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Synthesis of enantiomerically pure constrained γ-hydroxy-α-amino acids by directed hydroxylation

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Abstract: Efficient synthetic routes to enantiomerically pure (1*R*,3*R*,6*R*)- and (1*S*,3*S*,6*S*)-1-amino-3-hydroxy-6-phenylcyclohexane-1-carboxylic acids have been developed. The key step is a directed hydroxylation through an iodo-initiated *O*-functionalization reaction of methyl (1*S*,6*R*)- and (1*R*,6*S*)-1-aminocarbonyl-6-phenyl-3-cyclohexene-1-carboxylates, which can easily be obtained from the asymmetric Diels–Alder reactions of 1,3-butadiene with the (*E*)-2-cyanocinnamates of (*S*)-ethyl lactate and (*R*)-pantolactone, respectively.

The synthesis of conformationally constrained α-amino acids has attracted significant attention over the last few years since their important role in the generation of peptidomimetics and pseudopeptides was recognised.[1] In this context, and as a part of our research program on the racemic and asymmetric synthesis of conformationally constrained amino acids,[2] we have been interested in the synthesis of hydroxylated amino acids because the incorporation of a hydroxy group in a predetermined position of an amino acid opens the way into the field of glycobiology, a new area of research directed towards the synthesis of new glycosylated hydroxyamino acids, which are carbohydrate mimetics of great interest.[3] Recently, we have reported[4] the synthesis of racemic 1-amino-*t*-3-hydroxy-*t*-6-phenylcyclohexan-*r*-1-carboxylic acid *rac*-**8** (**8a** and its enantiomer **8b**), starting from the Diels–Alder reaction between 1,3-butadiene and (*Z*)-2-phenyl-4-benzylidene-5(4H)-oxazolone, followed by a methodology involving a directed hydroxylation step through an iodo-oxazination reaction.

We would like to report here the asymmetric synthesis of both enantiomers **8a** and **8b** of the γ-hydroxy-α-amino acid mentioned above, starting from the enantiomerically pure (1*S*,6*R*)- and (1*R*,6*S*)-1-cyano-6-phenyl-3-cyclohexen-1-carboxylic acids **1a,b** (see Scheme 1). Compounds **1a,b** are prepared from asymmetric Diels–Alder cycloadditions between 1,3-butadiene and the chiral (*E*)-2-cyanocinnamates of (*S*)-ethyl lactate and (*R*)-pantolactone respectively.[5] The use of these compounds as chiral starting materials in the synthesis of the required optically active γ-hydroxy-α-amino acids **8a** and **8b** is discussed, using a similar methodology[4] to that referenced above to achieve the directed hydroxylation.

In order to obtain the regio- and stereochemical control in the hydroxylation step[6] through an iodo-oxazination reaction, it is necessary to incorporate an oxygenated functional group in an axial position. This group must also be linked to the quaternary carbon atom and predisposed towards attack of the double bond in an electrophile-initiated intramolecular reaction. In order to achieve this, the cyano group of compounds **1a,b** was transformed into the corresponding amide group by hydrolysis in H_2O_2/NaOH at 50°C over 3 days. Further treatment with diazomethane in diethyl ether afforded the esters **2a,b** in 55% yield from **1a,b** (Scheme 1).

