (200 ml) and H_2O (200 ml). The organic layer was separated and the aqueous layer extracted with *n*-pentane (2 × 100 ml). The combined organic extracts were washed with 1 : 1 HCl (2 M aq, 100 ml)/brine (aq, sat, 100 ml), $NaHCO_3$ (aq, sat, 100 ml) and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by vacuum distillation (bp 54–56 °C, 21 mm Hg; lit.[8] 45 °C, 11 mm Hg) gave the title compound (27.5 g, 74%) as a colourless oil; δ_H (200 MHz, $CDCl_3$) 0.22 (9H, s, Si(CH_3)$_3$), 1.79–2.04 (2H, m, C(4)H_2), 2.12–2.31 (4H, m, C(3)H_2 and C(5)H_2), 4.63 (1H, br s, C(2)*H*), with all other spectroscopic data consistent with that previously reported.[18]

(ii) Preparation of (1′,1′-dimethylethyl)-1-cyclopentanone. To a stirred solution of titanium tetrachloride (14.1 ml, 0.13 mol) and *tert*-butyl chloride (15.7 ml, 0.143 mol) in DCM (100 ml) at −45 °C, was added dropwise a solution of 1-trimethylsilyloxycylopentene (20.1 g, 0.13 mol) in DCM (50 ml). After 2 h the reaction mixture was warmed to 0 °C and neutralised by addition of $NaHCO_3$ (aq, sat, 100 ml). The aqueous phase was separated and extracted with DCM (3 × 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by vacuum distillation (bp 86–88 °C, 18 mm Hg; lit.[9] 95 °C, 45 mm Hg) gave the title compound (7.1 g, 39%) as a colourless oil; δ_H (200 MHz, $CDCl_3$) 0.96 (9H, s, C(CH_3)$_3$), 1.50–2.50 (7H, m, C(2)*H*, C(3)H_2, C(4)H_2 and C(5)H_2), with all other spectroscopic data consistent with that previously reported.[29]

(iii) Preparation of methyl 2-oxo-3-(1′,1′-dimethylethyl)-1-cyclopentanecarboxylate. Sodium hydride (60% suspension in mineral oil, 3.00 g, 74.8 mmol) was first prepared for use by careful washing with *n*-pentane (3 × 20 ml) and discarding the supernatant. To a vigorously stirred solution of the liberated sodium hydride in DMF (50 ml) at 0 °C was added neat, dropwise, (1′,1′-dimethylethyl)-1-cyclopentanone (5.00 g, 35.6 mmol). The reaction was allowed to warm to rt whereat it was stirred for 3 h. Dimethyl carbonate (6.44 g, 71.5 mmol) was added and stirring continued for 12 h. The reaction was quenched by dropwise addition of H_2O (10 ml) and neutralised with NH_4Cl (aq, sat, *ca.* 50 ml). The aqueous phase was separated and extracted with Et_2O (3 × 50 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (10% Et_2O/*n*-pentane) gave **18** (5.02 g, 71%) as a colourless oil; major diastereoisomer: δ_H (200 MHz, $CDCl_3$) 1.00 (9H, s, C(CH_3)$_3$), 1.55–2.65 (5H, m, C(3)*H*, C(4)H_2 and C(5)H_2), 3.08 (1H, dd, *J* 11.8, 8.2, C(1)*H*), 3.76 (3H, s, OCH_3); minor diastereoisomer: δ_H (200 MHz, $CDCl_3$) 0.98 (9H, s, C(CH_3)$_3$), 1.55–2.65 (5H, m, C(3)*H*, C(4)H_2 and C(5)H_2), 3.26 (1H, m, C(1)*H*), 3.76 (3H, s, OCH_3), with all other spectroscopic data consistent with that previously reported.[19]

Preparation of *tert*-butyl (*RS*)-3-ethylcyclopentene-1-carboxylate 11

(i) Preparation of *tert*-butyl 2-hydroxy-3-ethylcyclopentane-1-carboxylate. The β-keto ester **9** (4.00 g, 18.8 mmol) in EtOH (30 ml) was treated with $NaBH_4$ (0.71 g, 18.8 mmol) in accordance with *general procedure 2*, giving the title compound (3.75 g, 93%) as a complex mixture of diastereoisomers. This material was used without purification, although for the purposes of analysis a small quantity was subjected to flash chromatography on silica gel (20% Et_2O/*n*-pentane) to give the title compound as a colourless oil; ν_{max}(film) 3473br s, 1705s, 1155m; major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.4, CH$_2$CH_3), 1.15–1.22 (2H, m, C(4)H_A and CH_AH$_B$CH$_3$), 1.45 (1H, m, C(5)H_A), 1.46 (9H, s, OC(CH_3)$_3$), 1.84 (1H, m, CH$_A$$H_BCH_3$), 1.90–2.04 (3H, m, C(3)*H*, C(4)H_B and C(5)H_B), 2.69 (1H, ddd, *J* 9.1, 8.5, 5.6, C(1)*H*), 3.17 (1H, br s, O*H*), 3.98 (1H, dd, *J* 5.6, 3.9, C(2)*H*); δ_C (50 MHz, $CDCl_3$) 12.3 (CH$_2$*C*H$_3$), 26.2 (*C*(5)), 26.7 (*C*H$_2$CH$_3$), 28.0 (OC(*C*H$_3$)$_3$), 28.6 (*C*(4)), 48.8 (*C*(1) and *C*(3)), 78.3 (*C*(2)), 81.0 (O*C*(CH$_3$)$_3$), 174.7 (*C*O$_2$^{t}Bu); minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.4, CH$_2$CH_3), 1.44 (1H, m, CH_AH$_B$CH$_3$), 1.47 (9H, s, OC(CH_3)$_3$), 1.50–1.71 (3H, m, C(3)*H*, C(4)H_A and CH$_A$$H_BCH_3$), 1.79–2.08 (3H, m, C(4)H_B and C(5)H_2), 2.69 (1H, app td, *J* 10.0, 3.5, C(1)*H*), 3.08 (1H, br s, O*H*), 4.25 (1H, app t, *J* 3.5, C(2)*H*); δ_C (50 MHz, $CDCl_3$) 12.7 (CH$_2$*C*H$_3$), 22.0 (*C*(5)), 25.2 (*C*H$_2$CH$_3$), 28.0 (OC(*C*H$_3$)$_3$ and *C*(4)), 47.6 (*C*(3)), 50.1 (*C*(1)), 74.3 (*C*(2)), 81.0 (O*C*(CH$_3$)$_3$), 174.9 (*C*O$_2$^{t}Bu); *m*/*z* (CI$^+$, NH$_3$) 215 (MH$^+$, 10), 176 (MNH$_4$$^+$–C$_4H_8$, 100), 159 (MH$^+$–C$_4H_8$, 20%); HRMS, found 215.1645; $C_{12}H_{23}O_3$ (MH$^+$) requires 215.1647.

(ii) Preparation of *tert*-butyl (*RS*)-3-ethylcyclopentene-1-carboxylate 11. *tert*-Butyl 2-hydroxy-3-ethylcyclopentane-1-carboxylate (3.00 g, 14.0 mmol) in THF (50 ml) was treated with PPh$_3$ (5.51 g, 21.0 mmol) and DIAD (3.60 ml, 18.3 mmol) in accordance with *general procedure 3*, giving (*RS*)-**11** (2.39 g, 87%) as a volatile, colourless liquid; ν_{max} (film) 1709s, 1631m, 1167m; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.4, CH$_2$CH_3), 1.37 (1H, m, CH_AH$_B$CH$_3$), 1.49 (9H, s, OC(CH_3)$_3$), 1.46–1.54 (2H, m, CH$_A$$H_BCH_3$ and C(4)H_A), 2.12 (1H, dddd, *J* 13.0, 8.6, 8.6, 4.5, C(4)H_B), 2.48 (1H, m, C(5)H_A), 2.53 (1H, m, C(5)H_B), 2.70 (1H, m, C(3)*H*), 6.61 (1H, app q, *J* 2.0, C(2)*H*); δ_C (50 MHz, $CDCl_3$) 12.0 (CH$_2$*C*H$_3$), 27.7

(CH_2CH_3), 28.0 (OC(CH_3)$_3$), 29.5 (*C*(5)), 30.8 (*C*(4)), 47.9 (*C*(3)), 79.9 (O*C*(CH$_3$)$_3$), 137.7 (*C*(1)), 146.2 (*C*(2)), 165.4 ($CO_2{}^t$Bu); *m*/*z* (CI$^+$, NH$_3$) 214 (MNH$_4{}^+$, 20), 197 (MH$^+$, 45), 158 (MNH$_4{}^+$–C$_4$H$_8$, 100), 141 (MH$^+$–C$_4$H$_8$, 10), 123 (MH$^+$-74, 35), 95 (MH$^+$-101, 55%); HRMS, found 197.1548; $C_{12}H_{21}O_2$ (MH$^+$) requires 197.1542.

Preparation of *tert*-butyl (*RS*)-3-benzylcyclopentene-1-carboxylate 12

(i) Preparation of *tert*-butyl 2-hydroxy-3-benzylcyclopentane-1-carboxylate. The β-keto ester **10** (4.00 g, 14.5 mmol) in EtOH (30 ml) was treated with NaBH$_4$ (0.55 g, 14.5 mmol) in accordance with *general procedure 2*, giving the title compound (3.63 g, 90%) as a complex mixture of diastereoisomers. This material was used without purification, although for the purposes of analysis a small quantity was subjected to flash chromatography on silica gel (20% Et$_2$O/*n*-pentane) to give the title compound as a colourless oil; ν_{max} (film) 3471br s, 1704s 1154m; major diastereoisomer: δ_H (400 MHz, CDCl$_3$) 1.28 (1H, m, C(4)H_A), 1.48 (9H, s, OC(CH_3)$_3$), 1.89–1.99 (3H, m, C(3)*H*, C(4)H_B and C(5)H_A), 2.31 (1H, m, C(5)H_B), 2.46 (1H, dd, *J* 13.6, 9.0, CH_AH$_B$Ph), 2.78–2.85 (2H, m, CH$_A$$H_B$Ph and C(1)*H*), 2.98 (1H, br s, O*H*), 4.03 (1H, dd, *J* 5.7, 4.4, C(2)*H*), 7.15–7.31 (5H, m, *Ph*); δ_C (50 MHz, CDCl$_3$) 26.2 (*C*(5)), 28.0 (OC(*C*H$_3$)$_3$), 28.3 (*C*(4)), 39.6 (*C*H$_2$Ph), 48.1 (*C*(3)), 48.2 (*C*(1)), 77.9 (*C*(2)), 81.2 (O*C*(CH$_3$)$_3$), 126.1 (*p*-Ar), 128.5 and 129.1 (*o*, *m*-Ar), 140.8 (*ipso*-Ar), 174.7 (*C*O$_2{}^t$Bu); minor diastereoisomer: δ_H (400 MHz, CDCl$_3$) 1.46 (9H, s, OC(CH_3)$_3$), 1.68–1.81 (2H, m, C(3)*H* and C(4)H_A), 1.89–2.10 (3H, m, C(4)H_B and C(5)H_2), 2.64 (2H, m, C(1)*H* and CH_AH$_B$Ph), 2.94 (1H, dd, *J* 13.5, 8.1, CH$_A$$H_B$Ph), 3.26 (1H, br s, O*H*), 4.15 (1H, app t, *J* 3.4, C(2)*H*), 7.15–7.31 (5H, m, *Ph*); δ_C (50 MHz, CDCl$_3$) 25.4 (*C*(5)), 28.0 (OC(*C*H$_3$)$_3$ and *C*(4)), 35.3 (*C*H$_2$Ph), 47.8 (*C*(3)), 49.8 (*C*(1)), 74.0 (*C*(2)), 81.2 (O*C*(CH$_3$)$_3$), 125.9 (*p*-Ar), 128.4 and 129.0 (*o*, *m*-Ar), 142.0 (*ipso*-Ar), 174.9 (*C*O$_2{}^t$Bu); *m*/*z* (CI$^+$, NH$_3$) 294 (MNH$_4{}^+$, 10), 277 (MH$^+$, 25), 238 (MNH$_4{}^+$–C$_4$H$_8$, 100), 221 (MH$^+$–C$_4$H$_8$, 30%); HRMS, found 277.1827; $C_{17}H_{25}O_3$ (MH$^+$) requires 277.1804.

(ii) Preparation of *tert*-butyl (*RS*)-3-benzylcyclopentene-1-carboxylate 12. *tert*-Butyl 2-hydroxy-3-benzylcyclopentane-1-carboxylate (3.00 g, 10.9 mmol) in THF (50 ml) was treated with PPh$_3$ (4.28 g, 16.3 mmol) and DIAD (2.79 ml, 14.2 mmol) in accordance with *general procedure 3*, giving (*RS*)-**12** (2.56 g, 91%) as a white crystalline solid; mp 32–34 °C; elemental analysis, found C, 78.9; H, 8.5%; $C_{17}H_{22}O_2$ requires C, 79.0; H, 8.6%; ν_{max} (film) 1707s, 1629m, 1167m; δ_H (400 MHz, CDCl$_3$) 1.49 (9H, s, OC(CH_3)$_3$), 1.61 (1H, m, C(4)H_A), 2.09 (1H, dddd, *J* 13.0, 8.8, 8.8, 4.5, C(4)H_B), 2.49 (1H, m, C(5)H_A), 2.56 (1H, m, C(5)H_B), 2.65 and 2.77 (2H, ABX system, J_{AB} 13.5, J_{AX} 8.0, J_{BX} 7.3, CH_2Ph), 3.10 (1H, m, C(3)*H*), 6.58 (1H, app q, *J* 2.0, C(2)*H*), 7.19–7.33 (5H, m, *Ph*); δ_C (50 MHz, CDCl$_3$) 28.1 (OC(*C*H$_3$)$_3$), 29.7 (*C*(5)), 30.7 (*C*(4)), 41.0 (*C*H$_2$Ph), 47.9 (*C*(3)), 80.1 (O*C*(CH$_3$)$_3$), 126.2 (*p*-Ar), 128.6 and 129.0 (*o*, *m*-Ar), 138.3 (*C*(1)), 140.7 (*ipso*-Ar), 145.5 (*C*(2)), 165.3 (*C*O$_2{}^t$Bu); *m*/*z* (CI$^+$, NH$_3$) 276 (MNH$_4{}^+$, 40), 259 (MH$^+$, 10), 220 (MNH$_4{}^+$–C$_4$H$_8$, 100), 203 (MH$^+$–C$_4$H$_8$, 10), 185 (MH$^+$-74, 10), 158 (MH$^+$-102, 20), 91 (C$_7$H$_7{}^+$, 60%).

