A Novel Synthetic Route to N^6-Methyl-L-lysine and N^5-Methyl-L-ornithine via N^3-Protected (*S*)-3-Aminolactams[1]

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(*S*)-3-Phthalimido- or (*S*)-3-tritylaminolactams, prepared from L-lysine and L-ornithine in two or three steps, are easily methylated at the endocyclic nitrogen atom by iodomethane/silver(I) oxide in dimethylformamide. Acid hydrolysis of the *N*-methylated lactams thus obtained affords N^6-methyl-L-lysine and N^5-methyl-L-ornithine hydrochlorides in high yield.

N^6-Methyl-L-lysine (**8b**) is a naturally occuring compound[2] and certainly plays important role in living organisms which is not yet fully understood.[2,3] Reported procedures[4-6] for the synthesis of **8b** require introduction and removal of two or three protecting groups. Poorly crystallizing intermediates and steps such as catalytic hydrogenolysis make these methods impractical for large scale synthesis. The absence of a simple preparative method results in the high cost of **8b** and limits its use as starting material in the synthesis of modified peptides and L-lysine analogs.

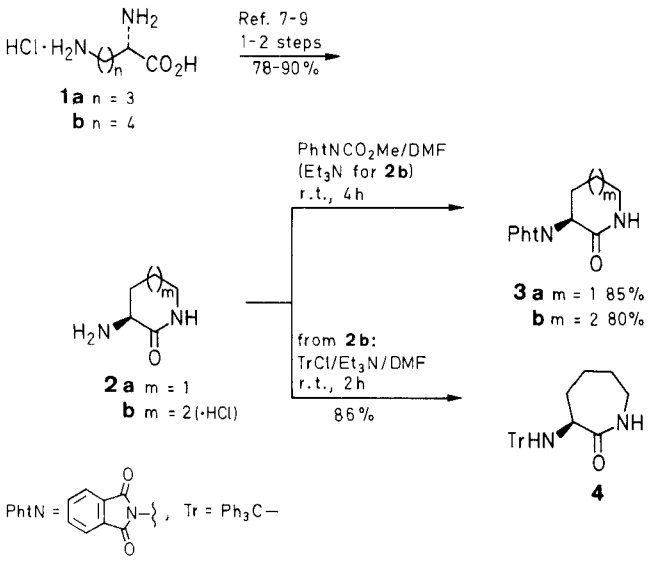
We report here a new and convenient synthetic route to **8b** from L-lysine via (*S*)-3-aminolactams which is also compatible with the synthesis of L-ornithine derivatives. The method is easily scaled up, and has allowed us to obtain almost 50 g of **8b** at once in one run.

The 3-aminolactams are easily prepared from the corresponding optically active diamino carboxylic acids (lysine, ornithine, diaminobutyric acid) or their esters without racemization.[7-9] Starting from the lactam **2b** the phthalimido, **3b**, and the tritylamino derivative **4** were obtained in high yield (Scheme 1).

