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# A modified palladium catalysed reductive amination procedure

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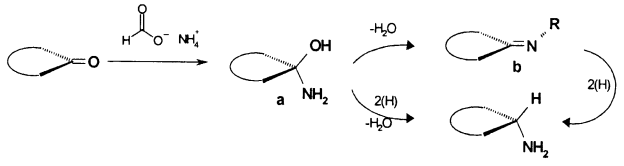
**Abstract**—New, extended applications of a modified palladium catalysed reductive amination procedure are described; a mechanistic hypothesis alternative to the common imine pathway is proposed. This versatile method advances the usual reductive amination processes in terms of yield and shows high stereoselectivity whether applied to constrained carbonyl compounds. 

## 1. Introduction

Reductive amination[1] is one of the most frequently used procedures for the preparation of alkylamines. In a recent paper[2] we described an improved procedure for the synthesis of 3-*endo*-tropanamine by a palladium catalysed reduction of tropanone in an aqueous/alcoholic medium; the proposed method employs the only ammonium formate salt both as hydrogen and nitrogen source. As far as we know, the use of formate salts coupled with palladium catalyst[3] has never been applied to the reductive amination reaction.

Compared with other known procedures[4,5] for transformation of ketones into primary amines, the described method shows several advantages in terms of feasibility and yield; the application to 3-*endo*-tropanamine synthesis allows to obtain the product with absolute stereoselectivity.

The aim of this paper is the description of new, extended synthetic applications of our procedure; starting from our experimental results a mechanistic alternative to imine reduction is hypothesised.

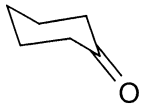
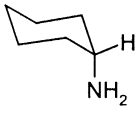
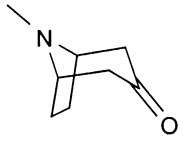
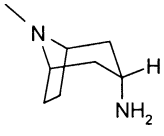
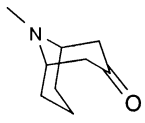
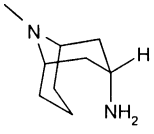
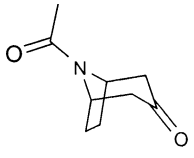
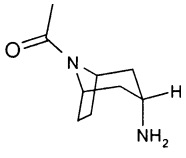
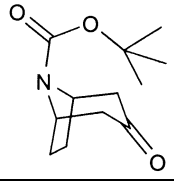
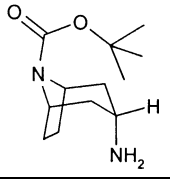



**Scheme 1.**

## 2. Results and discussion

In our previous work a direct transfer of the formate hydrogen to the hemiaminal intermediate **a** (Scheme 1) was suggested. The mechanistic hypothesis via hemiaminal was greatly preferred due to the instability of the alternative

**Table 1.** Ammonium formate reductive amination of ketones

| | Reagent | Product[a] | Yield (%) |
|---|---|---|---|
| (a) |  |  | 65 |
| (b) |  |  | 83 |
| (c) |  |  | 0 |
| (d) |  |  | 70 |
| (e) |  |  | 0 |

[a] Expected reductive amination product.

*Keywords*: reductive amination; palladium catalysis; tropanone; 3-*endo*-tropanamine; hemiaminal; ammonium formate.

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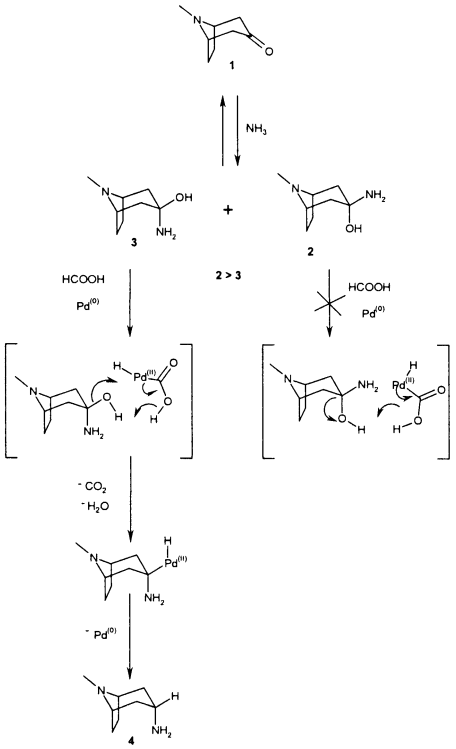


**Scheme 2.**

imine species **b** in the hydroalcoholic medium. Moreover, basing on our previous experiences and on the literature data,[6] the direct reduction of an imine intermediate could hardly justify the observed absolute stereoselectivity in tropanone reduction.

