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Asymmetric synthesis of conformationally constrained 4-hydroxyprolines and their applications to the formal synthesis of (+)-epibatidine

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Abstract

This report describes the synthesis of enantiomerically pure (1*S*,3*S*,4*R*)- and (1*S*,3*R*,4*R*)-3-hydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylic acids, two new conformationally constrained 4-hydroxyprolines, using a straightforward synthetic route and starting from (−)-8-phenylmenthyl 2-acetamidoacrylate. The easy transformation of the pure (1*S*,3*S*,4*R*)-3-hydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylic acid into (1*R*,4*S*)-*N*-Boc-7-azabicyclo[2.2.1]heptan-2-one constitutes a new formal synthesis of (+)-epibatidine.

1. Introduction

In recent years, several conformationally constrained analogues of bioactive peptides (peptidomimetics) have been developed with the aim of designing new pharmacological agents with more selective properties than the original peptides.[1] In order to synthesize this type of peptidomimetics, the systematic replacement of individual amino acids with the corresponding modified amino acid is well established.[2]

In this context, and as a part of our research program on the synthesis of new conformationally constrained α-amino acids,[3] we have been interested in the synthesis of hydroxy-α-amino acids[4] since they open the way to the synthesis of new glycosylated hydroxyamino acids.

In particular, 4-hydroxyproline[5] has received our attention due to its role as a key starting material in the synthesis of valuable products, such as chiral phosphine ligands,[6] carbapenems[7] and ACE inhibitors.[8] Moreover, it is a major constituent of several different proteins (collagen, gelatin...) and other

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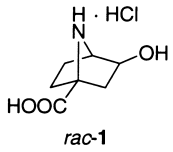


rac-**1**

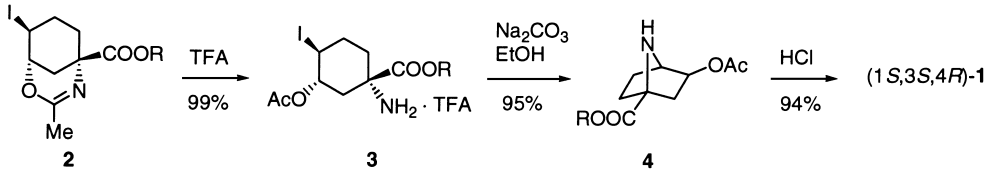
Figure 1. Constrained 4-hydroxyproline **1**

biodegradable synthetic polymers, which are expected to be useful in biomedical applications.[9] However, and in spite of their interest, there are very few examples of restricted 4-hydroxyprolines.[10]

In this context, we have recently reported the racemic synthesis of the conformationally constrained α-amino-γ-hydroxy acid *rac*-**1**, which is a derivative of 4-hydroxyproline with a 7-azabicyclo[2.2.1]heptane skeleton[11] (Fig. 1).

2. Results and discussion

We now report the synthesis of (1*S*,3*S*,4*R*)-**1**, using as starting material the iodo-1,3-oxazine **2**, obtained by iodo-oxazination of the Diels–Alder cycloadduct, synthesized by asymmetric reaction of 8-phenylmenthyl 2-acetamidoacrylate with 1,3-butadiene.[12] The initial step involves ring opening of the 1,3-oxazine intermediate **2** to give compound **3** in 99% yield, by the action of trifluoroacetic acid in water. In order to obtain **4** in good yield from **3**, several conditions were investigated and the best results were obtained with sodium carbonate in the presence of ethanol. The hydrolysis of **4** gave the required hydroxyproline (1*S*,3*S*,4*R*)-**1** in good yield (overall yield of 88% in three steps from **2**, Scheme 1).

