Tetrahydropyridinium Bromide: Useful Synthon to Functionalized Pyrrolidines

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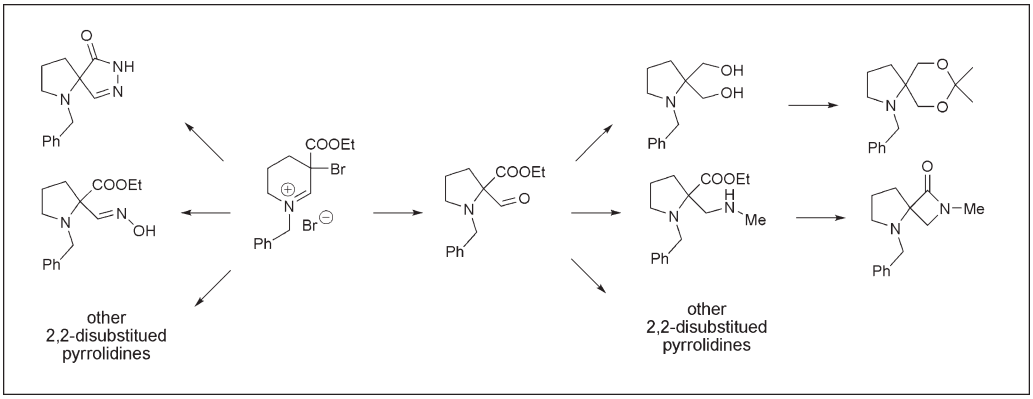

1-benzyl-5-(ethoxycarbonyl)-2,3,4,5-tetrahydropyridinium bromide undergoes ring contraction with a series of nucleophiles, getting 2,2-disubstitued pyrrolidines. Moreover, from some of the new 2,2-disubstitued pyrrolidines were synthesized spiro-pyrrolidines.

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INTRODUCTION

The pyrrolidine ring is a structural fragment present in many natural alkaloids such as nicotine, cocaine, and atropine. It is also present in the structure of proline, α-aminoacid unique in its conformational rigidity due to a secondary amino group. Moreover, proline and its derivatives are used as catalysts in asymmetric enantioselective synthesis [1], for example, in aldol reactions and Michael additions [2]. Finally, the pyrrolidine ring is present in several pharmaceutical compounds [3]: the most important example is the family of ACE inhibitors, widely used as antihypertensive. It is clear that the capability to obtain functionalized pyrrolidine rings is important in many aspects of synthetic chemistry.

In our continuing efforts to develop new and more general methods for the preparation of heterocycles with potential biological interest, we considered the synthesis of 2,2-disubstituted pyrrolidines. For the construction of this ring, there are several type of reactions, such as nucleophilic displacement [4] and ring expansion [5]. In addition, it is known that tetrahydropiridinium bromides **1** give a ring contraction reacting with OH^- sources, such as wet TEA or $NaHCO_{3(aq)}$ to give pyrrolidine aldehydes **2** (Scheme 1) [6,7]. As a further development, in this article, we consider the usefulness and the limits of this synthetic protocol for the preparation of a small library of proline-like compounds.

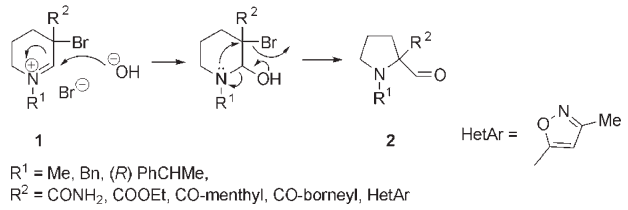
DISCUSSION AND RESULTS

The nature of the substituent in the nitrogen atom strongly affects the reaction path. In fact, when an electron withdrawing group is present, such as an acetyl group (**3**) [8,9], the formation of the correspondent tetrahydropyridinium bromides is completely prevented. Moreover, compounds **4** was the unexpected product, as a mixture of distereoisomers, obtained from the addition of bromine, in not anhydrous condition. (Scheme 2) Infrared spectrum showed the presence of a hydroxyl group and the absolute regioselectivity attack of water was confirmed by the signal shifts of C2 and C3 in ^{13}C-NMR spectra 80.8 and 74.8, respectively.

On the other hand, compound **1** can be easily achieved with three simple steps starting from ethyl nicotinate through *N*-alkylation [10], hydrogenation to get ethyl 1-benzyl-1,4,5,6-tetrahydronicotinate **5** and finally reactions with bromine, as reported in literature [7b] (Scheme 3).