The unusual stereoselectivity and the failed attempts to substitute formate with different hydrogen sources suggested a concerted hydrogen transfer step in the reaction pathway.[2]

Further results obtained studying the reactivity of bridged aminopiperidine derivatives (Table 1) support the hypothesis of a double steric effect influencing the reaction course in two different steps, as detailed in Scheme 2.

In the first step the hemiaminal is formed by direct attack of the amine on the carbonyl group according to the common pathway which also leads to the imine intermediate.

Looking at the tropanone reaction (Scheme 2), the attach of ammonia is favoured on the less hindered, equatorial face of the tropanic ring.[7] Hence, the major formation of the *exo*-hemiaminal **2** is plausible in the first step but, for the same reason, the hindrance of the axial position should greatly disfavour, in the second step, the Pd catalysed hydrogen transfer, avoiding therefore the *exo*-amine formation. In our view, the favoured reduction of the less hindered *endo*-hemiaminal **3**, drives the equilibrium towards 3-*endo*-tropanamine **4** with absolute stereoselectivity The concerted hydrogen transfer is probably in charge of the intermediate product of the well known $Pd^{(0)}$ oxidative insertion into formate.[8]

This hypothesis is confirmed by the opposite results obtained with pseudopelletierine (9-methyl-9-azabicyclo-[3.3.1]nonan-3-one) (entry c, Table 1). The higher degree of hindrance, due to the additional methylene group in the ring, makes the axial face completely unapproachable;[9] in this way the formation of the reactive *endo*-hemiaminal is forbidden. The formation of only the *exo*-hemiaminal, due to the steric hindrance during the hydrogenolytic step, is in agreement with observed lack of reactivity.

Results obtained starting from *N*-acylated tropanic rings (entries d and e, Table 1) further support the hypothesis of a relevant steric effect in the second step. The reductive amination of the *N*-acetyl derivative proceeds with good reactivity and stereoselectivity; the additional steric hindrance on the equatorial face makes the *N*-Boc tropinone absolutely unreactive because, according to the proposed mechanism, the concerted hydrogen transfer is not allowed.

Further evidence which supports the 'hemiaminal pathway' is the behaviour of secondary amines under our experimental conditions. Hydrogenolysis of the aminal intermediate is the commonly accepted pathway in the reductive amination of secondary amines,[10] due to the fact that conversion to the unstable iminium species is unlikely. The good reactivity of secondary amines (Table 2) in our conditions, strongly disfavouring the iminium formation because of the basic aqueous medium, is in agreement with the hypothesised hydrogenolytic pathway.

The results listed in Table 2 have been obtained using ammonium formate salts prepared 'in situ' from the corresponding primary or secondary amines; the process shows general applicability for the preparation of several alkylamines.

Stereoselectivity is absolutely maintained in the tropanone ring functionalization (entry e, Table 2). The observed unreactivity of diethylamine (entry f, Table 2) was expected on the basis of the mechanistic hypothesis due to the unlikely approach of the bulky secondary amines from the equatorial face of tropinone.

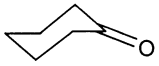
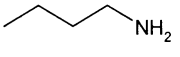
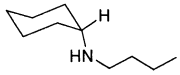
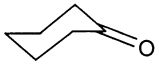
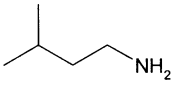
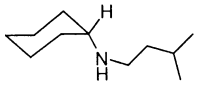
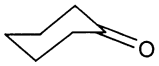
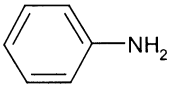
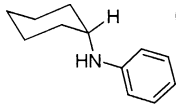
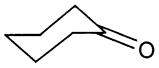
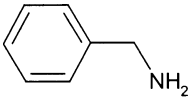
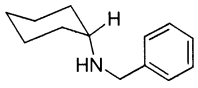
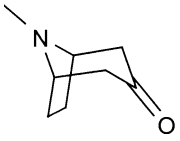
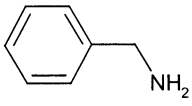
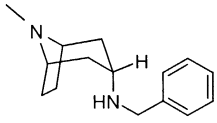
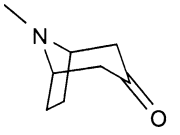
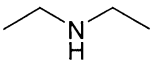
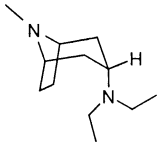
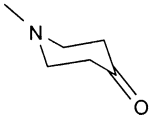
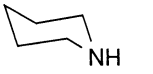
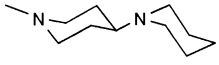
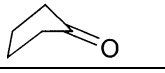
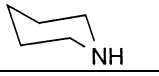
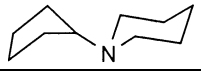
The ammonium formate excess, crucial to minimise the polyalkylation product formation, has been obviously avoided when operating with secondary amines.

