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The iodolactone approach to enantiopure oxiranes of constrained chiral cyclic β-amino acids

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ABSTRACT

A simple and efficient method has been developed for the synthesis of enantiopure epoxide derivatives of some constrained chiral cyclic β-amino acids via iodolactonization and alkaline de-iodation. Lower stereoselectivities were observed when the classical method using *m*CPBA was used when a bicyclic β-amino acid was involved leading to a quasi-inseparable mixture of two epoxides.

1. Introduction

Over recent years, the chemistry of β-amino acids and their use in medicinal chemistry have become areas of intense research activity.[1,2] In particular, there has been increasing interest with regards to the structure and function of conformationally constrained chiral cyclic β-amino acids and their oligomers. These compounds are present in many natural products and biologically active peptides. They are also useful starting materials in the synthesis of alkaloids and β-lactam antibiotics. Moreover, incorporation into peptides or peptidomimetics of cyclic β-amino acids induce conformational restriction and provides significant structural effects that can be used for structural and biomechanistic investigations.[3]

The availability of a large number of regio- and stereoisomers, together with the possibility of various ring sizes provide a significant structural diversity of chiral cyclic β-amino acids for designing therapeutic agents or new materials. This diversity has been further increased by additional substitutions on the amino acid ring and has found interesting applications. For example, in the foldamer field, the appending functionality in oligomers composed of chiral cyclic β-amino acids, which have an important effect on both their folding propensity and their biological activity.[4]

A valuable synthetic route to prepare various functionalized chiral cyclic β-amino acids consists of the ring opening of the corresponding chiral epoxide derivatives, because of their ring strain and high reactivity. The reaction of chiral epoxides with various nucleophiles (hydrides, organometallic reagents, oxygen and nitrogen containing derivatives) generally leads to high regio- and stereoselective ring opening products.

Consequently, the development of efficient methods for the stereochemical control of the epoxidation of unsaturated cyclic β-amino acids is of great interest.

Since Prilezhaev's discovery in 1910,[5] the interaction of peroxy acids with different olefins is the basis of a synthetic method that leads to the formation of the corresponding epoxides. Among its numerous applications, epoxidation of cyclic aminoalkenes containing a NH-carbamate protecting group with peracids [mainly metachloroperbenzoic acid (*m*CPBA)] is known to generally process with a high degree of *cis*-selectivity, presumably via a hydrogen binding interaction in the transition state during the reaction between the carbamate and the peracidic reagent.[6] Conversely, it has been reported that very high levels of *trans*-selectivity are obtained from the epoxidation of both N-diprotected cyclic allylic amines[6d] containing electron-withdrawing groups (e.g., Boc, Ts) or *N*-Boc protected cyclopentenyl lactams.[6h] In this case, the stereoselectivity is governed by steric factors as a consequence of the limited possibility of hydrogen bonding with peracid.

2. Results and discussion

In our previous studies,[7] we explored the asymmetric Diels Alder cycloaddition that involved the chiral acrylate (*R*)-**1** and several *N*-benzyloxycarbonyl (*Z*) protected aminodienes, that is, 1-(benzyloxycarbonylamino)butadiene **2**,[8] 1-(benzyloxycarbonylamino)cyclohexadiene **3**[9] and *N*-benzyloxycarbonyl-1,2-dihydropyridine **4**.[10]

The resulting Diels–Alder cycloadducts were obtained in high yield and in moderate to good selectivity using optimized conditions, especially when carrying out the reaction under microwave activation. In each case, using the acrylate with an (*R*)-configuration, the main Diels–Alder cycloadduct obtained was that resulted from an *endo* selective approach on the Cα *Si* face of the dienophile, and was isolated in pure form after column chromatography on

