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Asymmetric synthesis of the stereoisomers of 2-amino-5-carboxymethyl-cyclopentane-1-carboxylate

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The stereoisomers of 2-amino-5-carboxymethyl-cyclopentane-1-carboxylate may be prepared stereoselectively from diester derivatives of (*E*,*E*)-octa-2,6-diendioc acid, with the key step utilising the conjugate addition of homochiral lithium *N*-benzyl-*N*-α-methylbenzylamide. The *trans*-C(1)–C(2)-stereoisomers are readily prepared *via* a diastereoselective tandem conjugate addition cyclisation protocol with lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide, with subsequent hydrogenolysis and ester hydrolysis giving the (1*R*,2*R*,5*R*)- and (1*R*,2*R*,5*S*)-β-amino diacids in good yields. The preparation of the *cis*-C(1)–C(2)-stereoisomers utilises a protocol involving *N*-oxidation and Cope elimination of the major diastereoisomeric product arising from conjugate addition and cyclisation, giving homochiral (*R*)-5-carboxymethyl-cyclopentene-1-carboxylate. Conjugate addition of either lithium (*R*)- or (*S*)-*N*-benzyl-*N*-α-methylbenzylamide to (*R*)-5-carboxymethyl-cyclopentene-1-carboxylate, and diastereoselective protonation with 2,6-di-*tert*-butyl phenol gives, after hydrogenolysis and ester hydrolysis, the (1*S*,2*R*,5*R*)- and (1*R*,2*S*,5*R*)-β-amino diacids in good yield. The use of (*S*)-*N*-benzyl-*N*-α-methylbenzylamide in the initial conjugate addition and cyclisation reaction, and subsequent repetition of the elimination and conjugate addition strategy allows stereoselective access to all stereoisomers of 2-amino-5-carboxymethyl-cyclopentane-1-carboxylate.

Introduction

The asymmetric synthesis of polyfunctionalised cyclopentane derivatives has been widely pursued in organic synthesis, predominantly due to their incorporation in a variety of natural products including monoterpenes,[1] nepetalactones[2] and prostaglandins.[3] A range of methodologies for the asymmetric synthesis of cyclopentane derived β-amino acids has been devised, with much recent interest focusing around strategies for the asymmetric synthesis of the *cis*- and *trans*-diastereoisomers of 2-aminocylopentanecarboxylic acid (cispentacin **1** and transpentacin **2** respectively). The *cis*-diastereoisomer shows potent antifungal activity[4] while Fulop *et al*. have recently demonstrated that oligomers of cispentacin adopt a sheet type structure in DMSO.[5] Furthermore, Gellman *et al.* have demonstrated that short chain β-peptides derived from transpentacin adopt 12-membered helical stuctures in both the solid state and in solution,[6] while 3-substituted transpentacin derivatives fold in water, which should facilitate the design of β-peptides for biological applications (Fig. 1).[7]

We have previously employed the highly diastereoselective conjugate addition of homochiral lithium amides to α,β-unsaturated esters for the asymmetric synthesis of an extensive range of β-amino acid derivatives,[8] as illustrated in Scheme 1 for the synthesis of (1*R*,2*S*)-cispentacin **1** and (1*S*,2*S*)-transpentacin **2**.[9] Conjugate addition of homochiral lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **6** to *tert*-butyl cyclopentene-1-carboxylate **3** and subsequent *N*-deprotection and ester hydrolysis gives (1*R*,2*S*)-cispentacin **1**, while selective epimerisation of β-amino ester (1*R*,2*S*,α*S*)-**4** to the thermodynamic epimer (1*S*,2*S*,α*S*)-**5** and further deprotection gives (1*S*,2*S*)-transpentacin **2**.

To extend the generality of this methodology, and expand the diversity of both cis- and transpentacin derivatives available for secondary structural studies, the asymmetric synthesis of the stereoisomers of 2-amino-5-carboxymethyl-cyclopentane-1-carboxylate was investigated. Yamamoto *et al.* have previously demonstrated that the addition of achiral lithium *N*-benzyl-*N*-trimethylsilylamide to dimethyl (*E*,*E*)-octa-2,6-diendioate facilitates tandem conjugate addition and intramolecular cyclisation, generating the (1*RS*,2*RS*,5*RS*)-2-amino-5-carboxymethyl-cyclopentane-1-carboxylate skeleton.[10] It was predicted that the use of homochiral (*R*)- or (*S*)-lithium *N*-benzyl-*N*-α-methylbenzylamide in this protocol, coupled with further synthetic elaboration would give rise to the diastereo- and enantiocontrolled construction of the steroisomers of 2-amino-5-carboxymethyl-cyclopentane-1-carboxylate. The realisation of this synthetic strategy is contained herein, part of which has been communicated previously.[11]

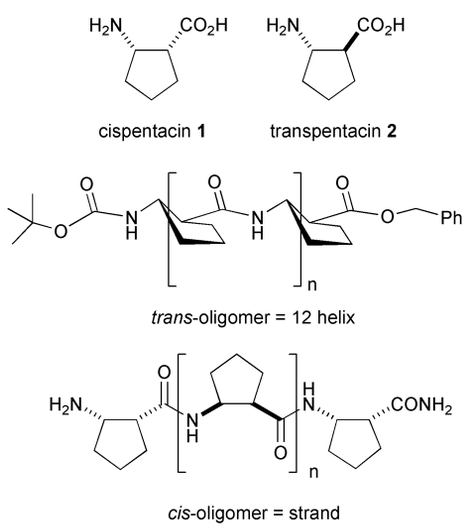

Fig. 1 Monomeric and oligomeric cispentacin and transpentacin.

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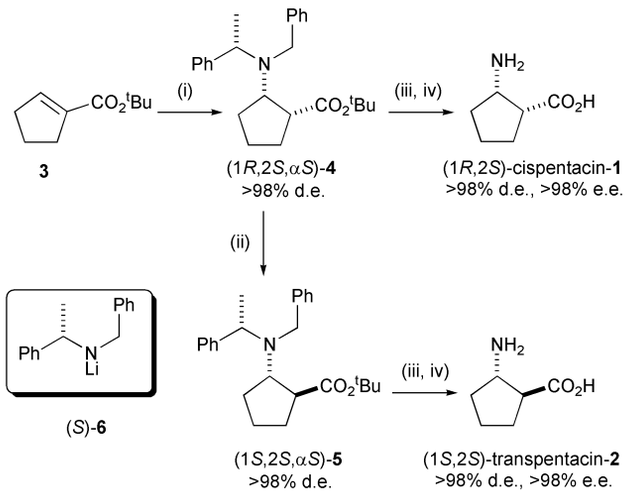
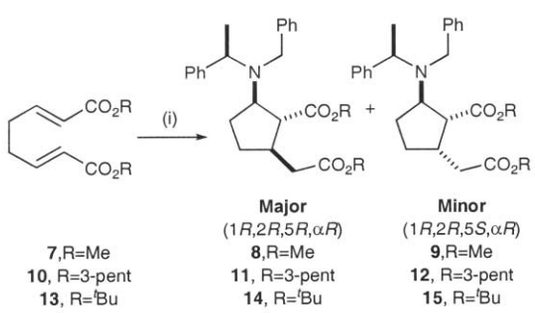


Scheme 1 *Reagents and conditions*: (i). Lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **6**, THF, −95 °C then 2,6-di-*tert*-butyl phenol; (ii). KO^{t}Bu, ^{t}BuOH, rt; (iii). Pd/C, MeOH, H_2 (5 atm), rt; (iv). TFA then Dowex 50X8-200.

Results and discussion

Asymmetric tandem conjugate addition cyclisation; synthesis of the *trans*-C(1)–C(2) stereoisomers

Initial studies concentrated upon studying the product distribution arising from the conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **6** to a range of diester derivatives of (*E*,*E*)-octa-2,6-diendioic acid. Conjugate addition of lithium amide (*R*)-**6** to dimethyl (*E*,*E*)-octa-2,6-diendioate **7** in THF at −78 °C gave a 91 : 9 mixture of the two C(5)-epimeric diastereoisomers (1*R*,2*R*,5*R*,α*R*)-**8** and (1*R*,2*R*,5*S*,α*R*)-**9**. Chromatographic purification enabled separation and characterisation of the two β-amino ester diastereoisomers **8** and **9**, in 86% overall yield, with none of the diamino ester product arising from double conjugate addition of lithium amide to (*E*,*E*)-**7** visible by spectroscopic analysis of the crude reaction mixture.[12] The generality of this protocol was explored further, *via* the conjugate addition of lithium amide (*R*)-**6** to either the di-3-pentyl or di-*tert*-butyl ester derivatives **10** and **13**, which furnished a 92 : 8 and a 93 : 7 mixture of the separable C(5) epimeric diastereoisomers **11** : **12** and **14** : **15** respectively in good yields (83% and 90% yield overall) after chromatographic purification (Scheme 2).



R	d.r.	Major	Yield (%)	Minor	Yield (%)
Me	91:9	**8**	80	**9**	6
3-Pent	92:8	**11**	77	**12**	6
^{t}Bu	93:7	**14**	83	**15**	7

Scheme 2 *Reagents and conditions*: (i). Lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **6**, THF, −78 °C.

In each case, the relative configuration within both the major and minor diastereoisomers was assigned on the basis of either ^{1}H NMR NOE difference or ^{1}H NMR ROESY experiments, with the absolute configuration at C(2) within (1*R*,2*R*,5*R*,α*R*)-**8** and (1*R*,2*R*,5*S*,α*R*)-**9** relative to the *N*-α-methylbenzyl stereocentre assigned by analogy with previous authenticated models developed to explain the stereoselectivity observed during addition of lithium amide **6** to α,β-unsaturated acceptors.[13] For instance, the major diastereoisomer (1*R*,2*R*,5*R*,α*R*)-**8** arising from cyclisation of dimethyl (*E*,*E*)-**7** showed a 4% NOE enhancement between C(1)**H** and one of the C(5)C**H**$_2$CO$_2$Me protons, a 9% NOE enhancement between C(1)**H** and one of the NC**H**$_2$Ph protons and a 5% enhancement between C(2)**H** and C(5)**H**, indicating the *anti*-configuration between both C(1)**H** and C(2)**H**, and C(1)**H** and C(5)**H**. For the minor diastereoisomer (1*R*,2*R*,5*S*,α*R*)-**9**, ^{1}H NMR ROESY experiments indicated a *syn*-relationship between C(1)**H** and C(5)**H**, and the *anti*-relationship between C(1)**H** and C(2)**H** (Fig. 2).

