Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 625–632

TETRAHEDRON: *ASYMMETRY*

Synthesis of enantiopure analogues of 3-hydroxyproline and derivatives

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Received 16 March 2002; accepted 25 March 2002

Abstract—All four enantiomerically pure 2-hydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylic acids, novel restricted analogues of 3-hydroxyproline, are described. The synthesis starts with the Diels–Alder reaction between methyl 2-benzamidoacrylate and Danishefsky's diene and uses as key steps a base-promoted internal nucleophilic displacement of the methanesulfonate group in the cyclohexane ring, followed by a resolution method that involves formation of diastereomers and further separation by crystallization. This synthetic route allowed us to obtain both enantiomers of the *N*-Boc-7-azabicyclo[2.2.1]heptan-2-ones, valuable ketones used as precursors of (−)- and (+)-epibatidine and other more interesting analogues. © 2002 Published by Elsevier Science Ltd.

1. Introduction

In recent years the synthesis and incorporation into peptides of conformationally constrained amino acids has become extremely important, since it represents a great advance in the creation of peptides with valuable physical properties and biological activity.[1–4] Proline has an enormous impact on the conformation of peptides owing to its ability to form *trans* as well as *cis* amide bonds, thus allowing the formation of turn structures. As a consequence, analogues of natural proline have attracted significant attention. For instance, the synthesis of hydroxyprolines[5–12] has been a matter of interest in order to incorporate such units into peptides, since this leads to enhanced stability of the collagen triple helix by hydrogen bonds between the hydroxyl group and the peptide backbone. The stability of the collagen helix depends strongly on the percentage of prolines and hydroxyprolines present. Moreover, 4-hydroxyproline is a common component in collagenous protein, although its isomer 3-hydroxyproline is a rare β-hydroxy-α-amino acid that has been found as a minor constituent in some proteins and both isomers, i.e. *cis* and *trans* are elements of the antibiotic teleomycin.[13–16]

On the other hand, 7-azabicyclo[2.2.1]heptane-1-carboxylic acid derivatives as proline analogues constitute a source of interesting compounds that include a novel class of HIV-1 protease inhibitor[17] and the boroarginine thrombin inhibitor.[18] Hence, the incorporation of a hydroxyl group in a predetermined position of these systems opens the way to new families of products of potential interest. In the main, three research groups (those of Rapoport, Avenoza and Cativiela) have developed the design of restricted amino acid analogues of proline that contain the 7-azabicyclo[2.2.1]heptane skeleton. For example, Rapoport and co-workers have synthesized *N*-protected 2- and 3-oxo-7-azabicyclo [2.2.1]heptane carboxylic esters **1**[19] and **2**[20] (interesting building blocks to obtain strained amino acids and precursors of epibatidine) and amino acid **3**,[20] starting from L-serine and L-glutamic acids and involving C–C bond formation onto the pyrrolidine ring as a key step. On the other hand, our groups have explored a synthetic route based on internal nucleophilic displacement, by an amide group, of a leaving group in a six-membered ring. The ring was created by a Diels–Alder reaction between α,β-didehydro-α-amino acid derivatives and Danishefsky's diene. In this way, compounds **2** and related derivatives[21,22] (starting materials in the synthesis of *cis*- and *trans*-4-hydroxyproline analogues) have been synthesized in racemic and enantiopure forms. Moreover, compounds **3**,[23] **4**,[24] **5**[25] and **6**[26]

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PII: S0957-4166(02)00158-1

have been obtained in good yields. Our present goal is to obtain the building block **1** as a starting material in the synthesis of new 'chimeras,' combinations of constrained proline and serine, or strained 3-hydroxyprolines (Fig. 1).

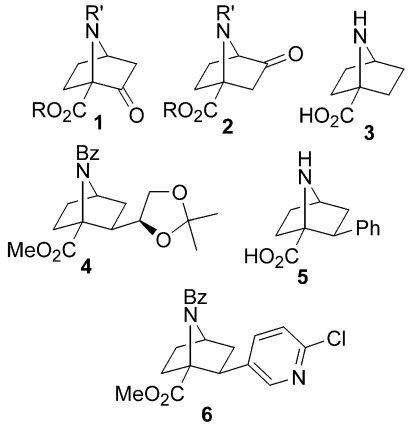
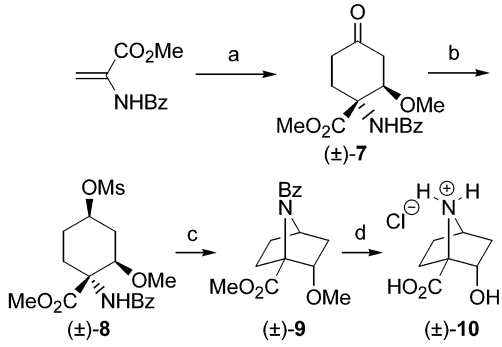


Figure 1. 7-Azabicyclo[2.2.1]heptane-1-carboxylic acid derivatives.

2. Results and discussion

2.1. Synthesis of 2-hydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylic acid hydrochloride (±)-10

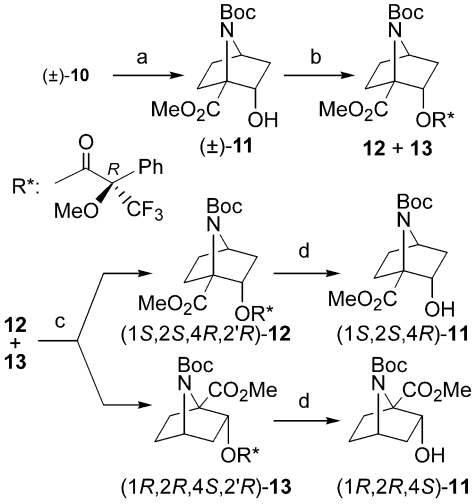
The starting material for our study was the *trans*-methoxycyclohexanone (±)-**7**, which was obtained by Diels–Alder reaction between methyl 2-benzamidoacrylate and Danishefsky's diene.[27] We have improved the yield of this reaction to 70% by using hydroquinone as a polymerization inhibitor and a 1:1 diene/dienophile ratio. Reduction of ketone (±)-**7** with L-Selectride® at −78°C in THF quantitatively gave the *trans* alcohol. Treatment of this alcohol with methanesulfonyl chloride in triethylamine (TEA) provided the corresponding methanosulfonate derivative (±)-**8**, which was used in the next reaction without further purification. Base-promoted internal nucleophilic displacement of the methanesulfonate group using ^{t}BuOK in THF, thereby yielding the 7-azabicyclo[2.2.1]heptane system of the constrained proline analogue, gave the desired compound (±)-**9** in high yield. The racemic hydrochloride amino acid (±)-**10** was obtained in a 95% yield by hydrolysis of compound (±)-**9** (Scheme 1).