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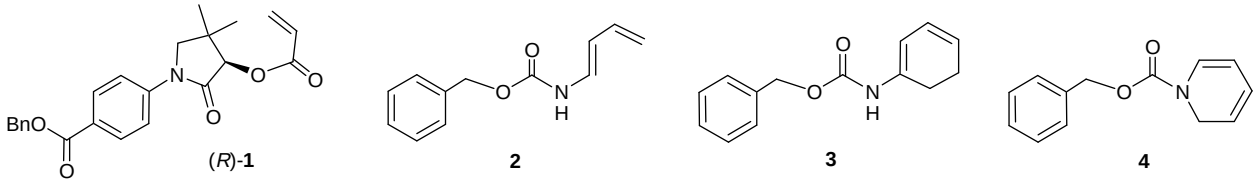
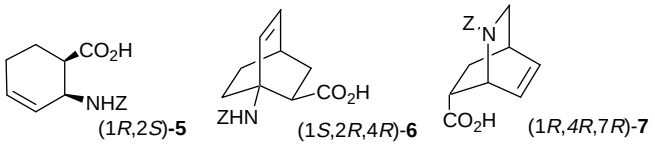
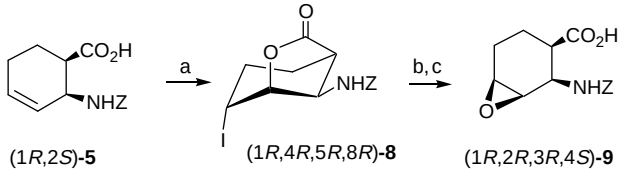


silica gel. Removal of the chiral auxiliary afforded three enantiopure constrained cyclic β-amino acids, that is, (1*R*,2*S*)-2-(benzyloxycarbonylamino)cyclohex-3-ene-1-carboxylic acid **5**, (1*S*,2*R*,4*R*)-1-benzyloxycarbonylaminobicyclo[2.2.2]oct-5-ene-2-carboxylic acid **6** and (1*R*,4*R*,7*R*)-(2-benzyloxycarbonyl)-2-azabicyclo[2.2.2]-oct-5-ene-7-carboxylic acid **7**.



To prepare the functionalized derivatives, we first studied the epoxidation of these three enantiopure constrained cyclic β-amino acids **5**, **6** and **7** having a *Z* amino protecting group, in the presence of *m*CPBA in dichloromethane.

As expected, the reaction of the cyclic β-amino acid **5** with *m*CPBA proceeded with high stereoselectivity, mainly providing the *cis*-epoxide due to the stereodirecting effect of the *Z* amino protecting group. The product was assigned as a *cis*-epoxide by analogy with the known stereochemistry obtained during epoxidation of 2-aminocyclohex-4-ene carboxylic acids.[6b,g] The *trans*-isomer could not be detected in the crude reaction mixture.



Scheme 1. Reagents and conditions: (a) I_2, KI, $NaHCO_3$, DCM, H_2O; (b) LiOH, THF, H_2O, rt; (c) H_3O^+, H_2O.

Although the reaction proceeded with high selectivity, isolation by chromatography of the pure *cis*-epoxide in good yield from the mixture containing *m*CPBA proved to be difficult. In the case of the bicyclic amino acids **6** and **7**, a lower selectivity was observed affording a quasi-inseparable mixture of the two epoxides in an 80:20 and 33:67 ratio, respectively.[11] It can be assumed that for these two compounds, steric and/or electronic effects were not sufficient enough to exclusively provide one epoxide.

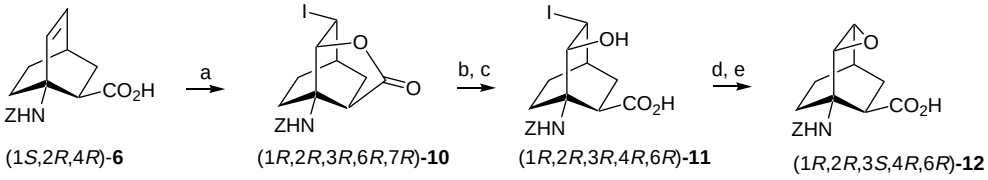
Consequently, we decided to explore an alternative route to oxirane formation based on the stereoselective transformation of the cyclic β-amino acid to its iodolactone that offered an excellent possibility for the exclusive formation of a single epoxide after basic treatment.