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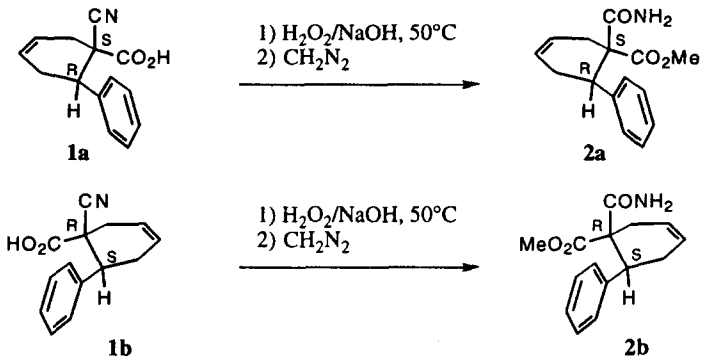
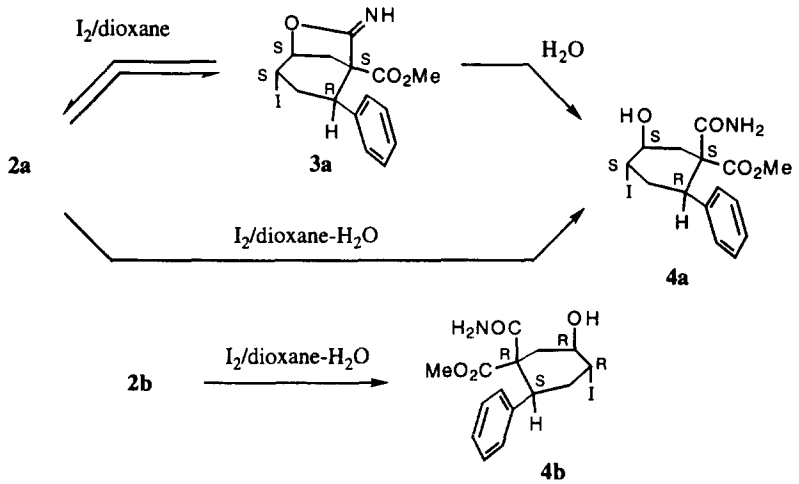


Scheme 1.

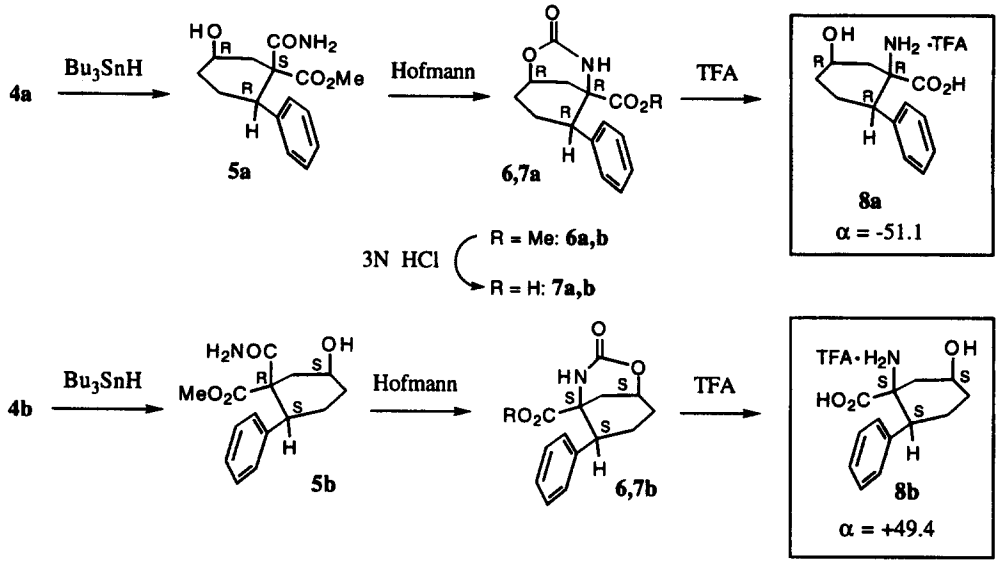
Compounds **2a,b** were used as starting materials in the iodo-cyclofunctionalization reaction in which addition of excess iodine in dioxane–water (7:3) gave the *O*-functionalization in a *syn* relationship to the amide group. In this way, the iodohydrins **4a,b** were obtained in good yield after elimination of the excess iodine with a 10% aqueous solution of $Na_2S_2O_3$ and further extraction with dichloromethane. The reactions proceed *via* the cyclic intermediates **3a,b** which could be identified by NMR techniques when the reactions were carried out in the absence of water. However, these intermediates could not be isolated because of their low stability, due to the fact that, in solution, the equilibrium lies towards the starting materials. When the reactions were carried out in dry dioxane and water was added later, the intermediates **3a,b** were observed prior to the formation of iodohydrins **4a,b** (Scheme 2).



Scheme 2.

