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# Regio- and stereoselective synthesis of the enantiomers of monoterpene-based β-amino acid derivatives

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**Abstract**—The regio- and stereospecific addition of chlorosulfonyl isocyanate to *cis*-δ-pinene enantiomers has furnished monoterpene-fused β-lactams. The observed regioselectivity can be explained by ab initio DFT modeling of transition state structures. In contrast with the less reactive α-pinane-fused β-lactam **4**, the resulting β-lactams **5** and **13** containing an amino group connected to a secondary carbon possess similar reactivity to the cycloalkane-fused analogues and can be 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 ester in moderate yield.


## 1. Introduction

The identification of new chiral building blocks and catalysts for asymmetric syntheses is of increasing importance in organic chemistry. Various powerful catalysts derived from monoterpenes, such as (+)-pulegone,[1] β-pinene,[2] fenchone-camphor,[3] and limonene,[4] have been reported to have been successfully used as chiral ligands in enantioselective syntheses.[5]

We recently described the transformations of enantiomerically pure α-pinene and 3-carene to β-amino acid derivatives, such as amino esters and amino alcohols, 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 diethylzinc with aromatic aldehydes.[6] These results revealed that a tertiary carbon next to the amino group dramatically decreases the reactivity of the synthons relative to those containing a secondary carbon next to the functional groups.[6]

Besides 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).[7] Icofungipen (PLD-118, (1*R*,2*S*)-2-amino-4-methylenecyclopentanecarboxylic acid), a β-amino acid, perturbs the biosynthesis of protein in *Candida albicans*.[8] β-Amino acids can also be used as building blocks for the preparation of modified analogues of pharmacologically active peptides. β-Amino acids and their foldameric oligomers are currently at the focus of research interest.[9]

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 (−)-δ-pinenes **2** and **13**.

## 2. Results and discussion

(+)- and (−)-*cis*-δ-pinenes **2** and **13** were synthesized from commercially available (−)- and (+)-isopinocampheols **1** and **12**, by modification of the literature method.[10] The tosylate of isopinocampheol **1** was prepared according to the Schmidt method.[11] Decomposition of the tosylate of isopinocampheol was carried out in DMF solution. This smoothly running reaction yielded a ternary mixture containing *cis*-δ-pinene **2** (45%), α-pinene **3** (45%), and unreacted starting material isopinocampheol **1** (10%). A simple bulb to bulb distillation resulted in a 1:1 mixture of alkenes **2** and **3**. Instead of the cumbersome fractional

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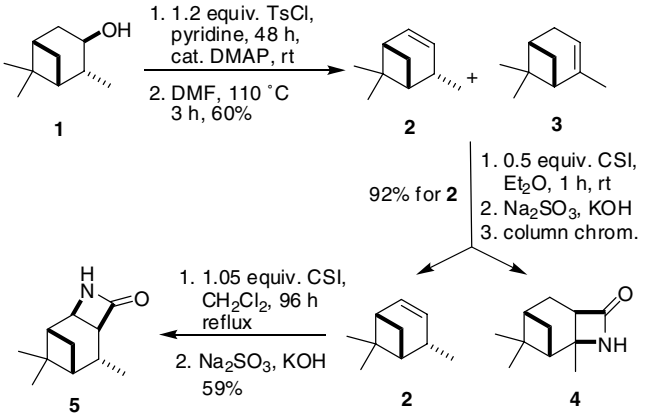
distillation of **2** and **3**,[10] the separation of the isomers was based on the different rates of the cycloaddition reaction of chlorosulfonyl isocyanate (CSI) (Scheme 1).




**Scheme 1.** Synthesis of azetidinone **5**.

When the progress of the cycloaddition of 0.5 equiv of CSI to the mixture of **2** and **3** was monitored, a marked difference in the reactivity of **2** and **3** was observed. In a dry ether solution at room temperature, the CSI addition to α-pinene **3** was completed within 1 h,[6a] whereas the addition to *cis*-δ-pinene **2** was negligible. After the usual work-up, *cis*-δ-pinene **2** and β-lactam **4** were easily separated by simple crystallization of the resulting azetidinone **4**. CSI addition to **2** was then successfully accomplished by refluxing the mixture in $CH_2Cl_2$ for 96 h. The NMR and GC studies on the crude product proved that the cycloaddition took place with high regio- and stereoselectivity (ee >99%), resulting in only β-lactam **5** (Scheme 1).[12]

The structure of azetidinone **5** was determined by X-ray crystallography (Fig. 1), while the relative stereochemistry was established by NOESY.

