Ring-opening Addition Reactions of 1-*tert*-Butoxycarbonyl-3,4-epoxypiperidine with Amine Nucleophiles

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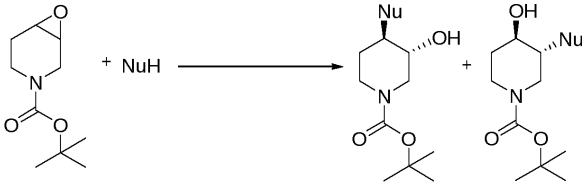
Ring-opening addition reactions of 1-*tert*-butoxycarbonyl-3,4-epoxypiperidine leading to the formation of the corresponding regioisomeric *trans*-β-aminoalcohols were carried out with three different types of amine nucleophiles under different reaction conditions with a view to study the reactivity and regioselectivity.

Key words: Epoxypiperidine, *trans*-β-Aminoalcohols, 4-Methoxyphenylpiperazine, 3-Methoxyaniline, Microwave Irradiation, Regioselectivity

Introduction

β-Amino alcohols are important organic compounds of considerable use in the synthesis of a vast range of biologically active natural and synthetic products, unnatural amino acids, and chiral auxiliaries for asymmetric synthesis [1]. One of the most practical and widely used routes for the synthesis of these compounds is the ring-opening addition reaction of 1,2-epoxides at elevated temperature with excess of ammonia or amines, and their synthetic equivalents [2]. Several useful modifications of the classical procedure using promoters or catalysts in different organic solvents [3], microwave irradiation [4] and solvent-free conditions [5] have been reported recently. The piperidine substructure is among the most important pharmacophores found in numerous natural products and biologically relevant targets under preclinical and clinical tests [6]. Substituted piperidines are found both in natural and synthetic products that exhibit antibiotic [7], antipsychotic [8], analgesic [9], and β-secretase inhibitory [10] activities. In continuation of our studies of piperidine derivatives of pharmacological interest, we became interested in the regioselective behavior of ring-opening addition reactions of amine nucleophiles *viz.* methylamine, 3-methoxyaniline and 1-(4-methoxyphenyl)-piperazine, with 1-*tert*-butoxycarbonyl-3,4-epoxypiperidine at elevated temperature and also under microwave condition, with or without $LiClO_4$ and $Zr(OBu)_4$ as catalysts. In the present investigation, we wished to verify whether the regioselectivity could be appreciably affected depending on the amine and/or the catalyst in such a way as to direct the regiochemistry of these reactions.



1 **2** **3** **4**

NuH = CH_3-NH_2, 1-(4-methoxyphenyl)-piperazine, 3-methoxyaniline

Scheme 1.

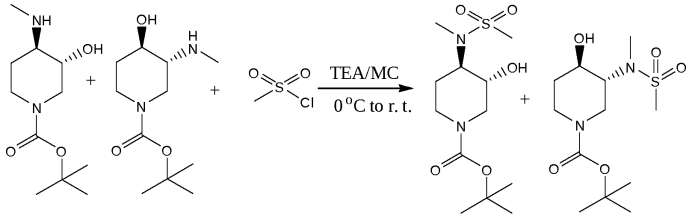
Results and Discussion

Treatment of 1-*tert*-butoxycarbonyl-3,4-epoxypiperidine (**1**) with amines **2** resulted in the formation of the corresponding *trans*-β-amino alcohols (**3**) and (**4**) as a mixture of regioisomers (Scheme 1). Initially, the ring-opening addition reaction of epoxypiperidine **1** was investigated with amine nucleophiles in the classical way without any catalyst in ethanol. Compound **1** was heated at 90 °C with methylamine hydrochloride (1.1 equivalents) and DBU (1.1 equivalents) in a sealed tube for 12 h to yield a mixture of regioisomers **3a** and **4a**. These two regioisomers could not be separated by column chromatography. However, after