Since we could not find examples in the literature of formate mediated, Pd catalysed hydrogenolysis of the C–O aminal bond, we decided to investigate the reactivity of stable aminal species in the studied conditions. A mixture of the compounds **5** and **6** has been obtained, according to a known procedure, by refluxing tropinone and ethanolamine in toluene over molecular sieves. The pure compounds have not been isolated and characterised but a 9:1 ratio of the two stereoisomers 5:6 has been detected by GC–MS analysis (Scheme 3).

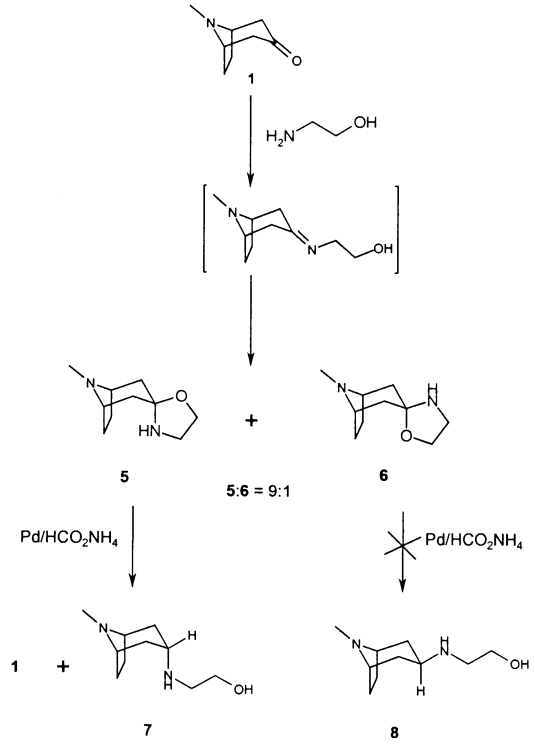
The formation of compound **5** has been assumed as favoured in the reaction conditions; the observed ratio exactly reflects the general reactivity of the tropinone imine derivatives.

In the hydroalcoholic $Pd/HCOONH_4$ hydrogenolytic

**Table 2.** Synthesis of secondary and tertiary amines via formate reductive amination

| | Reagents | | Product (expected) | Yield (%) |
|---|---|---|---|---|
| | Ketone | Amine[a] | | |
| (a) |  |  |  | 72 |
| (b) |  |  |  | 70 |
| (c) |  |  |  | 70 |
| (d) |  |  |  | 0 |
| (e) |  |  |  | 80 |
| (f) |  |  |  | 0 |
| (g) |  |  |  | 68 |
| (h) |  |  |  | 60 |

[a] Amine used to prepare the ammonium formate salt.




**Scheme 3.**

conditions, the hydrolysis to the starting tropinone is clearly competitive with the formation of the reduced aminoalcohol (see Section 4). The formation of only one of the two possible products has been observed (GC/MS); the obtained aminoalcohol has been isolated and characterised as the *endo*-isomer **7**. In order to confirm the stereochemistry of the isolated aminoalcohol, the synthesis of **7** has been performed by reacting pure **4** with 2-bromoethanol according standard procedures. The formation of the only *endo*-isomer **7** in the reaction conditions shows, according the proposed pathway, that: (1) the Pd/$HCOONH_4$ couple is a suitable reagent for the hydrogenolysis of aminal derivatives; (2) the concerted hydrogen transfer is affected by the steric hindrance on the axial face of the tropanic ring.

