Synthesis of 1-amino-4-hydroxycyclohexane-1-carboxylic acids

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The synthesis of both stereoisomers of 1-amino-4-hydroxycyclohexane-1-carboxylic acid (**1** and **2**), a new family of constrained hydroxy-α,α-disubstituted-α-amino acids, is achieved through selective transformations of the functional groups of the corresponding enone cycloadduct provided by the Diels–Alder cycloaddition of Danishefsky's diene to methyl 2-acetamidoacrylate. The stereochemistry of intermediates **8** and **9** in the synthesis of hydroxy-α-amino acids **1** and **2** was unambiguously confirmed by X-ray structure determination.

Introduction

In recent years, there has been an increasing interest in α,α-disubstituted-α-amino acids, due to their important role in the synthesis of peptides with altered physical properties and biological activity (pseudopeptides, peptidomimetics).[1] In this context, and as a part of our research program on the racemic and asymmetric synthesis of conformationally constrained α-amino acids, we have been interested in the synthesis of non-proteinogenic hydroxy-α-amino acids.[2]

Glycobiology is a research speciality of growing importance which has given rise to an increasing interest in carbohydrate mimetics.[3] The prospect of new hydroxylated α-amino acids becoming available will lead to the synthesis of new glycosylated hydroxyamino acids, and this area is our new research focus.

In the last few years, the syntheses of the monohydroxycyclohexane-α-amino acids have received considerable attention (Fig. 1).[4–6] Recently, we have reported the synthesis of a constrained homoserine analogue [(1*S*,3*R*)-1-amino-3-hydroxycyclohexane-1-carboxylic acid], through direct hydroxylation, *via* a dihydro-1,3-oxazine intermediate, from the unsaturated amino acid derivative, obtained by Diels–Alder cycloaddition of buta-1,3-diene with 8-phenylmenthyl 2-acetamidoacrylate.[6b]

In order to complete the stereoisomers of hydroxycyclohexane-α-amino acids and to further advance on our experience in the synthesis of constrained amino acids and the methodology involving the Diels–Alder reaction, we would now like to report the extension of this methodology to the synthesis of the two 1-amino-4-hydroxycyclohexane-1-carboxylic acids **1** and **2** as a new family of constrained hydroxyamino acids (Fig. 1).

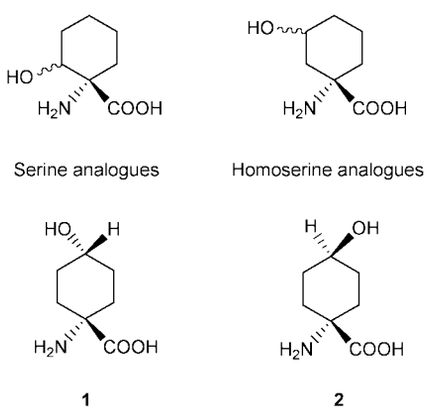


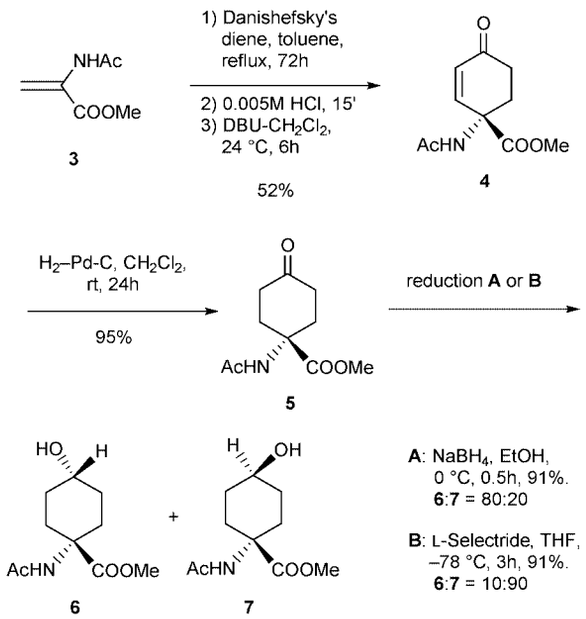
Fig. 1 All isomers of hydroxycyclohexane-α-amino acids.

