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# Synthesis of (2*R*,5*S*)- and (2*S*,5*S*)-2-Carboxy-1,4-diaza-[4.3.0]bicyclononane as Building Blocks for the Synthesis of New Potential HIV Protease Inhibitors.

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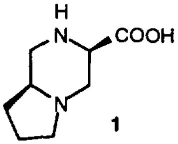
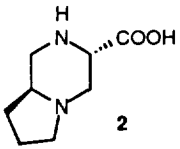
**Abstract**: A procedure for the preparation of optically active (2*R*,5*S*)- and (2*S*,5*S*)-2-Carboxy-1,4-diaza-[4.3.0]bicyclononane is described. The method is based on the reduction of diketopiperazines obtained from cyclization of Pro-L-Ser or Pro-D-Ser and occurs without loss of enantiomeric purity. The synthesis is based on readily available starting materials and can be easily arranged for multigram scale preparations.

Inhibitors of HIV protease have continued to receive much attention as potential therapeutic agents for the treatment of HIV infection.[1] Molecular modelling studies have recently demonstrated that the activity of these inhibitors is strictly dependent on the presence of 2-carboxypiperazine or 2-carboxydecahydroisoquinoline rings in their structures.[2] On this basis, we have directed our experience in the field of unnatural α-amino acids synthesis[3,4] to the preparation of bicyclic compounds **1** and **2** as potential building blocks for the preparation of new HIV protease inhibitors.



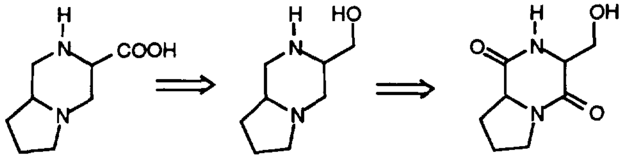
**1**



**2**

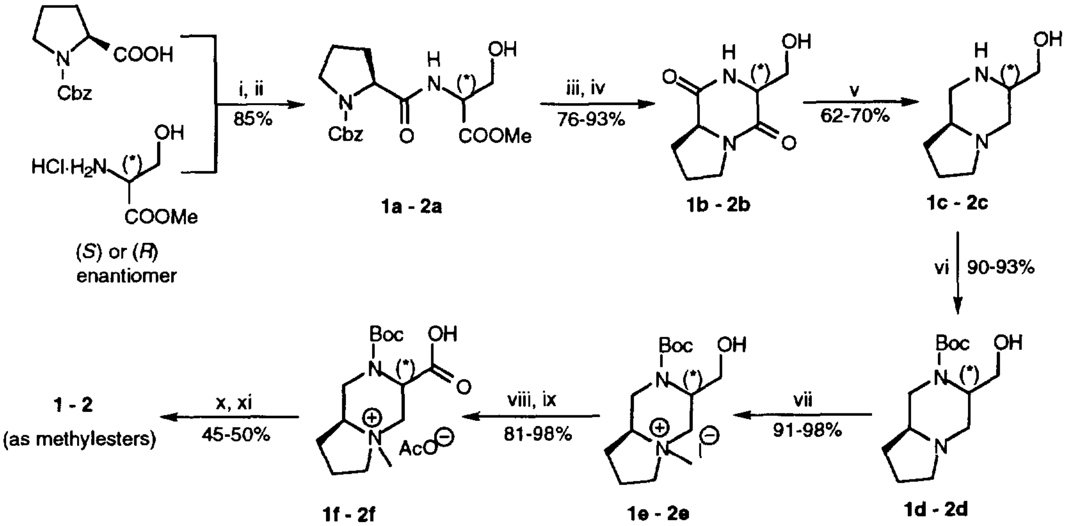
A possible retrosynthetic analysis for **1**-**2** suggested a correlation between the 2-substituted bicyclononane structure and a 2-hydroxymethyl piperazine, that can be prepared by reduction of simple *cyclo*-Pro-Ser (Scheme 1). The availability of the enantiomers of both the amino acids should enable the synthesis of all the four possible stereoisomers. For a synthesis that could be applied on a multigram scale and that could follow also the rule of atom economy, the main problem was to find suitable groups for the protection of the nitrogen atoms during the oxidation step: we decided to have a quaternary ammonium salt on the tertiary nitrogen atom and to use a Boc protective group on the secondary nitrogen atom. The complete synthesis of **1** and **2** is reported in Scheme 2: *S*)-*N*-benzyloxycarbonylproline (from L-proline, 99% ee) was condensed with L-serine methyl ester hydrochloride by using the mixed anhydride method affording dipeptide **1a** (85%) or with D-serine methyl ester hydrochloride affording dipeptide **2a** (85%).

