General and Versatile Approach to the Synthesis of Optically Active 5-Alkylpiperazine-2-carboxylic Acids

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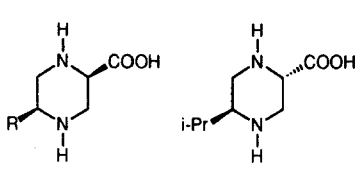
General and convenient syntheses of optically active 5-alkylpiperazine-2-carboxylic acids are described. The methods are based on cyclization of L- or D-serine with α-amino acids and occur without loss of optical purity. The presented procedures are based on readily available starting materials and can be arranged for multigram quantities.

The pharmacological action of the excitatory amino acids (EAA), L-glutamate and L-aspartate, is well documented.[1] In this context, 2-carboxy-4-(3-phosphonopropyl)piperazine (CPP) has been identified as a potent and selective antagonist of the *N*-methyl-D-aspartate (NMDA) subtype of the glutamate receptor.[2] Several syntheses of this compound have been described[3,4] however, the routes to the enantiomers of CPP or of 2-piperazinecarboxylic acid were essentially based on fractional crystallization of diastereomeric menthyl *N,N'*-dibenzylpiperazine-2-carboxylate[4] and only one synthesis of optically active (*R*)-piperazine-2-carboxylic acid has been reported until now.[4]

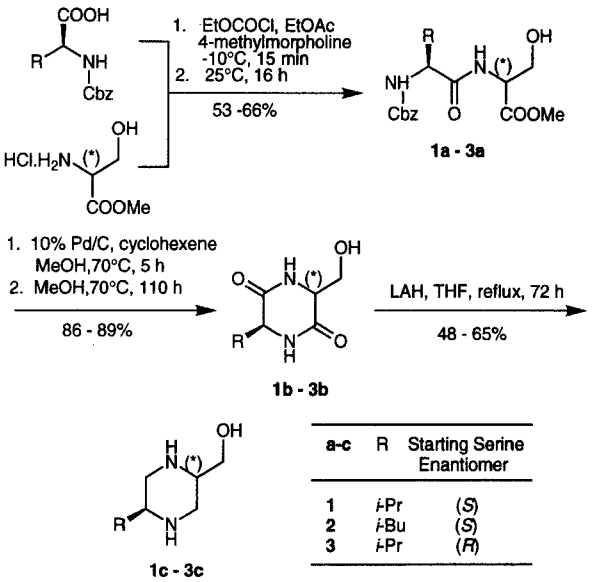


With this in mind, also taking into account the general importance of nonnatural chiral α-amino acids,[5] we have undertaken the synthesis of optically active 5-alkylpiperazine-2-carboxylic acids **1–3**, with high enantiomeric excess. It is worth noting that these compounds might represent useful starting materials for CPP analogs.

We thus required a synthesis which would be sufficiently versatile to obtain a range of structurally different amino acids. Attention was also directed to providing methods which would permit the preparation of any possible diastereomer. Our route to the key intermediates **1c–3c** is shown in Scheme 1.

Thus, a sample of (*S*)-*N*-benzyloxycarbonylvaline (from L-valine, 99% ee) was condensed, as previously published, with L-serine methyl ester hydrochloride by treatment with ethyl chloroformate and 4-methylmorpholine in ethyl acetate, to give the *N*-protected dipeptide **1a** in satisfactory yield (66%). Using the same procedure, dipeptides **2a** (65%) and **3a** (53%) were obtained.

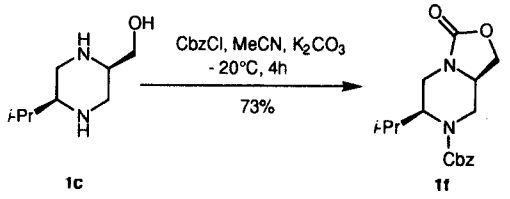
Removal of the benzyloxycarbonyl group in compounds **1a–3a** was carried out by transfer hydrogenation (10% Pd/C, cyclohexene, methanol, 70°C). After removal of any volatile product, the residue was suspended in absolute methanol[6] and heating was prolonged for 5 days to afford the dioxopiperazines **1b–3b** in excellent yields