Results and discussion

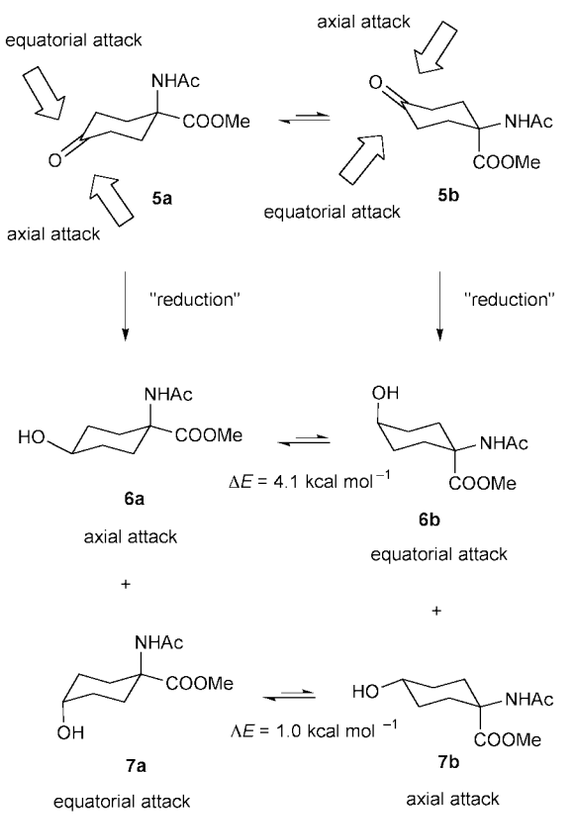
As there is a plane of symmetry in amino acids **1** and **2** there was no need to use a chiral dienophile, therefore the most convenient dienophile to use was methyl 2-acetamidoacrylate **3**. The direct diene precursor of this kind of 4-hydroxycyclohexane-α-amino acid is 2-methoxybuta-1,3-diene but the results obtained from the Diels–Alder reaction with methyl 2-acetamidoacrylate **3** were poor; we therefore changed this diene for another 2-hydroxy-functionalised one, which was more reactive than the first.[7] In our experiments the cycloaddition of Danishefsky's diene to methyl 2-acetamidoacrylate **3** worked with excellent results when the reaction was carried out in toluene at reflux for 72 h, allowing the obtention of the mixture of methyl 1-acetamido-*c*-2-methoxy-4-trimethylsilyloxycyclohex-3-ene-*r*-1-carboxylate and methyl 1-acetamido-*t*-2-methoxy-4-trimethylsilyloxycyclohex-3-ene-*r*-1-carboxylate, corresponding to *endo* and *exo* attack respectively. This mixture of products was treated with a 0.005 M HCl–THF (1:4) solution to give a mixture of methyl 1-acetamido-*t*-2-methoxy-4-oxocyclohexane-*r*-1-carboxylate and methyl 1-acetamido-4-oxocyclohex-2-ene-1-carboxylate **4** in a ratio of 1:1. Enone **4** was obtained from the easy elimination of the methoxy group of the *endo*-cycloadduct.[8] Subsequent addition of DBU–CH_2Cl_2 at 2 °C to the above reaction mixture gave the elimination of the methoxy group of the *exo*-cycloadduct, leaving only the corresponding enone **4** with an excellent yield. This enone was quantitatively hydrogenated in CH_2Cl_2 at room temperature, using 10% palladium–carbon as a catalyst to give ketone **5**, which is the direct precursor of the desired hydroxylated amino acids. The carbonyl group of compound **5** was reduced using sodium borohydride in ethanol at 0 °C to give a mixture of the equatorial and axial alcohols **6** and **7**, respectively, in an 80:20 ratio or by the action of L-Selectride® at −78 °C in THF to give the same mixture of alcohols **6** and **7**, but now in a 10:90 ratio (Scheme 1).

The stereochemical outcome of ketone reductions with metal hydrides depends strongly on the structure of the reagent and on the ketone, particularly in the case of cyclic ketones.[9]

In our case, it is of crucial importance to know the most stable chair conformation of the ketone **5**, since in the reduction reaction, the hydride attack on the same side in both conformations will lead to opposite results (Scheme 2). Due to this fact, several calculations were made on ketone **5** and on alcohols **6**



Scheme 1 Synthesis of alcohols **6** and **7** from dienophile **3**.