**Scheme 1**



Deblocking the benzyloxycarbonyl group was carried out by transfer hydrogenation using cyclohexene and 10% Pd/C. The catalyst was filtered off and any volatile product was removed, the residues were suspended in dry methanol and, according to previously reported diketopiperazines syntheses,[5] heating (65°C) was prolonged for 5 days to afford compounds **1b** (76%) or **2b** (93%). The reduction of DKPs **1b-2b** to piperazines **1c** (62%) and **2c** (70%) was carried out by using an excess of LAH in refluxing THF (72 h):[6] the recovery of the products from the reaction mixtures was optimised by carrying out the LAH hydrolysis by triethanolamine.[7]

**Scheme 2**



**Reagents and conditions:** i) 4-Methylmorpholine, EtOCOCl, $CH_2Cl_2$, -10 °C, 15 min. ii) 25 °C, 16 h. iii) Cyclohexene, 10% Pd/C, MeOH, 70 °C, 5 h. iv) MeOH, 70 °C, 110 h. v) LAH, THF, 65 °C, 72 h. vi) $(Boc)_2O$, aq $Na_2CO_3$ 20%, $CH_2Cl_2$, cat. $NH_2OH$, r.t., 18 h. vii) MeI, MeOH, rt., 12 h. viii) $NaIO_4$, Acetone/$H_2O$, cat. $RuCl_3$, 0 °C to rt., 2 h. ix) AcOH. x) Xylene/MeCN, 140°C, 72 h. xi) HCl(g), MeOH, rt., 24 h.

For the protection of the *N*-1 of products **1c-2c** we choose the *tert*-butylcarbamate group: treatment of **1c-2c** in 20% acq $Na_2CO_3$ with a stoichiometric amount of $(Boc)_2O$, in the presence of 10 mol% of hydroxylamine as catalyst, proved to be the best experimental procedure avoiding the formation of any by-products. The Boc piperazines **1d** (90%) or **2d** (93%) were obtained by simple washing with water the $CH_2Cl_2$

solution of the crude product. Measurements of $^{1}H$ and $^{13}C$ NMR carried out at various temperatures (from 20° to 50°C) indicated that compounds **1d-2d** have a diastereoisomeric purity ≥ 95%. The Boc amino alcohols **1d-2d** were treated by an excess of methyl iodide at rt in methanol. After 18 h the crude products were dissolved in water and washed with $CH_2Cl_2$ affording the pure ammonium salts **1e-2e** that were isolated in 98% and 91% yield respectively. The aminoalcohols **1e-2e** were then oxidised following Sharpless procedure[8] with sodium periodate in the presence of catalytic amounts of $RuCl_3$.[9] The oxidation mixtures were filtered through a Celite pad, affording, after removal of iodine, crude acids as light brown foams.[10] Attempts to carry out the demethylation of these crude acids using PhSNa[11] were unsuccessful. Thus demethylations was obtained by using acetate as the nucleophile: the crude oxidation products were then lyophilised from acetic acid solutions affording acetates **1f-2f**. Heating at 140°C for 72 h of compounds **1f** and **2f** in a mixture of xylene/acetonitrile affords the desired demethylated amino acids.[12] Attempts to recover **1** or **2** as free amino acids by using ion exchange chromatography gave unsatisfactory results; therefore, the target compounds **1** and **2** were recovered in satisfactory yields from the reaction mixture as methyl esters by treatment with HCl in MeOH at rt. Measurements of $^{1}H$ and $^{13}C$ NMR carried out at various temperatures (from 20° to 50°C) have indicated that **1** and **2** methyl esters have a diastereoisomeric purity ≥ 95%.

