Synthesis of 3- and 4-Hydroxy-2-aminocyclohexanecarboxylic Acids by Iodocyclization

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Starting from *cis*-7-azabicyclo[4.2.0]oct-4-en-8-one, novel routes have been developed for the synthesis of 2-amino-4-hydroxycyclohexanecarboxylic acid and its 3-hydroxy-substituted analog via iodooxazine, iodooxazoline or iodolactone intermediates. After CAL-B-catalyzed enzymatic transformation of the starting β-lactam, the iodolactone method was applied to the synthesis of 3-hydroxy-substituted β-amino acid enantiomers.

Introduction

The number of investigations on β-amino acids, and especially alicyclic compounds, has increased exponentially because of their growing chemical and biological applications.[1] Various new synthetic strategies involving transformations to heterocycles[2] or peptides and peptidomimetics[3] have been developed. Although alicyclic saturated amino acids have also proved to be of great importance, their partially saturated analogs provide scope for further functionalization of the alicyclic ring, for example, one or two hydroxy groups have been incorporated.

Hydroxyamino acids may serve as building blocks in the synthesis of peptide analogs and heterocycles; they can take part in enzymatic transformations and can be used as a scaffold in combinatorial chemistry.[4]

While the chemistry and pharmacology of hydroxy-substituted α-amino acids have been widely studied,[5] less attention has been paid to their β analogs.[6] The hydroxy-β-amino acid unit is the essential moiety of several well-known, naturally occurring products that possess powerful biological activity. For example, Taxol derivatives,[7] the immunological response modifier dipeptide bestatin,[8] and the highly potent HIV-1 protease inhibitor kynostatins[9,10] contain an α-hydroxy-β-amino acid unit.

The first alicyclic hydroxy-β-amino acid to be isolated was oryzoxymycin (Figure 1), which was extracted from a *Streptomyces* species by Hashimoto and co-workers and has been found to exhibit moderate activity in vitro against *Xanthomonas oryzae*.[11]

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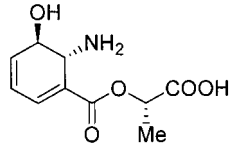

Figure 1. The structure of oryzoxymycin.

Since hydroxy-substituted β-amino acids are of both pharmacological and synthetic chemical interest, our aim was to synthesize saturated analogs of oryzoxymycin via iodooxazine or iodolactone intermediates. The enantiomerically pure forms of the hydroxy-β-amino acids may serve as chiral auxiliaries or additives; therefore we set out to prepare the enantiopure form of the 3-hydroxy-substituted β-amino acid derivative.

Results and Discussion

To achieve the desired iodocyclization of the unsaturated β-amino acid derivatives in the synthesis of 3- or 4-hydroxy derivatives, two pathways are available.[12] The cyclization reaction can be accomplished by attack of the activated double bond by the amide carbonyl of **3**, resulting in O,N-heterocycles (Scheme 1). Similarly, a five- or six-membered lactone ring can be produced by starting from *N*-Boc-protected amino acid **11** (Scheme 2). Recently we reported the regio- and diastereoselective functionalization of *cis*- and *trans*-2-amino-4-cyclohexenecarboxylic acids, regioisomers of compounds **3** and **11**, in the synthesis of 4- and 5-hydroxy-substituted 2-aminocyclohexanecarboxylic acids via 1,3-oxazine or γ-lactone intermediates.[13]

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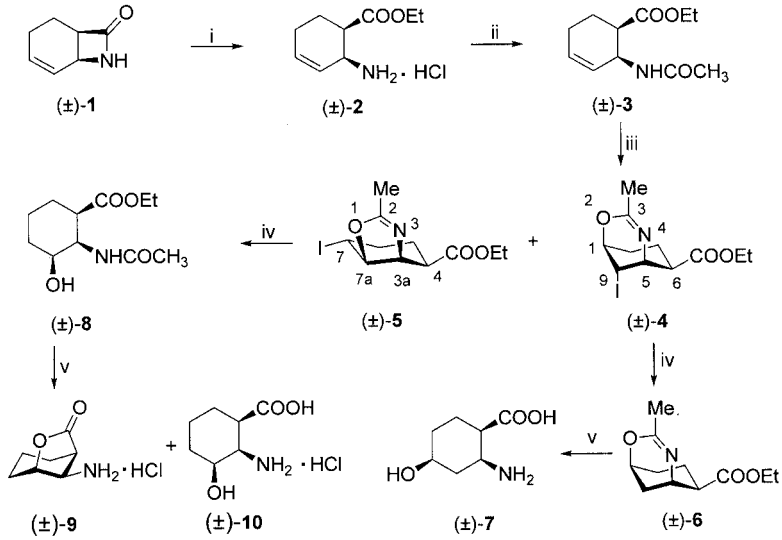
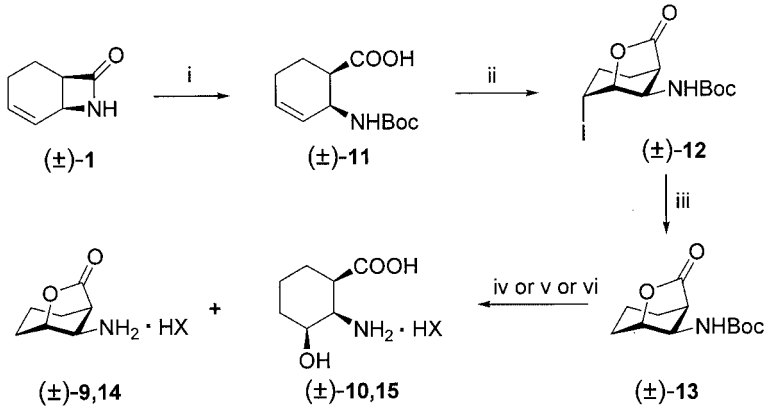


Scheme 1. Reagents and conditions: (i) 12% HCl, EtOH, reflux, 2 h, 76%; (ii) MeCOCl, Et_3N, $CHCl_3$, room temp., 2 h, 98%; (iii) NaI, I_2, $NaHCO_3$, CH_2Cl_2, 0 °C, 20 h, **4**: 27%, **5**: 63%; (iv) Bu_3SnH, AIBN, toluene, 60 °C, 6 h, N_2, followed by chromatography, **6**: 65%, **8**: 58%; (v) 10% HCl, H_2O, reflux, 30 h, **7**: 88%, a mixture (1:2) of **9** and **10**: 85%.