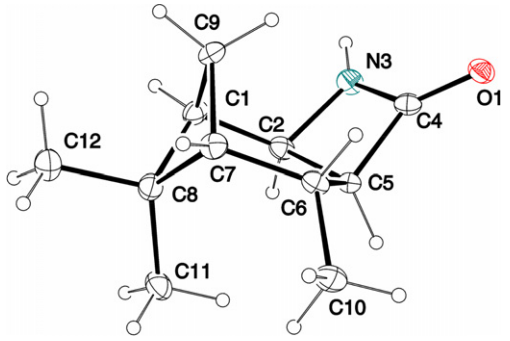



**Figure 1.** X-ray structure of azetidinone **5**.

The considerable difference in the rates of CSI addition to **2** and **3** can be explained on the basis of the ab initio theoretical results of Cossio et al.[13] CSI addition proceeds via [2+2] cycloaddition, where the transition state is partially asynchronous and has a zwitterionic nature. The partial positive charge that develops on the $sp^2$ carbon attacked by the nitrogen is significantly stabilized by any electron-donating substituent. For **3**, the attached methyl substituent can exert this stabilization effect, which rationalizes both the faster reaction toward **4** and the regiospecificity of the reaction.

It is more difficult to account for the regiospecificity of CSI addition to **2**. DFT calculations at the level of B3LYP/6-31+g(d,p) were performed to model the transition states A and B as shown in Figure 2.

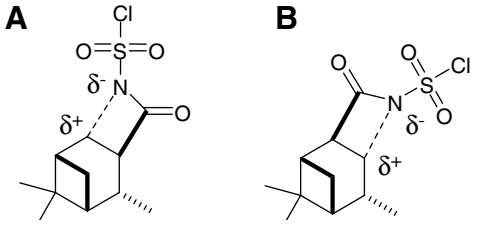



**Figure 2.** Possible transition states in CSI cycloaddition to **2**.

The transition state-searching algorithm implemented in Gaussian03 converged to stable saddle points for both models with single imaginary frequencies corresponding to the cycloaddition step. The single point energies were −1567.49232521 a.u. and −1567.48939210 a.u. for A and B, respectively, which means that transition state A is favored by 1.84 kcal/mol stabilization energy. Under the reaction conditions applied, this energy difference can explain the 20-fold higher reaction rate via transition state A, which is in good agreement with the experimental findings. To gain insight into the stereoelectronic features explaining the difference, NBO[14] calculations were performed (Fig. 3). The results revealed that the cycloaddition through A is less asynchronous, because the $n_{N3}$–$n^*_{C2}$ overlap occurs in the transition state, while B does not exhibit such an interaction. The synchronicity contributes to the increased stability of the transition state. Interestingly, an additional stabilizing $n_O$–$\sigma^*_{C6-H6}$ orbital overlap can be observed in A, while such an interaction does not build up in B. This partial electron donation from the oxygen lone pair to the antibonding orbital of the C–H single bond can be interpreted as an irregular C–H–O hydrogen-bond, which has been thoroughly studied in biological systems and has been shown to have significant stabilizing effect.[15]