Nucleophile	Reaction conditions	Yield (%)[a]	Ratio (3 : 4)[a]
CH_3-NH_2	DBU, EtOH/90 °C, 12 h	57	65[b] : 35[b]
1-(4-methoxy-phenyl)piperazine	DBU, EtOH/90 °C, 50 h	77	55[c] : 45[c]
3-methoxyaniline	EtOH/90 °C, 5 d	85	53 : 47

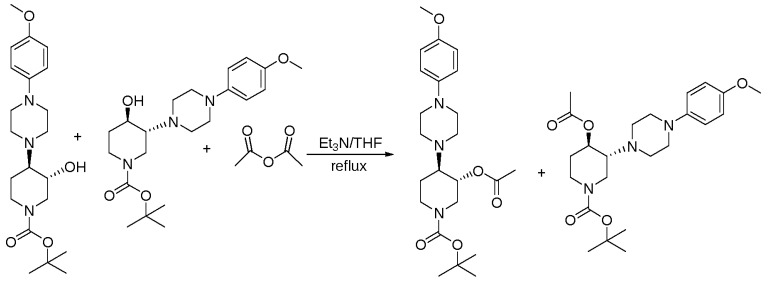
Table 1. Ratio of regioisomers for the ring opening in EtOH.

[a] Isolated yields; [b] as methane sulfonamide derivative; [c] as acetate derivative.



3a **4a** **5a** **6a**

Scheme 2.



3b **4b** **5b** **6b**

Scheme 3.

derivatization with methane sulfonyl chloride in the presence of triethylamine to give the methane sulfonamides, we found that the two isomers **5a** and **6a** could be separated by flash column chromatography (Scheme 2). Both regioisomers were obtained in a 65 : 35 ratio. Since the epoxide ring opening would result in a 3,4-*trans* relationship between the resulting hydroxyl group and the nucleophile, and the attack of the amine nucleophile on **1** would occur preferably at the less sterically hindered 4-position, compound **3a** was formed as expected as the major regioisomer. The ^{1}H NMR spectra of the separated regioisomers **5a** and **6a** were recorded and analyzed in detail. The splitting patterns and coupling constants of protons confirmed the *trans* configuration at C-3/4 in these regioisomers.

When the same reaction was carried out with 1-(4-methoxyphenyl)-piperazine dihydrochloride (1.1 equivalents) and DBU (2.2 equivalents) in ethanol for 50 h, we obtained 77 % of the mixture of regioisomer **3b** and **4b**, which were separated by derivatization with acetic anhydride as their acetates **5b** and **6b** (Scheme 3). The regioisomeric ratio in this case was found to be 55 : 45. Finally, the acetates **5b** and **6b** were subjected to alkaline hydrolysis to obtain the individual regioisomers **3b** and **4b** (Scheme 4). When **1** was subjected to the ring opening reaction with 3-methoxyaniline under the same conditions, regioisomers **3c** and **4c** were obtained in a 53 : 47 ratio, but the reaction took 5 d for completion. In this case, the regioisomers could be separated by flash column chromatography (Table 1).

The ring-opening addition reactions of **1** with the same amines in the presence of lithium perchlorate (1.1 equivalents) in acetonitrile containing zirconium tetrabutoxide (1.1 equivalents) in THF were also examined. The results obtained from this study are reported in Table 2. As can be seen from the Table, the catalysts not only reduce the reaction time drastically but also modulate the regiochemistry of the reaction markedly. The regioselectivity was reduced in the presence of catalysts with methylamine. Though the regioselectivity has remained more or less the same for 1-(4-methoxyphenyl)-piperazine in the presence of lithium perchlorate, it increased in the case of the zirconium tetrabutoxide-catalyzed reaction. An unusual regioselectivity was observed for 3-methoxyaniline in the presence of these catalysts. Regioselectivity was markedly increased, and the regioisomeric ratio was found to be reversed for the lithium perchlorate-catalyzed reaction.

The above mentioned reactions require rather long reaction time to reach complete conversion even in

Table 2. Ratio of regioisomers for the ring opening in the presence of $LiClO_4$ and $Zr(OBu)_4$.