## 3. Conclusions

The use of a modified procedure for the reductive amination of carbonyl compounds is described. This is a new, versatile method for the synthesis of a wide range of primary, secondary and tertiary amines which advances the well known reductive amination processes in terms of yield and stereoselectivity. It is well known that reductive amination reactions can follow several mechanisms to the final amine

product. In our point of view, the chosen experimental conditions allow to drive the reaction to the amine selectively through the hemiaminal pathway. In the presence of bulky substrates the concerted hydrogen transfer allows the absolute stereocontrol of the reaction.

The mechanistic hypothesis involves a concerted route in which the oxidative addition of palladium to formate is followed by concerted $CO_2$ elimination and reductive transfer of the metal co-ordinated hydride.

To our knowledge this is the first example in which ammonium salts are employed together with a palladium catalyst in a reductive amination reaction. The use of a cheap and versatile hydrogen source coupled with the catalyst in an aqueous medium, advances the previous methods due to the mild conditions and to the handy and cheap reagents required.

## 4. Experimental

### 4.1. General

Melting points were obtained using a Büchi 530 melting point apparatus and are uncorrected. Thin-layer chromatography was carried out with Macherey-Nagel-DURASIL-25 silica gel plates. Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker ARX-300 MHz. Commercially available reagents and solvents were used as received.

GC–MS analysis was performed using a Varian 3400 chromatograph (analytical column: SUPELWAX™-10 Fused Silica Capillary Column) and an Incos 50 XL (Finnigan Mat) spectrometer. Mass spectra were recorded on a Finnigan TSQ 700, a triple-quadrupole mass spectrometer, equipped with an electrospray ionization (ESI) source (Thermo Finnigan, San Jose, CA).

**4.1.1. 8-Azabicyclo[3.2.1]octan-3-one (intermediate for the below described ketones).** A stirred solution of 8-methyl-8-azabicyclo[3.2.1]octan-3-one (**1**, 5 g, 36.0 mmol) in 1,2-dichloroethane (50 mL) was cooled to 4°C, 1-chloroethyl chloroformate (4.3 mL, 39.5 mmol) was added and the solution was refluxed for 3 h. After cooling to room temperature, solvent was evaporated, the residue dissolved in MeOH (50 mL) and the solution refluxed 5 h more. After cooling to room temperature the solution was evaporated to half volume; by acetone addition (30 mL) 8-azabicyclo-[3.2.1]octan-3-one started to precipitate. After complete precipitation at 4°C for 12 h, the product was filtered, washed with acetone and dried at 40°C under vacuum to give 8-azabicyclo[3.2.1]octan-3-one (4.5 g, 35.9 mmol) as pale yellow oil in quantitative yield; mp 180–182°C; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 4.81 (m, 2H), 2.95 (dd, 2H, $J_1$=6 Hz, $J_2$=2 Hz), 2.60 (d, 2H, $J$=6 Hz), 2.25 (m, 2H), 1.97 (m, 2H). Anal. calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.18; H, 8.88; N, 11.17. ESI-MS $m/z$ 126 $[M+H]^+$.

**4.1.2. 8-*tert*-Butoxycarbonyl-8-azabicyclo[3.2.1]octan-3-one (entry e, Table 1, reagent).** To a stirred solution of triethylamine (2 mL) in MeOH (20 mL) 8-azabicyclo-[3.2.1]octan-3-one (1 g, 8 mmol) and di-*tert*-butyl dicarbonate (3.5 g, 15.98 mmol) were added. After heating the solution at 40–50°C for 30 min, the solvent was evaporated; 2N HCl (20 mL) and ethyl acetate (20 mL) were added to the residue. The two phases were separated; the aqueous one was extracted with ethyl acetate (3×40 mL). The collected organic extracts were dried over $Na_2SO_4$ to give, after evaporation of the solvent, pure 8-*tert*-butoxycarbonyl-8-azabicyclo[3.2.1]octan-3-one as a white powder (1.53 g, 6.8 mmol) in 85% yield; mp 68–70°C; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 4.65 (m, 2H), 2.88 (dd, 2H, $J_1$=6 Hz, $J_2$=2 Hz), 2.52 (d, 2H, $J$=6 Hz), 2.30 (m, 2H), 1.88 (d, 2H, $J$=6 Hz), 1.72 (m, 9H). Anal. calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.97; H, 8.50; N, 6.24. ESI-MS $m/z$ 226 $[M+H]^+$.