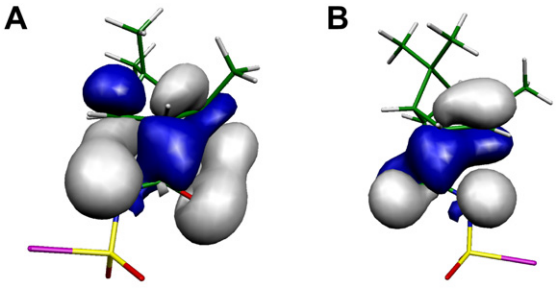
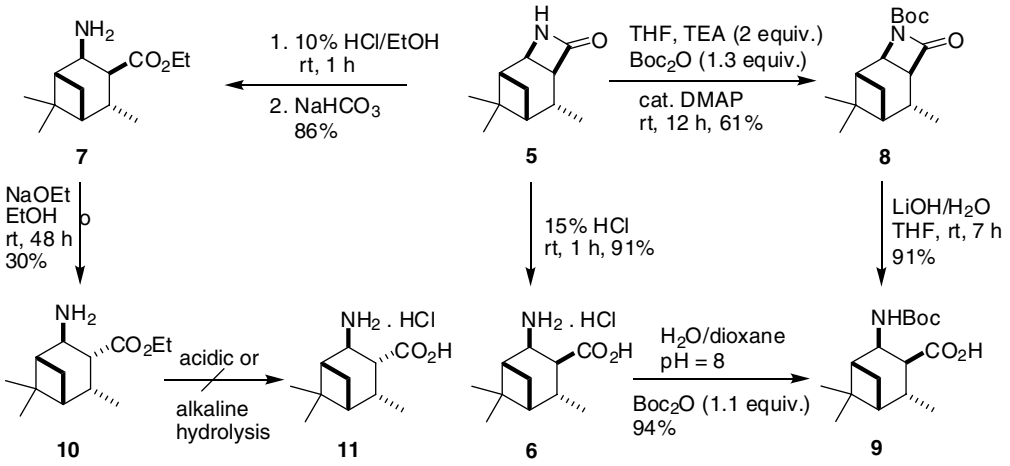



**Figure 3.** NBO analysis of DFT transition state models in CSI cycloaddition to **2**.




**Scheme 2.** Ring opening of **5** to β-amino acid derivatives.

Treatment of azetidinone **5** with hydrochloric acid resulted in amino acid **6** with excellent yield. Similarly, amino ester **7** was prepared by acid-catalyzed ethanolysis of **5** (Scheme 2). Our results suggest that a change in the position of the double bond of monoterpene, shifting the methyl group from the neighborhood of the functional groups, yields compounds with normal reactivity, similar to those with a cyclopentane or cyclohexane skeleton. These results differ significantly from those observed on α-pinene-based lactam **4**, where acidic hydrolysis was unsuccessful.

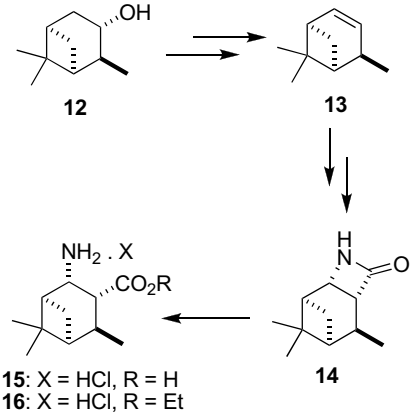
The *N*-Boc β-amino acid was prepared via two alternative pathways. Treatment of β-lactam **5** with di-*tert*-butyl dicarbonate resulted in the *N*-Boc β-lactam **8**, which was readily opened under mild conditions. The reaction of **8** with aqueous LiOH in THF gave *N*-Boc β-amino acid **9** in excellent yield (94%). Compound **9** was also prepared directly from amino acid **6** by Boc protection (Scheme 2).

Under strongly alkaline conditions, the *cis*-amino ester **7** underwent partial isomerization at the carboxylic function, resulting in a *cis*- and *trans*-amino ester mixture, from which **10** was isolated in low yield by chromatography.

Heating the reaction mixture or applying a stronger base than sodium ethoxide (e.g., potassium *tert*-butoxide) led to the decomposition of **7**. The acidic or alkaline hydrolysis of amino ester **10** to the corresponding amino acid **11** failed completely. When highly acidic (5 M hydrochloric acid solution) or alkaline (5 M sodium hydroxide solution) was applied, only the decomposition of ester **10** was observed (Scheme 2).

