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A Novel Strategy Towards the Asymmetric Synthesis of Orthogonally Funtionalised 2-*N*-Benzyl-*N*-α-methylbenzyl-amino-5-carboxymethyl-cyclopentane-1-carboxylic acid.

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Abstract: The asymmetric synthesis of the orthogonally funtionalised compounds *tert*-butyl 2-*N*-benzyl-*N*-α-methylbenzylamino-5-methoxycarbonylmethylcyclopentane-1-carboxylate and methyl 2-*N*-benzyl-*N*-α-methylbenzylamino-5–carboxymethylcyclo-pentane-1-carboxylate by a domino reaction of *tert*-butyl methyl (*E*,*E*)-octa-2,6-diendioate with lithium *N*-α-methylbenzyl-*N*-benzylamide initiated by a Michael addition, subsequent 5-*exo*-trig intramolecular cyclisation and posterior selective hydrolysis with trifluoroacetic acid is reported.

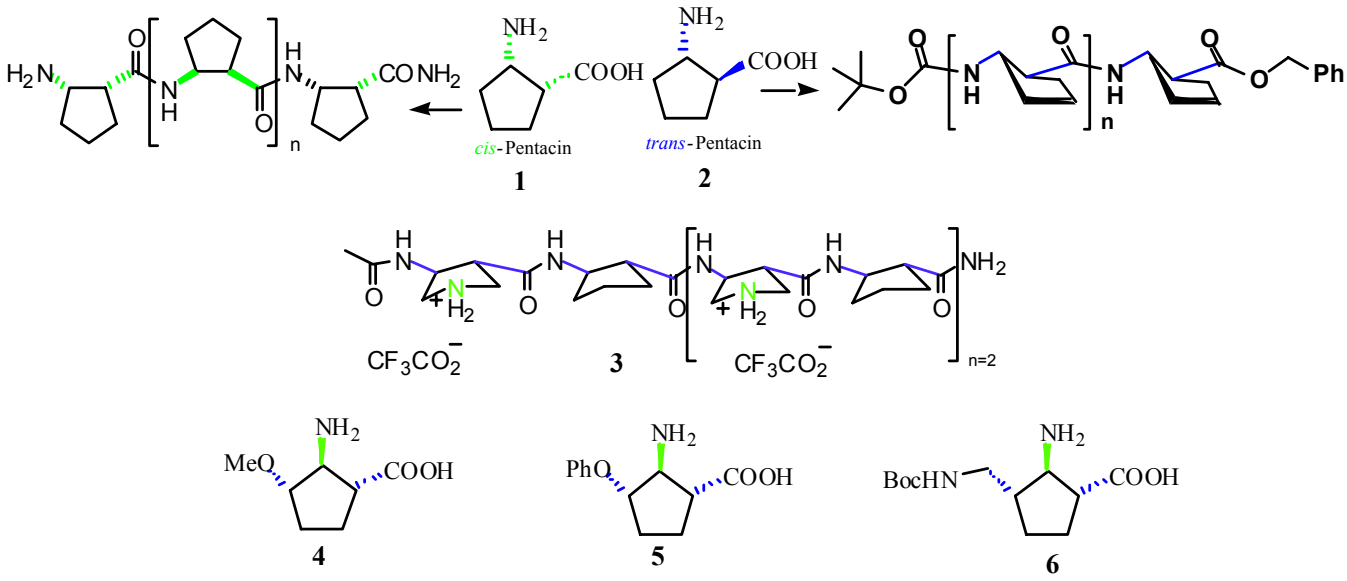
Keywords: Asymmetric synthesis, chiral lithium amide, β-amino acids, domino reaction, β-aminocyclopentane carboxilate, aminodiester orthogonal protection.

Introduction

The asymmetric synthesis of polyfunctionalised cyclopentane derivatives has been widely pursued in organic synthesis, with much recent interest focusing around strategies for the asymmetric synthesis of *cis*-pentacin (**1**) and *trans*-pentacin (**2**), respectively. The *cis*-diastereoisomer shows potent