Scheme 2. Reagents and conditions: (i) Boc_2O, Et_3N, DMAP, THF, room temp., 3 h, then LiOH, H_2O/THF, room temp., 5 h, 90%; (ii) I_2, NaI, $NaHCO_3$, CH_2Cl_2, 0 °C, 20 h, 91%; (iii) Bu_3SnH, AIBN, toluene, 60 °C, 20 h, N_2, 98%; (iv) HCl/H_2O, room temp., 12 h; (v) HBr/H_2O, room temp., 12 h; (vi) Me_3SiBr, phenol, CH_2Cl_2, room temp., Ar, 2 h, 65%; **9** and **10**: X = Cl; **14** and **15**: X = Br.

The ring-opening reaction of β-lactam (±)-**1**,[14–16] derived from cyclohexadiene, with ethanolic hydrogen chloride resulted in the corresponding amino ester hydrochloride salt **2**.[17] After the acylation of **2**, the iodocyclization of *N*-acylamino ester **3** with iodine and sodium iodide in a two-phase solvent system proved to be unselective, resulting in a 30:70 mixture of iodooxazine **4** and iodooxazoline **5**. Isomers **4** and **5** were successfully separated and fully characterized by NMR measurements. The relative positions of the iodine atoms were deduced from the *J* couplings and the NOESY spectra. For **4**, the *J* values for the 9-H atom are 3.0 and 4.3 Hz, which are typical for an equatorial–equatorial hydrogen arrangement between 9-H and 1-H and between 9-H and 5-H. The NOESY spectrum shows only 1-H and 6-H NOE cross-peaks for 9-H, which proves that the relative position of the iodine atom is axial. For **5**, the *J* values for the 7-H atom are 4.5, 7.1, and 10.6 Hz, which shows an axial–axial and an axial–equatorial hydrogen arrangement between 7-H and 7a-H, 7-H and 6_{ax}-H, and 7-H and 6_{eq}-H. The NOESY spectrum reveals a 5_{ax}-H NOE cross-peak for 7-H, which proves that the relative position of the iodine atom is equatorial. The structures were confirmed by molecular modeling. The conformational protocol comprised a stochastic search using the Merck molecular force field (MMFF94). Figure 2 depicts stereoviews of typical minimum-energy molecular structures of **4** and **5**. Compound **4** was deiodinated with tributyltin hydride in the presence of a catalytic amount of azobis(isobutyronitrile) (AIBN) under nitrogen. Hydrolysis of oxazine **6** resulted in 4-hydroxyamino acid **7** in a low overall yield.

When the deiodination of **5** was attempted, the oxazoline moiety proved unstable and only the ring-opened product **8** could be isolated. Hydrolysis of *N*-acetylamino ester **8** under acidic conditions furnished a mixture of hydroxyamino acid (±)-**10** and amino lactone **9** (Scheme 1). Lactone **9** proved to be very stable under acidic conditions (even when it was refluxed in 25% hydrogen chloride solution for several hours).

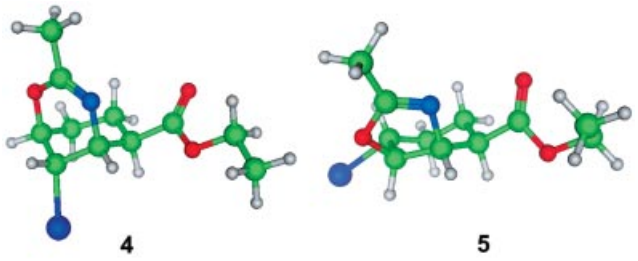


Figure 2. Stereoviews of typical minimum-energy structures of **4** and **5**.

Since the above procedure was not selective, even in two reaction steps, and only gave the 4-hydroxy derivative (±)-**7** in a low overall yield, we next focused on an iodolactonization protocol (Scheme 2). *N*-Boc protection of azetidinone (±)-**1** followed by hydrolysis with aqueous LiOH in THF gave *N*-Boc-amino acid (±)-**11**[16] in an excellent yield. The iodolactonization step was achieved under the same conditions as those used in the synthesis of iodooxazine, resulting in iodolactone (±)-**12** in 91% yield.[18] It appears that the chances of a five- or six-membered lactone ring being formed are the same, but in our case only the five-membered iodolactone (±)-**12** was obtained stereo- and regioselectively. The conversion of iodolactone (±)-**12** to *N*-Boc-lactone (±)-**13** was nearly quantitive in 20 h.

When ring-opening of the *N*-Boc-lactone (±)-**13** was attempted using different acidic reagents, similar to the hydrolysis of amido ester **8** (Scheme 1), a variable mixture of hydroxyamino acid (±)-**10** or **15** and deprotected stable amino lactone (±)-**9** or **14** was observed (Table 1). Deprotection of (±)-**13** with a mixture of bromotrimethylsilane and phenol under argon led to the formation of only the amino lactone **14**.

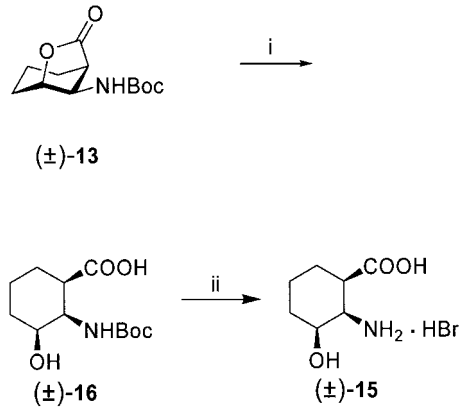
Table 1. Deprotection and hydrolysis of *N*-Boc-amino lactone (±)-**13**.