Since (+)-enantiomer **12** of isopinocampheol **1** is commercially available, we prepared the enantiomeric (−)-*cis*-δ-pinene **13**, β-lactam **14**, amino acid **15**, and amino ester **16** successfully by the methods presented in Schemes 1–3.

The enantiomeric purities of **2**, **5**, **7**, and **14** were measured by GC on a chiral column. Since there was no sign of the presence of any other diastereomer in the NMR spectra




**Scheme 3.** Synthesis of enantiomeric β-amino acid **15**.

of the crude products after the transformations, the high enantiomeric purity of the compounds prepared can be regarded as proven.

## 3. Conclusion

In conclusion, the highly regio- and stereospecific addition of CSI to *cis*-δ-pinene enantiomers resulted in β-lactam enantiomers. β-Lactams **5** and **14** and the corresponding β-amino acids **6** and **15** have similar reactivities to those of cyclopentane and cyclohexane. The lactams and β-amino acids prepared are highly valuable building blocks for the synthesis of bioactive compounds, combinatorial libraries and foldamers with exotic β-amino acid units.

## 4. Experimental

### 4.1. General experimental procedures

$^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer (400 and 68 MHz) in an

appropriate solvent. Chemical shifts are expressed in ppm ($\delta$) relative to TMS as the internal reference. $J$ values are given in Hz. FT-IR spectra were recorded on an AVATAR 330 FT-IR spectrometer (Thermo Nicolet, USA). Microanalyses were determined on a Perkin–Elmer 2400 elemental analyzer.

GC measurements were performed on a Perkin–Elmer Autosystem XL GC, consisting of a flame ionization detector and a Turbochrom Workstation data system (Perkin–Elmer Corporation, Norwalk, USA). The direct separation of enantiomers was carried out on a CHIRASIL-DEX CB column (2500 × 0.25 mm ID) at 60 °C (1 mL/min flow rate) for **2** and **13** and at 140 °C (1 mL/min flow rate) for **5** and **14**. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. Melting points were determined on a Kofler apparatus and are uncorrected. Chlorosulfonyl isocyanate (CSI) and (−)- and (+)-isopinocampheols **1** and **12** were purchased from Aldrich. Diethyl ether was dried over sodium wire, pyridine was dried over molecular sieve, and dichloromethane was distilled over phosphorus pentoxide before use. All the other solvents and reagents were used as received from commercial sources.

X-ray data for **5** have been deposited in Cambridge Crystallographic Data Centre (CCDC 658251).

### 4.2. (1*S*,4*S*,5*R*)-4,6,6-Trimethylbicyclo[3.1.1]hept-2-ene ((1*S*,4*S*,5*R*)-δ-pinene) 2

A 1:1 mixture of (1*S*,4*S*,5*R*)-δ-pinene **2** and (+)-(1*R*,5*R*)-α-pinene **3** (13.6 g, 100.0 mmol), prepared as described by Rykowski et al.,[10] and 7.15 g (50.51 mmol) of CSI was stirred in 300 mL of anhydrous diethyl ether for 1 h. Then 10.2 g of sodium sulfite in 70 mL of water was cautiously added dropwise to the solution. The pH was held at 7–8 by the addition of 20% aqueous potassium hydroxide. After the separation of the organic phase, the aqueous layer was extracted with diethyl ether (2 × 100 mL). The combined organic layer was dried over $Na_2SO_4$ and evaporated at 228 mm Hg and 45 °C. Crystalline compound **4** was isolated by simple filtration, washing of the crystals with *n*-hexane, and by recrystallization from isopropyl ether. All the physical and analytical data on the resulting azetidinone **4** matched exactly those reported in the literature.[6] The mother liquor containing the crude unreacted (1*S*,4*S*,5*R*)-δ-pinene **2** in *n*-hexane solution was filtered through a plug of silica gel, followed by distillation at 760 mm Hg, resulting in a colorless oily product **2**. Isolated compound **2**: 6.23 g (92%, calculated for 50% δ-pinene content of the starting mixture); bp: 156–158 °C (760 mm Hg; lit.:[10] 59–60 °C, 22 mm Hg); $[\alpha]_D^{20} = +66.0$ ($c$ 1.0, MeOH) ee = 95% (lit.[10] = +48.6, neat); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.00 (3H, s); 1.08 (3H, d, $J = 7.6$ Hz); 1.29 (3H, s); 1.30 (1H, d, $J = 8.4$ Hz); 2.00–2.11 (2H, m); 2.45 (1H, dt, $J = 5.7$, 8.5 Hz); 2.59–2.68 (1H, m); 5.53 (1H, d, $J = 8.7$ Hz); 6.06–6.13 (1H, m). $^{13}$C NMR ($CDCl_3$, 68 MHz): $\delta$ 18.4, 23.8, 27.4, 35.2, 37.9, 40.3, 42.1, 48.3, 129.7, 134.4. IR (KBr, cm$^{-1}$): 3363, 2940, 2360, 1366, 1250, 726. Anal. Calcd for $C_{10}H_{16}$ (136.23): C, 88.16; H, 11.84. Found: C, 88.31; H, 11.69.

