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Regio- and stereoselective synthesis of constrained enantiomeric β-amino acid derivatives

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ABSTRACT

Chlorosulfonyl isocyanate addition to (−)- and (+)-apopinene furnished monoterpene-fused β-lactams in highly regio- and stereospecific reactions. β-Lactams **5** and **13** exhibited reactivities similar to those of the cycloalkane-fused analogs and were easily converted to the β-amino acid and its protected derivatives. The base-catalyzed isomerization of the *cis*-amino ester afforded the corresponding *trans*-amino acid enantiomers in excellent yields. The complete isomerization is explained by the stability difference, which was estimated by ab initio calculations between the *cis*- and *trans*-diastereomers.

1. Introduction

There is an increasing demand for the production of new chiral building blocks and catalysts that can be widely used for asymmetric syntheses. These valuable chiral building blocks must be available in both enantiomeric forms, on at least a gram scale, and with high enantiomeric purity. Many natural monoterpenes, such as (+)-pulegone, myrtenal, fenchone-camphor, and α-pinene, have been prepared on a large scale with excellent enantiomeric excess. Various powerful catalysts derived from these monoterpenes have been reported as chiral ligands in enantioselective syntheses.[1]

We recently described the transformations of enantiomerically pure α-pinene and 3-carene to β-amino acid derivatives, which proved to be excellent building blocks for the syntheses of monoterpene-fused saturated 1,3-heterocycles, and were also applied as chiral auxiliaries in the enantioselective reactions of Et_2Zn with aromatic aldehydes.[2] These results revealed that a methyl substituent (present in the natural monoterpenes) next to the amino group dramatically decreases the reactivities of the synthons relative to those containing a secondary carbon next to the adjacent functional groups.[2] We previously reported the synthesis of *cis*-δ-pinene-based derivatives;[3] the amino acid derivatives described proved to be more reactive than the α-pinene-based compounds, but the strong steric hindrance of the ring system restricted their synthetic applications. In addition to the disadvantageous steric effect, it is well known that constrained pinane terpenoids in an acidic medium generally undergo numerous transformations, leading to complex mixtures of products; their facile rearrangement restricts the wide application of these compounds in organic syntheses.[4,5] These disadvantages may be reduced by removal of the 2-methyl substituent, resulting in *apo* derivatives.

In addition to the chemical importance of β-amino acids, some of them exert significant pharmacological effects, for example, the antifungal antibiotic (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid (cispentacin).[6] Icofungipen (PLD-118; (1*R*,2*S*)-2-amino-4-methylenecyclopentanecarboxylic acid), a β-amino acid, upsets the biosynthesis of protein in *Candida albicans*.[7] β-Amino acids can also be used as building blocks for the preparation of modified analogs of pharmacologically active peptides. β-Amino acids and their foldameric oligomers are currently the focus of research interest.[8]

Herein, we report the preparation and some transformations of a new family of monoterpene-based chiral β-lactams and β-amino acid derivatives derived from (−)- and (+)-apopinene **2** and **13**, in order to eliminate the disadvantageous steric effect of the 2-methyl substituent on the pinane ring system.[2,3]

2. Results and discussion

(−)-Apopinene **1** was synthesized from commercially available (−)-myrtenal via a literature method.[9] Chlorosulfonyl isocyanate (CSI) addition to **1** was successfully accomplished by stirring the mixture in dry Et_2O for 48 h.[10] The NMR and GC studies on the crude product proved that the cycloaddition took place highly regio- and stereospecifically (ee >98%), resulting in only β-lactam **2** (Scheme 1). Full crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data Centre (CCDC no. 705012).

The structure of azetidinone **2** was determined by X-ray crystallography (Fig. 1), and the relative stereochemistry established by NOESY.

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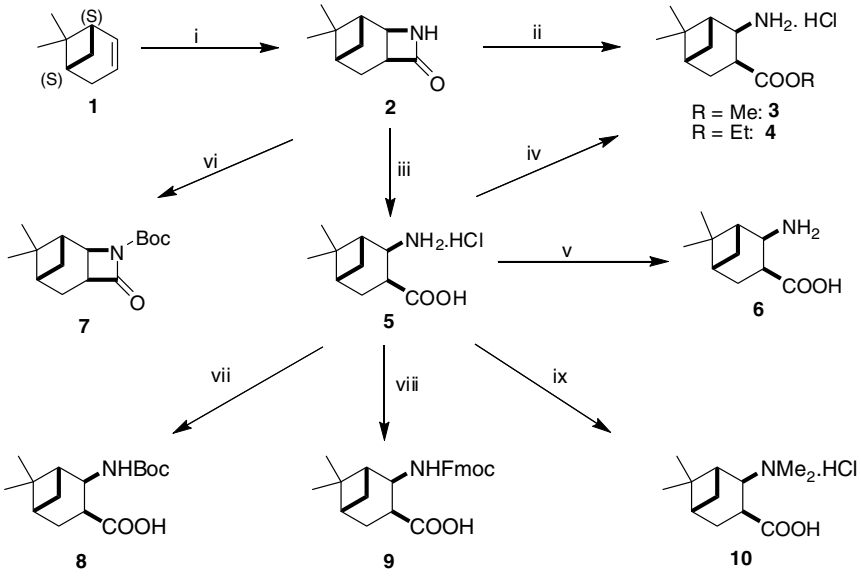


Scheme 1. Reaction conditions: (i) 1.01 equiv CSI, Et_2O, rt, 48 h, then Na_2SO_3/10% KOH soln, 2 h, 82%; (ii) **3**: 10% HCl/MeOH, **4**: 10% HCl/EtOH, rt, 1.5 h, 71–89%; (iii) 15% HCl/H_2O, rt, 1 h, 94%; (iv) 1.1 equiv $SOCl_2$, **3**: dry MeOH, **4**: dry EtOH, −12 °C, then 30 min, 0 °C, 3 h, rt, 80%; (v) 10% $NaHCO_3/H_2O$ to pH 7.4, 0 °C, 1 h, 58%; (vi) 1.3 equiv Boc_2O, THF, cat. DMAP, 2.6 equiv Et_3N, rt, 6 h, 89%; (vii) 3% NaOH/H_2O to pH 8.0, 1.1 equiv Boc_2O, 0 °C, rt, 6 h, then 5% HCl/H_2O, 61%; (viii) 10% $NaHCO_3/H_2O$ to pH 8.0, MeCN, 0 °C, 1.0 equiv Fmoc-OSu, then 12 h at rt, 63%; (ix) 2.2 equiv HCHO, H_2O, 10% Pd/C, 10 atm. H_2, rt, 12 h, 89%.