Preparation of *tert*-butyl (*RS*)-3-(1′-methylethyl)-cyclopentene-1-carboxylate 16

(i) Preparation of ethyl 2-hydroxy-3-(1′-methylethyl)-cyclopentane-1-carboxylate. The β-keto ester **15** (4.00 g, 20.2 mmol) in EtOH (30 ml) was treated with NaBH$_4$ (0.76 g, 20.2 mmol) in accordance with *general procedure 2*, giving the title compound (3.45 g, 85%) as a complex mixture of diastereoisomers. This material was used without purification, although for the purposes of analysis a small quantity was subjected to flash chromatography on silica gel (20% Et$_2$O/*n*-pentane) to give the title compound as a colourless oil; ν_{max} (film) 3485br s, 1716s and 1200m; major diastereoisomer: δ_H (400 MHz, CDCl$_3$) 0.88 (3H, d, *J* 6.6, CH(CH_{3A}CH$_{3B}$)), 0.97 (3H, d, *J* 6.6, CH(CH$_{3A}$CH_{3B})), 1.24 (1H, m, C(4)H_A), 1.28 (3H, t, *J* 7.1, CH$_2$CH_3), 1.52 (1H, m, C*H*(CH$_3$)$_2$), 1.70 (1H, m, C(3)*H*), 1.87–1.98 (3H, m, C(4)H_B and C(5)H_2), 2.52 (1H, br s, O*H*), 2.69 (1H, m, C(1)*H*), 4.03 (1H, m, C(2)*H*), 4.21 (2H, q, *J* 7.1, CH_2CH$_3$); δ_C (50 MHz, CDCl$_3$) 14.0 (OCH$_2$*C*H$_3$), 20.0 (*C*(5)), 21.0 (*C*(4)), 26.7 (CH(*C*H$_{3A}$CH$_{3B}$)), 27.1 (CH(CH$_{3A}$*C*H$_{3B}$)), 30.7 (*C*H(CH$_3$)$_2$), 49.4 (*C*(3)), 54.5 (*C*(1)), 60.5 (O*C*H$_2$CH$_3$), 76.3 (*C*(2)), 174.7 (*C*O$_2{}^t$Bu); *m*/*z* (CI$^+$, NH$_3$) 218 (MNH$_4{}^+$, 5), 201 (MH$^+$, 100), 183 (MH$^+$–H$_2$O, 20%); HRMS, found 201.1493; $C_{11}H_{21}O_3$ (MH$^+$) requires 201.1491.

(ii) Preparation of ethyl (*RS*)-3(1′-methylethyl)-cyclopentene-1-carboxylate. Ethyl 2-hydroxy-3-(1′-methylethyl)-cyclopentane-1-carboxylate (3.00 g, 15.0 mmol) in THF (50 ml) was treated with PPh$_3$ (5.90 g, 22.5 mmol) and DIAD (3.86 ml, 19.6 mmol) in accordance with *general procedure 3*, giving the title compound (2.24 g, 82%) as a colourless oil; ν_{max}(film) 1716s, 1634m; δ_H (400 MHz, CDCl$_3$) 0.90 (3H, d, *J* 7.1, CH(CH_{3A}CH$_{3B}$)), 0.94 (3H, d, *J* 7.1, CH(CH$_{3A}$CH_{3B})), 1.30 (3H, t, *J* 7.1, CH$_2$CH_3), 1.57–1.67 (2H, m, C*H*(CH$_3$)$_2$ and C(4)H_A), 2.07 (1H, dddd, *J* 13.0, 8.6, 8.6, 4.3, C(4)H_B), 2.49–2.65 (3H, m, C(3)*H* and C(5)H_2), 4.14–4.24 (2H, m, CH_2CH$_3$), 6.75 (1H, app q, *J* 2.0, C(2)*H*); δ_C (50 MHz, CDCl$_3$) 14.1 (OCH$_2$*C*H$_3$), 20.2 and 20.4 (CH(*C*H$_3$)$_2$), 27.3 (*C*(5)), 31.0 (*C*(4)), 32.1 (*C*H(CH$_3$)$_2$), 53.5 (*C*(3)), 60.1 (O*C*H$_2$CH$_3$), 136.7 (*C*(1)), 146.2 (*C*(2)), 165.9 (*C*O$_2$Et); *m*/*z* (CI$^+$, NH$_3$) 200 (MNH$_4{}^+$, 70), 183 (MH$^+$, 100%); HRMS, found 183.1391; $C_{11}H_{19}O_2$ (MH$^+$) requires 183.1385.

(iii) Preparation of *tert*-butyl (*RS*)-3-(1′-methylethyl)-cyclopentene-1-carboxylate 16. To a solution of ethyl (*RS*)-3-(1′-methylethyl)-cyclopentene-1-carboxylate (2.00 g, 10.0 mmol) in MeOH (20 ml) was added KOH (aq, 2 M, 20 ml) and the mixture heated at 60 °C for 12 h. Following cooling to rt the mixture was acidified to pH 1 by addition of HCl (aq, 2 M, ≈20 ml) then diluted with Et$_2$O (50 ml). The aqueous layer was separated and extracted with Et$_2$O (3 × 30 ml) and the combined organic extracts were dried (MgSO$_4$), filtered and concentrated *in vacuo* to afford the crude acid[30] (1.69 g, quantitative) as a pale yellow oil; δ_H (200 MHz, CDCl$_3$) 0.90 (3H, d, *J* 7.0, CH(CH_{3A}CH$_{3B}$)), 0.94 (3H, d, *J* 7.0, CH(CH$_{3A}$CH_{3B})), 1.56–1.73 (2H, m, C*H*(CH$_3$)$_2$ and C(4)H_A), 2.08 (1H, dddd, *J* 13.0, 8.5, 8.5, 4.5, C(4)H_B), 2.43–2.71 (3H, m, C(3)*H* and C(5)H_2), 6.90 (1H, app q, *J* 2.0, C(2)*H*). A solution of the crude acid (1.60 g, 10.4 mmol) in DCM (20 ml) was cooled to −78 °C and ≈20 ml of iso-butylene (condensed by passing the gas into a conical flask held at −78 °C) added, followed by H$_2$SO$_4$ (98%, 1 drop). The reaction mixture was held at −78 °C for 4 h, and then allowed to warm to rt overnight. The mixture was diluted with H$_2$O (10 ml) and the aqueous layer separated and extracted with DCM (3 × 20 ml). The combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (2% Et$_2$O/*n*-pentane) gave (*RS*)-**16** (1.22 g, 56% from ethyl (*RS*)-3-(1′-methylethyl)-cyclopentene-1-carboxylate) as a colourless oil; ν_{max} (film) 1709s, 1633m, 1171s; δ_H (400 MHz, CDCl$_3$) 0.90 (3H, d, *J* 6.7, CH(CH_{3A}CH$_{3B}$)), 0.94 (3H, d, *J* 6.7, CH(CH$_{3A}$CH_{3B})), 1.50 (9H, s, OC(CH_3)$_3$), 1.54–1.64 (2H, m, C*H*(CH$_3$)$_2$ and C(4)H_A), 2.05 (1H, dddd, *J* 13.0, 8.7, 8.7, 4.3, C(4)H_B), 2.44–2.60 (3H, m, C(3)*H* and C(5)H_2), 6.64 (1H, app q, *J* 2.0, C(2)*H*); δ_C (50 MHz, CDCl$_3$) 20.2 and 20.5 (CH(*C*H$_3$)$_2$), 27.4 (*C*(5)), 28.0 (OC(*C*H$_3$)$_3$), 31.1 (*C*(4)), 32.2 (*C*H(CH$_3$)$_2$), 53.5 (*C*(3)), 79.9 (O*C*(CH$_3$)$_3$), 138.3 (*C*(1)), 145.1 (*C*(2)), 165.4 (*C*O$_2{}^t$Bu); *m*/*z* (CI$^+$, NH$_3$) 228 (MNH$_4{}^+$, 15), 211 (MH$^+$, 30), 172 (MNH$_4{}^+$–C$_4$H$_8$, 100%); HRMS, found 211.1695; $C_{13}H_{23}O_2$ (MH$^+$) requires 211.1698.

Preparation of 19

(i) Preparation of methyl 2-hydroxy-3-(1′,1′-dimethylethyl)-cyclopentane-1-carboxylate. The β-keto ester **18** (4.00 g, 20.2 mmol) in EtOH (30 ml) was treated with NaBH$_4$ (0.76 g, 20.2 mmol) in accordance with *general procedure 2*, giving the title compound (3.72 g, 92%) as a complex mixture of diastereoisomers. This material was used without purification, although for the purposes of analysis a small quantity was subjected to flash chromatography on silica gel (20% Et_2O/*n*-pentane) to give the title compound as a colourless oil; ν_{max} (film) 3507br s, 1716s; major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.03 (9H, s, $C(CH_3)_3$), 1.43 (1H, br s, O*H*), 1.53 (1H, m, C(4)H_A), 1.68–1.86 (3H, m, C(3)*H*, C(4)H_B and C(5)H_A), 2.13 (1H, m, C(5)H_B), 2.52 (1H, m, C(1)*H*), 3.69 (3H, s, OCH_3), 4.48 (1H, m, C(2)*H*); δ_C (50 MHz, $CDCl_3$) 24.1 (*C*(5)), 26.1 (*C*(4)), 29.2 ($C(CH_3)_3$), 31.4 ($C(CH_3)_3$), 51.7 (CO_2Me), 53.9 (*C*(3)), 55.0 (*C*(1)), 77.5 (*C*(2)), 176.7 (CO_2Me); *m*/*z* (CI^+, NH_3) 218 (MNH_4^+, 50), 201 (MH^+, 20), 183 (MH^+–H_2O, 100%); HRMS, found 201.1487; $C_{11}H_{21}O_3$ (MH^+) requires 201.1491.

(ii) Preparation of ethyl (*RS*)-3-(1′,1′-dimethylethyl)-cyclopentene-1-carboxylate. Methyl 2-hydroxy-3-(1′,1′-dimethylethyl)-cyclopentane-1-carboxylate (3.00 g, 15.0 mmol) in THF (50 ml) was treated with PPh_3 (5.90 g, 22.5 mmol) and DIAD (3.86 ml, 19.6 mmol) in accordance with *general procedure 3*, giving the title compound (2.35 g, 86%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 0.90 (9H, s, $C(CH_3)_3$), 1.58–1.77 (1H, m, C(4)H_A), 1.97 (1H, dddd, *J* 13.1, 8.8, 8.8, 4.4, C(4)H_B), 2.50–2.69 (3H, m, C(3)*H* and C(5)H_2), 3.74 (3H, s, OCH_3), 6.78 (1H, app q, *J* 2.0, C(2)*H*), with all other spectroscopic data consistent with that previously reported.[19]

(iii) Preparation of *tert*-butyl (*RS*)-3-(1′,1′-dimethylethyl)-cyclopentene-1-carboxylate 19. To a solution of ethyl (*RS*)-3-(1′,1′-dimethylethyl)-cyclopentene-1-carboxylate (2.00 g, 11.0 mmol) in MeOH (20 ml) was added KOH (aq, 2 M, 20 ml) and the mixture heated at 60 °C for 12 h. Following cooling to rt the mixture was acidified to pH 1 by addition of HCl (aq, 2 M, ≈20 ml) then diluted with Et_2O (50 ml). The aqueous layer was separated and extracted with Et_2O (3 × 30 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude acid[10] (1.85 g, quantitative) as a pale yellow oil; δ_H (400 MHz, $CDCl_3$) 0.91 (9H, s, $C(CH_3)_3$), 1.73–1.80 (1H, m, C(4)H_A), 2.01 (1H, dddd, *J* 13.2, 8.8, 8.8, 4.4, C(4)H_B), 2.50–2.59 (2H, m, C(5)H_2), 2.69 (1H, m, C(3)*H*), 6.93 (1H, app q, *J* 2.0, C(2)*H*). A solution of the crude acid (1.80 g, 10.7 mmol) in DCM (20 ml) was cooled to −78 °C and ≈20 ml of isobutylene (condensed by passing the gas into a conical flask held at −78 °C) added, followed by H_2SO_4 (98%, 1 drop). The reaction mixture was held at −78 °C for 4 h, and then allowed to warm to rt overnight. The mixture was diluted with H_2O (10 ml) and the aqueous layer separated and extracted with DCM (3 × 20 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (2% Et_2O/*n*-pentane) gave (*RS*)-**19** (1.70 g, 71% from ethyl (*RS*)-3-(1′,1′-dimethylethyl)-cyclopentene-1-carboxylate) as a colourless oil; ν_{max} (film) 1710s, 1634m, 1168s; δ_H (400 MHz, $CDCl_3$) 0.89 (9H, s, $C(3)C(CH_3)_3$), 1.50 (9H, s, $OC(CH_3)_3$), 1.70 (1H, m, C(4)H_A), 2.01 (1H, dddd, *J* 13.2, 8.8, 8.8, 4.4, C(4)H_B), 2.42–2.60 (2H, m, C(5)H_2), 2.63 (1H, m, C(3)*H*), 6.65 (1H, app q, *J* 2.0, C(2)*H*); δ_C (50 MHz, $CDCl_3$) 25.2 (*C*(4)), 27.4 ($C(3)C(CH_3)_3$), 28.0 ($OC(CH_3)_3$), 31.2 (*C*(5)), 33.1 ($C(3)C(CH_3)_3$), 57.6 (*C*(3)), 79.9 ($OC(CH_3)_3$), 138.6 (*C*(1)), 144.5 (*C*(2)), 165.3 ($CO_2{}^tBu$); *m*/*z* (CI^+, NH_3) 242 (MNH_4^+, 5), 225 (MH^+, 20), 186 (MNH_4^+–C_4H_8, 100%); HRMS, found 225.1856; $C_{14}H_{25}O_2$ (MH^+) requires 225.1855.