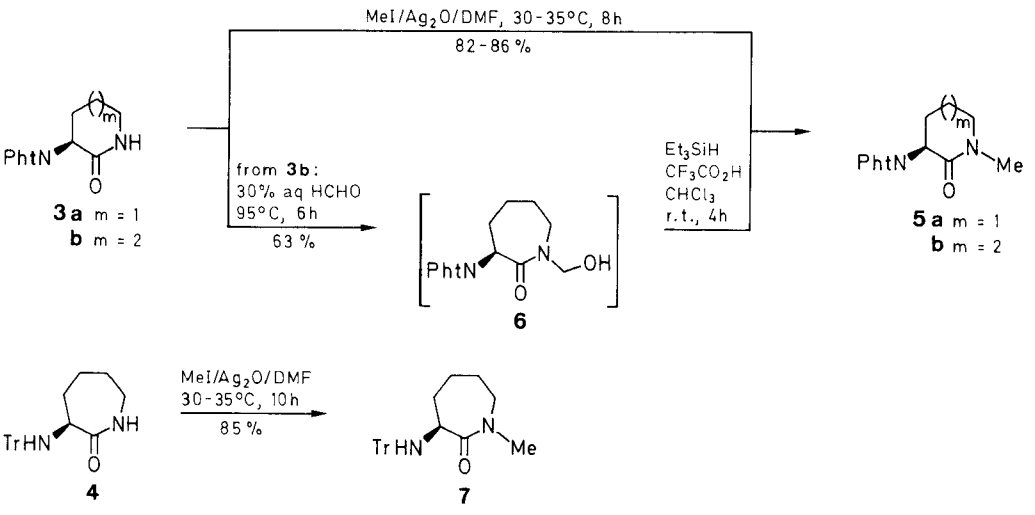
Several procedures for amide *N*-methylation under relatively mild conditions without the use of strong bases to avoid racemization of the α-carbon center are described in the literature. Thus, ε-caprolactam and lower homologs were successfully *N*-methylated with iodomethane in the presence of potassium fluoride on neutral aluminum oxide Alumina 90 (Merck).[10] We were able to obtain similar results with neutral aluminum oxide for TLC 5/40 (Lachema-Chemapol) but this method failed on the lactams **3b** and **4** which did not react under the conditions of ε-caprolactam methylation.

Amides can be *N*-methylated by reduction of *N*-hydroxymethyl derivatives prepared from amide and formaldehyde.[11] The *N*-hydroxymethyl derivative **6** was obtained by heating of lactam **3b** with 30% aqueous formaldehyde; reduction of **6** without further purification by triethylsilane/trifluoroacetic acid gave the *N*-methyllactam **5b** (Scheme 2).

The best results, however, were obtained with iodomethane/silver(I) oxide in dimethylformamide used earlier for the *N*-methylation of protected amino acid derivatives and peptides.[12,13] The treatment of lactam **3b**



Scheme 1

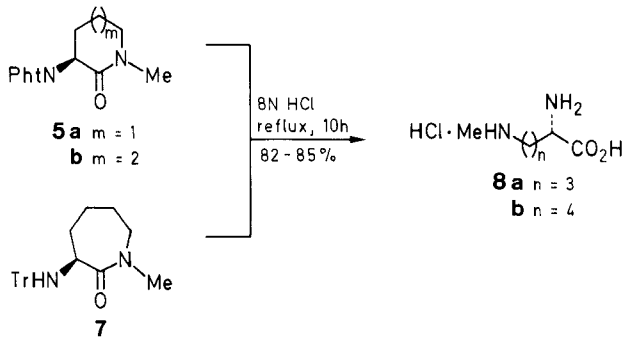


Scheme 2

with this reagent afforded, after an easy workup, pure **5b** in 86% yield. Completeness of methylation was shown by reversed phase HPLC to be 98–99%. This method was also compatible with the acid labile trityl derivative **4** which was methylated only at the endocyclic nitrogen N1 to give the *N*-methyllactam **7**. This conclusion was made from the results of the ^{1}H-NMR spectrum of **7** which showed the presence of only one *N*-methyl group and a doublet for the 3-amino group protons at $\delta = 3.85$, and also the absence of an amide proton triplet at $\delta \simeq 6$ (Scheme **2**).

The mixture of silver(I) oxide and silver iodide formed after methylation can be easily recycled.

No selective ring opening of the lactams **5b, 7** without simultaneous N^3-deprotection was achieved under hydrolytic conditions, i.e. diluted aqueous hydrochloric acid for the phthalimide derivative **5b** or up to 4N water/ethanolic sodium hydroxide under reflux for the trityl derivative **7**. Heating of **5b** or **7** in 8N hydrochloric acid under reflux afforded **8b** in $\simeq$ 50% overall yield from L-lysine **(1b)** (Scheme **3**).



Scheme 3

Application of the above procedure to L-ornithine **(1a)** allowed us to obtain N^5-methyl-L-ornithine **(8a)** via the 3-amino lactam **2a**, phthalimido derivative **3a** and *N*-methyllactam **5a** with the same overall yield.

