Facile Regio- and Diastereoselective Syntheses of Hydroxylated 2-Aminocyclohexanecarboxylic Acids

Ferenc Fülöp,*[a] Márta Palkó,[a] Enikő Forró,[a] Máté Dervarics,[a] Tamás A. Martinek,[a] and Reijo Sillanpää[b]

Dedicated to Professor András Lipták on the occasion of his 70th birthday

Keywords: Amino acids / Heterocycles / Diastereoselectivity / Structure elucidation

By means of total regio- and diastereoselective functionalizations of *cis*- and *trans*-2-amino-4-cyclohexenecarboxylic acid derivatives **1**, **9**, **12** and **16**, isomers of 2-amino-4-hydroxycyclohexanecarboxylic acid **8** and **11**, and 2-amino-5-hydroxycyclohexanecarboxylic acid **15** and **19** were prepared in good yields, via 1,3-oxazine or γ-lactone intermediates. The enantiomers of **8** and **15** were also prepared by the same pathway, resulting in products with *ee* > 99 %. The structures, stereochemistry and relative configurations of the synthesized compounds were proved by NMR, using some key vicinal couplings and characteristic NOEs.

Introduction

The continuously increasing interest in cyclic β-amino acids[1–3] is mainly connected with the importance of the naturally occurring cispentacin,[4] which exhibits strong anticandida activity. A further feature is the fact that Gellman′s group recently synthesized and investigated[5] *trans*-2-aminocyclopentane- and *trans*-2-aminocyclohexanecarboxylic acid oligomers, which clearly display a stable helical conformation. We have found that by inversion of the relative configurations of the *cis* oligomers, the preferred conformation can be switched from a helix to a single nonpolar strand.[6] Cyclic β-amino acids are widely used as starting substances for the preparation of heterocycles. Through their incorporation in place of an α-amino acid of a naturally occurring pharmacologically active peptide, the activities can be modified and the stabilities of the natural peptides can be increased. Changes of configuration and differences in ring size allow modification of the conformation of the peptides. They are also applicable in combinatorial syntheses.[7–10]

In recent years, a number of new syntheses of functionalized derivatives have been reported (see, for example, ref.[11]). Among them, hydroxy-substituted β-amino acids are of considerable importance because of their occurrence in many biologically active compounds (e.g. taxol and related molecules).[2,7] Our present aim was to introduce an extra hydroxy group at position 4 or 5 of the cyclohexane ring. For these syntheses, the readily available *cis*- and *trans*-2-amino-4-cyclohexenecarboxylic acids were used. For the derivatization, we considered two strategies: cyclization on an acylamino derivative via 1,3-oxazine formation, or cyclization on a carboxylic acid function via lactone formation (iodolactonization protocol).

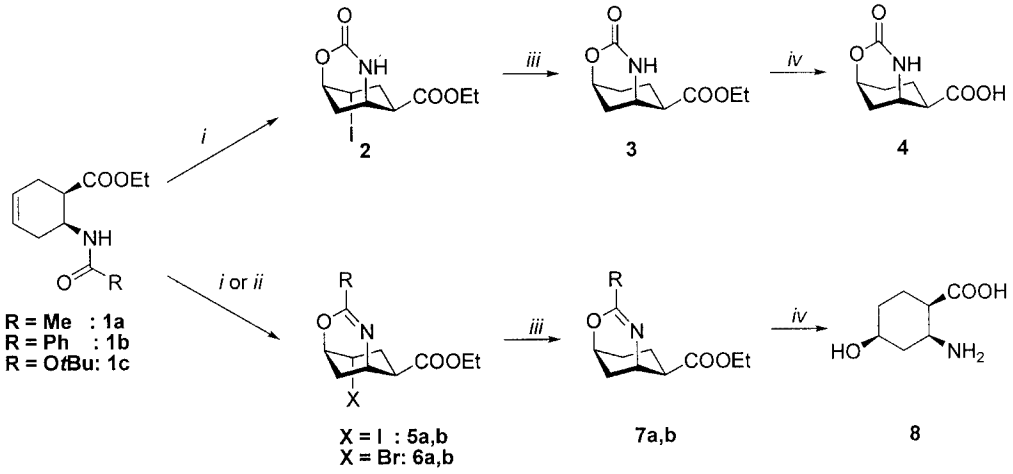
Results and Discussion

The starting *cis*-2-amino-4-cyclohexenecarboxylic acid was prepared by hypochlorite-mediated Hoffman degradation of the carboxamide obtained by ammonolysis of *cis*-1,2,3,6-tetrahydrophthalic anhydride.[12] The amino acid was esterified in the presence of ethanol and thionyl chloride and then acylated with acetic anhydride, benzoyl chloride, or *tert*-butoxy pyrocarbonate, resulting in *N*-acylated amino esters **1a-c**, respectively.

With *N*-iodo- (NIS) or *N*-bromosuccinimide (NBS) (for a related transformation, see, for example, ref.[13]), the *N*-Boc derivative **1c** gave oxazinone **2**, while the *N*-acetyl and *N*-benzoyl derivatives **1a** and **1b** furnished the corresponding methyl- or phenyl-substituted oxazines **5a,b** and **6a,b** regio- and diastereoselectively (Scheme 1). Not even traces of other regio- or diastereomers were observed in the crude product. Iodooxazinone **2** and bromooxazine derivatives **5a,b** or **6a,b** were dehalogenated with tributyltin hydride under argon, resulting in compounds **3** and **7a,b**, respectively.

[a] Institute of Pharmaceutical Chemistry, University of Szeged, P. O. Box 121, 6701 Szeged, Hungary
Fax: +36-62-545705
E-mail: fulop@pharma.szote.u-szeged.hu
[b] Department of Chemistry, University of Jyväskylä, 40351 Jyväskylä, Finland

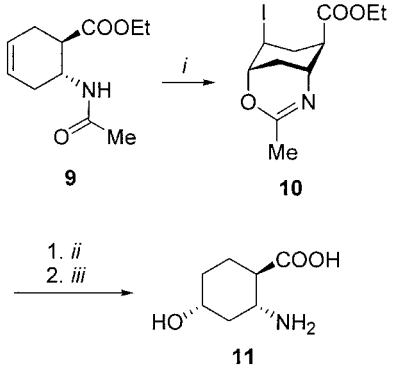
 DOI: 10.1002/ejoc.200500062



Scheme 1. (*i*) NIS, CH_2Cl_2, 14 h, room temp.; (*ii*) NBS, CH_2Cl_2, 14 h, room temp.; (*iii*) Bu_3SnH, CH_2Cl_2, 20 h, 40 °C; (*iv*) 20% HCl, 30 h reflux.

Acidic hydrolysis of **3** gave the stable oxazinonecarboxylic acid derivative **4**, which slowly decomposed on further heating. Hydrolysis of oxazines **7a,b** with 20% aqueous HCl, and removal of the HCl by ion-exchange chromatography led to **8**, the *all-cis* isomer of 2-amino-4-hydroxycyclohexanecarboxylic acid (Scheme 1).

The corresponding *trans*-2-amino-4-cyclohexenecarboxylic acid was prepared by Hoffman degradation of the carboxamide obtained by ammonolysis of *trans*-1,2,3,6-tetrahydrophthalic anhydride. The amino acid was esterified, and subsequent treatment with acetic anhydride resulted in *N*-acetylamino ester **9**. By a similar transformation as for the *cis* isomer **1a**, the *trans*-2-acetylamino-4-cyclohexenecarboxylic acid **9** reacted via the iodooxazine intermediate **10** to furnish the corresponding (*r*-1,*t*-2,*t*-4)-2-amino-4-hydroxycyclohexanecarboxylic acid **11** (Scheme 2).