Reagents[a]	(±)-**9** or **14** [%]	(±)-**10** or **15** [%]
iv	23	77
v	15	85
vi	100	0

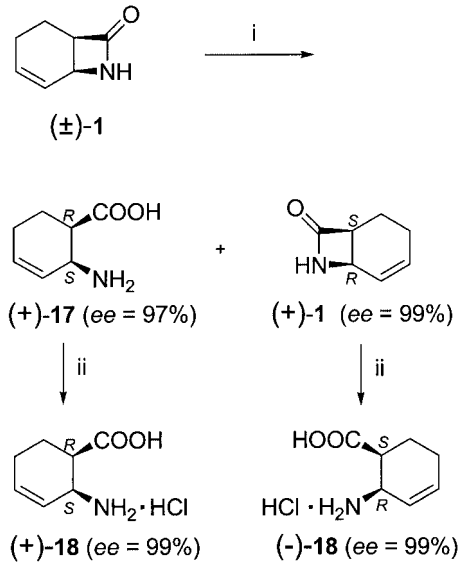
[a] Reagents and conditions: (iv) 10% HCl/H_2O, room temp., 12 h; (v) 10% HBr/H_2O, room temp., 12 h; (vi) Me_3SiBr, phenol, CH_2Cl_2, room temp., Ar, 2 h (see Scheme 2).

When the hydrolysis of (±)-**13** was carried out with aqueous LiOH in THF, the expected *N*-Boc-hydroxyamino acid (±)-**16** was obtained in an excellent yield. Deprotection of (±)-**16** with bromotrimethylsilane and phenol resulted in the desired 2-amino-3-hydroxycyclohexanecarboxylic acid (±)-**15** as the hydrobromide salt (Scheme 3).[19]

In order to synthesize the enantiopure hydroxy-substituted β-amino acids (+)-**15** and (–)-**15**, highly enantioselective CAL-B-catalyzed ring-opening of β-lactam (±)-**1** was performed ($E > 200$) (Scheme 4) following the literature procedure.[20] The enantiomers (+)-**1** and (+)-**17** obtained were transformed with 18% HCl into β-amino acid hydrochlorides (+)-**18** and (–)-**18**. After Boc protection, the hydroxyamino acid enantiomers (+)-**15** and (–)-**15** were synthesized following a procedure similar to that used for the synthesis of the racemic compound (±)-**15**.



Scheme 3. Reagents and conditions: (i) LiOH, H_2O, THF, room temp., 5 h, 98%; (ii) Me_3SiBr, phenol, CH_2Cl_2, room temp., 2 h, Ar atmosphere, 76%.



Scheme 4. Reagents and conditions: (i) CAL-B, H_2O (1 equiv.), iPr_2O, 65 °C; (ii) 18% HCl.

Conclusions

In summary, we have devised novel pathways to synthesize the 4-hydroxy-β-amino acid and its 3-hydroxy-substituted analog from 1,3-cyclohexadiene. Iodocyclization via **3** was not selective and gave only a low overall yield of 2-amino-4-hydroxycyclohexanecarboxylic acid **7**. On the other hand, iodolactonization proved to be an excellent protocol for the synthesis of either racemic or enantiomeric 2-amino-3-hydroxycyclohexanecarboxylic acid **15**. The β-amino acids that have been prepared are good starting materials for the synthesis of peptides and different heterocycles with potential biological activity.

Experimental Section

^1H and ^{13}C spectra were recorded with a Bruker Avance DRX 400 spectrometer [400 MHz, δ = 0 (TMS), in D_2O, DMSO, or $CDCl_3$]. Chemical shifts are expressed in ppm (δ relative to TMS as internal reference). *J* values are given in Hz. FTIR spectra were recorded with a Perkin–Elmer model 1000 spectrophotometer in KBr pellets. Microanalyses were determined with a Perkin–Elmer 2400 elemental analyzer.

Compounds (+)-**1**, (+)-**17**, (+)-**18**, and (–)-**18** were prepared by following literature methods.[18] Lipolase (lipase B from *Candida antarctica*), produced by submerged fermentation of a genetically modified *Aspergillus oryzae* microorganism and adsorbed onto a macroporous resin, was from Sigma–Aldrich (Catalog No. L4777). The *ee* values were determined by gas chromatography on a Chrompack Chirasil-Dex CB column (25 m) [without derivatization for (+)-**1**, (+)-**12**, (–)-**12**, (+)-**13**, and (–)-**13**; after derivatization with diazomethane for (+)-**11** and (–)-**11**; after double derivatization with diazomethane and acetic anhydride in the presence of 4-(dimethylamino)pyridine and pyridine for (+)-**15**, (–)-**15**, (+)-**16**, (–)-**16**, (+)-**17**, (+)-**18**, and (–)-**18**]. Optical rotations were measured with a Perkin–Elmer 341 polarimeter. Melting points were determined with a Kofler apparatus and are uncorrected.

(1*R,6*S**)-7-Azabicyclo[4.2.0]oct-4-en-8-one (1):** Compound **1** was synthesized following a modified literature method.[16a] 1,3-Cyclohexadiene (7.00 g, 87.0 mmol) in dry diethyl ether (100 mL) was added dropwise to a solution of chlorosulfonyl isocyanate (7.70 mL, 88.6 mmol) in dry diethyl ether (100 mL) over 10 min. After stirring for 30 min at room temperature, the reaction mixture was poured into a stirred solution of K_2CO_3 (35.93 g, 0.26 mol) and Na_2SO_3 (1.10 g, 8.7 mmol) in water (300 mL). The organic layer was separated, and the aqueous layer was washed with diethyl ether (2 × 500 mL) and then with chloroform (2 × 500 mL). The combined organic layers were dried with Na_2SO_4, and the solvents evaporated to dryness under reduced pressure. Recrystallization from ethyl acetate/*n*-hexane afforded pure compound **1**. Colorless crystals, 60% yield, m.p. 71–73 °C (ref.[16a] m.p. 70.5–71.5 °C). IR: $\tilde{\nu}_{max}$ = 1768, 3263 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.55–1.68 (m, 1 H, 2-H), 2.02–2.14 (m, 3 H, 2-H, 2 × 3-H), 3.45–3.53 (m, 1 H, 1-H), 4.01 (t, *J* = 4.8 Hz, 1 H, 6-H), 5.94 (dd, *J* = 4.5, 10.1 Hz, 1 H, 4-H), 6.08–6.16 (m, 1 H, 5-H), 6.81 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.2 (3-C), 22.3 (2-C), 44.7 (1-C), 50.1 (6-C), 126.6 (4-C), 134.7 (5-C), 172.8 (8-C) ppm. C_7H_9NO (123.15): calcd. C 68.27, H 7.37, N 11.37; found C 68.38, H 7.45, N 11.24.