In the cyclization of olefinic amides promoted by a halonium ion, the predominant product is the imino ether which subsequently hydrolyses to the corresponding lactone.[7] Given this, in our case, the cyclofunctionalization was produced by nucleophilic intramolecular attack by the oxygen atom of the amide group on the double bond activated by the iodo-substituent. This attack allows the formation of cyclic intermediate **3a** in the absence of water. In the presence of water, the heterocycle oxolan-2-imine was opened[8] to give the desired iodohydrin **4a**. There are numerous examples in the literature of the generation of bicyclic systems that use amide derivatives as oxygen nucleophiles but, to the best of our knowledge, in many cases secondary or tertiary amides were used, there are few examples with primary amides.[8,9]

The iodohydrins **4a,b** could be easily deiodinated under mild conditions to give the hydroxy-derivatives **5a,b**, using tributyltin hydride in dichloromethane.[10] After removal of organotin compounds by treatment with hexane, hydroxy-compounds **5a,b** were obtained in 80% yield (Scheme 3).

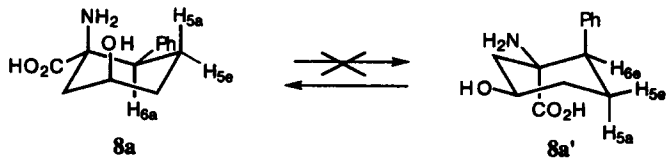


Scheme 3.

In order to achieve the desired enantiomerically pure γ-hydroxy-α-amino acids, the amide group of compounds **5a,b** was transformed into the amino group by a selective Hofmann rearrangement[11] using $Hg(OAc)_2$, methanol and NBS in DMF. This procedure gave the cyclic carbamates **6a,b** rather than the corresponding methyl carbamates. This result can be explained in terms of an intramolecular attack involving the hydroxy group, situated in an axial position at the C_3 carbon, on the isocyanate intermediate generated from the Hofmann rearrangement (Scheme 3).

The treatment of cyclic carbamates **6a,b** with 3N HCl under reflux led to the hydrolysis of the methyl ester group to give the corresponding carboxylic acids **7a,b**, which were subsequently converted into the optically active γ-hydroxy-α-amino acids **8a,b** by hydrolysis in trifluoroacetic acid under reflux[12] (Scheme 3).

The conformational rigidity of these γ-hydroxy-α-amino acids **8a,b** is attributed to the phenyl group attached to the cyclohexane ring, which plays a very important role, favouring the conformation that places this group in an equatorial position, so hydroxy and amino substituents are placed in axial positions. Evidences of this fact are provided by consideration of their NMR spectral data, in particular the multiplicity and the value of the coupling constants of H_6 proton. This proton shows a doublet of doublets due to couplings with H_{5a}, H_{5e} protons of 12.3 Hz and 3.4 Hz. The large coupling observed would only be explainable if the H_6 proton has an axial position, so the phenyl group has an equatorial position (Scheme 4).



Scheme 4.

In summary, starting from optically active cycloadducts **1a,b**, obtained by the asymmetric Diels–Alder reaction of the (*E*)-2-cyanocinnamates of (*S*)-ethyl lactate and (*R*)-pantolactone with 1,3-butadiene, and using a methodology that involves a hydroxylation in a *syn* relationship to the amide group, we have synthesised both enantiomers of γ-hydroxy-α-amino acid, which we have previously achieved in a racemic form starting from (*Z*)-2-phenyl-4-benzylidene-5(4H)-oxazolone using a different strategy.

Experimental section

Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using Silica gel 60 (230–400 mesh). ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker ARX-300. Deuterated chloroform was used as a solvent with tetramethylsilane as the internal standard and deuterated methanol with tetramethylsilane as the external standard using a coaxial microtube (the chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). Melting points were determined on a Büchi 530 and are uncorrected. Microanalyses were carried out on a Perkin–Elmer 2400 analyser and are in good agreement with the calculated values. Optical rotations were measured on a Perkin–Elmer 241-C using 1 and 0.5 dm cells of 1 and 3.4 mL capacity, respectively.

