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Synthesis of mono- and dihydroxy-substituted 2-aminocyclooctanecarboxylic acid enantiomers

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ABSTRACT

(1*R*,2*S*,6*R*)-2-Amino-6-hydroxycyclooctanecarboxylic acid (−)-**10** was synthesized from (1*R*,2*S*)-2-aminocyclooct-5-enecarboxylic acid (+)-**2** via an iodolactone intermediate, while (1*R*,2*S*,3*R*,4*S*)-2-amino-5,6-dihydroxycyclooctanecarboxylic acid (−)-**12** was prepared by using the OsO_4-catalysed oxidation of Boc-protected amino ester (−)-**5**. The stereochemistry and relative configurations of the synthesized compounds were determined by 1D and 2D NMR spectroscopy (based on 2D NOE cross-peaks and ^3J(H,H) coupling constants) and X-ray crystallography.

1. Introduction

The stereoselective synthesis of alicyclic β-amino acids,[1,2] derived from β-lactams,[3,4] has attracted attention because of their occurrence in many pharmacologically relevant compounds.[5] They can become important components for peptides with the aim of modifying their biological activities.[6] These compounds are to be found in various natural and synthetic biologically active molecules, for example, natural cispentacin and its synthetic 4-methylene analogue (Icofungipen, PLD-118) exhibit antifungal activity.[7–11] These molecules are also useful starting materials; as an example anatoxin-*a*,[12–14] a nicotinic acetylcholine receptor agonist, was efficiently synthesized from the β-lactam.[15]

Among the β-amino acids, hydroxy-functionalized counterparts also play an important role in medicinal chemistry because of their presence in many essential products, such as Paclitaxel (Taxol®) and its synthetic derivative Docetaxel (Taxotere®), which exert significant chemotherapeutic effects.[16–18] Some cyclic derivatives have antibiotic (oryzoxymycin) and antifungal activities.[19–22]

We earlier reported several methods for the mono- or dihydroxylation of the cyclopentene and cyclohexene rings, but there is no example involving mono- or dihydroxycyclooctane β-amino acids in the literature. By iodolactonization[23] and epoxidation[24,25] of the double bond or via dihydrooxazine[26] and oxazoline[27] derivatives, the corresponding monohydroxy β-amino acids can be efficiently synthesized. For dihydroxylation, well-known routes involve oxidation of the double bond with $KMnO_4$ or with catalytic OsO_4.[26,28]

Our present work focuses on functionalization of the double bond of N-protected *cis*-2-aminocyclooct-5-enecarboxylic acid derivatives and analysis of the structures of the newly prepared mono- and dihydroxy-substituted enantiopure and racemic molecules.

2. Results and discussion

The racemic β-lactam (±)-**1** was prepared by 1,2-cycloaddition of chlorosulfonyl isocyanate (CSI) in dry CH_2Cl_2 at room temperature by modification of a literature process.[29] The starting (1*R*,2*S*)-2-aminocyclooct-5-enecarboxylic acid (+)-**2** was synthesized from (±)-**1** by highly enantioselective Lipolase-catalysed ring opening with 1 equiv of H_2O in iPr_2O at 70 °C.[30]

The enantiopure amino acid (+)-**2** (ee >99%) was esterified in the presence of EtOH and $SOCl_2$ to furnish amino ester hydrochloride (−)-**4**, which was then reacted with *tert*-butoxy pyrocarbonate, affording the *N*-Boc-protected amino ester (−)-**5**. An alternative synthesis of (±)-**5**, which was used in the case of racemic compounds, comprised hydrolysis of (±)-**1** with 22% ethanolic HCl at room temperature to give (±)-**4**, which was then acylated by the above method (Scheme 1).

The starting material in the iodolactonization reaction was *cis*-2-*tert*-butoxycarbonylaminocyclooct-5-enecarboxylic acid (−)-**6**. Enantiopure (−)-**6** was prepared from (+)-**2** with Boc_2O, while (±)-**6** was synthesized by the ring opening of (±)-**1** with 18% aqueous HCl and after acylation with di-*tert*-butyl dicarbonate. The N-protected acid (−)-**6** was reacted with I_2/KI/aqueous