## Experimental

Melting and boiling points are uncorrected. Bulb to bulb distillations were carried out with a Büchi GRK-51 apparatus equipped with a vacuum controller Büchi B-168. Melting points were determined on a microscope Leitz LABORLUX S equipped with Leitz Microscope Heating Stage 350 and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 420 B analyser. Optical rotations were measured with a Perkin-Elmer 241 automatic polarimeter in a 1 dm tube. GC analyses of the reaction products were carried out on a Perkin-Elmer 8600 gas chromatograph on fused silica megabore columns (15 m x 0.53 mm) DB-1, DB-5 (J&W), operating with a He flow rate of 9 mL/min. The $^{1}H$ NMR (300 MHz) and $^{13}C$ NMR (75.4 MHz) Fourier transform spectra were obtained with a Varian VXR-300 spectrometer on $CDCl_3$ solutions (unless otherwise specified) and with TMS as internal standard. All reactions involving air sensitive materials were carried out under argon atmosphere; all reagents and solvents employed were reagent grade materials purified by standard methods and distilled before use. As chiral starting materials (*S*)-proline of "*BioChemica*" grade (chemical and enantiomeric purity >99%) purchased from Fluka Chemie AG was used; (*S*) and (*R*)-serine (enantiomeric purity >99%) purchased from Janssen were used. H-L-Ser-OMe·HCl {mp 162-165 °C, $[\alpha]_D^{25}$ +4.90 (c 1, MeOH)} and H-D-Ser-OMe·HCl {mp 164-166°C, $[\alpha]_D^{25}$ -4.97 (c 1, MeOH)} were prepared as previously reported for the *S* enantiomer.[13] (*S*)-*N*-(Benzyloxycarbonyl)proline were prepared according reported procedures; for the sample employed it was found:[14] mp 78-80°C, $[\alpha]_D^{25}$ -40.4 (c 1, EtOH).

**Products 1a-2a:** Under vigorous stirring and at -15°C, 4-methylmorpholine (32.9 mL, 30.3 g, 300 mmol) in $CH_2Cl_2$ (30 mL) and ethylchloroformate (28.2 mL, 32.0 g, 295 mmol) in $CH_2Cl_2$ (20 mL) were added to (*S*)-*N*-(benzyloxycarbonyl)proline acids, (73.4 g, 295 mmol) in $CH_2Cl_2$ (200 mL). The reaction mixtures were stirred at -15 °C for 15 min, then 4-methylmorpholine (32.9 mL, 30.3 g, 300 mmol) and (*S*)- or (*R*)-H-Ser-

OMe·HCl (44.2 g, 284 mmol, portionwise) were added; also $CH_2Cl_2$ (250 mL) was added. The resulting mixtures were stirred at -15 °C for 1 h, then 12 h at rt. The reaction mixtures were treated with water (200 mL). After separation of the organic layers, the aqueous phases were extracted with EtOAc (50 mL). The collected organic phases were washed with 10% aq $NaHCO_3$, sat. aq NaCl, 5% aq HCl and sat. aq NaCl (150 mL each) in that order, and dryed ($Na_2SO_4$). The solvent was evaporated under reduced pressure and the crude products were recrystallized from the suitable solvents giving pure (TLC) protected dipeptides **1b-2b**.

***N*-[*N'*-(Benzyloxycarbonyl)-(*S*)-prolyl]-(*S*)-serine methylester (Z-Pro-Ser-OMe), 1a:** 82% yield, recrystallized from EtOAc/hexane, mp 103-107 °C, $[\alpha]_D^{25}$ -28.95 (c 2, $CHCl_3$); $^1H$ NMR, δ: 7.43-7.23 (m, 6H, $C_6H_5$ + NH), 5.22-4.75 (q like, 2H, $CH_2$-Ph), 4.65-4.48 (m, 1H, NH-CH-CO of serine), 4.37-4.20 (m, 1H, N-CH-CO of proline), 4.00-3.84 (m, 2H, CH-$CH_2$-OH), 3.75 (s, 3H, $COOCH_3$), 3.68 (bs, 1H, OH), 3.62-3.42 (m, 2H, $CH_2$-N of proline), 2.24-2.03 (m, 3H), 1.95-1.80 ppm (m, 1H); $^{13}C$ NMR δ: 172.3, 170.7, 155.5, 136.4, 128.4, 128.0, 127.8, 67.3, 62.4, 60.7, 55.0, 52.5, 47.1, 29.3, 24.5 ppm. Calculated for $C_{17}H_{22}N_2O_6$: C, 58.28; H, 6.33; N, 8.00. Found: C, 58.43; H, 6.23; N, 8.08.