Methyl (1S,6R)-1-aminocarbonyl-6-phenyl-3-cyclohexene-1-carboxylate ***2a***

A 30% solution of hydrogen peroxide (10 mL) was added to a solution of **1a** (726 mg, 3.2 mmol) in 5% NaOH (10 mL) at a rate of 2 mL/12 h and the reaction mixture was stirred at 50°C. After 3 days, the resulting solution was cooled, acidified with 6N HCl and extracted with CH_2Cl_2 (3×20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and treated with an excess of CH_2N_2 in diethyl ether. After 10 min, the solvent was evaporated *in vacuo* and the residue was purified by a silica gel column chromatography eluting with hexane–ethyl acetate (7:3) to give 270 mg of the corresponding methyl ester of compound **1a** and 456 mg of amide **2a** as a white solid (55%). Mp: 116–117°C. $[\alpha]^{25}_D$=+212.3 (c=1.7, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 2.32 (br d, 1H, $J_{2e'-2a'}$=18.6, $H_{2e'}$); 2.43 (br d, 1H, $J_{5e'-5a'}$=18.0, $H_{5e'}$); 2.69 (br d, 1H, $J_{2a'-2e'}$=18.6, $H_{2a'}$); 2.76–2.87 (m, 1H, $H_{5a'}$); 3.75 (s, 3H, CO_2CH_3); 3.82 (br d, 1H, $J_{6a'-5a'}$=7.2, $H_{6a'}$); 5.81 (br s, 1H, CONH); 5.84–5.87 (m, 2H, H_3+H_4); 6.02 (br s, 1H, CONH); 7.22–7.33 (m, 5H, Arom.). ^{13}C-NMR ($CDCl_3$): δ 25.3, 30.2 (C_2, C_5); 43.2 (C_6); 53.1 (CO_2CH_3); 58.0 (C_1); 125.2, 126.8, 127.2, 128.3, 128.4, 141.6 (C_3, C_4, Arom.); 171.3, 173.4 (CO_2CH_3, $CONH_2$). Found C 69.70, H 6.72, N 5.52, Anal. calc. for $C_{15}H_{17}NO_3$ C 69.46, H 6.61, N 5.40.

Methyl (1R,6S)-1-aminocarbonyl-6-phenyl-3-cyclohexene-1-carboxylate ***2b***

In a similar way to that described for **2a** and starting from carboxylic acid **1b** (680 mg, 3.0 mmol), compound **2b** was obtained as a white solid in 57% yield. $[\alpha]^{25}_D$=−218.0 (c=1.7, $CHCl_3$) Found C 69.64, H 6.70, N 5.50, Anal. calc. for $C_{15}H_{17}NO_3$ C 69.46, H 6.61, N 5.40.

Methyl (1S,3S,4S,6R)-1-aminocarbonyl-3-hydroxy-4-iodo-6-phenylcyclohexane-1-carboxylate ***4a***

Method A

A mixture of compound **2a** (194 mg, 0.75 mmol) and iodine (952 mg, 3.75 mmol) in dry dioxane (50 mL) was stirred at room temperature. After 10 h, the solvent was evaporated to give compound **3a** as an oil, which was analysed by ^{1}H- and ^{13}C-NMR. The oil was dissolved in dioxane–water (7:3) (10 mL) and stirred for 6 h. Evaporation of the solvents gave a mixture of compounds **2a** and **4a** in a ratio 2:3. An analytical sample of **4a** was obtained, as an oil, after purification by silica gel column chromatography eluting with hexane–ethyl acetate (1:1). $[\alpha]^{25}_D$=+22.2 (c=2.8, $CHCl_3$) Compound **3a:** ^{1}H-NMR ($CDCl_3$): δ 2.40 (dd, 1H, J_{6x-6n}=16.2, J_{6x-5n}=4.5, H_{6x}); 2.58–2.76 (m, 2H, H_{8a}+H_{6n}); 3.13 (d, 1H, J_{8s-8a}=12.3, H_{8s}); 3.54 (s, 3H, CO_2CH_3); 3.64 (dd, 1H, J_{5n-6n}=13.2, J_{5n-6x}=4.5, H_{5n}); 4.50 (t, 1H, J_{7x-1} J_{7x-6n}=4.2, H_{7x}); 4.85 (dd, 1H, J_{1-8a}=6.0, J_{1-7x}=4.2, H_1); 7.21–7.35 (m, 6H, Arom.+NH). ^{13}C-NMR ($CDCl_3$): δ 28.9, 36.9, 43.7, 44.1, 52.5, 55.4 (C_4, C_5, C_6, C_7, C_8, CO_2CH_3); 77.2 (C_1);