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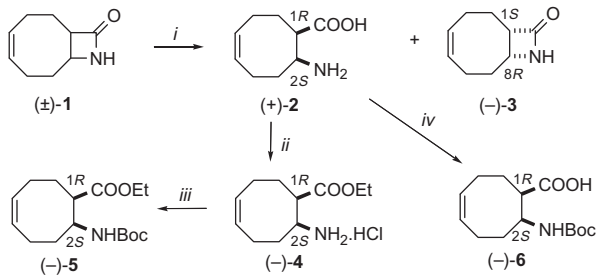
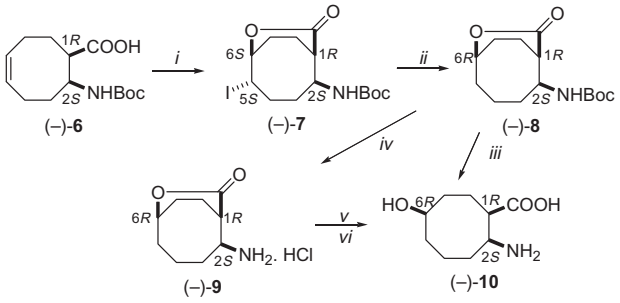


Scheme 1. Reagents and conditions: (i) Lipolase, *i*Pr_2O, 70 °C; (ii) $SOCl_2$, EtOH, 30 min, 0 °C, 3 h rt, 1 h, △, 88%; (iii) Et_3N, Boc_2O, THF, 2 h, rt, 91%; (iv) dioxane/H_2O, Boc_2O, 4 h, rt, 76%.

$NaHCO_3$ in CH_2Cl_2 to give iodolactone (−)-**7** regio- and diastereoselectively as a white crystalline product, in good yield. Reduction of the iodo group with Bu_3SnH in CH_2Cl_2 yielded lactone (−)-**8** which, after hydrolysis with microwave irradiation, gave (1*R*,2*S*,6*R*)-2-amino-6-hydroxycyclooctanecarboxylic acid ((−)-**10**) in good yield. When ring opening of the Boc–lactone (−)-**8** was attempted with hydrochloric acid, deprotected lactone (−)-**9** was observed, which was transformed to hydroxy-amino acid (−)-**10** upon microwave irradiation followed by heating in propylene oxide (Scheme 2). The presence of the lactone ring in (−)**7**-(−)-**9** was confirmed by the cross-peak between H-6 and the carbonyl carbon in the HMBC spectra. In the case of (−)-**10**, the NOE cross-peak between H-1 and H-6 suggests that the hydroxyl group should have a *cis* configuration relative to the carboxyl group. A small NOE cross-peak was also observed between H-2 and H-6, which indicates the conformational flexibility of the compound and also proves the orientation of the amino group. The stereochemistry of (±)-**7** and (±)-**9** was confirmed by X-ray diffraction (Figs. 1 and 2).



Scheme 2. Reagents and conditions: (i) I_2/KI, $NaHCO_3$, CH_2Cl_2, 20 h, rt, 71%; (ii) Bu_3SnH, CH_2Cl_2, 20 h, 40 °C, 76%; (iii) microwave irradiation, H_2O, 1 h, 150 °C, 67%; (iv) 10% HCl/H_2O, 24 h, 82%; (v) microwave irradiation, H_2O, 1 h, 150 °C, 65%; (vi) propylene oxide, 1 h, △, 62%.

(1*R*,2*S*,5*R*,6*S*)-2-Amino-5,6-dihydroxycyclooctane-carboxylic acid (−)-**12** was obtained by OsO_4-catalysed dihydroxylation. The oxidation of *N*-Boc ester (−)-**5** with catalytic OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) as the stoichiometric co-oxidant afforded the desired product (−)-**11** as a single diastereomer in good yield. After deprotection of the compound, microwave irradiation in water resulted in the corresponding dihydroxy-aminoacid (−)-**12** in good yield (Scheme 3). In the case of (−)-**11**, the all-*cis* stereochemistry of the substituents can be proved by the NOE cross-peaks between H-2 and H-5 and between H-1 and H-6. The presence of these NOE signals not only confirms the *cis* orientation of the functional groups, but also indicates the conformational flexibility of (−)-**11**. For (−)-**12**, a similar NOE pattern was observed which indicates the all-*cis* orientation of the functional groups and reveals that the microwave irradiation did not affect the stereochemistry. The stereochemistry of **12** was also confirmed by X-ray diffraction (Fig. 3). From a racemic mixture, a single enantiomer crystallized out in a zwitterionic form in the crystal investigated. However, the data did not permit confirmation of which enantiomer this was.