(1*R*,4*R*,5*S*)-Enantiomer **13** was prepared as described above, starting from a 1:1 mixture of (1*R*,4*R*,5*S*)-δ-pinene **13** and (−)-(1*S*,5*S*)-α-pinene; $[\alpha]_D^{20} = -58.0$ ($c$ 1.0, MeOH) ee = 90% [similar to the ee of the commercial (+)-isopinocampheol]; all the spectroscopic data were similar to those for **2**.

### 4.3. (1*R*,2*R*,5*S*,6*R*,7*R*)-6,8,8-Trimethyl-3-azatricyclo-[5.1.1.0$^{2,5}$]nonan-4-one 5

A mixture of (1*S*,4*S*,5*R*)-δ-pinene **2** (5.0 g, 37 mmol) and CSI (5.24 g, 37 mmol) was stirred and refluxed in 100 mL of anhydrous dichloromethane for 96 h. Anhydrous sodium sulfite (10.2 g, 81 mmol) in 70 mL of water was then cautiously added dropwise to the cooled solution. The pH was held at 7–8 by the addition of 20% aqueous potassium hydroxide. After 2 h stirring at the appropriate pH, the organic phase was separated and the aqueous layer extracted with dichloromethane (2 × 50 mL). The combined organic layer was dried over $Na_2SO_4$ and evaporated. The crude product obtained was purified by flash chromatography on a silica gel column (*n*-hexane/ethyl acetate = 1:1), resulting in a white crystalline product **5**.

Isolated compound **5**: 3.9 g (59%); mp: 115–117 °C (*n*-hexane); $[\alpha]_D^{20} = -85.0$ ($c$ 0.25, EtOH); ee = 99%; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.99 (3H, s); 1.12 (3H, d, $J = 7.5$ Hz); 1.31 (3H, s); 1.35 (1H, d, $J = 10.3$ Hz); 1.83–1.91 (1H, m); 2.12–2.23 (2H, m); 2.45–2.55 (1H, m); 3.05 (1H, dd, $J = 2.7$, 4.9 Hz); 4.02 (1H, t, $J = 4.1$ Hz); 5.50 (1H, br s). $^{13}$C NMR ($CDCl_3$, 68 MHz): $\delta$ 21.8, 21.9, 25.2, 27.8, 33.7, 40.5, 43.0, 48.4, 51.9, 52.8, 173.1. IR (KBr, cm$^{-1}$): 3287, 2952, 2360, 1734, 1698, 1474, 1342. Anal. Calcd for $C_{11}H_{17}NO$ (179.26): C, 73.70; H, 9.56; N, 7.81. Found: C, 73.95; H, 9.34; N, 7.99.

(1*S*,2*S*,5*R*,6*S*,7*S*)-Enantiomer **14** was prepared as described above, starting from (1*R*,4*R*,5*S*)-δ-pinene **13**; $[\alpha]_D^{20} = +76.0$ ($c$ 0.25, EtOH; ee = 90%); the spectroscopic data and mp were similar to those for **5**. Analysis found: C, 73.98; H, 9.79; N, 7.59.