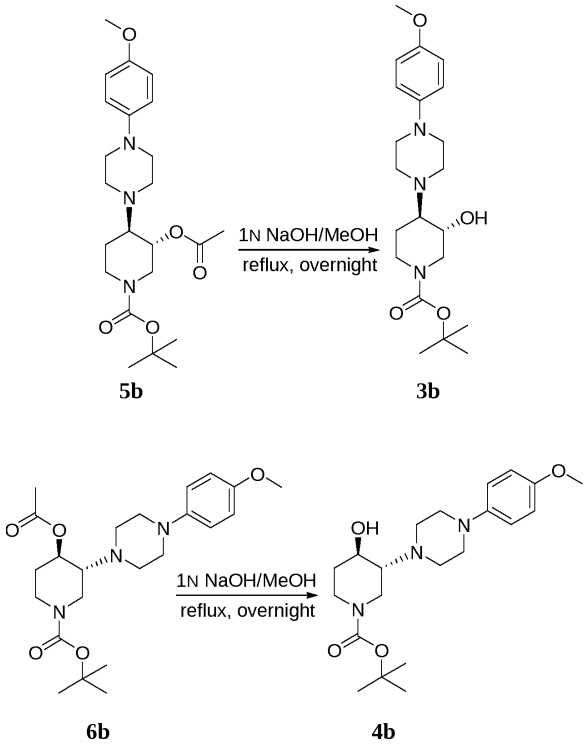
Nucleophile	Reaction conditions	Yield (%)[a]	Ratio (3 : 4)[a]
CH_3-NH_2	$LiClO_4$, DBU, CH_3CN/85 °C, 8 h	67	58[b] : 42[b]
CH_3-NH_2	$Zr(OBu)_4$, DBU, THF/80 °C, 8 h	68	61[b] : 39[b]
1-(4-methoxy-phenyl)piperazine	$LiClO_4$, DBU, CH_3CN/85 °C, 14 h	81	56[c] : 44[c]
1-(4-methoxy-phenyl)piperazine	$Zr(OBu)_4$, DBU, THF/80 °C, 25 h	67	63[c] : 37[c]
3-methoxyaniline	$LiClO_4$, CH_3CN/85 °C, 3 d	75	33 : 67
3-methoxyaniline	$Zr(OBu)_4$, THF/80 °C, 3 d	75	66 : 34

[a] Isolated yields; [b] as methane sulfonamide derivative; [c] as acetate derivative.

Table 3. Ratio of regioisomers for the ring opening in the presence of $LiClO_4$ and $Zr(OBu)_4$ under microwave condition.

Nucleophile	Reaction conditions	Yield (%)[a]	Ratio (3 : 4)[a]
CH_3-NH_2	$LiClO_4$, DBU, CH_3CN/100 °C, 35 min	68	59[b] : 41[b]
CH_3-NH_2	$Zr(OBu)_4$, DBU, THF/110 °C, 30 min	68	60[b] : 40[b]
1-(4-methoxy-phenyl)piperazine	$LiClO_4$, DBU, CH_3CN/130 °C, 35 min	76	55[c] : 45[c]
1-(4-methoxy-phenyl)piperazine	$Zr(OBu)_4$, DBU, THF/ 50 °C, 30 min	63	62[c] : 38[c]
3-methoxyaniline	$LiClO_4$,CH_3CN/130 °C, 35 min	58	38 : 62
3-methoxyaniline	$Zr(OBu)_4$, THF/150 °C, 30 min	77	74 : 26

[a] Isolated yields; [b] as methane sulfonamide derivative; [c] as acetate derivative.



Scheme 4.

the presence of catalysts. Therefore, any measure accelerating the process would be desirable for a high throughput conversion. Numerous reports have demonstrated that microwave irradiation can be used to speed up organic reactions in a variety of chemical transformations. We utilized microwave irradiation in the presence of lithium perchlorate and zirconium tetrabutoxide to achieve the above transformations with in a few minutes. Although the regioselectivity of the reaction of methylamine and 1-(4-methoxyphenyl)-piperazine was found to be quite similar, it was increased for 3-methoxyaniline (Table 3).