Melting points were determined on a Boëtius micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded at 100 MHz on a Tesla BS 567A spectrometer. Observed rotations at the Na-D line were obtained at 20°C using a EPL-01 polarimeter. TLC was carried out on plates precoated with silica gel Silufol UV-254 (Kavalier) using the following solvent systems: 2-propanol/HCO_2H/H_2O (75:13:12); EtOH/17% NH_3 (7:3); EtOAc/hexane (4:1); 0.1 M aq NaCl. HPLC were obtained on Milichrom instrument, UV detector at $\lambda = 254$, a Silasorb C18, 5 μ, 62 × 2 mm column and a mobile phase H_2O/MeCN (2:1), flow rate 0.1 mL/min. L-Lysine hydrochloride and L-ornithine hydrochloride were purchased from Reanal Chemical Co. *N*-Carbomethoxyphthalimide, Ph_3CCl, Et_3SiH and Ag_2O were prepared according to published procedures.[14–16] DMF was distilled over CaO before use.

(*S*)-3-Phthalimidopiperidin-2-one (3a):
A mixture of (*S*)-3-aminolactam **2a** (1.14 g, 10 mmol) and *N*-carbomethoxyphthalimide (2.05 g, 10 mmol) in DMF (10 mL) is stirred at r.t. for 4 h and then evaporated to half of the initial volume under reduced pressure. H_2O (ca. 30 mL) is added and the mixture is allowed to stand at 4°C overnight. The crystals are collected by suction filtration, washed with H_2O (ca. 10 mL) and dried in a vacuum desiccator (P_2O_5) to give **3a**; yield: 2.08 g (85%); mp 167°C (dec); $[\alpha]_D^{20}$ −36.5° (c = 1, $CHCl_3$).

$C_{13}H_{12}N_2O_3$	calc.	C 63.92	H 4.95	N 11.47
(244.3)	found	63.72	4.63	11.18

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.70–2.70 (m, 4H, CH_2CH_2), 3.40 (m, 2H, NCH_2), 4.75 (dd, 1H, J = 11.3, 6.3 Hz, CHCO), 6.75 (br s, 1H, NH), 7.78 (m, 4H_{arom}).

(*S*)-Hexahydro-3-phthalimido-2*H*-azepin-2-one (3b):
To a stirred solution of *N*-carbomethoxyphthalimide (2.05 g, 10 mmol) in DMF (10 mL) are added (*S*)-3-aminolactam hydrochloride **2b** (1.65 g, 10 mmol) and Et_3N (2.0 mL, 15 mmol). The mixture is stirred at r.t. for 4 h, then poured into cold H_2O (ca. 30 mL) and allowed to stand at 4°C overnight. The crystals are collected by suction filtration, washed with H_2O (ca. 15 mL) and dried in a vacuum desiccator (P_2O_5) to give **3b**; yield: 2.06 g (80%); dec. without melting; $[\alpha]_D^{20}$ +64.5° (c = 1, $CHCl_3$).

$C_{14}H_{14}N_2O_3$	calc.	C 65.11	H 5.46	N 10.85
(258.3)	found	65.28	5.61	11.03

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.5–2.9 (m, 6H, $CH_2CH_2CH_2$), 3.30 (m, 2H, NCH_2), 5.0 (dd, 1H, J = 12.2, 1.4 Hz, CHCO), 6.16 (br s, 1H, NH), 7.77 (m, 4H_{arom}).

(*S*)-Hexahydro-3-tritylamino-2*H*-azepin-2-one (4):
A solution of trityl chloride (3.1 g, 11 mmol) in $CHCl_3$ (20 mL) is added to **2b** (1.65 g, 10 mmol) and Et_3N (4.6 mL, 30 mmol) in DMF (5 mL) and stirred at r.t. for 2 h. The mixture is poured into H_2O (ca. 200 mL). The organic layer is washed with H_2O (2 × 100 mL), dried ($MgSO_4$) and the solvent evaporated. The oily residue is then recrystallized from EtOAc/pentane to give **4**; yield: 3.2 g (86%); mp 187°C; $[\alpha]_D^{20}$ +28.0° (c = 1, $CHCl_3$).

