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Parallel kinetic resolution of methyl (*RS*)-5-tris(phenylthio)methyl-cyclopent-1-ene-carboxylate for the asymmetric synthesis of (1*R*,2*S*,5*S*)- and (1*S*,2*R*,5*R*)-5-methyl-cispentacin

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ABSTRACT

Parallel kinetic resolution of methyl (*RS*)-5-tris(phenylthio)methyl-cyclopent-1-ene-carboxylate with a 50:50 pseudoenantiomeric mixture of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide provides an efficient entry to the corresponding homochiral methyl (1*R*,2*S*,5*S*)- and (1*S*,2*R*,5*R*)-2-amino-5-tris(phenylthio)methyl-cyclopentane-carboxylate derivatives in >98% de, with subsequent, sequential desulfurisation with Raney Nickel, *N*-debenzylation and ester hydrolysis furnishing (1*R*,2*S*,5*S*)- and (1*S*,2*R*,5*R*)-5-methyl-cispentacin in high yield, >98% de and >98% ee.

1. Introduction

The simple cyclic β-amino acid (1*R*,2*S*)-2-amino-cyclopentane-carboxylic acid (cispentacin) has attracted considerable synthetic attention,[1] with a number of efficient methodologies having been developed for its synthesis in enantioenriched form.[2] In order to enhance the structural diversity of monomeric cispentacin derivatives available for both secondary structural[3] and bioactivity studies,[4] we recently reported the efficient kinetic and parallel kinetic resolution of a range of 3- and 5-substituted cyclopent-1-ene-carboxylates, utilising the conjugate addition of either homochiral or a pseudoenantiomeric mixture of homochiral lithium amides, respectively, for the asymmetric synthesis of homochiral 3- and 5-substituted cispentacin and transpentacin derivatives.[5] We have also promulgated the view that a full understanding of the observed stereoselectivity in these systems is best achieved by initially evaluating the level of substrate control upon addition of an achiral lithium amide to the racemic α,β-unsaturated ester. For those substrates offering high facial selectivity upon conjugate addition, the levels of enantiorecognition between the chiral acceptor and chiral lithium amides was assessed through their mutual kinetic resolution (addition of racemic α,β-unsaturated ester to an excess of racemic lithium amide). If high enantiorecognition was seen between the reacting partners, then efficient kinetic and parallel kinetic resolution in these systems was expected. Upon application of this protocol to a range of methyl (*RS*)-5-substituted-cyclopent-1-ene-carboxylates **1**–**3** bearing an α-branched 5-substituent, high levels of substrate control were observed, promoting addition of lithium dibenzylamide **5** *anti* to the 5-substituent, with subsequent protonation of the resultant enolate occurring exclusively *anti* to the amino group, giving the corresponding 1,2-*syn*-diastereoisomers **6**, **8** and **10** as the major products.[5c] In the case of 5-methyl **4**, however, poor substrate control was noted, giving a 78:22 mixture of the 1,2-*syn*-diastereoisomers **12**:**13**. In accordance with the low levels of substrate control, attempted mutual kinetic resolution of (*RS*)-5-methyl **4** upon addition of lithium (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*RS*)-**14** gave an 80:20 mixture of the 1,2-*syn*-diastereoisomeric products **21**:**22**, consistent with $E = 4$,[6] indicating that **4** is not suitable for kinetic or parallel kinetic resolution via this conjugate addition protocol (Scheme 1).

In order to extend this parallel kinetic resolution methodology for the preparation of 5-methyl-cispentacin derivatives it was envisaged that the use of a latent methyl group equivalent, incorporating an α-branch, would give the desired substrate control during lithium amide conjugate addition; subsequent deprotection would then reveal the C(5)-methyl group. Details of these investigations are delineated herein.

2. Results and discussion

Dithianes and thio orthoesters have frequently been employed as acyl anion equivalents in synthesis.[7] In an elegant protocol, Smith et al. demonstrated that the tris(phenylthio)methyl group could act as a latent methyl group equivalent via exhaustive

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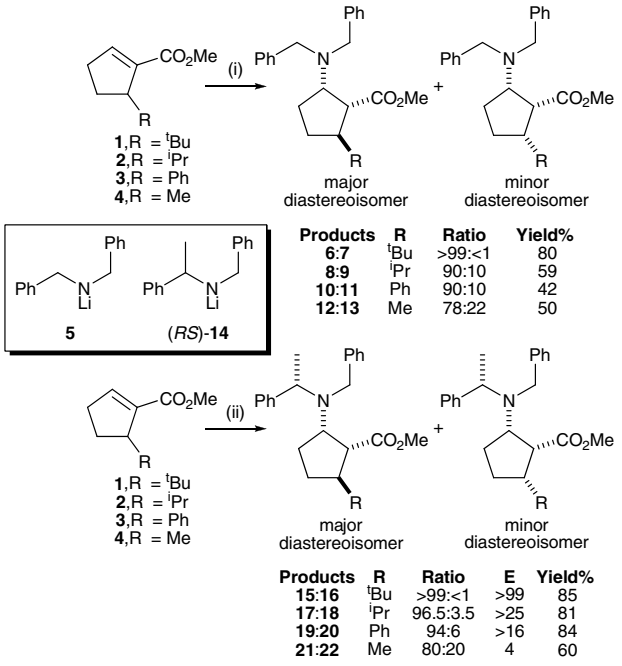
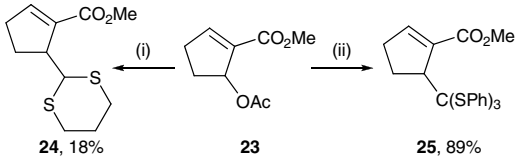


Products	R	Ratio	Yield%
6:**7**	^{t}Bu	>99:<1	80
8:**9**	^{i}Pr	90:10	59
10:**11**	Ph	90:10	42
12:**13**	Me	78:22	50

Products	R	Ratio	E	Yield%
15:**16**	^{t}Bu	>99:<1	>99	85
17:**18**	^{i}Pr	96.5:3.5	>25	81
19:**20**	Ph	94:6	>16	84
21:**22**	Me	80:20	4	60

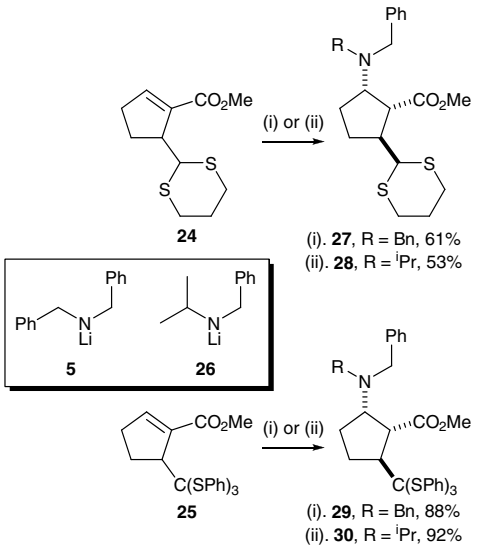
Scheme 1. Reagents and conditions: (i) lithium dibenzylamide **5**, THF, −78 °C, 2 h, then NH_4Cl (satd aq); (ii) lithium (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*RS*)-**14**, THF, −78 °C, 2 h, then NH_4Cl (satd aq).