In conclusion, a variation in reactivity and regioselectivity of the ring opening addition reaction of epoxypiperidine with methylamine, 1-(4-methoxyphenyl)-piperazine and 3-methoxyaniline has been demonstrated under classical and microwave conditions in the presence of catalysts. An unusual regioselectivity was observed for 3-methoxyaniline in the presence of lithium perchlorate. Microwave irradiation was proven to be highly effective for these transformations in shorter reaction times.

Experimental Section

All melting points were determined using a Thomas Hoover-Unimelt capillary melting point apparatus and are uncorrected. Amines were obtained from Sigma-Aldrich/ Alfa Aesar Chemical Co. and used as such. 1-*tert*-Butoxycarbonyl-3,4-epoxypiperidine was synthesized by the reported procedure [10]. ^1H NMR spectra were recorded on a Varian 300 MHz NMR spectrometer in $CDCl_3$. TMS was used as an internal standard.

*General method for the synthesis of 1-tert-butoxycarbonyl-trans-4-amino-3-hydroxy-piperidine (**3**) and 1-tert-butoxy-trans-3-amino-4-hydroxy-piperidine (**4**)*

Method A

A mixture of 1-*tert*-butoxycarbonyl-3,4-epoxypiperidine (**1**, 1 mmol), and an amine [methylamine hydrochloride

(**2a**, 1.1 mmol); DBU (1.1 mmol) or 1-(4-methoxyphenyl)-piperazine dihydrochloride (**2b**, 1.1 mmol); DBU (2.2 mmol) or 3-methoxyaniline (**2c**, 1.1 mmol)] was heated to reflux in absolute ethanol at 90 °C in a sealed tube. After completion of the reaction, the mixture was diluted with ethyl acetate and washed with water. The organic layer was dried (Na_2SO_4), and concentrated *in vacuo*. The remaining residue was purified by flash column chromatography to yield the desired product as a mixture of two regioisomers except in the case of 3-methoxyaniline where the two regioisomers were obtained separately.

Method B

A mixture of 1-*tert*-butoxycarbonyl-3,4-epoxypiperidine (**1**, 1 mmol), lithium perchlorate (1.1 mmol), and an amine [methylamine hydrochloride (**2a**, 1.1 mmol); DBU (1.1 mmol) or 1-(4-methoxyphenyl)-piperazine dihydrochloride (**2b**, 1.1 mmol); DBU (2.2 mmol) or 3-methoxyaniline (**2c**, 1.1 mmol)] was heated to reflux in acetonitrile at 85 °C in a sealed tube. After completion of the reaction, the mixture was diluted with ethyl acetate and washed with water. The organic layer was dried (Na_2SO_4), concentrated *in vacuo*, and the remaining residue was subjected to flash column chromatography to yield the desired product as a mixture two regioisomers except in the case of 3-methoxyaniline where the two regioisomers were obtained separately.

Method C

A mixture of 1-*tert*-butoxycarbonyl-3,4-epoxypiperidine (**1**, 1 mmol), zirconium tetrabutoxide (1.1 mmol), and an amine [methylamine hydrochloride (**2a**, 1.1 mmol) ; DBU (1.1 mmol) or 1-(4-methoxyphenyl)-piperazine dihydrochloride (**2b**, 1.1 mmol); DBU (2.2 mmol) or 3-methoxyaniline (**2c**, 1.1 mmol)] was heated to reflux in THF at 80 °C in a sealed tube. After completion of the reaction, the mixture was diluted with ethyl acetate and washed with water. The organic layer was dried (Na_2SO_4), and concentrated *in vacuo*. The flash column chromatography of the remaining residue afforded the desired product as a mixture of two regioisomers except in the case of 3-methoxyaniline where the two regioisomers were obtained separately.