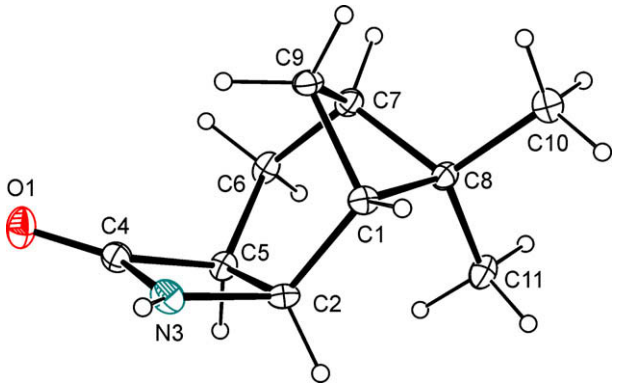


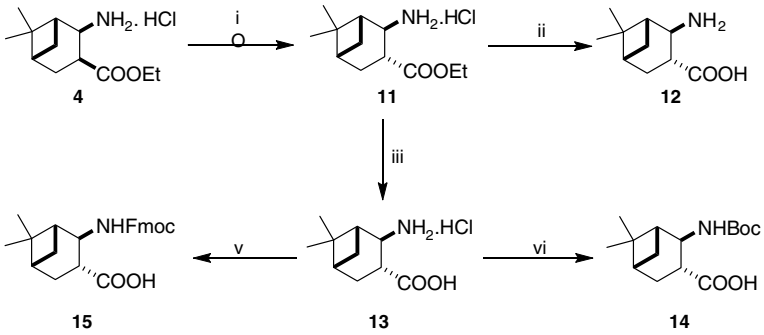
Figure 1. The Ortep plot of azetidinone **2** with thermal ellipsoids drawn at the 30% probability level.

Treatment of azetidinone **2** with aqueous HCl resulted in amino acid **5** in excellent yield. Amino esters **3** and **4** were prepared by acid-catalyzed alcoholysis of **2** (Scheme 1). Our results suggest that the absence of the methyl group at the 2-position of α-pinene (practically apopinene) yields compounds with normal reactivity, similar to those with a cyclopentane or cyclohexane skeleton.[6,11] These results differ significantly from those observed for the α-pinene-based lactam, where acidic hydrolysis was unsuccessful.[2]

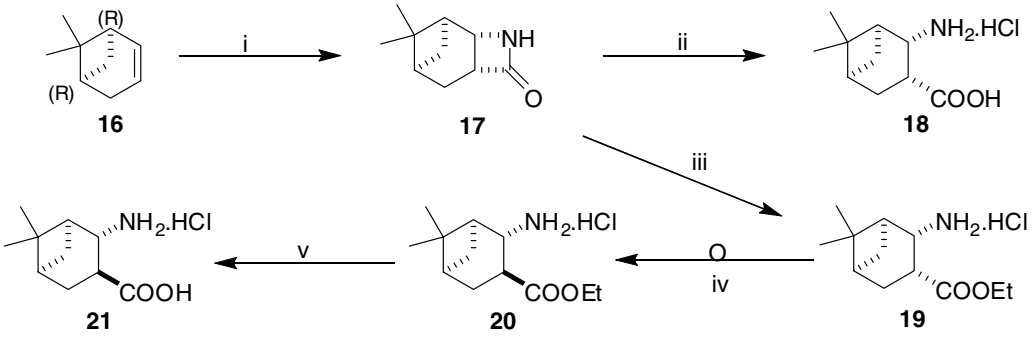
When the aqueous solution of amino acid hydrochloride **5** was adjusted to pH 7.4, the poorly water-soluble free amino acid **6** was isolated readily. Treatment of β-lactam **2** with di-*tert*-butyl dicarbonate resulted in the *N*-Boc β-lactam **7**. The *N*-Boc β-amino acid **8** was prepared in good yield (94%) directly from amino acid **5**. Similarly, Fmoc-protected amino acid **9** was prepared, resulting in promising building blocks for peptide chemistry. N,N-Disubstituted amino acid **10** was synthesized via the reductive methylation of amino acid **5** (Scheme 1).[12]

Under alkaline conditions, the *cis*-amino ester **4** underwent fast and complete isomerization at the carboxylic function, resulting in the *trans*-amino ester in excellent yield (Scheme 2).

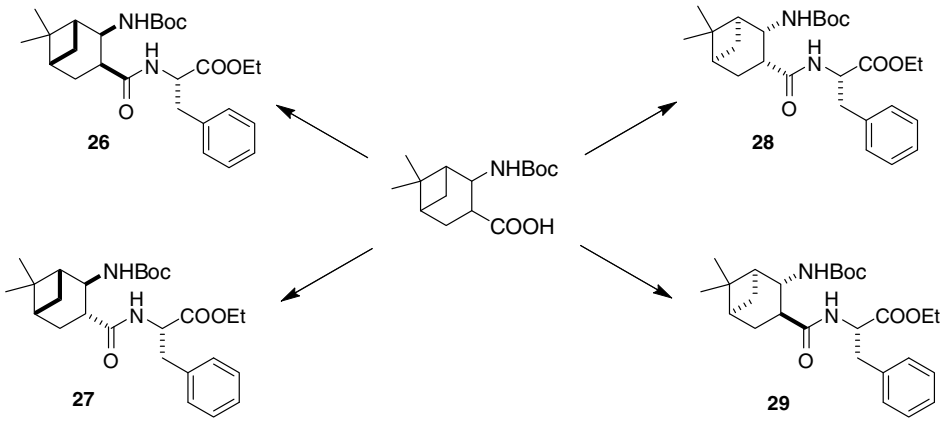
Complete *cis–trans* isomerization is not common among β-amino esters.[6,13] To explain this phenomenon, ab initio modelling was carried out on **3** and the methyl ester derivatives of **11** at the B3LYP/6-31G(d) level implemented in the GAUSSIAN program package.[14] Simplification of the ester group was not expected to affect the relative stabilities. After geometrical optimization, the final energies were −635.784040543 a.u. and −635.787701000 a.u. for **4** and **11**, respectively. This means that, under thermodynamic control, the estimated stability difference of 2.30 kcal/mol in favor of the methyl analog of **11** can lead to a 40-fold higher concentra-



Scheme 2. Reaction conditions: (i) 2.0 equiv NaOEt, dry EtOH, rt, 4 h, then 15% dry HCl/EtOH, 69%; (ii) 10% NaOH/H_2O, then dioxane/H_2O, 80 °C, 6 h, 65%; (iii) 10% HCl/H_2O, rt, 48 h, 85%; (iv) 3% NaOH/H_2O to pH 8.0, 1.1 equiv Boc_2O, rt, 6 h, then 5% HCl/H_2O, 65%; (v) 10% $NaHCO_3/H_2O$ to pH 8.0, MeCN, 0 °C, 1.0 equiv Fmoc-OSu, then 12 h at rt, 63%.



Scheme 3. Reaction conditions: (i) 1.01 equiv CSI, Et_2O, rt, 48 h, then Na_2SO_3/10% KOH soln, 2 h, 82%; (ii) 15% HCl/H_2O, rt, 1 h, 94%; (iii) 10% HCl/EtOH, 25 °C, 1.5 h, 89%; (iv) 2.0 equiv NaOEt, dry EtOH, then 15% dry HCl/EtOH, rt, 4 h, 69%; (v) 10% HCl/H_2O, rt, 48 h, 85%.



Scheme 4. Reaction conditions: 1.0 equiv (*S*)-phenylalanine ethyl ester, 1.0 equiv $ClCO_2iBu$, 1.0 equiv Et_3N, dry THF, −10 °C, then rt, 5 h, 67%.

tion for the *trans*-isomer under the conditions applied. This finding fully explains the unusual and complete transformation of **4** to **11**.