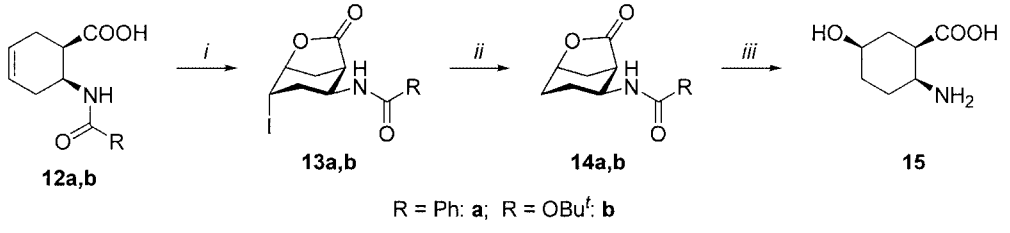


Scheme 2. (*i*) NIS, CH_2Cl_2, 14 h, room temp.; (*ii*) Bu_3SnH, CH_2Cl_2, 20 h, 40 °C; (*iii*) 20% HCl, 30 h reflux.

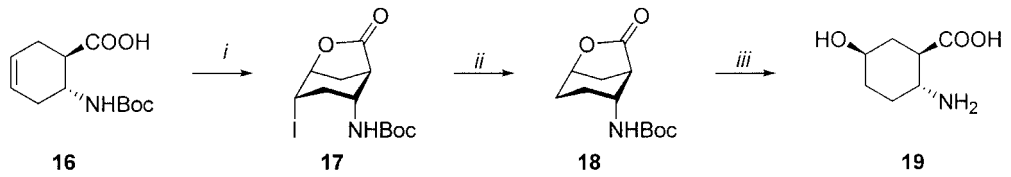
Stereoselective iodolactonization[7] was the key step in the synthesis of 2-amino-5-hydroxycyclohexanecarboxylic acid. The reactions of *N*-benzoyl- and *N*-Boc-protected *cis*-2-amino-4-cyclohexenecarboxylic acid **12a**,**b** with I_2/KI in slightly alkaline medium yielded the iodolactones **13a,b** in fairly good yields, with excellent regio- and diastereoselectivity. The products were reduced with tributyltin hydride to give lactones **14a**,**b**. The acidic hydrolysis of benzoyl derivative **14a** did not give the desired amino acid; instead, decomposition took place. When the *N*-Boc lactone **14b** was hydrolysed after ion-exchange chromatography, the *all-cis* isomer of 2-amino-5-hydroxycyclohexanecarboxylic acid **15** was obtained in 66% yield (Scheme 3).

By a similar transformation from *trans*-2-*tert*-butoxycarbonylamino-4-cyclohexenecarboxylic acid **16** via iodolactone **17**, the corresponding (*r*-1,*t*-2,*c*-5)-2-amino-5-hydroxycyclohexanecarboxylic acid **19** was prepared (Scheme 4).

The *cis* compounds (+)-**8** and (–)-**15** were synthesized from *rac*-7-azabicyclo[4.2.0]oct-3-en-8-one by CAL-B treatment with one equivalent of H_2O in isopropyl ether, as described earlier.[14] The enantiopure β-lactam obtained was transformed with 18% HCl into the (1*S*,2*R*)-2-amino-4-cyclohexenecarboxylic acid hydrochloride.[14] The syntheses of the 4-hydroxy- and 5-hydroxyamino acid derivatives (+)-**8** and (–)-**15** were carried out similarly as for the racemic compounds given in Scheme 1 and Scheme 3, resulting in the products with *ee* > 99%.



Scheme 3. (*i*) KI, I_2, $NaHCO_3$, CH_2Cl_2, 20 h, room temp.; (*ii*) Bu_3SnH, CH_2Cl_2, 20 h, 40 °C; (*iii*) 20% HCl, 30 h room temp.



Scheme 4. (*i*) KI, I_2, $NaHCO_3$, CH_2Cl_2, 20 h, room temp.; (*ii*) Bu_3SnH, CH_2Cl_2, 20 h, 40 °C; (*iii*) 20% HCl, 30 h, room temp.

The given stereochemistry and the relative configurations of the synthesized compounds were proved by using some key vicinal couplings and characteristic NOEs. For **8**, there are two small couplings, ^3J(H-1,H-2) = 4.2 Hz and ^3J(H-1,H-6ax) = 3.8 Hz, demonstrating an *equatorial* H-1. H-2 is in the *axial* position as it has a large coupling, ^3J(H-2,H-3ax) = 9.7 Hz. The H-4 signal has both large and small couplings: ^3J(H-4,H-3ax/H-5ax) = 9.1 Hz and ^3J(H-4,H-3eq/H-5eq) = 4.1 Hz. These suggest an *axial* H-4, which, together with the characteristic NOE signals between H-2, H-4 and H-6 and the likely chair ring conformation, proves the relative stereochemistry.

For **15**, there are small and large couplings, ^3J(H-1,H-2) = 4.2 Hz and ^3J(H-1,H-6ax) = 12.1 Hz, indicating an *axial* H-1. H-2 is in the *equatorial* position as it has two small couplings: ^3J(H-2,H-3ax) = 4.2 Hz and ^3J(H-1,H-2) = 3.8 Hz. The H-5 dddd multiplet exhibits both large and small couplings: ^3J(H-5,H-4ax/H-6ax) = 10.1 Hz and ^3J(H-5,H-4eq/H-6eq) = 4.1 Hz. These suggest an *axial* H-5, which, together with the characteristic NOE signals between H-1, H-3ax and H-5 and the likely chair ring conformation, proves the relative stereochemistry.

For **19**, there are large and small couplings: ^3J(H-1,H-2) = 11.2 Hz and ^3J(H-1,H-6ax) = 4.4 Hz, indicating an *axial* H-1. H-2 is in the *axial* position as it has large and small couplings: ^3J(H-1,H-2) = 11.2 Hz and ^3J(H-2,H-3ax) = 4.0 Hz. The H-5 signal has both large and small couplings: ^3J(H-5,H-4ax/H-6ax) = 11.1 Hz and ^3J(H-5,H-4eq/H-6eq) = 4.0 Hz. These suggest an *axial* H-5, which, together with the characteristic NOE signals between H-1, H-3ax and H-5 and the likely chair ring conformation, proves the relative stereochemistry.

The conformation might be sensitive to the solvent. The ^{1}H, COSY and NOESY spectra of **15** and **19** were therefore recorded in [D_4]methanol, too. In both cases, we found similar vicinal coupling and a similar NOE signal pattern as in D_2O, leading to the conclusion that these molecules have the same predominant conformers in D_2O and in [D_4]methanol. This finding corroborated our conclusions on the relative configurations and conformations. The relevant spectroscopic data obtained in [D_4]methanol are as follows:

19: *Axial* H-1, concluded from small and large couplings: ^3J(H-1,H-6ax) = 3.5 Hz and ^3J(H-1,H-2) = 12.0 Hz. *Axial* H-2 was indicated by the large and small couplings, ^3J(H-1,H-2) = 12.0 Hz and ^3J(H-1,H-2) = 3.8 Hz. The H-5 signal has both large and small couplings, ^3J(H-5,H-4ax/H-6ax) = 10.8 Hz and ^3J(H-5,H-4eq/H-6eq) = 4.0 Hz, which suggests an *axial* H-5. There are characteristic NOE signals between H-1, H-3ax and H-5.

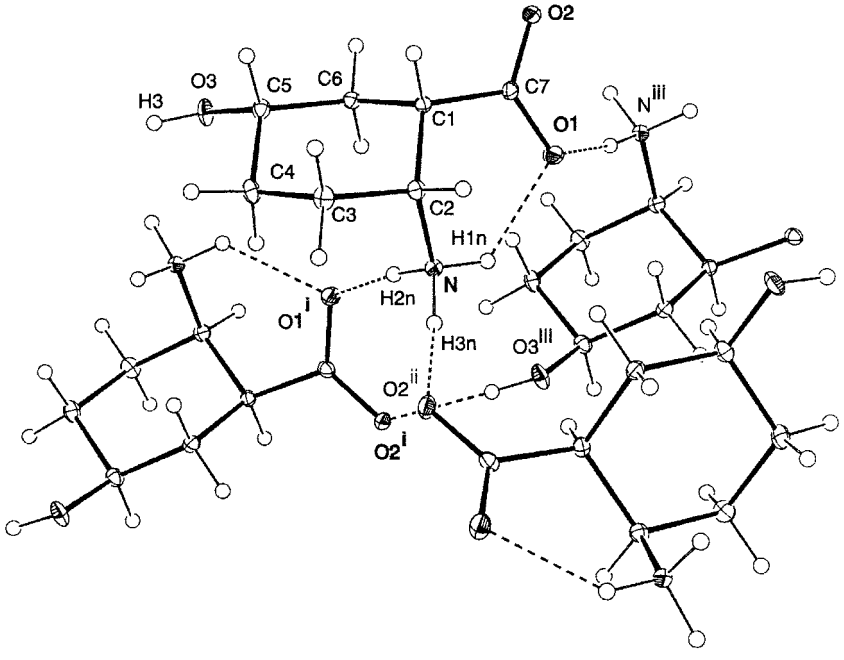


Figure 1. Crystal structure of **15**, showing the hydrogen bonding scheme. Thermal ellipsoids have been drawn at the 30% probability level. Symmetry codes: i = x + 1/2, $-y$ + 3/2, $-z$+2, ii = $-x$ + 3/2, $-y$+1, z + 1/2 and iii = x + 1/2, $-y$ + 3/2, $-z$+1.