It is important to say that, because of its instability and hygroscopicity, compound **1** must be used freshmade. For this reason, ethyl *N*-benzyl tetrahydronicotinate is the starting material for all the reactions that involve the use of compound **1**. The results of this investigations are reported in Scheme 4. The first nucleophile used was EtONa to get acetal **6**. On the other hand, the use of carbanions (methyl lithium or

Scheme 1



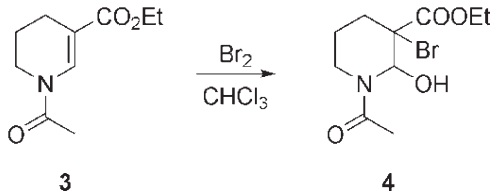
magnesium malonate) resulted in a debromination to the starting ethyl tetrahydronicotinate (Schemes 4 and 5). Nitrogen-based nucleophiles works, but the yields at this stage are very poor. However we obtained three new pyrrolidines as shown in Scheme 4. The use of the very reactive hydrazine disclosed the possibility to obtain the interesting spiro-compound **7**. X-ray analysis of this compound confirmed the assigned structure, as shown in Figure 1. Unfortunately hydroxylamine did not permit to get the corresponding spiro-compound, but only oxime **8**. ^{1}H NMR spectrum showed the presence of only one of the two possible stereoisomers, and from X-ray analysis the *E* configuration was assigned. (Fig. 1) Some attempts to convert **8** into the *Z* isomer were made, but without results [11].

The use of *ortho*-phenylendiamine did not permit to get the desired product, but the formation of benzimidazole and ethyl *N*-benzylproline was observed. Same result was obtained starting from aldehyde **2**. A possible reaction mechanism is shown in Scheme 6.

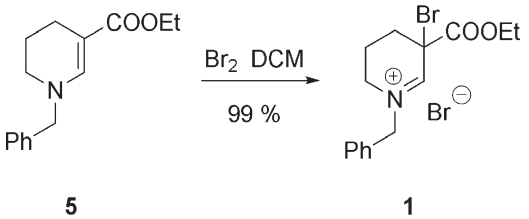
At this point, considering that bromide **1** gives the aldehyde **2** in good yield (Scheme 1), we decided to use this type of compound for the preparation of a family of pyrrolidines. Following this approach, we improved the yields for compounds **7** and **8** (Scheme 7). Furthermore, even protected α-aminoacids can be used, to give for instance imine **10**.

Using a reductive agent, such as sodium cyanoborohydride, together with methylamine or *ortho*-phenylendiamine it was possible to get compounds **11** and **12**, respectively. In addition, compound **2** can be selectively or totally reduced, using H_2/PtO_2 or $NaBH_4$ obtaining **13** and **14** respectively in good yields. Oxidation of **2** with I_2, in basic condition, offers the possibility to get **15** with quantitative yield.