(C_1); 127.8, 128.0, 128.7, 138.7 (Arom.); 153.4 (C_3), 170.4 (CO_2CH_3). Found C 65.56, H 6.34, N 5.18, Anal. calc. for $C_{15}H_{17}NO_4$ C 65.42, H 6.22, N 5.09.

*Methyl (1S,5S,6S)-6-*endo*-phenyl-2-oxa-4-azabicyclo[3.3.1]non-3-one-5-carboxylate* **6b**

Carbamate **6b** was obtained as a white solid in a similar way to that described for **6a**, starting from alcohol **5b** (249 mg, 0.9 mmol). Isolated yield, 222 mg (90%). $[\alpha]^{25}_D$=+44.1 (c=1.45, $CHCl_3$). Found C 65.61, H 6.38, N 5.21, Anal. calc. for $C_{15}H_{17}NO_4$ C 65.42, H 6.22, N 5.09.

(1R,3R,6R)-1-Amino-3-hydroxy-6-phenylcyclohexane-1-carboxylic acid trifluoroacetate **8a**

Compound **6a** (138 mg, 0.5 mmol) was treated with 3N HCl (8 mL) and the mixture was heated under reflux for 16 h. On cooling the reaction mixture was extracted with CH_2Cl_2 (3×5 mL) and the organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent evaporated to afford 120 mg (91%) of (1*R*,5*R*,6*R*)-6-*endo*-phenyl-2-oxa-4-azabicyclo[3.3.1]non-3-one-5-carboxylic acid **7a**, which was used in the next step without purification. ^{1}H-NMR ($CDCl_3$): δ 1.68–2.28 (m, 5H, H_{9a}+H_{7n}+H_{7x}+H_{8n}+H_{8x}); 2.37 (br d, 1H, J_{9s-9a}=15.0, H_{9s}); 3.20 (dd, 1H, J_{6x-7n}=12.6, J_{6x-7x}=3.9, H_{6x}); 4.79 (br s, 1H, H_1); 7.05–7.30 (m, 5H, Arom.); 7.39 (br s, 1H, NH); 9.32 (br s, 1H, CO_2H). ^{13}C-NMR ($CDCl_3$): δ 22.8 (C_7); 30.3 (C_8); 31.6 (C_9); 48.5 (C_6); 59.2 (C_5); 72.2 (C_1); 126.4, 127.4, 127.8, 137.9 (Arom.); 155.2 (C_3); 171.2 (CO_2H). Carboxylic acid **7a** (120 mg, 0.46 mmol) was treated with trifluoroacetic acid (2 mL) and water (0.2 mL) and the reaction mixture was heated at 50°C for 2 h. Removal of the solvent gave quantitatively the optically active γ-hydroxy-α-amino acid **8a** as a white solid. $[\alpha]^{25}_D$=−51.1 (c=3.3, CD_3OD) ^{1}H-NMR (CD_3OD): δ 2.48–2.91 (m, 5H, H_{2a}+H_{4a}+H_{4e}+H_{5a}+H_{5e}); 3.16 (br d, 1H, J_{2e-2a}=13.2, H_{2e}); 3.98 (dd, 1H, J_{6a-5a}=12.3, J_{6a-5e}=3.9, H_{6a}); 5.47 (br s, 1H, H_{3e}); 7.88–8.02 (m, 5H, Arom.). ^{13}C-NMR (CD_3OD): δ 24.1 (C_5); 31.6 (C_4); 33.2 (C_2); 50.1 (C_6); 61.1 (C_1); 73.9 (C_3); 127.8, 128.6, 128.7, 140.2 (Arom.); 172.2 (CO_2H). Found C 50.21, H 5.91, N 3.88, F 15.56, Anal. calc. for $C_{15}H_{18}NO_5F_3$ C 51.56, H 5.20, N 4.01, F 16.32.