15: *Axial* H-1, concluded from the small and large couplings: ^3J(H-1,H-2) = 3.9 Hz and ^3J(H-1,H-6ax) = 11.0 Hz. *Equatorial* H-2 was shown by its small coupling constants: ^3J(H-1,H-2) = 3.9 Hz and ^3J(H-1,H-2) = 4.2 Hz. The H-5 signal has both large and small couplings: ^3J(H-5,H-4ax/H-6ax) = 9.0 Hz and ^3J(H-5,H-4eq/H-6eq) = 4.0, which suggests an *axial* H-5. There are characteristic NOE signals between H-1, H-3ax and H-5.

X-ray diffraction studies confirmed the structure of **15**. All bonding parameters are in the usual ranges. The molecular structure and extensive hydrogen bonding system of **15** are presented in Figure 1.

Experimental Section

General Procedures: ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz in $CDCl_3$ or in [D_6]DMSO, at ambient temperature, with a Bruker AM 400 spectrometer. Chemical shifts are given in δ (ppm) relative to TMS ($CDCl_3$ or DMSO) 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.

The *ee* values of the synthesized enantiomers were determined by gas chromatography (GC) on Chromopak Chiralsil-Dex CB (CCD) or Chirasil-L-Val (CLV) columns. (1*S*,2*R*)-Ethyl 2-amino-4-cyclohexenecarboxylate: CCD column, after derivatization with acetic anhydride in the presence of 4-dimethylaminopyridine and pyridine [120 °C for 2 min → 190 °C (rate of temperature rise 10 °C/min; 100 kPa)], retention time (min): 10.86 (antipode: 10.77); **(+)-1a** and **(+)-14b**: CCD column [120 °C for 2 min → 190 °C (rate of temperature rise 10 °C/min; 100 kPa)], retention times (min) **(+)-1a**: 10.86 (antipode: 10.77), **(+)-14b**: 17.48 (antipode: 17.19); **(+)-12b**: CLV column, after derivatization with diazomethane [100 °C for 10 min → 160 °C (rate of temperature rise 10 °C/min; 45 kPa)], retention time **(+)-12b**: 26.61 (antipode: 26.49). The *ee* values of **(+)-8** and **(–)-15** were determined on a CCD column after double derivatization with (*i*) diazomethane; (*ii*) acetic anhydride in the presence of 4-dimethylaminopyridine and pyridine [120 °C for 2 min → 190 °C (rate of temperature rise 10 °C/min; 100 kPa)], retention times (min): **(+)-8**: 20.17 (antipode: 19.59); (–)-15: 18.34 (antipode: 17.82).

Ethyl *cis*-2-Acetylamino-4-cyclohexenecarboxylate (1a): To a suspension of ethyl *cis*-2-amino-4-cyclohexenecarboxylate hydrochloride (2.04 g, 10 mmol) in toluene (40 mL) were added triethylamine (2.04 g, 20 mmol) and acetyl chloride (0.94 g, 12 mmol), and the mixture was stirred at room temperature for 2 h, and then washed with water (2 × 10 mL). The aqueous layer was extracted with *n*-hexane (3 × 20 mL). The combined organic phase was dried (Na_2SO_4), and the solvents were evaporated. The residue was recrystallised from *n*-hexane/diisopropyl ether to give a white solid (1.15 g, 55% yield), m.p. 64–67 °C. ^{1}H NMR (DMSO): δ = 1.14 (t, *J* = 7.0 Hz, 3 H, C*H*$_3$CH$_2$), 1.77 (s, 3 H, COC*H*$_3$), 2.00 (d, *J* = 17.6 Hz, 1 H, H-5), 2.15 (d, *J* = 18.6 Hz, 1 H, H-2), 2.27 (d, *J* = 17.6 Hz, 1 H, H-5), 2.71-2.76 (m, 1 H, H-2), 4.28-4.34 (m, 1 H, H-6), 5.56 (d, *J* = 10.3 Hz, 1 H, H-4), 5.64 (d, *J* = 10.3 Hz, 1 H, H-3), 7.59 (d, *J* = 7.6 Hz, 1 H, NH) ppm. ^{13}C NMR (DMSO): δ = 14.9, 23.4, 24.6, 31.1, 41.8, 44.8, 60.6, 125.9, 125.1, 169.8, 173.4 ppm. $C_{11}H_{17}NO_3$ (211.26): calcd. C 62.54, H 8.11, N 6.63; found C 62.24, H 7.82, N 6.48.

Ethyl *cis*-2-Benzoylamino-4-cyclohexenecarboxylate (1b): Ethyl *cis*-2-amino-4-cyclohexenecarboxylate hydrochloride (2.04 g, 10 mmol) was benzoylated according to the Schotten–Baumann method. After separation, drying and evaporation of the toluene layer, an almost white crystalline product was obtained. After recrystallisation from *n*-hexane/EtOAc, a white crystalline product, 1.76 g (65%), was obtained. M.p. 105–106 °C. ^{1}H NMR (DMSO): δ = 1.13 (t, *J* = 7.0 Hz, 3 H, C*H*$_3$CH$_2$), 2.30–2.40 (m, 3 H, H-2, H-5), 2.47 (s, 1 H, H-2), 2.93–2.99 (m, 1 H, H-1), 3.97-4.1 (m, 2 H, CH$_3$C*H*$_2$), 4.43–4.50 (m, 1 H, H-6), 5.65 (q, *J* = 9.8 Hz, 2 H, H-3, H-4), 7.44 (t, *J* = 7.3 Hz, 2 H, *m*-Ph), 7.52 (t, *J* = 7.3 Hz, 1 H, *p*-Ph), 7.78 (d, *J* = 7.3 Hz, 2 H, *o*-Ph), 8.00 (d, *J* = 7.5 Hz, 1 H, NH) ppm. ^{13}C NMR (DMSO): δ = 14.4, 25.1, 29.5, 41.3, 45.6, 60.2, 124.8, 125.3, 127.8, 128.4, 131.4, 135.1, 166.7, 173.0 ppm. $C_{16}H_{19}NO_3$ (273.34): calcd. C 70.31, H 7.01, N 5.12; found C 70.44, H 7.27, N 5.48.

Ethyl *cis*-2-(*tert*-Butoxycarbonylamino)-4-cyclohexenecarboxylate (1c): Ethyl *cis*-2-amino-4-cyclohexenecarboxylate hydrochloride (2.04 g, 10 mmol) was dissolved in a mixture of toluene (25 mL) and NaOH solution (1 M, 25 mL), and *tert*-butoxypyrocarbonate (2.4 g, 11 mmol) was then added with stirring. Stirring was continued for 1 h, after which the toluene layer was separated off, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic phase was dried (Na_2SO_4), and the solvents were evaporated. The residue was recrystallised from *n*-hexane/diisopropyl ether to give a white solid (1.63 g, 61% yield), m.p. 70–72 °C. ^{1}H NMR (DMSO): δ = 1.17 (*t*, *J* = 7.0 Hz, 3 H, C*H*$_3$CH$_2$), 1.37 (*s*, 9 H, O*t*Bu), 2.02 (*d*, *J* = 17.9 Hz, 1 H, H-5), 2.13 (*d*, *J* = 17.9 Hz, 1 H, H-2), 2.27 (*d*, *J* = 17.9 Hz, 1 H, H-5), 2.41 (*d*, *J* = 17.9 Hz, 1 H, H-2), 2.74-2.80 (*m*, 1 H, H-1), 3.94-4.11 (*m*, 3 H, H-6, CH$_3$C*H*$_2$), 5.54 (*d*, *J* = 10.4 Hz, 1 H, H-4), 5.61 (*d*, *J* = 10.4 Hz, 1 H, H-3), 6.49 (*d*, *J* = 8.3 Hz, 1 H, NH) ppm. ^{13}C NMR (DMSO): δ = 14.4, 24.1, 28.5, 30.7, 41.4, 46.1, 60.1, 78.0, 124.4, 125.4, 155.4, 172.9 ppm. $C_{14}H_{23}NO_4$ (269.35): calcd. C 62.43, H 8.61, N 5.20; found C 62.84, H 8.32, N 5.55.