Scheme 2 Reduction of ketone **5**.

and **7**, obtained in these reductions. The lowest energy conformers of cyclohexanone **5** were calculated by molecular mechanics and dynamics (MM/MD)[10] and the relative energy of the conformer **5a** was 1.6 kcal mol^{-1} lower than the conformer **5b**[11] (Scheme 2).

The addition of the sodium borohydride to the carbonyl carbon of conformer **5a** takes place preferentially on the opposite side to the acetamide group to give alcohol **6** (resulting from the axial attack), in accordance with the Felkin–Ahn model.[12] By contrast, the preferential equatorial attack of bulky hydride L-Selectride® to the carbonyl group gives axial alcohol **7** as the major compound.

Alcohols **6** and **7** could not be separated by column chromatography. The mixture starting from $NaBH_4$ reduction was therefore treated with methanesulfonyl chloride in triethylamine to give the methanesulfonate derivatives **8** and **9**, which were separated by silica gel column chromatography, eluting with ethyl acetate. The stereochemistry of compounds **8** and **9** was unambiguously confirmed by X-ray analysis (Fig. 2).

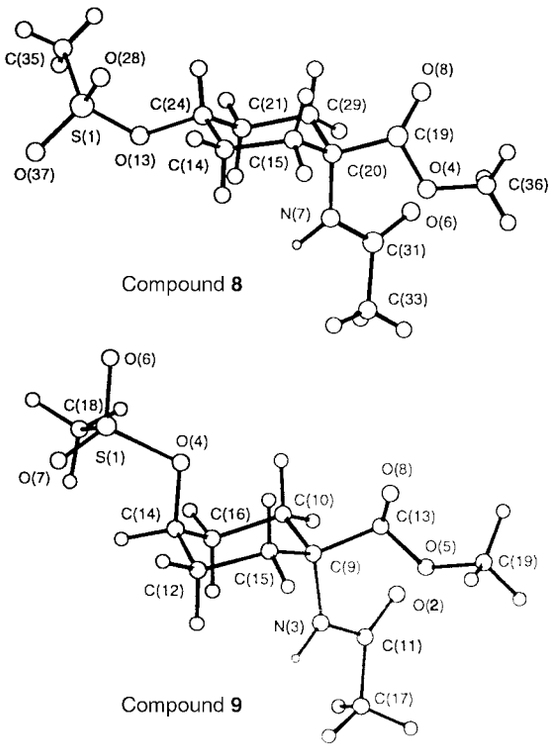


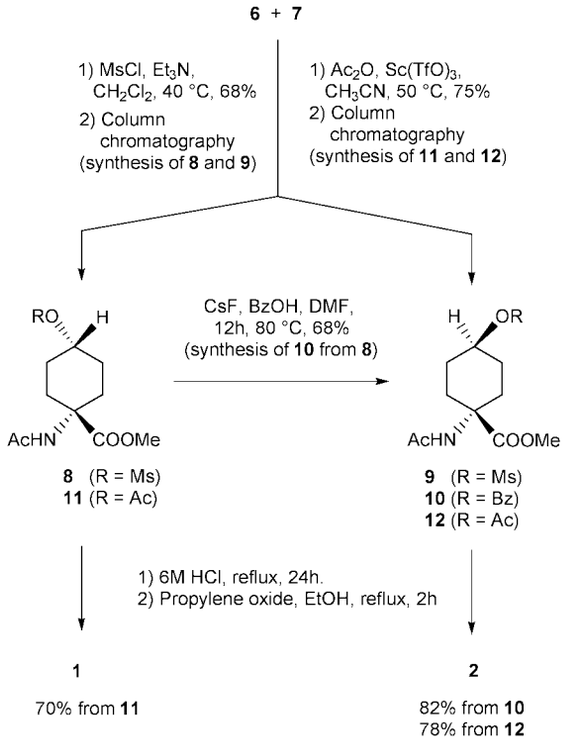
Fig. 2 X-Ray crystallographic projection of **8** and **9**.

To obtain the stereoisomer of 4-hydroxycyclohexane-α-amino acid **2**, in which the amino and hydroxy groups present an *anti* relationship, we attempted the inversion of methanesulfonate derivative **8** by means of the addition of CsF in DMF, achieving the inversion of the hydroxy group in the form of the benzoate derivative **10**. This compound was hydrolysed by the action of a 6 M HCl aqueous solution heated under reflux, giving the desired 1-amino-*c*-4-hydroxycyclohexane-*r*-1-carboxylic acid as a hydrochloride derivative. Further addition of propylene oxide in ethanol yielded the 4-hydroxycyclohexane-α-amino acid **2** (Scheme 3).