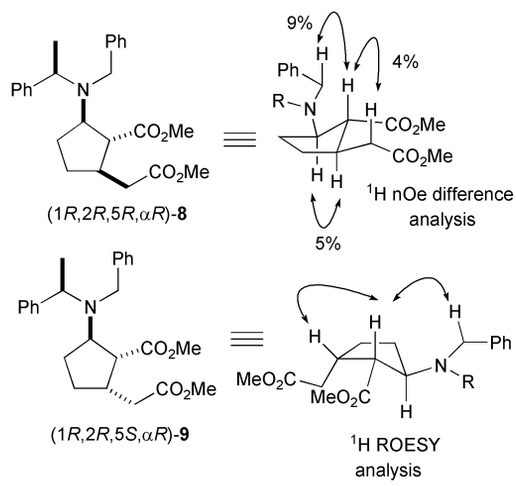


Fig. 2 ^{1}H NMR stereochemical analysis of major and minor diastereoisomers **8** and **9**.

This indicates that both diastereoisomers have identical configurations at C(1) and C(2), but differ at C(5), consistent with the expected high levels of stereocontrol in the initial lithium amide conjugate addition reaction, with the mixture of diastereoisomers arising upon cyclisation of the resultant (*Z*)-β-amino enolate.[14] The relative configuration within the major diastereoisomer (1*R*,2*R*,5*R*,α*R*)-**8** was further confirmed unambiguously by X-ray crystallographic analysis, with the absolute configuration arising from the known (*R*)-stereocentre of the α-methylbenzylamine derived fragment (Fig. 3).

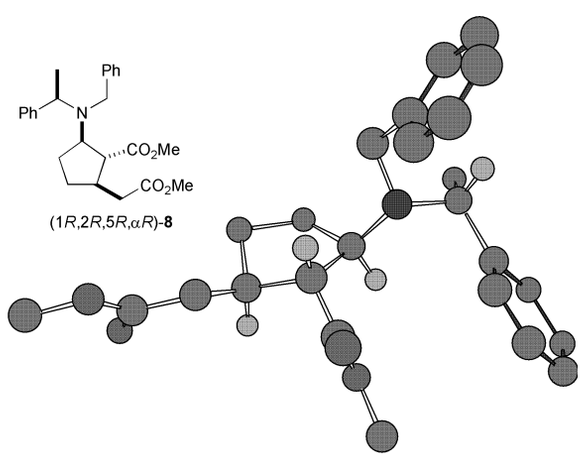
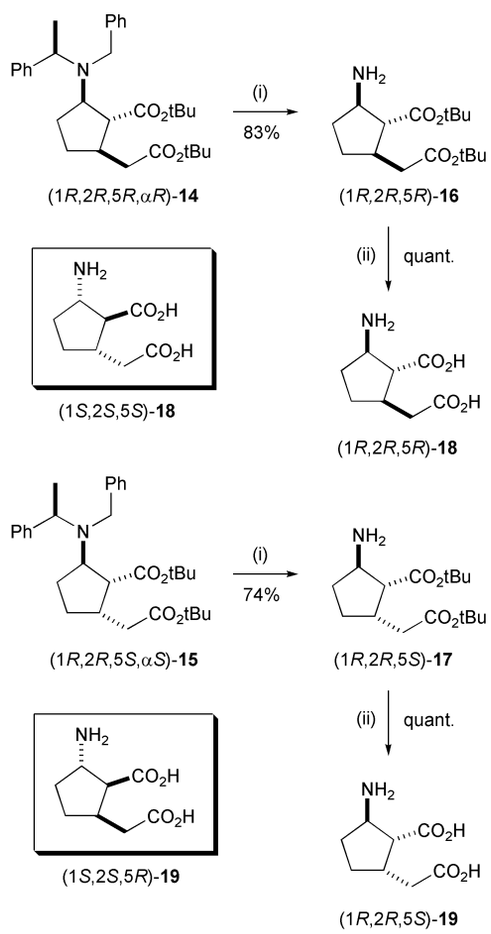


Fig. 3 Chem 3D representation of the X-ray crystal structure of (1*R*,2*R*,5*R*,α*R*)-**8** (some H omitted for clarity).

With a range of C(1)–C(2)-*trans* β-amino ester diastereoisomers in hand from this addition cyclisation protocol, the di-*tert*-butyl ester derivatives (1*R*,2*R*,5*R*,α*R*)-**14** and (1*R*,2*R*,5*S*,α*R*)-**15** were deprotected to their parent β-amino diacids.

Hydrogenolysis of β-amino esters **14** and **15** to the corresponding primary β-amino esters, a process we have previously demonstrated occurs without loss of stereochemical integrity,[15] furnished (1*R*,2*R*,5*R*)-**16** and (1*R*,2*R*,5*S*)-**17** in 83% and 74% yield respectively, and in >98% de in each case. Subsequent ester hydrolysis and purification by ion exchange chromatography gave the β-amino diacids (1*R*,2*R*,5*R*)-**18** {$[\alpha]_D^{26}$ +2.4 (*c* 1.0, H_2O)} and (1*R*,2*R*,5*S*)-**19** {$[\alpha]_D^{26}$ −35.0 (*c* 0.6, H_2O)} in quantitative yield and in >98% de in each case. With (1*R*,2*R*,5*R*)-**18** and (1*R*,2*R*,5*S*)-**19** in hand, the preparation of the enantiomeric β-amino diacids was investigated. Addition of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide to the diester **13** and subsequent manipulation furnished β-amino diacids (1*S*,2*S*,5*S*)-**18** {$[\alpha]_D^{26}$ − 2.7 (*c* 0.6, H_2O)} and (1*S*,2*S*,5*R*)-**19** {$[\alpha]_D^{26}$ +44.7 (*c* 1.0, H_2O)]} in good yield, enantiomeric, respectively, with (1*R*,2*R*,5*R*)-**18** and (1*R*,2*R*,5*S*)-**19** (Scheme 3).



Scheme 3 *Reagents and conditions*: (i). Pd/C, MeOH, H_2 (6 atm), rt; (ii). TFA, rt then Dowex 50 × 8–200.

Asymmetric synthesis of the C(1)–C(2)-*cis* diastereoisomers

With the asymmetric synthesis of the four C(1)–C(2)-*trans* 2-amino-5-carboxymethyl-cyclopentane-1-carboxylate stereoisomers complete, attention turned to the preparation of the set of stereoisomers with the *cis*-C(1)–C(2) configuration. Previous work from our laboratory has shown that conjugate addition of lithium amides to cyclic α-alkyl-α,β-unsaturated acceptors and subsequent diastereoselective protonation with the hindered proton source 2,6-di-*tert*-butyl phenol gives rise to the *cis*-C(1)–C(2) configuration with high levels of selectivity.[16] It was predicted that this methodology could be used to generate the *cis*-C(1)–C(2) configuration of the desired 2-amino-5-carboxymethyl-cyclopentane-1-carboxylate stereoisomers, through the conjugate addition of a chiral lithium amide to a homochiral 5-carboxyalkyl cyclopentene-1-carboxylate. Such chiral α,β-unsaturated acceptors are highly desirable in their own right, having previously been synthesised in both racemic and enantiomerically enriched form and used as building blocks for the synthesis of a range of monoterpenes such as dolichodial and mitsugashiwalactone.[17] It was envisaged that the desired acceptor would be readily available by *N*-oxidation and Cope elimination[18] of the *trans*-C(1)–C(2) diastereoisomeric products arising from tandem conjugate addition and cyclisation protocol (Fig. 4).[19]

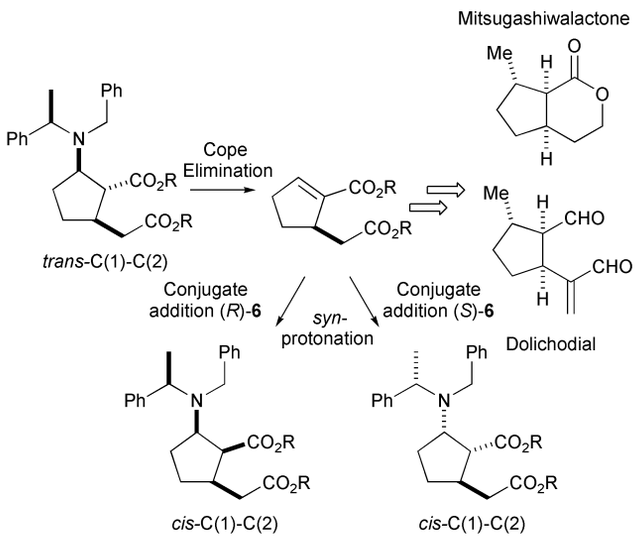
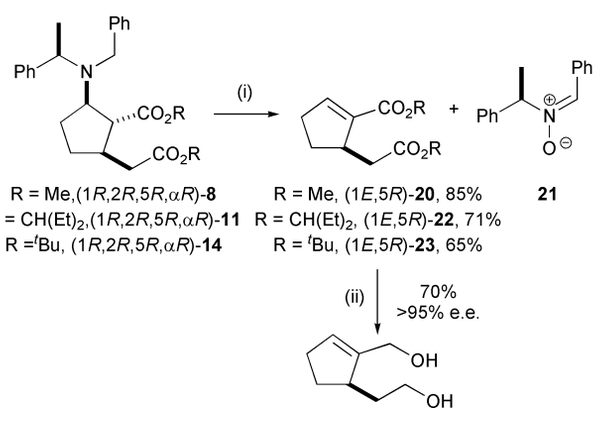


Fig. 4 Proposed route to *cis*-C(1)–C(2) stereoisomeric products.