Ethyl *trans*-2-Acetylamino-4-cyclohexenecarboxylate (9): Starting from ethyl *trans*-2-amino-4-cyclohexenecarboxylate hydrochloride, the procedure described for **1a** was followed to prepare **9:** yield 58%, white solid, m.p. 68–69 °C. ^{1}H NMR (DMSO): δ = 1.16 (t, *J* = 7.0 Hz, 3 H, C*H*$_3$CH$_2$), 1.76 (s, 3 H, COCH$_3$), 1.87–1.98 (m, 1 H, H-5), 2.19 (dt, *J* = 17.1, 4.3 Hz, 1 H, H-5), 2.25-2.29 (m, 2 H, H-2, H-1), 2.55 (dt, *J* = 10.1, 7.5 Hz, 1 H, H-2), 4.11-4.19 (m, CH$_3$C*H*$_2$, 3 H, H-6), 5.56–5.66 (m, 2 H, H-3, H-4), 7.85 (d, *J* = 8.3 Hz, 1 H, N*H*) ppm. ^{13}C NMR (DMSO): δ = 14.4, 23.0, 27.6, 31.1, 44.6, 45.9, 60.2, 125.2, 125.1, 168.7, 173.6 ppm. $C_{11}H_{17}NO_3$ (211.26): calcd. C 62.54, H 8.11, N 6.63; found C 62.63, H 8.42, N 6.91.

General Procedure for the Synthesis of Iodo- and Bromooxazines (2, 5a,b, 6a,b and 10): A solution of *N*-acylamino ester **1a**–**c** or **9** (3 mmol) in CH_2Cl_2 (40 mL) was treated with one equivalent of NIS or NBS, and the reaction mixture was stirred for 14 h at room temp. When the reaction was completed (monitored by TLC), the mixture was treated with aqueous NaOH solution (10%, 3 × 20 mL). The aqueous solution was extracted with CH_2Cl_2 (3 × 40 mL), the combined organic layer was dried (Na_2SO_4), and the solvents were evaporated. The residue was recrystallised from *n*-hexane/diisopropyl ether.

2: Yield 80%, a white crystalline solid, m.p. 199–201 °C. ^{1}H NMR (DMSO): δ = 1.21 (t, *J* = 7.0 Hz, 3 H, C*H*$_3$CH$_2$), 1.95 (ddt, *J* = 1.8, 14.1, 4.0 Hz, 1 H, H-9eq), 2.00–2.16 (m, 2 H, H-7), 2.55 (d, *J* = 14.1 Hz, 1 H, H-9ax), 2.85 (ddd, *J* = 1.5, 5.5, 11.1 Hz, 1 H, H-6), 3.81 (br. s, 1 H, H-5), 4.01–4.16 (m, 2 H, CH$_3$C*H*$_2$), 4.58–4.63 (m, 1 H, H-1), 4.73-4.79 (m, 1 H, H-8), 7.69 (d, *J* = 5.0 Hz, 1 H,

H-4) ppm. ^{13}C NMR (DMSO): δ = 14.3, 25.3, 28.1, 28.7, 43.1, 46.6, 60.9, 75.4, 152.6, 171.6 ppm. $C_{10}H_{14}INO_4$ (339.13): calcd. C 35.42, H 4.16, N 4.13; found C 35.13, H 4.27, N 3.98.

5a: This compound was very sensitive to air and was used in the dehalogenation step without further purification.

5b: Yield 80%, a white crystalline solid, m.p. 113–114 °C. ^{1}H NMR (DMSO): δ = 1.21 (t, J = 7.05 Hz, 3 H, CH_3CH$_2$), 1.83–1.96 (m, 2 H, H-7, H-9), 2.04 (d, J = 3.2 Hz, 1 H, H-7), 2.62 (dt, J = 14.1, 1.3 Hz, 1 H, H-9), 3.04 (ddd, J = 3.0, 4.0, 12.3 Hz, 1 H, H-6), 4.12 (q, J = 7.3 Hz, 2 H, CH$_3$CH_2), 4.16–4.20 (m, 1 H, H-6), 4.74–4.78 (m, 1 H, H-1), 4.85–4.89 (m, 1 H, H-8), 7.41 (t, J = 7.8 Hz, 2 H, *m*–Ph), 7.48 (t, J = 7.0 Hz, 1 H, *p*-Ph), 7.81 (d, J = 8.1 Hz, 2 H, *o*-Ph) ppm. ^{13}C NMR (DMSO): δ = 14.4, 24.4, 29.0, 29.3, 42.9, 48.8, 60.6, 73.3, 127.2, 128.5, 131.2, 132.8, 155.9, 172.0 ppm. $C_{16}H_{18}INO_3$ (399.23): calcd. C 48.14, H 4.54, N 3.51; found C 47.89, H 4.32, N 3.87.

6a: Yield 83%, a white crystalline solid, m.p. 68–69 °C. ^{1}H NMR (DMSO): δ = 1.22 (t, 3 H, J = 7.0 Hz, CH_3CH$_2$), 1.70 (ddt, J = 1.5, 13.8, 4.0 Hz, 1 H, H-9), 1.86 (s, 3 H, Me-3), 1.99–2.05 (m, 2 H, H-7), 2.35 (dt, J = 13.8, 1.5 Hz, 1 H, H-9), 2.93 (ddd, J = 2.8, 6.0, 10.3 Hz, 1 H, H-6), 3.89–3.94 (m, 1 H, H-5), 4.00–4.15 (m, 2 H, CH$_3$CH_2), 4.48-4.52 (m, 1 H, H-1), 4.64–4.68 (m, 1 H, H-8) ppm. ^{13}C NMR (DMSO): δ = 16.8, 23.6, 29.5, 38.6, 45.3, 61.7, 63.7, 64.5, 74.9, 172.7, 174.2 ppm. $C_{11}H_{16}BrNO_3$ (290.17): calcd. C 45.53, H 5.56, N 4.83; found C 45.89, H 5.72, N 4.37.

6b: Yield 81%, a white crystalline solid, mp. 119–120 °C. ^{1}H NMR (DMSO): δ = 1.22 (t, J = 7.0 Hz, 3 H, CH_3CH$_2$), 1.86 (ddt, J = 1.5, 13.8, 3.8 Hz, 1 H, H-9), 1.95–2.13 (m, 2 H, H-7), 2.49 (dt, J = 10.3, 1.5 Hz, 1 H, H-9), 3.07 (ddd, J = 2.8, 4.3, 11.8 Hz, 1 H, H-6), 4.13 (q, J = 7.0 Hz, 2 H, CH$_3$CH_2), 4.20–4.24 (m, 1 H, H-5), 4.47–4.78 (m, 1 H, H-1), 4.78–4.83 (m, 1 H, H-8), 7.41 (t, J = 7.55 Hz, 2 H, *m*-Ph), 7.49 (t, J = 7.3 Hz, 1 H, *p*-Ph), 7.81 (d, J = 7.3 Hz, 2 H, *o*-Ph) ppm. ^{13}C NMR (DMSO): δ = 14.4, 23.3, 27.6, 42.4, 48.6, 49.9, 60.6, 72.2, 127.2, 128.5, 131.2, 132.9, 155.6, 172.1 ppm. $C_{11}H_{18}BrNO_3$ (252.24): calcd. C 54.56, H 5.15, N 3.98; found C 54.41, H 5.49, N 4.22.