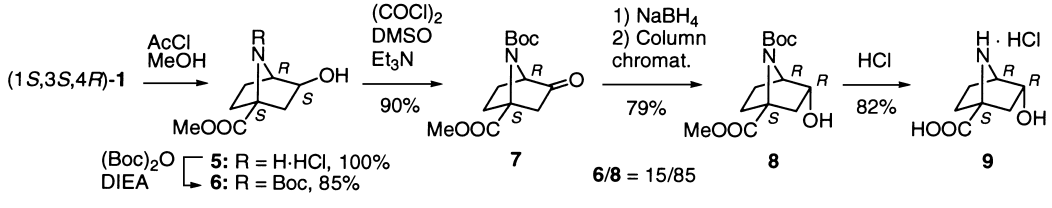


2 **3** **4**

R = (-)-8-phenylmenthyl

Scheme 1. Synthesis of constrained 4-hydroxyproline **1**

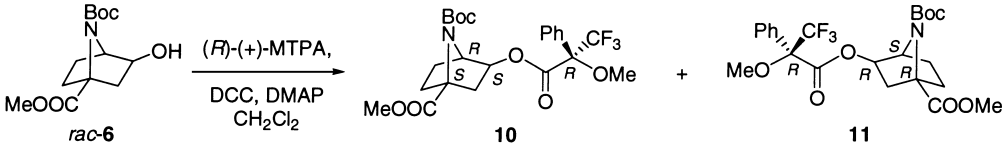
Starting from enantiomerically pure (1*S*,3*S*,4*R*)-**1** we synthesized another new conformationally constrained 4-hydroxyproline, (1*S*,3*R*,4*R*)-**9**, with an overall yield of 50%, using five steps: esterification with acetyl chloride in MeOH, protection of the amine group with $(Boc)_2O$ in the presence of diisopropylamine (DIEA), Swern oxidation, subsequent reduction of the carbonyl group with sodium borohydride and further hydrolysis (Scheme 2).



Scheme 2. Synthesis of constrained 4-hydroxyproline **9**

The stereoselective reduction of ketone **7** gave a mixture of alcohols **6** and **8** in a 15:85 ratio, respectively. The major isomer **8** was obtained in a 79% yield after separation by column chromatography (Scheme 2).

The enantiomeric purity of the intermediates in the synthesis of amino acids was examined by preparation of the Mosher ester of alcohol (1*S*,3*S*,4*R*)-**6**. According to the protocol described in the literature,[13] (1*S*,3*S*,4*R*)-**6** was coupled with (*R*)-(+)-methoxytrifluorophenylacetic acid [(*R*)-(+)-MTPA] in the presence of DCC and DMAP to give Mosher ester **10**. Analysis of the NMR spectra of ester **10** showed that the enantiomeric purity of compound (1*S*,3*S*,4*R*)-**6** was at least 96% (only one isomer was observed in the ^{1}H and ^{19}F NMR spectra). In order to be sure that compound (1*S*,3*S*,4*R*)-**6** was almost enantiomerically pure, we determined the cross-contamination by conversion of *rac*-**6** into its Mosher ester derivatives **10** and **11**, coupling *rac*-**6** in the same conditions, with (*R*)-(+)-MTPA (Scheme 3). The synthesis of *rac*-**6** was carried out using the same methodology described above for preparation of (1*S*,3*S*,4*R*)-**6** from (1*S*,3*S*,4*R*)-**1**, but now starting from *rac*-**1**.

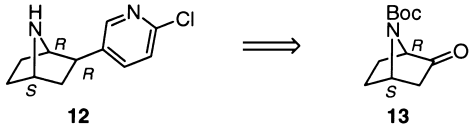


Scheme 3. Determination of enantiomeric purity of **6**

Next, we applied conformationally constrained 4-hydroxyproline (1*S*,3*S*,4*R*)-**1** to an asymmetric synthesis of (+)-epibatidine **12**, a nitrogen containing chiral building block with the 7-azabicyclo[2.2.1]heptane ring system, which constitutes a popular target for synthesis owing to its structural novelty and relevant pharmacological profile.

Since the discovery of epibatidine[14] by Daly et al. in 1992 and due to its potent non-opioid analgesic effect, this alkaloid has been the focus of intense synthetic interest over the past 7 years, despite its toxicity.[15]

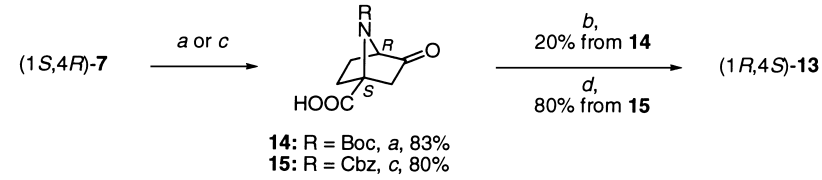
Nevertheless, although there have been many reports on its total synthesis,[16] there have been only a few reports on the asymmetric synthesis[17] of epibatidine **12**. Many different synthetic strategies have been developed for the preparation of this novel alkaloid and, in a number of syntheses, *N*-Boc-7-azabicyclo[2.2.1]heptan-2-one **13** has been used as an advanced key intermediate in the synthesis of epibatidine[17a–c,e,i,j,18] (Scheme 4).



Scheme 4. Retrosynthesis of (+)-epibatidine **12** from chiral ketone **13**

In this context, we planned to use the building block (1*S*,3*S*,4*R*)-**1** as the key chiral precursor for the preparation of ketone (1*R*,4*S*)-**13**, because it possesses the correct stereochemistry required to obtain (1*R*,2*R*,4*S*)-**12**.