Ethyl (1*R,2*S**)-2-Aminocyclohex-3-enecarboxylate Hydrochloride (2):** A solution of **1** (1.50 g, 12.0 mmol) in ethanol containing 12% HCl (50 mL) was refluxed for 2 h.[17] After removal of the solvent, amino ester **2** was obtained as the hydrochloride salt, which was recrystallized from ethanol/diethyl ether. Colorless crystals, 76% yield, m.p. 157–159 °C. IR: $\tilde{\nu}_{max}$ = 1718, 2860, 2902, 2977 cm^{-1}. ^1H NMR (D_2O): δ = 1.27 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.87–1.99 (m, 1 H, 6-H), 2.04–2.13 (m, 1 H, 6-H), 2.17–2.24 (m, 2 H, 2 × 5-H), 3.11 (dt, *J* = 3.5, 10.3 Hz, 1 H, 1-H), 4.13–4.29 (m, 3 H, 2-H, CH_2CH_3), 5.71–5.79 (m, 1 H, 3-H), 6.11–6.18 (m, 1 H, 4-H) ppm. ^{13}C NMR (D_2O): δ = 13.4 (CH_2CH_3), 20.6 (5-C), 23.5 (6-C), 40.9 (1-C), 46.2 (2-C), 62.4 (CH_2CH_3), 120.8 (3-C), 134.8 (4-C), 174.7 (C=O) ppm. $C_9H_{16}ClNO_2$ (205.09): calcd. C 52.56, H 7.84, N 6.81; found C 52.48, H 7.99, N 6.79.

Ethyl (1*R,2*S**)-2-Acetylaminocyclohex-3-enecarboxylate (3):** A solution of **2** (1.00 g, 5.9 mmol) in dry chloroform (30 mL) was treated with triethylamine (1.19 g, 11.8 mmol) and acetyl chloride (0.56 g, 7.1 mmol). After stirring for 2 h at room temperature, the reaction mixture was washed with water (2 × 20 mL). The combined aqueous layers were extracted with chloroform (2 × 30 mL), and the combined organic layers were dried (Na_2SO_4) and the solvent removed by evaporation under reduced pressure to afford **3**. Colorless crystals, 98% yield, m.p. 84–86 °C. IR: $\tilde{\nu}_{max}$ = 1724, 3257 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.24 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.88 (d, *J* = 6.3 Hz, 1 H, 6-H), 1.91 (d, *J* = 6.3 Hz, 1 H, 6-H), 1.93 (s, 3 H, Me), 2.00–2.07 (m, 2 H, 2 × 5-H), 2.80–2.86 (m, 1 H, 1-H), 4.06–4.16 (m, 2 H, CH_2CH_3), 4.82–4.89 (m, 1 H, 2-H), 5.56–5.62 (m, 1 H, 4-H), 5.76–5.81 (m, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.5 (CH_2CH_3), 22.6 (6-C), 23.5 (5-C), 23.8 (Me), 43.4 (1-C), 45.2 (2-C), 61.0 (CH_2CH_3), 127.7 (4-C), 129.7 (3-C), 169.7 (NHCOMe), 173.9 (COO) ppm. $C_{11}H_{17}NO_3$ (211.26): calcd. C 62.54, H 8.11, N 6.63; found C 62.62, H 8.23, N 6.54.

Iodocyclization of Carboxamide 3: A 0.5 M aqueous solution of $NaHCO_3$ (300 mL), NaI (34.48 g, 0.23 mol), and I_2 (14.83 g, 117.0 mmol) were added to a solution of carboxamide **3** (8.24 g, 39.0 mmol) in dry dichloromethane (200 mL) at 0 °C. After stirring for 20 h at room temperature, the excess of I_2 was decomposed with an aqueous 1 M $Na_2S_2O_3$ solution. The phases were separated and the organic phase was washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo to give a mixture of iodooxazine **4** and iodooxazoline **5** (in a ratio of 30:70, based on ^1H NMR measurements), which were separated by column chromatography (dichloromethane/ethyl acetate, 10:1).

Ethyl (1*S,5*R**,6*R**,9*S**)-9-Iodo-3-methyl-2-oxa-4-azabicyclo-[3.3.1]non-3-ene-6-carboxylate (4):** Yellowish crystals, 27% yield, m.p. 93–95 °C. IR: $\tilde{\nu}_{max}$ = 1031, 1225, 1655, 1731, 2930 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.27 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.71 (ddd, *J* = 5.0, 14.1 Hz, 1 H, 7-H), 1.77–1.86 (m, 1 H, 7-H), 1.96 (s, 3 H, Me), 2.03–2.11 (m, 1 H, 8-H), 2.40 (ddd, *J* = 1.8, 5.5, 14.9 Hz, 1 H, 8-H), 3.25 (ddd, *J* = 2.8, 4.5, 12.3 Hz, 1 H, 6-H), 4.11 (dd, *J* = 3.3, 5.8 Hz, 1 H, 5-H), 4.13–4.25 (m, 2 H, CH_2CH_3), 4.42–4.46 (m, 1 H, 1-H), 4.67 (dd, *J* = 3.0, 4.3 Hz, 1 H, 9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.8 (CH_2CH_3), 18.3 (7-C), 21.4 (Me), 26.7 (9-C), 27.9 (8-C), 43.3 (6-C), 55.1 (5-C), 61.5 (CH_2CH_3), 74.3 (1-C), 160.2 (3-C), 173.9 (COO) ppm. $C_{11}H_{16}INO_3$ (337.15): calcd. C 39.19, H 4.78, N 4.15; found C 39.51, H 4.52, N 4.45.