10: This compound is sensitive to air and was used in the next step without purification. ^{1}H NMR ($CDCl_3$): δ = 1.23 (t, J = 7.0 Hz, 3 H, CH_3CH$_2$), 1.64 (d, J = 14.1 Hz, 1 H, H-9), 1.90 (s, 3 H, Me), 2.24 (ddd, J = 3.5, 7.3, 16.4 Hz, 1 H, H-7), 2.44 (d, J = 16.4 Hz, 1 H, H-7), 2.53 (d, J = 14.1 Hz, 1 H, H-9), 2.73 (d, J = 6.1 Hz, 1 H, H-6), 3.83 (s, 1 H, H-5), 4.11 (q, J = 7.0 Hz, 2 H, CH$_3$CH_2), 4.52 (s, 1 H, H-1), 4.53 (s, 1 H, H-8) ppm. ^{13}C NMR (DMSO): δ = 14.8, 20.5, 21.6, 27.5, 41.1, 46.3, 49.5, 61.1, 72.9, 158.9, 172.8 ppm.

General Procedure for Dehalogenation of Iodo- and Bromooxazines 2, 5a,b, 6a,b and 10 to Oxazines 3, 7a and 7b: Tributyltin hydride (0.8 mL, 3 mmol) was added to a solution of iodo- or bromooxazine **2**, **5a**,**b**, **6a**,**b** or **10** (1.48 mmol) in dry CH_2Cl_2 (65 mL) under argon. The reaction mixture was stirred for 20 h at 40 °C. Except in the case of air-sensitive **10**, the solvent was evaporated, and the residue was purified by column chromatography on silica gel (eluent: *n*-hexane–EtOAc 10:1) to afford the 1,3-oxazine as a white crystalline solid (**3**, **7b**) or as an oil (**7a**). The reaction mixture of **10** was used without purification to form **11** upon addition of HCl (20 mL 20%) and refluxing (see below).

3: Yield 70%, a white crystalline solid, m.p. 150–153 °C. ^{1}H NMR (DMSO): δ = 1.20 (t, J = 7.0 Hz, 3 H, CH_3CH$_2$), 1.53–1.66 (m, 2 H, H-7, H-8), 1.71–1.78 (m, 1 H, H-8), 1.86–1.91 (m, 2 H, H-9), 1.91–1.97 (m, 1 H, H-7), 2.65 (ddd, J = 2.0, 4.5, 11.8 Hz, 1 H, H-6), 3.79 (br. s, 1 H, H-5), 4.00–4.13 (m, 2 H, CH$_3$CH_2), 4.49–4.55 (m, 1 H, H-1), 7.37 (d, J = 5.0 Hz, 1 H, H-4) ppm. ^{13}C NMR (DMSO): δ = 14.8, 18.7, 29.5, 30.9, 46.5, 47.4, 60.1, 72.6, 154.3, 173.1 ppm. $C_{10}H_{15}NO_4$ (213.24): calcd. C 56.33, H 7.09, N 6.57; found C 55.92, H 7.22, N 6.19.

7a: Yield 60%, a colourless oil, from iodooxazine **5a**, and 55% from bromooxazine **5b**. ^{1}H NMR (DMSO): δ = 1.18 (t, J = 7.3 Hz, 3 H, CH_3CH$_2$), 1.45 (ddt, J = 4.8, 12.6, 4.8 Hz, 1 H, H-7), 1.55 (ddd, J = 1.5, 4.8, 13.3 Hz, 1 H, H-8), 1.59–1.73 (m, 2 H, H-9), 1.82 (s, CH$_3$, 3 H, H-8), 1.93 (d, J = 13.3 Hz, 1 H, H-7), 2.67 (dt, J = 12.1, 3.0 Hz, 1 H, H-6), 3.85 (s, 1 H, H-5), 3.97–4.11 (m, 2 H, CH$_3$CH_2), 4.39 (s, 1 H, H-1) ppm. ^{13}C NMR (DMSO): δ = 14.1, 17.9, 20.9, 27.8, 31.1, 45.5, 48.1, 59.7, 59.8, 69.2, 158.6, 172.6 ppm. $C_{11}H_{17}NO_3$ (211.26): calcd. C 62.54, H 8.11, N 6.63; found C 63.00, H 8.24, N 6.32.

7b: Yield 65% from iodooxazine **6a**, and 62% from bromooxazine **6b**, a white crystalline solid, m.p. 64–65 °C. ^{1}H NMR (DMSO): δ = 1.21 (t, J = 7.0 Hz, 3 H, CH_3CH$_2$), 1.38–1.52 (m, 1 H, H-7), 1.63–1.74 (m, 2 H, H-7, H-8), 1.82–1.89 (m, 1 H, H-9), 1.93 (dt, J = 13.3, 1.8 Hz, 1 H, H-9), 2.01–2.12 (m, 1 H, H-8), 2.82 (dt, J = 12.1, 3.5 Hz, 1 H, H-6), 4.10 (q, J = 7.0 Hz, 2 H, CH$_3$CH_2), 4.17–4.20 (m, 1 H, H-5), 4.68–4.72 (m, 1 H, H-1), 7.39 (t, 7.5 Hz, 2 H, *m*-Ph), 7.46 (t, J = 7.3 Hz, 1 H, *p*-Ph), 7.81 (d, J = 7.3 Hz, 2 H, *o*-Ph) ppm. ^{13}C NMR (DMSO): δ = 14.5, 18.2, 28.1, 31.5, 46.1, 49.0, 60.1, 70.3, 127.1, 128.4, 130.8, 133.8, 156.8, 173.0 ppm. $C_{16}H_{19}NO_3$ (273.34): calcd. C 70.31, H 7.01, N 5.12; found C 70.39, H 6.87, N 5.43.

General Synthesis of Stereoisomeric 2-Amino-4-hydroxy Acids 8 and 11 and Oxazinonecarboxylic Acid 4: A solution of ester **3**, or **7a,b** or the reaction mixture of **10** (1 mmol in 20 mL 20% HCl) was refluxed for 30 h. The solvent was then evaporated to afford the crude amino acid hydrochloride. The free amino acid base was liberated by ion-exchange chromatography with Dowex 50.

(*r*-6,*c*-1,*c*-5)-2-Oxa-3-oxo-4-azabicyclo[3.3.1]nonane-6-carboxylic Acid (4): Yield 53% from **7a**, and 35% from **7b**, a white crystalline solid, m.p. 222–226 °C. ^{1}H NMR (DMSO): δ = 1.52–1.67 (m, 2 H, H-5, H-6), 1.69–1.80 (m, 1 H, H-6), 1.82–1.98 (m, 3 H, H-3, H-5), 2.51–2.59 (m, 1 H, H-1), 3.79 (br. s, 1 H, H-2), 4.51 (br. s, 1 H, H-4), 7.28 (d, J = 5.04 Hz, 1 H, OH) ppm. ^{13}C NMR (DMSO): δ = 18.4, 29.1, 30.1, 46.0, 46.7, 72.1, 153.8, 174.3 ppm. $C_8H_{11}NO_4$ (185.18): calcd. C 51.89, H 5.99, N 7.56; found C 51.92, H 5.57, N 7.92.

(*r*-1,*c*-2,*c*-4)-2-Amino-4-hydroxycyclohexanecarboxylic Acid (8): Yield 52%, a white crystalline solid, m.p. 220–225 °C. ^{1}H NMR (D_2O): δ = 1.41 (s, 1 H, H5), 1.55–1.67 (m, 1 H, H-6), 1.78–1.91 (m, 2 H, H-3, H-5), 2.06 (dt, J = 12.6, 3.5 Hz, 1 H, H-3), 2.10–2.22 (m, 1 H, H-6), 2.58 (dt, J = 4.4, 4.0 Hz, 1 H, H-2), 3.49 (dt, J = 13.6, 4.1 Hz, 1 H, H-1), 3.88 (m, 1 H, H-4) ppm. ^{13}C NMR (D_2O): δ = 22.9, 30.8, 34.7, 42.6, 49.0, 67.5, 180.3 ppm. $C_7H_{13}NO_3$ (159.19): calcd. C 52.82, H 8.23, N 8.80; found C 52.99, H 8.48, N 8.70.