Method D

A mixture of 1-*tert*-butoxycarbonyl-3,4-epoxypiperidine (**1**, 1 mmol), lithium perchlorate (1.1 mmol), and an amine [methylamine hydrochloride (**2a**, 1.1 mmol); DBU (1.1 mmol) or 1-(4-methoxyphenyl)-piperazine dihydrochloride (**2b**, 1.1 mmol); DBU (2.2 mmol) or 3-methoxyaniline (**2c**, 1.1 mmol)] in acetonitrile was taken in a Biotage vial containing a magnetic stirring bar. The vial was sealed, and the mixture was heated in the Biotage initiator Synthesizer to reflux in THF at 80 °C. After completion of the reaction, the mixture was diluted with ethyl acetate and washed with water. The organic layer was dried (Na_2SO_4), and concentrated *in vacuo*. The remaining residue was purified by flash column chromatography to yield the desired product as a mixture of two regioisomers except in the case of 3-methoxyaniline where the two regioisomers were obtained separately.

Method E

A mixture of 1-*tert*-butoxycarbonyl-3,4-epoxypiperidine (**1**, 1 mmol), zirconium tetrabutoxide (1.1 mmol), and an amine [methylamine hydrochloride (**2a**, 1.1 mmol); DBU (1.1 mmol) or 1-(4-methoxyphenyl)-piperazine dihydrochloride (**2b**, 1.1 mmol); DBU (2.2 mmol) or 3-methoxyaniline (**2c**, 1.1 mmol)] in acetonitrile was taken in a Biotage vial containing a magnetic stirring bar. The vial was sealed, and the resulting mixture was heated in the Biotage initiator Synthesizer to reflux in THF at 80 °C. After completion of the reaction, the mixture was diluted with ethyl acetate and washed with water. The organic layer was dried (Na_2SO_4), and concentrated *in vacuo*. The flash column chromatography of the remaining residue afforded the desired product as a mixture of two regioisomers except in the case of 3-methoxyaniline where the two regioisomers were obtained separately.

*1-tert-Butoxycarbonyl-trans-3-hydroxy-4-methylamino-piperidine (**3a**) and 1-tert-butoxy-carbonyl-trans-4-hydroxy-3-methylamino-piperidine (**4a**)*

Colorless solid. – ^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 9H), 1.46 (s, 9H), 1.90 – 2.06 (m, 3H), 2.22 – 2.35 (m, 3H), 2.45 (s, 3H), 2.48 (s, 3H), 2.51 – 2.64 (m, 2H), 2.66 – 2.84 (m, 6H), 3.25 – 3.40 (m, 2H), 4.00 – 4.10 (m, 2H), 4.20 – 4.30 (m, 2H).

*1-tert-Butoxycarbonyl-trans-3-hydroxy-4-[4-(4-methoxy-phenyl)-piperazin-1-yl]-piperidine (**3b**) and 1-tert-butoxy-carbonyl-trans-4-hydroxy-3-[4-(4-methoxy-phenyl)-piperazin-1-yl]-piperidine (**4b**)*

Colorless solid. – ^{1}H NMR($CDCl_3$): δ = 1.47 (s, 18H), 1.62 – 1.70 (m, 1H), 2.00 – 2.15 (m, 1H), 2.30 – 2.45 (m, 2H), 2.50 – 2.80 (m, 8H), 2.85 – 2.93 (m, 1H), 2.95 – 3.15 (m, 12H), 3.35 – 3.50 (m, 1H), 3.55 – 3.70 (m, 2H), 3.77 (s, 6H), 4.05 – 4.18 (m, 1H), 4.20 – 4.34 (m, 2H), 4.35 – 4.55 (m, 1H), 6.82 – 7.27 (m, 8H).

*1-tert-Butoxycarbonyl-trans-3-hydroxy-4-(3-methoxy-phenylamino)-piperidine (**3c**)*

Colorless solid, m. p. 55 – 56 °C. – ^{1}H NMR ($CDCl_3$): δ = 1.46 (s, 9H), 1.96 – 2.04 (m, 1H), 2.50 – 2.65 (m, 1H), 2.85 – 2.95 (m, 1H), 3.15 – 3.25 (m, 1H), 3.50 – 3.60 (m, 2H), 3.75 (s, 3H), 3.90 – 4.00 (m, 1H), 4.20 – 4.30 (m, 1H), 6.26 (s, 1H), 6.31 (d, 2H, J = 8.0 Hz), 7.08 (t, 1H, J = 8.0 Hz).