Since the (+)-enantiomer of myrtenal is not commercially available, it was prepared from available (+)-α-pinene according to a literature method.[15] (+)-Myrtenal was then transformed successfully via (+)-apopinene **16** to enantiomeric β-lactam **17**, amino acid **18** and to all the other amino acid derivatives **22**–**25** (Section 4) by the methods presented in Schemes 1–3.

The enantiomeric purities of **2**, **17**, **4**, and **19** were determined by GC on a chiral column. Since there was no sign of the presence of any other diastereomer in the NMR spectra of the crude products after the transformations, the high enantiomeric purities of the compounds prepared can be regarded as proven.

To prove the applicability of the resulting β-amino acid derivatives, starting from the *N*-Boc amino acid epimers, all four representative dipeptide derivatives **26**–**29** were prepared by coupling with phenylalanine methyl ester (Scheme 4).

3. Conclusion

The disadvantageous steric effect of the 2-methyl substituent on the pinane ring system was eliminated by the synthesis of apopinane enantiomers. The highly regio- and stereospecific addition of CSI to apopinene resulted in the successful large-scale preparation of β-lactam enantiomers. β-Lactams **2** and **17** and the corresponding constrained β-amino acids **5**, **13**, **18**, and **21** and their derivatives exhibited reactivities similar to those of cyclopentane and cyclohexane, apart from the facile isomerization of the *cis*-amino esters toward the *trans*-amino esters under alkaline conditions. The lactams and β-amino acids prepared are highly valuable building blocks for the synthesis of bioactive compounds and combinatorial libraries.

4. Experimental

4.1. General experimental procedures

^{1}H NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer at 400.13 MHz (^{1}H) and 100.61 MHz (^{13}C) [$\delta = 0$ (TMS)] in $CDCl_3$ or in D_2O in a 5-mm tube. Chemical shifts are expressed in ppm (δ) relative to TMS as the internal reference. *J* values are given in hertz. Microanalyses were performed on a Perkin–Elmer 2400 elemental analyzer. Optical rotations were obtained with a Perkin–Elmer 341 polarimeter. Melting points were determined on a Kofler apparatus and are uncorrected. Chromatographic separations were carried out on Merck Kieselgel 60 (230–400 mesh ASTM). Reactions were monitored with Merck Kieselgel 60 F_{254}-precoated TLC plates (0.25 mm thickness).

The enantiomeric purities of the prepared compounds were determined by means of GC measurements involving direct separation of the enantiomers on a CHIRASIL-DEX CB column (2500 × 0.25 mm I.D.) at 160 °C and 80 kPa for azetidinones **2** and **17**. IR spectra were measured with a FT-IR spectrometer.

Et_2O and THF were dried over Na wire; all other chemicals and solvents were used as supplied. (−)-(1*S*,5*S*)- and (+)-(1*R*,5*R*)-apopinene (**1** and **16**) were prepared by a literature method, and were identical with those reported therein.[9]

4.2. (1*R*,2*R*,5*S*,7*R*)-8,8-Dimethyl-3-azatricyclo[5.1.1.0^{2,5}]nonan-4-one 2

A mixture of 12.21 g (100.0 mmol) of (−)-(1*S*,5*S*)-apopinene **1** and 14.30 g (101.2 mmol) of chlorosulfonyl isocyanate was stirred in 300 mL of dry Et_2O for 48 h at room temperature. 20.4 g (162 mmol) of dry Na_2SO_3 in 140 mL of water was then cautiously

added dropwise to the solution. The pH was held at 7–8 by the addition of 20% aqueous KOH. After stirring for 2 h at the appropriate pH, the organic phase was separated off and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layer was dried (Na_2SO_4) and evaporated, and the white crystalline product obtained was recrystallized from iPr_2O. Isolated compound: 13.54 g (82%); mp: 68–72 °C; $[\alpha]_D^{20} = -80.0$ (*c* 0.5, MeOH) ee 98%; ^{1}H NMR ($CDCl_3$) δ (ppm): 0.88 (3H, s), 1.30 (3H, s), 1.50 (1H, d, *J* = 11.1 Hz), 1.82–1.98 (2H, m), 2.07–2.29 (3H, m), 3.28 (1H, dd, *J* = 4.8, 10.7 Hz), 3.95–4.00 (1H, m), 5.87 (1H, s); ^{13}C NMR ($CDCl_3$) δ (ppm): 19.7 (Me), 23.3 (CH_2), 24.7 (CH_2), 26.8 (Me), 40.0 (C_q), 41.9 (CH), 43.7 (CH), 44.9 (*C*H=O), 51.8 (CHN), 173.9 (C=O). IR = 3247, 2914, 1710, 1380, 1256, 1189 cm^{-1}. Anal. Calcd for $C_{10}H_{15}NO$ (165.23): C, 72.69; H, 9.15; N, 8.48. Found: C, 72.52; H, 9.27; N, 8.31.

4.3. (1*S*,2*S*,5*R*,7*S*)-8,8-Dimethyl-3-azatricyclo[5.1.1.0^{2,5}]nonan-4-one 17

The (1*S*,2*S*,5*R*,7*S*)-enantiomer **17** was synthesized analogously to **2**, from (+)-(1*R*,5*R*)-apopinene **16**; $[\alpha]_D^{20} = +61.5$ (*c* 0.5, MeOH) ee = 90%; all the spectroscopic data and mp were similar to those for the (−)-enantiomer **2**. Anal. Calcd for $C_{10}H_{15}NO$ (165.23): C, 72.69; H, 9.15; N, 8.48. Found: C, 72.57; H, 9.31; N, 8.25.

4.4. Methyl (1*R*,2*R*,3*S*,5*R*)-2-amino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylate hydrochloride 3

Method A: A solution of 2.0 g (12.1 mmol) of (1*R*,2*R*,5*S*,7*R*)-8,8-dimethyl-3-azatricyclo[5.1.1.0^{2,5}]nonan-4-one **2** in dry MeOH containing 10% anhydrous HCl (20 mL) was stirred at room temperature. After 1.5 h, the solution was evaporated to dryness and the resulting crystalline product was recrystallized from an iPr_2O/EtOAc mixture. Isolated compound: 1.98 g (71%); mp: 157–160 °C; $[\alpha]_D^{20} = +4.8$ (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.97 (3H, s), 1.35 (3H, s), 1.54 (1H, d, *J* = 11.1 Hz), 2.08–2.22 (3H, m), 2.36–2.45 (1H, m), 3.54 (1H, dt, *J* = 3.5, 10.1 Hz), 3.84 (3H, s), 4.09 (1H, d, *J* = 10.1 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.2, 25.3, 28.5, 38.7, 39.0, 43.6, 44.1, 47.8, 49.9, 53.1, 176.7. IR = 2926, 1724, 1498, 1205 cm^{-1}. Anal. Calcd for $C_{11}H_{20}ClNO_2$ (233.74): C, 56.52; H, 8.62; N, 5.99. Found: C, 56.73; H, 9.01; N, 6.17.

