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# Convenient Synthesis of (*R*)-3-[(*tert*-Butoxycarbonyl)amino]-piperidine and (*R*)-3-[(*tert*-Butoxycarbonyl)amino]azepane

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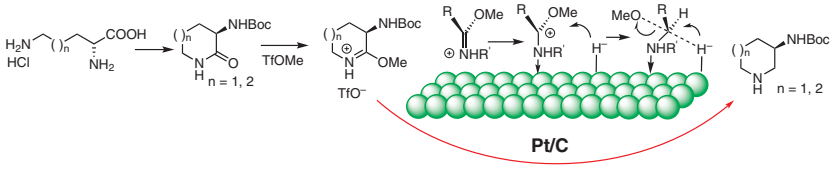


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**Abstract** (*R*)-3-[(*tert*-Butoxycarbonyl)amino]piperidine and (*R*)-3-[(*tert*-butoxycarbonyl)amino]azepane were prepared in two steps starting from D-ornithine and D-lysine, respectively. In the key step, *N*-Boc-protected 3-aminolactams were converted into imido esters by O-alkylation and then hydrogenated to amines, under mild conditions (5 bar $H_2$, room temperature) and without isolation, over a standard hydrogenation catalyst (5% Pt/C).

**Key words** amides, amines, hydrogenation, heterogeneous catalysis, chirality

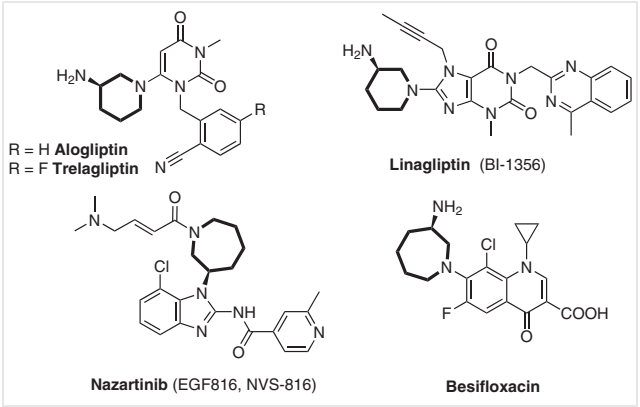


**Figure 1** (*R*)-3-Aminopiperidine and (*R*)-3-aminoazepane in antidiabetic, antibacterial, and anticancer drugs

Chiral amines are commonly found moieties in many natural and synthetic drugs and biologically active molecules. Of these, 3-amino cyclic amines have attracted intense attention over the past decades due to their wide potential as medicinal agents.[1] Optically active 3-aminopiperidine and 3-aminoazepane constitute core structures in many valuable pharmaceutical drugs such as alogliptin, trelagliptin, linagliptin, nazartinib, and besifloxacin (Figure 1). Furthermore, the number of potential drugs which possess these scaffolds grows continuously.[2–4] This is reflected in an increasing number of reports about active pharmaceutical ingredients (APIs) possessing significant potency that contain both building blocks.

The currently known methods for the synthesis of optically active 3-aminopiperidines and 3-aminoazepanes include the aluminum hydride reduction of lactams produced by cyclization of α-amino acids,[5] diamination of aldehydes,[6] enantioselective ring expansion of prolinol,[7] cyclization of chiral dimesylates,[8] and biocatalytic synthesis.[9] Although a number of protocols have been established, most suffer from the requirement for multistep syntheses, thereby leading to an explosion in production costs for these preparations. In this regard, an approach including the cyclization of natural amino acids, followed by reduction, appears to be the most convenient synthetic route for a large-scale, cost-efficient preparation. Consequently, the development of alternative synthetic approaches using hydrogen as the reducing agent is in urgent demand.