Scheme 1. (a) Ref. 23; (b) (i) L-Selectride®, THF, −78°C, 100%; (ii) MsCl, TEA, CH_2Cl_2, 35°C; (c) ^{t}BuOK, THF, −78°C, 76% two steps; (d) 12N HCl, 120°C, 95%.

2.2. Synthesis of methyl *N*-Boc-2-hydroxy-7-azabicyclo-[2.2.1]heptane-1-carboxylates (1*S*,2*S*,4*R*)-11 and (1*R*,2*R*,4*S*)-11

Esterification of (±)-**10** with acetyl chloride in MeOH and subsequent protection of the amine group with $(Boc)_2O$ in the presence of $Na_2CO_3{\cdot}10H_2O$ gave the protected alcohol (±)-**11**, which could be separated by resolution methods. The strategy used to resolve the racemic protected amino acid involved the reaction of (±)-**11** with (*R*)-(+)-methoxytrifluorophenylacetic acid [(*R*)-(+)-MTPA] in the presence of DCC and DMAP to give (1*S*,2*S*,4*R*,2′*R*)-**12** and (1*R*,2*R*,4*S*,2′*R*)-**13** as a diastereoisomeric mixture in 95% yield. These diastereoisomers were easily separated by crystallization, using octane as the solvent, to give crystals of the pure isomer (1*S*,2*S*,4*R*,2′*R*)-**12**. The purity of this material was determined by ^{19}F NMR (>95%). The filtrate was chromatographed to give the diastereoisomer (1*R*,2*R*,4*S*,2′*R*)-**13** and the purity of this compound was also determined by ^{19}F NMR (>95%). Hydrolysis of the chiral ester was achieved in MeONa/MeOH and gave enantiomerically pure isomers (1*S*,2*S*,4*R*)-**11** and (1*R*,2*R*,4*S*)-**11** (Scheme 2).



Scheme 2. (a) (i) AcCl, MeOH, 60°C, (ii) $(Boc)_2O$, $Na_2CO_3{\cdot}10H_2O$, THF/H_2O, rt 80%; (b) (*R*)-(+)-MTPA, DCC, DMAP, CH_2Cl_2, rt 95%; (c) separation by crystallization from octane; (d) MeONa, MeOH, rt, 87%.

2.3. Synthesis and determination of the absolute configurations of *N*-Boc-7-azabicyclo[2.2.1]heptan-2-ones (1*S*,4*R*)-16 and (1*R*,4*S*)-16

Single crystals of the diastereoisomers (1*S*,2*S*,4*R*,2′*R*)-**12** and (1*R*,2*R*,4*S*,2′*R*)-**13** could not be obtained and so we developed a route to identify the absolute configurations of the new enantiomers. Our proposal was to derivatize the alcohols (1*S*,2*S*,4*R*)-**11** and (1*R*,2*R*,4*S*)-**11** to obtain known chiral compounds. In this context, and taking into account the significance of *N*-Boc-7-azabicyclo[2.2.1]heptan-2-ones (1*S*,4*R*)- and (1*R*,4*S*)-**16** as precursors of (−)- and (+)-epibatidine and related analogues, we decided to undertake their synthesis.[28–30]

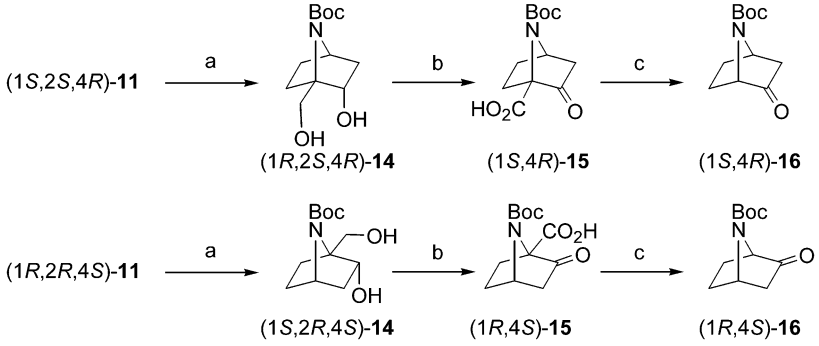
We attempted the cleavage of the methoxycarbonyl group of the azabicyclo[2.2.1]heptane system. The acid (1*S*,4*R*)-**15** was obtained from diol (1*R*,2*S*,4*R*)-**14** by oxidation using Jones' reagent. This diol was in turn obtained from alcohol (1*S*,2*S*,4*R*)-**11** by treatment with $NaBH_4/CaCl_2$ in THF/EtOH. The decarboxylation of (1*S*,4*R*)-**15** was carried out by formation of the acid chloride and subsequent coupling with *N*-hydroxy-2-thiopyridone. This compound was photolyzed in the presence of tributyltin hydride to give ketone (1*S*,4*R*)-**16** in 50% yield from (1*S*,4*R*)-**15**. The specific rotation of (1*S*,4*R*)-**16** was identical to that described in the literature[22] {$[\alpha]_D^{25}$ (*c* 1.03, $CHCl_3$) = +75.5}. The same procedure, starting from the alcohol (1*R*,2*R*,4*S*)-**11**, was followed to give the ketone (1*R*,4*S*)-**16** (Scheme 3).

These transformations constitute a formal synthesis of (−)- and (+)-epibatidine. In addition, and more importantly, taking into account that the activity of epibatidine is accompanied by high toxicity,[31] *N*-Boc-7-azabicyclo[2.2.1]heptan-2-ones (1*S*,4*R*)-**16** and (1*R*,4*S*)-**16** can also be considered as potential building blocks for the preparation of other analogues of epibatidine.

