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# Enantioselective synthesis of epimeric *cis*-3-carboxycyclopentylglycines

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**Abstract**—Two epimeric chiral cyclopentylglycines (−)-**16** and (+)-**17**, functionalised with a carboxy group cis to the amino acid group, were prepared starting from chiral 2-amino-3-oxo-norbornanecarboxylic acid derivative *exo*-**9** by combining two classical reactions such as the Diels–Alder and retro-Claisen reactions. Compounds **16** and **17** are non-proteinogenic amino acids of biological interest containing conformational constraints in which the skeletons of both 2-aminoadipic acid and 2-aminopimelic acid are included.
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## 1. Introduction

Cyclopentylglycines functionalised with a carboxy group at the 3-position of the cyclopentyl ring are non-proteinogenic amino acids of biological interest containing conformational constraints in which the skeletons of both 2-aminoadipic acid and 2-aminopimelic acid, two natural amino acids of biological importance, are included. The former amino acid is a constituent of penicillin N[1] and is an important analogue of glutamic acid.[2] The second amino acid is produced by *Asplenium unilaterale*[3] and was used for the preparation of small peptides characterised by antibacterial activity.[4] Recently, heterosubstituted 3-carboxycyclopentylglycines were prepared and their biological activity toward neuroaminidase evaluated.[5] The preparation of two racemic and epimeric 3-carboxycyclopentylglycine derivatives was reported by us.[6] In view of the potential biological interest in these compounds and their possible use for the preparation of modified bioactive peptidomimetics and by considering that the chirality of amino acids is of essential importance in biological interactions, we herein report on the chiral synthesis of the (1*S*,3*R*,1′*R*)-epimer and (1*S*,3*R*,1′*S*)-3-(amino-carboxymethyl)-cyclopentanecarboxylic acids (−)-**16** and (+)-**17**, respectively. The key reagent for our synthesis is the new chiral 2-amino-3-oxo-norbornanecarboxylic acid derivative *exo*-**9**, which was obtained from the Diels–Alder cycloadduct *exo*-**5** of acrylate **3** and cyclopentadiene **4**. The use of the (−)-8-phenylmenthyl group in acrylate **3** as chiral auxiliary allowed us to control the *exo*/*endo* selectivity in the Diels–Alder reaction, increasing the amount of *exo* adduct, the true starting material for the preparation of **16** and **17**. The facial diasteroselectivity was also improved and compound *exo*-**5** was obtained with an excellent diastereomeric excess (99%).

The above amino acids were obtained from (+)-*exo*-**9** by way of a retro-Claisen reaction that allowed us to control the cis-relationship between the two carbon residues on the cyclopentyl ring. The absolute configuration of each stereocentre of (−)-**16** and (+)-**17** was unequivocally assigned by X-ray analysis.

## 2. Results and discussion

The new (−)-8-phenylmenthyl derivative *exo*-**5** was prepared from cyclopentadiene **4** and the new chiral synthon (−)-8-phenylmenthyl 2-benzoylaminoacrylate *Z*-**3** by the way of the Diels–Alder reaction. Acrylate **3** was

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synthesised by reacting oxazolone **1** with (−)-8-phenylmenthol using bis-(dibutylchlorotin) oxide[7] as the catalyst and operating in toluene at reflux. Ester **2** (85%) was obtained and protected on the oxygen atom as the carbonate. Acrylate **3** was obtained in 93% yield (Scheme 1).

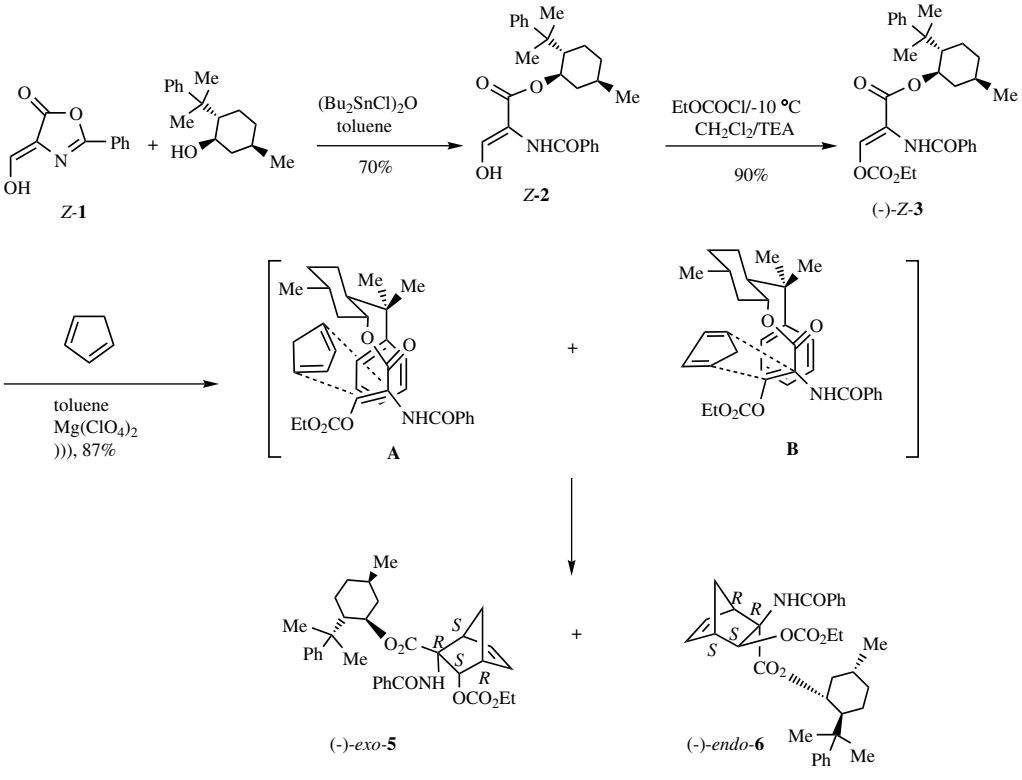
The cycloaddition reaction of **3** with cyclopentadiene **4** was performed using $Mg(ClO_4)_2$ as the catalyst and operating in toluene and with ultrasound (Scheme 1). The $^1H$ NMR analysis of the crude reaction mixture showed the presence of the diastereomers of the *exo* and *endo* series in a 7:1 ratio. In principle, the cycloaddition reaction can afford four diastereomers: two *exo* adducts and two *endo* adducts. HPLC analysis showed the presence of a main compound (85.5%), corresponding to ester *exo*-**5**, as well as a trace amount (0.3%) of the second *exo* isomer.