hydrogenolytic deprotection mediated by Raney Nickel.[8] In an analogous manner, exhaustive hydrogenolysis of 1,3-dithianes has been extensively reported.[9] Thus, two 5-substituted acceptors were identified and evaluated for their utility in this protocol: methyl 5-(1′,3′-dithian-2′-yl)cyclopent-1-ene-carboxylate **24** (bearing an α-branched 5-substituent) and methyl 5-tris(phenylthio)methyl-cyclopent-1-ene-carboxylate **25** (bearing a bis-α-branched 5-substituent). The required racemic 5-substituted cyclopent-1-ene-carboxylates **24** and **25** were readily prepared from 5-acetoxy-**23**.[5c,10] Under optimised conditions, treatment of **23** with the lithium anion of tris(phenylthio)methane gave **25** in 89% yield, whilst addition of the lithium anion of 1,3-dithiane to **23**[11] gave a complex mixture of products (potentially a result of competing 1,2-addition and Michael addition, and polymerisation)[12] from which **24** was isolated in 18% yield (Scheme 2).



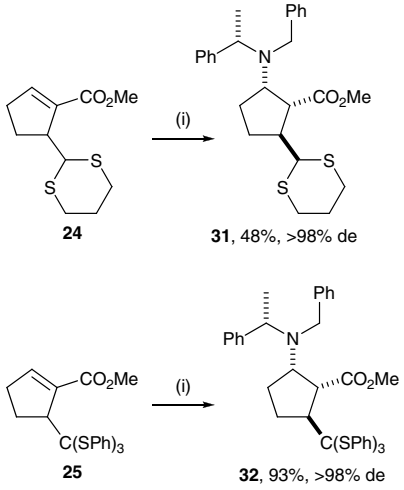
Scheme 2. Reagents and conditions: (i) BuLi, 1,3-dithiane, −78 °C to rt, 48 h; (ii) BuLi, tris(phenylthio)methane, THF, −78 °C to rt, 48 h.

The level of substrate control offered by **24** and **25** upon conjugate addition of a lithium amide was probed with achiral lithium dibenzylamide **5**[5,13] and lithium *N*-benzyl-*N*-isopropylamide **26**, the latter being employed as an even better mimic of the steric bias of the chiral lithium *N*-benzyl-*N*-(α-methylbenzyl)amide.[5c] Conjugate addition of both lithium amides **5** and **26** to (*RS*)-5-(1′,3′-dithian-2′-yl)-**24** gave quantitative conversion to the corresponding adducts (1*RS*,2*SR*,5*SR*)-**27** and (1*RS*,2*SR*,5*SR*)-**28** in >98% de in each case, which were isolated in 61% and 53% yield, respectively. Analogous conjugate addition of lithium amides **5** and **26** to (*RS*)-5-tris(phenylthio)methyl-**25** gave the corresponding adducts (1*RS*,2*SR*,5*SR*)-**29** and (1*RS*,2*SR*,5*SR*)-**30** as single diastereoisomers (>98% de) in 88% and 92% yield, respectively (Scheme 3). The relative configurations within **27**–**30** were assigned on the assumption that addition of the lithium amide occurs exclusively *anti* to the bulky 5-substituent,[5c] with protonation of the resultant β-amino enolate occurring exclusively *anti* to the amino group;[14] ^{1}H NMR NOE difference analysis of **27**, **29** and **30** corroborated this assignment.



Scheme 3. Reagents and conditions: (i) lithium dibenzylamide **5** (1.6 equiv), THF, −78 °C, 2 h, then NH_4Cl (satd aq); (ii) lithium *N*-benzyl-*N*-isopropylamide **26** (1.6 equiv), THF, −78 °C, 2 h, then NH_4Cl (satd aq).

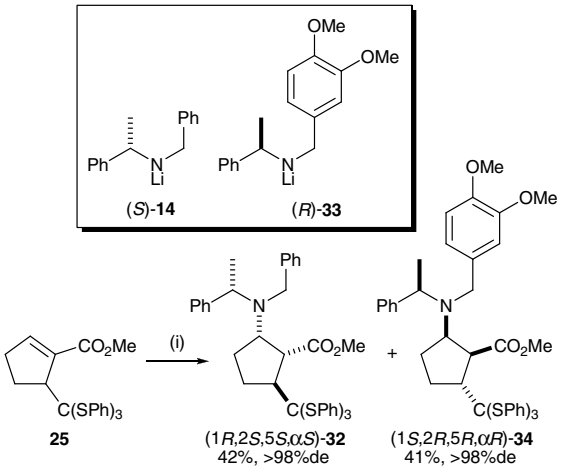
With high levels of substrate control displayed upon conjugate addition of both lithium dibenzylamide **5** and lithium *N*-benzyl-*N*-isopropylamide **26** to racemic α,β-unsaturated esters **24** and **25**, high levels of enantiorecognition between lithium (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*RS*)-**14**, and both **24** and **25** were anticipated. Under optimised conditions, conjugate addition of racemic lithium amide (*RS*)-**14** (4 equiv) to (*RS*)-5-(1′,3′-dithian-2′-yl)-**24** gave β-amino ester (1*RS*,2*SR*,5*SR*,α*SR*)-**31** in >98% de and 48% yield, whilst addition of (*RS*)-**14** to (*RS*)-5-tris(phenylthio)methyl-**25** gave β-amino ester (1*RS*,2*SR*,5*SR*,α*SR*)-**32** in >98% de and 93% yield, consistent with *E* >99[6] in both cases. The relative configurations of **31** and **32** were assigned by ^{1}H NMR NOE difference analysis and are consistent with high levels of enantiorecognition between the



Scheme 4. Reagents and conditions: (i) lithium (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*RS*)-**14** (4 equiv), THF, −78 °C, 2 h, then NH_4Cl (satd aq).

chiral α,β-unsaturated ester and chiral lithium amide, with addition of the lithium amide occurring exclusively *anti* to the bulky 5-substituent, and protonation of the resultant β-amino enolate occurring exclusively *anti* to the amino group[14] (Scheme 4).