The oxirane formation in two steps via iodolactolization has previously been described to obtain intermediates involved in the synthesis of α-multistriatin,[12] in some preparations of polyunsaturated fatty acids,[13] in the macrocyclic core synthesis of salicylihalamides A an B[14] as well as in the synthesis of 4,5-epoxy-α-amino acids from allyl or crotyl glycine.[15] Likewise, unsaturated cyclic β-amino acids have also been previously subjected to iodolactonization but rarely with the aim of oxirane synthesis.[6a,16]

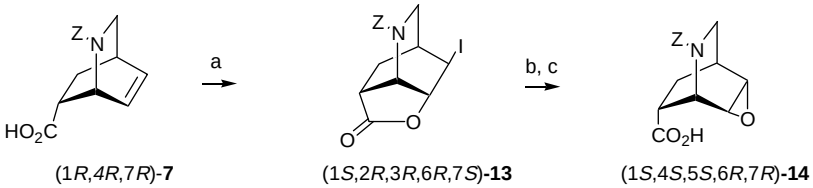
The reaction of the unsaturated cyclic β-amino acids **5**, **6** and **7** in a biphasic mixture with I_2/KI in a slightly alkaline medium, overnight, at room temperature yielded the corresponding iodolactones **8**, **10** and **13** with excellent regio and stereoselectivity (Schemes 1–3).

These iodolactones were isolated in pure form in 75–80% yield after column chromatography on silica gel using dichloromethane/ethyl acetate (9.5:0.5) as eluent. The structure of compounds **8**, **10** and **13** was characterized by ^1H and ^{13}C NMR and by MS analysis.

Treatment of iodolactone **8** with lithium hydroxide (3 equiv) in a THF/H_2O mixture for 4 h at room temperature resulted in the quantitative formation of the epoxide **9**, which was isolated in pure form by recrystallization from ethyl acetate (98% yield) (Scheme 1).



Scheme 2. Reagents and conditions: (a) I_2, KI, $NaHCO_3$, DCM, H_2O; (b) LiOH, THF, H_2O, rt; (c) H_3O^+, H_2O; (d) LiOH, THF, H_2O, 70 °C; (e) H_3O^+, H_2O.



Scheme 3. Reagents and conditions: (a) I_2, KI, $NaHCO_3$, DCM, H_2O; (b) LiOH, THF, H_2O, rt; (c) H_3O^+, H_2O.

The lactone ring opening intermediate was not detected by LC/MS analysis in the reaction mixture due to the fast epoxide formation.

Under the same experimental conditions for 2 h, the iodolactone **10** led to the corresponding iodo hydroxy-β-aminoacide **11** which was isolated in good yield (98%) after acidic treatment of the reaction mixture (Scheme 2). On the other hand, epoxide **12** was quantitatively formed when compound **11** was treated with an excess of lithium hydroxide (3 equiv) in a THF/H_2O mixture at 70 °C for 4 h. It was isolated in pure form after column chromatography on silica gel using dichloromethane/acetic acid (9.5:0.5) as eluent in 81% yield.

Opening of the lactone ring of compound **13** with lithium hydroxide (3 equiv) at room temperature was quantitative after 3 h, as determined by LC/MS analysis. The corresponding epoxide **14** was quantitatively formed overnight. Although the formation of epoxide **14** was slow, in this case, we were unable to isolate the iodo hydroxy-β-amino acid intermediate in its pure form.

Characterization of these three enantiopure epoxides **9**, **11** and **14** allowed us to unambiguously establish the structure of the main epoxide that was previously obtained when using *m*CPBA by comparison of the NMR data of the crude mixtures obtained using the two methods. As assumed, the *cis*-epoxide **9** was obtained by reaction of *m*CPBA on the cyclic β-amino acid **5**. In the case of the bicyclic β-amino acid **6**, the main product formed[17] was the epoxide **12** (80% yield), probably the result of a stereodirecting effect of the carboxyl group since an interaction in the transition state between the carbamate and the peracid seems improbable. Finally, epoxide **14** corresponds to the minor isomer[18] formed in 33% yield during the epoxidation of the amino acid **7** with *m*CPBA. Taking into account that a tertiary amine should not exert a stereodirecting effect,[6d,h] we assumed that in this case, the stereoselectivity is mainly governed by steric factors.