Ethyl (3a*R,4*R**,7*R**,7a*R**)-7-Iodo-2-methyl-3a,4,5,6,7,7a-hexahydrobenzoxazole-4-carboxylate (5):** White crystals, 63% yield, m.p. 170–173 °C. IR: $\tilde{\nu}_{max}$ = 1041, 1203, 1663, 1729, 2978 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.28 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.66–1.96 (m, 3 H, 5-H, 2 × 6-H), 2.00 (d, *J* = 1.8 Hz, 3 H, Me), 2.19–2.29 (m, 1 H, 5-H), 2.99 (dt, *J* = 5.3, 12.3 Hz, 1 H, 4-H), 3.89 (ddd, *J* = 4.5, 7.1, 10.6 Hz, 1 H, 7-H), 4.17–4.28 (m, 2 H, CH_2CH_3), 4.34–4.40 (m, 1 H, 3a-H), 4.90 (dd, *J* = 7.3, 8.1 Hz, 1 H, 7a-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.9 (CH_2CH_3), 15.2 (Me), 23.5 (6-C), 27.2 (7-C), 32.5 (5-C), 41.7 (4-C), 61.5 (CH_2CH_3), 66.5 (3a-C), 85.7 (7a-C), 161.4 (2-C), 173.5 (COO) ppm. $C_{11}H_{16}INO_3$ (337.15): calcd. C 39.19, H 4.78, N 4.15; found C 39.01, H 4.62, N 4.39.

Iodocyclization of *N*-Boc-Amino Acid Derivatives

(1*R,4*R**,5*R**,8*R**)-8-(*tert*-Butoxycarbonylamino)-4-iodo-6-oxabicyclo[3.2.1]octan-7-one [(±)-12]:** A 0.5 M aqueous solution of $NaHCO_3$ (300 mL), NaI (34.48 g, 0.23 mol), and I_2 (9.89 g, 78.0 mmol) were added to a solution of *N*-Boc-amino acid **11** (9.41 g, 39.0 mmol) in dry dichloromethane (200 mL) at 0 °C. After stirring for 20 h, the mixture was poured into an aqueous 1 M $Na_2S_2O_3$ solution (100 mL). The phases were separated and the organic phase was washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo to give iodolactone **12**. Colorless crystals, 91% yield (ethyl acetate/*n*-hexane), m.p. 132–134 °C. IR: $\tilde{\nu}_{max}$ = 1710, 2926, 3228 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.46 (s, 9 H,

OC*Me*$_3$), 1.87–1.97 (m, 1 H, 2-H), 1.99–2.13 (m, 2 H, 2-H, 3-H), 2.25–2.39 (m, 1 H, 3-H), 2.74 (s, 1 H, 1-H), 4.53 (t, J = 4.5 Hz, 1 H, 4-H), 4.71 (d, J = 4.0 Hz, 1 H, 5-H), 4.77 (br. s, 1 H, 8-H), 4.83 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.2 (4-C), 23.5 (2-C), 28.9 (3-C), 29.2 (OC*Me*$_3$), 45.9 (1-C), 58.0 (8-C), 81.0 (O*C*Me$_3$), 84.3 (5-C), 155.4 (COO), 176.9 (7-C) ppm.

(1*R*,4*R*,5*S*,8*R*)-8-(*tert*-Butoxycarbonylamino)-4-iodo-6-oxabicyclo-[3.2.1]octan-7-one [(+)-12]: The synthesis was accomplished according to the above procedure, starting from (+)-**11**. Colorless crystals, 89% yield (ethyl acetate/*n*-hexane), m.p. 134–135 °C, $[\alpha]_D^{20}$ = +6.8 (c = 0.5, MeOH). The ^{1}H NMR spectroscopic data were similar to those for (±)-**12**. $C_{12}H_{18}INO_4$ (367.18): calcd. C 39.25, H 4.94, N 3.81; found C 39.34, H 5.06, N 3.75.

(1*S*,4*S*,5*R*,8*S*)-8-(*tert*-Butoxycarbonylamino)-4-iodo-6-oxabicyclo-[3.2.1]octan-7-one [(–)-12]: The synthesis was accomplished according to the above procedure, starting from (–)-**11**. Colorless crystals, 86% yield (ethyl acetate/*n*-hexane), m.p. 134–135 °C, $[\alpha]_D^{20}$ = –7.0 (c = 0.5, MeOH). The ^{1}H NMR spectroscopic data were similar to those for (±)-**12**. $C_{12}H_{18}INO_4$ (367.18): calcd. C 39.25, H 4.94, N 3.81; found C 39.33, H 5.05, N 3.75.

General Procedure for the Deiodination Reaction: Tributyltin hydride (9.32 g, 32.0 mmol) and azobis(isobutyronitrile) (0.26 g, 1.60 mmol) were added to a solution of the iodo compound (16.0 mmol) in dry toluene (200 mL) under nitrogen. After stirring at 60 °C for 6 h under the inert atmosphere, the solvent was evaporated in vacuo. Compounds **6** and **8** were purified by column chromatography (toluene/ethanol 9:1), while **13** was crystallized from *n*-hexane.

Ethyl (1*S,5*R**,6*R**)-3-Methyl-2-oxa-4-azabicyclo[3.3.1]non-3-ene-6-carboxylate (6):** The synthesis was accomplished according to the general procedure, starting from **4**. A colorless oil, 65% yield. IR: $\tilde{\nu}_{max}$ = 1667, 1743, 2872, 2942 cm^{-1}. ^{1}H NMR (DMSO): δ = 1.18 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 1.26–1.38 (m, 1 H, 8-H), 1.45 (ddd, J = 4.3, 12.6 Hz, 1 H, 7-H), 1.52–1.82 (m, 3 H, 7-H, 8-H, 9-H), 1.83 (s, 3 H, CH_3), 1.89–1.97 (m, 1 H, 9-H), 2.68 (dt, J = 3.0, 12.1 Hz, 1 H, 6-H), 3.88 (s, 1 H, 5-H), 3.99–4.11 (m, 2 H, CH_2CH_3), 4.43 (s, 1 H, 1-H) ppm. ^{13}C NMR (DMSO): δ = 14.1 (CH_2CH_3), 17.9 (7-C), 21.0 (Me), 27.7 (8-C), 31.1 (9-C), 45.5 (6-C), 48.1 (5-C), 59.7 (CH_2CH_3), 69.2 (1-C), 158.6 (3-C), 172.6 (COO) ppm. $C_{11}H_{17}NO_3$ (211.26): calcd. C 62.54, H 4.11, N 6.63; found C 62.52, H 4.15, N 6.67.