The high levels of enantiorecognition observed between lithium amide (*RS*)-**14** and both 5-substituted cyclopent-1-ene-carboxylates **24** and **25** suggest that both are suitable for either kinetic or parallel kinetic resolution upon treatment with homochiral or a 50:50 pseudoenantiomeric mixture of homochiral lithium amides, respectively. Even with *E* >99, the parallel kinetic resolution protocol was investigated, not only as it is experimentally more facile but also, unlike a simple kinetic resolution, can be run to completion and requires no further optimisation studies. Additionally, both enantiomeric series of the desired 5-methyl-cispentacin derivatives are available from a parallel kinetic resolution method. Due to the superior yields obtained upon conjugate addition to (*RS*)-5-tris(phenylthio)methyl-**25**, its amenability to parallel kinetic resolution was chosen for investigation. Thus, addition of a 50:50 pseudoenantiomeric mixture of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**14** and lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide (*R*)-**33** to (*RS*)-**25** furnished a 50:50 mixture of β-amino esters (1*R*,2*S*,5*S*,α*S*)-**32** and (1*S*,2*R*,5*R*,α*R*)-**34** only, in >98% de in each case, which were isolated in 42% and 41% yield, respectively, after chromatography (Scheme 5). The relative configuration within β-amino ester **34** was unambiguously established via single crystal X-ray analysis, with the absolute (1*S*,2*R*,5*R*,α*R*)-configuration assigned from the known (*R*)-α-methylbenzyl stereocentre (Fig. 1).



Scheme 5. Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**14** (2 equiv), lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide (*R*)-**33** (2 equiv), THF, −78 °C, 2 h, then NH_4Cl (satd aq).

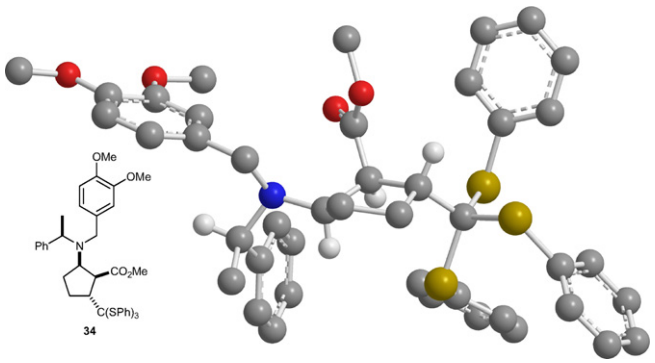
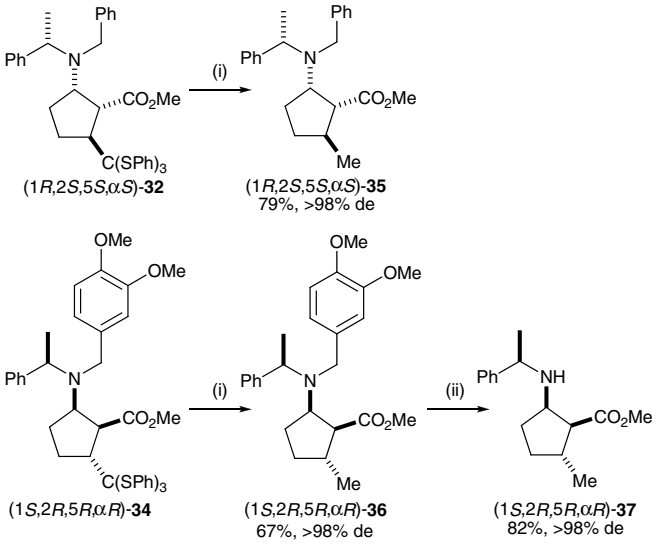


Figure 1. Chem 3D representation of the X-ray crystal structure of **34** (some H atoms removed for clarity).

Reduction of (1*R*,2*S*,5*S*,α*S*)-**32** with Raney Nickel resulted in desulfurisation furnishing β-amino ester (1*R*,2*S*,5*S*,α*S*)-**35** in 79% yield and >98% de. Analogous treatment of (1*S*,2*R*,5*R*,α*R*)-**34** with Raney Nickel gave β-amino ester (1*S*,2*R*,5*R*,α*R*)-**36** in >98% de and 67% isolated yield. Attempted epimerisation of **36** upon treatment with NaOMe in MeOH for 24 h returned only starting material.[5c] The recalcitrance of this class of compound to epimerisation at C(1) may be due to C(1)*H* and the carbonyl group being oriented approximately coplanar, as revealed in the X-ray crystal structure of **34**.[5c] Oxidative debenzylation of **36** with DDQ furnished (1*S*,2*R*,5*R*,α*R*)-**37** in >98% de and 82% yield (Scheme 6).



Scheme 6. Reagents and conditions: (i) Raney Nickel, THF, rt, 8 h; (ii) DDQ, DCM/H_2O (5:1), rt, 24 h.

Hydrogenolysis of (1*R*,2*S*,5*S*,α*S*)-**35** furnished β-amino ester (1*R*,2*S*,5*S*)-**38** in 91% yield, >98% de and >98% ee,[15] with ester hydrolysis and purification via ion-exchange chromatography furnishing β-amino acid (1*R*,2*S*,5*S*)-**39** in 95% yield and >98% de. Similarly, the enantiomeric β-amino acid (1*S*,2*R*,5*R*)-**39** was synthesised by hydrogenolysis of β-amino ester (1*S*,2*R*,5*R*,α*R*)-**37** to yield β-amino ester (1*S*,2*R*,5*R*)-**38** in 95% yield, >98% de and >98% ee.[15] Ester hydrolysis and ion exchange chromatography provided the β-amino acid (1*S*,2*R*,5*R*)-**39** in 93% yield and >98% de (Scheme 7). ^1H NMR NOESY analysis of **39** was supportive of the assigned 1,2-*syn*-1,5-*anti*-configuration, consistent with ester hydrolysis not being accompanied by epimerisation of the C(1)-stereocentre (vide supra).

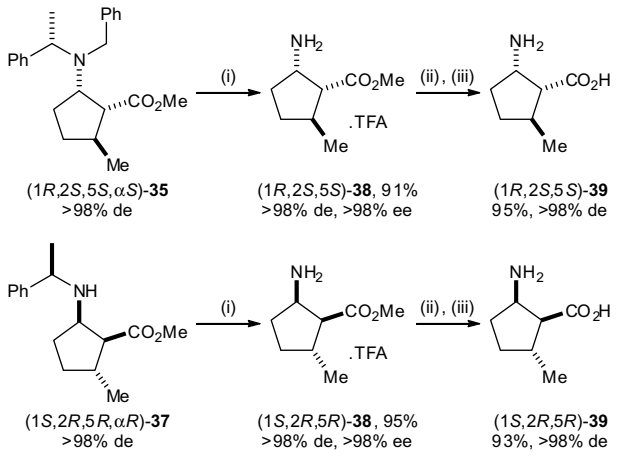
3. Conclusion

In conclusion, parallel kinetic resolution of methyl (*RS*)-5-tris(phenylthio)methyl-cyclopent-1-ene-carboxylate with a 50:50 pseudoenantiomeric mixture of homochiral lithium amides represents an efficient route to homochiral 5-substituted-cispentacin derivatives, which can be deprotected to furnish (1*R*,2*S*,5*S*)- and (1*S*,2*R*,5*R*)-5-methyl-cispentacin in high de and ee. The application of these substrates as organocatalysts, and as monomers for the construction of β-peptides is currently ongoing within our laboratory.