### 4.4. (1*R*,2*R*,3*S*,4*R*,5*R*)-2-Amino-4,6,6-trimethylbicyclo-[3.1.1]heptane-3-carboxylic acid hydrochloride 6

Azetidinone **5** (0.70 g, 3.9 mmol) was stirred in a solution of 15 mL of 15% hydrochloric acid at room temperature. When the mixture became clear (approximately 1 h), the solution was evaporated to dryness and the resulting white crystalline product **6** was filtered off and washed with acetone. Isolated compound **6**: 0.83 (91%); mp: 185–187 °C; $[\alpha]_D^{20} = -23.0$ ($c$ 0.25, EtOH); $^1$H NMR ($D_2O$ 400 MHz): $\delta$ 0.99 (3H, s); 1.07 (3H, d, $J = 7.1$ Hz); 1.24 (3H, s); 1.28 (1H, d, $J = 10.1$ Hz); 1.82 (3H, t, $J = 5.0$ Hz); 2.18–2.30 (3H, m); 3.05 (1H, t, $J = 9.1$ Hz); 3.82 (1H, d, $J = 9.1$ Hz); 8.05 (1H, br s), 12.94 (1H, br s). $^{13}$C NMR ($D_2O$, 68 MHz): $\delta$ 21.1, 22.1, 27.5, 27.6, 38.5, 38.8, 43.8, 44.5, 46.1, 49.1, 174.2. IR (KBr, cm$^{-1}$): 3216, 2915, 1705, 1519, 1373, 1197; Anal. Calcd for $C_{11}H_{20}ClNO_2$ (233.74): C, 56.52; H, 8.62; N, 5.99. Found: C, 56.79; H, 8.91; N, 5.67.

(1*S*,2*S*,3*R*,4*S*,5*S*)-Enantiomer **15** was prepared as described above, starting from (1*S*,2*S*,5*R*,6*S*,7*S*)-lactam **14**; $[\alpha]_D^{20} = +18.0$ (*c* 0.25, EtOH); the spectroscopic data and mp were similar to those for **6**. Analysis found: C, 56.81; H, 8.53; N, 6.24.

### 4.5. Ethyl (1*R*,2*R*,3*S*,4*R*,5*R*)-2-amino-4,6,6-trimethylbicyclo[3.1.1]heptane-3-carboxylate 7

Azetidinone **5** (1.20 g, 6.7 mmol) was dissolved in 80 mL of ethanol containing 10% dry hydrogen chloride. After stirring for 1 h at room temperature, the mixture was evaporated to dryness in vacuo. The residue was dissolved in water (30 mL), basified with cold saturated sodium hydrogencarbonate and extracted with chloroform (3 × 50 mL). The combined organic phase was dried over $Na_2SO_4$, filtered and evaporated. The oily residue obtained was purified by flash chromatography on a silica gel column (toluene/ethanol = 9:1). Isolated compound **7**: 1.30 g (86%) oil; $[\alpha]_D^{20} = -30$ (*c* 0.25, EtOH); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.99 (3H, d, $J = 8.1$ Hz); 1.02 (3H, s); 1.16 (1H, d, $J = 10.1$ Hz); 1.26 (3H, s); 3.31 (3H, t, $J = 7.1$ Hz); 1.43 (2H, br s); 1.82 (1H, t, $J = 6.0$ Hz); 2.21 (1H, dt, $J = 6.0$, 10.1 Hz); 2.49–2.59 (1H, m), 2.96 (1H, t, $J = 8.5$ Hz); 3.62–3.70 (1H, m); 4.21 (2H, dd, $J = 7.1$, 14.1 Hz). $^{13}$C NMR ($CDCl_3$, 68 MHz): $\delta$ 14.4, 21.7, 22.2, 28.1, 28.2, 37.2, 39.4, 47.0, 49.7, 49.9, 50.6, 60.2, 174.9. IR (KBr, cm$^{-1}$): 2904, 1732, 1470, 1375, 1181, 1037. Anal. Calcd for $C_{13}H_{23}NO_2$ (225.33): C, 69.29; H, 10.29; N, 6.22. Found: C, 69.51; H, 10.15; N, 6.53.