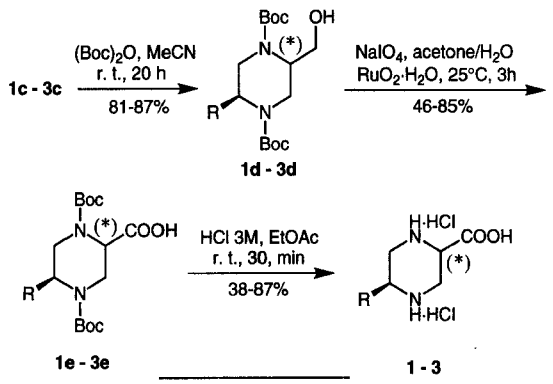
Scheme 1

(> 80%). Reduction of these compounds to the 5-alkyl-2-hydroxymethylpiperazines **1c–3c** was conducted by using an excess of lithium aluminum hydride in refluxing tetrahydrofuran. Recovery of the products from the reaction mixture was optimized during hydrolysis by using triethanolamine,[7] nevertheless, the yields were moderate (< 65%).

Our synthetic plan required double *N*-protection of the nitrogen atoms in the piperazine ring, followed by oxidation of the hydroxymethyl group. The benzyloxycarbonyl group (Cbz) appeared the most suitable, owing to its stability and the possibility of its removal in a non aqueous and nonacidic medium. Treatment of (*R*)-2-hydroxymethyl-4-methylpiperazine with benzyl chloroformate in acetonitrile at −20°C, according to a recent method,[8] gave 1-benzyloxycarbonyl-2-hydroxymethyl-4-methylpiperazine in excellent yield (87%).[9] Therefore, we tried to apply the same procedure to compound **1c**, surprisingly, no *N,N'*-dibenzyloxycarbonyl derivative was recovered. Analyses on the reaction product (73%) agree with the structure depicted in Scheme 2, moreover, we were unable to obtain the desired *N,N'*-di-Cbz derivative and the oxazolidinone **1f** was always recovered in variable yields using other methods.



Scheme 2



d-e	R	(*)
1	*i*-Pr	(*R*)
2	*i*-Bu	(*R*)
3	*i*-Pr	(*S*)

Scheme 3

Hence the readily cleaved *tert*-butoxycarbonyl was chosen as the *N*-protecting group and the synthetic path affording the title compound **1–3** is reported in Scheme 3. Thus, 2-hydroxymethyl-5-isopropylpiperazine **(1c)** in acetonitrile was treated with di-*tert*-butyldicarbonate [$(Boc)_2O$] to give the protected amino alcohol **1d** in good yield (87%). Compounds **2c** (81%) and **3d** (84%) were obtained analogously. In a previous run, compound **1d** was tentatively treated with pyridine chlorochromate (PCC) in dimethylformamide at 25°C for 48 h. After workup, compound **1d** was recovered unchanged. Ruthenium-catalyzed oxidation with sodium periodate,[10] which proceeds under mild conditions, was then adopted to give the *N,N'*-protected amino acids **1e–3e** in satisfactory yields (46–85%).

Complete deprotection of compounds **1e–3e** was accomplished using 3 M hydrochloric acid in ethyl acetate at room temperature and the 5-alkylpiperazine-2-carboxylic acids **1–3** were isolated as dihydrochlorides in moderate yields (38–87%).

The enantiomeric purity of **1–3** was determined by ^{19}F and ^1H NMR analysis of the reaction products of **3d** with (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.[11] A value of ≥ 94% was determined for the enantiomeric purity of the C–2 center which is very close to that of the starting serine. Moreover, in accordance with literature,[10] no evidence of epimerization at C–2 in the oxidative process was found. ^1H and ^{13}C NMR studies carried out at various temperatures (20° to 50°C) have shown that compounds **1–3** have a diastereoisomeric purity of ≥ 95%.

In conclusion, the data reported suggests that optically active 5-alkylpiperazine-2-carboxylic acids can be readily obtained from α-amino acids with negligible racemization.