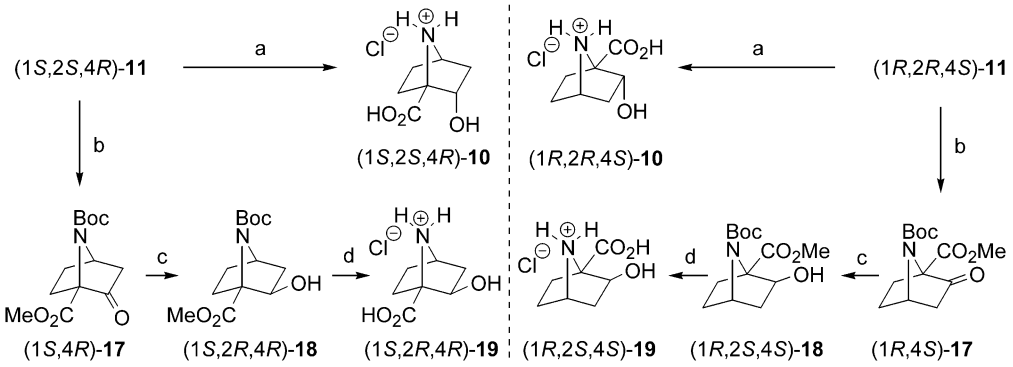
2.4. Synthesis of all four 2-hydroxy-7-azabicyclo[2.2.1]-heptane-1-carboxylic acids (1*S*,2*S*,4*R*)-10, (1*R*,2*R*,4*S*)-10, (1*S*,2*R*,4*R*)-19 and (1*R*,2*S*,4*S*)-19

Acid hydrolysis of the methyl ester and *N*-Boc groups in the compound (1*S*,2*S*,4*R*)-**11** quantitatively gave the required amino acid hydrochloride (1*S*,2*S*,4*R*)-**10**, in which the alcohol group is in the *endo* disposition. In order to obtain the alcohol in the *exo* disposition, we synthesized the enantiopure protected ketone (1*S*,4*R*)-**17** by treatment with Dess–Martin reagent in dichloromethane. This compound is an excellent building block for analogues of α-amino acids through further functionalization. Rapoport and Hart obtained the same building block, **1**, with other protective groups (*N*-Cbz and *tert*-butyl ester) in only 4% yield from L-serine, whereas our route gives an improved yield of 13% for the enantiopure (1*S*,4*R*)-**17** (from D,L-serine) (Scheme 4).

Reduction of the ketone (1*S*,4*R*)-**17** with sodium borohydride in the presence of $CeCl_3 \cdot 7H_2O$ at rt gave a mixture of *endo*/*exo* alcohols in a 7:3 ratio in favour of the *endo* compound (1*S*,2*S*,4*R*)-**11**. Surprisingly, the use of L-Selectride® at −78°C gave only the alcohol



Scheme 3. (a) $NaBH_4$, $CaCl_2$, THF/EtOH, 0°C to rt, 99%; (b) Jones' reagent, acetone, 0°C to rt, 90%; (c) (i) $(COCl)_2$, DMF, dichloroethane, rt, (ii) *N*-hydroxy-2-thiopyridone, TEA, THF, 0°C to rt, (iii) Bu_3SnH, hν, THF, 50% three steps.



Scheme 4. (a) 6N HCl, 60°C, 100%; (b) Dess–Martin reagent, CH_2Cl_2, rt, 89%; (c) L-Selectride®, THF, −78°C, 76%; (g) 6N HCl, 85°C, 100%.

(1*S*,2*R*,4*R*)-**18** with the hydroxy group in the *exo* disposition. Generally, reductions of similar substrates with L-Selectride® give *endo* isomers[28] and we believe that the influence of the methyl ester group in position 1 is critical to this selectivity. Hydrolysis of the alcohol (1*S*,2*R*,4*R*)-**18** led to the synthesis of the amino acid hydrochloride (1*S*,2*R*,4*R*)-**19**, which possesses the hydroxy group in the *exo* disposition (Scheme 4).

An identical procedure was used to obtain the corresponding enantiomers (1*R*,2*R*,4*S*)-**10** and (1*R*,2*S*,4*S*)-**19** from alcohol (1*R*,2*R*,4*S*)-**11**. The specific rotations measured for these compounds were in agreement with the isomers previously synthesized, but with opposite signs (Scheme 4).

3. Conclusions

In conclusion, we have developed a versatile route to synthesize, for the first time to the best of our knowledge, all four conformationally constrained analogues of 3-hydroxyproline that incorporate the 7-azabicyclo [2.2.1]heptane skeleton: (1*S*,2*S*,4*R*)-**10**, (1*R*,2*R*,4*S*)-**10**, (1*S*,2*R*,4*R*)-**19** and (1*R*,2*S*,4*S*)-**19**. Moreover, we have improved the yield in the synthesis of building block **1**, reported earlier by Rapoport, and obtained compounds (1*S*,4*R*)-**17** and (1*R*,4*S*)-**17**. This synthetic route also allows both enantiomers of the *N*-Boc-7-azabicyclo-[2.2.1]heptan-2-ones (1*S*,4*R*)-**16** and (1*R*,4*S*)-**16** to be obtained, and these are valuable building blocks for the synthesis of epibatidine analogues.

4. Experimental

4.1. General procedures

Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using silica gel 60 (230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard and in D_2O with TMS as the external standard using a coaxial microtube (chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). The assignment of all separate signals in the ^{1}H NMR spectra was made on the basis of coupling constants, selective proton–proton homonuclear decoupling experiments, proton–proton COSY experiments and proton–carbon HETCOR experiments. Melting points were determined on a Büchi SMP-20 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 341 polarimeter in 1.0 and 0.5 dm cells of 1.0 and 3.4 mL capacity, respectively. Microanalyses were carried out on a CE Instruments EA-1110 analyser and are in good agreement with the calculated values. IR spectra were recorded on a Perkin–Elmer FT-IR spectrum 1000 spectrophotometer.