Very recently, we have demonstrated that hydrogenolysis of amide acetals and imido esters proceeds under very mild conditions applying commercially available hydrogenation catalysts.[10] Herein, we present a method for the synthesis of optically active 3-aminopiperidine and 3-aminoazepane by O-alkylation of lactams prepared from amino acids and with hydrogenation directly to amines without intermediate isolation. In searching for optimal synthetic procedures toward lactams, we had found that protection of the 3-amino group by *N*-Boc had a positive impact on the lactam isolation procedure, as well as on the success of the activation of the amide group toward hydrogenation. Furthermore, protection of the 3-amino group is of use in the

 
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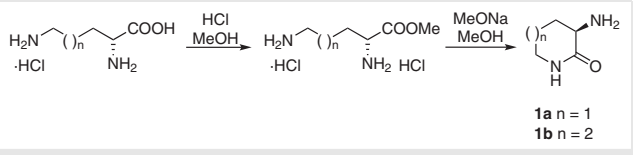
majority of published routes to APIs containing both building blocks.

To test the direct reduction of nonprotected 3-aminolactams, easy access to lactams **1a** and **1b** was first required. From several protocols for the cyclization of amino acids,[11] the base-mediated cyclization of amino esters appears to be the most convenient synthetic route for the large-scale and cost-efficient preparation of chiral lactams. 3-Aminolactams are prepared by esterification of amino acids with methanol/hydrochloric acid followed by heating the crude amino acid methyl esters under reflux with sodium methoxide in methanol for 4 hours (Scheme 1). Lactam **1a** can be isolated in fair yield after a time-consuming purification. Lactam **1b** was prepared as the free base in significantly lower yield. With the required lactams now in hand, the transformation into lactim esters was studied. Unfortunately, all attempts to produce lactim esters by O-alkylation using common alkylation agents were unsuccessful for both lactams **1a** and **1b**; therefore, an alternative synthetic approach was sought.

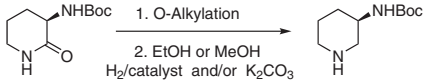



**Scheme 1** Synthesis of lactams **1a** and **1b**

Amongst the different protocols for the isolation of pure 3-aminopiperidine, Toshima and co-workers[11f] have reported an easy and practical method through protection of the amino groups with $(Boc)_2O$ and isolation of the 3-aminopiperidine as the *N*-Boc derivative. In this way, *N*-Boc-protected lactams **2a** and **2b** can be obtained on large scale as crystalline products without time-consuming purification procedures and in very good yields (Scheme 2).

In model experiments, the alkylation[10b] of lactam **2a** with common alkylating agents, such as ClCOOEt, $(Et_3O)BF_4$, and $CF_3SO_2OMe$, together with hydrogenation over Pd/C and Pt/C was studied (Table 1). The best result was achieved using $CF_3SO_2OMe$ as the alkylating agent and with hydrogenation over Pt/C. Fortunately, applying this method to **2b** succeeded in reduction to **3b** in high yield, while alkylation of **2b** with ClCOOEt failed. When the reaction was conducted on a 0.1 mol scale using significantly lower hydrogen pressure (5 bar), amines **3a** and **3b** were recovered in yields of 84% and 87% starting from **2a** and **2b**.

**Table 1** Evaluation of Alkylating Agents and Catalysts in the Reduction of 3-Aminopiperidone **2a**[a]



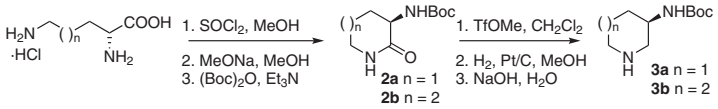

**2a** **3a**

| Run | Alkylation agent | Base | Catalyst | Yield[b] (%) |
|---|---|---|---|---|
| 1 | ClCOOEt | – | 5% Pd/C | 0 |
| 2 | ClCOOEt | $K_2CO_3$ | 5% Pd/C | 0 |
| 3 | ClCOOEt | – | 5% Pt/C | 67 |
| 4 | ClCOOEt | $K_2CO_3$ | 5% Pt/C | 76 |
| 5 | $(Et_3O)BF_4$ | – | 5% Pd/C | 0 |
| 6 | $(Et_3O)BF_4$ | $K_2CO_3$ | 5% Pd/C | 0 |
| 7 | $(Et_3O)BF_4$ | – | 5% Pt/C | 0 |
| 8 | $(Et_3O)BF_4$ | $K_2CO_3$ | 5% Pt/C | ~40 |
| 9 | $CF_3SO_2OMe$ | – | 5% Pd/C | 0 |
| 10 | $CF_3SO_2OMe$ | $K_2CO_3$ | 5% Pd/C | 0 |
| 11 | $CF_3SO_2OMe$ | – | 5% Pt/C | 99 |
| 12 | $CF_3SO_2OMe$ | $K_2CO_3$ | 5% Pt/C | 12 |