Boiling points are uncorrected. Bulb-to-bulb distillations were carried out with a Büchi GRK-51 apparatus. Melting points were determined on a microscope Leitz LABORLUX S and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 420 B analyser. All new compounds showed satisfactory microanalyses (within ± 0.3%). Optical rotations were measured with a Perkin-Elmer 241 automatic polarimeter. GC analyses of the reaction products were carried out on a Perkin-Elmer 8600 gas chromatograph on fused silica megabore column (15 m × 0.53 mm) DB-1 (J&W), operating with an He flow rate of 7 mL/min. ^1H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) FT spectra were obtained with a Varian VXR-300 spectrometer on $CDCl_3$ solutions with TMS as internal standard, on D_2O solutions of compounds **1–3** with deuterated sodium 3-(trimethylsilyl)propionate as internal standard and on DMSO-d_6 solutions of compounds **1a** and **1b–3b**. All reactions involving air sensitive materials were carried out under an Ar atmosphere. All reagents and solvents employed were reagent grade materials purified by standard methods and distilled before use. Chiral starting materials (*S*)-valine and (*S*)-leucine of *BioChemica* grade (chemical and enantiomeric purity > 99%) purchased from Fluka Chemie AG and (*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.[12] L-α-*N*-(Benzyloxycarbonyl)amino acids were prepared according to reported procedures; for the samples employed it was found: Z-Val-OH[13] mp 60–63°C, $[\alpha]_D^{25}$ +1.5 (*c* = 5, EtOH); Z-Leu-OH[14] oil, $[\alpha]_D^{25}$ −16.0 (*c* = 2, EtOH).

Benzyloxycarbonyl Dipeptide Methyl Esters 1a–3a; General Procedure:

Under vigorous stirring and at −15°C, 4-methylmorpholine (32.9 mL, 30.3 g, 300 mmol) in EtOAc (30 mL) and ethyl chloroformate (28.2 mL, 32.0 g, 295 mmol) in EtOAc (20 mL) were added to the Z-protected amino acid (295 mmol) in EtOAc (200 mL). The reaction mixture was stirred at −15°C for 15 min, then 4-methylmorpholine (32.9 mL, 30.3 g, 300 mmol) and L- or D-H-Ser-OMe · HCl (44.2 g, 284 mmol), were added portionwise along with EtOAc (250 mL). The resulting mixture was stirred at −15°C for 1 h, then 12 h at r. t. The mixture was treated with H_2O (200 mL) and EtOAc (200 mL). The organic and aq layers were separated and the aq layer extracted with EtOAc (2 × 50 mL). The organic phase was washed with 10% aq $NaHCO_3$, sat. aq NaCl, 5% aq HCl and sat. aq NaCl (150 mL each) in that order, and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the crude product recrystallized from a suitable solvent giving the pure (TLC: CH_2Cl_2/acetone, 85:15) protected dipeptide **1a–3a**.

5-Alkyl-2-hydroxymethyl-3,6-dioxopiperazines 1b–3b; General Procedure:

The protected dipeptide **1a–3a** (266 mmol) was suspended in absolute MeOH (150 mL) with 10% Pd on active charcoal (2.5 g) and cyclohexane (120 mL). The reaction mixture was refluxed for 5 h, then all the volatile products were evaporated under reduced pressure. The crude solid recovered was suspended in absolute MeOH (250 mL) and the resulting mixture heated at 62–65°C for 110 h. The solvent was evaporated under reduced pressure and the crude product dried and suspended in refluxing dry acetone for 3 h. Filtration afforded the pure (TLC: EtOH/acetone, 7:3) diketopiperazine **1b–3b**.