Both *endo*-isomers were also present (12% and 0.9%, respectively). The reaction mixture was chromatographed allowing us to isolate the main isomer *exo*-**5** (76%) and compound *endo*-**6** (11%) (pure compounds according to HPLC analyses). The minor diastereomers of the *exo*/*endo* series were not characterised.

The synthesis of the analogous menthyl derivatives, which has been previously reported,[7] suffered from some limitations: (i) the *exo*/*endo* ratio (7:3) and (ii) the de values for each couple of *exo* (de 80%) and *endo* (de 85%) compounds were not excellent. Accordingly, difficulties in the separation and purification of the single isomers had to be faced. It must be also underlined that improvement of the yields of the *exo* adduct is of synthetic relevance, because it is the starting material for the preparation of the keto compound **9**. In fact, as reported for the corresponding methyl ester,[6] it is impossible to deprotect the carbonate function of the *endo*-norbornane derivative, thus preventing preparation of the corresponding keto compound. Concerning the stereochemical outcome of the cycloaddition reaction using the (−)-8-phenylmenthyl group, as a chiral auxiliary with respect to the use of (−)-menthyl group some advantages have been obtained because the cycloaddition reaction (i) is more diastereoselective in terms of *exo*/*endo* selectivity (*exo*/*endo* = 7:1) and (ii) proceeds with a better face diasteroselectivity for each *exo* (de 99%) and *endo* (de 94%) couple.

The structure of the two major cycloadducts was confirmed by NMR ($^1H$, $^{13}C$, COSY, Hetcor reverse experiments) and the configuration by a NOESY experiment. For compound *exo*-**5**, spatial proximity was observed between H-3 (5.67 $\delta$) and the bridge proton at 1.70 $\delta$ as well as with H-4 (3.20 $\delta$). H-3 (5.30 $\delta$) of *endo*-**6** showed spatial proximity both with H-4 (2.96 $\delta$) and, importantly, with the olefinic proton H-5 (6.25 $\delta$), thus confirming its trans-position with respect to the bridge. As further confirmation of the *endo* configuration, a positive Overhauser effect was observed between NH (6.45 $\delta$) and the bridge proton at 2.03 $\delta$.

Literature data for the cycloaddition of (−)-phenylmenthyl 2-aminoacrylate[8] or acrylate esters[9] with butadiene




**Scheme 1.**

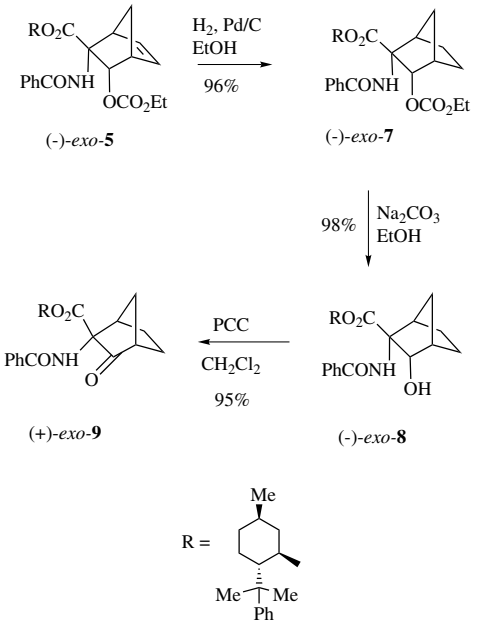
and cyclopentadiene, respectively, reported that the phenyl group of the menthyl substituent has a shielding effect on the $C_{\alpha Re}$ side of the double bond, thus favouring the addition of the diene on the *si* face. Based on these considerations and by comparison of the steric outcome of the cycloaddition reaction of (−)-menthyl 2-aminoacrylate derivative and cyclopentadiene (X-ray analyses are given),[7] we were able to assign the (1*S*,2*R*,3*S*,4*R*)- and (1*R*,2*R*,3*S*,4*S*)-absolute configuration at the stereocentres of the norbornene skeleton in the *exo*-**5** and *endo*-**6** compounds, respectively. The high face diasteroselectivity observed in the present case can be ascribed to secondary interactions between the diene and carbonyl functions of both amide and carbonate groups (intermediate **A**), which favour the formation of the *exo* cycloadduct **5**. Through intermediate **B**, the *endo* compound **6** is formed (Scheme 1).

The key starting material for the preparation of the epimeric 3-carboxy-cyclopentylglycines was the chiral (−)-phenylmenthyl 2-benzoylamino-3-oxo-bicylo[2.2.1]heptane-2-carboxylate (+)-*exo*-**9**. As depicted in Scheme 2, compound (+)-*exo*-**9** was prepared in 89% overall yield starting from *exo*-**5**. Compound *exo*-**5** was reduced to the norbornane derivative (−)-*exo*-**7**. The selective deprotection of the hydroxy group on C-3 with sodium carbonate in ethanol at room temperature gave the 3-hydroxy derivative (−)-*exo*-**8**, which was oxidised to ketone (+)-*exo*-**9** with pyridinium chlorochromate (PCC) in dichloromethane.

