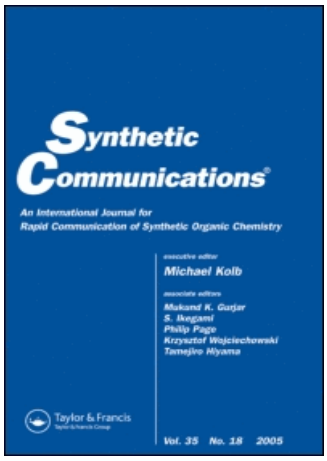

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Synthesis of the 3-(3,4,5-Trimethoxyphenyl)-pyrrolidine: A New Conformationally Constrained Mescaline Analogue

Ricardo de L. Barreto, Laura B. L. R. Nascimbem, and Carlos R. D. Correia
Chemistry Institute, State University of Campinas (UNICAMP), Campinas, São Paulo, Brazil

Abstract: The total synthesis of the 3-(3,4,5-trimethoxyphenyl)-pyrrolidine, a new and conformationally constrained mescaline analogue, was accomplished in a concise and efficient manner. The synthetic route encompassed only 4 steps from the starting N-Cbz-3-pyrrolidine, in 46% overall yield. The route features a highly effective Heck arylation of the non-activated olefin N-Cbz-3-pyrrolidine with the 3,4,5-trimethoxybenzene diazonium tetrafluoroborate. The hemiaminal (lactamol) Heck adduct was converted to the mescaline analogue in a sequence of reactions: (a) dehydration of the intermediate hemiaminal 3 with trifluoroacetic acid anhydride, (b) hydrogenation/hydrogenolysis of the endocyclic enecarbamate 6 with H2-Pd/C, and (c) formation of the rather stable mescaline analogue in the form of a hydrochloride salt. The target molecule constitutes a new mescaline analogue with potential activity towards 5-HT2 dopamine receptors.

Keywords: arenediazonium tetrafluoroborates, 3-aryl pyrrolidines, heck arylation, mescaline analogues

INTRODUCTION

Mescaline, an important hallucinogenic alkaloid, was discovered in 1896 by Heffer.[1] Mescaline is found in the small cactus peyote *Lophophora williamsii* (Cactaceae), and its structure corresponds to the rather simple alkaloid

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Address correspondence to Carlos Roque Duarte Correia, Instituto de Química, UNICAMP, P. O. Box 6154, Campinas, São Paulo, 13084-971 Brazil. E-mail: roque@iqm.unicamp.br

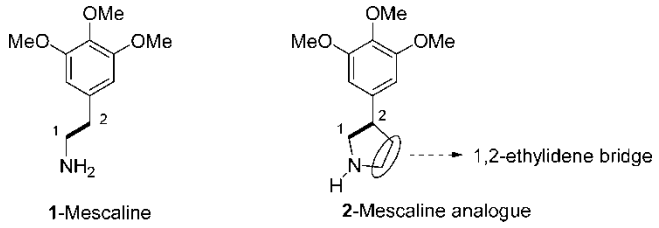
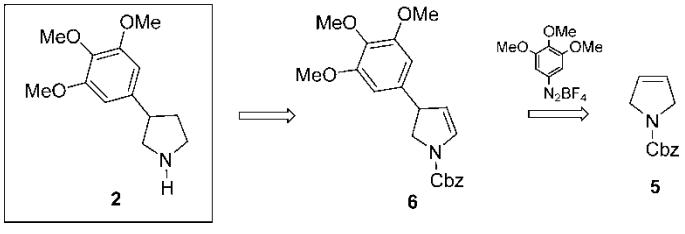


Figure 1. Mescaline and the target molecule **2**.



Scheme 1. Retrosynthesis of the new mescaline analogue **2.**

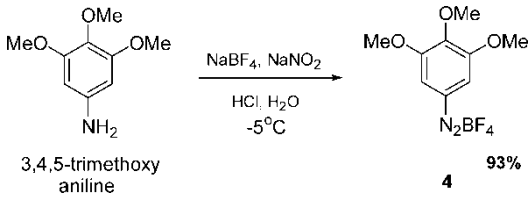
3,4,5-trimetoxyphenylethylamine shown in Fig. 1. Mescaline acts on the central nervous system (CNS) because of its interaction with dopamine receptors, especially with those of the $5HT_2$ type. These receptors mediate many important physiological processes, such as vascular and nonvascular contraction of the smooth muscle, humor perception, anxiety, and feed behavior.[2] Mescaline has been used as a hallucinogen in experimental psychiatry.