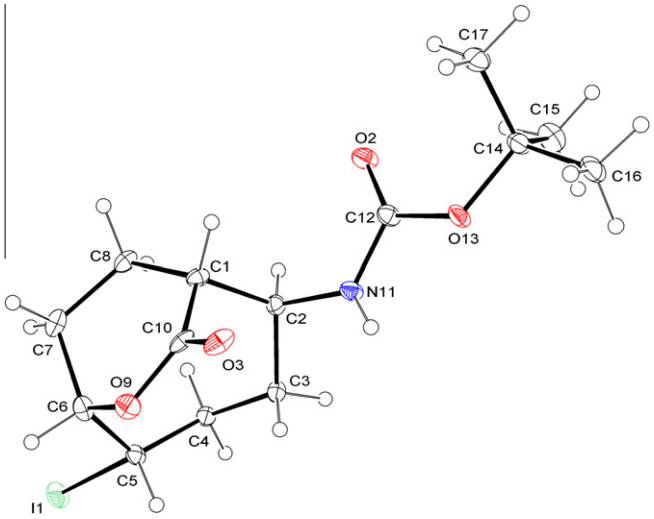


Figure 1. ORTEP plot of the X-ray structure of iodolactone (±)-**7**.

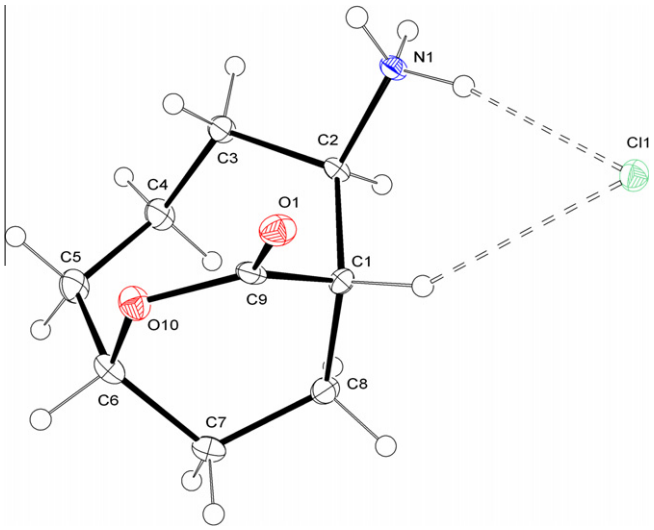
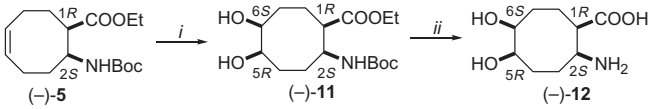


Figure 2. ORTEP plot of the X-ray structure of lactone (±)-**9**.



Scheme 3. Reagents and conditions: (i) 2.0% w/w solution of OsO_4 in *t*-BuOH, NMO, acetone, 4 h, rt, 91%; (ii) microwave irradiation, H_2O, 1 h, 150 °C, 69%.

3. Conclusions

In summary, we have successfully synthesized either racemic and enantiomeric 6-hydroxy- and 5,6-dihydroxy-2-aminocyclooctanecarboxylic acid derivatives by using iodolactonization and OsO_4-catalysed dihydroxylation. All the racemic and enantiopure derivatives produced can be used for further valuable transforma-

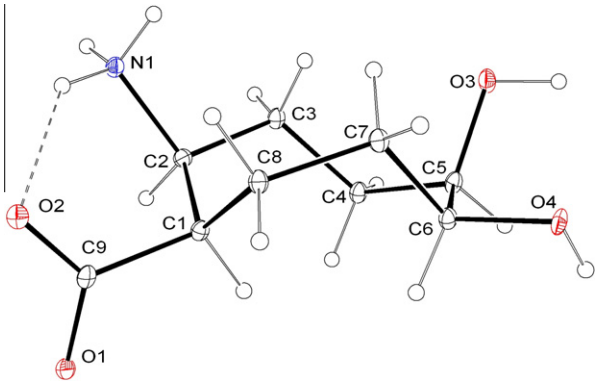


Figure 3. ORTEP plot of the X-ray structure of zwitterionic dihydroxy-substituted amino acid **12**.

tions, and they are good starting materials for the synthesis of peptides and different heterocycles with potential biological activity.

4. Experimental

4.1. General

The NMR spectra were recorded at ambient temperature in $CDCl_3$, DMSO-d_6 or D_2O with a Bruker AV 500 spectrometer at 500 MHz and at 125 MHz for ^1H and ^{13}C, respectively. Chemical shifts are given in δ (ppm) relative to TMS as an internal standard. Elemental analyses were performed with a Perkin–Elmer CHNS-2400 Ser II Elemental Analyzer. Melting points were measured with a Kofler melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin Elmer 341 polarimeter. Microwave reactions were performed in a CEM Discover LabMate MW reactor.