5-Alkyl-2-hydroxymethylpiperazines 1c–3c; General Procedure:

The diketopiperazine **1b–3b** (133 mmol) was added portionwise, over 30 min, with vigorous stirring, to a suspension of LAH (20.0 g, 526 mmol) in THF (800 mL) at 0°C. The reaction mixture was then heated at 65–68°C for 72 h. The heating bath was removed and triethanolamine (74 mL, 82 g, 550 mmol) added cautiously over 45 min. After 1 h stirring, H_2O (20 mL, 20 g, 1.1 mmol) was added. After a further 12 h stirring, the reaction mixture was filtered and the solvent removed under vacuum. The residue was distilled without fractionating and the oil obtained dissolved in 10% aq HCl (150 mL). The acid layer was washed with Et_2O (2 × 50 mL) then the aq solution basified with KOH (60 g) and extracted with CH_2Cl_2 (4 × 50 mL) several times. The organic phase was dried (Na_2SO_4) and the solvent evaporated under vacuum. The crude product was then distilled affording pure (GC) piperazine **1c–3c**.

5-Alkyl-1,4-di-(*tert*-butoxycarbonyl)-2-hydroxymethylpiperazines 1d–3d; General Procedure:

Solid $(Boc)_2O$ (13.1 g, 60 mmol) was added to a stirred solution of

Table. Compounds **1–3** Prepared

Product	Yield[a,b] (%)	mp (°C) or bp (°C/mbar)	$[\alpha]_D^{25}$ (*c*, solvent)	(Solvent) ^{1}H NMR δ, *J* (Hz)	(Solvent) ^{13}C NMR δ
1	87	199–201 (dec.)	−4.58 (1, H_2O)	(D_2O) 4.52–4.46 (m, 1H, CHCOOH), 3.98 (dd, 1H, CHCH(CH_3)$_2$, J_1 = 14, J_2 = 3), 3.68 (d, 1H, J = 11), 3.52 (dd, 1H, J_1 = 14, J_2 = 6), 3.38–3.20 (m, 2H), 2.00–1.82 (m, 1H, CH_3CHCH_3), 0.97 (d, 3H, CH_3CHCH_3, J = 7), 0.93 (d, 3H, CH_3CHCH_3, J = 7)	(D_2O) 170.8, 60.3, 54.6, 44.6, 43.3, 31.1, 19.9
1a	66	160–163[c]	+2.73 (3, $CHCl_3$)	(DMSO-d_6) 8.24 (m, 1H, NH), 7.44–7.30 (m, 6H, Ph + NH), 5.11–4.94 (m, 2H, $PhCH_2O$), 4.37–4.26 (m, 1H), 4.02–3.88 (m, 1H), 3.78–3.24 (m, 2H), 3.61 (s, 3H, $COOCH_3$), 3.37–3.24 (m, 1H, CH_2OH), 2.06–1.85 (m, 1H, CH_3CHCH_3), 0.97–0.71 (m, 6H, CH_3CHCH_3)	(DMSO-d_6) 171.2, 170.7, 156.0, 137.0, 128.2, 127.6, 127.5, 65.3, 61.1, 59.7, 54.6, 51.6, 30.4, 18.9, 17.8