(1*S*,2*S*,3*R*,4*S*,5*S*)-Enantiomer **16** was prepared as described above, starting from (1*S*,2*S*,5*R*,6*S*,7*S*)-lactam **14**; $[\alpha]_D^{20} = +22.0$ (*c* 0.25, EtOH); the spectroscopic data and mp were similar to those for **7**. Analysis found: C, 69.30; H, 10.03; N, 6.41.

### 4.6. (1*R*,2*R*,5*S*,6*R*,7*R*)-*N*-*tert*-Butoxycarbonyl-6,8,8-trimethyl-3-azatricyclo[5.1.1.0$^{2,5}$]nonan-4-one 8

To a stirred solution of azetidinone **5** (0.50 g, 2.8 mmol) and dry THF (14 mL), triethylamine (0.56 g, 5.5 mmol), di-*tert*-butyl dicarbonate (0.79 g, 3.6 mmol) and 10 mg of 4-dimethylaminopyridine were added. After stirring for 12 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/ethyl acetate = 4:1), resulting in a white crystalline product **8**. Isolated compound **8**: 0.48 g (61%): mp: 75–77 °C (*n*-hexane); $[\alpha]_D^{20} = -83$ (*c* 0.25, EtOH); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.99 (3H, s); 1.13 (3H, d, $J = 7.5$ Hz); 1.21 (1H, d, $J = 11.4$ Hz); 1.31 (3H, s); 1.50 (9H, s); 1.51–1.55 (1H, m); 1.86–1.91 (1H, m); 2.20–2.28 (1H, m); 2.47–2.55 (2H, m); 3.05 (1H, dd, $J = 2.7$, 6.0 Hz); 4.29 (1H, dd, $J = 3.8$, 5.6 Hz). $^{13}$C NMR ($CDCl_3$, 68 MHz): $\delta$ 21.7, 22.1, 25.6, 27.6, 28.1, 34.2, 39.7, 41.3, 48.2, 51.4, 55.2, 82.7, 148.0, 169.3; IR (KBr, cm$^{-1}$): 3310, 2925, 1743, 1665, 1407, 1181, 1055. Anal. Calcd for $C_{13}H_{23}NO_2$ (279.37): C, 69.29; H, 10.29; N, 6.22. Found: C, 69.45; H, 10.15; N, 6.51.

### 4.7. (1*R*,2*R*,3*S*,4*R*,5*R*)-2-*tert*-Butoxycarbonylamino-4,6,6-trimethylbicyclo[3.1.1]heptane-3-carboxylic acid 9

*Method A*: Amino acid hydrochloride **6** (0.30 g, 1.3 mmol) was dissolved in distilled water (5 mL) at 0 °C and the pH of the solution was adjusted to 8 with 3% sodium hydroxide solution in the presence of bromothymol blue indicator. Dioxane (5 mL) and di-*tert*-butyl dicarbonate (0.31 g, 1.4 mmol) were then added to the mixture. The reaction mixture was stirred at room temperature, with pH 8 being maintained with 3% sodium hydroxide solution. After stirring for 6 h at room temperature, the solution was cooled to 0 °C and acidified with 5% aqueous hydrochloric acid to pH 5, and the solution was then extracted with chloroform (3 × 30 mL). The combined organic layer was dried ($Na_2SO_4$) and evaporated, and the oily product obtained was purified by flash chromatography on a silica gel column (*n*-hexane/ethyl acetate = 4:1), resulting in compound **9**. In $CDCl_3$, $^1$H NMR and NOESY measurements showed the presence of two rotamers in a ratio of 73:27. Isolated compound **9**: 0.38 g (94%); mp: 121–123 °C; $[\alpha]_D^{20} = -7$ (*c* 0.25, EtOH); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.98 (3H, d, $J = 7.2$ Hz, major + minor rotamers); 1.03 (3H, s, major + minor rotamers); 1.25 (3H, s, major + minor rotamers); 1.28 (1H, d, $J = 10.6$ Hz, major + minor rotamers); 1.42 (9H, s, minor); 1.45 (9H, s, major); 1.78–1.88 (1H, m, major + minor rotamers); 1.95–2.08 (1H, m, major + minor rotamers); 2.22–2.32 (1H, m, major + minor rotamers); 2.46–2.51 (1H, m, minor); 2.61–2.72 (1H, m, major); 2.98 (1H, dd, $J = 7.5$, 10.1 Hz, major); 3.10–3.19 (1H, m, minor); 4.45 (1H, t, $J = 10.0$ Hz, major); 4.58 (1H, t, $J = 8.4$ Hz, minor); 5.30 (1H, br s, minor), 7.23 (1H, br s, major). $^{13}$C NMR ($CDCl_3$, 68 MHz): $\delta$ 21.6, 22.4, 27.7, 28.1, 28.3, 28.4, 29.7, 36.0, 38.9, 46.2, 46.4, 47.0, 47.3, 47.8, 48.9, 50.5, 80.8, 157.7, 177.5. IR (KBr, cm$^{-1}$): 3313, 2915, 1713, 1659, 1405, 1174, 1051. Anal. Calcd for $C_{16}H_{27}NO_4$ (297.39): C, 64.62; H, 9.15; N, 4.71. Found: C, 64.79; H, 9.37; N, 4.49.