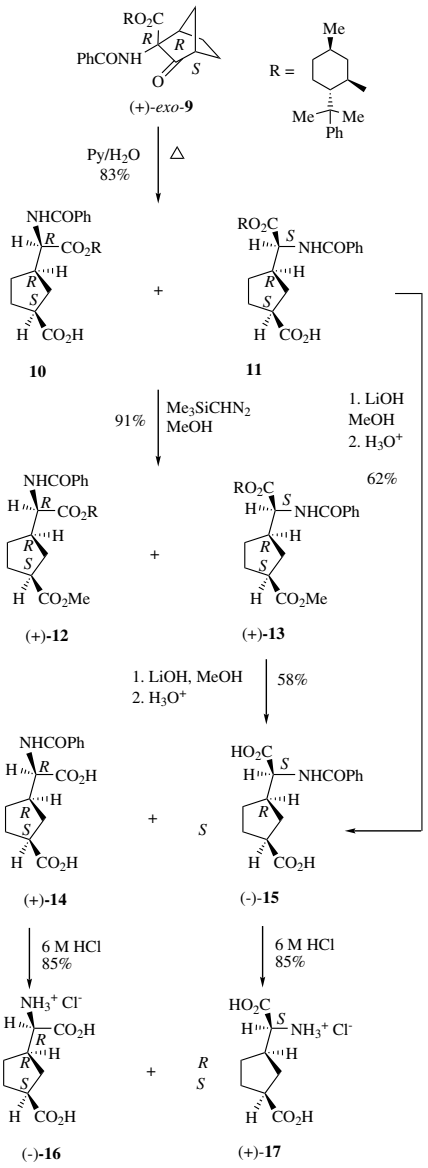
β-Keto ester **9** was successfully transformed into a mixture of epimeric cyclopentylglycines **10** and **11** (1:1 ratio, 83%) using a retro-Claisen reaction and operating in pyridine/$H_2O$ (2:1) at reflux (Scheme 3). These compounds could not be separated as such, but the target compound was obtained by transforming the carboxylic acids into the corresponding methyl esters. By reacting **10** and **11** with trimethylsilyldiazomethane, a mixture of methyl esters **12** and **13** was isolated in 91% yield (Scheme 3). Compounds (+)-**12** and (+)-**13** were obtained in their pure forms by semi-preparative HPLC separation.

As confirmed by NMR data, the cis-configuration of the carbon groups linked to the cyclopentyl ring was assured by the mechanism of retro-Claisen reaction. The $^1$H NMR spectra of compounds **10** and **11** and of the corresponding esters (+)-**12** and (+)-**13** are consistent with those reported in the literature for similar compounds.[6]

In order to unequivocally assign the stereochemistry of the amino acid centre, an X-ray analysis was performed on compound (+)-**12** characterised by the *R* configuration of C-α (Fig. 1).




**Scheme 2.**




**Scheme 3.**

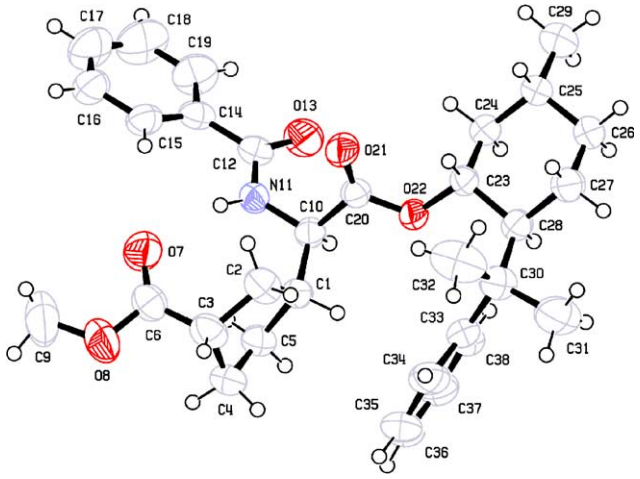



**Figure 1.** ORTEPIII projection of (+)-**12** with the crystallographic numbering scheme. Ellipsoids at 20% probability level. H atoms not to scale.

The hydrolysis of the (−)-8-phenyl-menthyl ester group of compounds **12** and **13** required basic conditions. Starting from **13** and operating in MeOH in the presence of LiOH (4 equiv) at room temperature, a mixture of amides was formed. $^1$H NMR analysis showed the presence of the expected epimer **15**, as the major compound, as well as isomer **14** (4:1, 58% yield) (Scheme 3).

Since epimerisation of the amino acid carbon could not be avoided when starting from pure compounds, we planned a direct hydrolysis of a mixture of **10** and **11**. Operating under the above reaction conditions, a mixture of dicarboxylic acids **14** and **15** was obtained (62% yield, 1:1 ratio). These compounds were separated by a flash column chromatography (see Section 4).

Finally, the hydrolysis of the amide functionality was performed under acidic conditions (6 M HCl). $^1$H NMR analysis of crude reaction mixtures showed that epimerisation of the amino acid function did not occur and pure amino acids (−)-**16** and (+)-**17** were isolated starting from the single epimer (+)-**14** and (−)-**15**, respectively.