3. Conclusion

In conclusion, an effective approach to the enantiopure oxirane derivatives of some constrained chiral cyclic β-amino acids has been developed, based on a stereoselective epoxidation involving the regio- and stereoselective iodolactonization, followed by opening of the lactone ring by alkaline treatment. These syntheses constitute the first preparation of these cyclic β-aminoacid derivatives and further studies concerning their transformation are currently in progress.

4. Experimental

4.1. General remarks

All reagents were used as purchased from commercial suppliers without further purification. Solvents were dried and purified by conventional methods prior to use. Melting points were determined with a Kofler Heizbank apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 341 polarimeter. ^1H or ^{13}C NMR spectra (DEPT, $^1H/^{13}C$ 2D-correlations) were recorded with a Bruker A DRX 400 spectrometer using the solvent as the internal reference. Data are reported as follows: chemical shifts (δ) in parts per million, coupling constants (J) in hertz (Hz). The ESI mass spectra were recorded with a platform II quadrupole mass spectrometer (Micromass, Manchester, UK) fitted with an electrospray source. HPLC analyses were performed with a Waters model 510 instrument or a Beckman System Gold 126 instrument with variable detector using column A: Symmetry Shield RP_{18}, 3.5μ, (50 × 4.6 mm), flow: 1 ml/min, H_2O (0.1% TFA)/CH_3CN (0.1% TFA), gradient 0→100% (15 min) and 100% (4 min); column B: Chiracel OD-RH, C_{18}, 5μ, (150 × 4.6 mm), flow: 1 ml/min, eluent I: H_2O (0.1% TFA)/CH_3CN (0.1% TFA) 60:40; eluent II: H_2O (0.1% TFA)/CH_3CN (0.1% TFA) 70:30; column C: (S,S)-Welk 01, flow: 1 ml/min, hexane/2-propanol: 90:10; column D: Chiracel OD, flow: 1 ml/min, hexane/2-propanol: 70:30.

The enantiopure (1*R*,2*S*)-2-(benzyloxycarbonylamino)cyclohex-3-ene-1-carboxylic acid **5**, (1*S*,2*R*,4*R*)-1-benzyloxycarbonylaminobicyclo[2.2.2]oct-5-ene-2-carboxylic acid **6** and (1*R*,4*R*,7*R*)-(2-benzyloxycarbonyl)-2-azabicyclo[2.2.2]oct-5-ene-7-carboxylic acid **7** were prepared as previously described.[7]

4.2. General procedure for synthesis of iodolactones 8, 10 and 13

To a solution of the N–Z β-amino acid (1 equiv) in CH_2Cl_2, KI (6 equiv), $NaHCO_3$ (3 equiv) and I_2 (2 equiv) in H_2O were added at 0 °C. After stirring for 24 h at room temperature, a solution of $Na_2S_2O_3$ was added in order to destroy the excess iodine. The mixture was then extracted with CH_2Cl_2 and the organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford the expected iodolactone.

4.3. (1*R*,4*R*,5*R*,8*R*)-8-(Benzyloxycarbonylamino)-4-iodo-6-oxabicyclo[3.2.1]octan-7-one (1*R*,4*R*,5*R*,8*R*)-8