We first studied the cleavage of the methoxycarbonyl group of (1*S*,4*R*)-**7**, easily available from (1*S*,3*S*,4*R*)-**1**. Treatment of (1*S*,4*R*)-**7** with lithium hydroxide in aqueous MeOH gave (1*S*,4*R*)-**14**. The synthesis of (1*R*,4*S*)-**13** required the decarboxylation of (1*S*,4*R*)-**14**, so sequential formation of the acid chloride of (1*S*,4*R*)-**14** was achieved by the action of oxalyl chloride, followed by coupling with *N*-hydroxy-2-thiopyridone (NHTP) to give the corresponding *O*-acyl thiohydroxamide. This compound was then photolyzed with tributyltin hydride, using a 200 W tungsten lamp, to give (1*R*,4*S*)-**13** in a 13% yield from (1*S*,3*S*,4*R*)-**1** in five steps (Scheme 5).



Scheme 5. Syntheses of chiral ketone **13**. Reagents: (a) LiOH, MeOH, H_2O; (b) i: $(COCl)_2$; ii: Et_3N, NHTP; iii: Bu_3SnH, hν; (c) i: HCl; ii: CbzCl, Na_2CO_3; (d) Campbell and Rapoport,[17c] two steps

In order to improve this yield, we attempted to change the Boc group for the Cbz group and using the same strategy as that described above, (1*R*,4*S*)-**13** was obtained from (1*S*,3*S*,4*R*)-**1** in an overall yield of 37% using six steps.

Better results were obtained by direct conversion of (1*S*,4*R*)-**7** into (1*R*,4*S*)-**13** via (1*S*,4*R*)-**15**. For this purpose, (1*S*,4*R*)-**7** was treated with HCl to obtain the corresponding amino acid hydrochloride, which was then protected with CbzCl in the presence of sodium carbonate to give (1*S*,4*R*)-**15**. The transformation of this compound into the required ketone (1*R*,4*S*)-**13** was obtained according to the protocol described in the literature by Campbell and Rapoport,[17c] and includes two steps with an overall yield of 80%: reductive radical decarboxylation and hydrogenolysis in MeOH containing $(Boc)_2O$. In this way, we obtained a 49% yield of (1*R*,4*S*)-**13** from (1*S*,3*S*,4*R*)-**1** in six steps (Scheme 5).

In conclusion, we have developed the asymmetric synthesis of two conformationally constrained 4-hydroxyprolines (1*S*,3*S*,4*R*)-**1** and (1*S*,3*R*,4*R*)-**9** from iodo-1,3-oxazine **2**. Moreover, chiral building block (1*S*,3*S*,4*R*)-**1** has been exploited as the precursor of chiral ketone (1*R*,4*S*)-**13**. This transformation constitutes a formal asymmetric synthesis of (+)-epibatidine. In addition and more importantly, taking into account that the activity of epibatidine is accompanied by high toxicity,[15] *N*-Boc-7-azabicyclo[2.2.1]heptan-2-one **13** has been brought further into consideration as a potential building block for the preparation of epibatidine analogues.

3. Experimental

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). ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard and in CD_3OD with TMS as the external standard using a coaxial microtube (chemical shifts are reported in ppm on the δ scale, coupling constants in hertz). The assignment of all separate signals in the ^1H 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 and 0.5 dm cells of 1 and 3.4 mL capacity, respectively. Microanalyses were carried out on a CE Instruments EA-1110 analyzer and are in good agreement with the calculated values. IR spectra were recorded on a Perkin–Elmer FT-IR Spectrum 1000 spectrometer.

3.1. (1′R,2′S,5′R)-8′-Phenylmenthyl (1S,3S,4S)-3-acetoxy-1-amino-4-iodo-1-cyclohexanecarboxylate trifluoroacetate **3**