1b	88	245–249 (dec.)	−85.52 (2, DMSO)	(DMSO-d_6) 8.07 (bs, 1H, NH), 7.92 (bs, 1H, NH), 4.95 (t, 1H, $CHCH_2OH$, J = 6), 3.82–3.77 (m, 1H), 3.70–3.52 (m, 2H), 3.33 (s, 1H, CH_2OH), 2.25–2.08 (m, 1H, CH_3CHCH_3), 0.94 (d, 3H, CH_3CHCH_3, J = 8), 0.84 (d, 3H, CH_3CHCH_3, J = 8)	(DMSO-d_6) 166.6, 166.2, 62.4, 59.4, 56.8, 31.6, 18.8, 17.4
1c	56	115–117/0.03	+14.56 (1, $CHCl_3$)	($CDCl_3$) 3.90 (dd, 1H, CH_2OH, J_1 = 12, J_2 = 9), 3.62 (dd, 1H, CH_2OH, J_1 = 12, J_2 = 4.5), 2.98–2.92 (m, 2H), 2.90–2.75 (m, 4H), 2.38–2.28 (m, 2H, NH), 2.50–2.00 (bm, 1H, CH_2OH), 1.75–1.61 (m, 1H, CH_3CHCH_3), 0.90 (d, 3H, CH_3CHCH_3, J = 7), 0.86 (d, 3H, CH_3CHCH_3, J = 7)	($CDCl_3$) 53.9, 52.5, 43.5, 38.2, 35.5, 20.8, 9.9, 9.7
1d	87	225/0.03[d]	+99.88 (2, $CHCl_3$)	($CDCl_3$, 50°C) 4.07–3.86 (m, 3H), 3.82–3.71 (m, 1H) 3.70–3.52 (m, 2H), 2.97–2.74 (m, 2H), 2.70–2.45 (bm, 1H, CH_2OH), 1.90–1.75 (m, 1H, CH_3CHCH_3), 1.43 (m, 18H, $C(CH_3)_3$), 0.88 (m, 6H, CH_3CHCH_3)	($CDCl_3$) 156.0, 155.5, 80.5, 79.9, 63.0, 58.1, 55.2, 41.0, 39.9, 30.5, 28.2, 19.1, 17.7
1e	85	61–65	+69.02 (2, $CHCl_3$)	($CDCl_3$) 9.20–8.80 (bm, 1H, COOH), 4.58–4.13 (m, 2H, 4.00–3.72 (m, 2H), 3.11–2.80 (m, 2H), 1.92–1.78 (m, 1H, CH_3CHCH_3), 1.60–1.29 (m, 18H, $C(CH_3)_3$, 1.00–0.83 (m, 6H, CH_3CHCH_3)	($CDCl_3$) 174.5, 155.2, 154.7, 81.0, 80.6, 58.4, 55.6, 40.0, 30.8, 28.1, 28.0, 19.0, 17.4
1f	73	250/0.02[d]	+10.42 (1, $CHCl_3$)	($CDCl_3$) 7.42–7.24 (m, 5H, Ph), 5.23–5.08 (m, 2H, $PhCH_2O$), 4.48–4.36 (m, 1H), 4.34–4.09 (m, 1H), 4.01–3.87 (m, 3H), 3.80–3.69 (m, 1H), 3.11–2.96 (m, 1H), 2.90–2.72 (m, 1H), 2.05–1.88 (m, 1H, CH_3CHCH_3), 1.12–0.98 (m, 3H, CH_3CHCH_3), 0.90–0.77 (m, 3H, CH_3CHCH_3)	($CDCl_3$) 158.5, 158.0, 155.5, 134.0, 128.5, 128.2, 128.0, 67.7, 65.3, 65.1, 57.4, 56.5, 52.2, 52.1, 43.0, 42.3, 41.4, 25.4, 20.1
2	38	168–170	+5.07 (3, D_2O)	(D_2O) 4.50–4.43 (m, 1H), 4.22–4.00 (m, 2H), 3.73–3.55 (m, 2H), 3.46–3.30 (m, 1H), 1.91–1.66 (m, 2H, CH_2CH_3)$_2$), 1.65–1.57 (m, 1H, CH_3CHCH_3), 1.04–0.90 (m, 6H, CH_3CHCH_3)	(D_2O) 170.6, 62.8, 53.8, 44.3, 41.1, 27.2, 26.3, 24.5, 24.1