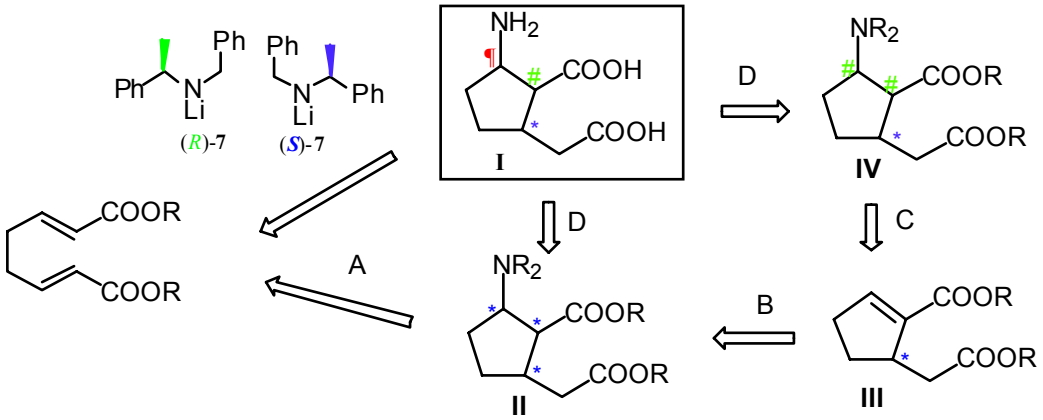
antifungal activity while Fülop *et al*. have recently demonstrated that oligomers of *cis*-pentacin adopt a sheet type structure in DMSO [1]. Furthermore, Gellman *et al.* have demonstrated that short chain β-peptides derived from *trans*-pentacin adopt 12-membered helical structures [2-5] and when a pyrrolidine–base β-amino acid is incorporated into the hexa-β-peptide **3**, it confers water solubility when the ring nitrogen is protonated [6-7]. In addition, oligomers composed of the 3-substituted *trans*-pentacin residues **4**, **5** and **6** fold in water, which should facilitate the design of β-peptides for biological applications (Figure 1)[8].

Figure 1



We have recently demonstrated the asymmetric synthesis of the eight stereoisomers of 2-amino-5-carboxymethyl-cyclopentane-1-carboxylate (**I**) using (*E*,*E*)-octa-2,6-diendioate as the only prochiral precursor [9], as shown in the retrosynthesis in Scheme 1. The set of *trans*-C(1)-C(2)-stereoisomeric β-amino diacids (**II**) are readily prepared via a diastereoselective tandem conjugate addition-cyclisation protocol with either (*R*)- or (*S*)-*N*-benzyl-*N*-α-methylbenzylamine [(*R*)- or (*S*)-**7**], hydrogenolysis and ester hydrolysis. The synthsis of 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 (**II**), giving homochiral (*R*)- or (*S*)-5-carboxymethylcyclo-pentene-1-carboxylate derivatives (**III**). Conjugate addition of either lithium (*R*)- or (*S*)-**7** 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 (**IV**). With the β-aminodiacids in hand the synthesis of the orthogonally protected aminodiester was envisaged in order to give further options when trying to link the monomer to build the β-peptide.

Scheme 1



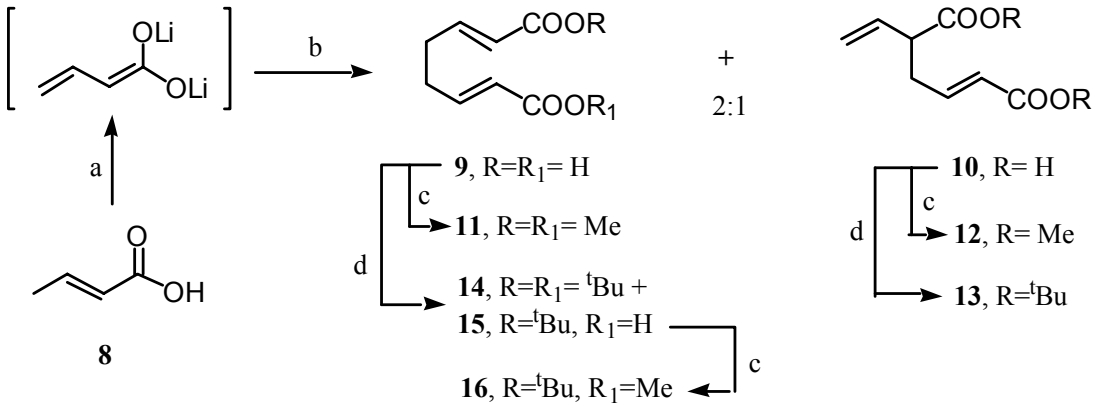
A:*domino* reaction: Michael addition/intramolecular 5-*exo*-cyclisation. B: Cope stereoespecific *sin* elimination. C: Stereoselective Michael conjugate addition . D: Deprotection.