(*r*-1,*t*-2,*t*-4)-2-Amino-4-hydroxycyclohexanecarboxylic Acid (11): Yield 48%, a white crystalline solid, m.p. 230–232 °C. ^{1}H NMR (D_2O): δ = 1.27-1.5 (m, 3 H, H-3, H-5, H-6), 2.02–2.08 (m, 1 H, H-5), 2.14-2.26 (m, 2 H, H-2, H-6), 2.28-2.34 (m, 1 H, H-3), 3.35 (ddd, J = 4.0, 10.8, 12.1 Hz, 1 H, H-1), 3.76 (tt, J = 4.0, 10.8 Hz, 1 H, H-4) ppm. ^{13}C NMR (D_2O): δ = 25.7, 35.2, 41.0, 45.8, 50.5, 67.5, 180.5 ppm. $C_7H_{13}NO_3$ (159.19): calcd. C 52.82, H 8.23, N 8.80; found C 52.54, H 8.73, N 8.49.

***cis*-2-Benzoylamino-4-cyclohexenecarboxylic Acid (12a):** 2-Amino-4-cyclohexenecarboxylic acid (1.41 g, 10 mmol) was dissolved in NaOH solution (10%, 15 mL), benzoyl chloride (1.54 g, 11 mmol) was added dropwise, and the solution was stirred at room tempera-

ture for 1 h. The solution was then acidified with aqueous HCl, and **12a** was precipitated, filtered off, washed with water and dried. Yield 2.05 g, 84%, a white crystalline solid, m.p. 188–189 °C (*n*-hexane–ethyl acetate). ^{1}H NMR (DMSO): δ = 2.30 (m, 1 H, H-2), 2.55 (m, 1 H, H-2), 2.90 (dd, *J* = 6.0, 9.5 Hz, 1 H, H-1), 4.41–4.48 (m, 1 H, H-6), 5.68 (d, *J* = 10.3 Hz, 1 H, H-3), 5.62 (d, *J* = 10.3 Hz, 1 H, H-4), 7.52 (t, *J* = 7.3 Hz, 1 H, *p*-Ph), 7.45 (t, *J* = 7.3 Hz, 2 H, *o*-Ph), 7.79 (d, *J* = 7.30 Hz, 2 H, *m*-Ph), 7.97 (d, *J* = 8.2 Hz, 1 H, NH), 12.28 (br. s, 1 H, OH) ppm. ^{13}C NMR (DMSO): δ = 26.1, 30.2, 41.6, 46.1, 125.4, 126.1, 128.2, 129.0, 131.9, 135.6, 167.0, 175.3 ppm. $C_{14}H_{15}NO_3$ (245.28): calcd. C 68.56, H 6.16, N 5.71; found C 68.94, H 7.43, N 5.39.

***cis*-2-*tert*-Butoxycarbonylamino-4-cyclohexenecarboxylic Acid (12b):** 2-Amino-4-cyclohexenecarboxylic acid (1.41 g, 10 mmol) was dissolved in a mixture of dioxane (20 mL) and water (10 mL), *tert*-butoxypyrocarbonate (2.4 g, 11 mmol) was added to the solution at 0 °C, and the mixture was stirred at room temperature for 4 h. The solvent was then evaporated down to half volume, and the mixture was diluted with ethyl acetate (20 mL) and acidified with H_2SO_4 (10%, pH = 2.5). The mixture was extracted with ethyl acetate (3 × 20 mL), the combined organic layer was dried (Na_2SO_4), and the solvents were evaporated. The residue was recrystallised from diisopropyl ether to give a white crystalline solid. Yield 75%, m.p. 58–60 °C. ^{1}H NMR ($CDCl_3$): δ = 1.44 (s, 9 H, O*t*Bu), 2.21 (dd, *J* = 18.1 Hz, 6.04 Hz, 1 H, H-2), 2.36 (d, *J* = 18.1 Hz, 2 H, H-5), 2.54 (d, *J* = 18.1 Hz, 1 H, H-2), 2.81–2.93 (m, 1 H, H-1), 4.11–4.23 (m, 1 H, H-6), 5.29 (d, *J* = 6.04 Hz, 1 H, NH), 5.55–5.70 (m, 2 H, H-3, H-4) ppm. ^{13}C NMR (DMSO): δ = 26.8, 28.9, 31.8, 42.6, 46.8, 80.1, 125.3, 125.7, 156.1, 179.1 ppm. $C_{12}H_{19}NO_4$ (241.29): calcd. C 59.73, H 7.94, N 5.80; found C 59.42, H 7.81, N 5.92.

***trans*-6-*tert*-Butoxycarbonylaminocyclohex-3-ene-carboxylic Acid (16):** The procedure described for **12b** was followed to prepare **16** from *trans*-6-aminocyclohex-3-ene-carboxylic acid. Yield 74%, a white crystalline solid, m.p. 120–122 °C. ^{1}H NMR (DMSO): δ = 1.36 (s, 9 H, O*t*Bu), 1.88–1.97 (m, 1 H, H-2), 2.15–2.23 (m, 3 H, H-2, H-5), 2.44–2.54 (m, 1 H, H-6), 3.6-3.72 (m, 1 H, H-1), 5.55–5.63 (m, 2 H, H-3, H-4), 6.76 (d, *J* = 8.6 Hz, 1 H, NH) ppm. ^{13}C NMR (DMSO): δ = 28.3, 28.6, 31.5, 44.6, 47.5, 77.8, 126.1, 125.3, 155.2, 175.5 ppm. $C_{12}H_{19}NO_4$ (241.29): calcd. C 59.73, H 7.94, N 5.80; found C 59.39, H 7.49, N 5.53.

General Procedure for the Synthesis of Iodolactones 13a,b and 17: To a solution of carboxylic acid derivative **12a,b** or **16** (5.75 mmol) in CH_2Cl_2 (50 mL), were added $NaHCO_3$ (0.5 N, 35 mL), KI (5.7 g, 34.5 mmol) and I_2 (2.9 g, 11.5 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 20 h and then poured into a saturated solution of $Na_2S_2O_3$ (100 mL). The mixture was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic layer was washed with saturated NaCl solution, dried (Na_2SO_4), and the solvents were evaporated. The residue was recrystallised from diisopropyl ether to give iodolactone **13a,b** or **17**.

13a: Yield 78%, a white crystalline solid, m.p. 185–189 °C. ^{1}H NMR (DMSO): δ = 2.22 (dd, *J* = 5.3, 15.8 Hz, 1 H, H-3), 2.51–2.80 (m, 3 H, H-8, H-3), 2.81 (d, *J* = 12.4 Hz, 1 H, H-1), 4.23–4.31 (m, 1 H, H-2), 4.75 (t, *J* = 4.8 Hz, 1 H, H-4), 4.89 (t, *J* = 4.8 Hz, 1 H, H-5), 7.48 (t, *J* = 7.3 Hz, 2 H, *m*-Ph), 7.55 (t, *J* = 7.3 Hz, 1 H, *p*-Ph), 7.83–7.87 (d, *J* = 7.3 Hz, 2 H, *o*-Ph), 8.53 (d, *J* = 7.0 Hz, 1 H, NH) ppm. ^{13}C NMR (DMSO): δ = 23.4, 33.4, 34.6, 43.9, 46.0, 79.3, 127.8, 128.6, 131.8, 134.3, 166.9, 175.9 ppm. $C_{14}H_{14}INO_3$ (371.18): calcd. C 45.30, H 3.80, N 3.77; found C 44.92, H 3.61, N 3.87.