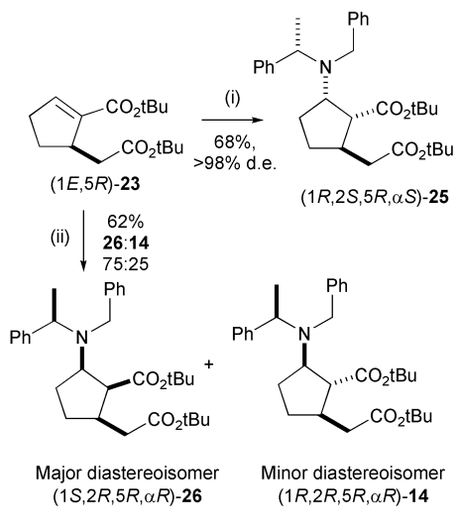
In this fashion, treatment of dimethyl β-amino ester (1*R*,2*R*,5*R*,α*R*)-**8** with *m*-CPBA in DCM gave, after chromatographic purification, the nitrone **21** in 59% yield {$[\alpha]_D^{26}$ −45.5 (*c* 1.19, $CHCl_3$), lit.,[20] $[\alpha]_D^{20}$ −48.2 (*c* 1.0, $CHCl_3$)} and (1*E*,5*R*)-5-carboxymethyl-cyclopentene carboxylate **20**[21] in 85% yield and in >95% de. The ee of (1*E*,5*R*)-**20** was determined as >95% by reduction to the diol (1*E*,5*R*)-**24** {$[\alpha]_D^{26}$ +11.3 (*c* 0.6, MeOH); lit.[17] $[\alpha]_D^{30}$ +9.2 (*c* 0.68, MeOH)} and subsequent derivatisation as the bis-Mosher's ester and comparison of the resulting spectra with an authentic racemic sample. In a similar fashion, treatment of β-amino esters (1*R*,2*R*,5*R*,α*R*)-**11** and (1*R*,2*R*,5*R*,α*R*)-**14** with *m*-CPBA gave the α,β-unsaturated acceptors **22** and **23** in 71% and 65% yield respectively, and in >95% de in each case (Scheme 4).



Scheme 4 *Reagents and conditions*: (i). *m*-CPBA, $CHCl_3$, 0 °C; (ii). $LiAlH_4$, THF, rt.

Having demonstrated the generality of this *N*-oxidation and elimination strategy, addition of lithium amides (*S*)- and (*R*)-**6** to **23** was investigated. Conjugate addition of lithium amide (*S*)-**6** to **23** proceeded to generate a single diastereoisomeric product (1*R*,2*S*,5*R*,α*S*)-**25**, isolated in 68% yield after chromatographic purification. Conjugate addition of lithium amide

(*R*)-**6** under identical conditions furnished a 75 : 25 mixture of the separable C(1) epimeric diastereoisomers (1*S*,2*R*,5*R*,α*R*)-**26** and (1*R*,2*R*,5*R*,α*R*)-**14**, isolated in 62% overall yield (Scheme 5). The minor diastereoisomer from the addition of lithium amide (*R*)-**6** in this protocol exhibited identical spectroscopic properties to the major diastereoisomer arising from the conjugate addition cyclisation protocol, while the relative configuration within β-amino esters (1*R*,2*S*,5*R*,α*S*)-**25** and (1*S*,2*R*,5*R*,α*R*)-**26** was proven by ^{1}H NMR experiments. In all cases, the absolute configuration at C(2) relative to the *N*-α-methylbenzyl stereocentre was assigned by analogy with the previous models developed to explain the observed stereoselectivity of lithium amide **6**, consistent with the reactions proceeding under the predominant stereocontrol of the chiral lithium amide, not the chiral acceptor **23**.

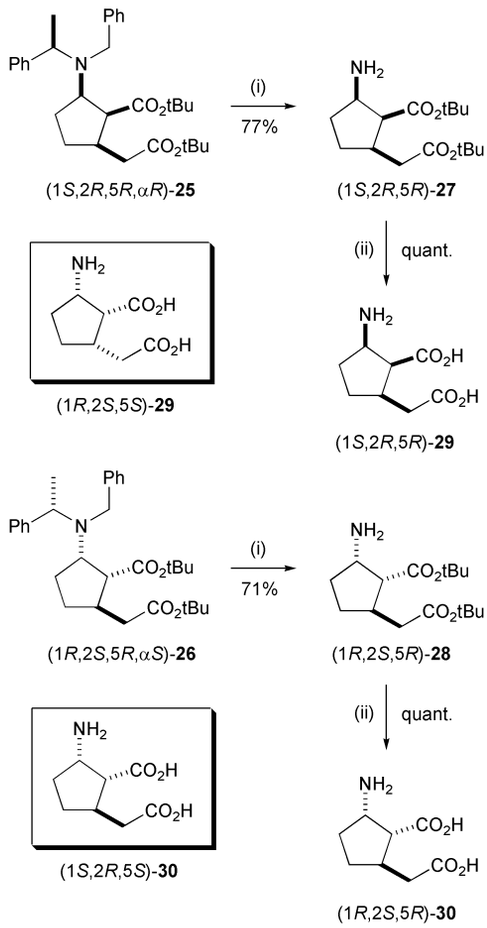


Scheme 5 *Reagents and conditions*: (i). Lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **6**, THF, −78 °C then 2,6-di-*tert*-butyl phenol, −78 °C to rt; (ii). Lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **6**, THF, −78 °C then 2,6-di-*tert*-butyl phenol, −78 °C to rt.

With C(1)–C(2)-*cis* β-amino esters (1*R*,2*S*,5*R*,α*S*)-**25** and (1*S*,2*R*,5*R*,α*R*)-**26** in hand, deprotection to the corresponding β-amino diacids was followed. Hydrogenolysis with Pd/C gave the primary β-amino esters **27** and **28** in 77% and 71% yield and in >95% de in each case, with ester hydrolysis and ion exchange chromatography giving (1*S*,2*R*,5*R*)-**29** {$[\alpha]_D^{26}$ +15.2 (*c* 0.3, 5.5 M $NH_{3(aq.)}$} and (1*R*,2*S*,5*R*)-**30** {$[\alpha]_D^{26}$ +24.6 (*c* 1.93, H_2O)} in >95% de. Repetition of this series of reactions in the enantiomeric series gave (1*R*,2*S*,5*S*)-**29** {$[\alpha]_D^{26}$ −31.9 (*c* 1.09, 5.5 M $NH_{3(aq.)}$} and (1*S*,2*R*,5*S*)-**30** {$[\alpha]_D^{26}$ − 25.1 (*c* 0.57, H_2O)} (Scheme 6).

Conclusions

In conclusion, the asymmetric synthesis of the eight stereoisomers of 2-amino-5-carboxymethyl-cyclopentane-1-carboxylate has been achieved. The set of *trans*-C(1)–C(2)-stereoisomeric β-amino diacids are readily prepared *via* a diastereoselective tandem conjugate addition cyclisation protocol with either lithium (*R*)- or (*S*)-*N*-benzyl-*N*-α-methylbenzylamide, hydrogenolysis and ester hydrolysis. The array of *cis*-C(1)–C(2)-stereoisomeric β-amino diacids utilises a protocol involving *N*-oxidation and Cope elimination of the major diastereoisomeric product arising from conjugate addition and cyclisation, giving homochiral (*R*)- or (*S*)-5-carboxymethyl-cyclopentene-1-carboxylate derivatives. Conjugate addition of either lithium (*R*)- or (*S*)-*N*-benzyl-*N*-α-methylbenzylamide and diastereoselective protonation with 2,6-di-*tert*-butyl phenol, hydrogenolysis and ester hydrolysis, gives the *cis*-C(1)–C(2)-stereoisomeric β-amino diacids. The extension of this strategy for the preparation of a range of substituted cyclopentane and cyclohexane derived β-amino acids is currently under investigation in our laboratory.



Scheme 6 *Reagents and conditions*: (i). Pd/C, MeOH, H_2 (6 atm), rt; (ii). TFA, rt then Dowex 50 × 8–200.

Experimental

General

^{1}H NMR spectra were recorded in $CDCl_3$ at 200 and 400 MHz on Varian 200 VX and BRUKER DRX 400 instruments, respectively. ^{13}C NMR spectra were recorded in $CDCl_3$ at 50 and 100 MHz on Varian 200 VX and BRUKER DRX 400 instruments, respectively in the deuterated solvent stated, and multiplicities were determined by DEPT experiments. IR spectra were registered using a BOMEM 100 FT IR spectrophotometer. Optical rotations were determined using a Perkin-Elmer 241 polarimeter in a 1 dm cell and are given in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are quoted in g per 100 ml. The electron impact (EI) mass spectra were run on a VG-TS 250 spectrometer at 70 eV ionising voltage. HRMS were recorded using a VG Platform (Fisons) spectrometer using Chemical Ionisation (ammonia as gas) or Fast Atom Bombardment (FAB) techniques. Thin layer chromatography (TLC) was performed on aluminium sheets coated with 60 F_{254} silica. Sheets were visualised using iodine, UV light or 1% aqueous $KMnO_4$ solution. Column chromatography was performed with Merck silica gel 60 (70–230 mesh). Solvents and reagents were generally distilled prior to use: THF from sodium benzophenone ketyl and dichloromethane from KOH.

General procedure 1

n-BuLi was added to a stirred solution of amine in THF at −78 °C and was stirred for 30 minutes prior to the addition of a solution of acceptor in THF at −78 °C. After two hours,

saturated aqueous NH_4Cl solution was added and the resultant solution warmed to rt, partitioned between DCM (3 × 50 ml) and brine, dried and concentrated *in vacuo*. Purification by chromatography on silica gel gave the desired product.

General procedure 2

m-CPBA was added to a stirred solution of the β-amino diester in DCM at 0 °C and was stirred for 24 hours before the addition of 5 ml saturated $Na_2S_2O_3$ solution. The resultant solution was partitioned between DCM (3 × 25 ml) and water, dried and concentrated *in vacuo*. Purification by chromatography on silica gel gave the desired product.