*1-tert-Butoxycarbonyl-trans-4-hydroxy-3-(3-methoxy-phenylamino)-piperidine (**4c**)*

Colorless solid, m. p. 47 – 48 °C. – ^{1}H NMR($CDCl_3$): δ = 1.46 (s, 9H), 2.05 – 2.10 (m, 1H), 2.65 – 2.85 (m, 2H), 3.15 – 3.25 (m, 2H), 3.35 – 3.45 (m, 1H), 3.75 (s, 3H), 3.99 (m, 1H), 4.20 – 4.30 (m, 1H), 6.24 (s, 1H), 6.25 – 6.35 (m, 2H), 7.06 (t, 1H, J = 8.0 Hz).

*General procedure for the synthesis of the methane sulfonamides **5a** and **6a***

The mixture of **2a** and **3a** (1 mmol) and triethyl amine (153 μL, 1.1 mmol) was dissolved in methylene chloride (3 mL) and cooled to 0 °C. A solution of methane sulfonyl chloride (0.126 g, 1.1 mmol) in methylene chloride (1 mL) was added dropwise with stirring to the cold solution. The reaction mixture was slowly warmed to r. t., and stirring was continued. After completion of the reaction, the mixture was diluted with ethyl acetate (15 mL), washed with saturated $NaHCO_3$ (2 × 10 mL), water (10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography of the resulting crude residue (silica gel) using EtOAc-Hex (1 : 1.5) as eluent afforded **5a** and **6a**.

*1-tert-Butoxycarbonyl-trans-3-hydroxy-4-(N-methane-sulfonyl-N-methylamino)-piperidine (**5a**)*

Colorless solid, m. p. 119 – 120 °C. – ^{1}H NMR ($CDCl_3$): δ = 1.44 (s, 9H), 1.64 – 1.72 (m, 5-H^1, 1H), 1.76 – 1.85 (dq, 5-H^2, 1H, J = 13.5, 3.3 Hz), 2.49 – 2.64 (ddd, 4-H, 1H, J = 11.1, 9.6, 3.9 Hz), 2.70 – 2.79 (m, 6-H^1, 1H), 2.85 (s, 3H), 2.95 (s, 3H), 2.97 (brs, 1H), 3.50 – 3.61 (d, 2-H^1, 1H, J = 5.7 Hz), 3.63 – 3.75 (tt, 6-H^2, 1H, J = 9.6, 5.1 Hz), 4.00 – 4.25 (m, 3-H, 1H), 4.30 – 4.44 (d, 2-H^2, 1H, J = 13.5 Hz).

*1-tert-Butoxycarbonyl-trans-4-hydroxy-3-(N-methane-sulfonyl-N-methylamino)-piperidine (**6a**)*

Colorless solid, m. p. 141 – 142 °C. – ^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 9H), 1.50 – 1.63 (m, 5-H^1, 1H), 2.01 – 2.14 (dq, 5-H^2, 1H, J = 13.2, 3.3 Hz), 2.59 – 2.68 (m, 3-H, 1H), 2.70 – 2.86 (m, 6-H^1, 1H), 2.89 (s, 3H), 2.96 (s, 3H), 2.98 (brs, 1H), 3.47 – 3.60 (d, 2-H^1, 1H, J = 5.4 Hz), 3.67 – 3.79 (tt, 6-H^2, 1H, J = 9.6, 5.1 Hz), 4.04 – 4.14 (ddd, 4-H, 1H, J = 11.1, 9.6, 3.9 Hz), 4.14 – 4.25 (d, 2-H^2, 1H, J = 13.5 Hz).