To obtain the other stereoisomer, in which the amino and hydroxy groups present a *syn* relationship, we tried the hydrolysis of the major compound **8**; however all attempts in acid media were unsuccessful because a mixture of elimination products was produced under these conditions. Consequently, we decided to convert the mixture of alcohols **6** and **7** (starting from $NaBH_4$ reduction) into the corresponding acetate derivatives **11** and **12**, using acetic anhydride and scandium triflate as the catalyst. This mixture was separated by column chromatography and the major product **11** was hydrolysed in an acid medium at reflux in order to obtain the desired 1-amino-*t*-4-hydroxycyclohexane-*r*-1-carboxylic acid **1**, according to the protocol described for the synthesis of 4-hydroxy-α-amino acid **2**. Alternatively, 4-hydroxy-α-amino acid **2** was obtained by hydrolysis, in an acid medium, of acetate derivative **12** (starting from L-Selectride® reduction of ketone **5** and further acetylation) (Scheme 3).

Conclusion

In summary, we have developed a strategy to synthesize both *cis* and *trans* constrained δ-hydroxy-α-amino acids with a cyclohexane structure, in order to complete the family of hydroxy-



Scheme 3 Synthesis of hydroxy-α-amino acids **1** and **2** from alcohols **6** and **7**.

cyclohexane-α-amino acids described in the literature. The Diels–Alder cycloaddition of methyl acetamidoacrylate with Danishefsky's diene is the key step to achieve these cyclic quaternary amino acids.

Experimental

The solvents were purified according to standard procedures. Analytical TLC was carried out using Polychrom SI F_{254} plates. Column chromatography was carried out using Silica gel 60 (230–400 mesh). ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker ARX-300 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard and in CD_3OD and D_2O with TMS as external standard using a coaxial microtube (chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). Melting points were determined on a Büchi SMP-20 melting point apparatus and are uncorrected. Microanalyses were carried out on a CE Instruments EA-1110 analyser and are in good agreement with the calculated values. IR spectra were recorded on a Perkin Elmer FT-IR Spectrum 1000 spectrometer.

Methyl 1-acetamido-4-oxocyclohex-2-ene-1-carboxylate (4)

Danishefsky's diene (2.4 g, 14.0 mmol) was added to a solution of methyl 2-acetamidoacrylate **3** (500 mg, 3.5 mmol) in dry toluene (50 mL) kept under an inert atmosphere. After stirring for 24 h, at reflux, another 3.5 mmol of **3** were added. After 2 more days stirring at the same temperature, the solvent was evaporated *in vacuo* and a solution of 0.005 M HCl–THF (1 : 4) (40 mL) was added to the residue. The reaction mixture was stirred for 15 h at 20 °C, the solvent was eliminated and the mixture was diluted with CH_2Cl_2 (30 mL). This solution was washed with brine (2 × 20 mL) and an aqueous solution of 5% $NaHCO_3$ (2 × 20 mL). The aqueous phases were washed again with CH_2Cl_2 (20 mL) and AcOEt (20 mL), the combined organic phases were dried over anhydrous $MgSO_4$ and filtered. Evaporation of the solvent gave a residue which corresponded to a mixture of methyl 1-acetamido-*t*-2-methoxy-4-oxocyclohexane-*r*-1-carboxylate and methyl 1-acetamido-4-oxocyclohex-2-ene-1-carboxylate **4** in a ratio of 1 : 1. The residue was dissolved in CH_2Cl_2 (40 mL) and DBU (0.525 mL, 3.5 mmol) was added. The reaction mixture was stirred for 24 h at 2 °C and the solution was washed with a solution of HCl 0.5 M (60 mL). The aqueous phase was extracted with CH_2Cl_2 (5 × 20 mL) and the combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was chromatographed on silica gel, eluting with ethyl acetate, to yield 770 mg of enone **4** as a white solid (52%). Mp: 94–95 °C. Calc. for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63; found C, 56.48; H, 6.23; N, 6.58%. IR (CH_2Cl_2, cm^{-1}): 3433 (NH), 1743 (COO + CO), 1685 (CON). ^{1}H-NMR ($CDCl_3$): δ 1.98 (s, 3H, MeCO), 2.40–2.59 (m, 4H, $H_{5a'}$ + $H_{5e'}$ + $H_{6a'}$ + $H_{6e'}$), 3.74 (s, 3H, MeOOC), 6.04 (d, 1H, H_3, J_{2-3}=12.0), 6.47 (br s, 1H, NH), 7.05 (d, 1H, H_2, J_{3-2} = 12.0). ^{13}C-NMR ($CDCl_3$): δ 22.7, 31.4, 33.5 (C_5, C_6, MeCO), 53.1 (MeOOC), 57.8 (C_1), 129.9 (C_3), 147.1 (C_2), 170.2, 171.2 (COO, CON), 197.4 (CO).