Synthesized according to the general procedure from (1*R*,2*S*)-2-(benzyloxycarbonylamino)cyclohex-3-ene-1-carboxylic acid **5** (605 mg, 2.2 mmol) in CH_2Cl_2 (20 ml), in the presence of KI (2.19 g, 13.2 mmol), $NaHCO_3$ (554 mg, 6.6 mmol) and I_2 (1.11 g, 4.4 mmol) in H_2O (15 ml). The expected pure iodolactone (1*R*,4*R*,5*R*,8*R*)-**8** was obtained as a white solid after column chromatography on silica gel with dichloromethane/ethyl acetate (9.5:0.5) and precipitation using diethyl ether (662 mg, 75%); mp 109 °C; $[\alpha]_D^{20} = +57$ (c 0.8, CH_2Cl_2); t_R (HPLC, column A) 9.6 min; t_R (HPLC, column B: eluent I) 18.0 min; MS (ESI) m/z: 402.0 [$(M+H)^+$]; ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.75–1.85 (m, 1H, 2-H), 1.85–2.00 (m, 2H, 2-H and 3-H), 2.15–2.25 (m, 1H, 3-H), 2.68 (s, 1H, 1-H), 4.40 (m, 1H, 4-H), 4.62 (s br, 1H, 5-H), 4.71 (d, J = 5.6 Hz, 1H, 8-H), 5.00 (s, 2H, CH_2O), 5.48 (d, J = 6.2 Hz, NH), 7.25 (m, 5H, CH-arom); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 21.52 (C-4), 22.92 (C-2), 28.52 (C-3), 45.20 (C-1), 57.91 (C-8), 67.22 (CH_2O), 83.73 (C-5), 128.26, 128.37, 128.49, 128.60 (CH-arom), 135.92 (C-arom), 155.57 (NHCOO), 176.15 (COO); HRMS (FAB) calcd for $C_{15}H_{17}INO_4$ (MH^+) 402.0202, found 402.0204.

4.4. (1*R*,2*R*,3*R*,6*R*,7*R*)-7-(Benzyloxycarbonylamino)-2-iodo-4-oxa-8-tricyclo[4.3.1.0^{3,7}]decan-5-one (1*R*,2*R*,3*R*,6*R*,7*R*)-10

Synthesized according to the general procedure from (1*S*,2*R*,4*R*)-1-benzyloxycarbonylaminobicyclo[2.2.2]oct-5-ene-2-carboxylic acid **6** (542 mg, 1.8 mmol) in CH_2Cl_2 (15 ml), in the presence of KI (1.80 g, 10.8 mmol), $NaHCO_3$ (445 mg, 5.4 mmol) and I_2 (910 mg, 3.6 mmol) in H_2O (10 ml). The expected pure iodolactone (1*R*,2*R*,3*R*,6*R*,7*R*)-**10** was obtained as a colourless oil after column chromatography on silica gel with dichloromethane/ethyl acetate (9.5:0.5) (615 mg, 80%); $[\alpha]_D^{20} = -55$ (c 0.9, CH_2Cl_2); t_R (HPLC, column A) 10.2 min; t_R (HPLC, column C) 29.4 min; MS (ESI) m/z: 428.0 [$(M+H)^+$]; ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.66 (br m, 1H, 9-H), 2.05 (m, 2H, 1-H and 10-H), 2.18 (m, 4H, 9-H, 10-H, 8-H), 2.82 (br d, J = 8.7 Hz, 1H, 6-H), 4.28 (br s, 1H, 2-H), 4.99 (s, 2H, CH_2O), 5.09 (s, 1H, 3-H), 5.26 (br s, 1H, NH), 7.15–7.30 (m, 5H, CH-arom); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 26.14 (C-9), 27.80 (C-2), 28.36 (C-8 and C-10), 31.96 (C-1), 40.84 (C-6), 58.57 (C-7), 66.85 (CH_2O), 87.35 (C-3), 128.17, 128.32, 128.61 (CH-arom), 135.91 (C-arom), 154.83 (NHCOO), 178.26 (COO); HRMS (FAB) calcd for $C_{17}H_{19}INO_4$ (MH^+) 428.0359, found 428.0362.

4.5. (1*S*,2*R*,3*R*,6*R*,7*S*)-8-(Benzyloxycarbonyl)-2-iodo-4-oxa-8-azatricyclo[4.3.1.0^{3,7}]decan-5-one (1*S*,2*R*,3*R*,6*R*,7*S*)-13