Scheme 2

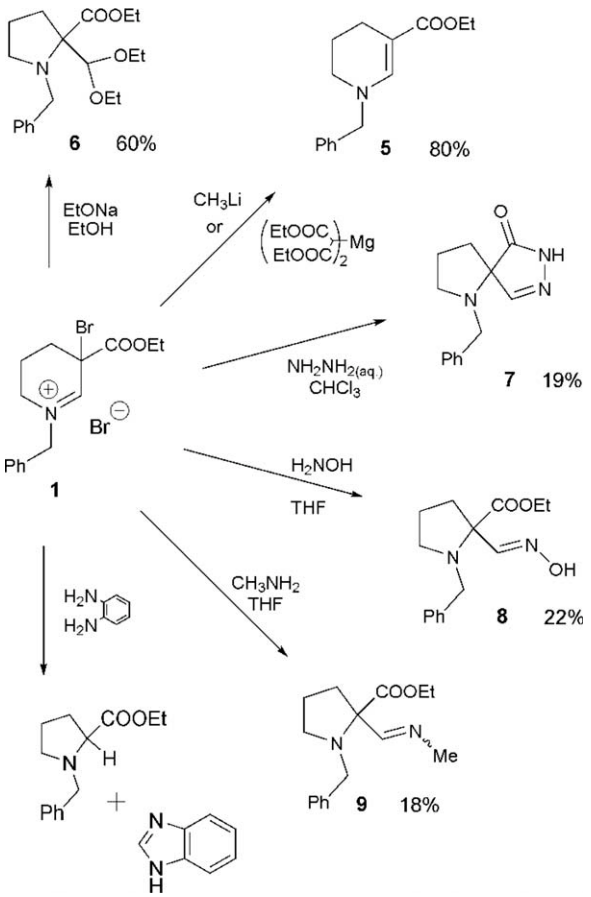


Scheme 3

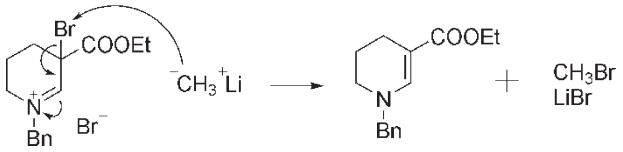


The biological activity of functionalized spiro-compounds, such as buspirone and spiperone, is often linked to structural and conformational rigidity, which gives enantiomeric selectivity in the interaction with the enzymes sites. For this reason and the good result with compound **7**, it was designed to synthesize additional spiro-compounds from 2,2-disubstituted pyrrolidines so far obtained. In particular using two equivalents of a strong base as LDA upon **11**, it was possible to get 5,4-spiro-pyrrolidine **16**. Starting from **14** with the use of p-toluensulfonic acid in acetone, we obtained 5,6-spiro-**17**. (Scheme 8). At the moment, further insight into the reactivity of compounds **12** and **15** is under investigation.

Scheme 4



Scheme 5. Debromination of **1** with carbanions.



CONCLUSIONS

The results presented here suggest that the conversion of ethyl 1-benzyl-1,4,5,6-tetrahydronicotinate into Δ^1-piperideinium salts or even into pyrrolidine derivatives discloses new interesting synthetic pathways to obtain proline-like derivatives. Moreover, the described strategy offers an efficient and simple method, often characterized by good yields, to synthetize compounds of generally difficult access like spiro-pyrrolidines.

EXPERIMENTAL

General. Melting points were determined with a Kofler hot stage and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 27°C ($CDCl_3$), unless otherwise stated, with a Bruker AC200 MHz instrument operating at 200.13 and 50.33 MHz, respectively, or with a Bruker Advance 400 MHz instrument operating at 400.13 and 100.62 MHz, respectively. Chemical shifts are reported in ppm from internal TMS. The ^{1}H NMR data are reported as follows: *s* = singlet, *d* = doublet, *t* = triplet, *m* = multiplet, bs = broad singlet, bt = broad triplet; coupling constant(s) in Hz. Mass spectra were recorded in the positive or negative ion mode with a LCQ-DECA Thermo instrument by using electrospray ionization. GC mass spectra were recorded with a mass spectrometer Varian Saturn 2000 coupled with a gas chromatograph Varian 3800 equipped with capillary column Rtx-5MS. All solvents were previously dried according to standard procedures. Analytical TLC was performed on silica gel 60 F254 plates. Flash column chromatography was carried out on silica gel (0.040–0.063 mm). Single crystals of **7** and **8** were submitted to X-ray data collections by using a Siemens P4 four-circle diffractometer (293K), equipped with a graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). The structures were solved by direct methods implemented in the SHELXS-97 program [12]. The refinements were carried out by full-matrix anisotropic least-squares on F^2 for all reflections for non-H atoms by means of the SHELXL-97 program [13]. Crystallographic data for the structures in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication n. CCDC-796487 (**4**), CCDC-796488 (**5**). Copies of the data can be obtained, free of charge via www.ccdc.cam.ac.uk/data_request/cif or by e-mailing data_request@ccdc.cam.ac.uk or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

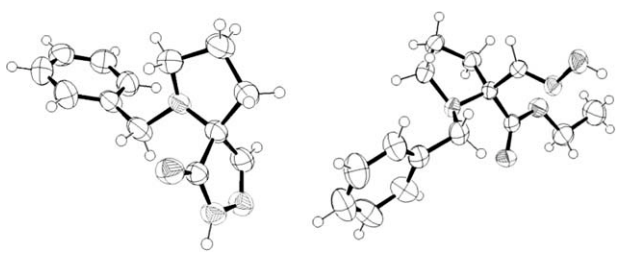
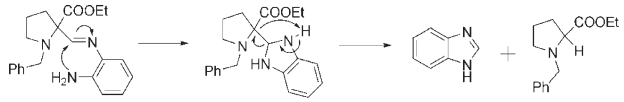


Figure 1. X-ray structures of compounds **7** and **8**.

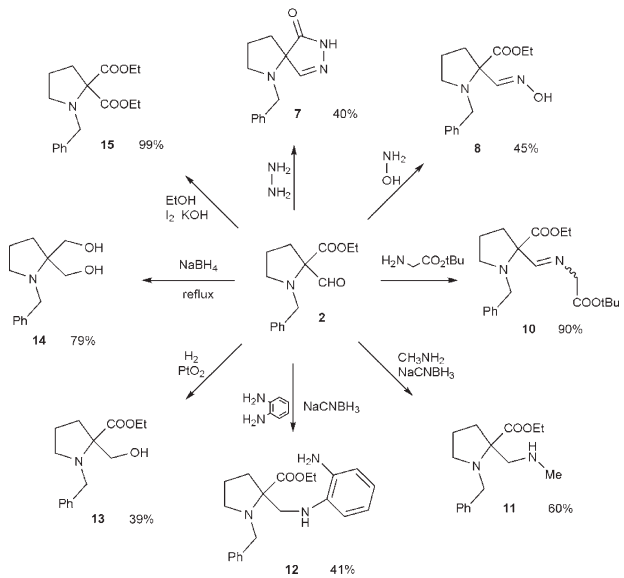
Scheme 6. Reaction of *ortho*-phenylendiamine.