**4.1.3. 8-Acetyl-8-azabicyclo[3.2.1]octan-3-one (entry d, Table 1, reagent).** A mixture of 8-azabicyclo[3.2.1]octan-3-one (0.45 g, 3.6 mmol) in acetic anhydride (1 mL) was heated at 70°C for 3 h. After cooling at room temperature, iced water (20 mL) was added. The mixture was refluxed for 30 min, cooled at room temperature and dichloromethane (20 mL) was added. After adding 1N NaOH until pH 9, the mixture was washed with 2N NaOH (2×20 mL), the organic phase was dried over $Na_2SO_4$ and evaporated under reduced pressure. After residue dissolution in ethyl acetate and cooling overnight at 4°C a white precipitate was obtained. The product was collected by filtration under vacuum and dried at 40°C to give 8-acetyl-8-azabicyclo[3.2.1]octan-3-one as a white powder (0.38 g, 2.27 mmol) in 63% yield; mp 75–78°C; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 4.77 (m, 2H), 2.95 (dt, 2H, $J_1$=6 Hz, $J_2$=2 Hz), 2.57 (t, 2H, $J$=6 Hz),2.42 (s, 3H), 2.25 (m, 2H), 1.95 (m, 2H). Anal. calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.83; N, 8.37. Found: C, 64.68; H, 7.81; N, 8.33. ESI-MS $m/z$ 168 $[M+H]^+$.

### 4.2. General procedure for amines synthesis

**4.2.1. 3-*endo*-Amino-8-methyl-8-azabicyclo[3.2.1]octane bis hydrochloride (4) (3-*endo*-tropanamine) (entry b, Table 1, product).** A solution of 8-methyl-8-azabicyclo-[3.2.1]octan-3-one (**1**, 6 g, 43.0 mmol) in MeOH (112 mL) was treated, under vigorous stirring, with ammonium formate (25 g, 0.40 mol) and water (12.5 mL). After complete dissolution, 10% Pd/C (5.1 g, 4.8 mmol) was added and the reaction mixture stirred overnight at room temperature. At the completion of the reaction (detected by TLC, eluent: EtOH/$NH_4OH$ 8:2), the catalyst was filtered off on Celite and the filtrate concentrated under reduced pressure; the oily residue obtained was dissolved in ethyl alcohol (100 mL) and 37% HCl (7.5 mL) was added dropwise. The solution was seeded and left stirring at room temperature for 1 h and at 4°C for 5 h. The resulting white precipitate was filtered and dried at 40°C under vacuum to give 3-*endo*-tropanamine (7.6 g, 35.6 mmol) in 83% yield; mp>250°C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.21–11.05 (bs, 1H), 8.75–8.22 (bs, 3H), 4.05–3.82 (bs, 2H), 3.75–3.55 (m, 1H), 2.85–2.55 (m, 5H), 2.40–2.05 (m, 6H). Anal. calcd for $C_8H_{18}N_2Cl_2$: C, 45.08; H, 8.51; N, 13.14; Cl, 33.26. Found: C, 45.09; H, 8.50; N, 13.12; Cl, 33.26. ESI-MS $m/z$ 141 $[M+H]^+$.

According to the same procedure above described and starting from the corresponding ketones, the following amines have been synthesised.

**4.2.2. 3-*endo*-Amino-8-acetyl-8-azabicyclo[3.2.1]octane hydrochloride (entry d, Table 1, product).** White powder (0.27 g, 1.59 mmol); mp>250°C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$, 4.65 (m, 1H), 4.08 (m, 1H), 3.46 (t, 1H, $J$=6 Hz), 2.32–2.10 (m, 3H), 2.10–1.83 (m, 6H), 1.70–1.47 (m, 3H). Anal. calcd for $C_8H_{18}N_2OCl_2$: C, 41.93; H, 7.92; N, 12.22; Cl, 30.94. Found: C, 41.94; H, 7.92; N, 12.22; Cl, 30.91. ESI-MS $m/z$ 169 $[M+H]^+$.