Preparation of *tert*-butyl (1*RS*,2*SR*,3*RS*)-3-ethyl-2-(*N*,*N*-dibenzylamino)-cyclopentane-1-carboxylate 20 and *tert*-butyl (1*SR*,2*SR*,3*RS*)-3-ethyl-2-(*N*,*N*-dibenzylamino)-cyclopentane-1-carboxylate 22

Following *general procedure 4*, *n*-BuLi (2.5 M, 0.61 ml, 1.53 mmol), dibenzylamine (0.29 ml, 1.53 mmol) in THF (5 ml) and (*RS*)-**11** (100 mg, 0.51 mmol) in THF (1 ml) gave, after quenching with NH_4Cl (aq, sat, 5 ml) and purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane), the diastereoisomeric products (1*RS*,2*SR*,3*RS*)-**20** and (1*SR*,2*SR*,3*RS*)-**22** as an 84 : 16 mixture (142 mg, 71%); NMR data for (1*RS*,2*SR*,3*RS*)-**20** (assigned from the diastereoisomeric mixture): δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.5, CH_2CH_3), 1.03 (1H, m, $CH_AH_BCH_3$), 1.13 (1H, m, C(4)H_A), 1.58 (9H, s, $OC(CH_3)_3$), 1.67–1.81 (2H, m, C(5)H_A and $CH_AH_BCH_3$), 1.91 (1H, m, C(5)H_B), 2.07 (1H, m, C(4)H_B), 2.34 (1H, app quintet of doublets, *J* 8.8, 4.0, C(3)*H*), 2.93 (1H, m, C(1)*H*) overlays 2.98 (1H, m, C(2)*H*), 3.80 and 3.86 (2 × 2H, AB system, J_{AB} 13.9, $N(CH_2Ph)_2$), 7.21–7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.3 (CH_2CH_3), 27.2 and 27.4 (CH_2CH_3 and *C*(5)), 28.1 ($OC(CH_3)_3$), 28.5 (*C*(4)), 40.4 (*C*(3)), 46.3 (*C*(1)), 54.4 ($N(CH_2Ph)_2$), 67.9 (*C*(2)), 80.2 ($OC(CH_3)_3$), 126.7 (*p*-Ph), 128.4 and 128.8 (*o*-, *m*-Ph), 140.4 (*ipso*-Ph), 175.6 ($CO_2{}^tBu$).

The mixture of (1*RS*,2*SR*,3*RS*)-**20** and (1*SR*,2*SR*,3*RS*)-**22** (120 mg, 0.31 mmol) was re-dissolved in *tert*-butanol and epimerised under thermodynamic conditions in accordance with *general procedure 6*. Purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane) gave (1*SR*,2*SR*,3*RS*)-**22** (118 mg, quantitative) as a pale yellow crystalline solid; mp 58–60 °C; elemental analysis, found C, 79.5; H, 8.7; N, 3.6%; $C_{26}H_{35}NO_2$ requires C, 79.4; H, 9.0; N, 3.6%; ν_{max} (KBr) 3059s, 3028s, 2974s, 2873s, 1717s, 1603m, 1495m, 1452m, 1363s, 1254m, 1145s, 1072m, 965m, 845m, 751s; δ_H (400 MHz, $CDCl_3$) 0.84 (1H, t, *J* 7.4, CH_2CH_3), 1.09 (1H, m, $CH_AH_BCH_3$), 1.32 (1H, m, C(4)H_A), 1.50 (9H, s, $OC(CH_3)_3$), 1.72–1.87 (5H, m, $CH_AH_BCH_3$, C(3)*H*, C(4)H_B and C(5)H_2), 2.90 (1H, app q, *J* 7.1, C(1)*H*), 3.17 (1H, dd, *J* 7.9, 7.5, C(2)*H*), 3.54 and 3.79 (2 × 2H, AB system, J_{AB} 13.8, $N(CH_2Ph)_2$), 7.21–7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.4 (CH_2CH_3), 26.6 (CH_2CH_3), 28.1 ($OC(CH_3)_3$), 29.2 and 29.3 (*C*(4) and *C*(5)), 44.4 (*C*(1)), 44.6 (*C*(3)), 54.9 ($N(CH_2Ph)_2$), 69.7 (*C*(2)), 79.8 ($OC(CH_3)_3$), 126.7 (*p*-Ph), 128.0 and 128.8 (*o*-, *m*-Ph), 140.2 (*ipso*-Ph), 176.5 ($CO_2{}^tBu$); *m*/*z* (ESI^+) 394 (MH^+, 100), 338 (MH^+–C_4H_8, 15%); HRMS, found 394.2750; $C_{26}H_{36}NO_2$ (MH^+) requires 394.2746.

Preparation of *tert*-butyl (1*RS*,2*SR*,3*SR*)-3-benzyl-2-(*N*,*N*-dibenzylamino)-cyclopentane-1-carboxylate 21 and *tert*-butyl (1*SR*,2*SR*,3*SR*)-3-benzyl-2-(*N*,*N*-dibenzylamino)-cyclopentane-1-carboxylate 23

Following *general procedure 4*, *n*-BuLi (2.5 M, 1.20 ml, 3.0 mmol), dibenzylamine (0.58 ml, 3.0 mmol) in THF (10 ml) and (*RS*)-**12** (200 mg, 1.0 mmol) in THF (2 ml) gave, after quenching with NH_4Cl (aq, sat, 5 ml) and purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane), the diastereoisomeric products (1*RS*,2*SR*,3*SR*)-**21** and (1*SR*,2*SR*,3*SR*)-**23** as an 83 : 17 mixture (350 mg, 77%); NMR data for (1*RS*,2*SR*,3*SR*)-**21** (assigned from the diastereoisomeric mixture): δ_H (400 MHz, $CDCl_3$) 1.19 (1H, m, C(4)H_A), 1.59 (9H, s, $OC(CH_3)_3$), 1.70 (1H, m, C(5)H_A), 1.87–1.92 (2H, m, C(4)H_B and C(5)H_B), 2.19 (1H, dd, *J* 13.6, 10.4, $C(3)CH_ACH_BPh$), 2.72 (1H, app quintet of doublets, *J* 8.8, 4.0, C(3)*H*), 2.99 (1H, td, *J* 8.0, 4.8, C(1)*H*), 3.09 (1H, dd, *J* 9.6, 8.0, C(2)*H*), 3.16 (1H, dd, *J* 13.6, 4.0, $C(3)CH_AH_BPh$), 3.85 and 3.98 (2 × 2H, AB system, J_{AB} 14.0, $N(CH_2Ph)_2$), 7.10–7.45 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.1 (*C*(5)), 28.2 ($OC(CH_3)_3$), 28.6 (*C*(4)), 40.6 ($C(3)CH_2Ph$), 40.9 (*C*(3)), 45.8 (*C*(1)), 54.6 ($N(CH_2Ph)_2$), 67.9 (*C*(2)), 80.3 ($OC(CH_3)_3$), 125.6 and 126.9 (*p*-Ph), 128.2, 128.9 and 129.0 (*o*-, *m*-Ph), 140.3 and 141.5 (*ipso*-Ph), 175.5 ($CO_2{}^tBu$).

The mixture of (1*RS*,2*SR*,3*SR*)-**21** and (1*SR*,2*SR*,3*SR*)-**23** (300 mg, 0.66 mmol) was re-dissolved in *tert*-butanol and epimerised under thermodynamic conditions (7 d, rt) in accordance with *general procedure 6*. Purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane) gave (1*SR*,2*SR*,3*SR*)-**23** (296 mg, quantitative) as a white crystalline solid; mp 86–88 °C; ν_{max} (KBr) 3058s, 3025s, 3004s, 2930s, 2866s, 2807s, 1715s, 1602m, 1494s, 1453s, 1362s, 1251m, 1151s, 967m, 877m, 747s, 697s; δ_H (400 MHz, $CDCl_3$) 1.36 (1H, m, C(4)H_A), 1.51 (1H, s, OC(CH_3)$_3$), 1.59 (1H, m, C(4)H_B), 1.80–1.84 (2H, m, C(5)H_2), 2.15–2.22 (2H, m, C(3)CH_AH_BPh and C(3)H), 2.96 (1H, m, C(1)H), 3.13 (1H, dd, J 13.6, 4.2, C(3)CH_AH_BPh), 3.26 (1H, dd, J 8.4, 7.2, C(2)H), 3.59 and 3.85 (2 × 2H, AB system, J_{AB} 13.7, N(CH_2Ph)$_2$), 7.04–7.44 (15H, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.6 (OC(CH_3)$_3$), 29.4 (*C*(5)), 29.9 (*C*(4)), 40.4 (C(3)CH_2Ph), 44.3 (*C*(1)), 45.7 (*C*(3)), 55.5 (N(CH_2Ph)$_2$), 70.2 (*C*(2)), 80.5 (O*C*(CH_3)$_3$), 126.1 and 127.3 (*p*-Ph), 128.6, 129.4, 140.6 and 142.3 (*o*-, *m*-Ph), 140.6 and 142.3 (*ipso*-Ph), 176.9 ($CO_2{}^t$Bu); *m*/*z* (ESI$^+$) 456 (MH^+, 100), 400 (MH^+-C_4H_8, 15%); HRMS, found 456.2901; $C_{31}H_{38}NO_2$ (MH^+) requires 456.2903.

Preparation of (*RS*), (*R*)- and (*S*)-*N*-benzyl-*N*-α-methylbenzylamine

Benzaldehyde (90.0 g, 0.85 mmol) was added to a stirred solution of (*RS*)-α-methylbenzylamine (100 g, 0.83 mol) in EtOH (400 ml) and heated at reflux for 3 h. Following cooling to 0 °C $NaBH_4$ (31.4 g, 0.83 mol) was added portionwise. The reaction mixture was warmed to rt whereat it was stirred for 3 d. The solvent was removed *in vacuo* and the residue partitioned between H_2O (100 ml) and DCM (150 ml). The aqueous phase was separated and extracted with DCM (3 × 100 ml) and the combined organic layers dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude amine as a colourless oil. The crude material was dissolved in Et_2O (1000 ml) and the solution treated with HCl (g). The collected white precipitate was recrystallised from DCM : *n*-pentane, furnishing the purified hydrochloride salt (192 g, 93%) which could be stored indefinitely. The free amine was regenerated by treatment with 1 M NaOH solution and extracted with DCM (3 × 100 ml) to give (*RS*)-*N*-benzyl-*N*-α-methylbenzylamine as a colourless oil as required; δ_H (200 MHz, $CDCl_3$) 1.44 (3H, d, J 6.6, C(α)*Me*), 1.86 (1H, br s, N*H*), 3.68 and 3.72 (2 × 1H, AB system, J_{AB} 13.2, NCH_2Ph), 3.90 (1H, q, J 6.6, C(α)*H*), 7.29–7.47 (10H, m, *Ph*). The (*R*)-enantiomer (184 g, 89%) {$[\alpha]_D^{24}$ +52.9 (c 1.0, $CHCl_3$)}, and (*S*)-enantiomer (186 g, 90%) {$[\alpha]_D^{23}$ −53.1 (c 1.0, $CHCl_3$), lit.[31] −53.6 (c 3.8, $CHCl_3$)}, were prepared on an identical scale and in an analogous fashion.

Preparation of *tert*-butyl (1*RS*,2*SR*,3*RS*,α*SR*)-3-ethyl-2-(*N*-benzyl-*N*-α-methylbenzylamino)-cyclopentane-1-carboxylate 24

Following *general procedure 4*, *n*-BuLi (1.6 M, 1.88 ml, 3.00 mmol), (*RS*)-*N*-benzyl-*N*-α-methylbenzylamine (636 mg, 3.00 mmol) in THF (20 ml) and (*RS*)-**11** (196 mg, 1.00 mmol) in THF (2 ml) gave, after quenching with 2,6-di-*tert*-butylphenol (660 mg, 3.20 mmol) in THF (5 ml), (1*RS*,2*SR*,3*RS*,α*SR*)-**24**, (1*SR*,2*SR*,3*RS*,α*SR*)-**27** and (1*SR*,2*RS*,3*SR*,α*SR*)-**30** in a 96.9 : 1.9 : 1.2 ratio. Purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane) gave (1*RS*,2*SR*,3*RS*,α*SR*)-**24** (279 mg, 71%) as a clear oil; elemental analysis, found C, 79.7; H, 8.8; N, 3.0%; $C_{27}H_{37}NO_2$ requires C, 79.6; H, 9.2; N, 3.4%; ν_{max} (film) 2965s, 1719s, 1493m, 1454m, 1366s, 1145s, 700s; δ_H (400 MHz, $CDCl_3$) 0.82 (3H, t, J 7.2, CH_2CH_3), 0.89–0.98 (1H, m, $CH_AH_BCH_3$), 1.00–1.09 (1H, m, C(4)H_A), 1.18 (3H, d, J 6.8, C(α)*Me*), 1.52 (9H, s, OC(CH_3)$_3$) overlays 1.50–1.54 (1H, m, C(5)H_A), 1.73 (1H, m, C(5)H_B), 1.86 (1H, m, $CH_AH_BCH_3$), 1.99 (1H, m, C(4)H_B), 2.07 (1H, m, C(3)*H*), 2.54 (1H, app td, J 7.2, 4.0, C(1)*H*), 2.92 (1H, dd, J 10.0, 7.6, C(2)*H*), 3.94 and 4.18 (2 × 1H, AB system, J_{AB} 15.6, NCH_2Ph) overlays 4.17 (1H, q, J 6.8, C(α)*H*), 7.20–7.49 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.5 (CH_2CH_3), 21.2 (C(α)*Me*), 27.2 (*C*(5)), 27.3 (CH_2CH_3), 27.8 (*C*(4)), 28.1 (OC(CH_3)$_3$), 41.8 (*C*(3)), 46.7 (*C*(1)), 51.0 (NCH_2Ph), 60.4 (*C*(α)H), 68.8 (*C*(2)), 78.0 (O*C*(CH_3)$_3$), 126.2 and 126.8 (*p*-Ph), 127.4, 127.7, 128.1 and 128.2 (*o*-, *m*-Ph), 143.6 and 145.4 (*ipso*-Ph), 176.1 ($CO_2{}^t$Bu); *m*/*z* (APCI$^+$) 408 (MH^+, 100), 352 (MH^+–C_4H_8, 10%); HRMS, found 408.2890; $C_{27}H_{38}NO_2$ (MH^+) requires 408.2903.

Preparation of *tert*-butyl (1*R*,2*S*,3*R*,α*S*)-3-ethyl-2-(*N*-benzyl-*N*-α-methylbenzylamino)-cyclopentane-1-carboxylate 24 via kinetic resolution

Following *general procedure 5*, *n*-BuLi (1.6 M, 0.56 ml, 0.9 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (191 mg, 0.9 mmol) in THF (20 ml) and (*RS*)-**11** (196 mg, 1.0 mmol) in THF (2 ml) gave, after quenching with 2,6-di-*tert*-butylphenol (409 mg, 1.98 mmol) in THF (5 ml), (1*R*,2*S*,3*R*,α*S*)-**24**, (1*S*,2*S*,3*R*,α*S*)-**27** and (1*S*,2*R*,3*S*,α*S*)-**30** in a 93.3 : 2.5 : 4.2 ratio. The amines were separated from the unused acceptor by dissolving the crude mixture in *n*-pentane (25 ml) and passing HCl (g) through the mixture. The *n*-pentane was decanted from the solid, neutralised ($NaHCO_3$) and concentrated *in vacuo* to give the crude acceptor, which was purified by flash chromatography on silica gel (2% Et_2O : *n*-pentane) furnishing (*S*)-**11** (71 mg, 36%) {$[\alpha]_D^{24}$ −68.3, (c 1.3, $CHCl_3$)}, with spectroscopic data identical to the racemate. The adducts (1*R*,2*S*,3*R*,α*S*)-**24**, (1*S*,2*S*,3*R*,α*S*)-**27** and (1*S*,2*R*,3*S*,α*S*)-**30** were neutralised (KOH) and purified by flash chromatography in the same manner as the racemate, to give the diastereoisomerically pure product (1*R*,2*S*,3*R*,α*S*)-**24** (130 mg, 32%) as a colourless oil; $[\alpha]_D^{23}$ −125.3 (c 1.1, $CHCl_3$), with spectroscopic data identical to the racemate.