The ee value for the starting (1*R*,2*S*)-2-aminocyclooct-5-enecarboxylic acid (+)-**2** was determined by using GC after double derivatization.[31]

The ee values for the HCl salts of the final products were determined by HPLC. A Chirobiotic TAG 5 μ column (0.46 cm × 25 cm) was used at room temperature; the mobile phase was MeOH containing 0.1% TEA and 0.1% AcOH; flow rate 1 mL/min; detection at 216 nm; retention times (min): (−)-**10**, 28.08 (antipode: 30.92) and (−)-**12**, 25.49 (antipode: 27.36).

4.2. Ethyl (1*R*,2*S*)-2-aminocyclooct-5-enecarboxylate hydrochloride (−)-4

Thionyl chloride (0.86 g, 7.27 mmol) was added dropwise with stirring to dry EtOH (5 mL) at −15 °C. Compound (+)-**2** (1 g, 6.61 mmol) was added in one portion to this mixture, which was then stirred at 0 °C for 30 min. After subsequent stirring at room temperature for a further 3 h, the mixture was refluxed for 1 h and then concentrated to give colourless crystals (1.5 g, 88%) mp 108–110 °C, lit. mp 112–117 °C,[29] $[\alpha]_D^{20} = -1.5$ (*c* 1, EtOH). The ^1H NMR data are in accordance with those reported in the literature.[29] ^{13}C NMR (125 MHz, $CDCl_3$, 27 °C): δ = 14.3, 23.2, 23.7, 27.0, 30.3, 44.5, 52.0, 61.4, 128.8, 130.2, 172.9 ppm.

4.3. Ethyl (1*R*,2*S*)-2-*tert*-butoxycarbonylaminocyclooct-5-enecarboxylate (−)-5

To a suspension of (−)-**4** (1.5 g, 6.42 mmol) in THF (50 mL) were added Et_3N (1.29 g, 12.84 mmol) and di-*tert*-butyl dicarbonate (1.54 g, 7.06 mmol) at 0 °C. Stirring was continued for 3 h at room temperature, after which the organic layer was diluted with EtOAc and washed with H_2O (2 × 20 mL). The aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic phase was dried (Na_2SO_4) and the solvents were evaporated off. The residue was purified by column chromatography (*n*-hexane/EtOAc 5:1) to afford a colourless oil (1.74 g, 91%), $[\alpha]_D^{20} = -53.4$ (*c* 1, EtOH). ^1H NMR (500 MHz, $CDCl_3$, 27 °C): δ = 1.28 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.43 (s, 9H, *t*Bu), 1.72–1.82 (m, 2H, H-3, H-8), 1.86–1.94 (m, 1H, H-3), 1.96–2.02 (m, 1H, H-4), 2.07–2.21 (m, 2H, H-7, H-8), 2.26–2.34 (m, 1H, H-4), 2.44–2.51 (m, 1H, H-7), 2.81–2.85 (m, 1H, H-1), 4.11–4.22 (m, 3H, H-2, CH_2CH_3), 4.99–5.05 (m, 1H, N*H*), 5.61–5.72 (m, 2H, H-5, H-6) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 27 °C): δ = 14.2, 23.3, 24.6, 27.3, 28.4, 32.9, 48.0, 50.2, 60.4, 79.2, 129.2, 130.4, 155.0, 174.2 ppm. Anal. Calcd for $C_{16}H_{27}NO_4$ (297.39): C, 64.62; H, 9.15; N, 4.71. Found: C, 64.57; H, 9.11; N, 4.84.