Results and Discussion

We have obtained dimethyl and di-(1-ethylpropyl)(*E*,*E*)-octa-2,6-diendioate on a multigram scale using the method published by Scheffer *et al.* [10]. Treatment of sebacic acid with thionyl chloride followed by bromine, while irradiating the entire apparatus with a 300-W sunlamp and then the addition of alcohol (methanol or 1-ethylpropanol) produces the appropriate dibromodiester, which yields the required diendioate upon refluxing with DMF. It was not possible to obtain the convenient di-*tert*-butyl diester using this procedure and we used the methodology developed by Mestres *et al.* [11-14] (Scheme 2) to obtain diunsaturated dicarboxylic acids by oxidative coupling of the dianions of unsaturated carboxylic acids.

The oxidative coupling of the dianion derived from crotonic acid (**8**), as shown in Scheme 3, afforded a 70% yield of a 2:1 mixture of (*E*,*E*)-octa-2,6-diendioic and (*E*)-5-vinyl-hex-2-endioic acids (**9** and **10**) that could be easily separated by crystallization of **9** [13]. Methylation of these diacids using diazomethane or methanol in acid media is quantitative. The di-*tert*-butyldiester **13** is obtained (67% after CC) by reaction of diacid **10** with trifluoroacetic anhydride and *tert*-butanol, but under the same conditions diacid **9** afforded an easily separable mixture of di-*tert*-butyl ester **14** (42%) and monoester **15** (57%) which upon further treatment with diazomethane produced the orthogonally protected *tert*-butyl methyl (*E*,*E*)-octa-2,6-diendioate **16**. Compound **14** has been used to synthesize the aforementioned β-aminocyclopentanoic acid [9] and **16** provided two differentiated Michael acceptors to be tested with the homochiral lithium amide.