4. Experimental

4.1. General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmo-



Scheme 7. Reagents and conditions: (i) $Pd(OH)_2/C$, H_2 (1 atm), MeOH/AcOH (40:1), rt, 2 h then TFA/DCM (1:1); (ii) LiOH, THF/H_2O, rt, 16 h; (iii) HCl then Dowex 50-WX8-200.

sphere using standard vacuum line techniques, and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[16] Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$ or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, UK. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent state. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

4.2. Methyl (*RS*)-5-(1′,3′-dithian-2′-yl)cyclopent-1-ene-carboxylate 24

BuLi (1.6 M in hexanes, 12.9 mL, 18.9 mmol) was added dropwise via syringe to a stirred solution of 1,3-dithiane (2.27 g, 18.9 mmol) in THF (10 mL) at −78 °C and stirred for 1.5 h. The mixture was then added dropwise via cannula to a stirred solution of **23** (1.0 g, 4.10 mmol) in THF (10 mL) at −78 °C. The resultant mixture was allowed to warm slowly to rt over 24 h before the addition of satd aq NH_4Cl (20 mL). The aqueous layer was separated and extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **24** as a yellow oil (430 mg, 18%); $C_{11}H_{16}O_2S_2$ requires: C, 54.1; H, 6.6. Found: C, 54.2; H, 6.65; ν_{max} (film) 1716 (C=O), 1628 (C=C); δ_H (400 MHz, $CDCl_3$) 1.65–1.76 (1H, m, C(5′)H_A), 1.99–2.03 (1H, m, C(5′)H_B), 2.04–2.07 (1H, m, C(4)H_A), 2.12–2.20 (1H, m, C(4)H_B), 2.33–2.42 (1H, m, C(3)H_A), 2.47–2.57 (1H, m, C(3)H_B), 2.69–2.79 (3H, m, C(4′)H_2, C(6′)H_A), 2.84–2.92 (1H, dt, *J* 2.5, 11.9, C(6′)H_B), 3.34–3.37 (1H, m, C(5)*H*), 3.68 (3H, s, O*Me*), 4.72 (1H, d, *J* 3.8, C(2′)H), 6.80–6.82 (1H, m, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 26.0 (*C*(4′), C(6′)), 30.2 (*C*(4)), 30.4 (*C*(5′)), 32.7 (*C*(3)), 49.1 (*C*(5)), 51.4 (O*Me*), 52.1 (*C*(2′)), 135.0 (*C*(1)), 146.3 (*C*(2)), 164.9 (CO_2Me); *m*/*z* (FI^+) 244 ($[M]^+$, 100%); HRMS (FI^+) $C_{11}H_{16}O_2S_2$ ($[M]^+$) requires: 244.0592; found, 244.0602.

4.3. Methyl (*RS*)-5-tris(phenylthio)methyl-cyclopent-1-ene-carboxylate 25

BuLi (1.6 M in hexanes, 3.08 mL, 4.92 mmol) was added dropwise via syringe to a stirred solution of tris(phenylthio)methane (1.27 g, 4.92 mmol) in THF (10 mL) at −78 °C and stirred for 1.5 h. The mixture was then added dropwise via cannula to a stirred solution of **23** (1.0 g, 4.10 mmol) in THF (10 mL) at −78 °C. The resultant mixture was allowed to warm slowly to rt over 24 h before the addition of satd aq NH_4Cl (30 mL). The aqueous layer was separated and extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **25** as a colourless, viscous oil (1.70 g, 89%); ν_{max} (film) 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 1.98–2.88 (4H, m, C(3)H_2, C(4)H_2), 3.60 (1H, d, *J* 8.8, C(5)*H*), 3.71 (3H, s, O*Me*), 6.76 (1H, s, C(2)*H*), 7.22–7.53 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 29.4 (*C*(4)), 32.8 (*C*(3)), 51.6 (*C*(5)), 55.7 (O*Me*), 81.9 (*C*($SPh)_3$), 128.3, 129.1, 132.0 (*o*-, *m*-, *p*-*Ph*), 135.4 (*C*(1)), 136.6 (*i*-*Ph*), 146.3 (*C*(2)), 167.1 (CO_2Me); *m*/*z* (ESI^+) 487 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{26}H_{24}NaO_2S_3^+$ ($[M+Na]^+$) requires: 487.0831; found, 487.0836.

4.4. General procedure for lithium amide conjugate addition

BuLi (as a solution in hexanes) was added dropwise via syringe to a stirred solution of the requisite amine (or 50:50 mixture of amines) in THF at −78 °C. After stirring for 30 min, a solution of the requisite α,β-unsaturated ester in THF at −78 °C was added dropwise via cannula. After stirring for a further 2 h at −78 °C, the reaction mixture was quenched with satd aq NH_4Cl and allowed to warm to rt before being concentrated in vacuo. The residue was partitioned between EtOAc (50 mL) and 10% aq citric acid (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), dried and concentrated in vacuo.

4.5. Methyl (1*RS*,2*SR*,5*SR*)-2-(*N*,*N*-dibenzylamino)-5-(1′,3′-dithian-2′-yl)cyclopentane-carboxylate 27

Following the *General procedure*, BuLi (1.6 M in hexanes, 0.4 mL, 0.64 mmol), dibenzylamine (0.12 mL, 0.66 mmol) in THF (2 mL), and **24** (100 mg, 0.41 mmol) in THF (2 mL) gave (1*RS*,2*SR*,5*SR*)-**27** in >98% de. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave (1*RS*,2*SR*,5*SR*)-**27** as a colourless viscous oil (110 mg, 61%, >98% de); ν_{max} (film) 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 1.50–1.61 (1H, m, C(4)H_A), 1.71–1.80 (1H, m, C(3)H_A), 1.81–2.10 (4H, m, C(3)H_B, C(4)H_B, C(5′)H_2), 2.76–2.88 (4H, m, C(4′)H_2, C(6′)H_2), 2.92–3.01 (1H, m, C(5)*H*), 3.20–3.27 (1H, m, C(1)*H*), 3.39–3.46 (1H, m, C(2)*H*), 3.69 (4H, s, N(*C*H_2Ph)$_2$), 3.75 (3H, s, O*Me*), 3.98 (1H, d, *J* 7.1, C(2′)*H*), 7.13–7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.9, 28.2, 28.3, 29.8, 30.0 (*C*(3), *C*(4), *C*(4′), *C*(5′), *C*(6′)), 46.3 (*C*(5)), 51.3 (*C*(1)), 51.9 (O*Me*), 52.7 (*C*(2′)), 56.0 (N(*C*H_2Ph)$_2$), 66.1 (*C*(2)), 126.7, 127.0, 128.2, 128.3, 128.5,

128.6 (*o*-, *m*-, *p*-*Ph*), 139.8, 140.2 (*i*-*Ph*), 174.7 (CO_2Me); *m*/*z* (ESI^+) 442 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{32}NO_2S_2^+$ requires: 442.1869; found, 442.1869.