Synthesized according to the general procedure from (1*R*,4*R*,7*R*)-(2-benzyloxycarbonyl)-2-azabicyclo[2.2.2] oct-5-ene-7-carboxylic acid **7** (224 mg, 0.78 mmol) in CH_2Cl_2 (6 ml), in the presence of KI (776 mg, 4.7 mmol), $NaHCO_3$ (196 mg, 2.3 mmol) and I_2 (406 mg, 1.6 mmol) in H_2O (5 ml). The expected pure iodolactone (1*S*,2R,3R,6*R*,7*S*)-**13** was obtained as a white solid after treatment and precipitation using diethyl ether (248 mg, 77%); mp 124 °C; $[\alpha]_D^{20} = +43$ (*c* 1.0, CH_2Cl_2); t_R (HPLC, column A) 10.1 min; t_R (HPLC, column D) 12.5 min; MS (ESI) *m/z*: 413.9 [(M+H)$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 2.00 and 2.05 (2 m (67/33)*, 1 H, 10-H), 2.14 and 2.21 (2 m (67/33)*, 1 H, 10-H), 2.28 and 2.34 (br m (67/33)*, 1 H, 1-H), 2.75 and 2.80 (2dd (67/33)*, *J* = 10.2 Hz and 5.2 Hz, 1 H, 6-H), 3.33 (m, 1 H, 9-H), 3.95 (m, 1 H, 9-H), 4.31 (br s, 1 H, 2-H), 4.70 and 4.85 (2 t (67/33)*, $J_1 = J_2$ = 5.2 Hz, 1 H, 7-H), 4.96 and 5.00 (2 d (67/33)*, *J* = 5.5 Hz, 2 H, 3-H), 5.14 (s, 2 H, OCH_2), 7.27 (m, 5 H, H-arom); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 25.14 and 25.56 (C-2)*, 26.87 (C-10), 33.32 and 33.43 (C-1)*, 36.32 and 36.50 (C-6)*, 47.76 and 47.89 (C-9)*, 48.53 and 49.12 (C-7)*, 67.72 and 67.91 (OCH_2)*, 83.47 and 83.68 (C-3), 127.93, 128.30, 128.52, 128.63 and 128.70 (CH-arom)*, 135.82 and 136.10 (C-arom)*, 154.72 and 155.50 (CO)*, 175.43 and 175.56 (CO)*; HRMS (FAB) Calcd for $C_{16}H_{17}INO_4$ (MH$^+$) 414.0202, found 414.0196. (*The NMR of this compound is complicated by the presence of carbamate rotamers.)

4.6. (1*R*,2*R*,3*R*,4*S*)-2-(Benzyloxycarbonylamino)-3,4-epoxycyclohexane-1-carboxylic acid (1*R*,2*R*,3*R*,4*S*)-9

To a solution of iodolactone (1*R*,4*R*,5*R*,8*R*)-**8** (207 mg, 0.516 mmol, 1 equiv) in THF (4 ml) was added a LiOH solution (1.55 mmol, 65.0 mg, 3 equiv) in H_2O (2 ml) and the mixture stirred for 4 h at room temperature. The organic solvent was removed in vacuo, the mixture diluted with water and acidified to pH 2, and extracted with CH_2Cl_2. The organic layer was then dried over anhydrous $MgSO_4$ and concentrated in vacuo.

The expected pure epoxide (1*R*,2*R*,3*R*,4*S*)-**9** was obtained as a white solid after crystallization with ethyl acetate (149.0 mg, 99%); mp 158 °C; $[\alpha]_D^{20} = +71$ (*c* 0.7, EtOH); t_R (HPLC, column A) 7.1 min; MS (ESI) *m/z*: 292.1 [(M+H)$^+$]; ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 1.40 (m, 1H, 6-H), 1.70 (m, 2H, 6-H and 5-H), 2.02 (m, 1H, 5-H), 2.48 (m, 1H, 1-H), 3.22 (m, 2H, 3-H and 4-H), 4.47 (m, 1H, 2-H), 5.03 (d, *J* = 12.7 Hz, 1H, CH_2O), 5.08 (d, *J* = 12.7 Hz, 1H, CH_2O), 7.2 (d, *J* = 9.4 Hz, 1H, NH), 7.35 (m, 5H, H-arom); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ 16.86 (C-6), 23.02 (C-5), 41.96 (C-1), 46.03 (C-2), 52.82 (C-4), 53.08 (C-3), 65.19 (CH_2O), 127.65, 127.73, 128.25, 128.32 (CH-arom), 137.00 (C-arom), 155.76 (NHCOO), 173.39 (COOH); HRMS (FAB) calcd for $C_{15}H_{18}NO_5$ (MH$^+$) 292.1185, found 292.1160.