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

Following *general procedure 6*, a solution of (1*R*,2*S*,3*R*,α*S*)-**24** (102 mg, 0.25 mmol) in ^{t}BuOH (10 ml) was treated with KO^{t}Bu and heated at reflux for 3 h. Purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane) gave (1*S*,2*S*,3*R*,α*S*)-**27** (100 mg, quantitative) in >98% de as a colourless oil; $[\alpha]_D^{25}$+21.2 (c 0.80, $CHCl_3$); ν_{max} (film) 2959s, 1720s, 1493m, 1454m, 1367m, 1154s, 700m; δ_H (400 MHz, $CDCl_3$) 0.83 (3H, t, J 7.4, CH_2CH_3), 1.16 (1H, m, $CH_AH_BCH_3$), 1.20 (1H, d, J 6.8, C(α)*Me*) overlays 1.21 (1H, m, C(4)H_A), 1.43 (9H, s, OC(CH_3)$_3$), 1.67–1.70 (4H, m, C(3)*H*, C(4)H_B and C(5)H_2), 1.73 (1H, m, $CH_AH_BCH_3$), 2.67 (1H, m, C(1)*H*), 3.27 (1H, dd, J 8.0, 5.5, C(2)*H*), 3.71 and 3.84 (2 × 1H, AB system, J_{AB} 15.8, NCH_2Ph) overlays 3.87 (1H, q, J 6.8, C(α)*H*), 7.20–7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.1 (CH_2CH_3), 22.6 (C(α)*Me*), 26.8 (*C*(5)), 28.6 (OC(CH_3)$_3$), 29.8 (CH_2CH_3), 31.0 (*C*(4)), 46.1 (*C*(3)), 47.0 (*C*(1)), 51.5 (NCH_2Ph), 62.2 (*C*(2)), 69.7 (*C*(α)H), 80.2 (O*C*(CH_3)$_3$), 126.8 and 127.1 (*p*-Ph), 127.9, 128.3, 128.5 and 128.6 (*o*-, *m*-Ph), 143.8 and 145.8 (*ipso*-Ph), 176.9 ($CO_2{}^t$Bu); *m*/*z* (APCI$^+$) 408 (MH^+, 100%); HRMS, found 408.2902; $C_{27}H_{38}NO_2$ (MH^+) requires 408.2903.

Preparation of *tert*-butyl (1*RS*,2*SR*,3*SR*,α*SR*)-3-benzyl-2-(*N*-benzyl-*N*-α-methylbenzylamino)-cyclopentane-1-carboxylate 25

Following *general procedure 4*, *n*-BuLi (1.6 M, 1.88 ml, 3.00 mmol), (*RS*)-*N*-benzyl-*N*-α-methylbenzylamine (636 mg, 3.00 mmol) in THF (20 ml) and (*RS*)-**12** (258 mg, 1.00 mmol) in THF (2 ml) gave, after quenching with 2,6-di-*tert*-butylphenol (660 mg, 3.20 mmol) in THF (5 ml), (1*RS*,2*SR*,3*SR*,α*SR*)-**25**, (1*SR*,2*SR*,3*SR*,α*SR*)-**28** and (1*SR*,2*RS*,3*RS*,α*SR*)-**31** in a 97.6 : 1.8 : 0.6 ratio. Purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane) gave (1*RS*,2*SR*,3*SR*,α*SR*)-**25** (347 mg, 74%) as a clear oil; ν_{max} (film) 3061w, 3026m, 2973s, 2870w, 1718s, 1602w, 1494m, 1453m, 1366s, 1146s, 700s; δ_H (400 MHz, $CDCl_3$) 1.10 (1H, m, C(4)H_A), 1.27 (3H, d, J 6.8, C(α)*Me*), 1.57 (9H, s, OC(CH_3)$_3$) overlays 1.58 (1H, m, C(5)H_A), 1.71–1.84 (2H, m, C(4)H_B and C(5)H_B), 2.06 (1H, dd, J 13.2, 11.2, C(3)CH_AH_BPh), 2.47 (1H, m, C(3)*H*), 2.64 (1H, m, C(1)*H*), 3.10 (1H, dd, J 10.3, 7.9, C(2)*H*), 3.33 (1H, dd, J 13.2, 3.0, C(3)CH_AH_BPh), 4.08 and 4.33 (2 × 1H, AB system, J_{AB} 16.0, NCH_2Ph) overlays 4.30 (1H, q, J 6.8, C(α)*H*), 6.98–7.63 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.0 (C(α)*Me*), 27.7 (*C*(4) and *C*(5)), 28.6 (OC(CH_3)$_3$), 41.4 (C(3)CH_2Ph), 43.0 (*C*(3)), 46.9 (*C*(1)), 51.5 (NCH_2Ph), 61.2 (*C*(α)H), 69.7 (*C*(2)), 80.6 (O*C*(CH_3)$_3$), 126.1, 126.8 and 127.4 (*p*-Ph), 127.9, 128.2, 128.6, 128.8, 128.9 and 129.2 (*o*-, *m*-Ph), 142.4, 144.0 and 145.9 (*ipso*-Ph), 176.3 ($CO_2{}^tBu$); *m*/*z* (APCI$^+$) 470 (MH$^+$, 100%); HRMS, found 470.3056; $C_{32}H_{40}NO_2$ (MH$^+$) requires 470.3059.

Preparation of *tert*-butyl (1*R*,2*S*,3*S*,α*S*)-3-benzyl-2-(*N*-benzyl-*N*-α-methylbenzylamino)-cyclopentane-1-carboxylate 25 via kinetic resolution

Following *general procedure 5*, *n*-BuLi (1.6 M, 0.38 ml, 0.60 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (127 mg, 0.60 mmol) in THF (20 ml) and (*RS*)-**12** (258 mg, 1.00 mmol) in THF (2 ml) gave, after quenching with 2,6-di-*tert*-butylphenol (272 mg, 1.32 mmol) in THF (5 ml), (1*R*,2*S*,3*S*,α*S*)-**25**, (1*S*,2*S*,3*S*,α*S*)-**28** and (1*S*,2*R*,3*R*,α*S*)-**31** in a 96.9 : 1.4 : 1.7 ratio. The amines were separated from the unused acceptor by dissolving the crude mixture in *n*-pentane (25 ml) and passing HCl (g) through the mixture. The *n*-pentane was decanted from the solid, neutralised ($NaHCO_3$) and concentrated *in vacuo* to give the crude acceptor, which was purified by flash chromatography on silica gel (2% Et_2O : *n*-pentane) furnishing (*R*)-**12** (101 mg, 39%) {$[\alpha]_D^{24}$ −74.2 (c 0.90, $CHCl_3$)}, with spectroscopic data identical to the racemate. The adducts (1*R*,2*S*,3*S*,α*S*)-**25**, (1*S*,2*S*,3*S*,α*S*)-**28** and (1*S*,2*R*,3*R*,α*S*)-**31** were neutralised (KOH) and purified by flash chromatography in the same manner as the racemate, to give the diastereoisomerically pure product (1*R*,2*S*,3*S*,α*S*)-**25** (192 mg, 41%) as a white crystalline solid; mp 86–88 °C; $[\alpha]_D^{23}$ −45.1 (c 1.0, $CHCl_3$); elemental analysis, found C, 81.6; H, 8.4; N, 3.0%; $C_{32}H_{39}NO_2$ requires C, 81.8; H, 8.4; N, 3.0%, with spectroscopic data identical to the racemate.

Preparation of *tert*-butyl (1*S*,2*S*,3*S*,α*S*)-3-benzyl-2-(*N*-benzyl-*N*-α-methylbenzylamino)-cyclopentane-1-carboxylate 28 via epimerisation

Following *general procedure 6*, a solution of (1*R*,2*S*,3*S*,α*S*)-**25** (117 mg, 0.25 mmol) in ^{t}BuOH (10 ml) and THF (10 ml) was treated with KO^{t}Bu and stirred at rt for 7 d. Purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane) gave (1*S*,2*S*,3*S*,α*S*)-**28** (116 mg, quantitative) in >98% de as a colourless oil; $[\alpha]_D^{25}$ +21.2 (c 0.80, $CHCl_3$); ν_{max} (film) 3041s, 3019s, 2929s, 2874s, 1717s, 1602w, 1491s, 1451s, 1359s, 1248m, 1149s, 738m, 699s; δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.4, C(α)*Me*) overlays 1.34 (1H, m, C(4)H_A), 1.48 (9H, s, OC(CH_3)$_3$), 1.57 (1H, m, C(4)H_B), 1.71–1.82 (2H, m, C(5)H_2), 2.14–2.21 (2H, m, C(3)CH_AH$_B$Ph and C(3)*H*), 2.94 (1H, m, C(1)*H*), 3.27 (1H, dd, *J* 13.6, 3.6, C(3)CH$_A$$H_B$Ph), 3.42 (1H, dd, *J* 8.4, 6.0, C(2)*H*), 3.83 and 3.91 (2 × 1H, AB system, J_{AB} 16.0, NCH_2Ph), 3.96 (1H, q, *J* 6.4, C(α)*H*), 7.02–7.43 (15H, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.8 (C(α)*Me*), 29.2 and 29.5 (*C*(4) and *C*(5)), 28.6 (OC(CH_3)$_3$), 40.5 (C(3)*C*H$_2$Ph), 44.5 (*C*(1)), 45.9 (*C*(3)), 53.3 (N*C*H$_2$Ph), 57.1 (*C*(α)H), 70.3 (*C*(2)), 80.6 (O*C*(CH$_3$)$_3$), 126.2, 126.3 and 127.3 (*p*-Ph), 127.8, 128.1, 128.5, 128.7, 128.9 and 129.3 (*o*-, *m*-Ph), 141.3, 144.2 and 144.9 (*ipso*-Ph), 175.6 ($CO_2{}^tBu$); *m*/*z* (APCI$^+$) 470 (MH$^+$, 100), 414 (MH$^+$–C_4H_8, 55%); HRMS, found 470.3048; $C_{32}H_{40}NO_2$ (MH$^+$) requires 470.3059.

Preparation of *tert*-butyl (1*RS*,2*SR*,3*SR*,α*SR*)-3-(1′-methylethyl)-2-(*N*-benzyl-*N*-α-methylbenzylamino)-cyclopentane-1-carboxylate 26

Following *general procedure 4*, *n*-BuLi (1.5 M, 0.96 ml, 1.44 mmol), (*RS*)-*N*-benzyl-*N*-α-methylbenzylamine (305 mg, 1.44 mmol) in THF (20 ml) and (*RS*)-**17** (100 mg, 0.48 mmol) in THF (2 ml) gave, after quenching with 2,6-di-*tert*-butylphenol (317 mg, 1.54 mmol) in THF (5 ml), (1*RS*,2*SR*,3*SR*,α*SR*)-**26**, (1*SR*,2*SR*,3*SR*,α*SR*)-**29** and (1*SR*,2*RS*,3*RS*,α*SR*)-**32** in a 94.1 : 5.2 : 0.7 ratio. Purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane) gave (1*RS*,2*SR*,3*SR*,α*SR*)-**26** (145 mg, 72%) as a clear oil; ν_{max} (film) 2961s, 1711s, 1603w, 1494m, 1454m, 1366m, 1261s, 1135s, 761m, 702s; δ_H (400 MHz, $CDCl_3$) 0.53 (3H, d, *J* 7.2, CH(CH_{3A}CH$_{3B}$)), 0.83 (3H, d, *J* 7.2, CH(CH$_{3A}$CH_{3B})), 1.16 (3H, d, *J* 6.8, C(α)*Me*) overlays 1.17 (1H, m, C(4)H_A), 1.39–1.44 (1H, m, C(5)H_A), 1.55 (9H, s, OC(CH_3)$_3$), 1.68–1.80 (2H, m, C(4)H_B and C(5)H_B), 2.03 (1H, app septet of doublets, *J* 7.2, 3.2, C*H*(CH$_3$)$_2$), 2.16 (1H, m, C(3)*H*), 2.63 (1H, app td, *J* 7.2, 3.6, C(1)*H*), 3.09 (1H, dd, *J* 10.8, 7.2, C(2)*H*), 3.92 and 4.24 (2 × 1H, AB system, J_{AB} 16.4, NCH_2Ph) overlays 4.23 (1H, q, *J* 6.8, C(α)*H*), 7.21–7.49 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.1 (CH(*C*H$_{3A}$CH$_{3B}$)), 21.3 (*C*(5)), 22.3 (CH(CH$_{3A}$*C*H$_{3B}$)), 22.7 (C(α)*Me*), 26.9 (*C*H(CH$_3$)$_2$), 28.0 (*C*(4)), 28.1 (OC(*C*H$_3$)$_3$), 45.8 (*C*(3)), 46.6 (*C*(1)), 50.8 (N*C*H$_2$Ph), 61.6 (*C*(2)), 66.2 (*C*(α)H), 80.0 (O*C*(CH$_3$)$_3$), 126.0 and 126.2 (*p*-Ph), 127.3, 127.6, 128.0 and 128.2 (*o*, *m*-Ph), 144.2 and 145.7 (*ipso*-Ph), 176.0 ($CO_2{}^tBu$); *m*/*z* (APCI$^+$) 422 (MH$^+$, 100), 366 (MH$^+$–C_4H_8, 60%); HRMS, found 422.3049; $C_{28}H_{40}NO_2$ (MH$^+$) requires 422.3059.