13b: Yield 84%, a white crystalline solid, m.p. 170–174 °C. ^{1}H NMR (DMSO): δ = 1.40 (s, 9 H, O*t*Bu), 2.09 (dd, *J* = 5.8, 16.1 Hz, 1 H, H-3), 2.27 (ddd, *J* = 5.8, 12.3, 16.1, 1 H, H-3), 2.46 (ddd, *J* = 1.5, 5.8, 12.6 Hz, 1 H, H-8), 2.55 (d, *J* = 12.6 Hz, 1 H, H-8), 2.67 (d, *J* = 6.3 Hz, 1 H, H-1), 3.69–3.79 (m, 1 H, H-2), 4.66 (t, *J* = 5.3 Hz, 1 H, H-4), 4.82 (dd, *J* = 4.3, 5.3 Hz, 1 H, H-5), 7.17 (d, *J* = 7.3 Hz, 1 H, N*H*CO) ppm. ^{13}C NMR (DMSO): δ = 23.2, 28.5, 33.2, 34.9, 44.2, 46.7, 78.8, 79.1, 155.2, 175.8 ppm. $C_{12}H_{18}INO_4$ (367.19): calcd. C 39.25, H 4.94, N 3.81; found C 38.93, H 4.65, N 3.72.

17: Yield 82%, a white crystalline solid, m.p. 125–127 °C. ^{1}H NMR (DMSO): δ = 1.41 (s, 9 H, O*t*Bu), 2.25–2.38 (m, 2 H, H-3, H-8), 2.41-2.48 (m, 1 H, H-3), 2.75 (t, *J* = 4.1 Hz, 1 H, H-8), 2.88 (d, *J* = 12.8 Hz, 1 H, H-1), 3.75 (s, 1 H, H-5), 4.42 (s, 1 H, H-4), 4.94 (dd, *J* = 3.3, 5.8 Hz, 1 H, H-2), 6.93 (br. s, 1 H, N*H*) ppm. ^{13}C NMR (DMSO): δ = 19.5, 28.0, 28.6, 33.3, 42.4, 46.0, 78.8, 81.2, 176.5 ppm. $C_{12}H_{18}INO_4$ (367.19): calcd. C 39.25, H 4.94, N 3.81; found C 39.37, H 5.22, N 3.68.

Reduction of Iodolactones 13a,b and 17 to Lactones 14a,b and 18: Tributyltin hydride (2.4 mL, 9 mmol) was added to a solution of iodolactone **13a**,**b** or **17** (4.5 mmol) in dry CH_2Cl_2 (65 mL) under argon. After stirring for 20 h at 40 °C, the solvent was evaporated, and the crude lactone was crystallized from *n*-hexane and recrystallised from isopropyl ether/ethyl acetate.

14a: Yield 68%, a white crystalline solid, m.p. 188–190 °C. ^{1}H NMR (DMSO): δ = 1.79–2.12 (m, 5 H, H-3, H-4, H-8), 2.50–2.57 (m, 1 H, H-8), 2.88 (d, *J* = 5.8 Hz, 1 H, H-1), 4.20-4.29 (m, 1 H, H-5), 4.94 (t, *J* = 4.8 Hz, 1 H, H-2), 7.60 (t, *J* = 7.3 Hz, 2 H, *m*-Ph), 7.67 (t, *J* = 7.3 Hz, 1 H, *p*-Ph), 7.98 (d, *J* = 7.3 Hz, 2 H, *o*-Ph), 8.50 (d, *J* = 7.0 Hz, 1 H, N*H*) ppm. ^{13}C NMR (DMSO): δ = 23.9, 27.4, 35.6, 43.6, 48.3, 77.0, 127.8, 128.5, 131.7, 134.5, 166.8, 176.9 ppm. $C_{14}H_{15}NO_3$ (245.28): calcd. C 68.56, H 6.16, N 5.71; found C 68.49, H 6.33, N 5.49.

14b: Yield 75%, a white crystalline solid, m.p. 115–119 °C. ^{1}H NMR (DMSO): δ = 1.40 (s, 9 H, O*tBu*), 1.45–1.56 (m, 1 H, H-3), 1.57–1.65 (m, 1 H, H-3), 1.75–1.9 (m, 3 H, H-4, H-8), 2.29–2.37 (m, 1 H, H-8), 2.62 (d, *J* = 4.8 Hz, 1 H, H-1), 3.56–3.65 (m, 1 H, H-5), 4.73 (t, *J* = 4.8 Hz, 1 H, H-2), 6.95 (d, *J* = 6.5 Hz, 1 H, N*H*) ppm. ^{13}C NMR (DMSO): δ = 24.3, 27.4, 28.5, 35.5, 43.8, 49.1, 76.7, 78.3, 155.1, 176.7 ppm. $C_{12}H_{19}NO_4$ (241.29): calcd. C 59.73, H 7.94, N 5.80; found C 59.92, H 8.21, N 5.37.

18: Yield 72%, a white crystalline solid, m.p. 82–86 °C. ^{1}H NMR (DMSO): δ = 1.40 (s, 9 H, O*t*Bu), 1.53–1.61 (dd, *J* = 6.3, 14.6 Hz, 1 H, H-8), 1.66–1.85 (m, 2 H, H-3, H-4), 2.05–2.18 (m, 2 H, H-4, H-8), 2.69 (t, *J* = 4.3 Hz, 1 H, H-1), 3.69–3.78 (m, 1 H, H-5), 4.81 (t, *J* = 4.3 Hz, 1 H, H-3), 7.48 (1 H, br. s, N*H*) ppm. ^{13}C NMR (DMSO): δ = 24.0, 24.8, 28.6, 31.0, 43.1, 45.6, 78.1, 78.56, 177.3 ppm. $C_{12}H_{19}NO_4$ (241.29): calcd. C 59.73, H 7.94, N 5.80; found C 59.56, H 7.83, N, 5.52.

General Procedure for 2-Amino-5-hydroxycarboxylic Acids 15 and 19 from Lactones 14b and 18: Lactone **14b** or **18** (0.72 g, 3 mmol) was dissolved in aqueous HCl (of 20%, 20 mL), and the solution was stirred at room temperature for 10 h. The solvent was evaporated, and the amino acid base was liberated from the residual hydrochloride by ion-exchange chromatography on Dowex 50.

(*r*-1,*c*-2,*c*-5)-2-Amino-5-hydroxycyclohexanecarboxylic Acid (15): Yield 66%, a white crystalline solid, mp, 255–256 °C. ^{1}H NMR (D_2O): δ = 1.43–1.54 (m, 1 H, H-4), 1.61 (q, *J* = 11.8 Hz, 2 H, H-6), 1.78 (tt, *J* = 4.3, 13.6 Hz, 1 H, H-3), 1.85–1.93 (m, 1 H, H-4), 2.02 (ddt, *J* = 4.3, 14.9, 4.3 Hz, 1 H, H-3), 2.15 (d, *J* = 13.6 Hz, 1 H, H-6), 2.62 (dt, *J* = 12.1, 3.8 Hz, 1 H, H-1), 3.64 (dt, *J* = 4.2,

3.8 Hz, 1 H, H-2), 3.75–3.84 (m, 1 H, H-5) ppm. ^{13}C NMR (D_2O): δ = 25.5, 27.9, 32.4, 43.7, 47.9, 68.2, 180.5 ppm. $C_7H_{13}NO_3$ (159.19): calcd. C 52.82, H 8.23, N 8.80; found C 52.67, H 8.49, N 8.31.

(*r*-1,t-2,*c*-5)-2-Amino-5-hydroxycyclohexanecarboxylic Acid (19): Yield 62%, a white crystalline solid, m.p. 275–280 °C. ^{1}H NMR (D_2O): δ = 1.32–1.44 (m, 2 H, H-4, H-6), 1.53 (ddt, J = 3.5, 12.8, 3.5 Hz, 1 H, H-3), 2.01–2.14 (m, 2 H, H-3, H-4), 2.31–2.40 (m, 2 H, H-1, H-6), 3.24 (dt, J = 3.8, 11.2 Hz, 1 H, H-2), 3.73 (tt, J = 4.0, 11.2 Hz, 1 H, H-5) ppm. ^{13}C NMR (D_2O): δ = 27.7, 32.0, 36.9, 46.8, 51.5, 68.8, 179.8 ppm. $C_7H_{13}NO_3$ (159.19): calcd. C 52.82, H 8.23, N 8.80; found C 52.55, H 8.43, N 8.21.