Iodo-1,3-oxazine **2** (300 mg, 0.57 mmol) was dissolved in THF:H_2O (9:1) (20 mL) and trifluoroacetic acid (72 mg, 0.63 mmol) was then added. After stirring for 5 h at rt, the reaction was quenched by removal of the water with the addition of anhydrous Na_2SO_4. The remaining filtrate was evaporated without warming the bath and the oily residue was then dissolved in Et_2O and the solvent and the residual trifluoroacetic acid distilled off in vacuo. This operation was repeated to ensure complete removal of the trifluoroacetic acid to give compound **3** (372 mg, 99%) as a white solid. Mp 75–76°C; $[\alpha]_D^{25}$=+28.3 (*c* 1.39, $CHCl_3$); ^{1}H NMR (CD_3OD): δ 0.85–1.03 (m, 4H), 1.09–1.56 (m, 12H), 1.61–1.82 (m, 4H), 1.90–2.21 (m, 7H), 2.22–2.32 (m, 1H, $H_{2'a}$), 2.43–2.52 (m, 1H, H_{2e}), 4.21–4.27 (m, 1H, H_{4e}), 5.09–5.19 (m, 2H, H_{3e}+$H_{1'a}$), 7.11–7.19 (m, 1H, p-arom), 7.26–7.41 (m, 4H, m,o-arom); ^{13}C NMR (CD_3OD): δ 20.7 (*Me*), 22.0 (*Me*CH), 25.8 (C_4), 26.4, 27.9, 28.3, 29.8, 30.6, 32.7, 35.1 (C_2), 35.2, 40.8 (*C*Me_2Ph), 42.9, 50.8 ($C_{2'}$), 59.6 (C_1), 73.2 ($C_{1'}$), 80.0 (C_3), 126.5, 129.6 (o,m,p-arom), 152.6 (ipso-arom), 170.8, 170.9 (COO); IR ($CHCl_3$): 3619, 3232 (NH_2), 1739 (C=O); ESI$^+$ (*m/z*): 542 [m−113]$^+$. Anal. calcd for $C_{27}H_{37}F_3INO_6$: C, 49.47; H, 5.69; N, 2.14. Found: C, 49.41; H, 5.75; N, 2.00.

3.2. (1′R,2′S,5′R)-8′-Phenylmenthyl (1S,3S,4R)-3-acetoxy-7-azabicyclo[2.2.1]heptane-1-carboxylate **4**

Trifluoroacetate **3** (400 mg, 0.61 mmol) was dissolved in EtOH (25 mL) and Na_2CO_3 (1.93 g, 18.3 mmol) was then added at rt. The suspension was stirred at 30°C for 24 h and the solvent evaporated. The residual solid was suspended in CH_2Cl_2, filtered off and the filtrate was evaporated to give an oil, which was purified by column chromatography (hexane:ethyl acetate, 6:4) to give **4** (240 mg, 95%) as a colourless oil. $[\alpha]_D^{25}$=+1.0 (*c* 2.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.79–0.92 (m, 4H), 0.97–1.14 (m, 2H), 1.15–1.77 (m, 14H), 1.82–1.95 (m, 2H, NH+$H_{6'e}$), 2.04–2.18 (m, 5H, *Me*CO+$H_{2'a}$+H_{2x}), 3.48 (d, 1H, J_{4-5x}=5.1 Hz, H_4), 4.73 (dd, 1H, J_{3n-2n}=6.9 Hz, J_{3n-2x}=2.4 Hz, H_{3n}), 4.89–5.01 (td, 1H, $J_{1'-2'}$=10.4 Hz, $J_{1'-6'e,6'a}$=4.1 Hz, $H_{1'}$), 7.08–7.17 (m, 1H, p-arom), 7.23–7.33 (m, 4H, m,o-arom); ^{13}C NMR ($CDCl_3$): δ 21.1 (*Me*CO), 21.6 (*Me*CH), 24.6, 25.8, 26.6, 27.4, 31.1, 32.1, 34.3 (C_5, C_6, $C_{3'}$, $C_{4'}$, $C_{5'}$, *Me*C, *Me′*C), 39.7 (CMe_2Ph), 41.4 ($C_{6'}$), 42.5 (C_2), 49.5 ($C_{2'}$), 60.8 (C_3), 67.5 (C_1), 75.1 ($C_{1'}$), 77.5 (C_4), 125.0 (p-arom), 125.4, 128.1 (m,o-arom), 151.6 (ipso-arom), 170.5, 171.8 (COO); IR ($CHCl_3$): 3295 (NH), 1724 (C=O). APCI$^+$ (*m/z*): 414.3. Anal. calcd for $C_{25}H_{35}NO_4$: C, 72.61; H, 8.53; N, 3.39. Found: C, 72.48; H, 8.57; N, 3.45.

3.3. (1S,3S,4R)-3-Hydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylic acid hydrochloride **1**