**4.2.3. Butylcyclohexylamine hydrochloride (entry a, Table 2, product).** White powder (0.923 g, 4.82 mmol); mp>250°C; $^1$H NMR (300 MHz, DMSO-$d_6$)) $\delta$, 8.85 (bs), 2.95–2.82 (m, 3H), 2.05–1.95 (m, 2H), 1.85–1.72 (m, 2H), 1.65–1.50 (m, 2H), 1.40–1.05 (m, 8H), 0.98 (t, 3H, $J$=7 Hz). Anal. calcd for $C_{10}H_{22}NCl$: C, 62.64; H, 11.56; N, 7.30; Cl, 18.49. Found: C, 62.64; H, 11.55; N, 7.32; Cl, 18.48. ESI-MS $m/z$ 156 $[M+H]^+$.

**4.2.4. 1-[(3-Methyl)butyl]cyclohexylamine hydrochloride (entry b, Table 2, product).** White powder (0.245 g, 1.19 mmol); mp>250°C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.70 (bs), 3.02–2.85 (m, 3H), 2.15–2.05 (m, 2H), 1.84–1.70 (m, 2H), 1.75–1.45 (m, 4H), 1.35–1.05 (m, 5H), 0.95 (d, 6H, $J$=7 Hz). Anal. calcd for $C_{11}H_{24}NCl$: C, 64.18; H, 11.75; N, 6.80; Cl, 17.22. Found: C, 64.16; H, 11.75; N, 6.81; Cl, 17.23. ESI-MS $m/z$ 170 $[M+H]^+$.

**4.2.5. *N*-Cyclohexylaniline hydrochloride (entry c, Table 2, product).** White powder (0.99 g, 4.69 mmol); mp 170–175°C; $^1$H NMR (300 MHz, $D_2O$) $\delta$ 7.35 (m, 3H), 7.25 (m, 2H), 3.35–3.25 (m, 1H), 1.75–1.85 (m, 2H), 1.65–1.55 (m, 2H), 1.45–1.35 (m, 1H), 1.30–0.85 (m, 6H). Anal. calcd for $C_{12}H_{18}NCl$: C, 68.07; H, 8.57; N, 6.61; Cl, 16.74. Found: C, 68.07; H, 8.55; N, 6.60; Cl, 16.77. ESI-MS $m/z$ 176 $[M+H]^+$.

**4.2.6. 3-*endo*-Benzylamino-8-methyl-8-azabicyclo[3.2.1]-octane hydrochloride (entry e, Table 2, product).** The hydrochloride (white powder; 0.88 g, 3.28 mmol) has been treated with 1N NaOH and extracted with dichloromethane to give the free base 3-endo-benzylamino-8-methyl-8-azabicyclo[3.2.1]octane as a transparent oil (0.738 g, 3.21 mmol) bp 128°C (2.5 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.40–7.10 (m, 5H), 3.71 (s, 2H), 3.10–3.00 (m, 2H), 2.90 (t, 1H, $J$=7 Hz), 2.24 (s, 3H), 2.10–1.90 (m, 6H), 1.56 (d, 2H, $J$=13.7 Hz), 0.95 (bs, 2H). Anal. calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.25; H, 9.75; N, 8.01. ESI-MS $m/z$ 231 $[M+H]^+$.

**4.2.7. *N*-(*N*′-Methyl-piperidinyl)piperidine bis hydrochloride (entry g, Table 2, product).** White powder (0.66 g, 2.58 mmol); mp>250°C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.30–8.10 (bs), 3.60–3.50 (m, 1H), 3.05–2.85 (m, 4H), 2.70 (s, 3H), 2.35–2.25 (m, 2H), 2.15–1.95 (m, 2H), 1.90–1.65 (m, 8H), 1.50–1.35 (m, 2 H); Anal. calcd for $C_{11}H_{24}N_2Cl_2$: C, 51.77; H, 9.48; N, 10.96; Cl, 27.78. Found: C, 51.77; H, 9.45; N, 10.98; Cl, 27.78. ESI-MS $m/z$ 183 $[M+H]^+$.

**4.2.8. *N*-Cyclopentyl-piperidine hydrochloride (entry h, Table 2, product).** White powder (0.65 g, 3.25 mmol); mp 210–215°C; $^1$H NMR (300 MHz, $D_2O$) $\delta$ 3.65–3.15 (m, 3H), 3.05–2.90 (m, 2H), 2.25–2.15 (m, 2H), 2.05–1.95 (m, 2H), 1.96–1.45 (m, 10H). Anal. calcd for $C_{10}H_{20}NCl$: C, 63.31; H, 10.63; N, 7.38; Cl, 18.69. Found: C, 63.30; H, 10.63; N, 7.38; Cl, 18.67. ESI-MS $m/z$ 166 $[M+H]^+$.