4.6. Methyl (1*RS*,2*SR*,5*SR*)-2-(*N*-benzyl-*N*-isopropylamino)-5-(1′,3′-dithian-2′-yl)cyclopentane-carboxylate 28

Following the *General procedure*, BuLi (1.6 M in hexanes, 0.4 mL, 0.64 mmol), *N*-benzyl-*N*-isopropylamine (0.12 mL, 0.66 mmol) in THF (2 mL), and **24** (100 mg, 0.41 mmol) in THF (2 mL) gave (1*RS*,2*SR*,5*SR*)-**28** in >98% de. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave (1*RS*,2*SR*,5*SR*)-**28** as a colourless viscous oil (85 mg, 53%, >98% de); ν_{max} (film) 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.6, CH_3CHCH$_3$), 0.99 (3H, d, *J* 6.6, CH_3CHCH_3), 1.49–1.60 (1H, m, C(5′)H_A), 1.66–1.72 (1H, m, C(3)H_A), 1.77–1.88 (2H, m, C(3)H_B, C(5′)H_B), 1.93–2.00 (1H, m, C(4)H_A), 2.02–2.08 (1H, m, C(4)H_B), 2.76–2.89 (5H, m, C(5)*H*, C(4′)H_2, C(6′)H_2), 3.03–3.17 (2H, m, C(1)*H*, NC*H*), 3.45–3.52 (1H, m, C(2)*H*), 3.63 (1H, d, *J* 14.4, NCH_A), 3.65 (1H, *J* 14.4, NCH_B), 3.70 (3H, s, O*Me*), 3.97 (1H, d, *J* 6.8, C(2′)*H*), 7.15–7.30 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.8 (CH_3CHCH$_3$), 19.0 (CH_3CHCH$_3$), 25.9, 28.2, 28.3, 29.9, 30.1 (*C*(3), *C*(4), *C*(4′), *C*(5′), *C*(6′)), 46.1 (*C*(5)), 49.6 (CH_3CHCH$_3$), 51.1 (NCH$_2$), 51.6 (O*Me*), 52.2 (*C*(1)), 52.8 (*C*(2)), 64.0 (*C*(2′)), 126.2, (*p*-*Ph*), 127.8, 127.9 (*o*-, *m*-*Ph*), 142.3 (*i*-*Ph*), 174.8 (CO_2Me); *m*/*z* (ESI^+) 394 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{32}NO_2S_2^+$ ($[M+H]^+$) requires: 394.1869; found, 394.1874.

4.7. Methyl (1*RS*,2*SR*,5*SR*)-2-(*N*,*N*-dibenzylamino)-5-tris(phenylthio)methyl-cyclopentane-carboxylate 29

Following the *General procedure*, BuLi (1.6 M in hexanes, 0.11 mL, 0.17 mmol), dibenzylamine (0.03 mL, 0.18 mmol) in THF (2 mL), and **25** (50 mg, 0.11 mmol) in THF (2 mL) gave (1*RS*,2*SR*,5*SR*)-**29** in >98% de. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave (1*RS*,2*SR*,5*SR*)-**29** as a white solid (64 mg, 88%, >98% de); mp 51–53 °C; ν_{max} (KBr) 1733 (C=O); δ_H (400 MHz, C_6D_6) 1.63–1.72 (1H, m, C(3)H_A), 1.89–2.11 (3H, m, C(3)H_B, C(4)H_2), 3.51 (3H, s, O*Me*), 3.70–3.76 (1H, m, C(2)*H*), 3.82 (4H, m, N(CH_2Ph)$_2$), 3.90–3.98 (1H, m, C(5)*H*), 4.18–4.21 (1H, m, C(1)*H*), 7.05–7.89 (25H, m, *Ph*); δ_C (125 MHz, C_6D_6) 27.4 (*C*(4)), 30.5 (*C*(3)), 31.7 (*C*(1)), 49.4 (O*Me*), 56.5 (*C*(5)), 67.1 (*C*(2)), 82.2 (*C*(SPh)$_3$), 127.2, 128.2, 128.9 (*o*-, *m*-, *p*-*Ph*), 134.7, 138.6 (*i*-*Ph*), 171.9 (CO_2Me); *m*/*z* (ESI^+) 662 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{40}H_{40}NO_2S_3^+$ ($[M+H]^+$) requires: 662.2216; found, 662.2216.

4.8. Methyl (1*RS*,2*SR*,5*SR*)-2-(*N*-benzyl-*N*-isopropylamino)-5-tris(phenylthio)methyl-cyclopentane-carboxylate 30

Following the *General procedure*, BuLi (1.6 M in hexanes, 0.11 mL, 0.17 mmol), *N*-benzyl-*N*-isopropylamine (0.03 mL, 0.18 mmol) in THF (2 mL), and **25** (50 mg, 0.11 mmol) in THF (2 mL) gave (1*RS*,2*SR*,5*SR*)-**30** in >98% de. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **30** as a white solid (62 mg, 92%, >98% de); mp 52–54 °C; ν_{max} (KBr) 1731 (C=O); δ_H (500 MHz, C_6D_6) 1.04 (3H, d, *J* 6.6, CH_3CHCH$_3$), 1.10 (3H, d, *J* 6.6, CH_3CHCH_3), 1.60–1.67 (1H, m, C(3)H_A), 1.82–1.93 (1H, m, C(3)H_B), 1.96–2.04 (1H, m, C(4)H_A), 2.11–2.22 (1H, m, C(4)H_B), 3.37–3.43 (1H, m, CH_3C*H*CH$_3$), 3.49 (3H, s, O*Me*), 3.61 (2H, m, NCH_2), 3.77–3.86 (2H, m, C(2)*H*, C(5)*H*), 4.01–4.06 (1H, m, C(1)*H*), 6.91–7.78 (20H, m, *Ph*); δ_C (125 MHz, C_6D_6) 16.4 (CH_3CHCH$_3$), 20.4 (*C*(4)), 28.5 (*C*(3)), 30.7 (*C*(1)), 50.2, 50.9, 51.3, 51.8, 53.2 (*C*(2), *C*(5), NCH$_2$, O*Me*, CH_3CHCH$_3$), 81.7 (*C*(SPh)$_3$), 132.8, 136.3 (*o*-, *m*-, *p*-*Ph*), 140.3 (*i*-*Ph*), 174.9 (CO_2Me); *m*/*z* (ESI^+) 614 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{36}H_{40}NO_2S_3^+$ ($[M+H]^+$) requires: 614.2216; found, 614.2216.