## 3. Conclusion

In conclusion, two epimeric chiral 3-carboxycyclopentylglycines (−)-**16** and (+)-**17** were successfully prepared using a very efficient protocol consisting in the synthesis of the chiral 2-amino-3-oxo-norbornanecarboxylic acid derivative *exo*-**9**, obtained in 99% de, through a Diels–Alder reaction followed by its transformation into the above amino acids by the way of a retro-Claisen reaction. The difficulties related to the separation, epimerisation of the amino acid stereocentre and deprotection of both ester and amide groups were overcome and the pure enantiomers isolated. The absolute configuration of the three stereocentres was unequivocally determined.

## 4. Experimental

Melting points were measured with a Büchi B-540 heating unit and are uncorrected. NMR spectra were recorded with an AVANCE 500 Bruker at 500 MHz for $^1$H NMR and 100 MHz for $^{13}$C NMR. Chemical shifts, relative to TMS as internal standard, are given in $\delta$ values. IR spectra were taken with a Perkin–Elmer 1725X FT-IR spectrophotometer. Optical rotations were measured with a Perkin–Elmer MODEL343 Plus Polarimeter. Flash chromatography was performed using a Biotage Flash+ Chromatography System. Ethanol-free $CH_2Cl_2$ was used in all experiments.

### 4.1. (−)-Phenylmenthyl (*Z*)-2-benzoylamino-3-hydroxy-acrylate *Z*-2

Operating under a nitrogen atmosphere, anhydrous oxazolone **1** (3.6 g, 19.0 mmol) was suspended in anhydrous toluene (30 mL). (−)-Phenylmenthol (2.7 g, 11.5 mmol) and bis-(dibutylchlorotin)oxide (1 g, 1.86 mmol) were added and the mixture refluxed for 24 h (TLC: $CH_2Cl_2$/$Et_2O$, 2:1). The solvent was evaporated and the crude reaction mixture chromatographed on silica gel ($CH_2Cl_2$) to give ester *Z*-**2** (3.4 g, 70%). Mp 195 °C (*i*-$Pr_2O$). $[\alpha]_D^{25} = -41$ (*c* 1, $CHCl_3$). $\nu_{max}$ (Nujol) 3360, 1650 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 12.00 (d, $J = 12.1$ Hz, 1H, exch., OH), 8.24 (br s, 1H, exch., NH), 7.90–7.10 (m, 10H, ArH), 6.39 (d, $J = 12.1$ Hz, 1H, H-3), 5.02–4.89 (m, 1H, OCH), 2.22–2.09 (m, 1H, $CH_{menth}$), 1.94–0.90 (m, 7H, $CH_{menth}$ and $CH_{2menth}$), 1.33 (s, 3H, Me), 1.12 (s, 3H, Me), 0.91 (d, $J = 6.2$ Hz, 3H, Me); $^{13}$C NMR ($CDCl_3$): $\delta$ 166.1, 164.7, 151.6, 147.2, 132.6, 132.3, 128.9, 128.2, 127.3, 125.2, 106.9, 75.8, 50.6, 41.8, 39.5, 34.6, 31.4, 29.0, 26.5, 23.8, 21.8. Anal. Calcd: C, 74.08; H, 7.41; N, 3.32. Found: C, 74.03; H, 7.44; N, 3.28.

### 4.2. (−)-Phenylmenthyl (*Z*)-2-benzoylamino-3-ethoxy-carbonyloxy-acrylate *Z*-3

Operating under a nitrogen atmosphere, ester **2** (3.4 g, 8.1 mmol) was dissolved in anhydrous $CH_2Cl_2$ (60 mL). The solution was cooled to −10 °C and ethyl chlorocarbonate (0.8 mL, 8.8 mmol) was added. A solution of TEA (1.1 mL, 8.8 mmol), dissolved in $CH_2Cl_2$ (4 mL), was added dropwise. After 3 h (TLC: cyclohexane/AcOEt, 4:1), the organic layer was washed with HCl (20 mL, 10%) and dried over $Na_2SO_4$. The solvent was evaporated and the crude reaction mixture crystallised to give pure compound **3** (3.6 g, 90%). Mp 133 °C (*i*-$Pr_2O$). $[\alpha]_D^{25} = -11.2$ (*c* 1, $CHCl_3$). $\nu_{max}$ (Nujol) 3580, 1780, 1650 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 7.82–7.05 (m, 10H, ArH), 7.42 (s, 1H, H-3), 6.70 (s, 1H, exch., NH), 5.08–4.95 (m, 1H, OCH), 4.34 (q, $J = 7.0$ Hz, 2H, $OCH_2$), 2.22–2.09 (m, 1H, $CH_{menth}$), 1.91–0.90 (m, 7H, $CH_{menth}$, $CH_{2menth}$), 1.38 (t, $J = 7.0$ Hz, 3H, $OCH_2$*Me*), 1.35 (s, 3H, Me), 1.22 (s, 3H, Me), 0.90 (d, $J = 6.2$ Hz, 3H, Me); $^{13}$C NMR ($CDCl_3$): $\delta$ 165.1, 163.4, 152.3,

151.4, 140.5, 134.0, 132.2, 128.8, 128.4, 127.9, 125.6, 125.1, 113.0, 75.8, 66.0, 50.7, 41.8, 39.7, 34.7, 31.6, 29.5, 26.6, 23.6, 22.0, 14.3. Anal. Calcd: C, 70.57; H, 7.15; N, 2.84. Found: C, 70.54; H, 7.17; N, 2.82.