4.1.1. Methyl 1-benzamido-*c*-4-methanesulfonyloxy-*c*-2-methoxycyclohexane-*r*-1-carboxylate (±)-8. Compound (±)-**7** (2.49 g, 8.16 mmol) was dissolved in dry THF (100 mL) and L-Selectride® (14.7 mL of a 1 M solution in THF, 14.7 mmol) was added dropwise at −78°C under an inert atmosphere. After 4 h stirring at the same temperature, the reaction was quenched by the addition of saturated aqueous NH_4Cl (50 mL). The resulting mixture was allowed to warm up to rt and washed with EtOAc (5×100 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue that was chromatographed on silica gel, eluting with EtOAc, to give 2.51 g of the *trans* alcohol as a white solid (100%). The alcohol was dissolved in dry CH_2Cl_2 (80 mL) under an inert atmosphere and TEA (2.84 mL, 20.4 mmol) and methanesulfonyl chloride (0.95 mL, 12.2 mmol) were added to the solution at 0°C. The solution was stirred at 35°C overnight. The mixture was washed with water (2×50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine. The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. After evaporation of the solvent, the residue (3.02 g) was used in the next reaction without further purification. In order to characterize the mesylate, a small portion of the residue was chromatographed on a silica gel column, eluting with hexane/EtOAc (1:9), to give compound (±)-**8**. Mp: 142°C. Anal. calcd for $C_{17}H_{23}NO_7S$; C, 52.97; H, 6.01; N, 3.63; S, 8.32. Found C, 52.78; H, 6.15; N, 3.81; S, 8.24%. IR (CH_2Cl_2, cm^{-1}): 3411 (NH); 1732 (COO); 1662 (CON). ^{1}H NMR ($CDCl_3$): δ 2.03–2.25 (m, 4H); 2.43–2.49 (m, 1H); 2.63–2.68 (m, 1H); 3.05 (s, 3H, CH_3SO_2); 3.35 (s, 3H, CH_3O); 3.86 (s, 3H, CH_3OCO); 4.32 (dd, 1H, $J_{a-e}=4.8$ Hz, $J_{a-a}=10.8$ Hz, H_2); 4.80–4.90 (m, 1H, H_4); 7.31 (br s, 1H, NH); 7.41–7.52 (m, 3H, arom), 7.75–7.80 (m, 2H, arom). ^{13}C NMR ($CDCl_3$): δ 26.4, 28.5, 33.0 (C_3, C_5, C_6); 38.6 (CH_3SO_2); 53.1 (CH_3OCO); 58.3 (CH_3O); 63.3 (C_1); 77.1 (C_2, C_4); 126.9, 128.7, 131.8, 134.6 (arom); 166.9; 172.1 (COO, CON).

4.1.2. Methyl *N*-benzoyl-7-azabicyclo[2.2.1]heptane-*endo*-2-methoxy-1-carboxylate (±)-9. To a solution of (±)-**8** (3.14 g, 8.16 mmol) in dry THF (100 mL) was added a 1 M solution of ^{t}BuOK in THF (9.8 mL, 9.8 mmol) under an inert atmosphere at −78°C. After stirring for 15 min at −78°C, the reaction was warmed up to rt and stirred at this temperature for 20 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (15 mL) and stirred for 15 min. The THF was evaporated and the resulting mixture was extracted with EtOAc (4×100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to give a residue, which was purified by silica gel column chromatography, eluting with hexane/EtOAc (1:1), to give (±)-**9** (1.80 g, 76% from ketone (±)-**7**) as a colorless oil. Anal. calcd for $C_{16}H_{19}NO_4$; C, 66.42; H, 6.62; N, 4.84. Found C, 66.32; H, 6.79; N, 4.77%. IR (CH_2Cl_2, cm^{-1}): 1737 (CO), 1648 (CON). ^{1}H NMR ($CDCl_3$): δ 1.30 (dd, 1H, $J_{3n-2x}=12.6$ Hz, $J_{3n-3x}=30$ Hz, H_{3n}); 1.61–1.78 (m, 2H, H_{5x}, H_{5n}); 2.24–2.29 (m, 1H, H_{6n}); 2.30–2.60 (m, 2H, H_{3x}, H_{6x}); 3.34 (s, 3H, CH_3O); 3.84 (s, 3H, CH_3OCO); 4.15–4.22 (m, 1H, H_4); 4.31–4.38 (m, 1H, H_{2x}); 7.36–7.50 (m, 3H, arom); 7.61–7.66 (m, 2H, arom). ^{13}C NMR ($CDCl_3$): δ 2.22 (C_6); 30.8 (C_5); 37.8 (C_3); 52.6 (CH_3OCO); 58.0 (CH_3O); 62.1 (C_4); 70.2 (C_1); 82.8 (C_2); 128.4, 128.6, 131.6, 134.0 (arom); 171.2, 172.3 (COO, CON).

4.1.3. *endo*-2-Hydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylic acid hydrochloride (±)-10. Compound (±)-**9** (614 mg, 2.12 mmol) was suspended in 12N HCl (25 mL) and the mixture was heated at 120°C for 7 days. The solvent was evaporated in vacuo, the residue was dissolved in water, washed with diethyl ether (3×10 mL) and the aqueous layer was evaporated to give 390 mg of the amino acid hydrochloride (±)-**10** (95%). Anal. calcd for $C_7H_{12}ClNO_3$: C, 43.42; H, 6.25; N, 7.23. Found: C, 43.58; H, 6.32; N, 7.38%. ^{1}H NMR (D_2O): δ 1.48 (dd, 1H, $J_{3n-2x}=14.1$ Hz, $J_{3n-3x}=3.6$ Hz, H_{3n}); 1.80–2.15 (m, 3H); 2.40–2.50 (m, 1H, H_{3x}); 2.55–2.65 (m, 1H); 4.13 ('t', 1H, $J_{4-3x}=J_{4-5x}=5.1$ Hz, H_4); 4.53–4.60 (m, 1H, H_2). ^{13}C NMR (D_2O): δ 24.3, 29.8, 38.6 (C_3, C_5, C_6); 61.3 (C_4); 72.7 (C_2); 76.2 (C_1); 173.6 (COO).