4.9. Methyl (1*RS*,2*SR*,5*SR*,α*SR*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-(1′,3′-dithian-2′-yl)cyclopentane-carboxylate 31

Following the *General procedure*, BuLi (1.6 M in hexanes, 0.4 mL, 0.64 mmol), (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (344 mg, 1.64 mmol) in THF (2 mL), and **24** (100 mg, 0.41 mmol) gave (1*RS*,2*SR*,5*SR*,α*SR*)-**31** in >98% de. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave (1*RS*,2*SR*,5*SR*,α*SR*)-**31** as a white solid (89 mg, 48%, >98% de); mp 59–61 °C; ν_{max} (KBr) 1727 (C=O); δ_H (400 MHz, C_6D_6) 1.19 (3H, d, *J* 6.8, C(α)*Me*), 1.33–1.43 (3H, m, C(3)H_A, C(4)H_A, C(5′)H_A), 1.45–1.50 (1H, m, C(5′)H_B), 1.74–1.92 (2H, m, C(3)H_B, C(4)H_B), 2.16–2.40 (4H, m, C(4′)H_2, C(6′)H_2), 3.05–3.15 (1H, m, C(5)*H*), 3.27 (1H, dd, *J* 6.5, 9.3, C(1)*H*), 3.36–3.45 (1H, m, C(2)*H*), 3.55 (3H, s, O*Me*), 3.58 (1H, d, *J* 6.8, C(2′)*H*), 3.65 (1H, d, *J* 14.4, NCH_A), 3.78 (1H, d, *J* 14.4, NCH_B), 4.22 (1H, q, *J* 6.8, C(α)*H*), 7.07–7.47 (10H, m, *Ph*); δ_C (125 MHz, C_6D_6) 15.6 (C(α)*Me*), 26.1 (*C*(5′)), 28.3, 28.5, 29.5, 30.1 (*C*(3), *C*(4), *C*(4′), *C*(6′)), 46.7 (*C*(5)), 51.5, 52.0, 52.1 (*C*(1), *C*(2), *C*(2′)), 57.5 (O*Me*), 59.2 (NCH$_2$), 64.2 (*C*(α)), 126.8, 127,8, 129.1 (*o*-, *m*-, *p*-*Ph*), 141.8, 143.3 (*i*-*Ph*), 174.8 (CO_2Me); *m*/*z* (ESI^+) 457 ($[M+H]^+$, 85%), 352 (100); HRMS (ESI^+) $C_{26}H_{34}NO_2S_2^+$ ($[M+H]^+$) requires: 456.2025; found, 456.2031.

4.10. Methyl (1*RS*,2*SR*,5*SR*,α*SR*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-tris(phenylthio)methyl-cyclopentane-carboxylate 32

Following the *General procedure*, BuLi (1.6 M in hexanes, 0.5 mL, 0.80 mmol), (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (180 mg, 0.84 mmol) in THF (2 mL), and **25** (100 mg, 0.21 mmol) in THF (2 mL) gave (1*RS*,2*SR*,5*SR*,α*SR*)-**32** in >98% de. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave (1*RS*,2*SR*,5*SR*,α*SR*)-**32** as a white solid (132 mg, 93%, >98% de); $C_{41}H_{41}NO_2S_3$ requires: C, 72.85; H, 6.1; N, 2.1; S, 14.2. Found: C, 72.8; H, 6.4; N, 1.9; S, 14.1; mp 53–55 °C; ν_{max} (KBr) 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.8, C(α)*Me*), 1.45–1.59 (3H, m, C(4)H_A, C(3)H_2), 1.63–1.67 (1H, m, C(4)H_B), 3.26–3.31 (1H, m, C(5)*H*), 3.37 (1H, d, *J* 15.6, NCH_A), 3.51–3.57 (1H, m, C(2)*H*), 3.62 (3H, s, OCH_3), 3.78 (1H, dd, *J* 3.8, 8.5, C(1)*H*), 3.92 (1H, d, *J* 15.6, NCH_B), 4.30 (1H, q, *J* 6.8, C(α)*H*), 7.24–7.41 (20H, m, *Ph*), 7.54–7.56 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.0 (C(α)*Me*), 27.5 (*C*(3)), 30.2 (*C*(4)), 50.7 (*C*(1)), 51.0 (NCH$_2$), 51.7 (O*Me*), 52.5 (*C*(5)), 57.9 (*C*(α)), 65.7 (*C*(2)), 80.7 (*C*(SPh)$_3$), 126.3, 126.3, 126.9, 127.6, 128.0, 128.0, 128.4, 128.5, 129.0 (*o*-, *m*-, *p*-*Ph*), 132.0 (*i*-*Ph*), 135.9 (*Ph*), 141.7, 142.5 (*i*-*Ph*), 175.3 (CO_2Me); *m*/*z* (ESI^+) 676 ($[M+H]^+$, 45%), 461 (100); HRMS (ESI^+) $C_{41}H_{42}NO_2S_3^+$ ($[M+H]^+$) requires: 676.2378; found, 676.2372.

4.11. Methyl (1*R*,2*S*,5*S*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-5-tris(phenylthio)methyl-cyclopentane-carboxylate 32 and methyl (1*S*,2*R*,5*R*,α*R*)-2-[*N*-(3,4-dimethoxybenzyl)-*N*-(α-methylbenzyl)amino]-5-tris(phenylthio)methyl-cyclopentane-carboxylate 34

Following the *General procedure*, BuLi (1.6 M in hexanes, 13.0 mL, 20.7 mmol), (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (2.25 mL, 10.8 mmol) and (*R*)-*N*-(3,4-dimethoxybenzyl)-*N*-(α-methylbenzyl)amine (2.90 mL, 10.8 mmol) in THF (20 mL), and **25** (2.50 g, 5.38 mmol) in THF (20 mL) gave a 50:50 mixture of (1*R*,2*S*,5*S*,α*S*)-**32** (>98% de) and (1*S*,2*R*,5*R*,α*R*)-**34** (>98% de) only. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave (1*R*,2*S*,5*S*,α*S*)-**32** as a white solid (1.52 g, 42%, >98% de); $[\alpha]_D^{23} = -81.9$ (*c* 1.0, $CHCl_3$). Further elution (eluent 30–40 °C petrol/Et_2O, 1:1) gave (1*S*,2*R*,5*R*,α*R*)-**34** as a white solid (1.60 g, 41%, >98% de); mp 54–56 °C; $[\alpha]_D^{23} = +72.0$ (*c* 1.0, $CHCl_3$);