*General procedure for the synthesis of acetates **5b** and **6b***

The isomeric mixture of **3b** and **4b** (1 mmol), triethyl-amine (418 μL, 3 mmol) and acetic anhydride (309 μL, 2.09 mmol) in THF (3 mL) was heated to reflux at 80 °C overnight. After completion of the reaction, the mixture was diluted with ethyl acetate (15 mL), washed with saturated $NaHCO_3$ (2 × 10 mL), water (10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The products **5b** and **6b** were separated by flash column chromatography (silica gel, EtOAc-Hex = 1 : 4) from the resulting crude residue.

*1-tert-Butoxycarbonyl-trans-3-acetoxy-4-[4-(4-methoxy-phenyl)-piperazin-1-yl]-piperidine (**5b**)*

Colorless solid, m. p. 115 – 116 °C. – ^{1}H NMR ($CDCl_3$): δ = 1.47 (s, 9H), 1.52 – 1.64 (m, 1H), 1.97 – 2.02 (m, 1H), 2.07 (s, 3H), 2.46 – 2.58 (m, 1H), 2.66 – 2.76 (m, 2H), 2.82 – 2.96 (m, 5H), 2.98 – 3.08 (m, 3H), 3.76 (s, 3H), 3.85 – 4.00 (m, 1H), 4.04 – 4.11 (m, 1H), 5.02 – 5.10 (m, 1H), 6.81 – 6.90 (m, 4H).

*1-tert-Butoxycarbonyl-trans-4-acetoxy-3-[4-(4-methoxy-phenyl)-piperazin-1-yl]-piperidine (**6b**)*

Colorless solid, m. p. 96 – 97 °C. – ^{1}H NMR($CDCl_3$): δ = 1.46 (s, 9H), 1.52 – 1.65 (m, 1H), 1.80 – 1.90 (m, 1H), 2.06 (s, 3H), 2.50 – 2.66 (m, 3H), 2.74 – 2.90 (m, 4H), 2.96 – 3.08 (m, 4H), 3.76 (s, 3H), 4.00 – 4.20 (m, 2H), 4.85 – 4.95 (m, 1H), 6.80 – 6.91 (m, 4H).

*General procedure for the hydrolysis of acetates **5b** and **6b***

To the solution of acetates **5b/6b** (1 mmol) in MeOH (5 mL), 1N NaOH solution (5 mL, 4 mmol) was added, and the resulting solution was heated to reflux. After completion of the reaction, the mixture was diluted with ethyl acetate (15 mL) and washed with water (2 × 15 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The resulting crude product (**3b/4b**) was purified by flash column chromatography (silica gel, EtOAc-Hex = 1 : 2).

*1-tert-Butoxy-trans-3-hydroxy-4-(1-[4-methoxyphenyl]-piperazino)-piperidine (**3b**)*

Colorless solid, yield 98 %, m. p. 145 – 146 °C. – ^{1}H NMR ($CDCl_3$): δ = 1.46 (s, 9H), 2.04 – 2.10 (m, 1H), 2.30 – 2.40 (m, 1H), 2.55 – 2.75 (m, 4H), 2.95 – 3.15 (m, 6H), 3.56 – 3.66 (m, 2H), 3.76 (s, 3H), 4.04 – 4.20 (m, 1H), 4.22 – 4.36 (m, 1H), 6.81 – 6.92 (m, 4H).

*1-tert-Butoxy-trans-4-hydroxy-3-(1-[4-methoxyphenyl]-piperazino)-piperidine (**4b**)*

Colorless solid, yield 91 %, m. p. 164 – 165 °C. – ^{1}H NMR ($CDCl_3$): δ = 1.46 (s, 9H), 1.75 – 1.85 (m, 1H), 2.33 – 2.42 (m, 1H), 2.50 – 2.70 (m, 5H), 2.85 – 2.95 (m, 2H), 3.03 – 3.16 (m, 4H), 3.40 – 3.48 (m, 1H), 3.76 (s, 3H), 4.16 – 4.34 (m, 1H), 4.38 – 4.50 (m, 1H), 6.81 – 6.93 (m, 4H).

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