4.1.4. Methyl *N*-(*tert*-butoxycarbonyl)-*endo*-2-hydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylate (±)-11. Acetyl chloride (0.57 mL, 8.1 mmol) was added dropwise to MeOH (30 mL) at 0°C. The mixture was stirred for 10 min and the amino acid hydrochloride (±)-**10** (521 mg, 2.7 mmol) was added. The resulting solution was stirred at 60°C for 12 h. The solvent was removed, the residual oil suspended in diethyl ether (20 mL) and the solvent was evaporated again. This process was repeated twice more and the corresponding pure methyl ester hydrochloride was obtained as a solid (560 mg, 100%). ^{1}H NMR (D_2O): δ 1.55 (dd, 1H, $J_{3n-3x}=14.1$ Hz, $J_{3n-2x}=3.6$ Hz, H_{3n}); 1.90–2.20 (m, 3H); 2.45–2.55 (m, 1H, H_{3x}); 2.60–2.73 (m, 1H); 3.84 (s, 3H, CH_3OCO); 4.23 ('t', 1H, $J_{4-3x}=J_{4-5x}=5.1$ Hz, H_4); 4.63 (ddd, 1H, $J_{2x-3x}=10.5$ Hz, $J_{2x-3n}=3.6$ Hz, $J_{2x-6x}=1.8$ Hz, H_{2x}). ^{13}C NMR (D_2O): δ 24.5, 29.9 (C_5, C_6); 38.7 (C_3); 56.4 (CH_3OCO); 61.7 (C_4); 72.8 (C_2); 76.0 (C_1); 171.9 (COO). The hydrochloride (380 mg, 1.8 mmol) was dissolved in water (10 mL) and $Na_2CO_3{\cdot}10H_2O$ (1.06 g, 3.7 mmol) was added. A solution of $(Boc)_2O$ (524 mg, 2.4 mmol) in THF (40 mL) was added to the mixture. The mixture was vigorously stirred at rt for 15 h, saturated aqueous NaCl (40 mL) was added and the resulting mixture was extracted with EtOAc (4×40 mL). The organic layer was dried, filtered and evaporated to give a residue, which was purified by column chromatography, eluting with hexane/EtOAc (1:1), to give (±)-**11** (400 mg, 80%) as a white solid. Mp: 95°C. Anal. calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.47; H, 7.70; N, 5.22%. IR (CH_2Cl_2, cm^{-1}) 3591 (OH); 1734 (COO); 1700 (CON). ^{1}H NMR ($CDCl_3$): δ 1.26 (dd, 1H, $J_{3n-3x}=12.9$ Hz, $J_{3n-2x}=3.9$ Hz, H_{3n}); 1.41 (s, 9H, $C(CH_3)_3$); 1.56–1.64 (m, 1H, H_5); 1.93–2.00 (m, 2H, H_5, H_6); 2.27–2.35 (m, 1H, H_{3x}); 2.45–2.55 (m, 1H, H_6); 3.82 (s, 3H, CH_3OCO); 4.21 ('t', 1H, $J_{4-3x}=J_{4-5x}=5.1$ Hz, H_4); 4.59 (ddd, 1H, $J_{2x-3x}=10.5$ Hz, $J_{2x-3n}=3.9$ Hz, $J_{2x-6x}=1.5$ Hz, H_{2x}). ^{13}C NMR ($CDCl_3$): δ 25.8 (C_6); 28.1 ($C(CH_3)_3$); 29.6 (C_5); 37.7 (C_3); 52.5 (CH_3OCO); 59.9 (C_4); 71.3 ($C(CH_3)_3$); 73.0 (C_2); 81.1 (C_1); 156.4 ($COOC(CH_3)_3$); 171.8 ($COOCH_3$).

4.1.5. Methyl *N*-(*tert*-butoxycarbonyl)-2-[2′-methoxy-2′-(trifluoromethyl)phenylacetyloxy] - 7 - azabicyclo[2.2.1]-heptane-1-carboxylates (1*S*,2*S*,4*R*,2′*R*)-12 and (1*R*,2*R*,4*S*,2′*R*)-13. To a solution of alcohol (±)-**11** (410 mg, 1.51 mmol), DCC (373 mg, 1.81 mmol) and DMAP (9 mg, 0.07 mmol) in dry CH_2Cl_2 (10 mL) at 0°C was slowly added a solution of (*R*)-(+)-MTPA (424 mg, 1.81 mmol) in dry CH_2Cl_2 (10 mL). The mixture was stirred at 0°C for 1 h and the reaction was warmed to rt and stirred at this temperature for 18 h. The resulting white suspension was filtered to remove the *N*,*N*′-dicyclohexylurea. The filtrate was concentrated in vacuo to give a white slurry and diethyl ether was added. The resulting suspension was filtered to remove the *N*-acyl-*N*′-cyclohexylurea and the solvent was evaporated. The residue was purified by column chromatography, eluting with hexane/EtOAc (7:3), to give the mixture of (1*S*,2*S*,4*R*,2′*R*)-**12** and (1*R*,2*R*,4*S*,2′*R*)-**13** as a colorless oil (700 mg, 95%). The diastereoisomers were separated by crystallization from octane to give (1*S*,2*S*,4*R*,2′*R*)-**12** (331 mg, 45%) as a white solid of high purity. The mother liquor containing (1*R*,2*R*,4*S*,2′*R*)-**13** was purified by column chromatography, using hexane/EtOAc (8:2) as an eluent, to give (1*R*,2*R*,4*S*,2′*R*)-**13** as a colorless oil (330 mg, 45%). The purity of the products was determined by ^{19}F NMR (>95%). (1*S*,2*S*,4*R*,2′*R*)-**12**: Mp: 88°C. $[\alpha]_D^{25}=+45.3$ (*c* 1.09, MeOH). Anal. calcd for $C_{23}H_{28}F_3NO_7$: C, 56.67; H, 5.79; N, 2.87. Found: C, 56.73; H, 5.82; N, 2.92%. IR (CH_2Cl_2, cm^{-1}) 1748 (COO); 1704 (CON). ^{1}H NMR ($CDCl_3$): δ 1.36 (dd, 1H, $J_{3n-3x}=13.2$ Hz, $J_{3n-2x}=3.0$ Hz, H_{3n}); 1.41 (s, 9H, $C(CH_3)_3$); 1.45–1.58 (m, 1H); 1.87–2.25 (m, 3H); 2.45–2.60 (m, 1H, H_{3x}); 3.51 (s, 3H, OCH_3); 3.76 (s, 3H, CH_3OCO); 4.32 ('t', 1H, $J_{4-3x}=J_{4-5x}=5.1$ Hz, H_4); 5.58 (ddd, 1H, $J_{2x-3x}=10.2$ Hz, $J_{2x-3n}=3.0$ Hz, $J_{2x-6x}=1.5$ Hz, H_{2x}); 7.35–7.45 (m, 3H, arom); 7.47–7.55 (m, 2H, arom). ^{13}C NMR ($CDCl_3$): δ 25.6 (C_6); 28.0 ($C(CH_3)_3$); 28.8 (C_5); 36.8 (C_3); 52.4 (CH_3OCO); 55.3 (OCH_3); 59.5 (C_4); 70.5 ($C(CH_3)_3$); 76.7 (C_2); 81.5 (C_1); 121.3 ($C(CF_3)$); 125.1 (CF_3); 127.4, 128.4, 129.7, 131.9 (arom); 155.6 ($COOC(CH_3)_3$); 165.7, 169.2 ($COOCH_3$, COO). ^{19}F NMR ($CDCl_3$): δ −72.06. (1*R*,2*R*,4*S*,2′*R*)-**13**: $[\alpha]_D^{25}=-7.4$ (*c* 1.07, MeOH). Anal. calcd for $C_{23}H_{28}F_3NO_7$: C, 56.67; H, 5.79; N, 2.87. Found: C, 56.49; H, 5.62; N, 2.78%. IR (CH_2Cl_2, cm^{-1}) 1747 (COO); 1704 (CON). ^{1}H NMR ($CDCl_3$): δ 1.36 (dd, 1H, $J_{3n-3x}=13.5$ Hz, $J_{3n-2x}=3.0$ Hz, H_{3n}); 1.34–1.48 (m, 10H, $C(CH_3)_3$, H_{5n}); 1.86–2.01 (m, 1H, H_{5x}); 2.02–2.15 (m, 1H, H_6); 2.16–2.28 (m, 1H, H_6); 2.46–2.59 (m, 1H, H_{3x}); 3.52 (s, 3H, OCH_3); 3.81 (s, 3H, CH_3OCO); 4.30 ('t', 1H, $J_{4-3x}=J_{4-5x}=5.1$ Hz, H_4); 5.52–5.60 (m, 1H, H_{2x}); 7.38–7.46 (m, 3H, arom); 7.47–7.56 (m, 2H, arom). ^{13}C NMR ($CDCl_3$): δ 26.4 (C_6); 28.0 ($C(CH_3)_3$); 28.6 (C_5); 37.2 (C_3); 52.4 (CH_3OCO); 55.3 (OCH_3); 59.5 (C_4); 70.2 ($C(CH_3)_3$); 76.1 (C_2); 81.6 (C_1); 121.4 ($C(CF_3)$); 125.2 (CF_3); 127.4, 128.4, 129.7, 131.9 (arom); 155.6 ($COOC(CH_3)_3$); 165.8, 169.3 ($COOCH_3$, COO). ^{19}F NMR ($CDCl_3$): δ −71.82.