ν_{max} (KBr) 1729 (C=O); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.7, C(α)*Me*), 1.49–1.59 (2H, m, C(3)H_A, C(4)H_A), 1.62–1.73 (2H, m, C(3)H_B, C(4)H_B), 3.30 (1H, dt, *J* 8.3, 4.0, C(5)*H*), 3.36 (1H, d, *J* 15.6, NCH_A), 3.50–3.56 (1H, m, C(2)*H*), 3.61 (3H, s, CO_2Me), 3.77 (1H, dd, *J* 4.0, 8.3, C(1)*H*), 3.85 (3H, s, ArO*Me*), 3.86 (1H, d, *J* 15.6, NCH_B), 3.92 (3H, s, ArO*Me*), 4.29 (1H, q, *J* 6.7, C(α)*H*), 6.75–6.81 (2H, m, *Ar*), 6.99–7.02 (1H, m, *Ar*), 7.25–7.58 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.5 (C(α)*Me*), 27.6, 30.0 (*C*(3), *C*(4)), 50.8 (*C*(1)), 50.8 (NCH_2), 51.7 (CO_2Me), 52.5 (*C*(5)), 55.8 (ArO*Me*), 55.9 (ArO*Me*), 57.5 (*C*(α)), 65.5 (*C*(2)), 80.7 (*C*(SPh)$_3$), 110.4, 110.6, 111.0, 119.3, 126.9, 128.0, 128.4, 129.0, 132.0, 134.8, 135.9, 141.9, 147.4, 148.8 (*Ar*, *Ph*), 175.4 (CO_2Me); *m*/*z* (ESI$^+$) 736 ([M+H]$^+$, 20%), 476 (100); HRMS (ESI$^+$) $C_{43}H_{46}NO_4S_3^+$ ([M+H]$^+$) requires: 736.2589; found, 736.2584.

4.12. X-ray crystal structure determination for 34

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 150 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.[17]

X-ray crystal structure data for **34** [$C_{43}H_{45}NO_4S_3$]: M = 736.03, orthorhombic, space group $P2_12_12_1$, a = 9.82860(10) Å, b = 17.4111(2) Å, c = 22.6109(3) Å, V = 3869.33(8) Å^3, Z = 4, μ = 0.23 mm^{-1}, colourless plate, crystal dimensions = 0.1 × 0.1 × 0.2 mm^3. A total of 8780 unique reflections were measured for $5 < \theta < 27$ and 6671 reflections were used in the refinement. The final parameters were wR_2 = 0.031 and R_1 = 0.029 [$I > 3\sigma(I)$]. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 665858. 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 e-mail: deposit@ccdc.cam.ac.uk].

4.13. Methyl (1*R*,2*S*,5*S*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-methyl-cyclopentane-carboxylate 35

Raney Nickel (50% slurry in H_2O, 8 mL) was added in five equal portions to a stirred solution of **32** (1.62 g, 2.40 mmol) in THF (40 mL) over a period of 8 h. The reaction mixture was filtered through Celite and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 12:1) gave **35** as a colourless oil (0.66 g, 79%, >98% de); $[\alpha]_D^{20} = -50.4$ (*c* 1.1, $CHCl_3$); ν_{max} (film) 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.3, C(5)*Me*), 1.04 (1H, m, C(4)H_A), 1.36 (3H, d, *J* 6.8, C(α)*Me*), 1.74 (1H, m, C(3)H_A), 1.74–2.09 (2H, m, C(3)H_B, C(4)H_B), 2.37–2.49 (2H, m, C(1)*H*, C(5)*H*), 3.53 (1H, m, C(2)*H*), 3.74 (3H, s, O*Me*), 3.87 (2H, m, NCH_2), 4.02 (1H, q, *J* 6.8, C(α)*H*), 7.23–7.30 (2H, m, *Ph*), 7.33–7.46 (8H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (C(5)*Me*), 20.7 (C(α)*Me*), 29.2 (*C*(3)), 33.1 (*C*(4)), 37.0 (*C*(5)), 51.4 (O*Me*), 51.9 (NCH_2), 56.5 (*C*(α)), 56.6 (*C*(1)), 61.8 (*C*(2)), 126.6, 127.8, 128.0, 128.1, 128.4 (*o*-, *m*-, *p*-*Ph*), 141.4, 143.5 (*i*-*Ph*), 174.9 (CO_2Me); *m*/*z* (ESI$^+$) 352 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{30}NO_2^+$ ([M+H]$^+$) requires: 352.2271; found, 352.2273.

4.14. Methyl (1*S*,2*R*,5*R*,α*R*)-2-[*N*-(3,4-dimethoxybenzyl)-*N*-(α-methylbenzyl)amino]-5-methyl-cyclopentane-carboxylate 36

Raney Nickel (50% slurry in H_2O, 4 mL) was added in five equal portions to a stirred solution of **34** (0.74 g, 0.34 mmol) in THF (20 mL) over a period of 8 h. The reaction mixture was filtered through Celite and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 6:1) gave **36** as a colourless oil (0.28 g, 67%, >98% de); $[\alpha]_D^{23} = +27.0$ (*c* 0.9, $CHCl_3$); ν_{max} (KBr) 2951 (N–H), 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.3, C(5)*Me*), 0.97–1.07 (1H, m, C(4)H_A), 1.31 (3H, d, *J* 6.8, C(α)*Me*), 1.70–1.77 (1H, m, C(3)H_A), 1.94–2.07 (2H, m, C(3)H_B, C(4)H_B), 2.38–2.43 (2H, m, C(1)*H*, C(5)*H*), 3.47–3.53 (1H, m, C(2)*H*), 3.64 (3H, s, CO_2Me), 3.75 (2H, s, NCH_2), 3.87 (3H, s, ArO*Me*), 3.93 (3H, s, ArO*Me*), 3.96 (1H, q, *J* 6.8, C(α)*H*), 6.79 (1H, d, *J* 8.2, C(6′)*H*), 6.87 (1H, dd, *J* 1.1, 8.2, C(5′)*H*), 7.11 (1H, d, *J* 1.1, C(3′)*H*), 7.21–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.6 (C(α)*Me*), 20.6 (C(5)*Me*), 28.8 (*C*(3)), 33.1 (*C*(4)), 37.0 (*C*(5)), 51.2 (CO_2Me), 51.7 (NCH_2), 55.8 (ArO*Me*), 55.8 (ArO*Me*), 56.9 (*C*(α)), 61.4 (*C*(2)), 110.5, 111.7, 120.3, 126.5, 127.7, 128.0, 133.8, 143.6, 147.6, 148.8 (*Ar*, *Ph*), 174.7 (CO_2Me); *m*/*z* (ESI$^+$) 412 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{34}NO_4^+$ ([M+H]$^+$) requires: 412.2483; found, 412.2488.