2a	65	103–106	−3.73 (10, $CHCl_3$)	($CDCl_3$) 7.38–7.26 (m, 6H, Ph + NH) 5.72 (bm, 1H, NH) 5.12 (d, 1H, J = 12, $PhCH_2O$), 5.0 (d, 1H, J = 12, $PhCH_2O$) 4.70–4.61 (m, 1H) 4.38–4.27 (m, 1H), 3.97–3.82 (m, 3H) 3.75 (s, 3H, $COOCH_3$) 3.80–3.65 (bm, 1H, CH_2OH), 1.77–1.48 (m, 3H, $CH_2CH(CH_3)_2$) 0.98–0.85 (m, 6H, CH_3CHCH_3)	($CDCl_3$) 172.9, 170.7, 156.6, 136.0, 128.4, 128.1, 128.0, 67.1, 62.6, 54.6, 53.6, 52.6, 41.4, 24.6, 22.8, 21.9
2b	86	231–233 (dec.)	−54.46 (0.6, DMF)	(DMSO-d_6) 8.22 (bs, 1H, NH), 7.92 (bs, 1H, NH), 5.15–5.06 (t, 1H, $CHCH_2OH$, J = 5), 3.75–3.62 (m, 2H), 3.54–3.43 (m, 1H), 3.34 (s, 1H, CH_2OH), 1.90–1.74 (m, 1H, CH_3CHCH_3), 1.69–1.51 (m, 2H, $CH_2CH(CH_3)_2$), 0.88 (d, 3H, CH_3CHCH_3, J = 7), 0.84 (d, 3H, CH_3CHCH_3, J = 7)	(DMSO-d_6) 168.1, 166.7, 62.3, 57.2, 52.7, 44.5, 23.3, 23.0, 21.6
2c	65	112–115/0.2	+4.90 (9, $CHCl_3$)	($CDCl_3$) 3.84–3.73 (m, 1H, CH_2OH), 3.62–3.52 (m, 1H, CH_2OH), 3.21–2.5 (m, 9H), 1.71–1.54 (m, 1H, CH_3CHCH_3), 1.4–1.15 (m, 2H, $CH_2CH(CH_3)_2$), 1.0–0.81 (m, 6H, CH_3CHCH_3)	($CDCl_3$) 62.1, 53.3, 52.8, 47.5, 46.3, 42.0, 24.1, 22.9, 22.3
2d	81	225/0.02[d]	+93.85 (4, $CHCl_3$)	($CDCl_3$) 4.08–3.90 (m, 4H), 3.70–3.63 (m, 2H), 3.61–3.53 (m, 1H), 2.92–2.77 (m, 3H), 2.80–2.50 (bm, 1H, CH_2OH), 1.61–1.48 (m, 1H, CH_3CHCH_3), 1.45 (m, 18H, $C(CH_3)_3$), 1.26–1.13 (m, 2H, $CH_2CH(CH_3)_2$), 0.94–0.85 (m, 6H, CH_3CHCH_3)	($CDCl_3$) 155.0, 154.1, 81.7, 80.0, 63.2, 56.0, 51.4, 43.5, 41.0, 38.6, 28.4, 28.3, 27.7, 24.4, 23.5, 21.9
2e	56	60–62	+11.17 (3, $CHCl_3$)	($CDCl_3$, 50°C) 9.62–9.20 (bm, 1H, COOH), 4.56–4.37 (m, 1H), 4.35–4.20 (m, 1H), 4.12–4.00 (m, 1H), 3.70–3.41 (m, 1H), 3.10–2.91 (m, 1H), 2.89–2.73 (m, 1H), 1.90–1.78 (m, 1H, CH_3CHCH_3), 1.58–1.37 (m, 18H, $C(CH_3)_3$), 1.34–1.10 (m, 2H, $CH_2CH(CH_3)_2$), 1.00–0.90 (m, 6H, CH_3CHCH_3)	($CDCl_3$) 174.0, 155.5, 154.2, 82.3, 81.0, 56.0, 52.0, 41.8, 38.9, 28.0, 27.8, 22.2, 23.7, 22.9, 21.8