General procedure 3

Pd/C (10% by mass) was added to a solution of β-amino ester in AcOH (12 ml) and under hydrogen (5 atm) and was stirred at rt overnight. After filtration through Celite (eluent DCM), the resultant solution was concentrated *in vacuo*, dissolved in DCM (3 × 50 ml) and washed with 10% $NaHCO_3$ (aq.) solution, dried and concentrated *in vacuo*. Purification by chromatography on silica gel gave the desired product.

General procedure 4

The β-amino diester was dissolved in TFA and stirred for 2 hours at rt before concentration *in vacuo*. HCl (1 M, 0.5 ml) was added and the resultant solution concentrated *in vacuo*. The residue was purified by ion exchange chromatography on Dowex 50X8-200.

Preparation of dimethyl (1*R*,2*R*,5*R*,α*R*)- and (1*R*,2*R*,5*S*,α*R*)-2-*N*-benzyl-*N*-α-methylbenzylamino-5-carboxymethyl-cyclopentane-1-carboxylate 8 and 9 respectively. Following general procedure 1, **7** (110 mg, 0.56 mmol) in THF (1 ml), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (135 mg, 0.64 mmol) in THF (11 ml) and *n*-BuLi (1.6 M, 0.37 ml, 0.58 mmol) gave, after chromatographic purification on silica (hexane–Et_2O 9 : 1), (1*R*,2*R*,5*R*,α*R*)-**8** (184 mg, 80%); $[\alpha]_D^{26}$ − 51.3 (*c* 0.97, $CHCl_3$); mp 82–84 °C (Et_2O–hexane); ν_{max} 2950, 1740, 1450; δ_H (400 MHz, C_6D_6) 1.02 (1H, m, *H*-4$_A$), 1.08 (3H, d, *J* = 6.9, C(α)*Me*), 1.35–1.5 (2H, m, C(3)H_2), 1.71 (1H, m, *H*-4$_B$), 2.02 (1H, dd, *J* = 12.6, 9.2, CH_AHCO$_2$Me), 2.25 (1H, dd, *J* = 12.6, 3.6, CH_BHCO$_2$Me), 2.40 (1H, m, *H*-5), 2. 45 (1H, app t, *J* = 10.1, *H*-1), 3.28 (3H, s, CO$_2$*Me*), 3.29 (3H, s, CO$_2$*Me*), 3.45 (1H, AB, J_{AB} = 12.6, NCH_AHPh), 3.55 (1H, dt, *J* = 10.1, 5.0, *H*-2), 3.65 (1H, AB, J_{AB} = 12.6, NCH$_A$$H_B$Ph), 3.81 (1H, q, *J* = 6.9, C(α)*H*), 7.01–7.33 (8H, m, Ar–*H*), 7.51–7.58 (2H, m, Ar–*H*); δ_C (100 MHz, $CDCl_3$) 14.1, 26.4, 30.9, 38.1, 38.8, 50.0, 51.4, 55.3, 56.7, 63.3, 126.5, 126.6, 127.0, 127.8, 127.9, 128.2, 128.5, 128.8, 141.1, 144.2, 172.4, 174.7; *m*/*z* (CI$^+$) 409 (M$^+$, 3), 394 (10), 250 (35), 146 (55), 105 (84), 91 (100), 77 (23), 51 (10); HRMS (CI$^+$) $C_{25}H_{32}NO_4$ requires 410.2331; found 410.2335. Further elution gave (1*R*,2*R*,5*S*,α*R*)-**9** (14 mg, 6%); $[\alpha]_D^{26}$ − 20.1 (*c* 2.05, $CHCl_3$); ν_{max} 2951, 1738, 1435, 710; δ_H (400 MHz, C_6D_6) 1.1 (3H, d, *J* = 7.0, C(α)*Me*), 1.25–1.32 (1H, m, *H*-4$_A$), 1.38–1.42 (1H, m, *H*-3$_A$), 1.51–1.59 (1H, m, *H*-3$_B$), 1.63–1.69 (1H, m, *H*-4$_B$), 2.11 (1H, dd, *J* = 15.2, 6.7, CH_AHCO$_2$Me), 2.35 (1H, dd, *J* = 15.2, 7.3, CH_BHCO$_2$Me), 2.38–2.45 (1H, m, *H*-5), 2.91 (1H, dd, *J* = 9.1, 5.9, *H*-1), 3.26 (3H, s, CO$_2$*Me*), 3.32 (3H, s, CO$_2$*Me*), 3.51 (2H, ABq, NCH_2Ph), 3.78 (1H, q, *J* = 7.0, C(α)*H*), 3.82 (1H, ddd, *J* = 9.1, 7.9, 3.8, *H*-2), 7.02–7.45 (10, m, Ar–*H*); δ_C (100 MHz, $CDCl_3$) 16.7, 29.4, 31.0, 33.7, 38.5, 49.9, 50.5, 51.0, 51.3, 58.2, 63.4, 126.5, 126.7, 127.5, 127.8, 128.1, 128.8, 141.6, 144.2, 172.7, 174.5; *m*/*z* (CI$^+$) 410 ((M + H)$^+$, 100), 307 (4), 306 (20); HRMS (CI$^+$) $C_{25}H_{32}NO_4$ requires 410.2331; found 410.2341.

X-Ray crystal structure data for 8

Data were collected using a Seifert 3003 SC diffractometer with graphite monochromated Cu–Kα radiation using standard procedures at room temperature. The structure was solved by direct methods, all non-hydrogen atoms were refined with anisotropic thermal parameters. The structure was refined using SHELTL™.[22] Crystal data for **8** [$C_{25}H_{31}NO_4$], colourless block, *M* = 409.51, orthorhombic, space group *P* 21 21 21, *a* = 18.0640(10) Å, *b* = 13.9610(10) Å, *c* = 9.1430(10) Å, *U* = 2305.8(3) Å^3, *Z* = 4, μ = 0.6343 mm^{-1}, crystal dimensions 1.0 × 0.7 × 0.8 mm. A total of 2087 unique reflections were measured for 4.00 < θ < 65.35 and 1934 reflections were used in the refinement. The final parameters were wR_2 = 0.1210 and R_1 = 0.0457 [$I > 2\sigma(I)$]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 220744. See http://www.rsc.org/suppdata/ob/b3/b313386a/ for crystallographic data in.cif or other electronic format.

Preparation of di-3-pentyl (1*R*,2*R*,5*R*,α*R*)- and (1*R*,2*R*,5*S*,α*R*)-2-*N*-benzyl-*N*-α-methylbenzylamino-5-carboxymethyl-cyclopentane-1-carboxylate 11 and 12 respectively. Following general procedure 1, **10** (631 mg, 2.03 mmol) in THF (3 ml), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (973 mg, 4.61 mmol) in THF (11 ml) and *n*-BuLi (1.6 M, 2.87 ml, 4.59 mmol) gave, after chromatographic purification on silica (hexane–Et_2O 49 : 1), (1*R*,2*R*,5*R*,α*R*)-**11** (816 mg, 77%); $[\alpha]_D^{26}$ −30.1 (*c* 1.55, $CHCl_3$); ν_{max} 2969, 1728, 1454, 1170, 974, 698; δ_H (400 MHz, $CDCl_3$) 0.78 (3H, t, *J* = 7.5, CH(CH$_2$*CH$_3$*)$_2$), 0.83 (6H, t, *J* = 7.5, CH(CH$_2$*CH$_3$*)$_2$), 0.94 (3H, t, *J* = 7.5, CH(CH$_2$*CH$_3$*)$_2$), 1.28 (3H, d, *J* = 6.8, C(α)*Me*), 1.40–1.72, 1.75–1.85, 1.91–2.01 (9H, m; 2H, m and 1H, m, 2 × CH(CH_2CH$_3$)$_2$, C(3)H_2 and C(4)H_2), 2.17 (1H, dd, *J* = 14.8, 9.6, CH_AHCO$_2$Me), 2.39 (1H, m, *H*-5), 2.50 (1H, dd, *J* = 9.6, 3.6, CH_BHCO$_2$Me), 2.53 (1H, app t, *J* = 10.0, *H*-1), 3.71 (1H, m, *H*-2), 3.75 (2H, ABm, NCH_2Ph), 3.86 (1H, q, *J* = 6.8, C(α)*H*), 4.58 (1H, quintet, *J* = 6.0, C*H*(CH$_2$CH$_3$)$_2$), 4.71 (1H, quintet, *J* = 6.0, C*H*(CH$_2$CH$_3$)$_2$), 7.11–7.51 (10H, m, Ar–*H*); δ_C (50 MHz, $CDCl_3$) 9.4, 9.5, 15.5, 25.8, 26.4, 26.7, 31.0, 39.0, 39.1, 50.0, 55.3, 58.0, 63.7, 76.6, 126.5, 126.6, 127.6, 128.1, 128.5, 141.6, 144.3, 171.7, 174.3; *m*/*z* (CI$^+$) 525 (8), 524 (52) 522 ((M + H)$^+$, 100), 510 (4), 508 (16), 419 82), 418 (10); HRMS (CI$^+$) $C_{33}H_{48}O_4N$ requires 522.3583; found 522.3582. Further elution gave (1*R*,2*R*,5*S*,α*R*)-**12** (64 mg, 6%); $[\alpha]_D^{26}$ −16.4 (*c* 0.87, $CHCl_3$); ν_{max} 2969, 1728, 1454, 1170, 957, 700; δ_H (400 MHz, $CDCl_3$) 0.83 (3H, t, *J* = 5.8, CH(CH$_2$*CH$_3$*)$_2$), 0.86 (6H, t, *J* = 6.0, CH(CH$_2$*CH$_3$*)$_2$), 0.97 (3H, t, *J* = 5.8, CH(CH$_2$*CH$_3$*)$_2$), 1.33 (3H, d, *J* = 6.8, C(α)*Me*), 1.35–1.70, 1.70–1.92 (10H, m and 2H, m, 2 × CH(CH_2CH$_3$)$_2$, C(3)H_2 and C(4)H_2), 2.17 (1H, dd, *J* = 15.2, 6.7, CH_AHCO$_2$Me), 2.37 (1H, dd, *J* = 15.2, 7.3, CH_BHCO$_2$Me), 2.48–2.56 (1H, m, *H*-5), 2.95 (1H, dd, *J* = 9.1, 6.1, *H*-1), 3.66–3.72 (1H, m, *H*-2), 3.73 (1H, AB, J_{AB} = 14.8, NCH$_A$), 3.83 (1H, AB, J_{AB} = 14.8, NCH$_B$), 3.88 (1H, q, *J* = 6.8, C(α)*H*), 4.66 (1H, quintet, *J* = 6.0, C*H*(CH$_2$CH$_3$)$_2$), 4.95 (1H, quintet, *J* = 6.0, C*H*(CH$_2$CH$_3$)$_2$), 7.15–7.55 (10H, m, Ar–*H*); δ_C (50 MHz, $CDCl_3$) 9.3, 9.5, 17.4, 25.7, 25.8, 26.3, 28.8, 31.1, 36.2, 38.9, 50.4, 51.3, 59.1, 64.0, 76.6, 126.5, 127.6, 128.0, 128.1, 142.0, 144.6, 172.4, 174.1; *m*/*z* (CI$^+$) 525 (3), 524 (25), 522 ((M + H)$^+$, 100), 432 (6); HRMS (CI$^+$) $C_{33}H_{48}O_4N$ requires 522.3571; found 522.3583.