***N*-[*N'*-(Benzyloxycarbonyl)-(*S*)-prolyl]-(*R*)-serine methylester (Z-Pro-D-Ser-OMe), 2a:** 83% yield, recrystallized from EtOAc, mp 123-125 °C, $[\alpha]_D^{25}$ -100.72 (c 1.5, $CHCl_3$); $^1H$ NMR, δ: 7.40-7.27 (m, 5H, $C_6H_5$), 7.23-7.17 (m, 0.6H, NH), 6.96-6.90 (m, 0.4H, NH), 5.26-5.00 (m, 2H, $CH_2$-Ph), 4.64-4.56 (m, 1H, NH-CH-CO of serine), 4.40-4.32 (m, 1H, N-CH-CO of proline), 3.99-3.85 (m, 2H, CH-$CH_2$-OH), 3.74 (s, 3H, $COOCH_3$), 3.65-3.43 (m, 2H, $CH_2$-N of proline), 3.20 (bs, 1H, OH), 2.27-2.15 (m, 2H) 2.0-1.85 ppm (m, 2H); $^{13}C$ NMR δ: (mixture of two conformers) 172.7, 171.8, 170.6, 136.1, 128.5, 128.1, 127.9, 67.5, 62.5, 61.0, 54.7, 54.2, 52.6, 47.5, 47.1, 31.1, 29.2, 24.4, 23.5 ppm. Calculated for $C_{17}H_{22}N_2O_6$: C, 58.28; H, 6.33; N, 8.00. Found: C, 58.35; H, 6.34; N, 8.02.

**Products 1b-2b:** Protected dipeptides **1a-2a** (92.8 g, 266 mmol) were suspended in absolute MeOH (150 mL) with 10% Pd on active charcoal (2.5 g) and cyclohexene (120 mL). The reaction mixtures were refluxed for 5 h. The resulting solutions were filtered on a celite pad and all the volatile products were eliminated under reduced pressure. The crude solids recovered were suspended in absolute MeOH (250 mL) and the resulting mixtures were heated at 62-65 °C for 110 h. The solvent was then eliminated under reduced pressure and the crude products were dryed in air and suspended in boiling dry acetone for 3 h. Filtration afforded pure (TLC) diketopiperazines **1b-2b**.

**(2*S*,5*S*)-2-Hydroxymethyl-3,6-diketo-1,4-diaza[4.3.0]bicyclononane (*cyclo*-Pro-Ser), 1b:**[6] 76% yield mp 134-136°C, $[\alpha]_D^{25}$ -114.8 (c 2, DMSO); $^1H$ NMR (DMSO $d_6$) δ: 7.83 (bs, 1H, NH), 4.77-4.71 (t like, 1H, OH), 4.21-4.10 (m, 1H, CH-$CH_2$-OH), 4.08-3.98 (m, 1H, CH-$CH_2$-$CH_2$), 3.79-3.58 (m, 2H, $CH_2$-OH), 3.50-3.21 (m, 2H, N-$CH_2$-$CH_2$), 2.23-2.0 (m, 1H), 0.93-0.62 ppm (m, 3H); $^{13}C$ NMR (DMSO $d_6$) δ: 169.1, 164.4, 60.1, 58.4, 56.7, 44.6, 27.9, 22.0 ppm. Calculated for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 52.07; H, 6.61; N, 15.20.