Method B: At first 0.31 mL (4.57 mmol) of $SOCl_2$ was added dropwise with stirring to 4 mL of dry MeOH, the internal temperature being kept below −12 °C during the addition. Next, 0.91 g (4.17 mmol) of (1*R*,2*R*,3*S*,5*R*)-2-amino-6,6-dimethylbicyclo[3.1.1]-heptane-3-carboxylic acid hydrochloride **5** was added to the solution in one portion and the mixture was stirred for 30 min at 0 °C, for 3 h at room temperature, and then for 30 min at the boiling point. The solution was finally evaporated to dryness and the resulting crude yellow product was recrystallized from an iPr_2O/EtOAc mixture. The isolated product **3** weighed 0.78 g (80%).

4.5. Ethyl (1*R*,2*R*,3*S*,5*R*)-2-amino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylate hydrochloride 4

Compound **4** was prepared by two methods.

Method A: A solution of 1.16 g (7.0 mmol) of (1*R*,2*R*,5*S*,7*R*)-8,8-dimethyl-3-azatricyclo[5.1.1.0^{2,5}]nonan-4-one **2** in dry EtOH containing 10% anhydrous HCl (20 mL) was stirred at room temperature. After 1.5 h, the solution was evaporated to dryness and the resulting crystalline product was recrystallized from an iPr_2O/EtOAc mixture. Isolated compound: 1.54 g (89%); mp: 138–139 °C; $[\alpha]_D^{20} = +23.0$ (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.97 (3H, s), 1.36 (3H, s), 1.35 (3H, t, *J* = 7.3 Hz), 1.56 (1H, d, *J* = 11.1 Hz), 2.08–2.23 (3H, m), 2.35–2.46 (2H, m), 3.51 (1H, dt, *J* = 3.0, 10.1 Hz), 4.08 (1H, d, *J* = 9.6 Hz), 4.24–4.35 (2H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 13.7 (Me), 19.7 (Me), 24.4 (CH_2), 25.8 (CH), 29.4 (CH_2), 34.7 (CH) 39.4 (C_q), 39.6 (Me), 44.2 (CH), 50.4 (CH), 63.0 (CH_2), 176.7 (C=O). IR = 2918, 1729, 1373, 1189 cm^{-1}. Anal. Calcd for $C_{12}H_{22}ClNO_2$ (247.76): C, 58.17; H, 8.95; N, 5.65. Found: C, 58.43; H, 9.26; N, 5.51.

Method B: 0.22 mL (3.05 mmol) of $SOCl_2$ was added dropwise to dry EtOH (4 mL) the internal temperature being kept below −12 °C during the addition. Next, 0.61 g (2.78 mmol) of (1*R*,2*R*,3*S*,5*R*)-2-amino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid hydrochloride **5** was added to the solution in one portion and the mixture was stirred for 30 min at 0 °C, for 3 h at room temperature, and then for 30 min at the boiling point. The solution was finally evaporated to dryness and the resulting crude yellow product was recrystallized from an iPr_2O/EtOAc mixture. The isolated product **4** weighed 0.56 g (81%).

4.6. Ethyl (1*S*,2*S*,3*R*,5*S*)-2-amino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylate hydrochloride 19

The (1*S*,2*S*,3*R*,5*S*)-enantiomer **19** was synthesized analogously to **4**, from the (1*S*,2*S*,5*R*,7*S*)-enantiomer **17**; $[\alpha]_D^{20} = -19.6$ (*c* 0.5, MeOH); all the spectroscopic data and the mp were similar to those for the (1*R*,2*R*,3*S*,5*R*)-enantiomer **4**. Anal. Calcd for $C_{12}H_{22}ClNO_2$ (247.76): C, 58.17; H, 8.95; N, 5.65. Found: C, 58.35; H, 9.07; N, 5.73.

4.7. (1*R*,2*R*,3*S*,5*R*)-2-Amino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid hydrochloride 5

A solution of 0.50 g (3.0 mmol) of (1*R*,2*R*,5*S*,7*R*)-8,8-dimethyl-3-azatricyclo[5.1.1.0^{2,5}]nonan-4-one **2** in 5 mL of 15% aqueous HCl was stirred at room temperature. When the mixture became clear (approx. 1 h), the solution was evaporated to dryness and the resulting white crystalline product was washed with acetone and filtered off. Isolated compound: 0.61 g (94%); mp: 248–249 °C; $[\alpha]_D^{20} = +22.5$ (*c* 0.5, MeOH); ^{1}H NMR (D_2O) δ (ppm): 0.89 (3H, s), 1.27 (3H, s), 1.48 (1H, d, *J* = 11.1 Hz), 2.04–2.16 (2H, m), 2.31–2.39 (2H, m) 3.39 (1H, dt, *J* = 3.6, 10.7 Hz), 3.98 (1H, d, *J* = 9.6 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.7 (Me), 24.3 (CH_2), 25.8 (Me), 29.4 (CH_2), 34.4 (CH), 39.3 (C_q), 39.6 (CH), 44.2 (CH), 50.2 (CH), 178.5 (C=O). IR = 2904, 1724, 1584, 1489, 1175 cm^{-1}. Anal. Calcd for $C_{10}H_{18}ClNO_2$ (219.71): C, 54.67; H, 8.26; N, 6.38. Found: C, 54.87; H, 8.02; N, 6.71.

4.8. (1*S*,2*S*,3*R*,5*S*)-2-Amino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid hydrochloride 18

(1*S*,2*S*,3*R*,5*S*)-2-Amino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid hydrochloride **18** was synthesized analogously to **5**, from the (1*S*,2*S*,5*R*,7*S*)-azetidinone enantiomer **17**; $[\alpha]_D^{20} = -21.6$ (*c* 0.5, MeOH); all the spectroscopic data and the mp were similar to those for the (1*R*,2*R*,3*S*,5*R*)-enantiomer **5**. Anal. Calcd for $C_{10}H_{18}ClNO_2$ (219.71): C, 54.67; H, 8.26; N, 6.38. Found: C, 54.75; H, 8.09; N, 6.35.

4.9. (1*R*,2*R*,3*S*,5*R*)-2-Amino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid 6

At first, 0.61 g (2.8 mmol) of (1*R*,2*R*,3*S*,5*R*)-2-amino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid hydrochloride **5** was dissolved in 5 mL of water and the solution was adjusted to pH 7.4 with a 10% solution of $NaHCO_3$ under ice cooling in the presence of methylthymol blue as indicator. After stirring for 1 h at 0 °C, the precipitated product **6** was filtered off and washed with a small amount of ice-cold distilled water. Isolated compound: 0.29 g (58%); mp: 270 °C; $[\alpha]_D^{20} = -1.6$ (*c* 0.50, MeOH); ^{1}H NMR

(CD_3OD) δ (ppm): 0.99 (3H, s), 1.36 (3H, s), 1.73 (1H, d, J = 10.6 Hz), 2.00–2.06 (1H, m), 2.12 (1H, dt, J = 2.0, 5.5 Hz), 2.26–2.39 (3H, m), 3.02 (1H, dt, J = 4.5, 9.6 Hz), 3.82 (1H, dt, J = 2.0, 9.6 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.9 (Me), 26.1 (CH_2), 27.6 (Me), 32.5 (CH_2), 37.8 (CH), 39.3 (C_q), 42.3 (CH), 47.2 (CH), 52.0 (CH), 183.1 (C=O). IR = 3243, 2972, 1625, 1576, 1474, 1382 cm^{-1}. Anal. Calcd for $C_{10}H_{17}NO_2$ (183.25): C, 65.54; H, 9.35; N, 7.64. Found: C, 65.48; H, 9.57; N, 7.42.