### 4.3. (−)-Phenylmenthyl 2-benzoylamino-3-ethoxycarbonyloxy-bicyclo[2.2.1]hept-5-ene-2-carboxylate *exo*-5 and *endo*-6

Operating in a sealed tube, acrylate *Z*-**3** (3.6 g, 7.3 mmol), diene **4** (3 mL, 36 mmol) and $Mg(ClO_4)_2$ (1.2 g, 9.9 mmol) were suspended in anhydrous toluene (65 mL) and the solution sonicated for 36 h (TLC: cyclohexane/AcOEt, 10:1). The crude reaction mixture was chromatographed on silica gel (cyclohexane/AcOEt, 100:1–5:1) to give two fractions containing pure adducts *exo*-**5** (3 g, 76%) and *endo*-**6** (430 mg, 11%), respectively, which were analysed by HPLC (Chiral Cel OD column: 250 × 4.6 mm; hexane/*i*-PrOH, 90:10; $T = 30$ °C, flow = 0.8 mL/min, $\lambda = 254$ nm).

**4.3.1. (1*S*,2*R*,3*S*,4*R*)-*exo*-5.** Oil. $[\alpha]_D^{25} = -29$ (*c* 1, $CHCl_3$). $\nu_{max}$ (Nujol) 3440, 1750, 1670 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.67–7.09 (m, 10H, ArH), 6.35–6.31 (m, 1H, H-5), 6.25–6.19 (m, 1H, H-6), 6.19 (s, 1H, exch., NH), 5.67 (d, $J = 3.6$ Hz, 1H, H-3), 4.97–4.84 (m, 1H, OCH), 4.21 (q, $J = 7.0$ Hz, 2H, $OCH_2$), 3.41 (br s, 1H, H-1), 3.20 (br s, 1H, H-4), 2.23–2.05 (m, 1H, $CH_{menth}$), 2.06–1.96 (m, 1H, $CH_{menth}$), 1.70, 1.57 (AB system, $J = 9.9$ Hz, 2H, H-7), 1.61–0.77 (m, 6H, $CH_{2menth}$), 1.27 (t, $J = 7.0$ Hz, 3H, $OCH_2Me$), 1.27 (s, 3H, $Me_{menth}$), 1.20 (s, 3H, $Me_{menth}$), 0.88 (d, $J = 6.2$ Hz, 3H, $Me_{menth}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ 171.3, 167.1, 154.1, 151.6, 137.3, 135.9, 134.4, 131.7, 128.7, 128.2, 127.3, 125.9, 125.3, 80.1, 77.8, 66.1, 64.5, 50.2, 49.5, 46.5, 43.8, 41.3, 40.3, 34.9, 31.6, 28.3, 27.5, 25.8, 22.0, 14.4. Anal. Calcd: C, 72.96; H, 7.38; N, 2.50. Found: C, 73.00; H, 7.33; N, 2.53.

**4.3.2. (1*R*,2*R*,3*S*,4*S*)-*endo*-6.** Oil. $[\alpha]_D^{25} = -20$ (*c* 1, $CHCl_3$). $\nu_{max}$ (Nujol) 3470, 1740, 1670 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.85–7.12 (m, 10H, ArH), 6.45 (s, 1H, exch., NH), 6.25 (br s, 2H, H-5, H-6), 5.30 (d, $J = 1.4$ Hz, 1H, H-3), 4.85–4.72 (m, 1H, OCH), 4.27–4.09 (m, 2H, $OCH_2$), 3.01 (br s, 1H, H-1), 2.96 (br s, 1H, H-4), 2.15–2.11 (m, 1H, $CH_{menth}$), 2.03, 1.78 (AB system, $J = 10.7$ Hz, 2H, H-7), 1.95–1.80 (m, 1H, $CH_{menth}$), 1.95–0.70 (m, 6H, $CH_{2menth}$) 1.28 (s, 3H, $Me_{menth}$), 1.26 (t, $J = 7.0$ Hz, 3H, $OCH_2Me$), 1.20 (s, 3H, $Me_{menth}$), 0.85 (d, $J = 4.2$ Hz, 3H, $Me_{menth}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ 170.1, 167.4, 154.2, 151.6, 137.4, 135.1, 134.7, 131.9, 129.4, 129.3, 128.9, 128.5, 128.3, 127.7, 127.5, 126.1, 125.8, 125.5, 78.8, 77.8, 65.9, 64.6, 50.4, 49.6, 48.7, 46.3, 41.4, 40.5, 35.0, 31.8, 29.6, 27.3, 24.8, 22.1, 14.4. Anal. Calcd: C, 72.96; H, 7.38; N, 2.50. Found: C, 72.92; H, 7.41; N, 2.48.

### 4.4. (−)-Phenylmenthyl (1*R*,2*R*,3*S*,4*S*)-2-benzoylamino-3-ethoxycarbonyloxy-bicyclo[2.2.1]heptane-2- carboxylate *exo*-7

Compound *exo*-**5** (3.0 g, 5.37 mmol) was suspended in EtOH (100 mL) and reduced with hydrogen using Pd/C (10%, 570 mg, 0.5 mmol) as the catalyst at 25 °C and 1 atm. After 2 h ($^1H$ NMR monitoring), the catalyst was filtered and the solvent eliminated. Pure compound *exo*-**7** (2.9 g, 96%) was obtained after crystallisation. Mp 135 °C (*i*-$Pr_2O$). $[\alpha]_D^{25} = -18$ (*c* 1, $CHCl_3$). $\nu_{max}$ (Nujol) 3450, 3400, 1738, 1673 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.79–7.07 (m, 10H, ArH), 6.62 (s, 1H, exch., NH), 5.13 (d, $J = 4.4$ Hz, 1H, H-3), 4.91–4.80 (m, 1H, OCH), 4.24 (q, $J = 7.0$ Hz, 2H, $OCH_2$), 3.00 (br s, 1H, H-1), 2.55 (br s, 1H, H-4), 2.27–2.09 (m 1H, $CH_{menth}$), 2.00–1.85 (m, 1H, $CH_{menth}$), 1.63 (d, $J = 11.0$, 1H, H-7), 1.59–0.73 (m, 11H, H-5, H-6, H-7, $CH_{2menth}$), 1.31 (t, $J = 7.0$ Hz, 3H, $OCH_2Me$), 1.18 (s, 3H, Me), 1.16 (s, 3H, Me), 0.86 (d, $J = 6.3$ Hz, 3H, Me); $^{13}C$ NMR ($CDCl_3$): $\delta$ 171.4, 167.2, 153.9, 151.4, 134.3, 131.8, 128.8, 128.2, 127.4, 125.9, 125.3, 78.0, 77.5, 64.6, 63.2, 50.3, 43.7, 41.2, 40.2, 40.1, 34.8, 33.8, 31.6, 28.6, 27.5, 25.4, 23.7, 21.0, 19.8, 14.5. Anal. Calcd: C, 72.75; H, 7.78; N, 2.49. Found: C, 72.79; H, 7.81 N; 2.45.