4.1.6. Methyl *N*-(*tert*-butoxycarbonyl)-2-hydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylate (1*S*,2*S*,4*R*)-11. Compound (1*S*,2*S*,4*R*,2′*R*)-**12** (546 mg, 1.12 mmol) was dissolved in MeOH (35 mL) and MeONa (30 mg, 0.56 mmol) was added. The mixture was stirred for 1 day at rt and a further quantity of MeONa (30 mg, 0.56 mmol) was added. The reaction mixture was stirred at rt for 3 days, quenched with Dowex 50W X8 and filtered. The residue was purified by column chromatography, using hexane/EtOAc (7:3) as eluent, to give (1*S*,2*S*,4*R*)-**11** (265 mg, 87%) as a white solid. $[\alpha]_D^{25}=+10.6$ (*c* 1.00, MeOH).

4.1.7. Methyl *N*-(*tert*-butoxycarbonyl)-2-hydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylate (1*R*,2*R*,4*S*)-11. Compound (1*R*,2*R*,4*S*,2′*R*)-**13** (500 mg, 1.02 mmol) was dissolved in MeOH (35 mL) and MeONa (27 mg, 0.51 mmol) was added. The mixture was stirred for 1 day at rt and a further quantity of MeONa (27 mg, 0.51 mmol) was added. The mixture was stirred for 3 days at rt, quenched with Dowex 50W X8 and filtered. The residue was purified by column chromatography, using hexane/EtOAc (7:3) as eluent, to give (1*R*,2*R*,4*S*)-**11** (241 mg, 87%) as a white solid. $[\alpha]_D^{25}=-10.3$ (*c* 0.99, MeOH).

4.1.8. *N*-(*tert*-Butoxycarbonyl)-2-hydroxy-1-hydroxymethyl-7-azabicyclo[2.2.1]heptane (1*R*,2*S*,4*R*)-14. To a suspension of methyl ester (1*S*,2*S*,4*R*)-**11** (320 mg, 1.18 mmol) and $CaCl_2$ (262 mg, 2.36 mmol) in EtOH/THF (6:4, 10 mL) at 0°C, was added $NaBH_4$ (179 mg, 4.72 mmol). The suspension was stirred at rt for 3 h. The mixture was diluted with EtOAc (20 mL) and extracted with 5% aqueous K_2CO_3 (30 mL), 0.5N HCl (30 mL), and brine (30 mL). The organic layer was dried, filtered and evaporated to give pure diol (1*R*,2*S*,4*R*)-**14** as a white solid (240 mg, 99%). Mp: 125°C. $[\alpha]_D^{25}=+14.7$ (*c* 1.00, MeOH). Anal. calcd for $C_{12}H_{21}NO_4$; C, 59.24; H, 8.70; N, 5.76. Found C, 59.38; H, 8.80; N, 5.81%. IR (CH_2Cl_2, cm^{-1}): 3610, 3400 (OH); 1668 (CON). ^1H NMR ($CDCl_3$): δ 1.05–1.15 (m, 1H, H_{3n}); 1.32–1.43 (m, 10H, $C(CH_3)_3$, H_6); 1.47–1.58 (m, 1H, H_5); 1.63–1.79 (m, 1H, H_5); 2.03–2.23 (m, 2H, H_{3x}, H_6); 3.73–3.98 (m, 2H, CH_2OH); 4.10 ('t', 1H, $J_{4-3x}=J_{4-5x}=5.1$ Hz, H_4); 4.18–4.30 (m, 2H, H_2, OH); 4.97–5.43 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 23.7 (C_6); 28.4 ($C(CH_3)_3$); 29.7 (C_5); 38.0 (C_3); 58.5 (C_4); 60.0 (CH_2OH); 69.7 (C_2); 71.4 ($C(CH_3)_3$); 80.5 (C_1); 155.2 ($COOC(CH_3)_3$).

4.1.9. *N*-(*tert*-Butoxycarbonyl)-2-hydroxy-1-hydroxymethyl-7-azabicyclo[2.2.1]heptane (1*S*,2*R*,4*S*)-14. As described for (1*R*,2*S*,4*R*)-**14**, compound (1*S*,2*R*,4*S*)-**14** (300 mg, 99%) was obtained starting from (1*R*,2*R*,4*S*)-**11** (337 mg, 1.24 mmol). $[\alpha]_D^{25}=-14.2$ (*c* 1.00, MeOH).