4.4. (1*R*,2*S*)-2-*tert*-Butoxycarbonylaminocyclooct-5-enecarboxylic acid (−)-6

Amino acid (+)-**2** (0.98 g, 4.76 mmol) was dissolved in a mixture of dioxane (10 mL) and water (5 mL), and 1 M NaOH (5 mL) and *tert*-butoxypyrocarbonate (1.14 g, 5.24 mmol) were added to the solution at 0 °C. The pH was adjusted to 8.5 with 1 M NaOH and the mixture was stirred at room temperature for 5 h. The solvent was then evaporated down to one-third volume, and the mixture was diluted with EtOAc (30 mL) and acidified with 10% H_2SO_4 (pH 2.5). The mixture was extracted with EtOAc (3 × 15 mL), the combined organic phase was dried ($NaSO_4$), and the solvents were evaporated off. The residue was recrystallized from iPr_2O to give a white crystalline solid (0.97 g, 76%), mp 125–127 °C, $[\alpha]_D^{20} = -59.0$ (*c* 1, EtOH). ^1H NMR (500 MHz, $CDCl_3$, 27 °C): δ = 1.45 (s, 9H, *t*Bu), 1.79–1.88 (m, 2H, H-3, H-8), 1.93–2.00 (m, 1H, H-3), 2.00–2.21 (m, 3H, H-4eq, H-7eq, H-8), 2.27–2.36 (m, 1H, H-4ax), 2.44–2.52 (m, 1H, H-7ax), 2.97 (s, 1H, H-1), 4.16–4.22 (m, 1H, H-2), 5.09 (s, 1H, N*H*), 5.68–5.74 (m, 2H, H-5, H-6) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 27 °C): δ = 22.9, 24.6, 27.6, 28.4, 33.0, 48.2, 50.0, 80.1, 129.6, 130.7, 155.8, 177.9 ppm.. Anal. Calcd for $C_{14}H_{23}NO_4$ (269.34): C, 62.43; H, 8.61; N, 5.20. Found: C, 62.36; H, 8.52; N, 5.14.

4.5. (1*R*,2*S*,5*S*,6*S*)-2-*tert*-Butoxycarbonylamino-5-iodo-7-oxabicyclo[4.2.2]decan-8-one (−)-7

To a solution of carboxylic acid derivative (−)-**6** (1 g, 3.71 mmol) in CH_2Cl_2 (25 mL) were added $NaHCO_3$ (0.5 M, 22 mL), KI (3.69 g, 22.26 mmol) and I_2 (1.88 g, 7.42 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 20 h, and saturated $Na_2S_2O_3$ (25 mL) was then added. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), in the extract was dried (Na_2SO_4), and the solvents were evaporated off. The residue was recrystallized from iPr_2O to give iodolactone (−)-**7** (1.04 g, 71%), mp 105–107 °C, $[\alpha]_D^{20} = -76.2$ (*c* 1, EtOH). ^1H NMR (500 MHz, $CDCl_3$, 27 °C): δ = 1.31–1.40 (m, 1H, H-3ax), 1.43 (s, 9H, *t*Bu), 2.00–2.14 (m, 3H, H-3eq, H-7, H-8), 2.26–2.37 (m, 2H, H-4ax, H-8), 2.47–2.54 (m, 1H, H-4eq), 2.53–2.56 (m, 1H, H-7), 3.04 (dt, *J* = 11.3, 2.5, 2.5 Hz, 1H, H-1), 3.82–3.89 (m, 1H, H-2), 4.55 (dt, *J* = 12.0, 4.0, 4.0 Hz, 1H, H-5), 5.02–5.06 (m, 2H, N*H*, H-6) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 27 °C): δ = 18.9, 22.5, 28.4, 31.7, 33.3, 34.2, 43.5, 55.4, 79.8, 82.7, 155.3, 172.0 ppm. Anal. Calcd for $C_{14}H_{22}INO_4$ (395.23): C, 42.54; H, 5.61; N, 3.54. Found: C, 42.46; H, 5.52; N, 3.56.

4.6. (1*R*,2*S*,6*R*)-2-*tert*-Butoxycarbonylamino-7-oxabicyclo[4.2.2]decan-8-one (−)-8

At first, Bu_3SnH (1.36 mL, 5.06 mmol) was added to a solution of iodolactone (−)-**7** (1 g, 2.53 mmol) in dry CH_2Cl_2 (35 mL) under argon. After stirring for 20 h at 40 °C, the solvent was evaporated off,

and the crude lactone was crystallized from *n*-hexane and recrystallized from iPr_2O (0.52 g, 76%), mp 102–105 °C, $[\alpha]_D^{20} = -93.1$ (*c* 0.5, EtOH). ^1H NMR (500 MHz, $CDCl_3$, 27 °C): δ = 1.34–1.47 (m, 10H, *t*Bu, H-3ax), 1.64–1.74 (m, 1H, H-4ax), 1.75–1.87 (m, 3H, H-4eq, H-5, H-7), 1.98–2.06 (m, 1H, H-8), 2.07–2.20 (m, 3H, H-3eq, H-5, H-7), 2.27 (ddd, *J* = 13.1, 11.4, 10.6 Hz, 1H, H-8), 2.99 (dt, *J* = 11.2, 2.7, 2.7 Hz, 1H, H-1), 3.81–3.87 (m, 1H, H-2), 4.84 (dt, *J* = 6.0, 3.0, 3.0 Hz, 1H, H-6), 5.14 (d, *J* = 7.6 Hz, 1H, N*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 27 °C): δ = 20.7, 22.3, 22.7, 28.2, 31.8, 35.3, 43.2, 55.8, 78.6, 79.5, 154.9, 173.1 ppm. Anal. Calcd for $C_{14}H_{23}NO_4$ (269.34): C, 62.43; H, 8.61; N, 5.20. Found: C, 62.35; H, 8.66; N, 5.15.