4.7. (1*R*,2*R*,3*R*,4*R*,6*R*)-1-(Benzyloxycarbonylamino)-2-hydroxy-3-iodobicyclo[2.2.2]octane-6-carboxylic acid (1*R*,2*R*,3*R*,4*R*,6*R*)-11

To a solution of iodolactone (1*R*,2*R*,3*R*,6*R*,7*R*)-**10** (180 mg, 0.42 mmol, 1 equiv) in THF (3 ml) was added a LiOH solution (1.27 mmol, 30 mg, 3 equiv) in H_2O (2 ml) and the mixture was stirred for 2 h at room temperature. The organic solvent was removed in vacuo, the mixture diluted with water (10 ml) and acidified to pH 2 and extracted with CH_2Cl_2 (4 × 10 ml). The organic layer was then dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford the iodo hydroxy β-aminoacid (1*R*,2*R*,3*R*,4*R*,6*R*)-**11** as a colourless semi-solid (185 mg, 98%); $[\alpha]_D^{20} = -30$ (*c* 0.8, CH_2Cl_2); t_R (HPLC, column A) 9.8 min; MS (ESI) *m/z*: 445.9 [(M+H)$^+$]; ^{1}H NMR (400 MHz, CD_3CN, 25 °C) δ 1.68 (br t, *J* = 10.2 Hz, 1H, 8-H), 2.00 (m, 4H, 8-H, 7-H, 5-H and 4-H), 2.15 (m, 1H, 5-H), 2.28 (m, 1H, 7-H), 3.12 (m, 1H, 6-H), 4.30 (s, 2H, 2-H and 3-H), 4.98 (d, *J* = 13.0 Hz, 1H, CH_2O), 5.10 (d, *J* = 13.0 Hz, 1H, CH_2O), 6.04 (s, 1H, NH), 7.40 (s, 5H, H-arom); ^{13}C NMR (100 MHz, CD_3CN, 25 °C) δ 22.33 (C-8), 28.28 (C-7), 28.84 (C-5), 35.01 (C-4), 37.94 (C-3), 39.93 (C-6), 55.54 (C-1), 65.64 (CH_2O), 80.95 (C-2), 127.62, 127.85, 128.46 (CH-arom), 137.28 (C-arom), 154.85 (NHCOO), 176.25 (COOH); HRMS (FAB) calcd for $C_{17}H_{21}INO_5$ (MH$^+$) 446.0464, found 446.0474.

4.8. (1*R*,2*R*,3*S*,4*R*,6*R*)-1-(Benzyloxycarbonylamino)-2,3-epoxybicyclo[2.2.2]octane-6-carboxylic acid (1*R*,2*R*,3*S*,4*R*,6*R*)-12

To a solution of iodo hydroxy β-amino acid (1*R*,2*R*,3*R*,4*R*,6*R*)-**11** (140 mg, 0.32 mmol, 1 equiv) in THF (4 ml) was added an LiOH solution (23 mg, 0.95 mmol, 3 equiv) in H_2O (2 ml) and the mixture was stirred for 4 h at 70 °C. The organic solvent was removed in vacuo, the mixture diluted with water (10 ml) and acidified to pH 2 and extracted with CH_2Cl_2 (4 × 10 ml). The organic layer was then dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford the iodo hydroxy β-amino acid (1*R*,2*R*,3*S*,4*R*,6*R*)-**12** as a colourless oil after column chromatography on silica gel with dichloromethane/ethyl acetate (9.5:0.5) (81 mg, 81%); $[\alpha]_D^{20} = -47$ (*c* 0.5, CH_2Cl_2); t_R (HPLC, column A) 8.1 min; MS (ESI) *m/z*: 318.1 [(M+H)$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.61 (m, 3H, 8-H and 5-H), 1.81 (m, 1H, 7-H), 2.12 (m, 2H, 4-H and 5-H), 1.30 (m, 1H, 7-H), 2.66 (dd, *J* = 12.3 and 4.8 Hz, 1H, 6-H), 3.32 (t, *J* = 4.8 Hz, 1H, 3-H), 3.51 (d, *J* = 5.0 Hz, 1H, 2-H), 5.00 (s, 1H, CH_2O), 6.25 (s, 1H, NH), 7.21 (m, 5H, H-arom); ^{13}C NMR (100 MHz, CD_3CN, 25 °C) δ 24.27 (C-8), 25.92 (C-5), 26.90 (C-4), 27.50 (C-7), 44.86 (C-6), 54.46 (C-3), 54.63 (C-2), 55.88 (C-1), 66.48 (CH_2O), 128.04, 128.50 (CH-arom), 136.50 (C-arom), 155.15 (NHCOO), 178.60 (COOH); HRMS (FAB) calcd for $C_{17}H_{20}NO_5$ (MH$^+$) 318.1341, found 318.1347.