Table. (continued)

Product	Yield[a,b] (%)	mp (°C) or bp (°C/mbar)	$[\alpha]_D^{25}$ (*c*, solvent)	(Solvent) ^{1}H NMR δ, *J* (Hz)	(Solvent) ^{13}C NMR δ
3	63	222–224 (dec.)	−16.05 (1, D_2O)	(D_2O) 4.06 (dd, 1H, J_1 = 13, J_2 = 4), 3.96 (dd, 1H, J_1 = 14.5, J_2 = 4), 3.84 (dd, 1H, J_1 = 13, J_2 = 3), 3.63–3.20 (m, 3H), 2.15–2.00 (m, 1H, $CH_3C\underline{H}CH_3$), 1.15–1.00 (m, 6H, $C\underline{H}_3CHC\underline{H}_3$)	(D_2O) 170.7, 59.8, 56.6, 45.5, 44.7, 31.1, 19.7, 19.4
3a	53	161–163	−29.37 (1, $CHCl_3$)	($CDCl_3$) 7.37–7.30 (m, 5H, Ph), 7.01–6.95 (bm, 1H, NH), 5.46–5.40 (bm, 1H, NH), 5.09 (s, 2H, $PhC\underline{H}_2O$), 4.69–4.61 (m, 1H, 4.13–4.06 (m, 1H), 4.00–3.85 (m, 2H), 3.76 (s, 3H, $COOC\underline{H}_3$), 2.79–2.61 (m, 1H, $CH_2O\underline{H}$), 2.24–2.12 (m, 1H, $CH_3C\underline{H}CH_3$), 1.00 (d, 3H, $CH_3CHC\underline{H}_3$, *J* = 7), 0.90 (d, 3H, $C\underline{H}_3CHCH_3$, *J* = 7)	($CDCl_3$) 171.5, 170.7, 156.6, 136.0, 128.5, 128.3, 128.1, 67.3, 62.9, 60.5, 54.6, 52.8, 30.8, 19.2, 17.6
3b	89	230–232 (dec.)	−23.88 (1, DMSO)	(DMSO-d_6) 8.01 (bs, 1H, NH), 5.04–4.97 (m, 1H, $CH_2O\underline{H}$), 3.79–3.70 (m, 2H), 3.64 (bs, 1H), 3.58–3.50 (m, 1H), 2.22–2.10 (m, 1H, $CH_3C\underline{H}CH_3$), 0.92 (d, 3H, $CH_3CHC\underline{H}_3$, *J* = 8), 0.82 (d, 3H, $C\underline{H}_3CHCH_3$, *J* = 8)	(DMSO-d_6) 167.7, 167.4, 62.5, 59.4, 56.6, 31.5, 18.3, 16.7
3c	48	80/45[c]	+5.61 (1, $CHCl_3$)	($CDCl_3$) 3.60 (dd, 1H, $C\underline{H}_2OH$, J_1 = 12, J_2 = 5), 3.43 (dd, 1H, $C\underline{H}_2OH$, J_1 = 12, J_2 = 7), 3.09 (dd, 1H, J_1 = 12, J_2 = 2), 2.98 (dd, 1H, J_1 = 12, J_2 = 2), 2.82–2.73 (m, 1H), 2.57–2.42 (m, 2H), 2.37–2.29 (m, 1H), 2.20–1.80 (bm, 3H, $CH_2O\underline{H}$ + NH), 1.61–1.48 (m, 1H, $CH_3C\underline{H}CH_3$), 0.95 (d, 3H, $CH_3CHC\underline{H}_3$, *J* = 7), 0.91 (d, 3H, $C\underline{H}_3CHCH_3$, *J* = 7)	($CDCl_3$) 64.3, 61.7, 57.0, 49.6, 49.1, 31.4, 19.0
3d	84	225/0.01[d]	−5.27 (1, $CHCl_3$)	($CDCl_3$) 4.30–3.86 (m, 3H), 3.75–3.43 (m, 3H), 3.05–2.85 (m, 2H), 2.30–2.00 (bm, 1H, $CH_2O\underline{H}$), 2.05–1.90 (m, 1H, $CH_3C\underline{H}CH_3$), 1.45 (m, 18H, $C(C\underline{H}_3)_3$), 1.03–0.95 (m, 3H, $CH_3CHC\underline{H}_3$), 0.87–0.78 (m, 3H, $C\underline{H}_3CHCH_3$)	($CDCl_3$) 155.9, 155.0, 80.2, 79.9, 59.2, 58.9, 55.9, 52.1, 50.9, 40.3, 38.8, 37.2, 28.3, 24.9, 20.0, 18.5
3e	46	150 (dec.)	−6.92 (1, $CHCl_3$)	($CDCl_3$) 9.80–9.60 (bm, 1H, COOH), 4.86–4.74 (m, 1H), 4.63–4.43 (m, 1H), 4.08–3.96 (m, 1H), 3.80–3.59 (m, 1H), 3.23–3.00 (m, 2H), 2.05–1.90 (m, 1H, $CH_3C\underline{H}CH_3$), 1.50–1.35 (m, 18H, $C(C\underline{H}_3)_3$), 1.03–0.95 (m, 3H, $C\underline{H}_3CHCH_3$), 0.85–0.77 (m, 3H, $CH_3CHC\underline{H}_3$)	($CDCl_3$) 174.6, 155.9, 154.8, 80.9, 80.0, 57.3, 55.5, 54.0, 52.7, 42.3, 40.9, 40.0, 38.9, 28.2, 25.1, 20.0, 18.9, 18.4