4.1.10. *N*-(*tert*-Butoxycarbonyl)-7-azabicyclo[2.2.1]-heptan-2-one-1-carboxylic acid (1*S*,4*R*)-15. A 2.5-fold excess of Jones' reagent was added dropwise to a solution of (1*R*,2*S*,4*R*)-**14** (225 mg, 0.92 mmol) in acetone (15 mL) at 0°C over 5 min. The mixture was stirred at 0°C for 1 h and for a further 4 h at rt. The excess Jones' reagent was quenched with 2-propanol. The mixture was then diluted with water (15 mL) and extracted with $CHCl_3$/2-propanol (4:1) (4×20 mL). The combined organic layers were dried and concentrated. The residual white solid (211 mg, 90%) was identified by NMR. Mp: 145°C. $[\alpha]_D^{25}=+1.8$ (*c* 0.97, $CHCl_3$). IR (CH_2Cl_2, cm^{-1}): 1779, 1750, 1713 (COO, CO, CON). ^1H NMR ($CDCl_3$): δ 1.40 (s, 9H, $C(CH_3)_3$); 1.57–1.72 (m, 1H, H_{5n}); 1.76–1.92 (m, 1H, H_{6n}); 1.93–2.09 (m, 1H, H_{5x}); 2.15 (d, 1H, $J_{3n-3x}=17.4$ Hz, H_{3n}); 2.22–2.36 (m, 1H, H_{6x}); 2.56–2.71 (m, 1H, H_{3x}); 4.55–4.65 (m, 1H, H_4); 10.66–11.04 (br s, 1H, COOH). ^{13}C NMR ($CDCl_3$): δ 25.9 (C_6); 27.8 ($C(CH_3)_3$); 28.2 (C_5); 44.8 (C_3); 57.1 (C_4); 75.9 ($C(CH_3)_3$); 82.9 (C_1); 155.8 ($COOC(CH_3)_3$); 171.2 (COO); 204.3 (C_2).

4.1.11. *N*-(*tert*-Butoxycarbonyl)-7-azabicyclo[2.2.1]-heptan-2-one-1-carboxylic acid (1*R*,4*S*)-15. As described for (1*S*,4*R*)-**15**, compound (1*R*,4*S*)-**15** (237 mg, 90%) was obtained starting from (1*S*,2*R*,4*S*)-**14** (250 mg, 1.03 mmol). $[\alpha]_D^{25}=-2.0$ (*c* 1.05, $CHCl_3$).

4.1.12. *N*-(*tert*-Butoxycarbonyl)-7-azabicyclo[2.2.1]-heptan-2-one (1*S*,4*R*)-16. To a suspension of acid (1*S*,4*R*)-**15** (196 mg, 0.77 mmol) in dichloroethane (13 mL) was added DMF (7 μL, 0.08 mmol) followed by oxalyl chloride (170 μL, 1.92 mmol). The mixture was stirred for 3 h at rt and evaporated to dryness. The residue was dissolved, in the dark, in THF (10 mL) and cooled to 0°C. *N*-Hydroxypyridine-2-thione (180 mg, 1.62 mmol) and TEA (240 μL, 1.69 mmol) were then added. The mixture was stirred for 2 h at rt and filtered. The residue was washed with cool THF and the solvent was evaporated, with protection from light, to give a yellow compound, which was used in the next step without purification. The yellow solid was dissolved in THF (30 mL) and Bu_3SnH (410 μL, 1.54 mmol) was added. The mixture was irradiated with a 200 W tungsten lamp at rt for 4 h. The solvent was removed and the residue was dissolved in CH_3CN (30 mL) and extracted with hexane (4×30 mL). The CH_3CN layer was evaporated and the residue was purified by column chromatography, using hexane/EtOAc (8:2), to give (1*S*,4*R*)-**16** as a colorless oil (82 mg, 50%). $[\alpha]_D^{25}=+75.5$ (*c* 1.03, $CHCl_3$). Anal. calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.49; H, 8.18; N, 6.72%. IR (CH_2Cl_2, cm^{-1}) 1760 (CO); 1690 (CON). ^1H NMR ($CDCl_3$): δ 1.44 (s, 9H, $C(CH_3)_3$); 1.50–1.68 (m, 2H); 1.92–2.08 (m, 2H); 2.00 (d, 1H, $J_{3n-3x}=17.4$ Hz, H_{3n}); 2.46 (dd, 1H, $J_{3x-3n}=17.4$ Hz, $J_{3x-4}=5.1$ Hz, H_{3x}); 4.21–4.27 (m, 1H, H_1); 4.52–4.57 (m, 1H, H_4). ^{13}C NMR ($CDCl_3$): δ 24.5, 27.6 (C_5, C_6); 28.3 ($C(CH_3)_3$); 45.3 (C_3); 56.1 (C_4); 64.0 (C_1); 80.9 ($C(CH_3)_3$); 155.2 ($COOC(CH_3)_3$); 209.7 (C_2).

4.1.13. *N*-(*tert*-Butoxycarbonyl)-7-azabicyclo[2.2.1]-heptan-2-one (1*R*,4*S*)-16. As described for (1*S*,4*R*)-**16**, compound (1*R*,4*S*)-**16** (83 mg, 50%) was obtained starting from (1*R*,4*S*)-**15** (200 mg, 0.78 mmol). $[\alpha]_D^{25}=-75.5$ (*c* 1.02, $CHCl_3$).

4.1.14. 2-Hydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylic acid hydrochloride (1*S*,2*S*,4*R*)-10. Compound (1*S*,2*S*,4*R*)-**11** (20 mg, 0.07 mmol) was suspended in 6N HCl (3 mL) and the mixture was heated at 60°C for 24

h. The solvent was evaporated in vacuo, the residue was dissolved in water, washed with diethyl ether (2×10 mL) and the aqueous layer was evaporated to give 14 mg of the amino acid hydrochloride (1*S*,2*S*,4*R*)-**10** (100%). $[\alpha]_D^{25}=+31.0$ (*c* 1.00, H_2O).

4.1.15. 2-Hydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylic acid hydrochloride (1*R*,2*R*,4*S*)-10. As described for (1*S*,2*S*,4*R*)-**10**, compound (1*R*,2*R*,4*S*)-**10** (15 mg, 100%) was obtained starting from (1*R*,2*R*,4*S*)-**11** (21 mg, 0.08 mmol). $[\alpha]_D^{25}=-31.3$ (*c* 1.07, H_2O).