Ethyl (1*R,2*R**,3*S**)-2-Acetylamino-3-hydroxycyclohexanecarboxylate (8):** The synthesis was accomplished according to the general procedure, starting from **5**. Colorless crystals, 58% yield (ethyl acetate/*n*-hexane), m.p. 125–128 °C. IR: $\tilde{\nu}_{max}$ = 1223, 1551, 1654, 1734, 2930, 3316 cm^{-1}. ^{1}H NMR (DMSO): δ = 1.27 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.37–1.66 (m, 6 H, 2×4-H, 2×5-H, 2×6-H), 1.81 (s, 3 H, Me), 2.45 (dt, J = 3.5, 12.1 Hz, 1 H, 1-H), 3.46–3.55 (m, 1 H, 3-H), 3.93 (dd, J = 7.6, 14.6 Hz, 2 H, CH_2CH_3), 4.48–4.51 (m, 1 H, 2-H), 7.30 (d, J = 9.8 Hz, 1 H, NH) ppm. ^{13}C NMR (DMSO): δ = 13.9 (CH_2CH_3), 21.3 (5-C), 21.8 (6-C), 22.8 (Me), 28.4 (4-C), 44.6 (1-C), 50.6 (2-C), 59.6 (CH_2CH_3), 69.3 (3-C), 169.6 (NHCO), 172.5 (COO) ppm. $C_{11}H_{19}NO_4$ (229.27): calcd. C 57.62, H 8.35, N 6.11; found C 57.85, H 8.07, N 6.45.

(1*R,5*R**,8*R**)-8-(*tert*-Butoxycarbonylamino)-6-oxabicyclo[3.2.1]-octan-7-one [(±)-13]:** The synthesis was accomplished according to the general procedure, starting from (±)-**12**. Colorless crystals, 98% yield (*n*-hexane), m.p. 145–147 °C. IR: $\tilde{\nu}_{max}$ = 1702, 1718, 3136, 3249 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.44 (s, 9 H, OC*Me*$_3$), 1.61–1.81 (m, 4 H, 2×2-H, 3-H, 4-H), 1.97–2.14 (m, 2 H, 3-H, 4-H), 2.67 (d, J = 3.5 Hz, 1 H, 1-H), 3.80 (d, J = 6.3 Hz, 1 H, 8-H), 4.71 (d, J = 4.8 Hz, 1 H, 5-H), 4.84 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.9 (2-C), 26.6 (3-C), 28.5 (4-C), 29.0 (OC*Me*$_3$), 46.2 (1-C), 60.5 (8-C), 81.1 (O*C*Me$_3$), 82.8 (5-C), 155.7 (COO), 177.7 (7-C) ppm. $C_{12}H_{19}NO_4$ (241.28): calcd. C 59.73, H 7.94, N 5.80; found C 59.82, H 7.99, N 5.72.

(1*R*,5*R*,8*R*)-8-(*tert*-Butoxycarbonylamino)-6-oxabicyclo[3.2.1]octan-7-one [(+)-13]: The synthesis was accomplished according to the general procedure, starting from (+)-**12**. Colorless crystals, 98% yield (*n*-hexane), m.p. 143–144 °C, $[\alpha]_D^{20}$ = +7.0 (c = 0.5, MeOH); *ee* = 99%. The ^{1}H NMR spectroscopic data were similar to those for (±)-**13**. $C_{12}H_{19}NO_4$ (241.28): calcd. C 59.73, H 7.94, N 5.80; found C 59.81, H 8.01, N 5.70.

(1*S*,5*S*,8*S*)-8-(*tert*-Butoxycarbonylamino)-6-oxabicyclo[3.2.1]octan-7-one [(–)-13]: The synthesis was accomplished according to the general procedure, starting from (–)-**12**. Colorless crystals, 96% yield (*n*-hexane), m.p. 143–144 °C, $[\alpha]_D^{20}$ = –6.9 (c = 0.5, MeOH); *ee* = 99%. The ^{1}H NMR spectroscopic data were similar to those for (±)-**13**. $C_{12}H_{19}NO_4$ (241.28): calcd. C 59.73, H 7.94, N 5.80; found C 59.80, H 7.97, N 5.71.

(1*R,2*S**,4*S**)-2-Amino-4-hydroxycyclohexanecarboxylic Acid (7):** A solution of **6** (0.20 g, 0.9 mmol) and 10% HCl in H_2O (20 mL) was refluxed for 30 h. The aqueous solvent was evaporated to afford the amino acid hydrochloride salt, which was purified on a resin column (Dowex 50) to give **7**. Colorless crystals, 88% yield (ethanol/diethyl ether), m.p. 140–141 °C. IR: $\tilde{\nu}_{max}$ = 1725, 3048, 3452 cm^{-1}. ^{1}H NMR (D_2O): δ = 1.41 (s, 1 H, 5-H), 1.55–1.67 (m, 1 H, 6-H), 1.78–1.91 (m, 2 H, 3-H, 5-H), 2.06 (dt, J = 3.5, 12.6 Hz, 1 H, 3-H), 2.10–2.22 (m, 1 H, 6-H), 2.58 (q, J = 4.4 Hz, 1 H, 2-H), 3.49 (dt, J = 4.1, 13.6 Hz, 1 H, 1-H), 3.88 (m, 1 H, 4-H) ppm. ^{13}C NMR (D_2O): δ = 22.9, 30.8, 34.7, 42.6, 49.0, 67.5, 180.3 ppm. $C_7H_{13}NO_3$ (159.18): calcd. C 52.82, H 8.23, N 8.80; found C 52.84, H 8.29, N 8.78.