[a] Yield of isolated pure products.
[b] Satisfactory microanalyses obtained: C ± 0.32, H ± 0.24, N ± 0.23.
[c] Compound purified by sublimation.
[d] Bulb-to-bulb distilled.

the piperazine **1c–3c** (15 mmol) in dry CH_3CN (30 mL) under an Ar atmosphere. The mixture was stirred at r.t. for 20 h, then the volatile products evaporated under reduced pressure. The residue was dissolved in Et_2O (100 mL) and washed with 5% aq citric acid (2 × 50 mL) and with sat. aq NaCl, with sat. aq $NaHCO_3$, and sat. aq NaCl (50 mL each) in that order, and dried (Na_2SO_4). The solvent was then evaporated under reduced pressure and the unreacted $(Boc)_2O$ was removed from the crude product by rectification with a 40 cm Vigreux column at 60 °C/0.1 mbar. The residue was cautiously bulb-to-bulb distilled affording the pure (TLC: EtOAc) di-Boc-piperazine **1d–3d**.

5-Alkyl-1,4-di-(*tert*-butoxycarbonyl)-piperazine-2-carboxylic Acids 1e–3e; General Procedure:

$NaIO_4$ (20 g, 94 mmol) in H_2O (50 mL) and $RuO_2 \cdot H_2O$ (0.45 g) were added to the protected piperazine **1d–3d** (13 mmol) in acetone (80 mL) with stirring at 0 °C. The mixture was stirred at r.t. for 4 h, then quenched with *i*-PrOH (50 mL). After 1 h, the mixture was filtered through a Celite pad and the filtrate concentrated under vacuum. The residue was dissolved in Et_2O (50 mL) and washed with 5% aq Na_2SO_3 and 5% aq citric acid (25 mL each) in that order, then the organic phase was treated with 10% aq NaOH (2 × 25 mL). The alkaline solution was washed with Et_2O (2 × 30 mL), acidified with solid citric acid (8 g), extracted several times with Et_2O (4 × 50 mL). The organic phase was dried (Na_2SO_4) and the solvent removed under reduced pressure affording the pure (TLC: EtOH/AcOH, 9:1) protected amino acid **1e–3e**.

5-Alkyl-2-carboxy-piperazines Dihydrochlorides 1–3; General Procedure:

The protected amino acid **1e–3e** (2 mmol) was treated at r.t. with 3 M HCl in EtOAc (6 mL); after 30 min the mixture was concentrated under reduced pressure affording the pure (TLC: EtOH/AcOH, 7:3) amino acid dihydrochloride **1–3**.

(2*R*,5*S*)-4-(Benzyloxycarbonyl)-5-isopropyl-7-oxo-1,4-diaza-8-oxabicyclo[4.3.0]nonane (1f):

Benzyl chloroformate (5.7 mL, 40 mmol) in dry CH_3CN (10 mL) was added dropwise at −20 °C to a well stirred suspension of powdered K_2CO_3 (12.0 g, 87 mmol) and piperazine **1c** (3.1 g, 18 mmol) in CH_3CN (40 mL). The mixture was stirred for 2 h at −20 °C, then H_2O (50 mL) was added and the aq phase extracted several times with $CHCl_3$ (4 × 15 mL). The organic layer was then washed with H_2O, 5% aq HCl and sat. aq NaCl (50 mL each) in that order. After drying (Na_2SO_4) the solvent was removed and the crude product was bulb-to-bulb distilled affording pure (TLC: acetone) bicyclic product **1f**.

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