### 4.5. (−)-Phenylmenthyl (1*R*,2*R*,3*S*,4*S*)-2-benzoylamino-3-hydroxy-bicyclo[2.2.1]heptane-2-carboxylate *exo*-8

Carbonate *exo*-**7** (2.9 g, 5.17 mmol) was dissolved in anhydrous EtOH (100 mL) and lyophilised $Na_2CO_3$ (841 mg, 7.9 mmol) added. The mixture was stirred at 25 °C for 24 h (TLC: $CH_2Cl_2/Et_2O$, 10:1). $Na_2CO_3$ was filtered over a Celite column and the solvent evaporated. After crystallisation of the crude reaction mixture, pure compound *exo*-**8** (2.4 g, 95%) was obtained. Mp 202 °C (*i*-$Pr_2O$). $[\alpha]_D^{25} = -12$ (*c* 1, $CHCl_3$). $\nu_{max}$ (Nujol) 3440, 1750, 1670 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.76–7.10 (m, 10H, ArH), 6.45 (s, 1H, exch., NH), 4.86–4.77 (m, 1H, OCH), 4.31 (br s 1H, H-3), 2.73–2.69 (m, 2H, 1 exch., OH and H-1), 2.38 (br s, 1H, H-4), 2.20–0.80 (m, 14H, H-5, H-6, H-7, $CH_{menth}$, $CH_{2menth}$), 1.25 (s, 3H, Me), 1.15 (s, 3H, Me), 0.90 (d, $J = 6.6$ Hz, 3H, Me); $^{13}C$ NMR ($CDCl_3$): $\delta$ 172.8, 168.8, 152.1, 134.5, 131.9, 128.7, 128.2, 127.4, 125.8, 125.1, 77.1, 74.3, 63.7, 50.0, 44.3, 41.7, 41.5, 40.0, 34.9, 33.7, 31.6, 27.5, 27.2, 26.5, 24.1, 22.0, 18.7. Anal. Calcd: C, 76.04; H, 8.03; N, 2.86. Found: C, 76.00; H, 8.07; N, 2.80.

### 4.6. (−)-Phenylmenthyl (1*R*,2*R*,4*S*)-2-benzoylamino-3-oxo-bicyclo[2.2.1]heptane-2-carboxylate *exo*-9

Compound *exo*-**8** (2.4 g, 4.9 mmol) was treated, under a nitrogen atmosphere, with PCC (6.3 g, 29.4 mmol) in anhydrous $CH_2Cl_2$ (150 mL). The solution was stirred at room temperature for 2 h (TLC: cyclohexane/AcOEt, 1:1). The reaction mixture was filtered through a silica gel column (cyclohexane/AcOEt, 1:1). Keto compound *exo*-**9** (1.6 g, 95%) was obtained and crystallised. Mp 128 °C (*i*-$Pr_2O$). $[\alpha]_D^{25} = +16$ (*c* 1, $CHCl_3$). $\nu_{max}$ (Nujol) 3440, 1750, 1670 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.81–7.10 (m, 10H, ArH), 6.65 (s, 1H, exch., NH), 5.03–4.90 (m, 1H, OCH), 3.73 (br s, 1H, H-4), 2.74 (d, $J = 3.7$ Hz, 1H, H-1), 2.22 (d, $J = 12.5$ Hz, 1H, H-7), 2.03–1.80 (m, 2H, $CH_{menth}$), 1.80–0.71 (m, 11H, H-5, H-6, H-7, $CH_{2menth}$), 1.27 (s, 3H, Me), 1.20 (s, 3H, Me), 0.86 (d, $J = 6.2$ Hz, 3H, Me); $^{13}C$ NMR ($CDCl_3$): $\delta$ 210.0,

167.6, 166.1, 150.7, 133.7, 132.2, 128.8, 128.3, 127.5, 125.9, 125.5, 78.3, 72.3, 50.5, 48.4, 44.2, 41.8, 40.5, 34.7, 34.6, 31.6, 29.9, 29.7, 27.6, 24.3, 22.3, 21.9. Anal. Calcd: C, 76.36; H, 7.65; N, 2.87. Found: C, 76.34; H, 7.65; N, 2.85.

### 4.7. Retro-Claisen reaction of ketone *exo*-9

Pure ketone *exo*-**9** (1 mmol) was dissolved in pyridine (3 mL) and $H_2O$ (1.5 mL). The reaction mixture was heated at reflux for 3 h (TLC: $CH_2Cl_2/Et_2O$, 2:1). The solvent was evaporated and the residue taken up with a HCl solution (10%, 10 mL). The aqueous layer was extracted with a mixture of THF/AcOEt (1:1, $3 \times 7$ mL). The organic layer was separated and dried over $Na_2SO_4$ to give a mixture of the two diastereomeric amino acid derivatives **10** and **11** (1:1, 420 mg, 83%). Any attempt to separate epimers **10** and **11** failed.