Preparation of *tert*-butyl (1*R*,2*S*,3*S*,α*S*)-3-(1′-methylethyl)-2-(*N*-benzyl-*N*-α-methylbenzylamino)-cyclopentane-1-carboxylate 26 via kinetic resolution

Following *general procedure 5*, *n*-BuLi (1.6 M, 1.76 ml, 2.8 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (592 mg, 2.8 mmol) in THF (50 ml) and (*RS*)-**17** (832 mg, 4.0 mmol) in THF (6 ml) gave, after quenching with 2,6-di-*tert*-butylphenol (1.27 g, 6.16 mmol) in THF (10 ml), (1*R*,2*S*,3*S*,α*S*)-**26**, (1*S*,2*S*,3*S*,α*S*)-**29** and (1*S*,2*R*,3*R*,α*S*)-**32** in a 93.8 : 4.7 : 1.5 ratio. The amines were separated from the unused acceptor by dissolving the crude mixture in *n*-pentane (50 ml) and passing HCl (g) through the mixture. The *n*-pentane was decanted from the solid, neutralised ($NaHCO_3$) and concentrated *in vacuo* to give the crude acceptor, which was purified by flash chromatography on silica gel (2% Et_2O : *n*-pentane) furnishing (*R*)-**17** (356 mg, 43%) {$[\alpha]_D^{24}$ −48.3 (c 0.80, $CHCl_3$)}, with spectroscopic data identical to the racemate. The adducts (1*R*,2*S*,3*S*,α*S*)-**26**, (1*S*,2*S*,3*S*,α*S*)-**29** and (1*S*,2*R*,3*R*,α*S*)-**32** were neutralised (KOH) and purified by repeated flash chromatography and fractional crystallisation to give the diastereoisomerically pure products: (1*R*,2*S*,3*S*,α*S*)-**26** (588 mg, 35%) as a white crystalline solid; mp 71–73 °C; $[\alpha]_D^{23}$ −89.5 (c 0.49, $CHCl_3$); elemental analysis, found C, 80.1; H, 9.3; N, 2.9%; $C_{28}H_{39}NO_2$ requires C, 79.8; H, 9.3; N, 3.3%, with spectroscopic data identical to the racemate; (1*S*,2*S*,3*S*,α*S*)-**29** (43 mg, 2.6%) as a colourless oil; $[\alpha]_D^{23}$ +19.2 (c 0.26, $CHCl_3$); ν_{max} (film) 2956s, 1721s, 1602w, 1494w, 1453m, 1367s, 1146s, 700s; δ_H (400 MHz, $CDCl_3$) 0.57 (3H, d, *J* 6.8, CH(CH_{3A}CH$_{3B}$)), 0.94 (3H, d, *J* 6.8, CH(CH$_{3A}$CH_{3B})), 1.19 (3H, d, *J* 6.8, C(α)*Me*), 1.33 (1H, m, C(4)H_A), 1.45 (9H, s, OC(CH_3)$_3$) overlays 1.46 (1H, m, C(5)H_A), 1.68–1.76 (3H, m, C(3)*H*, C(4)H_B and C(5)H_B), 2.06 (1H, septet of doublets, *J* 6.7, 4.3, C*H*(CH$_3$)$_2$), 2.69 (1H, app td, *J* 8.2, 4.1, C(1)*H*), 3.43 (1H, dd, *J* 9.1, 4.7, C(2)*H*), 3.72 and 3.89 (2 × 1H, AB system, J_{AB} 16.0, NCH_2Ph) overlays 3.88 (1H, q, *J* 6.8, C(α)*H*), 7.21–7.49 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.4 (CH(*C*H$_{3A}$CH$_{3B}$)), 22.8 (CH(CH$_{3A}$*C*H$_{3B}$)), 23.0 (C(α)*Me*), 23.8 (*C*(5)), 27.6 (*C*H(CH$_3$)$_2$), 28.1 (OC(*C*H$_3$)$_3$), 30.9 (*C*(4)), 45.2 (*C*(3)), 51.0 (*C*(1) and N*C*H$_2$Ph), 62.6 (*C*(2)), 66.4 (*C*(α)H), 79.7 (O*C*(CH$_3$)$_3$), 126.2 and 126.6 (*p*-Ph), 127.3, 127.8, 127.9 and 128.1 (*o*-, *m*-Ph), 143.7 and 145.4 (*ipso*-Ph), 176.4 ($CO_2{}^tBu$); *m*/*z* (APCI$^+$) 422 (MH$^+$, 100%); HRMS, found 422.3068; $C_{28}H_{40}NO_2$ (MH$^+$) requires 422.3059; (1*S*,2*R*,3*R*,α*S*)-**32** (6 mg, 0.4%) as a crystalline solid, with full spectroscopic data for the enantiomer, (1*R*,2*S*,3*S*,α*R*)-**32**, recorded below.

Preparation of *tert*-butyl (1*S*,2*S*,3*S*,α*S*)-3-(1′-methylethyl)-2-(*N*-benzyl-*N*-α-methylbenzylamino)-cyclopentane-1-carboxylate 29 via epimerisation

Following *general procedure 6*, a solution of (1*R*,2*S*,3*S*,α*S*)-**26** (105 mg, 0.25 mmol) in ^{t}BuOH (10 ml) was treated with KO^{t}Bu and heated at reflux for 3 h. Purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane) gave (1*S*,2*S*,3*S*,α*S*)-**29** (103 mg, quantitative) in >98% de as a colourless oil, with spectroscopic data identical to that recorded above.

Preparation of *tert*-butyl (1*SR*,2*SR*,3*SR*,α*SR*)-3-(1′,1′-dimethylethyl)-2-(*N*-benzyl-*N*-α-methylbenzylamino)-cyclopentane-1-carboxylate 34

Following *general procedure 4*, *n*-BuLi (2.5 M, 1.20 ml, 3.0 mmol), (*RS*)-*N*-benzyl-*N*-α-methylbenzylamine (636 mg, 3.0 mmol) in THF (20 ml) and (*RS*)-**19** (224 mg, 1.0 mmol) in THF (2 ml) gave, after quenching with 2,6-di-*tert*-butylphenol (317 mg, 1.54 mmol) in THF (5 ml), (1*RS*,2*SR*,3*SR*,α*SR*)-**33** and (1*SR*,2*SR*,3*SR*,α*SR*)-**34** in a 23.1 : 76.9 ratio. Purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane) gave the diastereoisomeric products (1*RS*,2*SR*,3*SR*,α*SR*)-**33** and (1*SR*,2*SR*,3*SR*,α*SR*)-**34** as an inseparable mixture (287 mg, 66%); selected NMR data for (1*RS*,2*SR*,3*SR*,α*SR*)-**33** (assigned from the diastereoisomeric mixture): δ_H (400 MHz, $CDCl_3$) 0.66 (2.1H, s, C(3)C(CH_3)$_3$), 1.15 (0.69H, d, *J* 6.8, C(α)*Me*), 1.61 (2.1H, s, OC(CH_3)$_3$), 2.47 (0.23H, m, C(1)*H*), 3.42 (0.23H, dd, *J* 10.1, 7.4, C(2)*H*), 4.20 and 4.31 (2 × 0.23H, AB system, J_{AB} 15.1, NCH_2Ph) overlays 4.17 (1H, q, *J* 6.8, C(α)*H*); δ_C (100 MHz, $CDCl_3$) 21.8 (C(α)*Me*), 26.2 (*C*(5)), 27.4 (C(3)C(CH_3)$_3$), 27.7 (OC(CH_3)$_3$), 30.6 (*C*(4)), 33.4 (C(3)*C*(CH_3)$_3$), 46.5 (*C*(3)), 50.3 (NCH_2Ph), 52.8 (*C*(1)), 61.9 (*C*(2)), 65.5 (*C*(α)H), 80.3 (O(CH_3)$_3$), 145.2 and 146.0 (*ipso*-Ph), 175.6 ($CO_2{}^t$Bu).

The mixture of (1*RS*,2*SR*,3*SR*,α*SR*)-**33** and (1*SR*,2*SR*,3*SR*,α*SR*)-**34** (250 mg, 0.57 mmol) was re-dissolved in *tert*-butanol and epimerised under thermodynamic conditions in accordance with *general procedure 6*. Purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane) gave (1*SR*,2*SR*,3*SR*,α*SR*)-**34** (246 mg, quantitative) in >98% de as a white crystalline solid; mp 103–105 °C; elemental analysis, found C, 79.9; H, 9.5; N, 3.2%; $C_{29}H_{41}NO_2$ requires C, 80.0; H, 9.5; N, 3.2%; ν_{max} (KBr) 3025w, 2968s, 2877m, 2798w, 1721s, 1600w, 1494m, 1452s, 1366s, 1148s, 849m, 742s, 707s; δ_H (400 MHz, $CDCl_3$) 0.87 (9H, s, C(3)C(CH_3)$_3$), 1.33 (3H, d, *J* 7.0, C(α)*Me*) overlays 1.36 (1H, m, C(4)H_A), 1.46 (9H, s, OC(CH_3)$_3$), 1.59 (1H, m, C(5)H_A), 1.70–1.84 (3H, m, C(3)*H*, C(4)H_B and C(5)H_B), 2.59 (1H, m, C(1)*H*), 3.59 and 3.99 (2 × 1H, AB system, J_{AB} 15.7, NCH_2Ph), 3.73 (1H, dd, *J* 6.9, 2.9, C(2)*H*), 3.83 (1H, q, *J* 7.0, C(α)*H*), 7.21–7.53 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.5 (C(α)*Me*), 27.3 (*C*(5)), 28.0 (C(3)C(CH_3)$_3$), 28.5 (OC(CH_3)$_3$), 31.2 (*C*(4)), 32.8 (C(3)*C*(CH_3)$_3$), 46.5 (*C*(3)), 50.8 (NCH_2Ph), 54.8 (*C*(1)), 61.6 (*C*(2)), 63.9 (*C*(α)H), 79.9 (O*C*(CH_3)$_3$), 126.5 and 127.0 (*p*-Ph), 127.9, 128.1, 128.4 and 128.7 (*o*-, *m*-Ph), 143.2 and 14.0 (*ipso*-Ph), 176.2 ($CO_2{}^t$Bu); *m*/*z* (APCI$^+$) 436 (MH$^+$, 100), 380 (MH$^+$–C_4H_8, 15%); HRMS, found 436.3219; $C_{29}H_{42}NO_2$ (MH$^+$) requires 436.3216.

Preparation of *tert*-butyl (1*S*,2*S*,3*S*,α*S*)-3-(1′,1′-dimethylethyl)-2-(*N*-benzyl-*N*-α-methylbenzylamino)-cyclopentane-1-carboxylate 34 via kinetic resolution and subsequent epimerisation

Following *general procedure 5*, *n*-BuLi (1.6 M, 0.44 ml, 0.70 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (148 mg, 0.70 mmol) in THF (20 ml) and (*RS*)-**19** (224 mg, 1.00 mmol) in THF (2 ml) gave, after quenching with 2,6-di-*tert*-butylphenol (318 mg, 1.54 mmol) in THF (5 ml), (1*R*,2*S*,3*S*,α*S*)-**33**, (1*S*,2*S*,3*S*,α*S*)-**34** and an unassigned mixture of (1*S*,2*R*,3*R*,α*S*) : (1*R*,2*R*,3*R*,α*S*)-**35** in a 31.9 : 66.9 : 1.2 (**33** : **34** : **35**) ratio. The amines were separated from the unused acceptor by dissolving the crude mixture in *n*-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 acceptor, which was purified by flash chromatography on silica gel (2% Et_2O : *n*-pentane) furnishing (*R*)-**19** (90 mg, 40%) {$[\alpha]_D^{24}$ −32.9 (c 0.45, $CHCl_3$)}, with spectroscopic data identical to the racemate. The adducts (1*R*,2*S*,3*S*,α*S*)-**33**, (1*S*,2*S*,3*S*,α*S*)-**34** and (1*S*,2*R*,3*R*,α*S*) : (1*R*,2*R*,3*R*,α*S*)-**35** were neutralised (KOH) and purified by flash chromatography in the same manner as the racemate, to give (1*R*,2*S*,3*S*,α*S*)-**33** and (1*S*,2*S*,3*S*,α*S*)-**34** as a 32.2 : 67.8 mixture (161 mg, 37%). The mixture of (1*R*,2*S*,3*S*)-**33** and (1*S*,2*S*,3*S*)-**34** (150 mg, 0.34 mmol) was re-dissolved in *tert*-butanol and epimerised under thermodynamic conditions in accordance with *general procedure 6*. Purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane) gave (1*S*,2*S*,3*S*)-**34** (147 mg, quantitative) as a white crystalline solid; mp 104–106 °C; $[\alpha]_D^{25}$ +18.1 (c 1.3, $CHCl_3$), with spectroscopic data identical to the racemate.

Preparation of (1*R*,2*S*,3*R*)-3-ethyl-2-aminocyclopentane-1-carboxylic acid 44

Following *general procedure 7*, $Pd(OH)_2$ on C (40 mg) was added to a stirred degassed solution of (1*R*,2*S*,3*R*,α*S*)-**24** (204 mg, 0.50 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. Although this material was used without purification, flash chromatography on silica gel (Et_2O) gave an analytical sample of *tert*-butyl (1*R*,2*S*,3*R*)-3-ethyl-2-aminocyclopentane-1-carboxylate (73 mg, 69%) as a colourless oil; $[\alpha]_D^{22}$ −44.7 (c 1.0, $CHCl_3$); ν_{max} (film) 3390br w, 2961s, 1722s, 1613w, 1462w, 1367m, 1153s; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.3, CH_2CH_3), 1.12–1.22 (2H, m, $CH_AH_BCH_3$ and C(4)H_A), 1.47 (9H, s, OC(CH_3)$_3$), 1.57–1.63 (2H, m, C(3)*H* and C(4)H_B), 1.88 (2H, br s, NH_2) overlays 1.82–2.02 (3H, m, $CH_AH_BCH_3$ and C(5)H_2), 2.80 (1H, app q, *J* 7.8, C(1)*H*), 3.07 (1H, m, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 12.6 (CH_2CH_3), 25.9 (*C*(5)), 27.0 (*C*(4)), 28.2 (OC(CH_3)$_3$), 29.3 (CH_2CH_3), 49.4 (*C*(3)), 50.3 (*C*(1)), 60.0 (*C*(2)), 80.2 (O*C*(CH_3)$_3$), 173.9 ($CO_2{}^t$Bu); *m*/*z* (APCI$^+$) 214 (MH$^+$, 15), 158 (MH$^+$–C_4H_8, 100%); HRMS, found 214.1808; $C_{12}H_{24}NO_2$ (MH$^+$) requires 214.1807.