**(2*R*,5*S*)-2-Hydroxymethyl-3,6-diketo-1,4-diaza[4.3.0]bicyclononane (*cyclo*-Pro-D-Ser), 2b:**[6] 93% yield, mp 248-250 °C (dec.), $[\alpha]_D^{25}$ -149.55 (c 0.7, DMSO); $^1H$ NMR (DMSO $d_6$) δ: 8.10 (bs, 1H), 5.29-5.23 (t like, 1H, OH), 4.15-4.06 (dd like, 1H, CH-$CH_2$-OH), 3.75-3.62 (m, 2H), 3.55-3.28 (m, 3H), 2.17-2.08 (m, 1H), 1.90-1.62 ppm (m, 3H); $^{13}C$ NMR (DMSO $d_6$) δ: 169.1, 164.7, 63.6, 59.6, 58.2, 44.9, 28.8, 21.6 ppm. Calculated for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 52.09; H, 6.63; N, 15.18.

**Products 1c-2c:** The diketopiperazines **1b-2b** (24.5 g, 133 mmol) were added portionwise, during 30 min, under vigorous stirring, to LAH (20.0 g, 526 mmol) suspensions in THF (800 mL) at 0 °C. The reaction mixures were then heated at 65-68 °C for 72 h. The heating bath was then removed and triethanolamine (74 mL, 82 g, 550 mmol) was added cautiously over 45 min. After 1 h stirring, $H_2O$ (20 mL, 20 g, 1.1 mmol) was added. After further 12 h stirring, the reaction mixtures were filtered and the solvent removed under vacuum. The residues were then distilled without fractionating and the oils obtained were dissolved in 10% aq HCl. The acid layers were washed with ether and then aqueous solutions made alkaline with solid KOH and continuosly extracted with $CH_2Cl_2$. The collected organic phases were dryed ($Na_2SO_4$) and the solvent removed under vacuum. The crude products were then distilled affording pure (GLC) piperazines **1c-2c**.

**(2*R*,5*S*)-2-Hydroxymethyl-1,4-diaza[4.3.0]bicyclononane, 1c**:[6] 62% yield bp 125-130°C/0.5 mBar, $[\alpha]_D^{25}$ +7.77 (c 1.88, $CHCl_3$); $^1$H NMR, δ: 3.95 (dd like, 1H, $C\underline{H}_2$-OH), 3.62 (dd like, 1H, $C\underline{H}_2$-OH), 3.05-2.89 (m, 5H), 2.8 (dd like, 1H), 2.35 (dd like, 1H), 2.12-1.99 (m, 1H), 1.97-1.58 (m, 5H), 1.44-1.29 ppm (m, 1H); $^{13}$C NMR δ: 64.2, 63.7, 54.6, 54.4, 52.3, 46.3, 27.4, 20.4 ppm. Calculated for $C_8H_{16}N_2O$: C, 61.51; H, 10.32; N, 17.93; . Found: C, 61.61; H, 10.22; N, 17.88.

**(2*S*,5*S*)-2-Hydroxymethyl-1,4-diaza[4.3.0]bicyclononane, 2c**:[6] 70% yield bp 112 °C/0.5 mBar, $[\alpha]_D^{25}$ +14.56 (c 1, $CHCl_3$); $^1$H NMR, δ 3.65-3.58 (dd, 1H), 3.50-3.43 (dd like, 1H, $C\underline{H}_2$-OH), 3.19-3.12 (dd like, 1H, $C\underline{H}_2$-OH), 3.09-2.88 (m, 4H), 2.58-2.49 (dd like, 1H), 1.96-1.63 (m, 6H), 1.44-1.30 ppm (m, 1H); $^{13}$C NMR δ 63.8, 63.1, 55.9, 54.8, 53.6, 49.0, 27.1, 20.8 ppm. Calculated for $C_8H_{16}N_2O$: C, 61.51; H, 10.32; N, 17.93. Found: C, 61.60; H, 10.35; N, 17.89.

**Products 1d-2d:** The solutions of the piperazines **1c-2c** (2.36 g, 15 mmol) in $CH_2Cl_2$ (15 mL) were added to stirred suspensions of $(Boc)_2O$ (3.27 g, 15 mmol) in $CH_2Cl_2$ (20 mL), aqueous $Na_2CO_3$ (20%, 15 mL) and $NH_2OH{\cdot}HCl$ (0.1 g, 1.5 mmol). After 24 h, the reaction mixtures were threated with $CH_2Cl_2$ (20 mL) and $H_2O$ (20 mL). The organic phase was then washed with $H_2O$ (2x30 mL) dryed ($Na_2SO_4$) and the solvent was eliminated under vacuum affording pure (TLC) protected piperazines **1d-2d**.