General Procedure for the Acidic Hydrolysis of 8 and 13: A solution of amide **8** (1.0 mmol) or *N*-Boc-amino lactone **13** (1.0 mmol) and 10% HCl in H_2O (20 mL, for **9** and **10**) or 10% HBr in H_2O (20 mL, for **14** and **15**) was stirred for 12 h at room temperature. The solution was then evaporated to dryness to give a mixture of **9** and **10** or a mixture of **14** and **15**. The ratio between the corresponding amino lactone and hydroxyamino acid was determined by NMR spectroscopy, based on integration of the 1-H singlets at δ = 3.04 ppm for **14** and at δ = 2.87 ppm for **15**. The attempted separation of the products was not successful.

(1*R,2*S**)-2-(*tert*-Butoxycarbonylamino)cyclohex-3-enecarboxylic Acid [(±)-11]:** Triethylamine (4.20 mL, 294.0 mmol), di-*tert*-butyl dicarbonate (7.86 g, 36.0 mmol), and a catalytic amount of DMAP were added to a stirred solution of azetidinone (±)-**1** (4.0 g, 30 mmol) and dry THF (100 mL). After stirring for 12 h at room temperature (the reaction was monitored by TLC), the mixture was evaporated to dryness. The oily residue obtained was purified by flash chromatography on a silica gel column (toluene/ethanol, 9:1), and the resulting white crystalline product (7.2 g, 97%) was dissolved in THF (75 mL) and treated with aqueous LiOH (4.40 g in 50 mL of water) at room temperature. The mixture was stirred at room temperature for 5 h. Then THF was removed in vacuo, water (50 mL) was added, and the solution was acidified to pH 3.5–4.0 with acetic acid and extracted with ethyl acetate (3×80 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to give (±)-**11**.[16a] Colorless crystals, 6.51 g, 90% yield (*n*-hexane), m.p. 119–121 °C (ref.[16a] m.p. 110–118 °C). IR: $\tilde{\nu}_{max}$ = 1710, 2932 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.44 (s, 9 H, OC*Me*$_3$), 1.87–2.21 (m, 4 H, 2×5-H, 2×6-H), 2.89 (s, 1 H, 1-H), 4.57 (s, 1 H, 2-H), 5.15 (d, J = 5.5 Hz, 1 H, NH), 5.60–5.86 (m, 2 H, 3-H, 4-H), 10.15

(br. s, 1 H, OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.8 (5-C), 23.7 (6-C), 29.0 (OC*Me*$_3$), 44.0 (2-C), 47.0 (1-C), 80.3 (O*C*Me$_3$), 128.2 (3-C), 129.8 (4-C), 156.1 (COO), 179.3 (COOH) ppm. $C_{12}H_{19}NO_4$ (241.28): calcd. C 59.73, H 7.94, N 5.80; found C 59.82, H 7.99, N 5.72.

(1*R*,2*S*)-2-(*tert*-Butoxycarbonylamino)cyclohex-3-enecarboxylic Acid [(+)-11]: An aqueous solution of NaOH (0.18 g, 4.5 mmol) was added to a solution of amino acid hydrochloride (+)-**18** (0.40 g, 2.3 mmol) in dioxane/water (2:1, 30 mL) at room temperature. After cooling to 0 °C, the solution was treated with di-*tert*-butyl dicarbonate (0.55 g, 2.5 mmol). The reaction mixture was then left to warm to room temperature and stirred for 4 h. The dioxane was removed under reduced pressure and the aqueous residue was acidified to pH 2.5 with dilute H_2SO_4 (10%). This solution was extracted with ethyl acetate (3 × 30 mL), dried (Na_2SO_4), and the solvent removed by evaporation. Colorless crystals, 88% yield (*n*-hexane), m.p. 122–123 °C, $[\alpha]_D^{20}$ = +22.3 (*c* = 0.5, MeOH). The ^{1}H NMR spectroscopic data were similar to those for (±)-**11**. $C_{12}H_{19}NO_4$ (241.28): calcd. C 59.73, H 7.94, N 5.80; found C 59.82, H 7.99, N 5.72.

(1*S*,2*R*)-2-(*tert*-Butoxycarbonylamino)cyclohex-3-enecarboxylic Acid [(–)-11]: The synthesis was accomplished as for (+)-**11**, starting from (–)-**18**. Colorless crystals, 85% yield (*n*-hexane), m.p. 122–123 °C, $[\alpha]_D^{20}$ = –22.1 (*c* = 0.5, MeOH). The ^{1}H NMR spectroscopic data were similar to those for (±)-**11**. $C_{12}H_{19}NO_4$ (241.28): calcd. C 59.73, H 7.94, N 5.80; found C 59.82, H 7.99, N 5.72.

(1*R,2*R**,3*R**)-8-Amino-6-oxabicyclo[3.2.1]octan-7-one Hydrobromide [(±)-14]:** The Boc group was removed as in the synthesis of (±)-**15** (see below), starting from (±)-**13**. Colorless crystals, 65% yield, m.p. 259–260 °C. IR: $\tilde{\nu}_{max}$ = 1718, 3132, 3245 cm^{-1}. ^{1}H NMR (D_2O): δ = 1.48–1.62 (m, 1 H, 2-H), 1.76–1.95 (m, 3 H, 2-H, 3-H, 4-H), 1.98–2.08 (m, 1 H, 3-H), 2.11–2.20 (m, 1 H, 4-H), 3.04, (s, 1 H, 1-H), 3.85 (s, 1 H, 8-H), 5.08 (d, *J* = 4.03 Hz, 1 H, 5-H) ppm. ^{13}C NMR (D_2O): δ = 16.8 (2-C), 26.0 (3-C), 27.3 (4-C), 44.2 (1-C), 59.2 (8-C), 81.5 (5-C), 178.9 (7-C) ppm. $C_7H_{12}BrNO_2$ (222.08): calcd. C 37.86, H 5.45, N 6.31; found C 37.78, H 5.52, N 6.24.