4.10. (1*R*,2*R*,5*S*,7*R*)-*N*-*tert*-Butoxycarbonyl-8,8-dimethyl-3-azatricyclo[5.1.1.0^{2,5}]nonan-4-one 7

To a stirred solution of 0.30 g (1.8 mmol) of (1*R*,2*R*,5*S*,7*R*)-8,8-dimethyl-3-azatricyclo[5.1.1.0^{2,5}]nonan-4-one **2** and dry THF (10 mL), Et_3N (0.47 g, 4.6 mmol), di-*tert*-butyl dicarbonate (0.51 g, 2.3 mmol) and a catalytic amount of DMAP (20 mg) were added. After stirring for 6 h at room temperature (the reaction was monitored by means of TLC), the mixture was evaporated to dryness. The oily residue obtained was purified by flash chromatography on a silica gel column (*n*-hexane/EtOAc = 9:1), which resulted in a white crystalline product. Compound **7**: 0.43 g (89%); mp: 64–66 °C; $[\alpha]_D^{20} = -41.1$ (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.89 (3H, s), 1.31 0.89 (3H, s), 1.35 (1H, d, J = 11.6 Hz), 1.50 (9H, s), 1.81–2.00 (2H, m), 2.14–2.25 (2H, m), 2.51–2.57 (1H, m), 3.29 (1H, dd, J = 6.2, 10.3 Hz), 4.27 (1H, dd, J = 4.0, 5.6 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 20.5 (Me), 24.3 (CH_2), 25.5 (CH_2), 27.3 (Me), 28.7 ((*Me*)$_3$C), 39.8 (C_q), 42.1 (CH), 42.5 (CH), 44.1 (CH), 55.5 (CH), 83.4 (C_q), 148.6 (C=O), 170.5 (C=O). IR = 2926, 1803, 1707, 1349, 1156 cm^{-1}. Anal. Calcd for $C_{15}H_{23}NO_3$ (265.35): C, 67.90; H, 8.74; N, 5.28. Found: C, 68.16; H, 8.54; N, 5.35.

4.11. (1*R*,2*R*,3*S*,5*R*)-(2-*tert*-Butoxycarbonylamino)-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid 8

At first, 0.66 g (3 mmol) of (1*R*,2*R*,3*S*,5*R*)-2-amino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid hydrochloride **5** was dissolved in 5 mL of distilled water at 0 °C and the pH of the solution was adjusted to pH 8 with 3% NaOH solution in the presence of bromothymol blue as indicator. Next 5 mL of dioxan and 0.72 g (3.3 mmol) of Boc_2O were added, and the reaction mixture was stirred at room temperature, with the pH being maintained at 8 with 3% NaOH solution. After stirring for 6 h at room temperature, the solution was cooled to 0 °C, acidified with 5% aqueous HCl solution to pH 5, and extracted with $CHCl_3$ (3 × 50 mL). The combined organic layer was dried (Na_2SO_4) and evaporated, and the white crystalline product obtained was recrystallized from *n*-hexane. The NMR measurements on the product revealed the presence of two rotamer populations in a ratio of 12:88. Isolated compound: 0.52 g (61%); mp: 151–153 °C; $[\alpha]_D^{20} = +46.0$ (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm) of major rotamer: 0.88 (3H, s), 1.24 (3H, s), 1.47 (9H, s), 1.75 (1H, d, J = 10.6 Hz), 1.84–1.99 (3H, m), 2.20–2.31 (2H, m), 3.21 (1H, dt, J = 2.5, 10.1 Hz), 4.31 (1H, t, J = 10.1 Hz), 7.33 (1H, d, J = 10.1 Hz), 11.30 (1H, br s). ^{13}C NMR ($CDCl_3$) δ (ppm): 20.6 (Me), 24.5 (CH_2), 26.5 (Me), 27.5 (CH2), 28.6 (C*Me*$_3$), 39.0 (CH), 39.3 (C_q), 39.6 (CH), 46.7 (CH), 50.5 (CH), 81.4 (*C*Me$_3$), 155.8 (NC=O), 179.8 (C=O). IR = 3255, 2914, 1711, 1654, 1407, 1171 cm^{-1}. Anal. Calcd for $C_{15}H_{25}NO_4$ (283.36): C, 63.58; H, 8.89; N, 4.94. Found: C, 63.79; H, 8.41; N, 5.19.

4.12. (1*S*,2*S*,3*R*,5*S*)-(2-*tert*-Butoxycarbonylamino)-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid 22

The (1*S*,2*S*,3*R*,5*S*)-enantiomer **22** was synthesized analogously to **8**, from the (1*S*,2*S*,3*R*,5*S*) = amino acid hydrochloride enantiomer **18**; $[\alpha]_D^{20} = -44.1$ (*c* 0.5, MeOH); all the spectroscopic data and the mp were similar to those for the (1*R*,2*R*,3*S*,5*R*)-enantiomer **8**. Anal. Calcd for $C_{15}H_{25}NO_4$ (283.36): C, 63.58; H, 8.89; N, 4.94. Found: C, 63.69; H, 8.57; N, 5.05.

4.13. (1*R*,2*R*,3*S*,5*R*)-2-(9*H*-Fluoren-9-yl-methoxycarbonylamino)-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid 9

At first, 0.34 g (1.56 mmol) of (1*R*,2*R*,3*S*,5*R*)-2-amino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid hydrochloride **5** was dissolved in 6 mL of distilled water at 0 °C. 0.50 g (6 mmol) of $NaHCO_3$, 5 mL of MeCN and 0.51 g (1.5 mmol) of Fmoc-OSu were added to the solution at 0 °C. After stirring for 12 h at room temperature, the solution was adjusted to pH 2 with 5% $NaHCO_3$ solution. After stirring overnight at room temperature, the solution was acidified with 10% aqueous HCl solution and, after stirring for 1 h, the reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over Na_2SO_4 and evaporated, and the crude product obtained was purified by flash chromatography on a silica gel column (*n*-hexane/EtOAc = 9:1, R_f = 0.35), resulting in a white crystalline product. Isolated compound: 0.40 g (63%); mp: 160–162 °C; $[\alpha]_D^{20} = +2.0$ (*c* 0.25, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.84 (3H, s), 1.23 (3H, s), 1.71 (1H, d, J = 10.4 Hz), 1.81–2.25 (5H, m), 3.08 (1H, t, J = 9.1 Hz), 4.00–4.47 (4H, m), 7.24–7.75 (8H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 20.8, 24.8, 26.8, 28.8, 39.1, 39.6, 39.9, 46.9, 47.9, 50.8, 68.2, 120.6, 125.6, 125.9, 127.7, 128.3, 142.0, 142.1, 144.5, 144.8, 158.7, 180.2. IR = 3260, 2908, 1711, 1652, 1414, 1332, 1201, 741 cm^{-1}. Anal. Calcd for $C_{25}H_{27}NO_4$ (405.49): C, 74.05; H, 6.71; N, 3.45. Found: C, 74.19; H, 6.45; N, 3.53.