**(2*R*,5*S*)-1-(*Tert*-butoxycarbonyl)-2-hydroxymethyl-1,4-diaza[4.3.0]bicyclononane, 1d**: 90% yield, waxy solid, $[\alpha]_D^{25}$ +64.7 (c 1, $CHCl_3$); $^1$H NMR, δ 4.35 (bs, 1H, $O\underline{H}$), 4.19-4.14 (dd like, 1H, $C\underline{H}_2OH$), 4.00-3.99 (dd like, $C\underline{H}_2OH$), 3.94-3.80 (m, 2H), 3.19-3.15 (d like, 1H), 3.08-3.02 (dt like, 1H), 2.98-2.88 (dd like, 1H), 2.36-2.31 (m, 1H), 2.02-1.67 (m, 5H), 1.43 (s, 9H, *t*-Bu group), 1.38-1.34 ppm (m, 1H); $^{13}$C NMR δ: (mixture of two rotomers) 155.3, 156.4, 79.9, 67.1, 66.9, 62.4, 53.9, 53.7, 51.3, 50.4, 47.3, 46.3, 28.3, 27.4, 21.1 ppm. Calculated for $C_{13}H_{24}N_2O_3$: C, 60.91; H, 9.44; N, 10.93. Found: C, 60.52; H, 9.36; N, 11.06.

**(2*S*,5*S*)-1-(*Tert*-butoxycarbonyl)-2-hydroxymethyl-1,4-diaza[4.3.0]bicyclononane, 2d**: 93% yield, waxy solid, $[\alpha]_D^{25}$ +66.1 (c 2, $CHCl_3$); $^1$H NMR, δ 4.32 (bs, 1H, $O\underline{H}$), 4.18-4.10 (dd like, 1H, $C\underline{H}_2OH$), 4.05-3.94 (dd like, $C\underline{H}_2OH$), 3.90-3.75 (m, 2H), 3.18-3.12 (d like, 1H), 3.06-2.98 (dt like, 1H), 2.95-2.83 (dd like, 1H), 2.32-2.25 (m, 1H), 2.00-1.65 (m, 5H), 1.45 (s, 9H, *t*-Bu group), 1.40-1.31 ppm (m, 1H); $^{13}$C NMR δ: (mixture of two confomers) 155.2, 154.8, 79.7, 66.6, 66.2, 62.4, 62.3, 53.8, 53.7, 51.4, 50.4, 47.2, 46.1, 28.3, 27.4, 21.0 ppm. Calculated for $C_{13}H_{24}N_2O_3$: C, 60.91; H, 9.44; N, 10.93. Found: C, 60.47; H, 9.37; N, 11.09.

**Products 1e-2e:** Methyliodide (2 mL, 2.82 g, 20 mmol) was added to the Boc-derivatives **1d-2d** (3.0 g, 11.7 mmol) in MeOH (20 mL). After 18 h under stirring all the volatile products were eliminated under reduced pressure and the residues were partitioned between $CH_2Cl_2$ and $H_2O$. The organic layers were discarded and the acqueous phases were concentrated under vacuum affording pure (TLC) ammonium salts **1e-2e**.

**(2*R*, 5*S*)-1-(*Tert*-butoxycarbonyl)-2-hydroxymethyl-1,4-diaza[4.3.0]bicyclononan-4-methylammonium iodide, 1e:** 98% yield, waxy solid, $[\alpha]_D^{25}$ +57.8 (c 2.5, $H_2O$); $^1$H NMR, ($D_2O$) & 4.36-4.18, (m, 2H, C$\underline{H}_2$OH) 3.90-3.81 (dd like, 1H), 3.80-3.62 (m, 3H), 3.61-3.51 (m, 2H), 3.26-3.14 (dd like, 1H), 3.09 (s, 3H, N$^+$-C$\underline{H}_3$), 2.37-2.23 (m, 1H), 2.18-2.06 (m, 3H), 1.84-1.74 (m, 1H), 1.43 ppm (s, 9H, *t*-Bu group); $^{13}$C NMR, ($D_2O$) & 156.0, 83.9, 75.1, 69.8, 61.9, 57.2, 53.3, 50.0, 42.4, 29.3, 28.2, 23.2 ppm. Calculated for $C_{14}H_{27}N_2O_3I$: C, 42.22; H, 6.83; N, 7.03. Found: C, 41.99; H, 6.77; N, 7.11.