4.9. (1*S*,4*S*,5*S*,6*R*,7R)-2-(Benzyloxycarbonyl)-2-azabicyclo[2.2.2]oct-5-ene-7-carboxylic acid (1*S*,4*S*,5*S*,6*R*,7*R*)-14

To a solution of iodolactone (1*S*,2*R*,3*R*,6*R*,7*S*)-**13** (190 mg, 0.46 mmol, 1 equiv) in THF (4 ml) was added a LiOH solution (1.38 mmol, 33 mg, 3 equiv) in H_2O (2 ml) and the mixture was stirred for 24 h at room temperature. The organic solvent was removed in vacuo, the mixture diluted with water and acidified to pH 2 and extracted with CH_2Cl_2. The organic layer was then dried over anhydrous $MgSO_4$, concentrated in vacuo, to afford the pure epoxide (1*S*,4*S*,5*S*,6*R*,7*R*)-**14** as a white solid (138 mg, 0 99%); mp 148 °C; $[\alpha]_D^{20} = -104$ (*c* 1.2, EtOH); t_R (HPLC, column A) 7.7 min; t_R (HPLC, column B: eluent II) 12.5 min; MS (ESI) *m/z*: 304.3 [(M+H)$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 1.59 (br m, 1H, 8-H), 2.18 and 2.23* (2br m, 1H, 8-H), 2.38 and 2.42* (2br m, 1H, 4-H), 2.65 (m, 1H, 7-H), 3.28 (m, 3H, 5-H and 3-H), 3.43 and 3.48* (t, $J_1 = J_2$ = 4.6 Hz, 1H, 6-H), 4.88 and 5.00* (t, $J_1 = J_2$ = 4.0 Hz, 1H, 1-H), 5.10 (s, 2H, CH_2O), 7.35 (m, 5H, H-arom); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 23.90 and 23.95* (C-8), 27.56 and 27.83 (C-4), 40.55 and 40.76 (C-7), 43.33 and 43.54* (C-3), 47.61 and 48.23* (C-1), 49.67 (C-5), 50.59 and 50.73* (C-6), 66.26 and 66.29* (CH_2O), 126.89, 127.03, 127.12, 127.16, 127.52, 127.57 (CH-arom), 136.39 and 136.48* (C-arom), 155.16 and 155.61* (COO), 177.53 and 177.59* (COOH); HRMS (FAB) calcd for $C_{16}H_{18}NO_5$ (MH$^+$) 304.1185, found 304.1161. (*The NMR of this compound is complicated by the presence of carbamate rotamers.)

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18. Some significant differences of the resonance signals on the ^{1}H and ^{13}C spectra were observed for the two epoxides obtained with *m*CPBA. For example, 8-*H*, 4-*H* and 1-*H* chemical shifts were, respectively, 1.92 and 1.98 ppm (2m)*; 3.00 and 3.06 ppm (2m)* and 4.74 and 4.85 ppm (2t)* for the major epoxide, and 1.59, 2.18 and 2.23 ppm (3m)*; 2.38 and 2.42 ppm (2br m)* and 4.88 and 5.00 ppm (2t)* for the minor epoxide. (*The NMR of this compound is complicated by the presence of carbamate rotamers.)