(1*R,2*R**,3*S**)-2-(*tert*-Butoxycarbonylamino)-3-hydroxycyclohexanecarboxylic Acid [(±)-16]:** *N*-Boc-lactone (±)-**13** (11.82 g, 49.0 mmol) was dissolved in THF (200 mL) and treated with LiOH (6.29 g, 0.15 mol) in water (150 mL). The mixture was stirred at room temperature for 5 h. The THF was removed in vacuo, and the aqueous residue was acidified to pH 3.5–4.0 with dilute acetic acid (10%) and extracted with ethyl acetate (3 × 200 mL). Drying (Na_2SO_4) and removal of the solvent in vacuo afforded (±)-**16**. Colorless crystals, 98% yield (*n*-hexane), m.p. 128–129 °C. IR: $\tilde{\nu}_{max}$ = 1706, 2938, 3318 cm^{-1}. ^{1}H NMR (D_2O): δ = 1.08–1.35 (m, 12 H, 4-H, 2 × 5-H, OC*Me*$_3$), 1.47–1.63 (m, 3 H, 4-H, 2 × 6-H), 2.51 (d, *J* = 12.0 Hz, 1 H, 1-H), 3.61 (s, 1 H, 2-H), 4.18 (s, 1 H, 3-H) ppm. ^{13}C NMR (D_2O): δ = 21.4 (6-C), 2 × 21.8 (4-C, 5-C), 27.9 (OC*Me*$_3$), 45.4 (1-C), 52.5 (2-C), 70.4 (3-C), 81.0 (O*C*Me$_3$), 158.4 (COO), 177.9 (COOH) ppm. $C_{12}H_{13}NO_5$ (251.23): calcd. C 55.58, H 8.16, N 5.40; found C 55.64, H 8.24, N 5.31.

(1*R*,2*R*,3*S*)-2-(*tert*-Butoxycarbonylamino)-3-hydroxycyclohexanecarboxylic Acid [(+)-16]: The synthesis was accomplished as for (±)-**16**, starting from (+)-**13**. Colorless crystals, 94% yield (*n*-hexane), m.p. 128–129 °C, $[\alpha]_D^{20}$ = +23.2 (*c* = 0.5, MeOH); *ee* = 99%. The ^{1}H NMR spectroscopic data were similar to those for (±)-**15**. $C_{12}H_{13}NO_5$ (251.23): calcd. C 55.58, H 8.16, N 5.40; found C 55.62, H 8.19, N 5.28.

(1*S*,2*S*,3*R*)-2-(*tert*-Butoxycarbonylamino)-3-hydroxycyclohexanecarboxylic Acid [(–)-16]: The synthesis was accomplished as for (±)-**16**, starting from (–)-**13**. Colorless crystals, 92% yield (*n*-hexane), m.p. 128–129 °C, $[\alpha]_D^{20}$ = –22.8 (*c* = 0.5, MeOH); *ee* = 99%. The ^{1}H NMR spectroscopic data were similar to those for (±)-**15**. $C_{12}H_{13}NO_5$ (251.23): calcd. C 55.58, H 8.16, N 5.40; found C 55.63, H 8.20, N 5.31.

(1*R,2*R**,3*S**)-2-Amino-3-hydroxycyclohexanecarboxylic Acid Hydrobromide [(±)-15]:** Compound (±)-**16** (1.14 g, 4.6 mmol) in dry dichloromethane (4 mL) was added to a solution of bromotrimethylsilane (1.04 g, 6.8 mmol) and phenol (0.03 g, 0.3 mmol) in dry dichloromethane (5 mL) at room temperature under argon. After stirring for 2 h, removal of the solvent afforded (±)-**15** as the hydrobromide salt. Colorless crystals, 76% yield (ethanol/diethyl ether), m.p. 243–244 °C. IR: $\tilde{\nu}_{max}$ = 1718, 3022, 3425 cm^{-1}. ^{1}H NMR (D_2O): δ = 1.37–1.52 (m, 2 H, 5-H, 6-H), 1.56–1.67 (m, 1 H, 4-H), 1.80–1.94 (m, 3 H, 4-H, 5-H, 6-H), 2.87 (dt, *J* = 3.5, 11.0 Hz, 1 H, 1-H), 3.82 (t, *J* = 3.0 Hz, 1 H, 2-H), 3.95–4.01 (m, 1 H, 3-H) ppm. ^{13}C NMR (D_2O): δ = 20.9 (5-C), 22.4 (6-C), 27.7 (4-C), 42.0 (1-C), 53.1 (2-C), 67.6 (3-C), 176.6 (COOH) ppm. $C_7H_{14}BrNO_3$ (240.09): calcd. C 35.02, H 5.88, N 5.83; found C 35.13, H 5.82, N 5.75.

(1*R*,2*R*,3*S*)-2-Amino-3-hydroxycyclohexanecarboxylic Acid Hydrobromide [(+)-15]: The synthesis was accomplished as for (±)-**15**, starting from (+)-**16**. Colorless crystals, 65% yield (ethanol/diethyl ether), m.p. 240–241 °C, $[\alpha]_D^{20}$ = +14.0 (*c* = 0.5, H_2O); *ee* > 98%. The ^{1}H NMR spectroscopic data were similar to those for (±)-**15**. $C_7H_{14}BrNO_3$ (240.09): calcd. C 35.02, H 5.88, N 5.83; found C 35.17, H 5.80, N 5.73.

(1*S*,2*S*,3*R*)-2-Amino-3-hydroxycyclohexanecarboxylic Acid Hydrobromide [(–)-15]: The synthesis was accomplished as for (±)-**15**, starting from (–)-**16**. Colorless crystals, 66% yield (ethanol/diethyl ether), m.p. 240–241 °C, $[\alpha]_D^{20}$ = –14.2 (*c* = 0.5, H_2O); *ee* = 99%. The ^{1}H NMR spectroscopic data were similar to those for (±)-**15**. $C_7H_{14}BrNO_3$ (240.09): calcd. C 35.02, H 5.88, N 5.83; found C 35.11, H 5.78, N 5.72.

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