Amino ester **4** (240 mg, 0.58 mmol) was suspended in 6N HCl (15 mL). The mixture was stirred at reflux for 14 h, the solvent evaporated and the excess of HCl removed in vacuo. The residual white solid was dissoved in water (15 mL) and washed with CH_2Cl_2 (2×15 mL). The aqueous phase was evaporated in vacuo to give **1** (106 mg, 94%) as a white solid. $[\alpha]_D^{25}$=−12.8 (*c* 1.9, MeOH); ^{1}H NMR (CD_3OD): δ 1.71–2.12 (m, 5H, H_{2x}+H_{5x}+H_{5n}+H_{6x}+H_{6n}), 2.50 (dd, 1H, J_{2n-2x}=13.8 Hz, J_{2n-3n}=6.9 Hz, H_{2n}), 3.96–4.01 (m, 1H, H_4), 4.20 (dd, 1H, J_{3n-2n}=6.9 Hz, J_{3n-2x}=2.1 Hz, H_{3n}); ^{13}C NMR (CD_3OD): δ 22.9, 31.0 (C_5+C_6), 42.8 (C_2), 66.5 (C_4), 71.9 (C_1), 72.1 (C_3), 170.7 (COOH); IR ($CHCl_3$): 1738 (C=O); ESI$^+$ (*m/z*): 158.4. Anal. calcd for $C_7H_{12}ClNO_3$: C, 43.42; H, 6.25; N, 7.23. Found: C, 43.31; H, 6.33; N, 7.15.

3.4. *Methyl (1*S*,3*S*,4*R*)-3-hydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylate hydrochloride **5**

Acetyl chloride (243.3 mg, 3.1 mmol) was added dropwise to methanol (10 mL) at 0°C. After stirring for 10 min, the amino acid hydrochloride **1** (200 mg, 1.03 mmol) was added. The resulting solution was stirred at 60°C for 12 h. The solvent was removed, the residual oil suspended in Et_2O (20 mL) and the solvent evaporated again. After repeating twice more, **5** (213 mg, 100%) was obtained pure as a white solid. $[\alpha]_D^{25}$=−12.0 (*c* 1.91, MeOH); ^{1}H NMR (CD_3OD): δ 1.74–1.86 (m, 1H, H_{6n}), 1.91–2.19 (m, 4H, H_{2x}+H_{5x}+H_{5n}+H_{6x}), 2.54 (dd, 1H, J_{2n-2x}=13.5 Hz, J_{2n-3n}=5.7 Hz, H_{2n}), 3.86 (s, 3H, COO*Me*), 4.01–4.07 (m, 1H, H_4), 4.20–4.27 (m, 1H, H_{3n}); ^{13}C NMR (CD_3OD): δ 22.8 (C_6), 31.0 (C_5), 42.8 (C_2), 53.8 (COO*Me*), 66.7 (C_4), 71.6 (C_1), 71.9 (C_3), 169.5 (*C*OOMe); IR ($CHCl_3$): 1755 (C=O); ESI$^+$ (*m/z*): 172.3 $[m-Cl]^+$. Anal. calcd for $C_8H_{14}ClNO_3$: C, 46.27; H, 6.80; N, 6.75. Found: C, 45.94; H, 6.71; N, 6.83.

3.5. *Methyl (1*S*,3*S*,4*R*)*-N-*(*tert-*butoxycarbonyl)-3-hydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylate **6**

Hydrochloride **5** (330 mg, 1.6 mmol) was dissolved in dry acetonitrile (25 mL) under an argon atmosphere. $(Boc)_2O$ (454 mg, 2.08 mmol) and DIEA (516 mg, 4 mmol) were added to the mixture. After stirring at 50°C for 24 h, the solvent was removed and the residual solid dissolved in CH_2Cl_2. The resulting suspension was washed with a saturated NaCl solution (30 mL) and a saturated $NaHCO_3$ solution (2×30 mL), dried and the solvent evaporated to give an oil, which was purified by column chromatography (hexane:ethyl acetate, 4:6) to give **6** (367 mg, 85%) as a colourless oil. $[\alpha]_D^{25}$=−33.1 (*c* 1.84, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.40–1.44 (m, 10H, C*Me*$_3$+H_{5n}), 1.49–1.54 (m, 1H, H_{6n}), 1.78–1.92 (m, 1H, H_{5x}), 1.94–2.02 (m, 2H, H_{2x}+H_{6x}), 2.13 (dd, 1H, J_{2n-2x}=12.9 Hz, J_{2n-3n}=6.9 Hz, H_{2n}), 2.32–2.46 (br s, 1H, OH), 3.78 (s, 3H, COO*Me*), 3.89–3.96 (dd, 1H, J_{3n-2n}=6.9 Hz, J_{3n-2x}=2.1 Hz, H_{3n}), 4.20 (d, 1H, J_{4-5x}=6.6 Hz, H_4); ^{13}C NMR ($CDCl_3$): δ 23.9 (C_5), 27.9 (C*Me*$_3$), 30.9 (C_6), 46.4 (C_2), 52.1 (COO*Me*), 66.1 (C_4), 67.9 (C_1), 73.3 (C_3), 81.1 (*C*Me$_3$), 156.8 (NCOO), 170.8 (*C*OOMe); IR ($CHCl_3$): 3599 (OH), 1742 (OC=O), 1702 (NC=O); ESI$^+$ (*m/z*): 294.3 $[m+Na]^+$. Anal. calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.48; H, 7.78; N, 5.22.