4.14. (1*S*,2*S*,3*R*,5*S*)-2-(9*H*-Fluoren-9-yl-methoxycarbonylamino)-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid 23

The (1*S*,2*S*,3*R*,5*S*) = enantiomer **23** was synthesized analogously to **9**, from the (1*S*,2*S*,3*R*,5*S*)-enantiomer **18**; $[\alpha]_D^{20} = -2.0$ (*c* 0.25, MeOH); all the spectroscopic data and the mp were similar to those for the (1*R*,2*R*,3*S*,5*R*)-enantiomer **9**. Anal. Calcd for $C_{25}H_{27}NO_4$ (405.49): C, 74.05; H, 6.71; N, 3.45. Found: C, 74.23; H, 6.51; N, 3.57.

4.15. (1*S*,2*S*,3*R*,5*S*)-2-Dimethylamino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid hydrochloride 10

At first, 0.50 g (2.27 mmol) of amino acid hydrochloride **5** was dissolved in 15 mL of distilled water, followed by the addition of 0.43 g (5.0 mmol) of 35% HCHO solution and 0.20 g of 10% Pd/C catalyst. The mixture was stirred at room temperature and 10 bar under a H_2 atmosphere for 12 h. The mixture was then filtered and the filtrate was evaporated to dryness. The resulting crystalline product was triturated with acetone, and then filtered off. Isolated compound: 0.50 g (89%); mp: 144–145 °C; $[\alpha]_D^{20} = +10.7$ (*c* 0.505, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.89 (3H, s), 1.35 (3H, s), 1.62 (1H, d, J = 11.1 Hz), 2.03–2.10 (1H, m), 2.21–2.56 (4H, m), 2.88 (3H, s), 2.92 (3H, s), 3.51 (1H, t, J = 9.3 Hz), 3.76 (1H, d, J = 8.6 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.4 (Me), 23.4 (CH_2), 25.9 (Me), 29.5 (CH_2), 34.3 (CH), 39.3 (CH), 40.3 (CH), 40.4 (C_q), 42.3 (Me), 44.1 (Me), 67.2 (CH), 179.9 (C=O). IR = 2952, 1709, 1458, 1186 cm^{-1}. Anal. Calcd for $C_{12}H_{22}ClNO_2$ (247.76): C, 58.17; H, 8.95; N, 5.65. Found: C, 58.23; H, 8.69; N, 5.37.

4.16. Ethyl (1*R*,2*R*,3*R*,5*R*)-2-amino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylate hydrochloride 11

To a solution of 0.23 g (10 mmol) of Na in 30 mL of dry EtOH, 1.05 g (5 mmol) of the base form of ethyl (1*R*,2*R*,3*S*,5*R*)-2-amino-

6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylate hydrochloride **4** was added in one portion. The solution was stirred at room temperature until the isomerization was complete (approximately 4 h; the isomerization process was monitored by means of TLC and GC). The solution was then evaporated to approximately 5 mL, diluted with ice-cold water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layer was dried over Na_2SO_4 and evaporated, and the hydrochloride salt **11**, prepared from the resulting amino ester base with a 15% solution of anhydrous HCl in dry EtOH, was recrystallized from iPr_2O. Isolated compound: 0.85 g (69%); mp: 147–148 °C; $[\alpha]_D^{20} = -32.4$ (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.88 (3H, s), 1.34 (3H, s), 1.36 (3H, t, *J* = 7.1 Hz), 1.56 (1H, d, *J* = 11.1 Hz), 2.05 (1H, dd, *J* = 9.1, 13.6 Hz), 2.10–2.23 (2H, m), 2.35–2.46 (2H, m), 3.05 (1H, dd, *J* = 9.1, 18.1 Hz), 4.10 (1H, d, *J* = 89.6 Hz), 4.33 (2H, dd, *J* = 7.1, 14.1 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 13.8 (Me), 19.1 (Me), 23.0 (CH_2), 25.8 (CH), 27.5 (CH_2), 38.4 (CH), 39.3 (Me), 39.7 (C_q), 43.4 (CH), 52.3 (CH), 63.0 (CH_2), 175.9 (C=O). IR = 2926, 1734, 1509, 1292, 1193 cm^{-1}. Anal. Calcd for $C_{12}H_{22}ClNO_2$ (247.76): C, 58.17; H, 8.95; N, 5.65. Found: C, 58.35; H, 8.78; N, 5.79.

4.17. Ethyl (1*S*,2*S*,3*S*,5*S*)-2-amino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylate hydrochloride 20

The (1*S*,2*S*,3*S*,5*S*) enantiomer **20** was synthesized analogously to **11**, from the 1*S*,2*S*,3*R*,5*S* enantiomer amino ester **19**; $[\alpha]_D^{20} = +31.0$ (*c* 0.5, MeOH); all the spectroscopic data and the mp were similar to those for the 1*R*,2*R*,3*R*,5*R* enantiomer **11**. Anal. Calcd for $C_{12}H_{22}ClNO_2$ (247.76): C, 58.17; H, 8.95; N, 5.65. Found: C, 58.27; H, 8.72; N, 5.83.

4.18. (1*R*,2*R*,3*R*,5*R*)-2-Amino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid 12

At first, 0.23 g (1.09 mmol) of the base liberated from ethyl (1*R*,2*R*,3*R*,5*R*)-2-amino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylate hydrochloride **11** was dissolved in a mixture of 10 mL of dioxan and 10 mL of distilled water, and the solution was heated at 80 °C with monitoring by means of TLC. When the reaction was complete (indicated by elimination of the starting ester), the mixture was evaporated to dryness and the resulting white crystalline product was triturated with acetone, filtered off, and recrystallized from an acetone/water mixture. Isolated compound: 0.13 g (65%); mp: 250–252 °C; $[\alpha]_D^{20} = -42.7$ (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.82 (3H, s), 1.26 (3H, s), 1.49 (1H, d, *J* = 10.8 Hz), 1.83–1.93 (1H, m), 1.98–2.11 (2H, m), 2.20–2.30 (2H, m), 2.61–2.70 (1H, m), 3.90 (1H, d, *J* = 8.6 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.1 (Me), 22.8 (CH_2), 25.8 (Me), 28.1 (CH_2), 39.7 (CH), 39.9 (C_q), 40.6 (CH), 43.4 (CH), 53.6 (CH), 181.5 (C=O). IR = 2924, 1624, 1552, 1404 cm^{-1}. Anal. Calcd for $C_{10}H_{17}NO_2$ (183.25): C, 65.54; H, 9.35; N, 7.64. Found: 65.21; H, 9.87; N, 7.19.