Following *general procedure 8*, TFA (5 ml) was added to a solution of crude *tert*-butyl (1*R*,2*S*,3*R*)-3-ethyl-2-aminocyclopentane-1-carboxylate (100 mg, 0.47 mmol) at rt and stirred for 16 h. Purification using Dowex® 50X8-200 resin gave (1*R*,2*S*,3*R*)-**44** (51 mg, 69% from **24**) as a white solid; mp 202–204 °C (decomposes); $[\alpha]_D^{24}$ −32.3 (c 1.1, H_2O); elemental analysis, found C, 61.2; H, 9.6; N, 8.6%; $C_8H_{15}NO_2$ requires C, 61.1; H, 9.6; N, 8.9%; ν_{max} (KBr) 3677–2360br s, 2956s, 2188m, 1644m, 1611m, 1566s, 1519s, 1414s, 1329m, 1308m, 1174m, 1132m, 845w, 745w; δ_H (400 MHz, D_2O) 0.76 (3H, t, *J* 7.4, CH_2CH_3), 1.11–1.22 (2H, m, $CH_AH_BCH_3$ and C(4)H_A), 1.38–1.44 (1H, m, $CH_AH_BCH_3$), 1.64–1.69 (1H, m, C(5)H_A), 1.81–1.96 (3H, m, C(3)*H*, C(4)H_B and C(5)H_B), 2.76 (1H, m, C(1)*H*), 3.23 (1H, dd, *J* 6.6, 5.0, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 11.7 (CH_2CH_3), 26.8 (CH_2CH_3), 28.1 (*C*(5)), 28.5 (*C*(4)), 45.3 (*C*(3)), 47.3 (*C*(1)), 57.5 (*C*(2)), 181.1 (CO_2H); *m*/*z* (APCI$^+$) 158 (MH$^+$, 80), 140 (MH$^+$–NH_3, 100%); HRMS, found 158.1180; $C_8H_{16}NO_2$ (MH$^+$) requires 158.1181.

Preparation of (1*S*,2*S*,3*R*)-3-ethyl-2-aminocyclopentane-1-carboxylic acid hydrochloride 47

Following *general procedure 7*, $Pd(OH)_2$ on C (25 mg) was added to a stirred degassed solution of (1*S*,2*S*,3*R*,α*S*)-**27** (110 mg, 0.27 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 gel (Et_2O), giving *tert*-butyl (1*S*,2*S*,3*R*)-3-ethyl-2-aminocyclopentane-1-carboxylate as a colourless oil (26 mg); $[\alpha]_D^{22}$ +36.1 (c 0.50, $CHCl_3$); ν_{max} (film) 3387br w, 2957s, 1726s, 1459w, 1366m, 1154s; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.4, CH_2CH_3), 1.11–1.21 (1H, m, $CH_AH_BCH_3$), 1.23–1.31 (1H, m, C(5)H_A), 1.45 (9H, s, OC(CH_3)$_3$) overlays 1.42–1.47 (1H, m, C(3)*H*), 1.69 (2H, br s, NH_2) overlays 1.63–1.71 (1H, m, $CH_AH_BCH_3$), 1.77–1.91 (3H, m, C(4)H_2 and C(5)H_B), 2.37 (1H, app q, *J* 8.8, C(1)*H*), 2.85 (1H, br t, *J* 8.8, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 12.4 (CH_2CH_3), 25.5 (CH_2CH_3), 26.1 (*C*(4)), 28.1 (OC(CH_3)$_3$), 28.5 (*C*(5)), 49.7 (*C*(3)), 54.3 (*C*(1)), 61.8 (*C*(2)), 80.2 (O*C*(CH_3)$_3$), 174.8 ($CO_2{}^t$Bu); *m*/*z* (ESI$^+$) 214 (MH$^+$, 100), 158 (MH$^+$–C_4H_8, 70%); HRMS, found 214.1806; $C_{12}H_{24}NO_2$ (MH$^+$) requires 214.1807.

TFA (5 ml) was added to a solution of crude *tert*-butyl (1*S*,2*S*,3*R*)-3-ethyl-2-aminocyclopentane-1-carboxylate (60 mg, 0.28 mmol) at rt and stirred for 16 h, in accordance with *general procedure 9*, furnishing (1*S*,2*S*,3*R*)-**47** (31 mg, 73% from **27**) as a clear glass; $[\alpha]_D^{25}$ +10.9 (c 1.0, H_2O); ν_{max} (film) 3411br s, 3321–2386br s, 2963s, 1716s, 1615m, 1516m, 1463w, 1412w, 1211s; δ_H (400 MHz, D_2O) 0.78 (3H, t, *J* 7.5, CH_2CH_3), 1.17 (1H, m, $CH_AH_BCH_3$), 1.32 (1H, m, C(4)H_A), 1.53 (1H, m, $CH_AH_BCH_3$), 1.74–1.93 (3H, m, C(3)*H*, C(4)H_B and C(5)H_A), 1.97–2.06 (1H, m, C(5)H_B), 2.86 (1H, app td, *J* 9.5, 7.8, C(1)*H*), 3.38 (1H, app t, *J* 8.1, C(2)*H*); δ_C (100 MHz, D_2O) 11.5 (CH_2CH_3), 25.2 (CH_2CH_3), 27.0 (*C*(5)), 28.5 (*C*(4)), 45.9 (*C*(3)), 48.4 (*C*(1)), 58.7 (*C*(2)), 177.4 (CO_2H); *m*/*z* (ESI$^+$) 158 (MH^+, 100), 140 (MH^+–NH_3, 20%); HRMS, found 158.1182; $C_8H_{16}NO_2$ (MH^+) requires 158.1181.

Preparation of (1*R*,2*S*,3*S*)-3-benzyl-2-aminocyclopentane-1-carboxylic acid 45

Following *general procedure 7*, $Pd(OH)_2$ on C (50 mg) was added to a stirred degassed solution of (1*R*,2*S*,3*S*,α*S*)-**25** (235 mg, 0.50 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. Although this material was used without purification, flash chromatography on silica gel (Et_2O) gave an analytical sample of *tert*-butyl (1*R*,2*S*,3*S*)-3-benzyl-2-aminocyclopentane-1-carboxylate (99 mg, 72%) as a colourless oil; $[\alpha]_D^{22}$ −32.5 (c 1.0, $CHCl_3$); elemental analysis, found C, 73.8; H, 8.7; N, 5.1%; $C_{17}H_{25}NO_2$ requires C, 74.1; H, 9.2; N, 5.1%; ν_{max} (film) 3389br w, 2973m, 1720s, 1603w, 1495w, 1453w, 1391w, 1366m, 1150s, 745w, 700m; δ_H (400 MHz, $CDCl_3$) 1.22 (1H, m, C(4)H_A), 1.39 (2H, br s, NH_2), 1.47 (9H, s, OC(CH_3)$_3$), 1.81–1.88 (3H, m, C(4)H_B and C(5)H_2), 2.04 (1H, m, C(3)*H*), 2.47 (1H, dd, *J* 13.5, 8.9, CH_AH_BPh), 2.83–2.90 (2H, m, C(1)*H* and CH_AH_BPh), 3.12 (1H, br t, *J* 7.4, C(2)*H*), 7.17–7.30 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.0 (*C*(5)), 28.2 (OC(CH_3)$_3$), 29.6 (*C*(4)), 40.2 (CH_2Ph), 49.2 (*C*(3)), 50.0 (*C*(1)), 59.8 (*C*(2)), 80.4 (O*C*(CH_3)$_3$), 125.8 (*p*-Ph), 128.3 and 128.9 (*o*-, *m*-Ph), 141.0 (*ipso*-Ph), 173.9 ($CO_2{}^tBu$); *m*/*z* (APCI$^+$) 276 (MH^+, 100%); HRMS, found 276.1954; $C_{17}H_{26}NO_2$ (MH^+) requires 276.1964.

Following *general procedure 8*, TFA (5 ml) was added to a solution of crude *tert*-butyl (1*R*,2*S*,3*S*)-3-benzyl-2-aminocyclopentane-1-carboxylate (80 mg, 0.47 mmol) at rt and stirred for 16 h. Purification using Dowex® 50X8-200 resin gave (1*R*,2*S*,3*S*)-**45** (45 mg, 72% from **25**) as a white solid; mp 210–212 °C (decomposes); $[\alpha]_D^{24}$ −15.0 (c 0.50, H_2O); elemental analysis, found C, 70.9; H, 7.5; N, 6.7%; $C_{13}H_{17}NO_2$ requires C, 71.1; H, 7.8; N, 6.4%; ν_{max} (KBr) 3742–2362br s, 3065s, 2966s, 2362m, 2114w, 1619m, 1658s, 1497m, 1407s, 1314m, 1204w, 727s, 698s; δ_H (400 MHz, D_2O) 1.30 (1H, m, C(4)H_A), 1.62–1.80 (2H, m, C(4)H_B and C(5)H_A), 1.97 (1H, m, C(5)H_B), 2.28 (1H, m, C(3)*H*), 2.50 (1H, dd, *J* 13.6, 8.9, CH_AH_BPh), 2.73 (1H, dd, *J* 13.6, 6.6, CH_AH_BPh), 2.85 (1H, m, C(1)*H*), 3.32 (1H, dd, *J* 6.6, 5.3, C(2)*H*), 7.13–7.26 (5H, m, *Ph*); δ_C (100 MHz, D_2O) 29.5 (*C*(5)), 30.0 (*C*(4)), 41.3 (CH_2Ph), 47.1 (*C*(3)), 47.9 (*C*(1)), 58.7 (*C*(2)), 127.8 (*p*-Ph), 130.0 and 130.4 (*o*-, *m*-Ph), 141.5 (*ipso*-Ph), 181.9 (CO_2H); *m*/*z* (APCI$^+$) 220 (MH^+, 100), 202 (MH^+–NH_3, 60%); HRMS, found 220.1340; $C_{13}H_{18}NO_2$ (MH^+) requires 220.1338.

Preparation of (1*S*,2*S*,3*S*)-3-benzyl-2-aminocyclopentane-1-carboxylic acid hydrochloride 48

Following *general procedure 7*, $Pd(OH)_2$ on C (25 mg) was added to a stirred degassed solution of (1*S*,2*S*,3*S*,α*S*)-**28** (120 mg, 0.26 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 gel (Et_2O), giving *tert*-butyl (1*S*,2*S*,3*S*)-3-benzyl-2-aminocyclopentane-1-carboxylate as a colourless oil (33 mg); $[\alpha]_D^{23}$ +44.2 (c 1.2, $CHCl_3$); ν_{max} (film) 3391br w, 2971m, 1723s, 1493w, 1451w, 1367m, 1148s; δ_H (400 MHz, $CDCl_3$) 1.36–1.42 (1H, m, C(4)H_A), 1.46 (9H, s, OC(CH_3)$_3$), 1.71–1.91 (3H, m, C(4)H_B and C(5)H_2), 1.99 (2H, br s, NH_2) overlays 1.92–2.01 (1H, m, C(3)*H*), 2.49–2.56 (2H, m, CH_AH_BPh and C(1)*H*), 2.95 (1H, dd, *J* 13.2, 5.6, CH_AH_BPh), 3.08 (1H, br t, *J* 8.4, C(2)*H*), 7.17–7.29 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.7 (*C*(5)), 28.1 (OC(CH_3)$_3$), 29.2 (*C*(4)), 39.7 (CH_2Ph), 48.9 (*C*(3)), 53.1 (*C*(1)), 61.1 (*C*(2)), 80.6 (O*C*(CH_3)$_3$), 126.0 (*p*-Ph), 128.4 and 128.8 (*o*-, *m*-Ph), 140.7 (*ipso*-Ph), 171.3 ($CO_2{}^tBu$); *m*/*z* (ESI$^+$) 276 (MH^+, 100), 220 (MH^+–C_4H_8, 95%); HRMS, found 276.1964; $C_{17}H_{26}NO_2$ (MH^+) requires 276.1964.

TFA (5 ml) was added to a solution of crude *tert*-butyl (1*S*,2*S*,3*S*)-3-benzyl-2-aminocyclopentane-1-carboxylate (80 mg, 0.29 mmol) at rt and stirred for 16 h, in accordance with *general procedure 9*, furnishing (1*S*,2*S*,3*S*)-**48** (49 mg, 77% from **28**) as a white solid; mp 203–205 °C; $[\alpha]_D^{24}$ +13.9 (c 1.2, H_2O); ν_{max} (KBr) 3397m, 3329–2403br s, 3126s, 2938s, 1708s, 1602w, 1484m, 1481m, 1453m, 1424s, 1283m, 1200s, 866m, 742s, 702s, 683s; δ_H (400 MHz, D_2O) 1.37 (1H, m, C(4)H_A), 1.67 (1H, m, C(4)H_B), 1.78 (1H, m, C(5)H_A), 1.92–2.01 (1H, m, C(5)H_B), 2.21 (1H, m, C(3)*H*), 2.48 (1H, dd, *J* 13.5, 9.7, CH_AH_BPh), 2.86 (1H, dd, *J* 13.5, 5.1, CH_AH_BPh) overlays 2.89 (1H, m, C(1)*H*), 3.52 (1H, app t, *J* 7.7, C(2)*H*), 7.15–7.27 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.9 (*C*(5)), 29.0 (*C*(4)), 38.2 (CH_2Ph), 45.9 (*C*(3)), 48.5 (*C*(1)), 58.5 (*C*(2)), 126.9 (*p*-Ph), 129.1 and 129.4 (*o*-, *m*-Ph), 140.1 (*ipso*-Ph), 177.2 (CO_2H); *m*/*z* (ESI$^+$) 220 (MH^+, 100), 202 (MH^+–NH_3, 55%); HRMS, found 220.1335; $C_{13}H_{18}NO_2$ (MH^+) requires 220.1338.

Preparation of (1*R*,2*S*,3*S*)-3-(1′-methylethyl)-2-aminocyclopentane-1-carboxylic acid 46

Following *general procedure 7*, $Pd(OH)_2$ on C (40 mg) was added to a stirred degassed solution of (1*R*,2*S*,3*S*,α*S*)-**26** (200 mg, 0.48 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. Although this material was routinely used without purification, flash chromatography on silica gel (Et_2O) gave an analytical sample of *tert*-butyl (1*R*,2*S*,3*S*)-3-(1′-methylethyl)-2-aminocyclopentane-1-carboxylate (70 mg, 64%) as a colourless oil; $[\alpha]_D^{22}$ −20.0 (c 0.35, $CHCl_3$); ν_{max} (film) 3385br w, 2958s, 2873m, 1723s, 1468w, 1392m, 1367s, 1249w, 1221w, 1152s; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* 6.5, CH($CH_{3A}CH_{3B}$)), 0.99 (3H, d, *J* 6.5, CH($CH_{3A}CH_{3B}$)), 1.23 (1H, m, C(4)H_A), 1.48 (9H, s, OC(CH_3)$_3$), 1.76 (2H, br s, NH_2) overlays 1.60–1.93 (5H, m, C*H*(CH_3)$_2$, C(3)*H*, C(4)H_B and C(5)H_2), 2.72 (1H, m, C(1)*H*), 3.30 (1H, dd, *J* 7.1, 5.7, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 19.2 (CH($CH_{3A}CH_{3B}$)), 21.5 (CH($CH_{3A}CH_{3B}$)), 26.4 (*C*(5)), 26.9 (*C*(4)), 28.1 (OC(CH_3)$_3$), 30.6 (*C*H(CH_3)$_2$), 51.3 (*C*(3)), 54.9 (*C*(1)), 57.2 (*C*(2)), 80.3 (O*C*(CH_3)$_3$), 173.8 ($CO_2{}^tBu$); *m*/*z* (APCI$^+$) 228 (MH^+, 15), 172 (MH^+–C_4H_8, 100%); HRMS, found 228.1954; $C_{13}H_{26}NO_2$ (MH^+) requires 228.1964.