### 4.8. (1*S*,3*R*,1′*R*)- and (1*S*,3*R*,1′*S*)-3-(Benzoylamino-phenylmenthoxycarbonyl-methyl)cyclopentanecarboxylic acids 10 and 11

Mixture of epimers (1:1). $\nu_{max}$ (Nujol) 3300, 1725, 1660 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.82–7.10 (m, 20H, ArH), 6.95 (**10**: d, $J = 8.4$ Hz, 1H, exch., NH), 6.59 (**11**: d, $J = 8.0$ Hz, 1H, exch., NH), 4.87–4.79 (m, 2H, OCH), 4.59 (**10**: dd, $J = 8.4$, 4.4 Hz, 1H, CHN), 4.17 (**11**: dd, $J = 8.0$, 5.4 Hz, 1H, CHN), 2.84–2.71 (m, 2H, H-1), 2.17–0.79 (m, 30H, H-2, H-3, H-4, H-5, $CH_{menth}$, $CH_{2menth}$), 1.31 (s, 6H, Me), 1.28 (s, 3H, Me), 1.21 (s, 3H, Me), 0.89 (d, $J = 6.4$ Hz, 3H, Me), 0.87 (d, $J = 6.4$ Hz, 3H, Me).

### 4.9. Esterification reaction of 10 and 11

To a solution of **10** and **11** (1:1, 100 mg, 0.2 mmol) in MeOH (6 mL), $(CH_3)_3SiCH_2N_2$ (2 M in $Et_2O$, 1 mmol, 0.5 mL) was added. After stirring under $N_2$ for 30 min, the solvent was removed under vacuum and a mixture of methyl esters **12** and **13** (1:1, 94 mg, 91%) was obtained. It was possible to separate **12** (40 mg, 0.07 mmol, 40%) from **13** (30 mg, 0.06 mmol, 30%) by semi-preparative HPLC (Supelco C18 column; $250 \times 10$ mm; 10 μm, MeCN/$H_2O$, 70:30; $T = 30$ °C, flow = 5 mL/min, $\lambda = 254$ nm; **12**: $t_R = 14.1$ min; **13**: $t_R = 15.4$ min).

### 4.10. Methyl (1*S*,3*R*,1′*R*)-3-(benzoylamino-(−)-phenylmenthoxy carbonyl-methyl)cyclopentanecarboxylate 12

Mp 131 °C ($Et_2O$). $[\alpha]_D^{25} = +23$ (*c* 1, $CHCl_3$). $\nu_{max}$ (Nujol) 3340, 1730, 1700, 1665 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.90–7.04 (m, 11H, ArH and NH), 4.93–4.80 (m, 1H, OCH), 4.60 (dd, $J = 8.0$, 4.4 Hz, 1H, CHN), 3.66 (s, 3H, OMe), 2.85–2.79 (m, 1H, H-1), 2.32–0.77 (m, 15H, H-2, H-3, H-4, H-5, $CH_{menth}$, $CH_{2menth}$), 1.28 (s, 3H, Me), 1.20 (s, 3H, Me), 0.85 (d, $J = 6.3$, 3H, Me); $^{13}C$ NMR ($CDCl_3$): $\delta$ 177.6, 171.4, 167.8, 151.0, 134.3, 131.8, 128.7, 128.2, 127.5, 125.8, 125.6, 77.0, 55.2, 52.2, 49.8, 43.3, 41.8, 40.6, 40.2, 34.7, 31.6, 30.4, 29.9, 28.7, 28.1, 27.3, 26.4, 22.0. Anal. Calcd: C, 73.63; H, 7.77; N, 2.77; Found: C, 73.59; H, 7.80; N, 2.73. X-ray data for compound (+)-**12** are available (CCDC deposition number 265248).

### 4.11. Methyl (1*S*,3*R*,1′*S*)-3-(benzoylamino-(−)-phenylmenthoxy carbonyl-methyl)cyclopentanecarboxylate 13

Oil. $[\alpha]_D^{25} = +10$ (*c* 1, $CHCl_3$). $\nu_{max}$ (Nujol) 3340, 1730, 1700, 1664 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.84–7.10 (m, 10H, ArH), 6.59 (d, $J = 8.4$ Hz, 1H, exch., NH), 4.87–4.74 (m, 1H, OCH), 4.19 (dd, $J = 8.4$, 5.1 Hz, 1H, CHN), 3.60 (s, 3H, OMe), 2.75–2.68 (m, 1H, H-1), 2.17–0.87 (m, 15H, H-2, H-3, H-4, H-5, $CH_{menth}$, $CH_{2menth}$), 1.31 (s, 3H, Me), 1.22 (s, 3H, Me), 0.88 (d, $J = 6.5$ Hz, 3H, Me); $^{13}C$ NMR ($CDCl_3$): $\delta$ 177.3, 171.4, 168.8, 151.0, 134.2, 131.8, 128.8, 127.4, 125.5, 76.4, 54.2, 51.9, 50.7, 43.4, 42.8, 41.6, 39.7, 34.7, 33.2, 31.5, 28.0, 26.9, 26.7, 24.5, 22.0. Anal. Calcd: C, 73.63; H, 7.77; N, 2.77. Found: C, 73.56; H, 7.73; N, 2.72.