**(2*S*, 5*S*)-1-(*Tert*-butoxycarbonyl)-2-hydroxymethyl-1,4-diaza[4.3.0]bicyclononan-4-methylammonium iodide, 2e:** 91% yield, waxy solid, $[\alpha]_D^{25}$ +60.9 (c 1.5, $H_2O$); $^1$H NMR, ($D_2O$) & 4.33-4.15, (m, 2H, C$\underline{H}_2$OH) 3.87-3.79 (dd like, 1H), 3.75-3.62 (m, 3H), 3.61-3.51 (m, 2H), 3.27-3.15 (dd like, 1H), 3.08 (s, 3H, N$^+$-C$\underline{H}_3$), 2.38-2.27 (m, 1H), 2.24-2.05 (m, 3H), 1.86-1.75 (m, 1H), 1.40 ppm (s, 9H, ); $^{13}$C NMR, ($D_2O$) δ: 155.2, 83.0, 74.2, 68.9, 60.0, 56.3, 52.5, 49.2, 41.5, 28.5, 27.4, 22.4 ppm. Calculated for $C_{14}H_{27}N_2O_3I$: C, 42.22; H, 6.83; N, 7.03. Found: C, 42.03; H, 6.76; N, 7.09.

**Products 1f-2f:** Under stirring at 0 °C, $NaIO_4$ (18.5 g, 86 mmol) in water (40 mL) and $RuCl_3$ hydrate (0.55 g) were added to ammonium salts **1e-2e** (3.5 g, 8.8 mmol) in acetone (60 mL). The reaction mixtures were stirred 1 h at 0°C and 1 h at r.t., then quenched with *iso*-propanol (10mL). After 2 h, the reaction mixtures were filtered through a Celite pad and the filtrates were concentrated under vacuum. The residues were dissolved in $H_2O$ (10 mL) and were washed with $CCl_4$ (2x25 mL) and with $CH_2Cl_2$ (2x25 mL), then the organic phases were discarded and the aqueous solutions were evaporated. The crude acids thus obtained were treated with glacial acetic acid (0.6 g, 10 mmol). After 3 h the acetic solutions were lyophilised affording pure (TLC) protected aminoacids **1e-2e**.

**(2*R*, 5*S*)-1-(*Tert*-butoxycarbonyl)-2-carboxy-1,4-diaza[4.3.0]bicyclononan-4-methylammonium acetate, 1f:** 81% yield, $[\alpha]_D^{25}$ -43.8 (c 1.3, AcOH); $^1$H NMR, (DMSO $d_6$, 50°C) δ: 9.5 (very bs, 1H, COO$\underline{H}$), 4.21-4.14 (m, 1H), 4.11-4.02 (dd like, 1H), 3.65-3.44 (m, 3H), 3.42-3.32 (m, 1H), 3.27-3.13 (m, 1H), 3.04 (s, 3H, N$^+$-C$\underline{H}_3$), 2.31-2.20 (m, 1H), 2.13-2.00 (m, 2H), 1.85 (s, 3H, C$\underline{H}_3$COO$^-$), 1.83-1.72 (m, 1H), 1.39 ppm (s, 9H, *t*-Bu group); $^{13}$C NMR, (DMSO $d_6$) δ: 176.1, 168.2, 154.3, 89.6, 78.9, 69.8, 63.8, 57.8, 51.8, 40.7, 27.8, 25.2, 22.0, 19.5 ppm. Calculated for $C_{16}H_{28}N_2O_6$: C, 55.80; H, 8.19; N, 8.13. Found: C, 55.10; H, 8.19; N, 8.16.