*Method B*: *N*-Boc lactam **8** (0.30 g, 1.3 mmol) was dissolved in THF (8 mL) and treated with LiOH (0.18 g in 3 mL of water) at room temperature. The mixture was stirred at room temperature for 7 h. The THF was removed in vacuo, water (10 mL) was added, and the solution was acidified to pH 3.5–4.0 with acetic acid and extracted with ethyl acetate (3 × 30 mL). The combined organic phase was dried over $Na_2SO_4$, and evaporated to give a colorless viscous oil, which was purified by flash chromatography on a silica gel column (*n*-hexane/ethyl acetate = 4:1), resulting in compound **9**, 0.37 g (91%).

### 4.8. Ethyl (1*R*,2*R*,3*R*,4*R*,5*R*)-2-amino-4,6,6-trimethylbicyclo[3.1.1]heptane-3-carboxylate 10

To a solution of sodium (0.23 g, 10 mmol) in 30 mL of dry ethanol, (1*R*,2*R*,3*S*,4*R*,5*R*)-aminoester **7** (1.13 g, 5 mmol) was added in one portion. The solution was stirred at room temperature for 3 days (the isomerization process was monitored by means of TLC and GC). The solution was next evaporated to approximately 5 mL, diluted with ice-cold water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was dried over

$Na_2SO_4$ and evaporated. The oily residue obtained was purified by flash chromatography on a silica gel column (toluene/ethanol = 9:1). Isolated compound **10**: 0.38 g (30%) oil; $[\alpha]_D^{20} = -17$ (*c* 0.25, EtOH); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.99 (3H, d, $J = 8.1$ Hz); 1.02 (3H, s); 1.22 (3H, s); 1.25–1.29 (1H, m); 1.30 (3H, t, $J = 7.1$ Hz); 1.49 (2H, br s); 1.80 (1H, t, $J = 5.0$ Hz); 1.92–1.99 (1H, m); 2.13–2.20 (1H, m); 2.57–2.67 (1H, m); 2.76 (1H, dd, $J = 7.1$, 11.1 Hz); 3.73–3.77 (1H, m); 4.20 (2H, dd, $J = 7.1$, 14.1 Hz). $^{13}$C NMR ($CDCl_3$, 68 MHz): $\delta$ 14.2, 16.7, 22.0, 25.4, 28.0, 29.5, 34.6, 48.0, 48.5, 49.3, 50.8, 60.1, 174.5. IR (KBr, $cm^{-1}$): 2925, 1732, 1470, 1375, 1253, 1181; Anal. Calcd for $C_{13}H_{23}NO_2$ (225.33): C, 69.29; H, 10.29; N, 6.22. Found: C, 69.56; H, 10.01; N, 6.65.

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