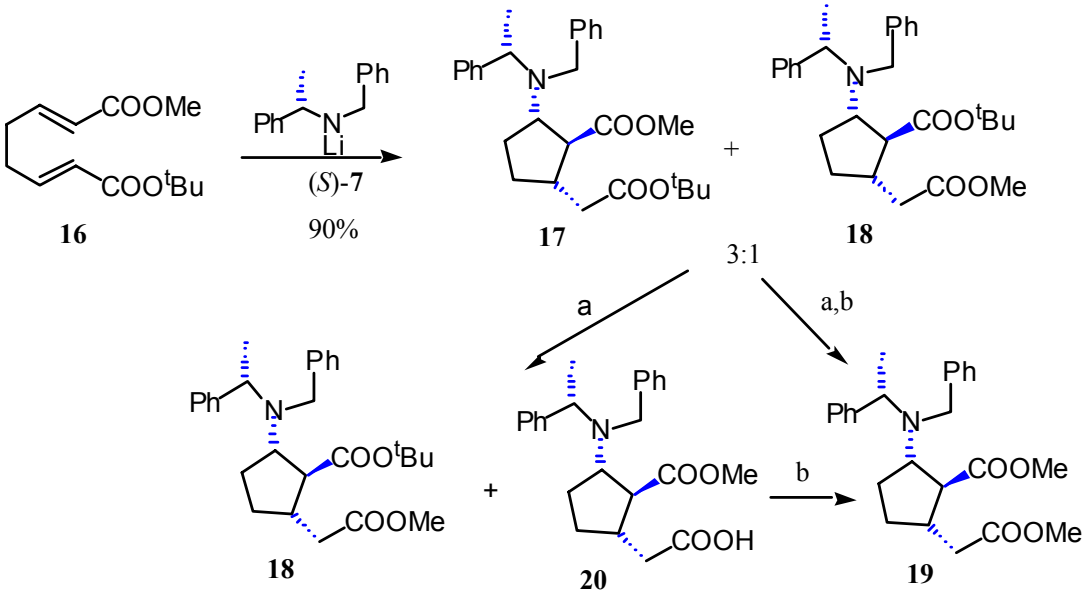
Scheme 2



a: $LiNEt_2$. b: I_2. c: MeOH,HCl ó CH_2N_2. d: TFAA, ^tBuOH

Addition of *tert*-butyl methyl (*E*,*E*)-octa-2,6-diendioate **16** to homochiral lithium (*S*)- *N*-benzyl-*N*-α-methylbenzylamine [(*S*)-**7**] gave a 90% yield of a 3:1 mixture of **17** and **18** (Scheme 3). The ratio was determined by integration of the respective methyl group signals of each compound observed at 3.44 and 3.62 ppm in the ^{1}H-NMR spectra (*vide infra*). The absolute configuration of this compound was established by obtaining **19** ($[\alpha]_D^{26}$ +50.5; lit. [9] –51.3 for the enantiomer) by reaction of the **17**/**18** mixture with trifluoroacetic acid and then diazomethane. Therefore both compounds have the same configuration, consistent with the asymmetric addition of the lithium amine and anti alkylation of the enolate produced. The only difference being the chemoselectivity observed due to the different alkyl group in each Michael acceptor, giving a favorable addition to the less bulky methyl.

Scheme 3

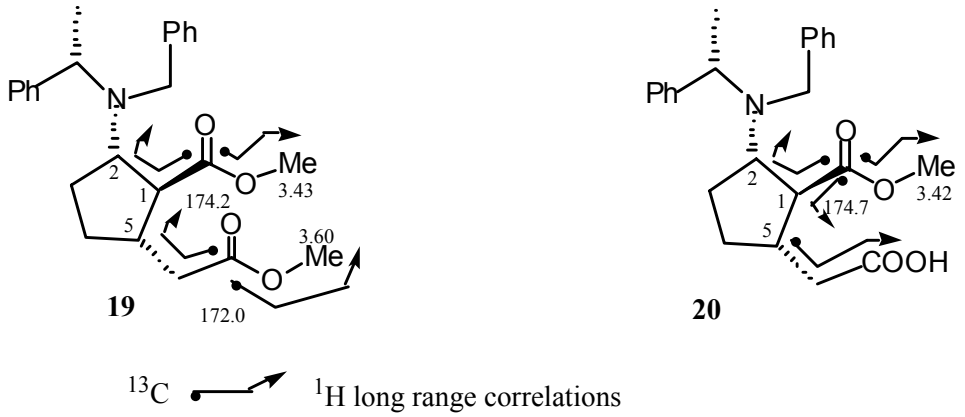


a: TFA. b: CH_2N_2.

The X-ray structure of **19** [9] shows the carbonyl on C-1 almost perpendicular to the ring plane, consequently very shielded by the adjacent groups at C-2 and C-5. So the **18**/**19** mixture could be easily resolved upon treatment with trifluoroacetic acid in a short period of time, as only the lateral *tert*-butyl ester at C-5 is hydrolyzed, giving rise to the straightforwardly separable unreacted diester **18** (21%) and the acid compound **20** (61%) from which **19** is obtained as well by methylation with diazomethane.

All the spectroscopic assignments of **20** and **19** have been unambiguously established by ^{1}H-NMR techniques, including 2-dimensional homonuclear COSY, heteronuclear HMQC and HMBC (noteworthy signals are shown in Figure 2, each methyl group is clearly differentiated), nOe and ROESY experiments.

Figure 2



Conclusions

Crotonic acid is an excellent starting material to obtain the orthogonally substituted *tert*-butyl, methyl (*E*,*E*)-octa-2,6-diendioate, which upon treatment with lithium *N*-α-methylbenzyl-*N*-benzylamine stereoselectively yields both methyl 2-*N*-benzyl-*N*-α-methylbenzylamino-5-*tert*-butoxy-carbonylmethylcyclopentane-1-carboxylate and *tert*-butyl 2-*N*-benzyl-*N*-α-methylbenzylamino-5-methoxycarbonylmethylcyclopentane-1-carboxylate in a 3:1 ratio, resulting from a domino reaction started by a chemoselective asymmetric Michael addition and subsequent 5-*exo*-trig intramolecular cyclization. A chemo- and stereoselective *tert*-butyl hydrolysis of the mixture of reaction with trifluoroacetic acid provides the easily separable unreacted diester **20** (21%) and the acid compound methyl 2-*N*-benzyl-*N*-α-methylbenzylamino-5-carboxymethylcyclopentane-1-carboxylate (**21**) (61%).

Here we demonstrate an efficient strategy towards the synthesis of a cyclopentane β-aminodiester with three different orthogonal protecting groups on each functionality, which can then submitted to appropriate modifications for use in β-peptide synthesis. The extension of this strategy to the preparation of a range of different orthogonally substituted cyclopentane and cyclohexane derived β-amino acids is currently under investigation in our laboratory.