Methyl 1-acetamido-4-oxocyclohexane-1-carboxylate (5)

A solution of enone **4** (211 mg, 1 mmol) in dry CH_2Cl_2 (10 mL) was hydrogenated at atmospheric pressure for 24 h at 30 °C; using 10% palladium–carbon (30 mg) as a catalyst. After the removal of the catalyst and the solvent, the residue was chromatographed on silica gel eluting with hexane–ethyl acetate (1 : 9), to yield 204 mg of compound **5** as a white solid (95%). Mp: 133–134 °C. Calc. for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57; found C, 56.67; H, 6.95; N, 6.25%. IR (CH_2Cl_2, cm^{-1}): 3433 (NH), 1741 (COO), 1720 (CO), 1686 (CON). ^{1}H-NMR ($CDCl_3$): δ 2.03 (s, 3H, MeCO), 2.32–2.49 (m, 8H, H_{2a} + H_{2e} + H_{3a} + H_{3e} + H_{5a} + H_{5e} + H_{6a} + H_{6e}), 3.74 (s, 3H, MeOOC), 6.34 (br s, 1H, NH). ^{13}C-NMR ($CDCl_3$): δ 22.7 (MeCO), 31.9, 36.4 (C_2, C_3, C_5, C_6), 52.4 (MeOOC), 57.4 (C_1), 171.0, 173.2 (COO, CON), 209.5 (CO).

Reduction of cyclohexanone 5

Method A. Sodium borohydride (91 mg, 2.4 mmol) was added to a stirred solution of ketone **5** (170 mg, 0.80 mmol) in dry ethanol (10 mL) kept under an inert atmosphere at 0 °C. After 30 min at 0 °C, water (2 mL) and a 2 M HCl solution were added dropwise. The solvent was evaporated and the residue washed with CH_2Cl_2 (2 × 20 mL) and THF (2 × 20 mL). Evaporation of the solvent gave a diastereoisomeric mixture (157 mg, 91%) of alcohols **6** and **7**, as a colourless solid, in a ratio 80 : 20, used without purification in the succeeding procedures.

Method B. Compound **5** (100 mg, 0.47 mmol) was dissolved in dry THF (8 mL) and L-Selectride® (0.7 mL of 1 M solution in THF, 0.7 mmol) was added dropwise, at −78 °C, under an inert atmosphere. After 3 h stirring at the same temperature, the reaction was quenched by the addition of a saturated NH_4Cl solution (2 mL). The resulting mixture was allowed to warm up to room temperature, the solvent evaporated and the residue washed with CH_2Cl_2 (2 × 10 mL) and THF (2 × 10 mL). Evaporation of the solvent gave an unpurified mixture (110 mg) of compounds **6** and **7,** in a 10 : 90 ratio, used without purification in the succeeding procedures. The ratio of alcohols **6** and **7** was determined by the integration of the next ^{1}H-NMR signals: ^{1}H-NMR ($CDCl_3$): δ 3.62–3.72 (m, 4H, MeOOC + H_{3ax} **6**), 3.86–3.94 (m, 1H, H_{3eq} **7**), 5.96 (br s, 1H, NH **6**), 6.09 (br s, 1H, NH **7**).

Methyl 1-acetamido-*t*-4-methylsulfonyloxycyclohexane-*r*-1-carboxylate (8)

The mixture of alcohols **6** and **7** obtained from the reduction of ketone **5** using method A (157 mg, 0.73 mmol) was dissolved in dry CH_2Cl_2 (15 mL) under an inert atmosphere; triethylamine (111 mg/0.153 mL, 1.09 mmol) and methanesulfonyl chloride (124.8 mg/0.084 mL, 1.09 mmol) were added to this solution.