3.6. *Methyl (1*S*,4*R*)*-N-*(*tert-*butoxycarbonyl)-7-azabicyclo[2.2.1]heptan-3-one-1-carboxylate **7**

To a solution of oxalyl chloride (145.6 mg, 1.14 mmol) in CH_2Cl_2 (20 mL) at −78°C was added dropwise DMSO (149 mg, 1.91 mmol). After 10 min stirring at −78°C, alcohol **6** (260 mg, 0.95 mmol) in CH_2Cl_2 (5 mL) was added to the solution. The reaction mixture was stirred, at −78°C, for 20 min and then Et_3N (388 mg, 3.83 mmol) was added. The solution was allowed to warm to rt. After 1 h stirring, the reaction was quenched by addition of water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2×15 mL) and the combined organic layers were dried. The solvent was evaporated to give an oil, which was purified by column chromatography (hexane:ethyl acetate, 6:4) to give **7** (234 mg, 91%) as a colourless oil. $[\alpha]_D^{25}$=−58.8 (*c* 1.48, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.40 (s, 9H, C*Me*$_3$), 1.66 (ddd, 1H, J_{5n-5x}=13.2 Hz, J_{5n-6n}=9.0 Hz, J_{5n-6x}=4.3 Hz, H_{5n}), 1.87 (ddd, 1H, J_{6n-6x}=12.3 Hz, J_{6n-5n}=9.0 Hz, J_{6n-5x}=4.5 Hz, H_{6n}), 2.10–2.23 (m, 1H, H_{5x}), 2.30 (d, 1H, J_{2n-2x}=17.7 Hz, H_{2n}), 2.31–2.42 (m, 1H, H_{6x}), 2.85 (dd, 1H, J_{2x-2n}=17.7 Hz, J_{2x-6x}=2.7 Hz, H_{2x}), 3.83 (s, 3H, COO*Me*), 4.34 (d, 1H, J_{4-5x}=5.7 Hz, H_4); ^{13}C NMR ($CDCl_3$): δ 23.7 (C_5), 27.9 (C*Me*$_3$), 31.8 (C_6), 47.1 (C_2), 52.6 (COO*Me*), 67.0 (C_4), 68.4 (C_1), 82.2 (*C*Me$_3$), 155.5 (NCOO), 169.3 (*C*OOMe), 207.2 (C_3); IR ($CHCl_3$): 1766, 1747, 1710 (NC=O, OC=O, C=O); ESI$^+$ (*m/z*): 270.3. Anal. calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.29; H, 7.18; N, 5.23.

3.7. Methyl (1S,3R,4R)-N-(tert-butoxycarbonyl)-3-hydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylate **8**

To a solution of ketone **7** (240 mg, 0.89 mmol) in dry MeOH (25 mL) at −78°C was added $NaBH_4$ (168 mg, 4.45 mmol). After stirring at −78°C for 1 h, the reaction was quenched with the addition of water (10 mL) and then the solvent was evaporated. The residual solid was dissolved in CH_2Cl_2 (40 mL), washed with a saturated NaCl solution (20 mL) and a saturated $NaHCO_3$ solution (2×20 mL), dried and the solvent was evaporated to give an oil, which was purified by column chromatography (hexane:ethyl acetate, 6:4) to give **6** (34 mg, 14%) and **8** (191 mg, 79%) as colourless oils. $[\alpha]_D^{25}$=−9.2 (*c* 1.27, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.36–1.44 (m, 10H, C*Me*$_3$+H_{2n}), 1.69–1.86 (m, 2H, H_{5x}+H_{6n}), 2.10–2.27 (m, 2H, H_{5n}+H_{6x}), 2.28–2.50 (br s, 1H, OH), 2.50–2.62 (m, 1H, H_{2x}), 3.76 (s, 3H, COO*Me*), 4.21 ('t', 1H, J_{4-5x}=J_{4-3x}=4.6 Hz, H_4), 4.38–4.46 (m, 1H, H_{3x}); ^{13}C NMR ($CDCl_3$): δ 20.7 (C_5), 27.9 (C*Me*$_3$), 32.8 (C_6), 42.7 (C_2), 52.1 (COO*Me*), 63.0 (C_4), 69.3 (C_3), 69.4 (C_1), 81.1 (*C*Me$_3$), 156.2 (NCOO), 171.1 (*C*OOMe); IR ($CHCl_3$): 3606 (OH), 1741 (OC=O), 1701 (NC=O); ESI$^+$ (*m/z*): 310.3 [m+K]$^+$. Anal. calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.42; H, 7.83; N, 5.19.