$C_{25}H_{26}N_2O$	calc.	C 81.05	H 7.07	N 7.56
(370.5)	found	80.76	6.97	7.40

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.9–1.9 (m, 6H, $CH_2CH_2CH_2$), 2.86 (m, 2H, NCH_2), 3.33 (m, 1H, CHCO), 3.87 (d, 1H, J = 5.9 Hz, NH_{amine}), 6.22 (t, 1H, J = 6.1 Hz, NH_{amide}), 7.22 (m, 12H_{arom}), 7.48 (m, 6H_{arom}).

(*S*)-1-Methyl-3-phthalimidopiperidin-2-one (5a) and (*S*)-Hexahydro-1-methyl-3-phthalimido-2*H*-azepin-2-one (5b):
To a stirred solution of lactam **3a** or **3b** (10 mmol) in DMF (10 mL) are added Ag_2O (2.89 g, 12.5 mmol) and MeI (1.54 mL, 25 mmol). The mixture is stirred at 30–35°C for 8 h. The solid is separated by filtration and washed with MeCN (ca. 2 mL). The combined filtrate and washings are evaporated *in vacuo* almost to dryness. The residue and the former solid are treated with $CHCl_3$ (15 mL) under reflux. The insoluble material is filtered off and washed with $CHCl_3$ (5 mL). The resulting solution is washed with H_2O (2 × 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield a thick slurry, which is diluted with hexane (15 mL). The crystals are collected, washed with hexane and dried to give **5a** or **5b**.

5a: Yield: 2.12 g (82%); mp 174°C (dec); $[\alpha]_D^{20}$ −32.0° (c = 1, $CHCl_3$).

$C_{14}H_{14}N_2O_3$	calc.	C 65.11	H 5.46	N 10.85
(258.3)	found	65.33	5.12	10.47

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.8–2.7 (m, 4H, CH_2CH_2), 3.00 (s, 3H, NCH_3), 3.38 (m, 2H, NCH_2), 4.76 (dd, 1H, J = 11.6, 6.0 Hz, CHCO), 7.76 (m, 4H_{arom}).

5b: Yield: 2.34 g (86%); dec. without melting; $[\alpha]_D^{20}$ +69.0° (c = 1, $CHCl_3$).

$C_{15}H_{16}N_2O_3$	calc.	C 66.61	H 5.92	N 10.29
(272.3)	found	66.67	5.98	10.36

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.6–2.8 (m, 6H, $CH_2CH_2CH_2$), 3.02 (s, 3H, NCH_3), 3.61 (m, 2H, NCH_2), 5.05 (dd, 1H, J = 11.4, 1.7 Hz, CHCO), 7.77 (m, 4H_{arom}).

5b via the Hydroxymethyl Derivative 6:
Lactam **3b** (0.52 g, 2 mmol) is suspended in 30% aq HCHO (3.2 mL) and stirred at 95°C for 6 h. The resulting solution is cooled to r.t., diluted with H_2O (20 mL) and extracted with $CHCl_3$

(2 × 15 mL). To the dried ($MgSO_4$) organic layer are added CF_3CO_2H (1.48 mL, 20 mmol) and Et_3SiH (0.47 mL, 3 mmol). The mixture is stirred at r.t. for 4 h, washed with 30% aq $NaHCO_3$ (3 × 30 mL) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure and recrystallization on the residue from EtOAc give pure **5b**; yield: 0.35 g (63%); dec. without melting: $[\alpha]_D^{20}$ + 69.0° (*c* = 1, $CHCl_3$).