Acknowledgements

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Experimental

General

^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ at 200 and 400 MHz (^{1}H) or 50 and 100 MHz (^{13}C) on Varian 200 VX and BRUKER DRX 400 instruments, respectively. Multiplicities were determined by DEPT experiments. IR spectra were registered using a BOMEM 100 FTIR 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 100mL. The electron impact (EI) mass spectra were run on a VG-TS 250 spectrometer using a 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 (CC) 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 (DCM) from KOH. Compounds **9**-**12** were prepared according to the published procedures [13-14].

Preparation of (E)-di-tert-butyl-5-vinylhex-2-enedioate (**13**)**.**

The diacid **10** (208 mg, 1.22 mmol) was dissolved in trifluoroacetic acid (TFAA, 1 mL) at 0 ºC and the solution was stirred for 30 min. and then *tert*-BuOH (1 mL) was added. The mixture was stirred for 5 h, then water (10 mL) was added and the crude product extracted with Et_2O. The combined organic extracts were washed with $NaHCO_3$ 5%, water and brine. After drying and concentration the residue was purified by chromatography (95:5 n-hexanol-EtOAc) to give **13** (231 mg, 67%); IR (film) ν (cm^{-1}) 2980, 2934, 1728, 1657, 1460, 1360, 1258, 982, 849; ^{1}H-NMR (200 MHz) 1.42-1.45 (18H, C(C*H*$_3$)$_3$), 2.39 (1H, ddd, *J* = 13.0, 6.5 y 6.5Hz, *H*-4A), 2.58 (1H, ddd, *J* = 13.0, 6.5 y 6.5Hz, *H*-4B), 3.10 (1H, c, *J* = 6.5Hz, *H*-5), 5.15 (2H, dd, *J* =15.5 y 2.0Hz, *H*-2'A), 5.19 (2H, dd, *J* =7.5 y 2.0Hz, *H*-2'B), 5.75 (1H, d, J= 16.0Hz, *H*-2), 5.80 (1H, ddd, *J* = 15.5, 7.5 y 6.5Hz, *H*-1'), 6.75(1H, dt, *J* = 16.0 y 6.5Hz, *H*-3); ^{13}C-NMR (50 MHz) 27.9 and 28.1(3CH$_3$, C(*C*H$_3$)$_3$), 34.4 (CH$_2$, *C*-4), 49.7 (CH, *C*-5), 80.0 (C, *C*(CH$_3$)$_3$), 81.0 (C, *C*(CH$_3$)$_3$), 117.3 (CH$_2$, *C*-2'), 125.0 (CH, *C*-2), 135.3 (CH, *C*-1'), 143.7 (CH, *C*-3), 165.5 (C, *C*-1), 171.9 (C, *C*-6).

Preparation of di-tert-butyl (E,E)-octa-2,6-diendioate and tert-butyl and hydrogen (E,E)-octa-2,6-diendioates **14** *and* **15**.

To the diacid **9** (593 mg, 3.5 mmol) at 0˚C was added TFAA (1.5 mL) and, after stirring for 30 min., *tert*-BuOH (1.5 mL) and the mixture was kept at room temperature for 5 h. The reaction product was partitioned between 10% $NaHCO_3$ (70 mL) and EtOAc (3 x 40 mL). The organic extracts were washed with water and brine. After drying and concentration compound **14** (407 mg, 42%) was obtained. The $NaHCO_3$ solution was treated with 6M HCl to pH = 2 and extracted with Et_2O. The organic extracts were washed with water and brine to give, after drying and concentration, compound **15** (450 mg, 57%).

Compound **14**: IR (film) ν (cm^{-1}) 2980, 1723, 1655, 1559, 1368, 1329, 1142, 1028, 982; ^{1}H-NMR (200 MHz) 1.45 (18H, s, C(CH_3)$_3$), 2.45 (4H, m, *H*-4 y *H*-5), 5.75 (2H, d, *J* = 15.0Hz, *H*-2 y *H*-7), 6.8 (2H, dt, *J* = 15.6 y 6.6Hz, *H*-3 y *H*-6); ^{13}C-NMR (50 MHz) 28.1 (6CH_3, C(CH_3)$_3$), 30.3 (2CH_2, *C*-4 and *C*-5), 80.0 (2C, *C*(CH_3)$_3$), 124.0 (2CH, *C*-2 y *C*-7), 149.9 (2CH, *C*-3 and *C*-6), 165.6 (2C, *C*OOR).