3.8. (1S,3R,4R)-3-Hydroxy-7-azabicyclo[2.2.1]heptane-1-carboxylic acid hydrochloride **9**

Alcohol **8** (192 mg, 0.70 mmol) was suspended in 6N HCl (12 mL). The mixture was stirred at reflux for 16 h, the solvent evaporated and the excess of HCl removed in vacuo. The residual white solid was dissolved in water (12 mL) and washed with CH_2Cl_2 (2×10 mL). The aqueous phase was evaporated in vacuo to give **9** (112 mg, 82%) as a white solid. $[\alpha]_D^{25}$=+2.5 (*c* 1.23, MeOH); ^{1}H NMR (CD_3OD): δ 1.74 (dd, 1H, J_{2n-2x}=13.6 Hz, J_{2n-3x}=3.4 Hz, H_{2n}), 1.91–2.04 (m, 1H, H_{5x}), 2.12–2.21 (m, 2H, H_{6x}+H_{6n}), 2.43–2.62 (m, 2H, H_{5n}+H_{2x}), 4.10 ('t', 1H, J_{4-3x}=J_{4-5x}=4.6 Hz, H_4), 4.48–4.57 (m, 1H, H_{3x}); ^{13}C NMR (CD_3OD): δ 20.3 (C_5), 31.7 (C_6), 40.5 (C_2), 62.5 (C_4), 68.4 (C_3), 73.4 (C_1), 170.9 (COOH); IR ($CHCl_3$): 1737 (C=O); ESI$^+$ (*m/z*): 158.4. Anal. calcd for $C_7H_{12}ClNO_3$: C, 43.42; H, 6.25; N, 7.23. Found: C, 43.48; H, 6.21; N, 7.28.

3.9. (1S,3S,4R,2′R)- and (1R,3R,4S,2′R)-Methyl N-(tert-butoxycarbonyl)-3-(2′-methoxy-2′-(trifluoromethyl)phenylacetyloxy)-7-azabicyclo[2.2.1]heptane-1-carboxylates **10** and **11**

To a solution of alcohol *rac*-**6** (160 mg, 0.59 mmol), DCC (129 mg, 0.62 mmol) and DMAP (8 mg, 0.065 mmol) in dry CH_2Cl_2 (6 mL) was added a solution of (*R*)-(+)-MTPA (157 mg, 0.67 mg) in dry CH_2Cl_2 (4 mL). After stirring the mixture at rt for 6 h, the resulting white suspension was filtered to remove the *N*,*N*′-dicyclohexylurea. The filtrate was concentrated in vacuo to give a white slurry, to which Et_2O 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 (hexane:ethyl acetate, 7:3) to give **10**+**11** (187 mg, 65%) as an oil in a 1:1 ratio; ^{1}H NMR ($CDCl_3$): δ 1.31 (s, 9H, C*Me*$_3$), 1.34 (s, 9H, C*Me*$_{3'}$), 1.43–1.71 (m, 4H), 1.89–2.36 (m, 8H), 3.53 (s, 3H, OMe), 3.57 (s, 3H, OMe′), 3.78 (s, 3H, COO*Me*), 3.79 (s, 3H, COO*Me*′), 4.37–4.43 (m, 1H, H_4), 4.47–4.53 (m, 1H, $H_{4'}$), 4.98–5.04 (m, 2H, H_3+$H_{3'}$), 7.35–7.60 (m, 10H, arom); ^{13}C NMR ($CDCl_3$): δ 24.5 (C_5+$C_{5'}$), 27.9 (C*Me*$_3$+C*Me*$_{3'}$), 31.7 (C_6+$C_{6'}$), 42.1 (C_2), 42.6 ($C_{2'}$), 52.3, 52.4 (COO*Me*), 55.4, 55.5 (O*Me*), 62.7 (C_4), 63.0 ($C_{4'}$), 67.5 (C_1+$C_{1'}$), 77.5 (C_3), 77.8 ($C_{3'}$), 81.1, 81.2 (*C*Me$_3$), 121.2 (*C*(CF_3)), 125.0 (*C*F_3), 127.3, 127.4, 128.4, 129.6, 131.8 (arom), 155.1 (NCOO), 166.5, 166.6 (RCOO), 170.0 (*C*OOMe); IR ($CHCl_3$): 3599 (OH), 1742 (OC=O), 1702 (NC=O); ESI$^+$ (*m/z*): 388.3 [m−101]$^+$. Anal. calcd for $C_{23}H_{28}F_3NO_7$: C, 56.67; H, 5.79; N, 2.87. Found: C, 56.52; H, 5.72; N, 2.91.