After 36 h stirring at reflux, the solution was left to reach room temperature and washed with an aqueous solution of 5% $NaHCO_3$, dried over anhydrous $MgSO_4$ and filtered. After evaporation of the solvent the residue was chromatographed on a silica gel column, eluting with ethyl acetate, to obtain 110 mg of compound **8** (52%) and 35 mg (16%) of compound **9**, both of them as white solids (62% overall from **5**). Mp: 120–123 °C. Calc. for $C_{11}H_{19}NO_6S$: C, 45.04; H, 6.53; N, 4.77; S, 10.93; found C, 46.29; H, 6.78; N, 4.47; S, 10.13%. IR (CH_2Cl_2, cm^{-1}): 3436 (NH), 1740 (COO), 1683 (CON). ^{1}H-NMR ($CDCl_3$): δ 1.80–1.93 (m, 2H, H_{3a} + H_{5a}), 1.94–2.12 (m, 7H, H_{2a} + H_{3e} + H_{5e} + H_{6a} + MeCO), 2.13–2.22 (m, 2H, H_{2e} + H_{6e}), 3.05 (s, 3H, $MeSO_2$), 3.70 (s, 3H, MeOOC), 4.66–4.76 (m, 1H, H_4), 6.73 (br s, 1H, NH). ^{13}C-NMR ($CDCl_3$): δ 23.1 (MeCO), 27.8 (C_3, C_5), 29.6 (C_2, C_6), 38.6 ($MeSO_2$), 52.5 (MeOOC), 57.3 (C_1), 79.0 (C_4), 170.2, 173.5 (COO, CON).

Methyl 1-acetamido-*c*-4-methylsulfonyloxycyclohexane-*r*-1-carboxylate (9)

Compound **9** was obtained as a white solid in a similar way to that described for compound **8**, starting from the mixture of alcohols **6** and **7** obtained from the reduction of ketone **5** using method B (110 mg, 0.47 mmol). Isolated yield, 102 mg (74%). Mp: 138–139 °C. Calc. for $C_{11}H_{19}NO_6S$: C, 45.04; H, 6.53; N, 4.77; S, 10.93; found C, 45.32; H, 6.45; N, 4.62; S, 11.01%. IR (CH_2Cl_2, cm^{-1}): 3436 (NH), 1740 (COO), 1684 (CON). ^{1}H-NMR ($CDCl_3$): δ 1.76–1.90 (m, 2H, H_{3a} + H_{5a}), 1.91–2.07 (m, 7H, H_{2a} + H_{3e} + H_{5e} + H_{6a} + MeCO), 2.15–2.31 (m, 2H, H_{2e} + H_{6e}), 3.03 (s, 3H, $MeSO_2$), 3.72 (s, 3H, MeOOC), 4.87–4.95 (m, 1H, H_4), 5.75 (br s, 1H, NH). ^{13}C-NMR ($CDCl_3$): δ 23.3 (MeCO), 26.9 (C_3, C_5), 27.4 (C_2, C_6), 38.8 ($MeSO_2$), 52.6 (MeOOC), 57.9 (C_1), 77.0 (C_4), 170.4, 173.6 (COO, CON).

Methyl 1-acetamido-*c*-4-benzoyloxycyclohexane-*r*-1-carboxylate (10)

A mixture of caesium fluoride (216 mg, 1.77 mmol) and benzoic acid (270 mg, 1.77 mmol) dissolved in dry DMF (8 mL), under an inert atmosphere, was stirred for 20 min at room temperature. Compound **8** (104 mg, 0.35 mmol) dissolved in dry DMF (2 mL) was then added. After 12 h stirring at 80 °C, a mixture of ethyl acetate and ice–water (4:1) (50 mL) was added to the solution and the organic phase was washed with an aqueous solution of 5% $NaHCO_3$ (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was chromatographed on a silica gel column, eluting with ether–ethyl acetate (9:1) to obtain 77 mg of compound **10** (68%) as an oilish solid. Calc. for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39; found C, 62.97; H, 6.76; N, 4.13%. IR (CH_2Cl_2, cm^{-1}): 3438 (NH), 1740, 1714 (COO), 1683 (CON). ^{1}H-NMR ($CDCl_3$): δ 1.81–2.10 (m, 9H, H_{3a} + H_{5a} + H_{2a} + H_{3e} + H_{5e} + H_{6a} + MeCO), 2.25–2.40 (m, 2H, H_{2e} + H_{6e}), 3.75 (s, 3H, MeOOC), 5.19–5.26 (m, 1H, H_4), 5.98 (br s, 1H, NH), 7.41–7.50 (m, 2H, *m*-arom), 7.52–7.61 (m, 1H, *p*-arom), 8.01–8.09 (m, 2H, *o*-arom). ^{13}C-NMR ($CDCl_3$): δ 23.2 (MeCO), 25.8 (C_3, C_5), 28.1 (C_2, C_6), 52.5 (MeOOC), 58.2 (C_1), 69.2 (C_4), 128.4, 129.5 (*o*,*m*,-arom), 130.3 (*ipso*-arom), 133.0 (*p*-arom), 165.9, 170.3, 174.0 (PhCOO, MeCOO, CON).