To evaluate the structure–activity relationship (SAR), many analogues of the prototype mescaline have been investigated.[3–7] Hence, structural modifications of its basic framework are of importance to optimize biological activity and develop new drugs for treatment of CNS disorders, such as schizophrenia and depression.[2,8,9] Herein we describe the total synthesis of a new analogue of mescaline bearing a pyrrolidine ring as the conformational constraining element.

Our synthetic strategy was centered on a Heck arylation of the protected 3-pyrroline **5** with an electron-rich arenediazonium salt to furnish the intermediate endocyclic enecarbamate **6**. Catalytical hydrogenation of enecarbamate **6** followed by hydrogenolysis would then provide the target molecule **2** (Scheme 1).

RESULTS AND DISCUSSION

The synthetic route was initiated with the preparation of the trimethoxybenzenediazonium tetrafluoroborate **4** following the protocol of Schiemann.[10] It

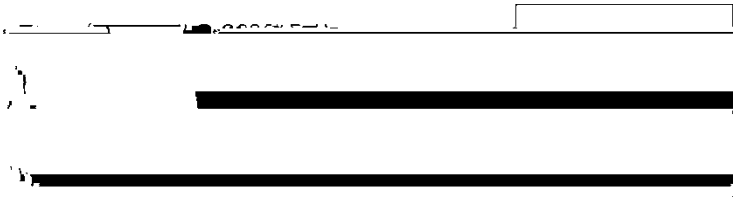


Scheme 2. Preparation of the arenediazonium tetrafluoroborate **4**.

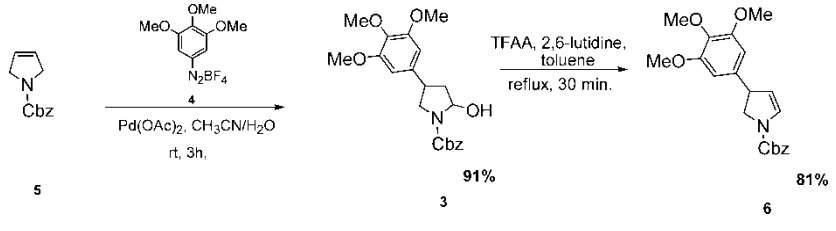
involved the diazotization reaction of 3,4,5-trimethoxyaniline in an acidic medium with sodium tetrafluoroborate (Scheme 2). The average yield for this reaction was 93%. Trimethoxybenzenediazonium tetrafluoroborate **4** was obtained as a stable, crystalline solid. Diazotation of 3,4,5-trimethoxyaniline can also be carried out under neutral conditions following Milner's protocol, albeit in slightly lower yields.[11]

With the 3,4,5-trimethoxybenzenediazonium tetrafluoroborate in hand, we then prepared the olefin *N*-Cbz-3-pyrroline by means of olefin metathesis following Grubbs's protocol.[12] As described in Scheme 3, diallylamine was converted into the desired 3-pyrroline in 95% isolated yield after two steps (*N*-protection and olefin metathesis).

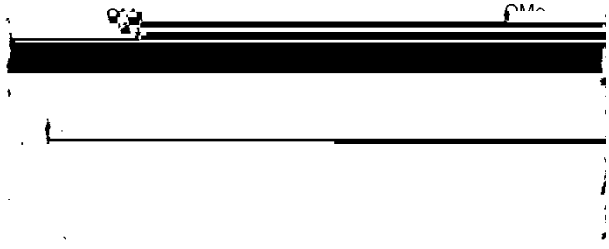
The critical step in the overall route involved a Heck arylation of *N*-Cbz-3-pyrroline **5** with arenediazonium salt **4** (Scheme 4). Heck arylation was accomplished by employing the conditions developed by Correia and coworkers,[13] under base-free conditions and using palladium acetate as catalyst to provide



Scheme 3. Protection and metathesis of diallylamine.



Scheme 4. Heck arylation of *N*-Cbz-pyrroline and dehydration of lactamol.