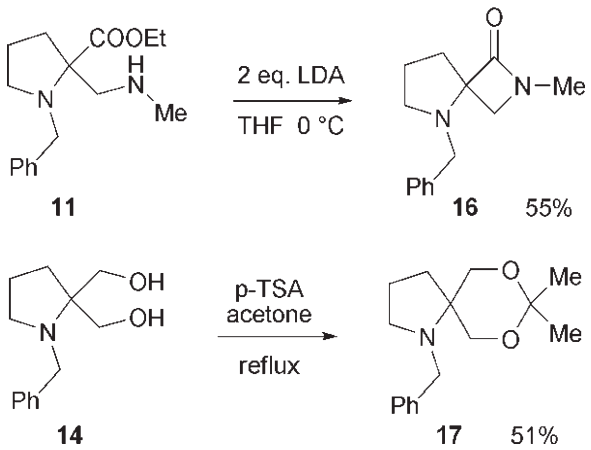
Ethyl 1-acetyl-2-bromo-3-hydroxypiperidine-3-carboxylate (4). Ethyl 1-acetyl-1,4,5,6-tetrahydropyridine-3-carboxylate **3** [8] (0.58 g, 2.94 mmol) was dissolved in $CHCl_3$ (ethanol free) (12 mL), then a solution of Br_2 (150 µL, 2.94 mmol) in $CHCl_3$ (ethanol free) (3 mL) was added slowly drop-by-drop. After 1 h stirring, solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (DCM/MeOH 95:5) getting **4** as a white solid (0.62 g, 1.74 mmol, 59%). M.p.: 126°C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.31 (t, ^3J = 7.3 Hz, 6H, CH_2CH_3), 1.78 (m, 4H, H5 + H5′), 2.10 (s, 3H, $COCH_3$), 2.20 (s, 3H, $COCH_3'$), 2.38 (m, 4H, H4 + H4′), 2.89 (m, 1H, H6), 3.46 (m, 2H, H6 + H6′), 4.28 (q, ^3J = 7.3 Hz, 4H, CH_2CH_3), 4.38 (m, 1H, H6′), 5.75 (s, 1H, H2), 6.40 (s, 1H, H2′). ^{13}C-NMR (200 MHz, $CDCl_3$): δ 13.8; 20.3; 21.1; 21.4; 21.9; 28.2; 30.7; 34.9; 40.2; 60.9; 62.1; 62.4; 74.8; 80.8; 169.3; 169.7; 170.9; 171.4. MS (ESI): *m/z* = 294/296 $[M + H]^+$, 316/318 $[M + Na]^+$. $C_{10}H_{16}BrNO_4$ (294,14): calcd. C 40.83; H 5.48; Br 27.17; N 4.76; found C 40.87; H 5.52; Br 27.16; N 4.79.

Ethyl 1-benzyl-2-(diethoxymethyl)pyrrolidine-2-carboxylate (6). 1-Benzyl-5-bromo-5-(ethoxycarbonyl)-2,3,4,5-tetrahydropyridinium bromide **1** (2.23 g, 5.5 mmol) was dissolved in ethanol (20 mL) and it was added EtONa in EtOH (Na° 253

Scheme 7



Scheme 8



mg, 11 mmol, in EtOH 10 mL) and stirred for 2 h at room temperature. After this time, the solvent was evaporated under vacuum, and the residue was treated with cyclohexane (30 mL), filtered and evaporated getting **6** (0.94 g, 2.8 mmol, 51%) as a yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.27 (m, 9H, $COOCH_2CH_3$ + OCH_2CH_3), 1.78 (m, 2H, 4-CH_2), 2.23 (m, 2H, 3-CH_2), 2.81 (m, 2H, 5-CH_2), 3.69 (q, ^3J = 7 Hz, 4H, OCH_2CH_3), 3.83 (AB system, ^2J = 13 Hz, 2H, NCH_2Ph), 4.19 (q, ^3J = 7 Hz, $COOCH_2CH_3$), 4.84 (s, 1H, *CH*), 7.22 (s, 5H, Ph). GC-MS (EI): *m/z* = 336 $[M + H]^+$. $C_{19}H_{29}NO_4$ (335,44): calcd. C 68.03; H 8.71; N 4.18; found C 68.05; H 8.74; N 4.19.