$C_{15}H_{16}N_2O_3$	calc.	C 66.61	H 5.92	N 10.29
(272.3)	found	66.97	6.02	10.25

(*S*)-Hexahydro-1-methyl-3-tritylamino-2*H*-azepin-2-one (7):
To a stirred solution of lactam **4** (1.85 g, 5 mmol) in DMF (5 mL) are added Ag_2O (1.46 g, 6.3 mmol) and MeI (1.27 mL, 12.5 mmol). The mixture is stirred at 30–35 °C for 10 h. The solid is separated by filtration and washed with boiling $CHCl_3$ (30 mL). The combined filtrate is washed with H_2O (3 × 30 mL), dried ($MgSO_4$) and filtered. Evaporation of the solvent under reduced pressure and recrystallization of the residue from pentane (– 40 °C) give pure **7**; yield: 1.63 g (85%); mp 89 °C; $[\alpha]_D^{20}$ + 17.5° (*c* = 1, $CHCl_3$).

$C_{26}H_{28}N_2O$	calc.	C 81.21	H 7.34	N 7.29
(384.5)	found	81.66	7.48	7.06

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.1–2.0 (m, 6H, $CH_2CH_2CH_2$), 2.67 (s, 3H, NCH_3), 2.97 (m, 2H, NCH_2), 3.35 (m, 1H, CHCO), 3.89 (br d, 1H, NH_{amine}), 7.21 (m, 12H, H_{arom}), 7.50 (m, 6H, H_{arom}).

N^5-Methyl-L-ornithine Hydrochloride (8a) and N^6-Methyl-L-lysine Hydrochloride (8b); General Procedure:
1-Methyllactam **5a, 5b** or **7** (10 mmol) is heated under reflux in 8 N HCl (40 mL) for 4 h. Then 12 N HCl (6 mL) is added, the mixture is refluxed for 6 h, cooled to 4 °C and allowed to stand overnight. The precipitate is removed by filtration and the filtrate is evaporated *in vacuo* at 95–100 °C to dryness. The residue is dissolved in EtOH (5 mL), evaporated to dryness again and dissolved in EtOH (25 mL). The resulting solution is neutralized with Et_3N and allowed to stand at 4 °C for 4 h. The precipitated product is isolated by suction, washed with EtOH (3 × 3 mL) and dried in a vacuum desiccator (P_2O_5) to give **8a** or **8b**.

8a: Yield: 1.46 g (80%); mp 245 °C; $[\alpha]_D^{20}$ + 25.5° (*c* = 2, 6 N HCl). [Lit.[5] mp 252 °C; $[\alpha]_D^{25}$ + 34.3° *c* = 0.5, 6 N HCl)[5]; $[\alpha]_D^{29}$ + 19.7° (*c* = 2, 6 N HCl)[4]].

$C_6H_{15}ClN_2O_2$	calc.	C 39.45	H 8.28	N 15.34
(182.6)	found	39.74	8.26	15.22

^{1}H-NMR (D_2O): δ = 1.89 (m, 4H, CH_2CH_2), 2.72 (s, 3H, NCH_3), 3.08 (br t, 2H, *J* = 7.0 Hz, NCH_2), 3.78 (t, 1H, *J* = 5.5 Hz, CH).

8b: Yield: 1.65 g (84%) from **5b**, 1.62 g (82%) from **7**; mp 254–255 °C (dec); $[\alpha]_D^{20}$ + 19.9 ± 2 (*c* = 2, 6 N, HCl). [Lit.[5] mp 240 °C; $[\alpha]_D^{25}$ + 27.1° (*c* = 0.5, 6 N, HCL)[5]; $[\alpha]_D^{23}$ + 21.9° (*c* = 2, 6 N HCl)[4]]; Aldrich sample is reported in catalog to have mp 250 °C (dec); $[\alpha]_D^{25}$ + 19.7° (*c* = 2, 6 N HCl).

$C_7H_{17}ClN_2O_2$	calc.	C 42.75	H 8.71	Cl 18.03
(196.7)	found	42.87	8.53	18.12

^{1}H-NMR (D_2O): δ = 1.2–2.0 (m, 6H, $CH_2CH_2CH_2$), 2.70 (s, 3H, NCH_3), 3.02 (m, 4H, NCH_2), 3.74 (t, 1H, *J* = 5.9 Hz, CH).

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