Scheme 5. Synthesis of the mescaline constrained analogue **2** in the hydrochloride form.

lactamol **3** in 91% yield as a rather stable oil. Most probably, enecarbamate **6** is the primary adduct of this Heck reaction. However, as observed previously, the reaction medium turns acidic as arylation proceeds. Under acidic conditions, the *N*-acyl enamine moiety undergoes hydration to form the lactamol **3**. Formation of the lactamol **3** during the Heck arylation is a critical event that prevents further arylation of the electron-rich olefin present in enecarbamate **6**.[13] Also noteworthy is that these Heck arylations of *N*-pyrroline are amenable to multigram-scale production.

Having the stable lactamol in hand, dehydration was cleanly and efficiently carried out using trifluoroacetic anhydride and 2,6-lutidine in refluxing toluene[14] to give the desired endocyclic enecarbamate **6** in good overall yields (~72% yield over two steps).

The last steps in the synthetic route involved a simultaneous Cbz removal and an enamine reduction. These transformations were carried out on a single step employing H_2/Pd-C; that is, hydrogenolysis followed by catalytic hydrogenation provided the target 2-aryl-pyrrolidine **2** in 65% isolated yield in the form of a stable hydrochloride after acidification of the medium with 6M HCl (Scheme 5).

CONCLUSION

A new and conformationally constrained analogue of mescaline was synthesized in a straightforward and concise manner. The key step was an efficient Heck arylation of a *N*-protected 3-pyrroline using an electron-rich arenediazonium tetrafluoroborate, which provided the key lactamol intermediate **3** in good yield. Lactamol **3** was cleanly converted into the unsaturated mescaline analogue after dehydration to provide the endocyclic enecarbamate **4**. A concomitant hydrogenolysis–catalytic hydrogenation of enecarbamate **4** provided the new mescaline analogue **2**. The overall synthesis involved only four steps from *N*-Cbz-3-pyrrolidine and was carried out in 46% overall yield.

Biological essays of this new potential 5-HT_2 ligand are ongoing, and results will be disclosed in due course.

EXPERIMENTAL

General Procedures

Unless noted otherwise, reactions were carried out under an atmosphere of dry nitrogen or argon, in oven-dried glassware. Methylene chloride, hexane, and triethylamine were distilled from CaH_2 prior to use. Acetonitrile was used as ACS-grade solvent without any further purification. All the reagents were purchased from traditional commercial sources and were used without further purification. Flash column chromatography was performed employing Merck silica gel 60 (230–400 mesh). Thin-layer chromatography (TLC) was performed on Merck silica-gel 60/F-254 aluminum-backed plates and was visualized by UV radiation and/or phosphomolybdic acid. Analytical high-performance liquid chromatography (HPLC) was carried out on an HP 1100 series chromatograph equipped with a UV detector. Capillary GLC analyses were performed on a Hewlett-Packard 6890 chromatograph equipped with fused-silica-gel capillary column (30 m × 0.32 mm) wall coated with HP-5. Melting points were measured on a Thomas Hoover capillary melting-point apparatus and are uncorrected. Nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded as solutions in the indicated solvents on Varian Gemini 300 or Brucker AC-300P spectrometer. Chemical shifts are reported in parts per million (δ units) relative to tetramethylsilane as internal standard (^{1}H NMR). Infrared spectra were recorded on a Thermo Nicolet 200 spectrometer. Low-resolution mass spectra were obtained on a Shimadzu QP5000 spectrometer, equipped with a HP-1 column (0.20 mm × 20 m) or on a ESI Applied Biosystems MDS SCIEX, model Q Trap LC/MS/MS System, and high-resolution mass spectra on a VG Autospec Instrument.