4.19. (1*R*,2*R*,3*R*,5*R*)-2-Amino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid hydrochloride 13

At first, 0.74 g (3.0 mmol) of ethyl (1*R*,2*R*,3*R*,5*R*)-2-amino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylate hydrochloride **11** was dissolved in a 10% solution of aqueous HCl, and the solution was stirred at room temperature for 48 h (the reaction was monitored by means of ^{1}H NMR). When the hydrolysis was complete, the solution was evaporated to dryness and the resulting crystalline product was triturated with acetone, and then filtered off. Compound **13**: 0.56 g (85%); mp: 241–242 °C; $[\alpha]_D^{20} = -32.6$ (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.88 (3H, s), 1.34 (3H, s), 1.56 (1H, d, *J* = 11.1 Hz), 2.05 (1H, dd, *J* = 8.8, 13.8 Hz), 2.13 (1H, dd, *J* = 4.8, 9.8 Hz), 2.20 (1H, t, *J* = 5.5 Hz), 2.35–2.45 (2H, m), 2.99–3.07 (1H, m), 4.08 (1H, d, *J* = 8.6 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.1 (Me), 23.0 (CH_2), 25.8 (Me), 27.4 (CH_2), 38.2 (CH), 39.4 (CH), 39.8 (C_q), 43.4 (CH), 52.4 (CH), 177.7 (C=O). IR = 2913, 1716, 1511, 1247 cm^{-1}. Anal. Calcd for $C_{10}H_{18}ClNO_2$ (219.71): C, 54.67; H, 8.26; N, 6.38. Found: C, 54.79; H, 8.39; N, 6.21.

4.20. (1*S*,2*S*,3*S*,5*S*)-2-Amino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid hydrochloride 21

The 1*S*,2*S*,3*S*,5*S* enantiomer **21** was synthesized analogously to **13**, from the 1*S*,2*S*,3*S*,5*S* amino ester enantiomer **20**; $[\alpha]_D^{20} = +30.1$ (*c* 0.5, MeOH); all the spectroscopic data and the mp were similar to those for the (1*R*,2*R*,3*R*,5*R*)-enantiomer **13**. Anal. Calcd for $C_{10}H_{18}ClNO_2$ (219.71): C, 54.67; H, 8.26; N, 6.38. Found: C, 54.83; H, 8.35; N, 6.19.

4.21. (1*R*,2*R*,3*R*,5*R*)-(2-*tert*-Butoxycarbonylamino)-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid 14

Compound **14** was synthesized analogously to **8**, from 0.66 g (3 mmol) of (1*R*,2*R*,3*R*,5*R*)-2-amino-6,6-dimethylbicyclo[3.1.1]-heptane-3-carboxylic acid hydrochloride **13**. Isolated compound: 0.55 g (65%); mp: 85–87 °C; $[\alpha]_D^{20} = -43.3$ (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.94 (3H, s), 1.23 (3H, s), 1.35 (1H, d, *J* = 10.1 Hz), 1.43 (9H, s), 1.94–2.21 (5H, m), 2.53–2.64 (1H, m), 4.26–4.36 (1H, m), 4.73 (1H, br s). ^{13}C NMR ($CDCl_3$) δ (ppm): 20.1, 24.1, 27.2, 28.4, 29.0, 40.2, 40.4, 42.7, 46.7, 52.1, 81.0, 155.7, 179.8. IR = 3336, 2923, 1711, 1659, 1366, 1176 cm^{-1}. Anal. Calcd for $C_{15}H_{25}NO_4$ (283.36): C, 63.58; H, 8.89; N, 4.94. Found: C, 63.84; H, 8.99; N, 5.26.

4.22. (1*S*,2*S*,3*S*,5*S*)-(2-*tert*-Butoxycarbonylamino)-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid 24

The (1*S*,2*S*,3*S*,5*S*)-enantiomer **24** was synthesized analogously to **14**, from 0.66 g (3 mmol) of (1*S*,2*S*,3*S*,5*S*)-2-amino-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid hydrochloride **21** prepared as above, $[\alpha]_D^{20} = +41.1$ (*c* 0.5, MeOH); all the spectroscopic data and the mp were similar to those for the (1*R*,2*R*,3*R*,5*R*)-enantiomer **14**. Anal. Calcd for $C_{15}H_{25}NO_4$ (283.36): C, 63.58; H, 8.89; N, 4.94. Found: C, 63.71; H, 9.13; N, 5.15.

4.23. (1*R*,2*R*,3*R*,5*R*)-2-(9*H*-Fluoren-9-yl-methoxycarbonylamino)-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid 15

The (1*R*,2*R*,3*R*,5*R*)-enantiomer **15** was synthesized analogously to **9**, from the (1*R*,2*R*,3*R*,5*R*)-amino acid hydrochloride enantiomer **13**; mp: 155–157 °C; $[\alpha]_D^{20} = -4$ (*c* 0.25, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.90 (3H, s), 1.20 (3H, s), 1.34 (1H, d, *J* = 10.6 Hz), 1.81–2.14 (5H, m), 2.56–2.62 (1H, m), 4.17 (1H, t, *J* = 6.5 Hz), 4.28–4.46 (3H, m), 4.97 (1H, br s), 7.20–7.80 (8H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 20.1, 24.2, 27.2, 28.4, 32.1, 40.2, 42.6, 46.7, 47.9, 52.5, 67.5, 120.6, 125.8, 127.7, 128.3, 142.0, 144.6, 148.5, 179.8.); IR = 3340, 2926, 1693, 1536, 1450, 1252, 739 cm^{-1}. Anal. Calcd for $C_{25}H_{27}NO_4$ (405.49): C, 74.05; H, 6.71; N, 3.45. Found: C, 74.27; H, 6.52; N, 3.49.

4.24. (1*S*,2*S*,3*S*,5*S*)-2-(9*H*-Fluoren-9-yl-methoxycarbonylamino)-6,6-dimethylbicyclo[3.1.1]heptane-3-carboxylic acid 25

The (1*S*,2*S*,3*S*,5*S*)-enantiomer **25** was synthesized analogously to **15**, from the (1*S*,2*S*,3*S*,5*S*)-amino acid hydrochloride enantiomer **21**; $[\alpha]_D^{20} = +6$ (*c* 0.25, MeOH); all the spectroscopic data and the mp were similar to those for the 1*R*,2*R*,3*R*,5*R* enantiomer **15**. Anal.

Calcd for $C_{25}H_{27}NO_4$ (405.49): C, 74.05; H, 6.71; N, 3.45. Found: C, 74.23; H, 6.49; N, 3.57.

4.25. Ethyl (2*S*,1′*R*,2′*R*,3′*S*,5′*R*)-2-[(2′-*tert*-butoxycarbonylamino)-6′,6′-dimethylbicyclo[3.1.1]heptane-3′-carbonyl)]amino-3-phenylpropionate 26