Following *general procedure 8*, TFA (5 ml) was added to a solution of crude *tert*-butyl (1*R*,2*S*,3*S*)-3-(1′-methylethyl)-2-aminocyclopentane-1-carboxylate (60 mg, 0.26 mmol) at rt and stirred for 16 h. Purification using Dowex® 50X8-200 resin gave (1*R*,2*S*,3*S*)-**46** (26 mg, 61% from **26**) as a white solid; mp 200–202 °C (decomposes); $[\alpha]_D^{23}$ +11.7 (c 1.1, H_2O); ν_{max} (KBr) 3672–2361br s, 3420m, 2958s, 2362w, 2125w, 1650m, 1575s, 1524m, 1469w, 1449w, 1414s, 1310m, 1207w, 1148m; δ_H (400 MHz, D_2O) 0.71 (3H, d, *J* 6.7, CH($CH_{3A}CH_{3B}$)), 0.78 (3H, d, *J* 6.7, CH($CH_{3A}CH_{3B}$)), 1.30 (1H, m, C(4)H_A), 1.50 (1H, app septet, *J* 6.7, C*H*(CH_3)$_3$), 1.58–1.68 (1H, m, C(5)H_A), 1.70–1.81 (2H, m, C(3)*H* and C(4)H_B), 1.85–1.94 (1H, m, C(5)H_B), 2.67 (1H, app td, *J* 10.4, 7.2, C(1)*H*), 3.40 (1H, dd, *J* 7.2, 3.4, C(2)*H*); δ_C (100 MHz, D_2O) 18.3 (CH($CH_{3A}CH_{3B}$)), 20.6 (CH($CH_{3A}CH_{3B}$)), 26.1 (*C*(4)), 28.6 (*C*(5)), 30.2 (*C*H(CH_3)$_2$), 48.2 (*C*(1)), 50.7 (*C*(3)), 55.4 (*C*(2)), 175.0 (CO_2H); *m*/*z* (APCI$^+$) 172 (MH^+, 65), 154 (MH^+–NH_3, 100%); HRMS, found 172.1333; $C_9H_{18}NO_2$ (MH^+) requires 172.1338.

Preparation of (1*S*,2*S*,3*S*)-3-(1′-methylethyl)-2-aminocyclopentane-1-carboxylic acid hydrochloride 49

Following *general procedure 7*, $Pd(OH)_2$ on C (25 mg) was added to a stirred degassed solution of (1*S*,2*S*,3*S*,α*S*)-**29** (80 mg, 0.19 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 gel (Et_2O), giving *tert*-butyl (1*S*,2*S*,3*S*)-3-(1′-methylethyl)-2-aminocyclopentane-1-carboxylate as a colourless oil (18 mg); $[\alpha]_D^{23}$ +30.6 (c 0.50, $CHCl_3$); ν_{max} (film) 3387br w, 2956s, 2875s, 1725s, 1365s, 1153s; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.6, $CH(CH_{3A}CH_{3B})$), 0.96 (3H, d, *J* 6.7, $CH(CH_{3A}CH_{3B})$), 1.46 (9H, s, $OC(CH_3)_3$) overlays 1.41–1.46 (1H, m, $C(4)H_A$), 1.67–1.84 (4H, m, $CH(CH_3)_2$, C(3)*H*, $C(4)H_B$ and $C(5)H_A$), 1.99 (2H, br s, NH_2) overlays 1.92–2.01 (1H, m, $C(5)H_B$), 2.66 (1H, app q, *J* 8.4, C(1)*H*), 3.26 (1H, br t, *J* 7.6, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 17.9 ($CH(CH_{3A}CH_{3B})$), 21.7 ($CH(CH_{3A}CH_{3B})$), 24.9 ($CH(CH_3)_2$), 26.8 (*C*(5)), 28.0 ($OC(CH_3)_3$), 28.7 (*C*(4)), 52.1 (*C*(1) and *C*(3)), 57.6 (*C*(2)), 80.9 ($OC(CH_3)_3$), 173.8 ($CO_2{}^tBu$); *m*/*z* (ESI$^+$) 228 (MH$^+$, 100), 172 (MH$^+$–C_4H_8, 65%); HRMS, found 228.1963; $C_{13}H_{26}NO_2$ (MH$^+$) requires 228.1964.

TFA (5 ml) was added to a solution of crude giving *tert*-butyl (1*S*,2*S*,3*S*)-3-(1′-methylethyl)-2-aminocyclopentane-1-carboxylate (40 mg, 0.18 mmol) at rt and stirred for 16 h, in accordance with *general procedure 9*, furnishing (1*S*,2*S*,3*S*)-**49** (20 mg, 69% from **29**) as a clear glass; $[\alpha]_D^{24}$ +14.8 (c 0.50, H_2O); ν_{max} (film) 3332–2386br s, 1709s, 1604w, 1492m, 1206s; δ_H (400 MHz, D_2O) 0.75 (3H, d, *J* 6.8, $CH(CH_{3A}CH_{3B})$), 0.83 (3H, d, *J* 6.8, $CH(CH_{3A}CH_{3B})$), 1.45 (1H, m, $C(4)H_A$), 1.63–1.86 (4H, m, $CH(CH_3)_2$, C(3)*H*, $C(4)H_B$ and $C(5)H_A$), 1.93–2.03 (1H, m, $C(5)H_B$), 2.85 (1H, app td, *J* 9.3, 7.6, C(1)*H*), 3.55 (1H, app t, *J* 7.8, C(2)*H*); δ_C (100 MHz, D_2O) 17.0 ($CH(CH_{3A}CH_{3B})$), 21.0 ($CH(CH_{3A}CH_{3B})$), 24.7 ($CH(CH_3)_2$), 27.5 (*C*(5)), 28.2 (*C*(4)), 50.4 (*C*(1) and *C*(3)), 56.6 (*C*(2)), 177.3 (CO_2H); *m*/*z* (ESI$^+$) 172 (MH$^+$, 100), 154 (MH$^+$–NH_3, 90%); HRMS, found 172.1334; $C_9H_{18}NO_2$ (MH$^+$) requires 172.1338.

Preparation of (1*S*,2*S*,3*S*)-3-(1′,1′-dimethylethyl)-2-aminocyclopentane-1-carboxylic acid hydrochloride 50

Following *general procedure 7*, $Pd(OH)_2$ on C (25 mg) was added to a stirred degassed solution of (1*S*,2*S*,3*S*,α*S*)-**34** (75 mg, 0.17 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 gel (Et_2O), giving *tert*-butyl (1*S*,2*S*,3*S*)-3-(1′,1′-dimethylethyl)-2-aminocyclopentane-1-carboxylate as a colourless oil (15 mg); $[\alpha]_D^{23}$ +34.2 (c 0.70, $CHCl_3$); ν_{max} (film) 3389br w, 2958 s, 2869s, 1724s, 1466w, 1389m, 1364s, 1149s; δ_H (400 MHz, $CDCl_3$) 0.92 (9H, s, $C(3)C(CH_3)_3$), 1.46 (9H, s, $OC(CH_3)_3$), 1.50–1.60 (2H, m, C(3)*H* and $C(4)H_A$), 1.64–1.78 (2H, m, $C(4)H_B$ and $C(5)H_A$), 1.80–1.88 (1H, m, $C(5)H_B$), 2.41 (2H, br s, NH_2) overlays 2.38–2.47 (1H, m, C(1)*H*), 3.25 (1H, br, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 27.6 (*C*(5)), 27.9 ($C(3)C(CH_3)_3$), 28.1 ($OC(CH_3)_3$), 30.9 (*C*(4)), 32.6 ($C(3)C(CH_3)_3$), 46.1 (*C*(3)), 55.5 (*C*(1)), 57.2 (*C*(2)), 80.3 ($OC(CH_3)_3$), 174.4 ($CO_2{}^tBu$); *m*/*z* (ESI$^+$) 242 (MH$^+$, 100), 186 (MH$^+$–C_4H_8, 95%); HRMS, found 242.2122; $C_{14}H_{28}NO_2$ (MH$^+$) requires 242.2120.

TFA (5 ml) was added to a solution of crude *tert*-butyl (1*S*,2*S*,3*S*)-3-(1′,1′-dimethylethyl)-2-aminocyclopentane-1-carboxylate (30 mg, 0.12 mmol) at rt and stirred for 16 h, in accordance with *general procedure 9*, furnishing (1*S*,2*S*,3*S*)-**50** (13 mg, 61% from **34**) as a clear glass; $[\alpha]_D^{24}$ +18.2 (c 0.50, H_2O); ν_{max} (film) 3591–2384br s, 2917s, 2163br m, 1661s, 1516m, 1416m, 1371m, 1251w, 1203w; δ_H (400 MHz, D_2O) 0.80 (9H, s, $C(CH_3)_3$), 1.51–1.62 (1H, m, $C(4)H_A$), 1.68–1.85 (3H, m, C(3)*H*, $C(4)H_B$ and $C(5)H_A$), 1.88–1.98 (1H, m, $C(5)H_B$), 2.88 (1H, m, C(1)*H*), 3.70 (1H, app t, *J* 6.3, C(2)*H*); δ_C (100 MHz, D_2O) 26.7 (*C*(4)), 26.9 ($C(CH_3)_3$), 28.4 (*C*(5)), 32.1 ($C(CH_3)_3$), 50.5 (*C*(1)), 54.7 (*C*(3)), 55.7 (*C*(2)), 177.2 (CO_2H); *m*/*z* (ESI$^+$) 186 (MH$^+$, 100%); HRMS, found 186.1495; $C_{10}H_{20}NO_2$ (MH$^+$) requires 186.1494.

Preparation of *tert*-butyl (1*S*,2*S*,3*S*,α*S*)-3-(1′-methylethyl)-2-(*N*-α-methylbenzylamino)-cyclopentane-1-carboxylate 40

In accordance with the literature procedure,[26] CAN (1.73 g, 3.15 mmol) and (1*S*,2*S*,3*S*,α*S*)-**29** (632 mg, 1.5 mmol) in 5 : 1 MeCN–H_2O (6 ml) at rt overnight gave, after purification by flash chromatography on silica gel (20% Et_2O : *n*-pentane), (1*S*,2*S*,3*S*,α*S*)-**40** (353 mg, 71%) as a colourless oil; $[\alpha]_D^{25}$ +32.6 (c 0.90, $CHCl_3$); ν_{max} (film) 2958s, 2871s, 1722s, 1455m, 1367m, 1277m, 1255m, 1147s, 761m, 701m; δ_H (400 MHz, $CDCl_3$) 0.62 (3H, d, *J* 6.7, $CH(CH_{3A}CH_{3B})$), 0.81 (3H, d, *J* 6.7, $CH(CH_{3A}CH_{3B})$), 1.34 (3H, d, *J* 6.7, C(α)*Me*), 1.41 (9H, s, $OC(CH_3)_3$) overlays 1.38–1.42 (2H, m, C(3)*H* and $C(4)H_A$), 1.57–1.68 (2H, m, $CH(CH_3)_2$ and $C(4)H_B$), 1.73–1.81 (1H, m, $C(5)H_A$), 1.82–1.90 (1H, m, $C(5)H_B$), 2.55 (1H, ddd, *J* 8.9, 8.9, 4.4, C(1)*H*), 2.86 (1H, dd, *J* 7.3, 4.9, C(2)*H*), 3.84 (1H, q, *J* 6.7, C(α)*H*), 7.19–7.31 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.1 ($CH(CH_{3A}CH_{3B})$), 22.1 ($CH(CH_{3A}CH_{3B})$), 25.0 (C(α)*Me*), 26.1 (*C*(4)), 28.0 ($OC(CH_3)_3$), 28.8 (*C*(5)), 29.0 ($CH(CH_3)_2$), 53.0 (*C*(1)), 54.5 (*C*(3)), 56.2 (*C*(α)H), 63.0 (*C*(2)), 79.8 ($OC(CH_3)_3$), 126.8 (*p*-Ph), 126.9 and 128.1 (*o*-, *m*-Ph), 145.5 (*ipso*-Ph), 175.8 ($CO_2{}^tBu$); *m*/*z* (APCI$^+$) 332 (MH$^+$, 50), 276 (MH$^+$–C_4H_8, 100), 172 (70), 105 (40%); HRMS, found 332.2592; $C_{21}H_{34}NO_2$ (MH$^+$) requires 332.2590.

Preparation of *tert*-butyl (*R*)-3-(1′-methylethyl)-cyclopentene-1-carboxylate 17

Methyl iodide (3 ml) was added neat, dropwise, to (1*S*,2*S*,3*S*,α*S*)-**40** (320 mg, 0.97 mmol) and the reaction mixture stirred for 2 d at rt. After the addition of $NaHCO_3$ (aq, sat, 10 ml), the mixture was extracted with Et_2O (3 × 20 ml) and the combined organic phases dried ($MgSO_4$), filtered and concentrated *in vacuo* to give *tert*-butyl (1*S*,2*S*,3*S*,α*S*)-3-(1-methylethyl)-2-(*N*-methyl-*N*-α-methylbenzylamino)cyclopentane-1-carboxylate as a yellow oil. This crude material (355 mg) was subsequently dissolved in $CHCl_3$ (5 ml) and a solution of *m*CPBA (50% by mass, 415 mg) in $CHCl_3$ (5 ml) added dropwise. After stirring at rt overnight, $NaHCO_3$ (aq, sat, 10 ml) was added and the aqueous layer separated and extracted with $CHCl_3$ (3 × 15 ml). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane) gave (*R*)-**17** (86 mg, 42% from **40**) as a volatile oil; $[\alpha]_D^{25}$ +51.2 (c 0.75, $CHCl_3$). The material was judged to be >98% ee by chiral shift NMR spectroscopy using 4 eq by mass $Eu(hfc)_3$, with spectroscopic data consistent with that obtained for the racemate.