3.10. (1S,4R)-N-(tert-Butoxycarbonyl)-7-azabicyclo[2.2.1]heptan-3-one-1-carboxylic acid **14**

$LiOH \cdot H_2O$ (318 mg, 7.6 mmol) was added to a solution of ketone **7** (204 mg, 0.76 mmol) in a mixture MeOH:H_2O, 3:2 (30 mL). The reaction mixture was stirred under reflux (70°C) for 12 h and the solvent was evaporated. The residual white solid was dissolved in water and washed with CH_2Cl_2 (2×20 mL). The aqueous phase was acidified and extracted with CH_2Cl_2 (2×20 mL). The organic phase was dried and the solvent evaporated to give **14** (161 mg, 83%) as a white solid. Mp 147–148°C. $[\alpha]_D^{25}=-33.5$ (*c* 1.46, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.42 (s, 9H, C*Me*$_3$), 1.71 (ddd, 1H, J_{5n-5x}=12.9 Hz, J_{5n-6n}=9.0 Hz, J_{5n-6x}=4.2 Hz, H_{5n}), 1.92–2.05 (m, 1H, H_{6n}), 2.11–2.24 (m, 1H, H_{5x}), 2.35–2.46 (m, 2H, H_{2n}+H_{6x}), 2.87 (dd, 1H, J_{2x-2n}=18.0 Hz, J_{2x-6x}=2.4 Hz, H_{2x}), 4.37 (d, 1H, J_{4-5x}=8.7 Hz, H_4), 10.33 (br s, 1H, COO*H*); ^{13}C NMR ($CDCl_3$): δ 23.7 (C_5), 27.8 (C*Me*$_3$), 31.7 (C_6), 47.0 (C_2), 67.0 (C_4), 68.4 (C_1), 82.7 (*C*Me$_3$), 155.6 (NCOO), 173.8 (COOH) 207.1 (C_3); IR ($CHCl_3$): 1764, 1712 (C=O); ESI$^-$ (*m/z*): 154.1. Anal. calcd for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.60; H, 6.80; N, 5.42.

3.11. (1R,4S)-N-(tert-Butoxycarbonyl)-7-azabicyclo[2.2.1]heptan-2-one **13**

A mixture of Et_3N (257 mg, 2.54 mmol), *N*-methyl-2-chloropyridinium iodide (324 mg, 1.26 mmol) and *N*-hydroxy-2-thiopyridone (203 mg, 1.59 mmol) was added to a solution of acid **7** (270 mg, 1.06 mmol) in dry CH_2Cl_2 (20 mL). After stirring under reflux for 12 h, the solvent was evaporated to give an oil, which was purified by a filtration with silica gel (hexane:ethyl acetate, 1:1) to give a protected acid derivative, which was dissolved in dry CH_2Cl_2 (10 mL) under an argon atmosphere. Bu_3SnH (617 mg, 2.12 mmol) was then added and the mixture was irradiated for 2 h using a tungsten lamp (200 W), with external cooling to keep the reaction mixture at rt. The solvent was evaporated to give an oil, which was purified by column chromatography (hexane:ethyl acetate, 9:1) to give **13** (45 mg, 20%) as a colourless oil. $[\alpha]_D^{25}=-75.5$ (*c* 1.00, $CHCl_3$). Anal. calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.68; H, 8.08; N, 6.52. Spectral data were identical to those reported in the literature.[17b]

3.12. (1S,4R)-N-(Benzyloxycarbonyl)-7-azabicyclo[2.2.1]heptan-3-one-1-carboxylic acid **15**

Ketone **7** (200 mg, 0.74 mmol) was suspended in 6N HCl (15 mL). The mixture was stirred under reflux for 14 h, the solvent evaporated and the excess of HCl removed in vacuo. The residual white solid, without purification, was dissolved in water (12 mL) at 0°C. Na_2CO_3 (258 mg, 2.44 mmol) and benzyloxycarbonyl chloride (164 mg, 0.96 mmol) was added at 0°C. After stirring at 35°C for 36 h, ice water (10 mL) was added and the mixture washed with CH_2Cl_2 (2×20 mL). The aqueous phase was acidified to pH 3 using 2N HCl and extracted with CH_2Cl_2 (2×20 mL). The organic phases were dried and the solvent evaporated to give **15** (220 mg, 80%) as a colourless oil. $[\alpha]_D^{25}=-43.3$ (*c* 1.30, $CHCl_3$). Anal. calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.35; H, 5.20; N, 4.79. Spectral data were identical to those reported in the literature.[17c]

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