[a] Reaction conditions: alkylation:[10b] **2a** (2.5 mmol); ClCOOEt (5 mmol), 50 °C, 3 h; $(Et_3O)BF_4$ (5 mmol), $CH_2Cl_2$, 25 °C, 16 h; $CF_3SO_2OMe$ (3 mmol), $CH_2Cl_2$, 25 °C, 4 h; hydrogenation: 5% Pd/C (212 mg, 2 mol%), 5% Pt/C (390 mg, 1 mol%), $K_2CO_3$ (5 mmol), MeOH or EtOH (5 mL), $H_2$ (40 bar), 25 °C, 4 h.
[b] Yields were determined by GC.

It should be noted that amino acids and their esters are racemized at elevated temperatures under strong acidic conditions.[10c,12] Lysine and ornithine were therefore esterified to their methyl esters using thionyl chloride in methanol at low temperature to prevent a possible racemization. The enantiomeric purity of the final products **3a** (98% ee) and **3b** (96% ee) was determined by $^{19}F$ NMR and GC analysis of the diastereomeric MTPA amides (see the Supporting Information). Careful examination of the enantiomeric purity of the starting D-ornithine (98% ee) and D-lysine (96% ee) by GC analysis revealed that all steps of the synthesis (Scheme 2) proceed without racemization.

In conclusion, (*R*)-3-[(*tert*-butoxycarbonyl)amino]-piperidine (**3a**) and (*R*)-3-[(*tert*-butoxycarbonyl)amino]azepane (**3b**) have been prepared in two steps starting from D-ornithine and D-lysine, respectively. In the key step, intermediate lactams were converted into imido esters by O-alkylation using methyl triflate, followed by hydrogenation




**Scheme 2** Synthesis of amines **3a** and **3b**

over a standard hydrogenation catalyst (5% Pt/C) without isolation and under mild reaction conditions (5 bar hydrogen pressure, room temperature, 2–4 h).

All reactions were performed under moisture-free conditions. Powder catalysts from Evonik[10a] were dried at 80 °C in vacuum for 4 h. Solvents were dried over freshly activated 3 Å molecular sieves. D-Ornithine hydrochloride and D-lysine hydrochloride were purchased from VWR and TCI, and used without further purification. (*S*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride [(*S*)-(+)-MTPA-Cl, (*S*)-Mosher's acid chloride] was obtained from TCI (99%, >99% ee). Methyl triflate was prepared as described in the literature[13] and the raw material was distilled off at reduced pressure (400–200 mbar) using an efficient condenser. Pure methyl triflate (bp 98–99 °C) was obtained by redistillation at atmospheric pressure using a 25-cm Vigreux column. The enantiopurity of the starting amino acids was determined by GC using a Chirasil-Val fused-silica capillary column (25 m, 0.25 mm, 0.12 µm; Agilent) as previously described.[14] The melting points of all synthesized compounds were determined in open capillaries and are uncorrected. NMR spectra were recorded on a Bruker Avance 600 ($^1$H: 601 MHz, $^{13}$C: 151 MHz) spectrometer; chemical shifts are given in δ ppm. Optical rotations were measured on a Gyromat-HP polarimeter.