Preparation of the Arenediazonium Tetrafluoroborate 4

To a solution of 1 g of trimethoxyaniline (5.5 mmol) in 1.5 mL of water, 1.5 mL of concentrated HCl were added. The mixture was stirred vigorously for ~20 min and then placed in a salted ice bath at −5°C. To the cooled solution, a freshly prepared aqueous solution of $NaNO_2$ (0.49 g of $NaNO_2$ dissolved in 1 mL of H_2O) was slowly added. After 15 min, an aqueous solution of $NaBF_4$ (0.845 g of $NaBF_4$ dissolved in 1.7 mL of H_2O) was added at once, causing the formation of a precipitate. The reaction mixture was filtered, and the solid was washed with cold Et_2O. The solid was collected and dissolved in 16.5 mL of acetone, and the resulting solution was filtered. To the filtrate, 11 mL of cold Et_2O were added, causing the precipitation of the arenediazonium tetrafluoroborate. The mixture was filtered and the solid dried in air to provide 1.43 g of the arenediazonium tetrafluoroborate **4** (93% yield). MW (g/mol): 282.0; mp: 114–116°C; IR (λ_{max}, film, cm^{-1}): 3105, 2277, 1587, 1493, 1475, 1425, 1314, 1243, 1129, 1022, 980;

^{1}H NMR (300 MHz, $CDCl_3$, δ): 4.0 (6H, s); 4.2 (3H, s); 8.2 (2H, s). ESI-MS (M+): 195.2.

Preparation of *N*-Cbz-3-pyrroline 5[12]

To a solution of diallylamine (1.55 g, 2 mL, 16 mmol) in 50 mL of dry dichloromethane, 4.5 mL of triethylamine (32 mmol) were added. The solution was cooled in an ice bath, and benzyl chloroformate was added (2.73 g, 2.3 mL, 16 mmol). The ice bath was removed, and the reaction mixture was stirred for 12 h. The reaction mixture was diluted with 20 mL of CH_2Cl_2 and transferred to a separatory funnel. The organic layer was separated and then washed successfully with water, saturated $NaHCO_3$, and brine. Next, the organic layer was dried with anhydrous sodium sulfate and filtered, and the solvent was removed in vacuo. A colorless oil corresponding to *N*-(Cbz)-diallylamine was obtained in quantitative yield.

The *N*-(Cbz)-diallylamine prepared previously (1.237 g, 5.35 mmol) was dissolved in 10 mL of dry dichloromethane and transferred to a flask containing a solution of the Grubbs catalyst (91 mg, 0.11 mmol) in 40 mL of dry dichloromethane. The reaction mixture was stirred under argon for 5 h at room temperature, after which the rubber septum was removed, and the reaction was left stirring for an addition hour to deactivate the catalyst. The solvent was then evaporated in vacuo, and the product was purified by flash chromatography (hexane/EtOAc = 80:20), furnishing 1.031 g of the *N*-Cbz-pyrroline **5** as homogeneous material by TLC in 95% yield. MW: 203.24 g/mol; IR (λ_{max}, film, cm^{-1}): 3095, 3077, 3043, 2961, 2909, 2863, 1708, 1627, 1435, 1360, 1331, 1209, 1128, 977; ^{1}H NMR (300 MHz, $CDCl_3$, δ): 4.2 (4H, brs); 5.2 (2H, s); 5.78 (2H, m); 7.3–7.4 (5H, m).

Preparation of Lactamol 3

To a solution of 540 mg of the *N*-Cbz-pyrroline **5** (2.7 mmol) in 13 mL of CH_3CN/H_2O (1:1; v/v), 1.125 g of the arenediazonium salt **4** (4.0 mmol) and 60 mg of $Pd(OAc)_2$ (10 mol %) were added. The reaction mixture was stirred for 3 h at room temperature, when total consumption of the pyrroline was observed by TLC analysis. The reaction mixture was then diluted with ethylacetate ($\sim$40 mL), transferred to a separatory funnel, and extracted with saturated $NaHCO_3$ and NaCl. The organic layer was collected, dried over anhydrous Na_2SO_4, and filtered, and the solvent was evaporated in vacuo. The product was purified by flash chromatography (hexane/EtOAc = 1:1) to provide 0.936 g (91% yield) of an oil (homogeneous by TLC), corresponding to a mixture of diastereomeric lactamols **3** (cis and trans). MW: 387.43 g/mol; Rf = 0.32 (hexane/EtOAc = 1:1), IR (λ_{max}, film, cm^{-1}): 3440, 2937, 2838, 1698, 1589, 1509, 1450, 1419, 1357, 1328, 1238, 1184, 1124, 1008, 698. ^{1}H

NMR (300 MHz, $CDCl_3$, δ): 2.3 (2H, m); 3.3–3.5 (1H, m); 3.85 (9H, s, OMe); 4.0 (2H, m); 5.15 (2H, s); 5.65 (1H, dd, $J = 5.1, 11.3$ Hz); 6.45 (2H, m, Ar); 7.4 (5H, m, Ar). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 155.3 (C), 153.4 (C), 136.0 (C), 128.2 (CH), 104.2 (CH), 82.0 (CH), 67.1 (CH_2), 60.8 (CH_3), 56.2 (OCH_3), 52.4 (CH_2), 42.9 (CH), 40.2 (CH_2).