1-Benzyl-1,7,8-triazaspiro[4.4]non-8-en-6-one (7). Hydrazine freshly distilled (170 μL, 5.4 mmol) was dissolved in $CHCl_3$ (5 mL), then a solution of ethyl 1-benzyl-2-formylpyrrolidine-2-carboxylate **2** (0.4 g, 1.53 mmol) in $CHCl_3$ (15 mL) was added slowly drop-by-drop. The mixture was refluxed and stirred for 48 h. After this time, the reaction was diluted in $CHCl_3$ (30 mL) and washed with H_2O (2 × 15 mL). The organic phase was dried over Na_2SO_4, filtrated and evaporated under vacuum getting a yellow oil. The residue was sublimated under vacuum at 100°C getting **7** (0.14 g, 0.61 mmol, 40%) as a white solid; m.p.: 78°C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.96 (m, 2H, 4-CH_2), 2.14 (m, 2H, 3-CH_2), 3.03 (m, 2H, 5-CH_2), 3.65 (s, 2H, NCH_2Ph), 7.11 (s, 1H, CH=N), 7.26 (s, 5H, Ph), 8.86 (bs, 1H, NH). ^{13}C-NMR (200 MHz, $CDCl_3$): δ 22.7; 32.6; 51.8; 54.6; 71.9; 127.3; 128.2; 128.7; 138.4; 154.9; 178.1. GC-MS (EI): *m/z* = 229 $[M]^+$. $C_{13}H_{15}N_3O$ (229,28): calcd. C 68.10; H 6.59; N 18.33; found C 68.08, H 6.62; N 18.36.

(E)-Ethyl 1-benzyl-2-((hydroxyimino)methyl) pyrrolidine-2-carboxylate (8). Ethyl 1-benzyl-2-formylpyrrolidine-2-carboxylate **2** (0.4 g, 1.53 mmol) was dissolved in dry THF (10 mL), then were added hydroxylamine hydrochloride (0.38 g, 5.51 mmol) and TEA freshly distilled (0.77 mL, 5.51 mmol). The mixture was refluxed for 16 h. After this time, the reaction was filtered, diluted in DCM (40 mL) and washed with H_2O (3 × 15 mL). The organic phase was dried over Na_2SO_4, filtrated and concentrated under vacuum. The residue was treated with cyclohexane/Et_2O 3:1 getting **8** (0.19 g, 0.69mmol, 45%) as a yellow solid; m.p.: 120°C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.30 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 1.85 (m, 2H, 4-CH_2), 2.29 (m, 2H, 3-CH_2), 2.80 (m, 2H, 5-CH_2), 3.85 (AB system, ^2J = 13.5 Hz, 2H, NCH_2Ph), 4.23 (q, ^3J = 7.1 Hz, CH_2CH_3), 7.28 (m, 5H, Ph), 7.59 (s, 1H, *CH*N), 8.30 (bs, 1H, N*OH*). ^{13}C-NMR (200 MHz, $CDCl_3$): δ 14.3; 22.1; 34.8; 50.9; 54.1; 61.1; 70.9; 126.9; 128.2; 128.4; 139.8; 151.6; 172.3. MS (ESI): *m/z* = 277 $[M + H]^+$, 299 $[M + Na]^+$. $C_{15}H_{20}N_2O_3$ (276,33): calcd. C 65.20; H 7.30; N 10.14; found C 65.19; H 7.32; N 10.17.

Ethyl 1-benzyl-2-((methylimino)methyl)pyrrolidine-2-carboxylate (9). 1-Benzyl-5-bromo-5-(ethoxycarbonyl)-2,3,4,5-tetrahydropyridinium bromide **1** (1.22 g, 3 mmol) was dissolved in dry EtOH (15 mL), it was added methylamine in EtOH 33% p/p (1.31 mL, 10.5 mmol), and the reaction was stirred at r.t. After 12 h solvent was evaporated, the residue was dissolved in Et_2O (50 mL) and washed with H_2O (3 × 15 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether/Et_2O 1:1) obtaining **9** (0.15 g, 0.54 mmol, 18%) as brown–yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.25 (t, ^3J = 7 Hz, 3H, CH_2CH_3), 1.56 (m, 2H, 4-CH_2), 2.08 (m, 2H, 3-CH_2), 2.27 (s, 3H, NCH_3), 2.75 (m, 2H, 5-CH_2), 3.83 (AB system, ^2J = 12.5 Hz, 2H, NCH_2Ph), 4.21 (q, ^3J = 7 Hz, 2H, CH_2CH_3), 7.25 (m, 5H, Ph), 7.85 (s, 1H, *CH*=N). MS (ESI): *m/z* = 275 $[M + H]^+$. $C_{16}H_{22}N_2O_2$ (274,36): calcd. C 70.04; H 8.08; N 10.21; found C 70.07; H 8.10; N 10.18.