4.7. (1*R*,2*S*,6*R*)-2-Amino-7-oxabicyclo[4.2.2]decan-8-one hydrochloride (−)-9

A solution of lactone (−)-**8** (0.6 g, 2.23 mmol) was dissolved in aqueous HCl (10%; 20 mL) and the mixture was stirred for 24 h at rt. The solvent was then evaporated off to afford the crude amino lactone hydrochloride which was recrystallized from EtOH/Et_2O (0.33 g, 68%), mp 250–252 °C, $[\alpha]_D^{20} = -23.9$ (*c* 0.4, H_2O). ^1H NMR (500 MHz, DMSO, 27 °C): δ = 1.37 (ddd, *J* = 14.0, 11.5, 9.8 Hz, 1H, H-3ax), 1.67–1.87 (m, 4H, H-4, H-4, H-5, H-7), 1.89–2.08 (m, 3H, H-5, H-7, H-8), 2.09–2.16 (m, 1H, H-3eq), 2.20 (ddd, *J* = 12.7, 11.3, 8.9 Hz, 1H, H-8), 3.09 (dt, *J* = 11.1, 2.5, 2.5 Hz, 1H, H-1), 3.45 (ddd, *J* = 10.8, 4.6, 2.8 Hz, 1H, H-2), 4.81–4.84 (m, 1H, H-6), 8.08 (s, 3H, N*H*) ppm. ^{13}C NMR (125 MHz, DMSO, 27 °C): δ = 19.0, 21.0, 21.6, 29.1, 34.5, 40.5, 55.0, 78.3, 170.9 ppm. Anal. Calcd for $C_9H_{16}ClNO_2$ (205.09): C, 52.56; H, 7.84; Cl, 17,24; N, 6.81. Found: C, 52.35; H, 7.66; Cl, 17,43; N, 7.05.

4.8. (1*R*,2*S*,6*R*)-2-Amino-6-hydroxycyclooctanecarboxylic acid (−)-10

4.8.1. Method A

The lactone (−)-**8** (178 mg, 0.66 mmol) was dissolved in water (4 mL) in a 10-mL pressurized reaction vial, and the mixture was then stirred at 150 °C for 60 min at max. One hundred and fifty watts microwave irradiation. After cooling, the mixture was diluted with acetone (6 mL) and the product crystallized out from the solvent. The crude amino acid was recrystallized from H_2O/acetone to afford a pale-yellow crystalline solid (83 mg, 67%), mp 211–213 °C (dec).

4.8.2. Method B

Lactone (−)-**9** (205 mg, 1 mmol) was dissolved in water (4 mL) in a 10-mL pressurized reaction vial, and the reaction mixture was then stirred at 150 °C for 60 min at max. One hundred and fifty watts microwave irradiation. The solvent was evaporated off, the residue was dissolved in propylene oxide (10 mL) and the mixture was refluxed for 1 h. The product crystallized out from the solvent. The crude amino acid was recrystallized from H_2O/acetone to afford a pale-yellow crystalline product (116 mg, 62%), mp 210–212 °C (dec), $[\alpha]_D^{20} = -9.0$ (*c* 0.4, H_2O), ee >99%. ^1H NMR (500 MHz, D_2O, 27 °C): δ = 1.36–1.44 (m, 1H, H-4), 1.51–1.58 (m, 1H, H-5), 1.67–1.98 (m, 8H, H-3, H-3, H-4, H-5, H-7, H-7, H-8, H-8), 2.62 (dt, *J* = 10.1, 3.7, 3.7 Hz, 1H, H-1), 3.46 (dt, *J* = 10.0, 4.0, 4.0 Hz, 1H, H-2), 3.82–3.87 (m, 1H, H-6) ppm. ^{13}C NMR (125 MHz, D_2O, 27 °C): δ = 19.1, 22.6, 28.9, 32.3, 34.3, 44.5, 51.2, 70.3, 180.9 ppm. Anal. Calcd for $C_9H_{17}NO_3$ (187.24): C, 57.73; H, 9.15; N, 7.48. Found: C, 57.68; H, 9.22; N, 7.45.