**(2*S*, 5*S*)-1-(*Tert*-butoxycarbonyl)-2-carboxy-1,4-diaza[4.3.0]bicyclononan-4-methylammonium acetate, 2f:** 98% yield, $[\alpha]_D^{25}$ +10.7 (c 2.8, AcOH); $^1$H NMR, (DMSO $d_6$) δ: 9.9 (very bs, 1H, COO$\underline{H}$), 4.27-4.19 (m, 1H), 4.12-4.02 (dd like, 1H), 3.91-3.85 (m, 1H), 3.73-3.56 (m, 2H), 3.43-3.38 (m, 1H), 3.25-3.07 (m, 1H), 3.05 (s, 3H, N$^+$-C$\underline{H}_3$), 2.28-2.20 (m, 1H), 2.13-2.02 (m, 2H), 1.89 (s, 3H, C$\underline{H}_3$COO$^-$), 1.83-1.75 (m, 1H), 1.38 ppm (s, 9H, *t*-Bu group); $^{13}$C NMR, (DMSO $d_6$, 50°C) δ: 175.0, 168.3, 154.0, 89.0, 78.9, 69.8, 67.7, 57.8, 51.7, 40.3, 27.8, 25.1, 22.0, 19.5. Calculated for $C_{16}H_{28}N_2O_6$: C, 55.80; H, 8.19; N, 8.13. Found: C, 55.22; H, 8.11; N, 8.12.

**Products 1-2**

The protected acetates **1f-2f** (1.5 g, 4.4 mmol) were suspended in xylene/acetonitrile (85/15, 100 mL) and heated, under stirring, at 140°C. After 26 h, the reaction mixtures were evaporated under vacuum and the residues were treated with $H_2O$ (30 mL) and extracted with $Et_2O$ (2x25 mL). The organic phases were discarded and the acqueous layers were recovered and evaporated under vacuum. The residues were dissolved in dry MeOH (30 mL) and gaseous HCl (0.55 g, 15 mmol) was added. After 24 h at room temperature the reaction mixtures were reduced to half of the volume and treated with ion exchange resin ($OH^-$ form) until pH 8-

9. The resin was then filtered off and the methanolic solutions were dried off. The residues were partitioned between $CH_2Cl_2$ (30 mL) and $H_2O$ (5 mL), the organic phases were than dried ($Na_2SO_4$) and the solvent was eliminated under vacuum affording pure (TLC) methylesters **1**-**2**

**(2*R*,5*S*)-2-carboxymethyl-1,4-diaza[4.3.0]bicyclononane, 1:** 45% yield, $[\alpha]_D^{25}$ -9.4 (c 0.6, AcOH); $^1$H NMR, δ: 3.80-3.73 (m, 1H), 3.70-3.55 (m, 3H), 3.35-3.29 (m, 1H), 3.24-3.06 (m, 3H), 3.25 (s, 3H, $COOC\underline{H}_3$), 2.32-2.01 ppm (m, 4H); $^{13}$C NMR, δ: 172.9, 66.8, 63.5, 54.9, 52.2, 47.8, 45.1, 23.0, 18.2 ppm. Calculated for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.2. Found: C, 58.98; H, 8.49; N, 15.14.

**(2*S*,5*S*)-2-carboxymethyl-1,4-diaza[4.3.0]bicyclononane, 2:** 50% yield, $[\alpha]_D^{25}$ +3.5 (c 0.5, AcOH); $^1$H NMR, δ: 3.80-3.73 (m, 1H), 3.70-3.55 (m, 3H), 3.38-3.31 (m, 1H), 3.25-3.07 (m, 3H), 3.22 (s, 3H, $COOC\underline{H}_3$), 2.30-2.09 ppm (m, 4H); $^{13}$C NMR, δ: 174.5, 67.8, 66.6, 56.0, 53.7, 46.9, 44.2, 23.3, 17.8 ppm. Calculated for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.2. Found: C, 58.89; H, 8.62; N, 15.09.

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## References and notes

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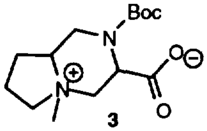

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