Ethyl 1-benzyl-2-((2-*tert*-butoxy-2-oxoethylimino) methyl)pyrrolidine-2-carboxylate (10). Ethyl 1-benzyl-2-formylpyrrolidine-2-carboxylate **2** (0.2 g, 0.77 mmol) was dissolved in dry $CHCl_3$ (10 mL), then were added *tert*-butyl glycine hydrochloride (0.14 g, 0.85 mmol) and DMAP (0.11 g, 0.92 mmol). The mixture was refluxed for 12 h. After this time, the solvent was evaporated under reduced pressure, and it was added Et_2O (10 mL). The precipitate was filtered off and the solvent was evaporated, getting **10** (0.26 g, 0.69 mmol, 90%) as an orange oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.27 (t, ^3J = 7.2 Hz, 3H, CH_2CH_3), 1.42 (s, 9H, Boc), 1.84 (m, 2H, 4-CH_2), 2.31 (m, 2H, 3-CH_2), 2.75 (m, 1H, 5-CH_2), 2.90 (m, 1H, 5-CH_2), 3.89 (AB system, ^2J = 13.6 Hz, 2H, NCH_2Ph), 4.12 (AB system, ^2J = 15.4 Hz, 2H, $NCH_2COOtBu$), 4.22 (q, ^3J = 7.2 Hz, 2H, CH_2CH_3), 7.17–7.33 (m, 5H, Ph), 7.74 (s, 1H, CHN). MS (ESI): *m/z* = 375 $[M + H]^+$, 397 $[M + Na]^+$. $C_{21}H_{30}N_2O_4$ (374,47): calcd. C 67.35; H 8.07; N 7.48; found C 67.38; H 8.10; N 7.47.

Ethyl 1-benzyl-2-((methylamino)methyl)-pyrrolidine-2-carboxylate (11). Ethyl 1-benzyl-2-formylpyrrolidine-2-carboxylate **2** (1.04 g, 4 mmol) was dissolved in dry EtOH (2.5 mL), then were added methylamine in EtOH 33% p/p (3 mL, 24 mmol) and $NaCNBH_3$ (0.16 g, 2.4 mmol). The solution was acidified with HCl 5N in ethanol to pH 5 and stirred at r.t. for 72 h. After this time, the solvent was evaporated under reduced pressure, the residue was treated with H_2O (50 mL) and extracted with Et_2O (2 × 20 mL). The aqueous phase was basified with KOH 4N to pH > 10 and extracted with Et_2O (2 × 20 mL). The organic fractions were reunited and dried over Na_2SO_4, filtered and evaporated under vacuum getting **11** (0.66 g, 2.4 mmol, 60%) as a yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.31 (t, ^3J = 7 Hz, 3H, CH_2CH_3), 1.63 (bs, 1H, NH), 1.81 (m, 2H, 4-CH_2), 2.15 (m, 2H, 3-CH_2), 2.43 (s, 3H, $NHCH_3$), 2.70 (m, 2H, 5-CH_2), 2.82 (AB system, ^2J = 11.9 Hz, 2H, CH_2NHCH_3), 3.66 (AB system, ^2J = 13.7 Hz, 2H,

N*CH*$_2$Ph), 4.21 (q, ^3J = 7 Hz, 2H, *CH*$_2$CH$_3$), 7.25 (m, 5H, Ph). ^{13}C-NMR (200 MHz, $CDCl_3$): δ 14.5; 22.5; 33.7; 37.0; 52.3; 53.6; 55.0; 60.2; 70.6; 126.8; 128.2; 129.0; 140.3; 174.7. MS (ESI): m/z = 277 $[M + H]^+$. $C_{16}H_{24}N_2O_2$ (276,37): calcd. C 69.53; H 8.75; N 10.14; found C 69.54; H 8.72; N 10.16.