4.1.16. Methyl *N*-(*tert*-butoxycarbonyl)-7-azabicyclo [2.2.1]heptan-2-one-1-carboxylate (1*S*,4*R*)-17. Dess–Martin periodinane (162 mg, 0.38 mmol) was added to a solution of alcohol (1*S*,2*S*,4*R*)-**11** (80 g, 0.29 mmol) in CH_2Cl_2 (10 mL) and the reaction mixture was stirred at rt for 18 h. 1N $Na_2S_2O_3$ (10 mL) was added to the reaction and, after stirring for 10 min, the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with 5% aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4 and evaporated. The mixture was purified by column chromatography, using hexane/EtOAc (7:3), to give (1*S*,4*R*)-**17** as a white solid (70 mg, 89%). Mp: 97°C. $[\alpha]_D^{25}=-7.2$ (*c* 1.11, MeOH). Anal. calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.69; H, 7.16; N, 5.28%. IR (CH_2Cl_2, cm^{-1}) 1777 (CO); 1742, 1710 (COO, CON). ^1H NMR ($CDCl_3$): δ 1.43 (s, 9H, $C(CH_3)_3$); 1.59–1.72 (m, 1H, H_{5n}); 1.81–1.93 (m, 1H, H_{6n}); 1.97–2.11 (m, 1H, H_{5x}); 2.15 (d, 1H, $J_{3n-3x}=17.7$ Hz, H_{3n}); 2.25–2.39 (m, 1H, H_{6x}); 2.66 (dd, 1H, $J_{3x-3n}=17.7$ Hz, $J_{3x-4}=5.1$ Hz, H_{3x}); 3.84 (s, 3H, CH_3OCO); 4.62 (t, 1H, $J_{4-3x}=J_{4-5x}=5.1$ Hz, H_4). ^{13}C NMR ($CDCl_3$): δ 25.7 (C_6); 27.9 ($C(CH_3)_3$); 28.2 (C_5); 44.8 (C_3); 52.6 (CH_3OCO); 57.0 (C_4); 76.1 ($C(CH_3)_3$); 82.0 (C_1); 155.6 ($COOC(CH_3)_3$); 166.8 (COO); 204.4 (C_2).

4.1.17. Methyl *N*-(*tert*-butoxycarbonyl)-7-azabicyclo [2.2.1]heptan-2-one-1-carboxylate (1*R*,4*S*)-17. As described for (1*S*,4*R*)-**17**, compound (1*R*,4*S*)-**17** (88 mg, 89%) was obtained starting from (1*R*,2*R*,4*S*)-**11** (100 mg, 0.37 mmol). $[\alpha]_D^{25}=+7.0$ (*c* 0.98, MeOH).

4.1.18. Methyl *N*-(*tert*-butoxycarbonyl)-2-hydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylate (1*S*,2*R*,4*R*)-18. To a solution of ketone (1*S*,4*R*)-**17** (70 mg, 0.26 mmol) in dry THF (10 mL) at −78°C was added L-Selectride® (310 μL of 1 M solution in THF, 0.31 mmol). The reaction mixture was stirred at −78°C for 2 h and then quenched by the addition of saturated aqueous NH_4Cl (8 mL). The resulting mixture was allowed to warm to rt, diluted with water and the residue washed with EtOAc (3×20 mL). The combined organic layers were dried, filtered, and the solvent was evaporated to give an oil, which was purified by column chromatography, using hexane/EtOAc (1:1), to give (1*S*,2*R*,4*R*)-**18** as a colorless oil (54 mg, 76%). $[\alpha]_D^{25}=-3.4$ (*c* 0.87, MeOH). Anal. calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.68; H, 7.67; N, 5.28%. IR (CH_2Cl_2, cm^{-1}) 3539 (OH); 1723, 1702 (COO, CON). ^1H NMR ($CDCl_3$): δ 1.20–1.34 (m, 1H, H_{5n}); 1.38 (s, 9H, $C(CH_3)_3$); 1.43–1.55 (m, 1H, H_6); 1.69–1.90 (m, 3H, H_{3x}, H_{3n}, H_{5x}); 2.09–2.22 (m, 1H, H_6); 3.61 (d, 1H, $J_{OH-2n}=1.8$ Hz, OH); 3.83 (s, 3H, CH_3OCO); 4.13–4.20 (m, 1H, H_{2n}); 4.31 (t, 1H, $J_{4-3x}=J_{4-5x}=4.8$ Hz, H_4). ^{13}C NMR ($CDCl_3$): δ 28.2 ($C(CH_3)_3$); 28.8 (C_5); 30.6 (C_6); 39.7 (C_3); 52.5 (CH_3OCO); 57.3 (C_4); 70.9 ($C(CH_3)_3$); 75.7 (C_2); 80.8 (C_1); 156.5 ($COOC(CH_3)_3$); 171.9 (COO).

4.1.19. Methyl *N*-(*tert*-butoxycarbonyl)-2-hydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylate (1*R*,2*S*,4*S*)-18. As described for (1*S*,2*R*,4*R*)-**18**, compound (1*R*,2*S*,4*S*)-**18** (65 mg, 76%) was obtained starting from (1*R*,4*S*)-**17** (85 mg, 0.31 mmol). $[\alpha]_D^{25}=+3.7$ (*c* 0.57, MeOH).

4.1.20. 2-Hydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylic acid hydrochloride (1*S*,2*R*,4*R*)-19. Alcohol (1*S*,2*R*,4*R*)-**18** (50 mg, 0.18 mmol) was suspended in 6N HCl (5 mL). The mixture was stirred at 85°C for 24 h, the solvent evaporated and the excess HCl removed in vacuo. The residual white solid was dissolved in water (10 mL) and washed with diethyl ether (2×10 mL). The aqueous phase was evaporated to give (1*S*,2*R*,4*R*)-**19** as a white solid (35 mg, 100%). $[\alpha]_D^{25}=-7.1$ (*c* 1.06, H_2O). Anal. calcd for $C_7H_{12}ClNO_3$: C, 43.42; H, 6.25; N, 7.23. Found: C, 43.57; H, 6.15; N, 7.30%. ^1H NMR (D_2O): δ 1.67–1.79 (m, 1H); 1.85–2.10 (m, 4H); 2.32 (dd, 1H, $J_{3n-3x}=14.4$ Hz, $J_{3n-2n}=7.5$ Hz, H_{3n}); 4.23 (t, 1H, $J_{4-3x}=J_{4-5x}=5.1$ Hz, H_4); 4.38 (d, 1H, $J_{2n-3n}=7.5$ Hz, H_{2n}). ^{13}C NMR (D_2O) δ 27.8, 28.7 (C_5, C_6); 41.4 (C_3); 59.5 (C_4); 74.5 (C_2); 79.4 (C_1); 172.7 (COOH).

4.1.21. 2-Hydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylic acid hydrochloride (1*R*,2*S*,4*S*)-19. As described for (1*S*,2*R*,4*R*)-**19**, compound (1*R*,2*S*,4*S*)-**19** (28 mg, 100%) was obtained starting from (1*R*,2*S*,4*S*)-**18** (40 mg, 0.15 mmol). $[\alpha]_D^{25}=+6.7$ (*c* 0.84, H_2O).

Acknowledgements

We thank the Comisión Interministerial de Ciencia y Tecnología (CICYT) and the Comisión Euopea (project 2FD97-1530), the Gobierno de La Rioja (project ANGI-2001) and the Universidad de La Rioja (project API-01/B02). J.I.B. thanks the Comunidad Autónoma de La Rioja for a doctoral fellowship.

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