**4.2.9. 3-*endo*-(2′-Hydroxy-ethyl)amino-8-methyl-8-azabicyclo[3.2.1]octane bis hydrochloride (7) (Scheme 3).** *Intermediates **5** and **6** mixture*. A stirred solution of 8-methyl-8-azabicyclo[3.2.1]octan-3-one (**1**, 1.4 g, 10.0 mmol) in toluene (10 mL) was heated at reflux temperature, ethanolamine (0.75 mL, 13.5 mmol) added and the resulting solution refluxed overnight. After cooling at room temperature, the solvent was evaporated, ethanolamine in excess distilled off in vacuum and the crude residue analysed by GC–MS.

GC–MS: analytical column (SUPELWAXTM-10 Fused Silica Capillary Column, 30 m×0.32 mm ID, 0.25 μm film thickness); temperature column: initial $T$=80°C (3 min), rate=1°C/min, final 1$T$=100°C (1 min), rate=30°C/min, final 2$T$=250°C (5 min); injector temperature $T$=250°C; injection volume=1 μL (split 1:30); carrier gas: helium (1 mL/min); run time 20 min; MS-source (EI; source temperature $T$=180°C); MS-transfer line ($T$=250°C); MS-scan mode (full scan $m/z$: 50–600) retention time (min): 15.3 ($m/z$ 182); 16.1 ($m/z$ 182).

**5/6** calculated ratio 9:1; residual **1** not observed (GC).

**4.2.10. 3-*endo*-(2′-Hydroxy-ethyl)amino-8-methyl-8-azabicyclo[3.2.1]octane bis hydrochloride (7).** The crude residue of intermediates **5** and **6** (0.18 g, 1.0 mmol) was dissolved in methanol (20 mL) and formic acid (0.4 mL, 10.0 mmol); triethylamine (1.5 mL, 10.0 mmol) and 10% Pd/C (100 mg) were added. The mixture was left stirring overnight at room temperature. The catalyst was filtered off and the solvent evaporated under vacuum. The crude residue was diluted with dichloromethane (15 mL) and the organic phase washed with 32% NaOH (2×15 mL) and water (3×20 mL). The organic phase was dried over $Na_2SO_4$ to give, after evaporation of the solvent, 3-*endo*-(2′-hydroxy-ethyl)amino-8-methyl-8-azabicyclo[3.2.1]-octane as an oil. The oily residue was dissolved in ethyl alcohol (20 mL) and 37% HCl (0.17 mL) was added dropwise with vigorous stirring; the pure bis hydrochloride was recovered by filtration as a white powder (0.08 g, 0.3 mmol).

Mp>250°C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.80–6.60 (bs), 5.10–4.9 (bs), 3.65–3.60 (t, 2H, $J$=6 Hz), 3.10–3.00 (bs, 2H), 2.85–2.80 (t, 1H, $J$=7 Hz), 2.75–2.04 (t, 2H, $J$=7 Hz), 2.25 (s, 3H), 2.20–1.80 (m, 6H), 1.65–1.50 (m, 2H). GC–MS: analytical column (SUPELWAX™-10 Fused Silica Capillary Column, 30 m×0.32 mm ID, 0.25 μm film thickness); temperature column: initial $T$=80°C (3 min), rate=1°C/min, final 1$T$=100°C (1 min), rate=30°C/min, final 2$T$=250°C (5 min); injector temperature $T$=250°C; injection volume=1 μL (split 1:30); carrier gas: helium (1 mL/min); run time=20 min; MS-source (EI; source temperature: $T$=180°C); MS-transfer line ($T$=250°C); MS-scan

mode (full scan *m/z*: 50–600) retention time (min): 7.1 (*m/z* 139, **1**), 15.3 (*m/z* 182, unreacted **5**), 16.1 (*m/z* 182, residual **6**), 16.6 (*m/z* 184, **7**). Anal. calcd for $C_{10}H_{22}N_2OCl_2$: C, 51.25; H, 7.88; N, 9.96; Cl, 25.21. Found: C, 51.22; H, 7.87; N, 9.96; Cl, 25.24. ESI-MS *m/z* 184 $[M+H]^+$.

**1/5/6/7** calculated ratio 5:0.5:0.5:4 (GC). Yield on isolated **7**: 30%.

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