Ethyl 2-((2-aminophenylamino)methyl)-1-benzyl pyrrolidine-2-carboxylate (12). Ethyl 1-benzyl-2-formylpyrrolidine-2-carboxylate **2** (0.5 g, 1.92 mmol), ortho phenylendiamine (0.23 g, 2.11mmol) and sodium cyanoborohydride (0.13 g, 2.11 mmol) were dissolved in dry THF (12 mL) and stirred at r.t. for 16 h. It was added HCl 2N (1 mL) and stirred for 1h at r.t. After this time, the mixture was diluted with Et_2O (40 mL) and washed with H_2O (3 × 20 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether/ Et_2O 1:1) getting **12** (0.28 g, 0.79 mmol, 41%) as a brown yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.39 (t, ^3J = 7 Hz, 3H, CH_2CH_3), 1.90 (m, 2H, 4-CH_2), 2.19 (m, 1H, 3-CH_2), 2.35 (m, 1H, 3-CH_2), 2.86 (m, 1H, 5-CH_2), 3.06 (m, 1H, 5-CH_2), 3.43 (AB system, ^2J = 11.9 Hz, 2H, *CH*$_2$NH), 3.70 (AB system, ^2J = 13.1 Hz, 2H, N*CH*$_2$Ph), 4.30 (q, ^3J = 7 Hz, 2H, *CH*$_2$CH$_3$), 6.78 (m, 4H, NHAr), 7.30 (m, 5H, Ph). ^{13}C-NMR (200 MHz, $CDCl_3$) δ 14.4; 22.4; 33.7; 45.1; 51.8; 52.9; 60.4; 70.0; 111.6; 116.0; 118.2; 120.3; 126.8; 128.2; 128.3; 134.5; 137.8; 139.4; 174.3. MS (ESI): m/z = 354 $[M + H]^+$, 376 $[M + Na]^+$. $C_{21}H_{27}N_3O_2$ (353,46): calcd. C 71.36; H 7.70; N 11.89; found C 71.38; H 71.73; N 11.88.

Ethyl 1-benzyl-2-(hydroxymethyl)pyrrolidine-2-carboxylate (13). PtO_2 (70 mg) was suspended in dry EtOH (10 mL) and activated under hydrogen pressure (50 p.s.i.) at r.t. for 10 minutes. After this time, ethyl 1-benzyl-2-formylpyrrolidine-2-carboxylate **2** (0.28 g, 1.07 mmol) in dry EtOH (10 mL) was added, and hydrogenated (50 p.s.i.) for 16 h. At the end of the reaction, the catalyst was removed by filtration and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (1° eluent = petroleum ether/Et_2O 2:1, 2° eluent = Et_2O/MeOH 1:1) getting **13** (0.11 g, 0.42 mmol, 39%) as a yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.31 (t, ^3J = 7 Hz, CH_2CH_3), 1.81 (m, 2H, 4-CH_2), 2.14 (m, 2H, 3-CH_2), 2.82 (m, 2H, 5-CH_2), 3.65 (AB system, ^2J = 13.2 Hz, 2H, *CH*$_2$OH), 3.71 (s, 2H, N*CH*$_2$Ph), 4.22 (q, ^3J = 7 Hz, *CH*$_2$CH$_3$), 7.28 (m, 5H, Ph). MS (ESI): m/z = 264 $[M + H]^+$. $C_{15}H_{21}NO_3$ (263,33): calcd. C 68.42; H 8.04; N 5.32; found C 68.43; H 8.06; N 5.31.

(1-Benzylpyrrolidine-2,2-diyl)dimethanol (14). Ethyl 1-benzyl-2-formylpyrrolidine-2-carboxylate **2** (0.28 g, 1.07 mmol) and sodium cyanoborohydride (0.67 g, 10.7 mmol) were dissolved in dry EtOH (8 mL) and refluxed for 3 h. After this time, the solvent was evaporated under reduced pressure and the residue was suspended in H_2O (30 mL) and extracted with DCM (4 × 10 mL). The organic fractions were reunited and dried over Na_2SO_4, filtered and evaporated under vacuum. The residue was purified by chromatography on silica gel (1° eluent = petroleum ether/Et_2O 2:1, 2° eluent = Et_2O/MeOH 1:1) getting **14** (0.19 g, 0.85 mmol, 79%) as a brown–yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.69 (m, 2H, 4-CH_2), 1.93 (m, 2H, 3-CH_2), 2.74 (t, ^3J = 6.5 Hz, 2H, 5-CH_2), 3.03 (bs, 2H, OH), 3.57 (m, 4H, *CH*$_2$OH), 3.76 (s, 2H, N*CH*$_2$Ph), 7.28 (s, 5H, Ph). ^{13}C-NMR (200 MHz, $CDCl_3$): δ 21.5; 31.4; 52.2; 52.3; 63.6; 68.6; 126.8; 128.2; 128.3; 128.4; 139.8. MS (ESI): m/z = 222 $[M + H]^+$. $C_{13}H_{19}NO_2$ (221,30): calcd. C 70.56; H 8.65; N 6.33; found C 70.54; H 8.66; N 6.35.