**(3*R*)-3-[(*tert*-Butoxycarbonyl)amino]-2-piperidone (2a)**

Thionyl chloride (30 mL, 0.41 mol) was added dropwise to a slurry of D-ornithine hydrochloride (33.7 g, 0.2 mol) in MeOH (200 mL) keeping the internal temperature within a range of –60 to –40 °C. The temperature of the mixture was allowed to rise to room temperature, and the mixture was further vigorously stirred for 12 h obtaining a clear solution. The reaction mixture was concentrated on a rotary evaporator at 40 °C and dissolved in MeOH (300 mL); 30% MeONa in MeOH (82 mL, 0.44 mol) was carefully added and the mixture was refluxed for 4 h. Ammonium chloride (10.7 g, 0.2 mol) was added and the mixture was allowed to stand overnight. Filtration and concentration gave a solid which was slurried in $CH_2Cl_2$ (200 mL) and $NEt_3$ (30.6 mL, 0.22 mol), cooled in an ice bath, and di-*tert*-butyl dicarbonate (46 g, 0.21 mol) then added in small portions; the reaction mixture was stirred overnight at room temperature. After concentration, the residue was treated with ethyl acetate (40 mL), then hexane (10 mL) was added forming a turbid solution which was filtered through a short pad of silica. The solvents were evaporated under reduced pressure, and the solid obtained was slurried in ice-cold hexane (80 mL) and filtered with suction, washed with ice-cold hexane, and vacuum-dried. An analytically pure sample was obtained by recrystallization (diethyl ether). The NMR spectroscopic data of **2a** match those previously described.[11f,15]

Yield: 37.3 g (87%); colorless solid; mp 102–104 °C (Lit. 101–103 °C,[15a] 112–115 °C,[15b] 100–101 °C[15c]).

$[\alpha]_D^{22}$ –3.9 (*c* 1.0, $CHCl_3$) [Lit. $[\alpha]_D^{24}$ –57.4 (*c* 1.07, $CHCl_3$);[11f] (3*S*): $[\alpha]_D$ –10.6 (*c* 1.22, MeOH),[15a] (3*S*): $[\alpha]_D$ –9.5 (*c* 1.22, MeOH)[15c]].

$^1$H NMR (601 MHz, $CDCl_3$): δ = 6.66 (s, 1 H), 5.46 (s, 1 H), 4.05–3.84 (m, 1 H), 3.25 (ddd, *J* = 7.4, 4.8, 2.4 Hz, 2 H), 2.38 (s, 1 H), 1.91–1.72 (m, 2 H), 1.54 (qd, *J* = 11.9, 4.7 Hz, 1 H), 1.38 (s, 9 H).

$^{13}$C NMR (151 MHz, $CDCl_3$): δ = 172.04, 155.89, 79.50, 51.37, 41.62, 28.35, 27.81, 21.02.

MS (EI): *m*/*z* (%) = 159 (42), 158 (41), 141 (53), 113 (25), 69 (48), 57 (100).

**(3*R*)-3-[(*tert*-Butoxycarbonyl)amino]hexahydro-2*H*-azepin-2-one (2b)**

The title compound was prepared using the same procedure as for **2a**, from D-lysine hydrochloride (36.5 g, 0.2 mol). The crude product was dissolved in warm ethyl acetate (200 mL) and formed a turbid solution which was filtered through a short pad of silica. The solvents were removed under reduced pressure and the solid obtained vacuum-dried. An analytically pure sample was obtained by recrystallization (diethyl ether). The NMR spectroscopic data of **2b** match those previously described.[15d,16a]

Yield: 34.7 g (76%); colorless solid; mp 110–111 °C (Lit. 105 °C,[16b] 150–151 °C[16c]).

$[\alpha]_D^{22}$ –31.2 (*c* 1.0, $CHCl_3$) [Lit. $[\alpha]_D^{25}$ –39.2 (*c* 1.2, $CHCl_3$);[16c] (3*S*): $[\alpha]_D^{21}$ +21.1 (*c* 0.59, $CHCl_3$)[16a]].

$^1$H NMR (601 MHz, $CDCl_3$): δ = 6.95 (br s, 1 H), 5.91 (br s, 1 H), 4.28 (d, *J* = 11.1 Hz, 1 H), 3.32–3.16 (m, 2 H), 2.14–1.90 (m, 2 H), 1.87–1.68 (m, 2 H), 1.57–1.28 (m, 11 H).

$^{13}$C NMR (151 MHz, $CDCl_3$): δ = 176.00, 155.17, 79.32, 53.22, 42.05, 32.21, 28.90, 28.38, 28.10.

MS (EI): *m*/*z* (%) = 172 (20), 155 (53), 143 (54), 111 (23), 83 (59), 57 (100).