Preparation of di-*tert*-butyl (1*R*,2*R*,5*R*,α*R*)- and (1*R*,2*R*,5*S*,α*R*)-2-*N*-benzyl-*N*-α-methylbenzylamino-5-carboxymethyl-cyclopentane-1-carboxylate 14 and 15 respectively. Following general procedure 1, **13** (650 mg, 2.44 mmol) in THF (10 ml), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (878 mg, 4.14 mmol) in THF (5 ml) and *n*-BuLi (1.6 M, 2.44 ml, 3.90 mmol) gave, after chromatographic purification on silica (hexane–Et_2O 9 : 1), (1*R*,2*R*,5*R*,α*R*)-**14** (1.0 g, 83%); $[\alpha]_D^{26}$ − 33.2 (*c* 0.57, $CHCl_3$); ν_{max} 2974, 1728, 1454, 1386, 1148, 874, 748, 698; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* = 6.8, C(α)*Me*), 1.38 (18H, s, CO$_2$C(CH_3)$_3$), 1.43–1.47 (1H, m, *H*-4$_A$), 1.71–1.77 (2H, m, C(3)H_2), 1.90–1.95 (1H, m, *H*-4$_B$), 2.03 (1H, dd, *J* = 14.7, 9.7,

$CH_AHCO_2{}^tBu$), 2.19–2.25 (1H, m, *H*-5), 2.34 (1H, dd, *J* = 14.7, 4.3, $CH_BHCO_2{}^tBu$), 2.35 (1H, dd, *J* = 9.9, 8.9, *H*-1), 3.59 (1H, app q, *J* = 8.9, *H*-2), 3.67 (1H, AB, J_{AB} = 14.6, NCH_A), 3.79 (1H, AB, J_{AB} = 14.6, NCH_B), 3.86 (1H, q, *J* = 6.8, C(α)*H*), 7.1–7.5 (10H, Ar–*H*); δ_C (50 MHz, $CDCl_3$) 15.0, 26.3, 28.0, 28.2, 30.5, 39.0, 39.9, 49.9, 55.7, 57.5, 63.0, 80.0, 80.2, 126.4, 126.6, 127.8, 127.9, 128.0, 128.5, 141.6, 144.1, 171.6, 179.3; *m*/*z* (EI^+) 493 (3), 388 (10), 332 (4), 250 (18), 217 (20), 153 (40), 105 (55), 77 (100); HRMS (EI^+) $C_{31}H_{43}O_4N$ requires 493.3192; found 493.3151. Further elution gave (1*R*,2*R*,5*S*,α*R*)-**15** (82mg, 7%); $[a]_D^{26}$ −21.5 (*c* 0.93, $CHCl_3$); ν_{max} 2974, 2932, 1728, 1454, 1368, 1148, 698; δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* = 6.8, C(α)*Me*), 1.37 (9H, s, $CO_2C(CH_3)_3$), 1.40 (9H, s, $CO_2C(CH_3)_3$), 1.59–1.67 (2H, m, *H*-3_A, *H*-4_A), 1.70–1.76 (1H, m, *H*-4_B), 1.84–1.90 (1H, m, *H*-3_B), 2.13 (1H, dd, *J* = 15.7, 8.4, $CH_AHCO_2{}^tBu$), 2.34 (1H, dd, *J* = 15.7, 6.6, $CH_BHCO_2{}^tBu$), 2.38–2.44 (1H, m, *H*-5), 2.80–2.84 (1H, dd, *J* = 8.9, 5.4, *H*-1), 3.70–3.74 (1H, td, *J* = 8.9, 3.8, *H*-2), 3.77 (1H, AB, J_{AB} = 14.6, NCH_AHPh), 3.80 (1H, d, J_{AB} = 14.6, NCH_BHPh), 3.86 (1H, q, *J* = 6.8, C(α)*H*), 7.10–7.60 (10H, Ar–*H*); δ_C (100 MHz, $CDCl_3$) 17.8, 28.1, 29.2, 30.9, 37.2, 39.2, 50.4, 51.2, 59.1, 64.0, 80.1, 126.5, 127.6, 128.0, 142.1, 144.8, 171.9, 173.9; *m*/*z* (EI^+) 493 (M^+,2), 388 (10), 338 (9), 250 (18), 153 (25), 105 (100), 77 (94); HRMS (EI^+) $C_{31}H_{43}O_4N$ requires 493.3192, found 493.3226.

Preparation of di-*tert*-butyl (1*S*,2*S*,5*S*,α*S*)- and (1*S*,2*S*,5*R*,α*S*)-2-*N*-benzyl-*N*-α-methylbenzylamino-5-carboxymethyl-cyclopentane-1-carboxylate 14 and 15 respectively. Following general procedure 1, **13** (590 mg, 2.1 mmol) in THF (3 ml), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (973 mg, 4.6 mmol) in THF (11 ml) and *n*-BuLi (1.6 M, 2.9 ml, 4.6 mmol) gave, after chromatographic purification on silica (hexane–Et_2O 9 : 1) (1*S*,2*S*,5*S*,α*S*)-**14** (878 g, 85%); $[a]_D^{26}$ +33.1 (*c* 0.54, $CHCl_3$); further elution gave (1*S*,2*S*,5*R*,α*S*)-**15** (41 mg, 4%); $[a]_D^{26}$ +24.5 (*c* 0.73, $CHCl_3$).

Preparation of di-*tert*-butyl (1*R*,2*R*,5*R*)-2-amino-5-carboxymethyl-cyclopentane-1-carboxylate 16. Following general procedure 3, (1*R*,2*R*,5*R*,α*R*)-**14** (147mg, 0.3 mmol) in AcOH (12 ml), Pd/C (10% by mass, 59 mg) and hydrogen (5 atm) at rt gave, after purification by column chromatography ($CHCl_3$–MeOH 95 : 5), (1*R*,2*R*,5*R*)-**16** (74mg, 83%); $[a]_D^{26}$ +5.7 (*c* 1.86, $CHCl_3$); ν_{max} 3380, 2976, 2934, 1723, 1458, 1393, 1258, 1154, 972, 845; δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, $C(CH_3)_3$), 1.46 (9H, s, $C(CH_3)_3$), 1.66 (2H, br s, NH_2), 1.85–1.89 (1H, m, *H*-4_A), 1.90–1.95 (2H, m, C(3)H_2), 1.96–1.99 (1H, m, *H*-4_B), 2.01 (1H, dd, *J* = 9.1, 14.1, $CH_AHCO_2{}^tBu$), 2.13–2.20 (1H, dd, *J* = 10.0, 11.0, *H*-1), 2.47–2.53 (1H, m, *H*-5), 2.52 (1H, dd, *J* = 14.1, 3.6, $CH_BHCO_2{}^tBu$), 3.41 (1H, app q, *J* = 7.4, *H*-2); δ_C (100 MHz, $CDCl_3$) 28.2, 28.3, 29.0, 34.0, 38.7, 41.2, 56.6, 60.1, 80.4, 81.7, 172.0, 173.8; *m*/*z* (EI^+) 299 (M^+, 2), 242 (2), 186 (31), 170 (38), 126 (35), 107 (15), 77 (32); HRMS (EI^+) $C_{16}H_{30}O_4N$ 300.2175, found 300.2220.

Preparation of di-*tert*-butyl (1*S*,2*S*,5*S*)-2-amino-5-carboxymethyl-cyclopentane-1-carboxylate 16. Following general procedure 3, (1*S*,2*S*,5*S*,α*S*)-**14** (130 mg, 0.27 mmol) in AcOH (8 ml), Pd/C (10% by mass, 53 mg) and hydrogen (5 atm) at rt gave, after purification by column chromatography ($CHCl_3$–MeOH 95 : 5), (1*S*,2*S*,5*S*)-**16** (64mg, 81%); $[a]_D^{26}$ − 6.3 (*c* 1.73, $CHCl_3$).

Preparation of di-*tert*-butyl (1*R*,2*R*,5*S*)-2-amino-5-carboxymethyl-cyclopentane-1-carboxylate 17. Following general procedure 3, (1*R*,2*R*,5*S*,α*R*)-**15** (58 mg, 0.12 mmol) in AcOH (8 ml), Pd/C (10% by mass, 23 mg) and hydrogen (5 atm) at rt gave, after purification by column chromatography ($CHCl_3$–MeOH 95 : 5), (1*R*,2*R*,5*S*)-**17** (26 mg, 74%); $[a]_D^{26}$ −25.2 (*c* 1.25, $CHCl_3$); ν_{max} 2978, 1728, 1368, 1258, 1154, 845; δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, $C(CH_3)_3$), 1.46 (9H, s, $C(CH_3)_3$), 1.68–1.76 (2H, m, C(4)H_2), 1.91–1.96 (1H, m, *H*-3_A), 2.06–2.14 (1H, m, *H*-3_B), 2.14 (1H, dd, *J* = 15.4, 9.7, $CH_AHCO_2{}^tBu$), 2.40 (1H, dd, *J* = 15.4, 3.6, $CH_AHCO_2{}^tBu$), 2.50 (1H, dd, *J* = 8.5, 5.6, *H*-1), 2.70–2.76 (1H, m, *H*-5), 3.52–3.57 (1H, m, *H*-2); δ_H (100 MHz, $CDCl_3$) 28.1, 28.2, 29.8, 35.0, 37.5, 37.7, 55.4, 57.9, 80.1, 80.5, 171.8, 172.9; *m*/*z* (EI^+) 300 (M^+, 1), 242 (12), 186 (80), 170 (100), 126 (46), 96 (8), 82 (40); HRMS (EI^+) $C_{16}H_{29}O_4N$ requires 299.2097; found 299.2113.