Methyl 1-acetamido-*t*-4-acetyloxycyclohexane-*r*-1-carboxylate (11)

The mixture of alcohols **6** and **7** from the reduction of ketone **5** using method A (215 mg, 1 mmol) was dissolved in dry acetonitrile, under an inert atmosphere, and acetic anhydride (306 mg/0.284 mL, 3 mmol) and scandium triflate (1.87 mL of a 0.01 M solution, 18.7 μmol) were added to the solution. After stirring for 16 h, at 50 °C, the reaction was left to reach room temperature and was quenched adding saturated aq. $NaHCO_3$ (20 mL). The mixture was extracted with dicloromethane (3 × 20 mL) and the organic phase dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was chromatographed on a silica gel column, eluting with hexane–ethyl acetate (3:7) to obtain 145 mg of compound **11** (57%) and 45 mg (18%) of compound **12**, both of them as white solids (75% overall). Mp: 140–142 °C. Calc. for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44; found C, 55.32; H, 7.31; N, 5.42%. IR (CH_2Cl_2, cm^{-1}): 3439 (NH), 1734 (COO), 1682 (CON). ^{1}H-NMR ($CDCl_3$): δ 1.47–1.62 (m, 2H, H_{3a} + H_{5a}), 1.85–2.06 (m, 10H, H_{2a} + H_{3e} + H_{5e} + H_{6a} + MeCON + MeCOO), 2.07–2.20 (m, 2H, H_{2e} + H_{6e}), 3.68 (s, 3H, MeOOC), 4.66–4.76 (m, 1H, H_4), 5.96 (br s, 1H, NH). ^{13}C-NMR ($CDCl_3$): δ 21.2, 23.1 (MeCOO, MeCON), 26.5 (C_3, C_5), 29.6 (C_2, C_6), 52.4 (MeOOC), 57.7 (C_1), 70.9 (C_4), 170.1, 170.3, 173.8 (MeCOO, COOMe, CON).

Methyl 1-acetamido-*c*-4-acetyloxycyclohexane-*r*-1-carboxylate (12)

Compound **12** was obtained as a white solid in a similar way to that described for compound **11**, starting from the mixture of alcohols **6** and **7** which came from the reduction of ketone **5** using method B (150 mg, 0.69 mmol). Isolated yield, 120 mg (68%). Mp: 156–158 °C. Calc. for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44; found C, 56.25; H, 7.23; N, 5.51%. IR (CH_2Cl_2, cm^{-1}): 3437 (NH), 1732 (COO), 1682 (CON). ^{1}H-NMR ($CDCl_3$): δ 1.68–1.91 (m, 6H, H_{2a}+ H_{3a} + H_{5a} + H_{6a} + H_{3e} + H_{5e}), 1.97 (s, 3H, MeCO), 2.03 (s, 3H, MeCO), 2.12–2.23 (m, 2H, H_{2e} + H_{6e}), 3.70 (s, 3H, MeOOC), 4.87–4.93 (m, 1H, H_4), 6.00 (br s, 1H, NH). ^{13}C-NMR ($CDCl_3$): δ 21.3, 23.2 (*Me*CON, *Me*COO), 25.7 (C_3, C_5), 28.0 (C_2, C_6), 52.4 (*Me*OOC), 58.1 (C_1), 68.7 (C_4), 170.3, 170.6, 174.0 (MeCOO, COOMe, CON).