At first, 0.05 g of Et_3N and 0.065 g of isobutyl chloroformate were added to a solution of 0.14 g (0.49 mmol) of the (1*R*,2*R*,3*S*,5*R*)-Boc-protected amino acid **8** in 5 mL of dry THF at −10 °C with vigorous stirring. After stirring for 10 min, 2 mL of a dry THF solution of 0.095 g (0.49 mmol) of (*S*)-phenylalanine ethyl ester was added dropwise to the mixture at −10 °C. The mixture was stirred at room temperature for a further 5 h, and then evaporated to dryness. The resulting crude oily product was dissolved in $CHCl_3$ (30 mL), and the organic solution was washed first with an ice-cold 5% solution of $NaHCO_3$ (20 mL), and then with an ice-cold 5% aqueous HCl solution (20 mL). The organic layer was next dried over Na_2SO_4 and evaporated, and the oily product obtained was purified by flash chromatography on a silica gel column (*n*-hexane/EtOAc = 6:1, R_f = 0.35). Isolated compound: 0.15 g (67%), viscous oil; $[\alpha]_D^{20} = +22.5$ (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.88 (3H, s), 1.22 (6H, s overlapped with t), 1.36 (9H, s), 1.62–2.20 (7H, m), 3.01 (1H, dt, *J* = 3.5, 10.1 Hz), 3.10 (1H, dd, *J* = 3.5, 10.1 Hz), 3.21 (1H, dd, *J* = 3.5, 10.1 Hz), 4.14 (2H, q, *J* = 7.1, 14.1 Hz), 4.35 (1H, t, *J* = 10.0 Hz), 4.74 (1H, q, *J* = 6.1, 12.1 Hz), 5.28 (1H, d, *J* = 10.1 Hz), 6.19 (1H, d, *J* = 6.5 Hz), 7.9 (2H, d, *J* = 7.1 Hz), 7.20–7.30 (3H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.7 (Me), 20.9 (Me), 25.4 (CH_2), 26.8 (Me), 29.0 (C*Me*$_3$), 29.8 (CH_2), 38.6 (CH_2), 39.8 (C_q), 40.0 (Me), 40.5 (CH), 46.9 (CH), 49.5 (CH), 54.5 (CH), 62.1 (CH_2), 79.6 (*C*Me$_3$), 127.7 (CH_{ar}), 129.1 (CH_{ar}), 130.1 (CH_{ar}), 136.7 (C_q), 156.1 (C═O, Boc), 171.6 (C═O), 175.4 (C═O). IR = 3411, 2978, 1711, 1497, 1366, 1161, 701 cm^{-1}. Anal. Calcd for $C_{26}H_{38}N_2O_5$ (458.59): C, 68.10; H, 8.35; N, 6.11. Found: C, 67.76; H, 8.53; N, 6.38.

4.26. Ethyl (2*S*,1′*R*,2′*R*,3′*R*,5′*R*)-2-[[(2′-*tert*-butoxycarbonylamino)-6′,6′-dimethylbicyclo[3.1.1]heptane-3′-carbonyl)]amino]-3-phenylpropionate 27

The (2*S*,1′*R*,2′*R*,3′*R*,5′*R*)-enantiomer **27** was synthesized analogously to **26**, from 0.14 g (0.49 mmol) of the (1*R*,2*R*,3*R*,5*R*)-enantiomer **14**. Isolated compound: 0.09 g (40%); mp: 185–188 °C; $[\alpha]_D^{20} = -15$ (*c* 0.25, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.79 (3H, s), 1.19 (3H, t, *J* = 7.1 Hz), 1.20 (3H, s), 1.30 (1H, d, *J* = 10.5 Hz), 1.46 (9H, s), 1.90–2.19 (5H, m), 2.33–2.47 (1H, m), 3.04–3.17 (2H, m), 4.12 (2H, dd, *J* = 7.1, 14.2 Hz), 4.20–4.29 (1H, m), 4.25 (1H, t, *J* = 8.6 Hz), 4.77–4.86 (1H, m), 7.17–7.32 (5H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.8, 20.1, 24.2, 27.0, 28.2, 29.1, 30.4, 38.7, 40.3, 43.6, 47.3, 51.9, 54.5, 61.9, 80.7, 127.5, 129.1, 130.1, 137.4, 156.2, 172.6, 174.4. IR = 3270, 2926, 1750, 1684, 1651, 1558, 1196 cm^{-1}. Anal. Calcd for $C_{26}H_{38}N_2O_5$ (458.59): C, 68.10; H, 8.35; N, 6.11. Found: C, 68.51; H, 7.96; N, 6.47.

4.27. Ethyl (2*S*,1′*S*,2′*S*,3′*R*,5′*S*)-2-[(2′-*tert*-butoxycarbonylamino)-6′,6′-dimethylbicyclo[3.1.1]heptane-3′-carbonyl)]amino-3-phenylpropionate 28

The (2*S*,1′*S*,2′*S*,3′*R*,5′*S*)-enantiomer **28** was synthesized analogously to **26**, from the (1*S*,2*S*,3*R*,5*S*)-enantiomer **22**. Isolated compound: 0.12 g (54%); oil; $[\alpha]_D^{20} = -10.0$ (*c* 0.25, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.90 (3H, s), 1.15 (3H, t, *J* = 7.1 Hz), 1.23 (3H, s), 1.38 (9H, s), 1.74 (1H, d, *J* = 10.1 Hz), 1.87–2.21 (5H, m), 2.93 (1H, dd, *J* = 7.1, 14.1 Hz), 3.03 (1H, dt, *J* = 4.0, 10.1 Hz), 3.21 (1H, dd, *J* = 5.0, 14.1 Hz), 4.09 (2H, dd, *J* = 7.1, 14.1 Hz), 7.10–7.31 (5H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.7, 20.9, 25.5, 26.9, 29.2, 29.8, 30.4, 39.3, 40.0, 40.4, 47.2, 49.6, 54.2, 62.0, 79.9, 127.8, 129.3, 130.0, 136.4, 156.1, 172.0, 175.3. IR = 3306, 2923, 2852, 1744, 1681, 1500, 1330, 1160, 1042 cm^{-1}. Anal. Calcd for $C_{26}H_{38}N_2O_5$ (458.59): C, 68.10; H, 8.35; N, 6.11. Found: C, 68.45; H, 8.01; N, 6.43.

4.28. Ethyl (2*S*,1′*S*,2′*S*,3′*S*,5′*S*)-2-[[(2′-*tert*-butoxycarbonylamino)-6′,6′-dimethylbicyclo[3.1.1]heptane-3′-carbonyl)]amino]-3-phenylpropionate 29

The (2*S*,1′*S*,2′*S*,3′*S*,5′*S*)-enantiomer **29** was synthesized analogously to **26**, from 0.14 g (0.49 mmol) of the (1*S*,2*S*,3*S*,5*S*)-enantiomer **24**. Isolated compound: 0.10 g (45%); mp: 186–188 °C; $[\alpha]_D^{20} = +18$ (*c* 0.25, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.93 (3H, s), 1.21 (3H, t, *J* = 7.1 Hz), 1.22 (3H, s), 1.26 (9H, s), 1.31 (1H, d, *J* = 11.1 Hz), 1.94–2.18 (5H, m), 2.29 (1H, m), 3.08 (1H, dd, *J* = 6.0, 14.1 Hz), 3.20 (1H, dd, *J* = 6.0, 14.1 Hz), 4.13 (2H, dd, *J* = 7.1, 14.1 Hz), 4.23–4.32 (1H, m), 4.66 (1H, br s), 4.81–4.91 (1H, m), 6.89 (1H, br s), 7.09–7.30 (5H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.8, 20.1, 23.4, 27.2, 29.0, 29.4, 30.0, 32.6, 38.5, 40.3, 43.7, 47.2, 54.3, 62.0, 80.3, 127.5, 129.0, 130.0, 137.0, 156.0, 172.6, 174.1. IR = 3310, 2926, 1692, 1645, 1557, 1182 cm^{-1}. Anal. Calcd for $C_{26}H_{38}N_2O_5$ (458.59): C, 68.10; H, 8.35; N, 6.11. Found: C, 68.39; H, 8.05; N, 6.28.

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