(1S,3S,6S)-1-Amino-3-hydroxy-6-phenylcyclohexane-1-carboxylic acid trifluoroacetate **8b**

Carboxylic acid **7b** was obtained as a white solid in a similar way to that described for **7a**, starting from compound **6b** (138 mg, 0.5 mmol). Isolated yield, 118 mg (90%). Optically active γ-hydroxy-α-amino acid **8b** was quantitatively obtained as a white solid in a similar way to that described for **8a**, starting from compound **7b** (120 mg, 0.46 mmol). $[\alpha]^{25}_D$=+49.4 (c=2.73, CD_3OD). Found C 50.33, H 6.03, N 3.81, F 15.61, Anal. calc. for $C_{15}H_{18}NO_5F_3$ C 51.56, H 5.20, N 4.01, F 16.32.

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127.7, 127.9, 128.5, 138.9 (Arom.); 168.2, 171.3 (CO_2CH_3, C_3). Compound **4a:** ^{1}H-NMR ($CDCl_3$): δ 2.04–2.08 (m, 1H, H_{5e}); 2.25 (dd, 1H, J_{2e-2a}=15.3, J_{2e-3e}=3.3, H_{2e}); 2.69 (ddd, 1H, J_{5a-5e}=14.4, J_{5a-6a}=10.8, J_{5a-4e}=3.3, H_{5a}); 3.02 (dd, 1H, J_{2a-2e}=15.3, J_{2a-3e}=4.8, H_{2a}); 3.88 (s, 3H, CO_2CH_3); 4.02 (dd, 1H, J_{6a-5a}=10.8, J_{6a-5e}=3.3, H_{6a}); 4.10 (br s, 1H, H_{3e}); 4.65 (br s, 1H, H_{4e}); 5.58 (br s, 1H, CONH); 6.76 (br s, 1H, CONH); 7.18–7.32 (m, 5H, Arom.). ^{13}C-NMR ($CDCl_3$): δ 14.2 (C_4); 29.6, 32.3 (C_2, C_5); 44.7 (C_6); 53.4 (CO_2CH_3); 59.0 (C_1); 70.5 (C_3); 127.7, 128.5, 128.8, 139.5 (Arom.); 173.2, 173.8 (CO_2CH_3, $CONH_2$). Found C 44.80, H 4.61, N 3.59, I 31.63, Anal. calc. for $C_{15}H_{18}NO_4I$ C 44.68, H 4.50, N 3.47, I 31.47.

Method B

A solution of compound **2a** (388 mg, 1.5 mmol) and iodine (1.9 g, 7.5 mmol) in dioxane–water (7:3) (10 mL) was stirred at room temperature for 10 h. The excess iodine was eliminated by addition of 10% $Na_2S_2O_3$ (5 mL) and the crude mixture was then extracted with CH_2Cl_2 (3×20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to give 544 mg of iodohydrin **4a** as an oil (90%).

*Methyl (1R,3R,4R,6S)-1-aminocarbonyl-3-hydroxy-4-iodo-6-phenylcyclohexane-1-carboxylate **4b***

Iodohydrin **4b** was obtained as an oil in a similar way to that described in method B for **4a**, starting from amide **2b** (388 mg, 1.5 mmol). Isolated yield, 532 mg (88%). $[\alpha]^{25}_D$=−23.9 (c=5.0, $CHCl_3$). Found C 44.84, H 4.64, N 3.61, I 31.66, Anal. calc. for $C_{15}H_{18}NO_4I$ C 44.68, H 4.50, N 3.47, I 31.47.