4.15. Methyl (1*S*,2*R*,5*R*,α*R*)-2-[*N*-(α-methylbenzyl)amino]-5-methyl-cyclopentane-carboxylate 37

DDQ (0.67 g, 2.90 mmol) was added portionwise to a stirred solution of β-amino ester **36** (0.60 g, 1.47 mmol) in a solution of DCM (60 mL) and H_2O (8 mL) at rt. The resultant mixture was stirred for 18 h before the addition of satd aq $NaHCO_3$ (50 mL). The aqueous layer was separated and extracted with DCM (2 × 50 mL). The combined organic layers were washed with brine (150 mL), dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 5:1) gave **37** as a colourless oil (0.31 g, 82%, >98% de); $[\alpha]_D^{20} = +126$ (*c* 1.0, $CHCl_3$). ν_{max} (film) 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 0.99 (3H, d, *J* 6.6, C(5)*Me*), 1.02 (1H, m, C(4)H_A), 1.25 (3H, d, *J* 6.7, C(α)*Me*), 1.52 (1H, m, C(3)H_A), 1.67 (1H, br s, N*H*), 1.80–1.90 (2H, m, C(3)H_B, C(4)H_B), 2.49 (1H, t, *J* 8.0, C(1)*H*), 3.22 (1H, m, C(2)*H*), 3.69 (1H, q, *J* 6.7, C(α)*H*), 3.76 (3H, s, O*Me*), 7.25 (1H, m, *Ph*), 7.30–7.33 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.6 (C(5)*Me*), 24.8 (C(α)*Me*), 32.2 (*C*(4)), 34.2 (*C*(3)), 37.7 (*C*(5)), 51.4 (O*Me*), 54.9 (*C*(1)), 56.7 (*C*(α)H), 59.5 (*C*(2)), 126.7, 126.8, 128.3 (*o*-, *m*-, *p*-*Ph*), 146.1 (*i*-*Ph*), 175.4 (*C*=O); *m*/*z* (ESI$^+$) 262 ([M+H]$^+$, 97%); HRMS (ESI$^+$) $C_{16}H_{23}NNaO_2^+$ ([M+Na]$^+$) requires: 284.1621; found, 284.1620.

4.16. Methyl (1*R*,2*S*,5*S*)-2-ammonio-5-methyl-cyclopentane-carboxylate trifluoroacetate (1*R*,2*S*,5*S*)-38

$Pd(OH)_2$/C (20 mg) was added to a degassed solution of **35** (95 mg, 0.35 mmol) in AcOH/MeOH (40:1, 5 mL) and stirred for 2 h under H_2 (1 atm). The reaction mixture was filtered through Celite and concentrated in vacuo. The residue was redissolved in DCM (2 mL) and treated with TFA (2 mL). After 15 min stirring the solution was concentrated in vacuo. This process was repeated twice to give (1*R*,2*S*,5*S*)-**38** as a colourless oil (67 mg, 91%, >98% de, >98% ee); $[\alpha]_D^{20} = +29.8$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 1700 (C=O); δ_H (400 MHz, CD_3OD) 1.14 (3H, d, *J* 6.5, C(5)*Me*), 1.33–1.37 (1H, m, C(4)H_A), 1.78–1.83 (1H, m, C(3)H_A), 2.03–2.10 (1H, m, C(4)H_B), 2.19–2.25 (1H, m, C(3)H_B), 2.34–2.41 (1H, m, C(5)*H*), 2.65 (1H, dd, *J* 2.3, 7.5, C(1)*H*), 3.76 (3H, s, O*Me*), 3.85 (1H, q, *J* 6.5, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 18.5 (C(5)*Me*), 30.4 (*C*(3)), 31.3 (*C*(4)), 37.7 (*C*(5)), 51.7 (O*Me*), 53.0 (*C*(2)), 53.1 (*C*(1)), 116.2 (q, $^1J_{C-F}$ 280, *C*F$_3$), 160.3 (q, $^2J_{C-F}$ 37, CF$_3$*C*O), 173.3 (*C*=O); *m*/*z* (ESI$^+$) 158 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_8H_{16}NO_2^+$ ([M+H]$^+$) requires: 158.1176; found, 158.1175.

4.17. Methyl (1*S*,2*R*,5*R*)-2-ammonio-5-methyl-cyclopentane-carboxylate trifluoroacetate (1*S*,2*R*,5*R*)-38

$Pd(OH)_2$/C (26 mg) was added to a degassed solution of **37** (110 mg, 0.41 mmol) in AcOH/MeOH (40:1, 5 mL) and stirred for

2 h under H_2 (1 atm). The reaction mixture was filtered through Celite and concentrated in vacuo. The residue was redissolved in DCM (2 mL) and treated with TFA (2 mL). After 15 min stirring the solution was concentrated in vacuo. This process was repeated twice to give (1*S*,2*R*,5*R*)-**38** as a colourless oil (100 mg, 95%, >98% de, >98% ee); $[\alpha]_D^{17} = -30.0$ (*c* 1.0, $CHCl_3$).

4.18. (1*R*,2*S*,5*S*)-2-Amino-5-methyl-cyclopentane-carboxylic acid (1*R*,2*S*,5*S*)-39

LiOH (2 M, 0.75 mL, 1.5 mmol) was added to a stirred solution of (1*R*,2*S*,5*S*)-**38** (82 mg, 0.3 mmol) in THF (3 mL) at rt and stirred for 16 h. The reaction mixture was concentrated in vacuo, re-dissolved in 1 M aq HCl (5 mL) and then concentrated in vacuo. Purification via ion exchange chromatography (Dowex 50WX8-200 resin) gave (1*R*,2*S*,5*S*)-**39** as a white solid (41 mg, 95%, >98% de); mp >360 °C; $[\alpha]_D^{17} = +19.0$ (*c* 1.0, H_2O); ν_{max} (film) 1695 (C=O); δ_H (400 MHz, D_2O) 1.03 (3H, d, *J* 6.6, C(5)*Me*), 1.22–1.26 (1H, m, C(4)H_A), 1.66–1.70 (1H, m, C(3)H_A), 1.93–1.97 (1H, m, C(4)H_B), 2.07–2.17 (2H, m, C(5)*H*, C(3)H_B), 2.27 (1H, dd, *J* 6.6, 10.1, C(1)*H*), 3.69–3.75 (1H, m, C(2)*H*); δ_C (125 MHz, D_2O) 18.8 (C(5)*Me*), 29.6 (*C*(3)), 30.5 (*C*(4)), 37.4 (*C*(5)), 53.1 (*C*(2)), 55.2 (*C*(1)), 180.4 (*C*=O); *m/z* (ESI^-) 142 ($[M-H]^-$, 89%); HRMS (ESI^+) $C_7H_{13}NNaO_2^+$ ($[M+Na]^+$) requires: 166.0838; found, 166.0837.

4.19. (1*S*,2*R*,5*R*)-2-Amino-5-methyl-cyclopentane-carboxylic acid (1*S*,2*R*,5*R*)-39

LiOH (2 M, 0.5 mL, 1.0 mmol) was added to a stirred solution of (1*S*,2*R*,5*R*)-**38** (49 mg, 0.18 mmol) in THF (3 mL) at rt and stirred for 16 h. The reaction mixture was concentrated in vacuo, re-dissolved in 1 M aq HCl (5 mL) and then concentrated in vacuo. Purification via ion exchange chromatography (Dowex 50WX8-200 resin) gave (1*S*,2*R*,5*R*)-**39** as a white solid (24 mg, 93%, >98% de); $[\alpha]_D^{17} = -18.8$ (*c* 1.0, H_2O).

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