Preparation of *tert*-butyl (1*R*,2*S*,3*S*,α*R*)-3-(1′-methylethyl)-2-(*N*-benzyl-*N*-α-methylbenzylamino)-cyclopentane-1-carboxylate 32 and *tert*-butyl (1*S*,2*S*,3*S*,α*R*)-3-(1′-methylethyl)-2-(*N*-benzyl-*N*-α-methylbenzylamino)-cyclopentane-1-carboxylate 41

Following *general procedure 4*, *n*-BuLi (1.5 M, 0.72 mmol, 0.48 ml), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (153 mg, 0.72 mmol) in THF (5 ml) and (*R*)-**17** (50 mg, 0.24 mmol) in THF (1 ml) gave, after quenching with 2,6-di-*tert*-butylphenol (326 mg, 1.58 mmol) in THF (4 ml), (1*R*,2*S*,3*S*,α*R*)-**32**, (1*S*,2*S*,3*S*,α*R*)-**41** and (1*S*,2*R*,3*R*,α*R*)-**42** in an 88.0 : 11.1 : 0.9 ratio. Purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane) and subsequent recrystallisation from *n*-pentane gave a sample of pure (1*R*,2*S*,3*S*,α*R*)-**32** (29 mg, 29%) as a white crystalline solid; mp 102–104 °C; $[\alpha]_D^{24}$ −19.1 (c 0.50, $CHCl_3$); ν_{max} (KBr) 3028w, 2952s, 2881m, 2870m, 1710s, 1602w, 1454m, 1366s, 1213m, 1138s, 748s, 698s; δ_H (400 MHz, $CDCl_3$) 0.11 (3H, d, *J* 6.7, $CH(CH_{3A}CH_{3B})$), 0.83 (3H, d, *J* 6.7, $CH(CH_{3A}CH_{3B})$), 1.18–1.24 (1H, m, $C(4)H_A$), 1.50 (3H, d, *J* 6.9, C(α)*Me*), 1.55 (9H, s,

$OC(CH_3)_3$) overlays 1.48–1.53 (1H, m, C(5)H_A), 1.74–1.83 (3H, m, CH(CH$_3$)$_2$, C(4)H_B and C(5)H_B), 2.36 (1H, m, C(3)H), 2.85 (1H, app td, J 6.9, 1.6, C(1)H), 2.92 (1H, dd, J 10.7, 6.8, C(2)H), 3.81 and 4.19 (2 × 1H, AB system, J_{AB} 14.1, NCH_2Ph), 4.01 (1H, q, J 6.9, C(α)H) 7.17–7.40 (10H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.1 and 14.2 (CH(CH_{3A}CH$_{3B}$) and C(α)Me), 20.0 (C(5)), 22.9 (CH(CH$_{3A}$$CH_{3B}$)), 26.4 ($C$H(CH$_3$)$_2$), 28.1 and 28.2 (OC($CH_3$)$_3$ and C(4)), 44.3 (C(3)), 49.4 (C(1)), 50.4 (NCH$_2$Ph), 56.1 (C(α)H), 63.3 (C(2)), 80.0 (OC(CH$_3$)$_3$), 126.5 and 126.6 (p-Ph), 127.7, 128.2, 128.3 and 128.8 (o-, m-Ph), 141.6 and 143.7 ($ipso$-Ph), 176.2 (CO$_2$^{t}Bu); m/z (APCI$^+$) 422 (MH$^+$, 100%); HRMS, found 422.3058; $C_{28}H_{40}NO_2$ (MH$^+$) requires 422.3059.

A mixed fraction of (1R,2S,3S,αR)-**32** and (1S,2S,3S,αR)-**41** (34 mg, 34%) as a colourless oil, was also obtained. This material was subsequently re-dissolved in *tert*-butanol (5 ml) and epimerised under thermodynamic conditions in accordance with *general procedure 6*. Purification by flash chromatography on silica gel (2% Et_2O : n-pentane) gave (1S,2S,3S,αR)-**41** in >98% de as a colourless oil (33 mg, quantitative); $[\alpha]_D^{25}$ −0.93 (c 0.75, $CHCl_3$); ν_{max} (film) 3086w, 3062w, 3029m, 2956s, 2872s, 1721s, 1602w, 1494m, 1453m, 1367s, 1274m, 1255m, 1148s, 749s, 733s, 698s; δ_H (400 MHz, $CDCl_3$) 0.26 (3H, d, J 6.8, CH(CH_{3A}CH$_{3B}$)), 0.81 (3H, d, J 6.8, CH(CH$_{3A}$$CH_{3B}$)), 1.27–1.32 (1H, m, C(4)H_A), 1.36 (3H, d, J 6.8, C(α)Me), 1.40–1.44 (1H, m, C(5)H_A), 1.52 (9H, s, OC(CH_3)$_3$), 1.63–1.69 (1H, m, CH(CH$_3$)$_2$), 1.70–1.82 (3H, m, C(3)H, C(4)H_B and C(5)H_B), 2.83 (1H, m, C(1)H), 3.34 (1H, dd, J 9.3, 5.2, C(2)H), 3.69 and 3.80 (2 × 1H, AB system, J_{AB} 14.2, NCH_2Ph), 3.90 (1H, q, J 6.8, C(α)H), 7.17–7.46 (10H, m, Ph); δ_C (100 MHz, $CDCl_3$) 13.2 (C(α)Me), 15.8 (CH(CH_{3A}CH$_{3B}$)), 22.9 (CH(CH$_{3A}$$CH_{3B}$)), 23.2 ($C$(5)), 27.0 ($C$H(CH$_3$)$_2$), 28.1 (OC($CH_3$)$_3$), 31.0 ($C$(4)), 45.8 ($C$(1)), 50.5 (N$CH_2$Ph), 51.0 ($C$(3)), 56.3 ($C$(α)H), 63.0 ($C$(2)), 79.9 (O$C$(CH$_3$)$_3$), 126.5 and 126.7 ($p$-Ph), 127.8, 127.9, 128.1 and 128.7 (o-, m-Ph), 141.5 and 144.2 ($ipso$-Ph), 176.5 (CO$_2$^{t}Bu); m/z (ESI$^+$) 422 (MH$^+$, 100%); HRMS, found 422.3057; $C_{28}H_{40}NO_2$ (MH$^+$) requires 422.3059.

X-ray crystal structure determination for 32†

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Cu–Kα radiation using standard procedures at 190 K. 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 structure was refined using CRYSTALS.[32]

X-ray crystal structure data for **32** [$C_{28}H_{39}NO_2$]: M = 421.62, monoclinic, space group P 1 21 1, a = 10.0382(3) Å, b = 10.7600(3) Å, c = 11.6779(4) Å, V = 1261.05(7) Å^3, Z = 2, μ = 0.068 mm^{-1}, colourless block, crystal dimensions = 0.1 × 0.1 × 0.1 mm. A total of 3011 unique reflections were measured for $5 < \theta < 27$ and 2299 reflections were used in the refinement. The final parameters were $wR_2 = 0.043$ and $R_1 = 0.045$ [$I > 2\sigma(I)$]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or deposit@ccdc.cam.ac.uk].

Preparation of *tert*-butyl (1*R*,2*S*,3*S*)-3-(1′-methylethyl)-2-aminocyclopentane-1-carboxylate 43 by hydrogenolysis of (1*R*,2*S*,3*S*,α*R*)-32

Following *general procedure 7*, $Pd(OH)_2$ on C (8 mg) was added to a degassed solution of (1R,2S,3S,αR)-**43** (20 mg, 0.05 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 gel (Et_2O) gave (1R,2S,3S)-**32** as a colourless oil (7 mg, 64%); $[\alpha]_D^{22}$ −18.1 (c 0.35, $CHCl_3$), with spectroscopic data consistent with that obtained for the same compound reported above.

† CCDC reference number 237688. See http://www.rsc.org/suppdata/ob/b4/b407559e/ for crystallographic data in .cif or other electronic format.

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References and notes

1 For representative examples see K. Gademann, A. Hane, M. Rueping, B. Jaun and D. Seebach, *Angew. Chem. Int. Ed.*, 2003, **42**, 1534; D. Seebach, M. Overhand, F. N. M. Kuehnle and B. Martinoni, *Helv. Chim. Acta*, 1996, **79**, 913; D. Seebach, P. E. Ciceri, M. Overhand, B. Jaun, D. Rigo, L. Oberer, U. Hommel, R. Amstutz and H. Widmer, *Helv. Chim. Acta*, 1996, **79**, 2043; D. Seebach, K. Gademann, J. V. Schreiber, J. L. Matthews, T. Hintermann, B. Jaun, L. Oberer, U. Hommel and H. Widmer, *Helv. Chim. Acta*, 1997, **80**, 2033; D. Seebach and J. L. Matthews, *Chem. Commun.*, 1997, 2015; D. Seebach, S. Abele, J. V. Schreiber, B. Martinoni, A. K. Nussbaum, H. Schild, H. Schulz, H. Hennecke, R. Woessner and F. Bitsch, *Chimia*, 1998, **52**, 734.

2 For representative examples see A. M. Brueckner, P. Chakraborty, S. H. Gellman and U. Diederichsen, *Angew. Chem. Int. Ed.*, 2003, **42**, 4395; B. R. Huck, J. D. Fisk, I. A. Guzei, H. A. Carlson and S. H. Gellman, *J. Am. Chem. Soc.*, 2003, **125**, 9035; J. M. Langenhan, I. A. Guzei and S. H. Gellman, *Angew. Chem. Int. Ed.*, 2003, **42**, 2402; M. Schinnerl, J. K. Murray, J. M. Langenhan and S. H. Gellman, *Eur. J. Org. Chem.*, 2003, **4**, 721; M. G. Woll, J. D. Fisk, P. R. LePlae and S. H. Gellman, *J. Am. Chem. Soc.*, 2002, **124**, 12447; R. P. Cheng, S. H. Gellman and W. F. DeGrado, *Chem. Rev.*, 2001, **101**, 3219; Y. J. Chung, L. A. Christianson, H. E. Stanger, D. R. Powell and S. H. Gellman, *J. Am. Chem. Soc.*, 1998, **120**, 10555.

3 G. P. Dado and S. H. Gellman, *J. Am. Chem. Soc.*, 1994, **116**, 1054; 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.

4 T. A. Martinek, G. K. Táth, E. Vass, M. Hollósi and F. Fülop, *Angew. Chem. Int. Ed.*, 2002, **41**, 1718.

5 A. Hayen, M. A. Schmitt, F. N. Ngassa, K. A. Thomasson and S. H. Gellman, *Angew. Chem., Int. Ed.*, 2004, **43**, 505; S. De Pol, C. Zorn, C. D. Klein, O. Zerbe and O. Reiser, *Angew. Chem., Int. Ed.*, 2004, **43**, 511.

6 For example see 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, *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.

7 S. Bailey, S. G. Davies, A. D. Smith and J. M. Withey, *Chem. Commun.*, 2002, 2910; M. E. Bunnage, A. M. Chippendale, S. G. Davies, R. M. Parkin, A. D. Smith and J. M. Withey, *Org. Biomol. Chem.*, 2003, 3698.

8 A. Horeau, *Tetrahedron*, 1975, **31**, 1307.

9 This approach is valid on the assumption that there are no non-linear effects operating in the reaction. For a review concerned with non-linear effects in asymmetric synthesis see H. B. Kagan, *Adv. Synth. Catal.*, 2001, 343. For other 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.

10 S. M. Brown, S. G. Davies and J. A. A. de Sousa, *Tetrahedron: Asymmetry*, 1991, **2**, 511; S. M. Brown, S. G. Davies and J. A. A. de Sousa, *Tetrahedron: Asymmetry*, 1993, **4**, 813; S. C. Case-Green, J. F. Costello, S. G. Davies, N. Heaton, C. J. R. Hedgecock and J. C. Prime, *Chem. Commun.*, 1993, 1621; S. C. Case-Green, J. F. Costello, S. G. Davies, N. Heaton, C. J. R. Hedgecock, V. M. Humphries, M. R. Metzler and J. C. Prime, *J. Chem. Soc., Perkin Trans 1*, 1994, 933; S. P. Bew, S. G. Davies and S.-I. Fukuzawa, *Chirality*, 2000, **12**, 483.

11 For the parallel kinetic resolutions of 5-alkyl-cyclopentene carboxylates with a pseudoenantiomeric mixture of lithium amides

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.
12 J. H. Babler and S. J. Sarussi, *J. Org. Chem.*, 1987, **52**, 3462.
13 D. Henderson, K. A. Richardson, R. J. K. Taylor and J. Saunders, *Synthesis*, 1983, 996.
14 X. Wang, J. F. Espinosa and S. H. Gellman, *J. Am. Chem. Soc.*, 2000, **122**, 4821.
15 A. Barco, S. Benetti and G. P. Pollni, *Synthesis*, 1973, 316.
16 K. Sisido, K. Utimoto and T. Isida, *J. Org. Chem.*, 1964, **29**, 2781; J. Wright, G. J. Drtina, R. A. Roberts and L. A. Paquette, *J. Am. Chem. Soc.*, 1988, **110**, 5806.
17 Attempted alkylation of the mono-enolate of *tert*-butyl 2-oxo-cyclopentene-1-carboxylate with 2-iodopropane also returned only starting materials.
18 H. O. House, L. J. Czuba, M. Gall and H. D. Olmstead, *J. Org. Chem.*, 1969, **34**, 2324.
19 L. A. Paquette, A. T. Hamme II, L. H. Kuo, J. Doyon and R. Kreuzholz, *J. Am. Chem. Soc.*, 1997, **119**, 1242.
20 The *syn*-1,2-*anti*-2,3-arrangement within β-amino esters **20** and **21** and the *anti*-1,2-*anti*-2,3-arrangement within **22** and **23** were assumed by analogy to that proven unambiguously in the 3-methyl series; see ref. 7.
21 The relative configurations within the observed β-amino esters were readily assigned by analogy to the selectivity observed in the related (*RS*)-3-methyl substrate; see ref. 7 for full details.
22 A total of four diastereoisomeric compounds were identified in the kinetic resolution crude reaction mixture in this case, with the combined sum (by ^{1}H NMR integration) of the two minor diastereo-isomeric products being 1.2% of the total.
23 As shown by ^{1}H NMR chiral shift experiments with commercially available Eu(hfc)$_3$ (Aldrich) and reference to an authentic racemic sample.
24 Prepared by epimerisation of the major diastereoisomeric product **26** from kinetic resolution.
25 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.
26 We have previously used this, and related procedures, to effect a range of asymmetric transformations; 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; S. G. Davies, C. A. P. Smethurst, A. D. Smith and G. D. Smyth, *Tetrahedron: Asymmetry*, 2000, **11**, 2437.
27 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.
28 E. Stahl, *Thin Layer Chromatography*, Springer-Verlag, Berlin, 1969, p. 873.
29 T. H. Chan, I. Paterson and J. Pinsonnault, *Tetrahedron Lett.*, 1977, **15**, 4183; M. Reetz and W. Maier, *Angew. Chem., Int. Ed. Engl.*, 1978, **7**, 48.
30 L. A. Paquette, K. Dahnke, J. Doyne, W. He, K. Wyant and D. Friedrich, *J. Org. Chem.*, 1991, **56**, 6199.
31 C. M. Main, R. P. C. Cousins, G. Coumbarides and N. S. Simpkins, *Tetrahedron*, 1990, **46**, 523.
32 D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge and R. I. Cooper, *CRYSTALS*, 2001, Issue 11, Chemical Crystallography Laboratory, Parks Road, Oxford.