Compound **15**: IR (film) ν (cm^{-1}) 3650, 1717, 1653, 1559, 1458, 1154; ^{1}H-NMR (200 MHz) 1.49 (9H, s, C(CH_3)$_3$), 2.45(4H, m, *H*-4 y *H*-5), 5.80(2H, d, *J* = 15.0Hz, *H*-2 and *H*-7), 6.85(1H, dt, *J* = 15.6 and 6.6Hz *H*-6), 7.15(1H, dt, *J* = 15.6 y 6.6Hz, *H*-3); ^{13}C-NMR (50 MHz) 28.1 (3CH_3, C(CH_3)$_3$), 30.1 (CH_2, *C*-5), 30.5 (CH_2, *C*-4), 80.0 (C, *C*(CH_3)$_3$), 121.4 (CH, *C*-7), 124.2 (CH, *C*-2), 146.3 (CH, *C*-3), 149.6(CH, *C*-6), 165.6(C, *C*-8), 170.4(C, *C*-1).

Preparation of tert-butyl methyl (E,E)-octa-2,6-diendioate (**16**).

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Compound **15** (12 mg, 0.053 mmol) was treated with a solution of gaseous CH_2N_2 in ether. The reaction product was concentrated *in vacuo* to give **16** (12 mg, 95%); IR (film) ν (cm^{-1}) 2978, 1705, 1653, 1559, 1458, 1150 ; ^{1}H-NMR (200 MHz) 1.47 (9H, s, C(CH_3)$_3$), 2.45 (4H, m, *H*-4 and *H*-5), 3.73 (3H, s, CH_3), 5.61 (2H, d, *J* =16.0Hz, *H*-2 and *H*-7), 6.88 (2H, dd, *J* =16.0 y 6.5Hz, *H*-3 and *H*-6); ^{13}C-NMR (50 MHz) 28.0 (3CH_3, C(CH_3)$_3$), 30.2 and 30.4 (CH_2, *C*-4 and *C*-5), 51.2 (CH_3, COOCH_3), 80.1 (C, *C*(CH_3)$_3$), 121.8 and 124.1 (2CH, *C*-2 and *C*-7), 145.6 and 147.1 (2CH, *C*-3 and *C*-6), 165.6 and 166.6 (C, *C*-1 and *C*-8).

Preparation of methyl (1S,2S,5S,αS)-2-N-benzyl-N-α-methylbenzylamino-5-tert-butoxycarbonyl-methylcyclopentane-1-carboxylate (**17**) *and tert-butyl (1S,2S,5S,αS)-2-N-benzyl-N-α-methylbenzyl-amino-5-methoxycarbonylmethyl-cyclopentane-1-carboxylate* (**18**).

n-BuLi (1.6 M, 0.50 mL, 0.80 mmol) was added to a stirred solution of (*R*)-*N*-benzyl-*N*-α-methyl-benzylamine (182 mg, 0.86 mmol) in THF (3 mL) at –78˚C and stirred for 30 minutes prior to the addition of a solution of **16** (122 mg, 0.50 mmol) in THF (0.5 mL) at –78˚C. After two hours, saturated

aqueous NH_4Cl solution was added and the resulting solution warmed to r.t., partitioned between DCM (3 x 50 mL) and brine, dried and concentrated *in vacuo* gave a 3:1 mixture of **17**/**18** (203 mg, 90%), as deduced by integration of the methyl ester signals in the ^{1}H-NMR at 3.44 and 3.62 ppm respectively.

Preparation of methyl (1S,2S,5S,αS)-2-N-benzyl-N-α-methylbenzylamino-5-methoxycarbonylmethyl-cyclopentane-1-carboxylate (**19**).