4.9. Ethyl (1*R*,2*S*,5*R*,6*S*)-2-*tert*-butoxycarbonylamino-5,6-dihydroxycyclooctanecarboxylate (−)-11

OsO_4 (1 mL, 0.08 mmol; a 2.0% w/w solution in *t*BuOH) was added to a stirred solution of *N*-methylmorpholine *N*-oxide (1.18 g, 10.13 mmol) and (−)-**5** (0.5 g, 1.68 mmol) in acetone (20 mL) and the mixture was stirred at room temperature for a further 4 h. When the reaction was complete (monitored by TLC), the mixture was treated with saturated aqueous Na_2SO_3 (20 mL). The aqueous layer was next extracted with EtOAc (3 × 20 mL), the combined organic layer was dried (Na_2SO_4) and the solvent was removed by evaporation under reduced pressure. Compound (−)-**11** was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 1:1) to afford a colourless oil (0.5 g, 91%), $[\alpha]_D^{20} = -27.2$ (*c* 1, EtOH). ^1H NMR (500 MHz, DMSO, 27 °C): δ = 1.16 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.30–1.40 (m, 11H, *t*Bu, H-4, H-7), 1.42–1.48 (m, 1H, H-3), 1.53–1.60 (m, 1H, H-8), 1.80–1.96 (m, 3H, H-3, H-4, H-8), 1.98–2.06 (m, 1H, H-7), 2.62 (dt, *J* = 11.0, 3.5, 3.5 Hz, 1H, H-1), 3.60 (t, *J* = 6 Hz, 1H, H-6), 3.65 (br s, 1H, H-5), 3.91–4.04 (m, 3H, CH_2CH_3, H-2), 4.22 (d, *J* = 3.3 Hz, 1H, O*H*), 4.30 (d, *J* = 4.6 Hz, 1H, O*H*), 6.61 (d, *J* = 9.2 Hz, 1H, N*H*) ppm. ^{13}C NMR (125 MHz, DMSO, 27 °C): δ = 14.0, 20.3, 26.1, 27.7, 28.1, 28.2, 44.5, 50.1, 59.8, 71.5, 71.5, 77.5, 154.8, 173.9 ppm. Anal. Calcd for $C_{16}H_{29}NO_6$ (331.40): C, 57.99; H, 8.82; N, 4.23. Found: C, 57.81; H, 8.89; N, 4.12.

4.10. (1*R*,2*S*,5*R*,6*S*)-2-Amino-5,6-dihydroxycyclooctanecarboxylic acid (−)-12

Dihydroxy ester (−)-**11** (0.2 g, 0.9 mmol) was dissolved in water (4 mL) in a 10-mL pressurized reaction vial and the reaction mixture was stirred at 150 °C for 60 min at max. One hundred and fifty watts microwave irradiation. After cooling, the mixture was diluted with acetone (5 mL) and the product crystallized out from the solvent. The crude amino acid was recrystallized from H_2O/acetone to afford a pale-yellow crystalline solid (126 mg, 69%), mp 207–210 °C (dec), $[\alpha]_D^{20} = -7.6$ (*c* 0.5, H_2O), ee >99%. ^1H NMR (500 MHz, D_2O, 27 °C): δ = 1.57–1.66 (m, 2H, H-4, H-7), 1.76–1.87 (m, 2H, H-3, H-8), 1.89–2.06 (m, 4H, H-3, H-4, H-7, H-8), 2.62 (dt, *J* = 10.1, 3.5, 3.5 Hz, 1H, H-1), 3.54 (ddd, *J* = 10.3, 5.0, 3.5 Hz, 1H, H-2), 3.84 (dt, *J* = 8.6, 2.2, 2.2 Hz, 1H, H-6), 3.92 (dt, *J* = 7.4, 2.3, 2.6 Hz, 1H, H-5) ppm. ^{13}C NMR (125 MHz, D_2O, 27 °C): δ = 22.3, 23.5, 25.9, 27.1, 43.8, 50.9, 71.1, 72.1, 181.0 ppm. Anal. Calcd for $C_9H_{17}NO_4$ (203.24): C, 53.19; H, 8.43; N, 6.89. Found: C, 53.01; H, 8.57; N, 6.78.

4.11. Racemic compounds

All the reactions were first optimized for the racemic compounds. The ^1H and ^{13}C NMR spectroscopic data and elemental analyses on the racemic derivatives are in accordance with those for the enantiomers.