**Lactam Reduction; General Procedure**

Methyl triflate (13.6 mL, 0.12 mol) was added dropwise to a solution of lactam (0.1 mol) in anhyd $CH_2Cl_2$ (100 mL) cooled in an ice bath, then allowed to warm to ambient temperature, stirred for 4 h, and then concentrated under vacuum. The residue was dissolved in anhyd MeOH (60 mL) and transferred via capillary tubing into a 100-mL autoclave containing dry 5% Pt/C (3.9 g, 1 mol%) under argon. The autoclave was pressurized with hydrogen to 5 bar and stirred at constant pressure until no hydrogen consumption (2–4 h) was observed. The autoclave was depressurized and the reaction mixture filtered through Celite. The solids were washed with MeOH and the combined filtrates concentrated on a rotary evaporator. The residue was treated with chilled 2 M aq NaOH solution (50 mL) and extracted with diethyl ether (5 × 25 mL). The combined organic layers were dried over $K_2CO_3$ and concentrated on a rotary evaporator. The solid product was slurried in hexane, stored in a refrigerator to complete crystallization, suction-filtered, washed with ice-cold hexane, and vacuum-dried.

**(3*R*)-3-[(*tert*-Butoxycarbonyl)amino]piperidine (3a)**

Prepared according to the general procedure, from **2a** (21.4 g, 0.1 mol). An analytically pure sample was obtained by recrystallization (diethyl ether/pentane). The NMR spectroscopic data of **3a** match those previously described.[8]

Yield: 16.8 g (84%); colorless solid; mp 104–105 °C.

$[\alpha]_D^{22}$ +10.9 (*c* 1.0, $CHCl_3$) [Lit.[8] (3*S*): $[\alpha]_D^{25}$ –13.3 (*c* 1.0, EtOH)].

$^1$H NMR (601 MHz, $CDCl_3$): δ = 4.73 (br s, 1 H), 3.51 (br s, 1 H), 2.99 (dd, *J* = 11.8, 3.1 Hz, 1 H), 2.81–2.71 (m, 1 H), 2.59 (t, *J* = 22.9 Hz, 1 H), 2.47 (s, 1 H), 2.03 (s, 1 H), 1.81–1.71 (m, 1 H), 1.67–1.56 (m, 1 H), 1.46–1.28 (m, 2 H), 1.37 (s, 9 H).

$^{13}$C NMR (151 MHz, $CDCl_3$): δ = 155.27, 79.10, 51.79 ($CH_2$), 47.02 (CH), 46.28 ($CH_2$), 30.77 ($CH_2$), 28.42 (Me), 24.24 ($CH_2$).

MS (EI): *m*/*z* (%) = 127 (10), 83 (100), 70 (20), 57 (44).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{20}N_2O_2$: 201.1603; found: 201.1606.

**(3*R*)-3-[(*tert*-Butoxycarbonyl)amino]azepane (3b)**

Prepared according to the general procedure, from **2b** (22.8 g, 0.1 mol). An analytically pure sample was obtained by vacuum sublimation.

Yield: 18.6 g (87%); colorless solid; mp 96–98 °C.

$[\alpha]_D^{22}$ +9.2 (*c* 1.0, $CHCl_3$) [Lit.[8] (3*S*): $[\alpha]_D^{25}$ –12.1 (*c* 1.0, EtOH)].

$^1$H NMR (601 MHz, $CDCl_3$): δ = 4.98 (br s, 1 H), 3.65 (br s, 1 H), 2.92–2.80 (m, 2 H), 2.78–2.67 (m, 2 H), 1.79–1.68 (m, 2 H), 1.65–1.50 (m, 4 H), 1.50–1.35 (m, 1 H), 1.34 (s, 9 H).

$^{13}$C NMR (151 MHz, $CDCl_3$): δ = 155.25, 78.79, 53.56 ($CH_2$), 50.87 (CH), 49.34 ($CH_2$), 34.31 ($CH_2$), 30.31 ($CH_2$), 28.44 (Me), 22.07 ($CH_2$).

MS (EI): *m*/*z* (%) = 157 (11), 141 (14), 97 (100), 82 (32), 57 (71).

HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{22}N_2O_2$: 215.1759; found: 215.1756.

## Conflict of Interest

The authors declare no conflict of interest.

## Acknowledgment

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## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1526-7657 and contains full experimental details for **1a** and **1b**, determination of the enantiomeric excess of **3a** and **3b**, and $^1$H and $^{13}$C NMR spectra of compounds.

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