The **17**/**18** mixture (58 mg, 0.13 mmol) was dissolved in TFA (0.5 mL) and stirred for 2 hours at rt before concentration in vacuo to give 40 mg of product, which upon treatment with a solution of gaseous CH_2N_2 in ether gave **19** (49 mg, 95%) after concentration *in vacuo* (yield 72% after crystallization from 7:3 hexane-Et_2O); $[\alpha]_D^{26}$ +50.5 (c 1.21, $CHCl_3$); m.p. 82-84 ºC; $C_{25}H_{31}NO_4$ requires C, 73,32; H. 7,63; N. 3,42; found: C, 73,45; H. 7,46; N. 3,59; IR (film) ν (cm^{-1}) 2950, 1920, 1840, 1740, 1490, 1450; ^{1}H-NMR (400 MHz) 1.31 (1H, m, *H*-4$_A$), 1.29 (3H, d, *J* = 6.8, C(α)*Me*), 1.70-1.85 (2H, m, *H*-3), 1.95 (1H, m, *H*-4$_B$), 2.21 (1H, dd, *J* = 12.0, 8.4, C*H*$_A$HCO$_2$Me), 2.29-2.39 (2H, m, *H*-5 and C*H*$_B$HCO$_2$Me), 2. 48 (1H, app t, *J* = 9.8, *H*-1), 3.43 (3H, s, CO$_2$*Me*), 3.52 (1H, dt, *J* = 9.8, 5.0, *H*-2), 3.60 (3H, s, CO$_2$*Me*), 3.68 (1H, AB, J_{AB} = 12.4, NC*H*$_A$HPh), 3.80 (1H, q, *J* = 6.8, C(α)*H*), 3.83 (1H, AB, J_{AB} = 12.4, NCH$_A$*H*$_B$Ph), 7.10-7.38 (8H, m, Ar-*H*), 7.48-7.52 (2H, m, Ar-*H*); ^{13}C-NMR (100 MHz) 14.1 (CH$_3$, C(α)*Me*), 26.5 (CH$_2$, *C*-3), 30.9 (CH$_2$, *C*-4), 38.1 (CH, *C*-5), 38.8 (CH$_2$, *C*H$_2$COOMe), 50.0 (CH$_2$, N*C*H$_2$), 50.0 (CH$_3$, CO$_2$*Me*), 51.4 (CH$_3$, CH$_2$CO$_2$*Me*), 55.3 (CH, *C*-1), 56.7 (CH, *C*α), 63.5 (CH, *C*-2), 126.5, 126.8, 127.0, 127.8, 127.9, 128.2, 128.6, 128.8 (CH, *Ar*), 141.1 (C, *Cipso*CH$_2$N), 144.2 (C, *Cipso*Cα), 172.4 (C,CH$_2$*C*O$_2$Me), 174.6 (C, *C*O$_2$Me); EIMS *m/z* (%) 409 (M$^+$, 5), 394 (8), 250 (30), 146 (50), 105 (78), 91 (100), 77 (22); HRMS (EI) $C_{25}H_{32}NO_4$ requires 410.2331; found 410.2329.

Preparation of methyl (1S,2S,5S,αS)-2-N-benzyl-N-α-methylbenzylamino-5-carboxymethylcyclo-pentane-1-carboxylate (**20**).

The **18**/**19** mixture (40 mg, 0.09 mmol) was dissolved in TFA (0.2 mL) and stirred for 15 min. at 0ºC. Then water (1 mL) was added and the mixture was extracted with DCM (3 x 20 mL). The combined organic layers were washed with water and brine and dried over Na_2SO_4. Concentration followed by flash chromatography on silica gel (7:3 *n*-hexane-EtOAc: gave **18** (8.4 mg, 21%) and **20** (22 mg, 61%).

Compound **18:** $[\alpha]_D^{26}$ +37.0 (c 0.26, $CHCl_3$); IR (film) ν (cm^{-1}) 2967, 1734, 1653, 1373, 1148, 667.; ^{1}H-NMR (400 MHz) 1.31 (1H, m, *H*-4$_A$), 1.35 (3H, d, *J* = 6.9, C(α)*Me*), 1.39 (9H, s, C(C*H*$_3$)$_3$), 1.58 (1H, m, *H*-3$_A$), 1.76 (1H, m, *H*-3$_B$), 1.95 (1H, m, *H*-4$_B$), 2.16 (1H, dd, *J* = 12.2, 6.8, C*H*$_A$HCO$_2$Me), 2.29 (1H, m, *H*-5), 2.38 (1H, app t, *J* = 10.0, *H*-1), 2.43 (1H, dd, *J* = 12.2, 3.0, C*H*$_B$HCO$_2$Me), 3.62 (3H, s, CO$_2$*Me*), 3.63 (1H, m, *H*-2), 3.65 (1H, AB, J_{AB} = 15.7, NC*H*$_A$HPh), 3.75 (1H, AB, J_{AB} = 15.7, NCH$_A$*H*$_B$Ph),3.85 (1H, q, *J* = 6.9, C(α)*H*), 7.10-7.40 (8H, m, Ar-*H*), 7.45-7.50 (2H, m, Ar-*H*); ^{13}C-