4.11.1. (1*R**,2*S**)-9-Azabicyclo[6.2.0]dec-4-en-10-one (±)-1

To a solution of 1,5-cyclooctadiene (30 g, 0.28 mol) in dry CH_2Cl_2 (250 mL) was added dropwise a solution of CSI (39.63 g, 0.28 mol) in dry CH_2Cl_2 (150 mL) at room temperature. After stirring for a further 72 h, the resulting liquid was poured into a stirred solution of Na_2SO_3 (54.5 g, 0.43 mol) in water (148 mL), and the pH was adjusted to 8–9 with 20% KOH solution. The mixture was stirred at room temperature for 3 h, after which the organic layer was separated off and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The resulting yellow solid was recrystallized from iPr_2O to give (17.78 g, 42%) of pure (±)-**1**, mp 110–113 °C, lit. 112–113 °C.[29] The ^1H NMR, ^{13}C NMR and elemental analysis data are in accordance with those reported in the literature.[30]

4.11.2. (1*R**,2*S**)-2-Aminocyclooct-5-enecarboxylic acid hydrochloride (±)-2·HCl

A solution of β-lactam (±)-**1** (1.5 g, 9.92 mmol) in H_2O containing 18% of HCl (15 mL) was refluxed for 1 h. After removal of the

solvent, amino acid hydrochloride (±)-**2**·HCl was obtained, which was recrystallized from EtOH to Et_2O. Colourless crystals (1.67 g, 82%), mp 229–231 °C, lit. mp 218–220 °C.[29] The ^1H NMR, ^{13}C NMR and elemental analysis data are in accordance with those reported in the literature.[30]

4.11.3. Ethyl (1*R**,2*S**)-2-aminocyclooct-5-enecarboxylate hydrochloride (±)-4

A solution of β-lactam (±)-**1** (3 g, 19.84 mmol) in EtOH containing 22% HCl (30 mL) was stirred for 2 h at room temperature. After removal of the solvent, amino ester hydrochloride **3** was obtained, which was recrystallized from EtOH to Et_2O. Colourless crystals (4.13 g, 89%), mp 108–110 °C, lit. mp 112–117 °C.[29] The ^1H NMR, ^{13}C NMR and elemental analysis data are in accordance with those reported in the literature.[30]

4.11.4. Representative data on the racemates (±)-5-(±)-12

4.11.4.1. Ethyl (1*R,2*S**)-2-*tert*-Butoxycarbonylaminocyclooct-5-enecarboxylate (±)-5.** Colourless oil.

4.11.4.2. (1*R,2*S**)-2-*tert*-Butoxycarbonylaminocyclooct-5-enecarboxylic acid (±)-6.** White crystals, mp 119–123 °C.

4.11.4.3. (1*R,2*S**,5*S**,6*S**)-2-(*tert*-Butoxycarbonylamino)-5-iodo-7-oxabicyclo-[4.2.2]decan-8-one (±)-7.** White crystals mp, 144–146 °C.

4.11.4.4. (1*R,2*S**,6*R**)-2-(*tert*-Butoxycarbonylamino)-7-oxabicyclo-[4.2.2]decan-8-one (±)-8.** Pale-yellow crystals, mp 86–88 °C.

4.11.4.5. (1*R,2*S**,6*R**)-2-Amino-6-hydroxycyclooctanecarboxylic acid (±)-9.** White crystals, mp 255–258 °C.

4.11.4.6. (1*R,2*S**,6*R**)-2-Amino-6-hydroxycyclooctanecarboxylic acid (±)-10.** White crystals, mp 220–222 °C (dec).

4.11.4.7. Ethyl (1*R,2*S**,5*R**,6*S**)-2-*tert*-butoxycarbonylamino-5,6-dihydroxycyclooctanecarboxylate (±)-11.** Colourless crystals, mp 90–93 °C.

4.11.4.8. (1*R,2*S**,5*R**,6*S**)-2-Amino-5,6-dihydroxycyclooctanecarboxylic acid (±)-12.** White crystals, mp 262–264 °C (dec).

5. X-ray crystallographic studies

All single-crystals for **7**, **9**, and **12** were obtained from racemic mixtures. Compound **12** crystallized as a single enantiomer. Crystallographic data were collected at 123 K with a Nonius-Kappa CCD area detector diffractometer, using graphite-monochromatized MoK radiation (λ = 0.71073 Å) as reported earlier,[32] except that the absorption corrections were carried out with SADABS[33] The structures were solved by direct methods, and full-matrix, least-squares refinements on F^2 were performed with the SHELXL-97 program.[34] The CH hydrogen atoms were included at fixed distances with fixed displacement parameters from their host atoms. The NH hydrogen atoms were refined isotropically with fixed displacement parameters.

The deposition numbers CCDC 769713–769715 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

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