Diethyl 1-benzylpyrrolidine-2,2-dicarboxylate (15). Ethyl 1-benzyl-2-formylpyrrolidine-2-carboxylate **2** (0.28 g, 1.07 mmol) was dissolved in dry EtOH (5 mL). At 0°C, it was added KOH 1N in EtOH (3 mL) and I_2 (0.34 g, 1.34 mmol) dissolved in EtOH (2 mL). The reaction was stirred at r.t. for 60 h. After this time, it was added sodium thiosulfate (1 mL) and stirred for 5 minutes. The solvent was removed under reduced pressure and the residue was suspended in H_2O (30 mL) and extracted with $CHCl_3$ (3 × 10 mL). The organic fractions were reunited and dried over Na_2SO_4, filtered and evaporated under vacuum getting **15** (0.32 g, 1.05 mmol, 98%) as a brown–yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.27 (t, ^3J = 7.3 Hz, 6H, CH_2CH_3), 1.84 (m, 2H, 4-CH_2), 2.38 (m, 2H, 3-CH_2), 2.77 (t, ^3J = 6.8 Hz, 2H, 5-CH_2), 3.87 (s, 2H, N*CH*$_2$Ph), 4.23 (q, ^3J = 7.3 Hz, 4H, *CH*$_2$CH$_3$), 7.29 (m, 5H, Ph). MS (ESI): m/z = 306 $[M + H]^+$. $C_{17}H_{23}NO_4$ (305,37): calcd. C 66.86; H 7.59; N 4.59; found C 66.87; H 7.60; N 4.62.

5-Benzyl-2-methyl-2,5-diazaspiro[3.4]octan-1-one (16). Ethyl 1-benzyl-2-((methylamino)methyl)pyrrolidine-2-carboxylate **11** (0.30 g, 1.08 mmol) was dissolved in dry THF (2 mL) and added in a round bottom flask containing LDA 1.8 M (1.2 mL, 2.16 mmol) at −20°C. The mixture was stirred at −20°C for 1 h, and then at room temperature for 12 h. After this time, it was added H_2O (10 mL) and extracted with DCM (4 × 5 mL). The organic fractions were reunited and dried over Na_2SO_4, filtered and evaporated under vacuum. The residue was purified by chromatography on silica gel (eluent = Et_2O) getting **16** (0.14 g, 0.59 mmol, 56%) as a yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.82 (m, 2H, 4-CH_2), 2.13 (m, 2H, 3-CH_2), 2.28 (m, 2H, 5-CH_2), 2.76 (s, 3H, NCH_3), 3.20 (AB system, ^2J = 5.7 Hz, 2H, *CH*$_2$NCH$_3$), 3.76 (AB system, ^2J = 13.3 Hz, 2H, N*CH*$_2$Ph), 7.27 (m, 5H, Ph). ^{13}C-NMR (200 MHz, $CDCl_3$): δ 22.2; 28.0; 31.8; 52.7; 53.8; 53.9; 79.6; 126.9; 128.1; 128.5; 139.2; 172.4. MS (ESI): m/z = 231 $[M + H]^+$ 253 $[M + Na]^+$. $C_{14}H_{18}N_2O$ (230,31): calcd. C 73.01; H 7.88; N 12.16; found C 72.98; H 7.91; N 12.19.

1-Benzyl-8,8-dimethyl-7,9-dioxa-1-azaspiro[4.5] decane (17). In a test tube (1-benzylpyrrolidine-2,2-diyl)dimethanol **14** (0.15 g, 0.68 mmol) was dissolved in dry acetone (10 mL), it was added p-toluensulfonic acid (40 mg, 0.23 mmol) and some 4Å activated MS. The tube was sealed and refluxed for 96 h. After this time, the reaction was filtered, concentrated under vacuum, and neutralized with $NaHCO_3$ sat. sol. It was added H_2O (10 mL) and extracted with $CHCl_3$ (3 × 5 mL). The organic fractions were reunited and dried over Na_2SO_4, filtered and evaporated under vacuum. The residue was purified by chromatography on silica gel (eluent = Et_2O) getting **17** (91 mg, 0.34 mmol, 51%) as a yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 6H, CH_3), 1.70 (m, 2H, 4-CH_2), 1.84 (m, 2H, 3-CH_2), 2.64 (t, ^3J = 6.6 Hz, 2H, 5-CH_2), 3.78 (AB system, ^2J = 11.7 Hz, 4H, OCH_2), 3.97 (s, 2H, N*CH*$_2$Ph), 7.31 (m, 5H, Ph). MS (ESI): m/z = 262 $[M+ H]^+$. $C_{16}H_{23}NO_2$ (261,36): calcd. C 73.53; H 8.87; N 5.36; found C 73.50; H 8.89; N 5.37.

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