NMR (100 MHz) 15.2 (CH_3, C(α)*Me*), 26.3 (CH_2, *C*-3), 28.1 ($3CH_3$, $C(CH_3)_3$), 29.6 (CH_2, *C*-4), 38.4 (CH, *C*-5), 38.6 (CH_2, CH_2COOMe), 49.9 (CH_2, NCH_2), 51.3 (CH_3, CO_2Me), 55.7 (CH, *C*-1), 57.6 (CH, *C*α), 63.2 (CH, *C*-2), 80.0 (C, $C(CH_3)_3$), 126.5, 126.6, 127.5, 127.7, 127.8, 128.0, 128.1, 128.5 (CH, *Ar*), 141.6 (C, *Cipso*CH_2N), 144.1 (C, *Cipso*Cα), 172.6 (C,CH_2CO_2Me), 173.8 (C, $CO_2{}^tBu$); EIMS *m/z* (%) (M^+, 2), 346 (8), 290 (12), 256 (13), 199 (100), 149 (13), 105 (42), 69 (48); HRMS (EI) $C_{28}H_{37}O_4N$ requires 451.2723; found 451.2720.

Compound **20**: $C_{24}H_{29}O_4N$ requires C, 72,89; H. 7,39; N. 3,54; found: C, 72,97; H. 7,15; N. 3,65; IR (film) ν (cm^{-1}) 3600-2600 (broad), 1738, 1710, 1495, 1454, 1373, 1283, 1157, 1028, 912; ^{1}H-NMR (400 MHz,) 1.30 (3H, d, *J* = 6.9, C(α)*Me*), 1.35 (1H, m, *H*-4_A), 1.68-1.78 (2H, m, *H*-3), 1.99 (1H, m, *H*-4_B), 2.25 (1H, dd, *J* = 12.2, 7.2, CH_AHCO_2H), 2.30 (1H, m, *H*-5), 2.43 (1H, dd, *J* = 12.2, 3.0, CH_BHCO_2H), 2.50 (1H, app t, *J* = 10.0, *H*-1), 3.42 (3H, s, CO_2Me), 3.55 (1H, q, *J* = 7.5, *H*-2), 3.70 (1H, AB, J_{AB} = 15.7, NCH_AHPh), 3.85 (1H, AB, J_{AB} = 15.7, NCH_AH_BPh), 3.87 (1H, q, *J* = 6.9, C(α)*H*), 7.10-7.40 (8H, m, Ar-*H*), 7.45-7.50 (2H, m, Ar-*H*); ^{13}C-NMR (100 MHz) 13.7 (CH_3, C(α)*Me*), 26.2 (CH_2, *C*-3), 30.9 (CH_2, *C*-4), 37.7 (CH, *C*-5), 38.5 (CH_2, CH_2COOH), 49.8 (CH_2, NCH_2), 51.5 (CH_3, CO_2Me), 55.3 (CH, *C*-1), 56.4 (CH, *C*α), 62.9 (CH, *C*-2), 80.0 (C, $C(CH_3)_3$), 126.4, 126.8, 127.7, 127.8, 128.2, 128.7 (CH, *Ar*), 140.9 (C, *Cipso*CH_2N), 144.0 (C, *Cipso*Cα), 174.7 (C, CO_2Me), 177.0 (C, CO_2H); EIMS *m/z* (%) 395(M^+,2), 290(5), 251(5), 196(100), 149(9), 91(80), 69(15); HRMS (EI) $C_{24}H_{29}O_4N$ requires 395.2097; found 395.2125. In a separate experiment compound **19** (36 mg, 0.091 mmol) was treated with a solution of gaseous CH_2N_2 in ether. The reaction product was concentrated *in vacuo* to give **20** (36 mg, 96%).

Preparation of (1S,2S,5S,αS)-2-N-benzyl-N-α-methylbenzylamino-5-methoxycarbonylmethylcyclo-pentane- 1-carboxylic acid (**21**).

The **18**/**19** mixture (100 mg, 0.22 mmol) was dissolved in TFA (1 mL) and stirred for 30 min. at rt. Water (2 mL) was then added and the mixture was extracted with DCM (3 x 40 mL). The combined organic layers were washed with water and brine and dried over Na_2SO_4. Concentration followed by flash chromatography on silica gel (7:3 *n*-hexane-EtOAc) gave **18** (12 mg, 12%), **20** (29 mg, 45%) and an inseparable 1:1 mixture of **20**/**21** (13 mg, 22%), from which compound **21** could not be isolated, but its structure is proposed to be that of the title compound.

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