(1*S*,2*R*,4*R*)-2-Amino-4-hydroxycyclohexanecarboxylic Acid (+)-(8): The same synthesis was followed as for the racemic compound (±)-**8**, starting from (1*S*,2*R*)-2-amino-4-cyclohexenecarboxylic acid hydrochloride, via intermediate **5a**. The ^{1}H NMR spectroscopic data on the intermediates and products were similar to those for the racemates. Representative data on the enantiomers isolated:

(1*S*,2*R*)-Ethyl 2-Amino-4-cyclohexenecarboxylate: Colourless crystals, m.p. 125–128 °C, $[\alpha]_D^{20}$ = +19 (c, 1.0, EtOH), *ee* > 99%.

(+)-1a. A colourless oil, $[\alpha]_D^{20}$ = +58 (c, 0.6, MeOH), *ee* > 99%.

(+)-7a. A colourless oil, $[\alpha]_D^{20}$ = +28 (c, 0.4, MeOH).

(+)-(8). Colourless crystals, m.p. 140–145 °C, $[\alpha]_D^{20}$ = +17 (c, 0.23, H_2O), *ee* > 99%.

(1*S*,2*R*,5*R*)-2-Amino-5-hydroxycyclohexanecarboxylic Acid (–)-(15): The same synthesis was followed as for the racemic compound (±)-**15**, starting from (1*S*,2*R*)-2-amino-4-cyclohexenecarboxylic acid hydrochloride, via intermediate **13b**. The ^{1}H NMR spectroscopic data on the intermediates and products were similar to those for the racemates. Representative data on the enantiomers isolated:

(+)-(12b). Colourless crystals, m.p. 118–123 °C, $[\alpha]_D^{20}$ = +19.4 (c, 0.5, MeOH), *ee* > 99%.

(+)-(13b). Colourless crystals, m.p. 185–190 °C, $[\alpha]_D^{20}$ = +92.5 (c, 0.6, MeOH).

(+)-(14b). Colourless crystals, m.p. 135–140 °C, $[\alpha]_D^{20}$ = +104 (c, 0.1, MeOH), *ee* > 99%.

(–)-(15). Colourless crystals, m.p. 247–250 °C, $[\alpha]_D^{20}$ = –26 (c, 0.15, H_2O), *ee* > 99%.

X-ray Data Collection and Processing: Crystallographic data for **15** were collected at 173 K on a Nonius Kappa CCD area-detector diffractometer, using graphite monochromatized MoK_α radiation (λ = 0.71073 Å). The data collection was performed using ϕ and ω scans. The data were processed using DENZO-SMN v0.93.0.[15] The structures were solved by direct methods with the *SHELXS* program[16] and full-matrix least-squares refinements on F^2 were performed using the *SHELXL-97* program.[16] All heavy atoms were refined anisotropically. The OH and NH hydrogens were refined anisotropically. The CH hydrogen atoms were included at fixed distances with fixed displacement parameters from their host atoms. Figure 1 was drawn with *ORTEP-III for Windows*.[17]

Acknowledgments

We thank the Hungarian Research Foundation (OTKA No. T 049407 and TS 04888) for financial support.

[1] F. Fülöp, *Chem. Rev.* **2001**, *101*, 2181–2204.
[2] *Enantioselective Synthesis of* β-*Amino Acids*, (Ed.: E. Juaristi); Wiley-VCH, New York, **1997**.
[3] F. Fülöp "The Chemistry of 2-Aminocyclopentanecarboxylic Acid" in *Studies in Natural Product Chemistry* (Ed.: Atta-ur-Rahman), Elsevier Science Publishers, **2000**, pp. 273–306.
[4] a) M. Konishi, M. Nishio, K. Saitoh, T. Miyaki, T. Oki, H. Kawaguchi, *J. Antibiotics* **1989**, *42*, 1749–1755; b) T. Iwamoto, E. Tsujii, M. Ezaki, A. Fujie, S. Hashimoto, M. Okuhara, M. Kohsaka, H. Imanaka, K. Kawabata, Y. Inamoto, K. Sakane, *J. Antibiotics* **1990**, *43*, 1–7.
[5] a) D. H. Appella, L. A. Christianson, D. A. Klein, D. R. Powell, X. Huang, J. J. Barchi, S. H. Gellman, *Nature* **1997**, *387*, 381–384; b) D. H. Appella, L. A. Christianson, I. L. Karle, D. R. Powell, S. H. Gellman, *J. Am. Chem. Soc.* **1996**, *118*, 13071–13072; c) D. H. Appella, S. L. Durell, J. J. Barchi, S. H. Gellman, *J. Am. Chem. Soc.* **1999**, *121*, 2309–2310; d) J. J. Barchi, X. Huang, D. H. Appella, L. A. Christianson, S. R. Durell, S. H. Gellman, *J. Am. Chem. Soc.* **2000**, *122*, 2711–2718.
[6] T. A. Martinek, G. K. Tóth, E. Vass, M. Hollósi, F. Fülöp, *Angew. Chem. Int. Ed.* **2002**, *41*, 1719–1721.
[7] a) K. Gademann, T. Hintermann, J. V. Schreiber, *Current Med. Chem.* **1999**, *6*, 905–925; b) A. F. Abdel-Magid, J. H. Cohen, C. A. Maryanoff, *Current Med. Chem.* **1999**, *6*, 955–969; c) E. Juaristi, H. Lopez-Ruiz, *Current Med. Chem.* **1999**, *6*, 983–1004.
[8] a) S. G. Davies, O. Ichihara, I. A. S. Walters, *Synlett* **1993**, 461–462; b) S. G. Davies, O. Ichihara, I. Lenoir, I. A. S. Walters, *J. Chem. Soc. Perkin Trans. 1* **1994**, 1411–1415; c) S. G. Davies, G. Bhalay, *Tetrahedron: Asymmetry* **1996**, *7*, 1595–1596.
[9] F. Fülöp, G. Bernáth, K. Pihlaja, *Adv. Heterocyclic Chem.* **1998**, *69*, 349–477.
[10] a) S. Gedey, J. Van der Eycken, F. Fülöp, *Org. Lett.* **2002**, *4*, 1967–1969; b) S. Gedey, P. Vainiotalo, I. Zupkó, P. A. M. de Witte, F. Fülöp, *J. Heterocycl. Chem.* **2003**, *40*, 951–956; c) S. Gedey, J. Van der Eycken, F. Fülöp, *Lett. Org. Chem.* **2004**, *1*, 215–217.
[11] a) P. Wipf, X. Wang, *Tetrahedron Lett.* **2000**. *41*, 8747–8751; b) F. Fringuelli, F. Pizzo, M. Rucci, L. Vaccaro, *J. Org. Chem.* **2003**, *68*, 7041–7045; c) K. Tatsuta, M. Takahashi, N. Tanaka, K. Chikauchi, *J. Antibiot.* **2000**, *53*, 1231–1234; d) Y. Ichikawa, M. Ohbayashi, K. Hirata, R. Nishizawa, M. Isobe, *Synlett* **2001**, 1763–1766; e) K. Wright, M. Crisma, C. Toniolo, R. Török, A. Péter, M. Wakselman, J. P. Mazaleyrat, *Tetrahedron Lett.* **2003**, *44*, 3381–3384; f) I. B. Masesane, P. G. Steel, *Tetrahedron Lett.* **2004**, *45*, 5007–5009.
[12] G. Bernáth, G. Stájer, A. E. Szabó, F. Fülöp, P. Sohár, *Tetrahedron* **1985**, *41*, 1353–1365.
[13] a) A. Avenoza, C. Cativiela, M. A. Fernandez-Recio, M. J. Peregrina, *Tetrahedron: Asymmetry* **1996**, *7*, 721–728; b) A. Avenoza, C. Cativiela, M. A. Fernandez-Recio, M. J. Peregrina, *Synthesis* **1997**, 165–167.
[14] E. Forró, F. Fülöp, *Tetrahedron: Asymmetry* **2004**, *15*, 2875–2880.
[15] Z. Otwinowski, W. Minor, *Methods in Enzymology*, vol. 276, *Macromolecular Crystallography*, *Part A* (Eds.: C. W. Carter, R. M. Sweet), pp. 307–326, Academic Press, New York, **1997**.
[16] G. M. Sheldrick, SHELX-97, University of Göttingen, Germany (**1997**).
[17] L. J. Farrugia, *J. Appl. Cryst.* **1997**, *30*, 565.

Received: January 26, 2005