*Methyl (1S,3R,6R)-1-aminocarbonyl-3-hydroxy-6-phenylcyclohexane-1-carboxylate **5a***

A 3.72 M solution of tributyltin hydride (1.7 mL, 6.25 mmol) was added to a solution of iodohydrin **4a** (503 mg, 1.25 mmol) in dry CH_2Cl_2 (25 mL) under an inert atmosphere. After stirring for 24 h at 25°C the solvent was evaporated and the residue was treated with hexane. The resulting precipitate was filtered off and purified by silica gel column chromatography eluting with hexane–ethyl acetate (7:3) to afford 280 mg of alcohol **5a** as a white solid (81%). Mp: 117–9°C. $[\alpha]^{25}_D$=−9.9 (c=2.1, $CHCl_3$) ^{1}H-NMR ($CDCl_3$): δ 1.68–1.81 (m, 2H, H_{5e}+H_{4a}); 1.97–2.06 (m, 1H, H_{4e}); 2.34–2.49 (m, 3H, H_{5a}+H_{2e}+H_{2a}); 3.47 (dd, 1H, J_{6a-5a}=11.1, J_{6a-5e}=3.3, H_{6a}); 3.79 (s, 3H, CO_2CH_3); 4.01–4.07 (m, 1H, H_{3e}); 5.74 (br s, 1H, OH); 5.92 (br s, 1H, $CONH_aH_b$); 6.67 (br s, 1H, $CONH_aH_b$); 7.17–7.30 (m, 5H, Arom.). ^{13}C-NMR ($CDCl_3$): δ 23.1 (C_5); 33.3 (C_4); 37.4 (C_2); 47.5 (C_6); 53.0 (CO_2CH_3); 59.1 (C_1); 64.1 (C_3); 127.4, 128.3, 128.6, 141.2 (Arom.); 173.5, 174.3 (CO_2CH_3, $CONH_2$). Found C 65.04, H 7.01, N 5.12, Anal. calc. for $C_{15}H_{19}NO_4$ C 64.95, H 6.91, N 5.05.

*Methyl (1R,3S,6S)-1-aminocarbonyl-3-hydroxy-6-phenylcyclohexane-1-carboxylate **5b***

Alcohol **5b** was obtained as a white solid in a similar way to that described for **5a**, starting from iodohydrin **4b** (503 mg, 1.25 mmol). Isolated yield, 271 mg (79%).$[\alpha]^{25}_D$=+10.1 (c=2.2, $CHCl_3$). Found C 65.09, H 7.06, N 5.16, Anal. calc. for $C_{15}H_{19}NO_4$ C 64.95, H 6.91, N 5.05.

*Methyl (1R,5R,6R)-6-*endo*-phenyl-2-oxa-4-azabicyclo[3.3.1]non-3-one-5-carboxylate **6a***

Dry MeOH (864 mg, 27 mmol) and a solution of NBS (208 mg, 1.17 mmol) in dry DMF (3 mL) were added, at room temperature, to a solution of compound **5a** (249 mg, 0.9 mmol) and anhydrous $Hg(OAc)_2$ (344 mg, 1.08 mmol) in dry DMF (10 mL). The reaction mixture was stirred for 12 h at room temperature and the solvents were evaporated *in vacuo*. The solid residue was treated with CH_2Cl_2 (20 mL), the resulting precipitate was filtered off and the filtrate was extracted with 5% NaOH (3×10 mL) to eliminate the succinimide. The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent removed to afford 227 mg (92%) of cyclic carbamate **6a** as a white solid. Mp: 168–170°C. $[\alpha]^{25}_D$=−43.1 (c=1.35, $CHCl_3$) ^{1}H-NMR ($CDCl_3$): δ 1.79–1.92 (m, 2H, H_{8n}+H_{7x}); 2.12–2.23 (m, 2H, H_{9a}+H_{7n}); 2.29–2.42 (m, 2H, H_{9s}+H_{8x}); 3.19 (dd, 1H, J_{6x-7n}=12.9, J_{6x-7x}=3.6, H_{6x}); 3.57 (s, 3H, CO_2CH_3); 4.80–4.83 (m, 1H, H_1); 5.96 (br s, 1H, NH); 7.14–7.32 (m, 5H, Arom.). ^{13}C-NMR ($CDCl_3$): δ 23.1 (C_7); 31.3 (C_8); 32.8 (C_9); 50.2 (C_6); 52.7 (CO_2CH_3); 61.0 (C_5); 72.4