Preparation of di-*tert*-butyl (1*S*,2*S*,5*R*)-2-amino-5-carboxymethyl-cyclopentane-1-carboxylate 17. Following general procedure 3, (1*S*,2*S*,5*R*,α*S*)-**15** (130 mg, 0.26 mmol) in AcOH (8 ml), Pd/C (10% by mass, 52 mg) and hydrogen (5 atm) at rt gave after purification by column chromatography ($CHCl_3$–MeOH 95 : 5), (1*S*,2*S*,5*R*)-**17** (59 mg, 76%); $[a]_D^{26}$ +28.9 (*c* 1.09, $CHCl_3$).

Preparation of (1*R*,2*R*,5*R*)-2-amino-5-carboxymethyl-cyclopentane-1-carboxylate 18. Following general procedure 4, (1*R*,2*R*,5*R*)-**16** (58 mg, 0.19 mmol) and TFA (1 ml) gave, after ion exchange chromatography (Dowex 50X8-200), (1*R*,2*R*,5*R*)-**18** (36 mg, quant.); $[a]_D^{26}$ +2.4 (*c* 1, H_2O); $C_8H_{13}NO_4$ requires C, 51.33; H, 7.00; N, 7.48; found: C, 51.08; H, 6.99; N, 8.21; ν_{max} 3600–2500 (br), 2974, 1719, 1406, 1235, 665; δ_H (200 MHz, D_2O) 1.36–1.44 (1H, m, *H*-4_A), 1.52–1.58 (1H, m, *H*-4_B), 1.80–2.10 (2H, m, C(3)H_2), 2.25–2.60 (4H, m, *H*-1, *H*-5 and CH_2CO_2H), 3.75 (1H, q, *J* = 7.8, *H*-2); δ_H (50 MHz, D_2O) 31.6, 31.8, 41.1, 41.8, 56.4, 57.1, 178.5, 179.2; *m*/*z* (EI^+) 188 (M^+, 48), 115 (28), 93 (100), 75(28); HRMS (EI^+) $C_8H_{14}O_4N$ 188.0923; found 188.0935.

Preparation of (1*S*,2*S*,5*S*)-2-amino-5-carboxymethyl-cyclopentane-1-carboxylate 18. Following general procedure 4, (1*S*,2*S*,5*S*)-**16** (55 mg, 0.18 mmol) and TFA (1.0 ml) gave, after ion exchange chromatography (Dowex 50X8-200), (1*S*,2*S*,5*S*)-**18** (35 mg, quant.); $[a]_D^{26}$ −2.7 (*c* 0.62, H_2O); $C_8H_{13}NO_4$ requires C, 51.33; H, 7.00; N, 7.48; found: C, 51.12; H, 6.95; N, 7.77%; HRMS (EI^+) $C_8H_{14}O_4N$ 188.0923; found 188.0922.

Preparation of (1*R*,2*R*,5*S*)-2-amino-5-carboxymethyl-cyclopentane-1-carboxylate 19. Following general procedure 4, (1*R*,2*R*,5*S*)-**17** (11 mg, 0.04 mmol) and TFA (0.5 ml) gave, after ion exchange chromatography (Dowex 50X8-200), (1*R*,2*R*,5*S*)-**19** (7 mg, quant.); $[a]_D^{26}$ −35.0 (*c* 0.6, H_2O); ν_{max} 3600–2400 (br), 1717, 1233, 1018, 667; δ_H (200 MHz, D_2O): 1.37–1.43 (1H, m, *H*-4_A), 1.52–1.58 (1H, m, *H*-4_B), 1.88–1.93 (1H, m, *H*-3_A), 2.15–2.20 (1H, m, *H*-3_B), 2.32 (2H, AB, *J* = 7.6, CH_2CO_2H), 2.72–2.77 (1H, m, *H*-5), 2.98 (1H, dd, *J* = 8.5, 6.2, *H*-1), 3.90 (1H, app q, *J* = 7.0, *H*-2); δ_C (50 MHz, D_2O) 31.9, 32.4, 38.3, 40.0, 53.9, 56.0, 177.7, 179.1; *m*/*z* (EI^+) 188 (M^+, 100), 172 (22), 142 (15), 125 (16), 105 (30), 93 (75), 75 (28), 57 (38); HRMS (EI^+) $C_8H_{14}O_4N$ requires 188.0923; found 188.0940.

Preparation of (1*S*,2*S*,5*R*)-2-amino-5-carboxymethyl-cyclopentane-1-carboxylate 19. Following general procedure 4, (1*S*,2*S*,5*R*)-**17** (45 mg, 0.15 mmol) and TFA (1.0 ml) gave, after ion exchange chromatography (Dowex 50X8-200), (1*S*,2*S*,5*R*)-**19** (28 mg, quant.); $[a]_D^{26}$ +44.7 (*c* 1.03, H_2O), $C_8H_{14}O_4N$ requires 188.0923; found 188.0919.

Preparation of dimethyl (1*E*,5*R*)-5-carboxymethyl-cyclopentene-1-carboxylate 20 and (*R*)-*N*-benzylidene-*N*-α-methylbenzylamine-*N*-oxide 21. Following general procedure 2, (1*R*,2*R*,5*R*,α*R*)-**8** (173 mg, 0.42 mmol) in DCM (10 ml) and *m*-CPBA (146 mg, 0.84 mmol) gave, after chromatographic purification on silica gel (hexane–EtOAc 4 : 1), (1*E*,5*R*)-**20** (70 mg, 85%); $[a]_D^{26}$ +30.7 (*c* 0.6, $CHCl_3$); ν_{max} 2953, 1738, 1628, 1098, 756; δ_H (400 MHz, $CDCl_3$) 1.60–1.80 (2H, m, C(4)H_2), 2.31 (1H, dd, *J* = 15.6, 10.3, CH_AHCO_2Me), 2.41–2.63 (2H, m, C(3)*H*), 2.87 (1H, dd, *J* = 15.6, 3.8, CH_BHCO_2Me), 3.34–3.40

(1H, m, *H*-5), 3.68 (3H, s, CO_2Me), 3.74 (3H, s, CO_2Me), 6.83 (1H, br s, *H*-2); δ_C (50 MHz, $CDCl_3$) 29.9, 31.4, 38.3, 40.9, 51.3, 51.4, 138.1, 145.1, 165.1, 173.0. Further elution gave **21** (56 mg, 59%); $[\alpha]_D^{26}$ − 45.5 (*c* 1.19, $CHCl_3$), [lit.,[20] $[\alpha]_D^{20}$ −48.2 (*c* 1.0, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 1.90 (3H, d, *J* = 6.8, C(α)*Me*), 5.21 (1H, q, *J* = 6.8, C(α)*H*), 7.31–7.52 (10H, m, Ar–*H*), 8.20–8.26 (1H, m, NC*H*Ph).

Preparation of dimethyl (1*E*,5*S*)-5-carboxymethyl-cyclopentene-1-carboxylate 20. Following general procedure 2, (1*S*,2*S*,5*S*,α*S*)-**8** (49 mg, 0.12 mmol) in DCM (10 ml) and *m*-CPBA (30 mg, 0.17 mmol) gave, after chromatographic purification on silica gel (hexane–Et_2O 9 : 1), (1*E*,5*S*)-**20** (20 mg, 84%); $[\alpha]_D^{26}$ −26.5 (*c* 1.0, $CHCl_3$).

Preparation of di-3-pentyl (1*E*,5*R*)-5-carboxymethyl-cyclopentene-1-carboxylate 22. Following general procedure 2, (1*R*,2*R*,5*R*,α*R*)-**11** (430 mg, 0.82 mmol) in DCM (36 ml) and *m*-CPBA (373 mg, 2.16 mmol) gave, after chromatographic purification on silica gel (hexane–Et_2O 9 : 1), (1*E*,5*R*)-**22** (182 mg, 71%) $[\alpha]_D^{26}$ +31.2 (*c* 1.12, $CHCl_3$); ν_{max} 2971, 1711, 1630, 1260, 1096, 932, 750; δ_H (200 MHz, $CDCl_3$) 0.80–1.00 (12H, m, 2 × $CH(CH_2CH_3)_2$), 1.45–1.65 (8H, m, 2 × $CH(CH2CH_3)_2$), 1.65–1.80 (2H, m), 2.24 (1H, dd, *J* = 15.6, 10.5, CH_AHCO_2), 2.38–2.58 (2H, m, C(3)H_2), 2.89 (1H, dd, *J* = 15.6, 3.2, CH_B-HCO_2), 3.30–3.45 (1H, m, *H*-5), 4.76 (1H, quintet, *J* = 6.0, $CH(CH_2CH_3)_2$), 4.82 (1H, quintet, *J* = 6.0, $CH(CH_2CH_3)_2$), 6.78 (1H, br s, *H*-2); δ_C (50 MHz, $CDCl_3$) 9.5, 26.4, 29.6, 31.3, 38.7, 41.1, 76.3, 76.5, 138.8, 144.0, 164.6, 172.4; *m*/*z* (EI^+) 310 (M^+, 5), 223 (7), 151 (100), 123 (70); HRMS (EI^+) $C_{18}H_{30}O_4$ requires 310.2144, found 310.2132; further elution gave nitrone **21** (90 mg, 50%).