### 4.12. Deprotection of the carboxylic group

To a solution of pure (+)-**13** (516 mg, 1 mmol) or a mixture of **10** and **11** (1:1, 502 mg, 1 mmol) in MeOH (10 mL), LiOH (**13**: 96 mg, 4 mmol, **10**; **11**: 48 mg, 2 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated and the crude reaction mixture taken up with $H_2O$ (10 mL) and extracted with AcOEt ($3 \times 5$ mL). The aqueous layer was acidified with 2 M HCl (3 mL) and extracted with THF/AcOEt (1:1, $3 \times 5$ mL). The organic layer was dried over $Na_2SO_4$ and evaporated under vacuum to obtain a mixture of the free carboxylic derivatives (+)-**14**/(−)-**15** (from (+)-**13**: 168 mg, 58%, 1:4; from **10**/**11**: 180 mg, 62%, 1:1). It was possible to separate compound **14** from **15** by a flash chromatography (Flash+Cartridge column: 25+M, $CH_2Cl_2$/MeOH/AcOH, 10:1:0.1, flow: 20 mL/min; **14**: $R_f = 0.15$; **15**: $R_f = 0.08$).

### 4.13. (1*S*,3*R*,1′*R*)-3-(Benzoylamino-carboxy-methyl)-cyclopentanecarboxylic acid 14

Mp 210 °C ($CH_2Cl_2$). $[\alpha]_D^{25} = +20$ (*c* 1, MeOH). $\nu_{max}$ (KBr) 3450, 1707, 1640 $cm^{-1}$; $^1H$ NMR ($CD_3OD$): $\delta$ 7.95–7.42 (m, 5H, ArH), 4.54 (d, $J = 6.9$ Hz, 1H, CHN), 2.95–2.75 (m, 1H, H-1), 2.75–2.45 (m, 1H, H-3), 2.20–1.50 (m, 6H, H-2, H-4, H-5); $^{13}C$ NMR ($CD_3OD$): $\delta$ 184.3, 177.9, 168.6, 134.7, 131.3, 128.3, 127.3, 58.6, 47.8, 43.0, 32.9, 30.4, 28.8. Anal. Calcd: C, 61.85; H, 5.88; N, 4.81. Found: 61.68; H, 6.05; N, 4.70.

### 4.14. (1*S*,3*R*,1′*S*)-3-(Benzoylamino-carboxy-methyl)-cyclopentanecarboxylic acid 15

Mp 193 °C ($CH_2Cl_2$). $[\alpha]_D^{25} = -14.5$ (*c* 1, MeOH). $\nu_{max}$ (KBr) 3450, 1707, 1640 $cm^{-1}$; $^1H$ NMR ($CD_3OD$): $\delta$ 7.90–7.35 (m, 5H, ArH), 4.54 (d, $J = 7.7$ Hz, 1H, CHN), 2.95–2.75 (m, 1H, H-1), 2.68–2.40 (m, 1H, H-3), 2.25–2.00 (m, 1H, H-2), 1.98–1.50 (m, 5H, H-2, H-4, H-5); $^{13}C$ NMR ($CD_3OD$): $\delta$ 185.4, 179.0, 169.7, 136.0, 132.6, 129.6, 128.6, 59.6, 48.7, 44.8, 36.0, 30.7, 28.7. Anal. Calcd: C, 61.85; H, 5.88; N, 4.81. Found: 61.71; H, 6.00; N, 4.74.

### 4.15. Deprotection of the amino group

In a sealed tube, pure compound (+)-**14** or (−)-**15** (291 mg, 1 mmol) was suspended in 6 N HCl (6 mL) and heated at 100 °C for 12 h. The reaction mixture was cooled at 0 °C and the precipitated benzoic acid was filtered. The aqueous layer was washed with $Et_2O$ (3 × 4 mL) and evaporated under vacuum allowing to obtain the pure amino acid hydrochloride (−)-**16** (159 mg, 85%) or (+)-**17** (159 mg, 85%).

### 4.16. (1*S*,3*R*,1′*R*)-3-(Amino-carboxy-methyl)-cyclopentanecarboxylic acid hydrochloride 16

Oil. $[\alpha]_D^{25} = -5$ (*c* 1, $H_2O$). $\nu_{max}$ (Nujol) 3340, 1660 $cm^{-1}$; $^1H$ NMR ($D_2O$): $\delta$ 3.84 (d, $J = 7.0$ Hz, 1H, CHN), 2.91–2.75 (m, 1H, H-1), 2.43–2.28 (m, 1H, H-3), 2.15–1.98 (m, 1H, H-2), 1.82–1.39 (m, 5H, H-2, H-4, H-5); $^{13}C$ NMR ($D_2O$): $\delta$ 180.8, 172.0, 56.4, 43.1, 40.6, 32.4, 29.1, 28.0. Anal. Calcd: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.26; H, 7.08; N, 7.41.

### 4.17. (1*S*,3*R*,1′*S*)-3-(Amino-carboxy-methyl)-cyclopentanecarboxylic acid hydrochloride 17

Oil. $[\alpha]_D^{25} = +9$ (*c* 1, $H_2O$); $\nu_{max}$ (Nujol) 3340, 1660 $cm^{-1}$; $^1H$ NMR ($D_2O$): $\delta$ 3.85 (d, $J = 8.3$ Hz, 1H, CHN), 2.88–2.72 (m, 1H, H-1), 2.43–2.28 (m, 1H, H-3), 2.19–1.87 (m, 1H, H-2), 1.80–1.59 (m, 5H, H-2, H-4, H-5); $^{13}C$ NMR ($D_2O$): $\delta$ 180.6, 171.9, 56.4, 43.1, 40.5, 32.5, 28.5, 27.9. Anal. Calcd: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.21; H, 7.10; N, 7.38.

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