1-Amino-*c*-4-hydroxycyclohexane-*r*-1-carboxylic acid (2)

Compound **10** (128 mg, 0.40 mmol) was suspended in a 6 M HCl aqueous solution (10 mL) and heated under reflux for 24 h. The solvent was evaporated *in vacuo*, the residue was dissolved in water, washed with diethyl ether (2 × 10 mL) and the aqueous layer evaporated. This residue of amino acid hydrochloride was dissolved in ethanol (3 mL) and propylene oxide (1 mL) was added. The mixture was heated under reflux for 2 h and after removal of the solvent, the residue was dissolved in distilled water (2 mL) and eluted through a C_{18} reverse-phase Sep-pak cartridge which, after removal of water, gave 52 mg (82%) of 4-hydroxy-α-amino acid **2** as a white solid. Alternatively, and using the same conditions as above, amino acid **2** was obtained in 78% yield starting from compound **12**. Calc. for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80; found C, 53.44; H, 7.98; N, 8.67%. IR (MeOH, cm^{-1}): 1772 (CO). ^{1}H-NMR (D_2O): δ 1.82–2.11 (m, 8H, H_{2a} + H_{2e}+ H_{3a} + H_{3e} + H_{5a} + H_{5e} + H_{6a} + H_{6e}), 4.80–4.85 (m, 1H, H_4). ^{13}C-NMR (D_2O): δ 24.8, 27.8 (C_2, C_3, C_5, C_6), 53.9 (C_1), 77.3 (C_4), 177.3 (COO).

1-Amino-*t*-4-hydroxycyclohexane-*r*-1-carboxylic acid (1)

Amino acid **1** was obtained as an oil in a similar way to that described for amino acid **2**, starting from compound **11** (145 mg, 0.56 mmol). Isolated yield, 63 mg (70%). Calc. for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80; found C, 53.20; H, 8.41; N, 8.76%. IR (MeOH, cm^{-1}): 1736 (CO). ^{1}H-NMR (D_2O): δ 1.38–1.54 (m, 2H, H_{3a}+ H_{5a}), 1.98–2.16 (m, 6H, H_{2a} + H_{2e} + H_{3e} + H_{5e} + H_{6a} + H_{6e}), 3.75–3.87 (m, 1H, H_4). ^{13}C-NMR (D_2O): δ 28.6, 29.8 (C_3, C_5, C_2, C_6), 60.4 (C_1), 67.9 (C_4), 177.1 (COO).

Crystal data for compound 8 †

Single crystals of **8** were recrystallised from dichloromethane–hexane. $C_{11}H_{19}NO_6S$ (293.33), triclinic, space group $P\bar{1}$,

† CCDC reference number 207/365. See http://www.rsc.org/suppdata/p1/1999/3375 for crystallographic files in .cif format.

$a = 5.928$ (6), $b = 13.671$ (15), $c = 18.592$ (2) Å, $V = 1451.4$ (3) Å^3, $Z = 4$. Mo-Kα radiation, $\lambda = 0.71069$ Å, graphite monochromator, $\omega/2\theta$ scan technique. A total of 6240 reflections were measured, and merged to 6240 unique reflections. Temperature of data collection at 293(2) K. Absorption coefficient (μ, mm^{-1}) 0.244. The structure was solved by direct methods. Software used, SHELXL 97,[13] SHELXS 97.[14] Least-squares (full matrix) refinement yielded R and R_w-values of 0.0765 and 0.1878 respectively. All calculations were performed on a Pentium PC.

Crystal data for compound 9 †

Single crystals of **9** were recrystallised from dichloromethane–hexane. $C_{11}H_{19}NO_6S$ (293.33), monoclinic, space group $C2/c$, $a = 34.154$ (10), $b = 8.581$ (2), $c = 9.984$ (3) Å, $V = 2923.26$ (14) Å^3, $Z = 4$. Mo-Kα radiation, $\lambda = 0.71069$ Å, graphite monochromator, $\omega/2\theta$ scan technique. A total of 3355 reflections were measured, and merged to 3355 unique reflections. Temperature of data collection at 293(2) K. Absorption coefficient (μ, mm^{-1}) 0.260. The structure was solved by direct methods. Software used, SHELXL 97,[13] SHELXS 97.[14] Least-squares (full matrix) refinement yielded R and R_w-values of 0.0450 and 0.1252 respectively. All calculations were performed on a Pentium PC.

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