Preparation of di-3-pentyl (1*E*,5*S*)-5-carboxymethyl-cyclopentene-1-carboxylate 22. Following general procedure 2, (1*S*,2*S*,5*S*,α*S*)-**11** (187 mg, 0.36 mmol) in DCM (16 ml) and *m*-CPBA (175 mg, 1.01 mmol) gave, after chromatographic purification on silica gel (hexane–Et_2O 95 : 5), (1*E*,5*S*)-**22** (91 mg, 81%); $[\alpha]_D^{26}$ −29.6 (*c* 1.33, $CHCl_3$).

Preparation of di-*tert*-butyl (1*E*,5*R*)-5-carboxymethyl-cyclopentene-1-carboxylate 23. Following general procedure 2, (1*R*,2*R*,5*R*,α*R*)-**14** (547 mg, 1.1 mmol) in DCM (40 ml) and *m*-CPBA (572 mg, 3.3 mmol) gave, after chromatographic purification on silica gel (hexane–EtOAc 4 : 1), (1*E*,5*R*)-**23** (209 mg, 65%); $[\alpha]_D^{26}$ +36.4 (*c* 2.2, $CHCl_3$); ν_{max} 2978, 2934, 1732, 1705, 1628, 1458, 1393, 1368, 1298, 1165, 851, 755; δ_H (400 MHz, $CDCl_3$) 1.43, 1.48 (2 × 9H, s, C(CH_3)$_3$), 1.65–1.85 (2H, m, C(4)H_2), 2.12 (1H, dd, *J* = 15.6, 10.5, $CH_AHCO_2{}^tBu$), 2.30–2.40 (2H, m, C(3)H_2), 2.89 (1H, dd, *J* = 15.6, 3.2, $CH_BHCO_2{}^tBu$), 3.30 (1H, m, *H*-5), 6.78 (1H, br s, *H*-2); δ_C (100 MHz, $CDCl_3$) 28.0, 29.4, 31.1, 39.6, 41.1, 79.8, 80.0, 139.9, 143.1, 164.0, 171.8; *m*/*z* (EI^+) 282 (M^+, 5), 245 (10), 225 (12), 185 (25), 169 (28), 151 (35), 123 (16), 105 (9), 71 (12), 77 (12), 57 (100); HRMS (EI^+) $C_{16}H_{27}O_4$ requires 283.1909; found 283.1903.

Preparation of di-*tert*-butyl (1*E*,5*S*)-5-carboxymethyl-cyclopentene-1-carboxylate 23. Following general procedure 2, (1*S*,2*S*,5*S*,α*S*)-**14** (474 mg, 0.96 mmol) in DCM (24 ml) and *m*-CPBA (504 mg, 2.9 mmol) gave, after chromatographic purification on silica gel (hexane–EtOAc 95 : 5), (1*E*,5*S*)-**23** (232 mg, 86%); $[\alpha]_D^{26}$ −35.3 (*c* 1.5, $CHCl_3$).

Preparation of (1*E*,5*R*)-2-(2-hydroxymethyl-cyclopent-2-enyl)-ethanol 24. $LiAlH_4$ (30 mg) was added to a solution of (1*E*,5*R*)-**20** (66 mg, 0.34 mmol) in Et_2O (4 ml) at 0 °C and stirred at rt overnight before the addition of EtOAc and H_2O (3 ml). The resultant solution was partitioned between EtOAc and H_2O, dried and concentrated *in vacuo*. Chromatographic purification on silica gel (EtOAc) gave (1*E*,5*R*)-**24** (39 mg, 70%); $[\alpha]_D^{26}$ +11.3 (*c* 0.6, MeOH); *lit.*[17] $[\alpha]_D^{30}$ +9.2 (*c* 0.68, MeOH); ν_{max} 3366, 2934, 2864, 1456, 1030, 1050, 806; δ_H (400 MHz, $CDCl_3$) 2.65 (2H, m, H-3), 2.8 (1H, m, H-5), 3.75 (2H, m, CH_2OH, C-8), 4.23 (2H, br s, CH_2OH, H-6), 5.68 (1H, br s, H-2); δ_C (50 MHz, $CDCl_3$) 30.7, 30.8, 36.6, 41.9, 60.7, 61.5, 126.8, 147.0.

Preparation of (*S*)-2-(2-hydroxymethyl-cyclopent-2-enyl)-ethanol 24. $LiAlH_4$ (30 mg) was added to a solution of (1*E*,5*S*)-**20** (20 mg, 0.10 mmol) in Et_2O (4 ml) at 0 °C and stirred at rt overnight before the addition of EtOAc and H_2O (3 ml). The resultant solution was partitioned between EtOAc and H_2O, dried and concentrated *in vacuo*. Chromatographic purification on silica gel (EtOAc) gave (1*E*,5*S*)-**24** (12 mg, 71%); $[\alpha]_D^{26}$ −14.0 (*c* 0.3, MeOH).

Preparation of di-*tert*-butyl (1*R*,2*S*,5*R*,α*S*)-2-*N*-benzyl-*N*-α-methylbenzylamino-5-carboxymethyl-cyclopentane-1-carboxylate 25. Following general procedure 1, (1*E*,5*R*)-**23** (98 mg, 0.35 mmol) in THF (2 ml), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (161 mg, 0.75 mmol) in THF (5 ml) and *n*-BuLi (1.6 M, 0.47 ml, 0.75 mmol) gave, after chromatographic purification on silica (hexane–Et_2O 49 : 1), (1*R*,2*S*,5*R*,α*S*)-**25** (116 mg, 68%); $[\alpha]_D^{26}$ −46.8 (*c* 1.72, $CHCl_3$); ν_{max} 2976, 1728, 1456, 1393, 1256, 1150, 735, 700; δ_H (400 MHz, $CDCl_3$) 1.05 (1H, m, *H*-4_A), 1.36 (3H, d, *J* = 6.8, C(α)*Me*), 1.43, 1.52 (2 × 9H, s, C(CH_3)$_3$), 1.57 (1H, m, *H*-3_A), 1.84 (1H, m, *H*-3_B), 1.97 (1H, m, *H*-4_B), 2.02–2.10 (1H, dd, *J* = 14.7, 7.6, $CH_AHCO_2{}^tBu$), 2.18 (1H, dd, *J* = 14.7, 6.9, $CH_BHCO_2{}^tBu$), 2.55–2.65 (1H, m, *H*-5), 2.60–2.65 (1H, dd, *J* = 9.9, 6.9, *H*-1), 3.25 (1H, ddd, *J* = 11.0, 8.4, 6.8, *H*-2), 3.54 (1H, AB, J_{AB} = 15.3, NCH_A), 4.03 (1H, AB, J_{AB} = 15.3, NCH_B), 4.25 (1H, q, *J* = 6.8, C(α)*H*), 7.25–7.40 (10H, m, Ar–*H*); δ_C (100 MHz, $CDCl_3$) 17.0, 28.1, 28.3, 29.7, 38.6, 42.3, 51.7, 54.4, 57.8, 63.9, 80.1, 126.2, 126.7, 127.9, 128.0, 142.5, 142.6, 171.5, 173.9; *m*/*z* (EI^+) 493 (M^+,8), 472 (11), 387 (24), 332 (11), 250 (52), 216(2), 146 (50), 105 (100), 77 (15); HRMS (EI^+) $C_{31}H_{43}O_4N$ requires 493.3192. found 493.3139.

Preparation of di-*tert*-butyl (1*S*,2*R*,5*S*,α*R*)-2-*N*-benzyl-*N*-α-methylbenzylamino-5-carboxymethyl-cyclopentane-1-carboxylate 25. Following general procedure 1, (1*E*,5*S*)-**23** (127 mg, 0.45 mmol) in THF (2 ml), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (304 mg, 1.44 mmol) in THF (3 ml) and *n*-BuLi (1.6 M, 0.87 ml, 1.39 mmol) gave, after chromatographic purification on silica (hexane–Et_2O 49 : 1), (1*R*,2*S*,5*R*,α*S*)-**25** (143 mg, 65%); $[\alpha]_D^{26}$ +50.3 (*c* 0.99, $CHCl_3$).

Preparation of di-*tert*-butyl (1*S*,2*R*,5*R*,α*R*)- and (1*R*,2*R*,5*R*,α*R*)-2-*N*-benzyl-*N*-α-methylbenzylamino-5-carboxymethyl-cyclopentane-1-carboxylate 26 and 14 respectively. Following general procedure 1, (1*E*,5*R*)-**23** (83 mg, 0.29 mmol) in THF (2 ml), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (136 mg, 0.65 mmol) in THF (5 ml) and *n*-BuLi (1.6 M, 0.4 ml, 0.65 mmol) gave, after chromatographic purification on silica (hexane–Et_2O 49 : 1), (1*S*,2*R*,5*R*,α*R*)-**26** (63 mg, 44%); $[\alpha]_D^{26}$ +42.1 (*c* 1.26, $CHCl_3$); ν_{max} 2976, 1728, 1493, 1454, 1368, 1258, 1154, 1028, 847, 746, 700; δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, *J* = 6.8, C(α)*Me*), 1.43, 1.51 (2 × 9H, s, C(CH_3)$_3$), 1.56–1.62 (2H, m, C(4)H_2), 1.70–1.80 (1H, m, *H*-3_A), 1.92–2.02 (1H, m, *H*-3_B), 2.18–2.38 (3H, m, *H*-5 and $CH_AH_BHCO_2{}^tBu$), 3.03 (1H, dd, *J* = 5.6, 5.1, *H*-1), 3.25 (1H, ddd, *J* = 11.2, 8.0, 6.5, *H*-2), 3.45 (1H, AB, J_{AB} = 15.3, NCH_AHPh), 3.97 (1H, AB, J_{AB} = 15.3, NCH_BHPh), 4.27 (1H, q, *J* = 6.8, C(α)*H*), 7.16–7.38 (10m, Ar–*H*); δ_C (100 MHz, $CDCl_3$) 17.7, 27.8, 28.1, 28.2, 28.8, 37.0, 37.8, 51.4, 52.3, 58.2, 65.8, 80.1, 80.4, 126.1, 126.8, 127.8, 128.0, 142.3, 143.1, 171.8, 172.5; *m*/*z* (EI^+) 493 (M^+,8), 478 (10), 388 (35), 332 (14), 250 (62), 218 (16), 146 (50), 105 (100), 77 (15); HRMS (EI^+) $C_{31}H_{43}O_4N$ requires 493.3192; found 493.3215. Further elution gave (1*R*,2*R*,5*R*,α*R*)-**14** (26 mg, 18%) with identical spectroscopic properties to that previously obtained.

Preparation of di-*tert*-butyl (1*R*,2*S*,5*S*,α*S*)- and (1*S*,2*S*,5*S*,α*S*)-2-*N*-benzyl-*N*-α-methylbenzylamino-5-carboxymethyl-cyclopentane-1-carboxylate 26 and 14 respectively. Following general procedure 1, (1*E*,5*S*)-**23** (97 mg, 0.34 mmol) in THF (2 ml), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (232 mg, 1.1 mmol) in THF (6 ml) and *n*-BuLi (1.6 M, 0.69 ml, 1.1 mmol) gave, after chromatographic purification on silica (hexane–Et_2O 49 : 1), (1*R*,2*S*,5*S*,α*S*)-**26** (82 mg, 48%); $[\alpha]_D^{26}$ −43.0 (*c* 1.6, $CHCl_3$); further elution gave (1*S*,2*S*,5*S*,α*S*)-**14** (35 mg, 21%); $[\alpha]_D^{26}$ +33.2 (*c* 0.54, $CHCl_3$).

Preparation of di-*tert*-butyl (1*S*,2*R*,5*R*)-2-amino-5-carboxymethyl-cyclopentane-1-carboxylate 27. Following general procedure 3, (1*S*,2*R*,5*R*,α*R*)-**25** (41 mg, 0.08 mmol) in AcOH (6 ml), Pd/C (10% by mass, 17 mg) and hydrogen (5 atm) at rt gave after purification by column chromatography ($CHCl_3$–MeOH 95 : 5), (1*S*,2*R*,5*R*)-**27** (19 mg, 77%); $[\alpha]_D^{26}$ +25.8 (*c* 1.47, $CHCl_3$); ν_{max} 3350, 2976, 1728, 1458, 1368, 1258, 1154; δ_H (200 MHz, $CDCl_3$) 1.43 (9H, s, C(CH_3)$_3$), 1.47 (9H, s, C(CH_3)$_3$), 1.60–1.82 (3H, m, C(4)H_2, *H*-3$_A$), 1.96–2.04 (1H, m, *H*-3$_B$), 2.21–2.50 (3H, m, C$H_A H_B$COO^{t}Bu, H-5), 2.81–2.85 (1H, app t, *J* = 6.0, 6.4, *H*-1), 3.40–3.58 (1H, m, *H*-2); δ_C (50 MHz, $CDCl_3$) 28.2, 28.3, 28.6, 29.6, 38.0, 38.2, 51.7, 52.8, 80.3, 81.1, 171.7, 171.9; *m*/*z* (EI$^+$) 299 (M$^+$, 1), 242 (7), 186 (42), 170 (60), 142 (15), 126 (30), 107 (20), 82 (30), 57 (100); HRMS (EI$^+$) $C_{16}H_{29}O_4N$ requires 299.2097; found: 299.2109.

Preparation of di-*tert*-butyl (1*R*,2*S*,5*S*)-2-amino-5-carboxymethyl-cyclopentane-1-carboxylate 27. Following general procedure 3, (1*R*,2*S*,5*S*,α*S*)-**25** (71 mg, 0.14 mmol) in AcOH (8 ml), Pd/C (10% by mass, 29 mg) and hydrogen (5 atm) at rt gave after purification by column chromatography ($CHCl_3$–MeOH 95 : 5), (1*R*,2*S*,5*S*)-**27** (36 mg, 84%); $[\alpha]_D^{26}$ −30.1 (*c* 1.07, $CHCl_3$).

Preparation of di-*tert*-butyl (1*R*,2*S*,5*R*)-2-amino-5-carboxymethyl-cyclopentane-1-carboxylate 28. Following general procedure 3, (1*R*,2*S*,5*R*,α*S*)-**26** (100 mg, 0.21 mmol) in AcOH (8 ml), Pd/C (10% by mass, 42 mg) and hydrogen (5 atm) at rt gave, after purification by column chromatography ($CHCl_3$–MeOH 95 : 5), **28** (43 mg, 71%); $[\alpha]_D^{26}$ +28.4 (*c* 1.45, $CHCl_3$); ν_{max} 3390, 2976, 1728, 1393, 1368, 1258, 1154, 845; δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, C(CH_3)$_3$), 1.46 (9H, s, C(CH_3)$_3$), 1.75–2.10 (4H, m, C(3)H_2 and C(4)H_2), 2.14 (1H, dd, *J* = 14.8, 8.7, CH_AHCO$_2$^{t}Bu), 2.40–2.46 (1H, m, *H*-1), 2.46 (1H, dd, *J* = 14.8, 5.4, CH_BHCO$_2$^{t}Bu), 2.64–2.72 (1H, m, *H*-2), 3.62 (2H, br s, NH_2); δ_C (100 MHz, $CDCl_3$) 28.0, 28.2, 29.4, 34.4, 37.0, 40.8, 54.8, 56.0 m, 80.1, 80.5, 171.7, 172.5; *m*/*z* (EI$^+$) 299 (M$^+$, 1), 242 (7), 186 (54), 170 (76), 152 (12), 126 (32), 82 (22), 57 (100); HRMS (EI$^+$) $C_{16}H_{29}O_4N$ requires 299.2097, found 299.2113.

Preparation of di-*tert*-butyl (1*S*,2*R*,5*S*)-2-amino-5-carboxymethyl-cyclopentane-1-carboxylate 28. Following general procedure 3, (1*S*,2*R*,5*S*,α*R*)-**26** (141 mg, 0.28 mmol) in AcOH (12 ml), Pd/C (10% by mass, 56 mg) and hydrogen (5 atm) at rt gave, after purification by column chromatography ($CHCl_3$–MeOH 95 : 5), (1*S*,2*R*,5*S*)-**28** (72 mg, 84%); $[\alpha]_D^{26}$ −30.9 (*c* 1.95, $CHCl_3$).

Preparation of (1*S*,2*R*,5*R*)-2-amino-5-carboxymethyl-cyclopentane-1-carboxylate 29. Following general procedure 4, (1*S*,2*R*,5*R*)-**27** (36 mg, 0.12 mmol) and TFA (0.5 ml) gave, after ion exchange chromatography (Dowex 50X8-200), (1*S*,2*R*,5*R*)-**29** (23 mg, quant.); $[\alpha]_D^{26}$.+15.2 (*c* 0.3, 5.5M NH_3 aq.); ν_{max} 3600–2400 (br), 1714, 1418, 1198, 799, 665; δ_C (200 MHz, D_2O) 1.49–1.53 (1H, m, *H*-4$_A$), 1.77–1.83 (1H, m, *H*-3$_A$), 1.90–1.98 (1H, m, *H*-4$_B$), 2.07–2.14 (1H, m, *H*-3$_B$), 2.40–2.70 (3H, m, CH_2CO$_2$H and *H*-5), 3.20 (1H, app t, *J* = 6.8, *H*-1), 3.75 (1H, app q, J = 8.1, *H*-2); δ_C (50 MHz, D_2O) 27.5, 27.7, 35.8, 37.5, 48.5, 52.0, 174.4, 176.7; *m*/*z* (EI$^+$) 188 (M$^+$, 1), 185 (50), 93 (100), 75 (30); HRMS (EI$^+$) $C_8H_{13}O_4N$ requires 188.0923; found 188.0922.

Preparation of (1*R*,2*S*,5*S*)-2-amino-5-carboxymethyl-cyclopentane-1-carboxylate 29. Following general procedure 4, (1*R*,2*S*,5*S*)-**27** (9 mg, 0.03 mmol) and TFA (0.5 ml) gave, after ion exchange chromatography (Dowex 50X8-200), (1*R*,2*S*,5*S*)-**29** (6 mg, quant.); $[\alpha]_D^{26}$ −31.9 (*c* 1.09, 5.5M NH_3 aq.); HRMS (EI$^+$) $C_8H_{13}O_4N$ requires 188.0923; found 188.09238.

Preparation of (1*R*,2*S*,5*R*)-2-amino-5-carboxymethyl-cyclopentane-1-carboxylate 30. Following general procedure 4, (1*R*,2*S*,5*R*)-**28** (36 mg, 0.12 mmol) and TFA (0.6 ml) gave, after ion exchange chromatography (Dowex 50X8-200), (1*R*,2*S*,5*R*)-**30** (23 mg, quant.); $[\alpha]_D^{26}$ +24.6 (*c* 1.93, H_2O); $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. found: C, 51.25; H, 7.11; N, 7.65%; ν_{max} 3600–2400 (br), 1715, 1418, 1198, 799, 665; δ_H (200 MHz, D_2O) 1.32–1.38 (1H, m, *H*-4$_A$), 1.71–1.79 (1H, m, *H*-4$_B$), 2.11–2.18 (2H, m, C(3)H_2), 2.40–2.70 (3H, m, CH_2CO$_2$H, *H*-5), 2.79 (1H, dd, *J* = 8.5, 7.8, *H*-1), 3.85 (1H, app q, *J* = 5.8, *H*-2); δ_C (50 MHz, D_2O) 26.6, 27.6, 35.9, 36.4, 48.4, 50.7, 173.3,174.7; *m*/*z* (EI$^+$) 188 (M$^+$, 18), 137 (5), 115 (100), 93 (52), 75(8); HRMS (EI$^+$) $C_8H_{13}O_4N$ 188.0923; found 188.0904.

Preparation of (1*S*,2*R*,5*S*)-2-amino-5-carboxymethyl-cyclopentane-1-carboxylate 30. Following general procedure 4, (1*S*,2*R*,5*S*)-**28** (32 mg, 0.10 mmol) and TFA (1 ml) gave, after ion exchange chromatography (Dowex 50X8-200), (1*S*,2*R*,5*S*)-**30** (19 mg, quant.); $[\alpha]_D^{26}$ −25.1 (*c* 0.57, H_2O); HRMS (EI$^+$) $C_8H_{13}O_4N$ requires 188.0923; found 188.0941.

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