Preparation of the Enecarbamate 6

To a solution of 90 mg of the lactamol (0.23 mmol) in 2.3 mL of dry toluene, 115 μL (5.0 equiv) of 2,6-lutidine (1.0 mol) and 0.3 mL (0.7 mmol) of a 7M solution of trifluoroacetic anhydride were added under argon in an ice bath at 0°C. The reaction was allowed to reach rt. After 2 h at rt, the reaction mixture was refluxed for 30 min, then cooled to room temperature, diluted with 20 mL of EtOAc, transferred to a separatory funnel, and extracted with saturated solutions of $NaHCO_3$ and NaCl. The organic layer was separated, dried over anhydrous Na_2SO_4, and filtered, and the solvent was evaporated in vacuo. Flash chromatography (hexane/EtOAc = 60:40) provided 67.3 mg of enecarbamate **6** as homogeneous material by TLC, in 81% yield. MW: 369.41 g/mol; Rf = 0.28 (hexane/EtOAc = 8:2) phosphomolybdic acid; IR (λ_{max}, film, cm^{-1}): 2937, 2834, 2358, 1704, 1616, 1589, 1508, 1455, 1417, 1336, 1234, 1124, 1008, 759, 698. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.7 (1H, m); 3.9 (9H, s, OMe); 4.1 (1H, m); 5.1 (1H, brs); 5.2 (2H, d, $J = 7.7$ Hz); 6.4 (2H, s, Ar); 6.7–6.9 (1H, d, $J = 3.7$ Hz); 7.4 (5H, m, Ar). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 153.5 (C), 152.0 (C), 140.0 (C), 128.5 (CH), 111.9 (CH), 104.1 (CH), 67.3 (CH_2), 60.1 (CH_3), 56.1 (CH_3), 53.9 (CH_2), 49.0 (CH), 45.7 (CH); MS: m/z (rel. intensity) 369 (82.5) $[M]^+$, 325 15, 234 (17.5), 205 (22.5), 91 100, 65 (14). HRMS m/z calcd. for $C_{21}H_{23}NO_5$, 369.15762; found 369.15758.

Preparation of 3-(3,4,5-Trimethoxyphenyl)-pyrrolidine 2

To a solution of 180 mg of the enecarbamate **6** (0.49 mmol) in 4 mL of EtOAc, 52 mg of Pd-C 10 mol % (0.5 mmol) were added. The resulting suspension was purged with H_2 for ~10 min and then stirred under hydrogen (a filled balloon) for 2 h. When TLC analysis indicated complete consumption of the enecarbamate, the reaction mixture was filtered through a short pad of Celite,® and the solvent was partially evaporated to a ~5-mL volume. To this concentrated EtOAc solution of the free amine, a drop (~0.2 mL) of a 6M HCl solution was added, and the mixture was cooled in ice to give 75 mg of a white precipitate after filtration, corresponding to the hydrochloride **2** (65% yield). MW: 273.60 g/mol; mp: >220°C (decomp.). Rf = 0.12 ($CHCl_3$/MeOH = 9:1). IR: 2933, 2872, 2839, 1687, 1589, 1507, 1458, 1421, 1319, 1237, 1119, 1004, 824. ^{1}H NMR (300 MHz, D_2O, δ): 2.0 (2H,

m); 2.3 (1H, m); 3.1 (2H, t, $J = 11.0$ Hz); 3.2–3.5 (2H, m); 3.6 (2H, s); 3.7 (6H, s); 6.6 (2H, s). ^{13}C NMR (75 MHz, D_2O, δ): 152.3 (C), 135.5 (C), 104.4 (CH), 61.4 (C), 60.5 (CH_3), 55.8 (CH_3), 50.3 (CH_2), 46.6 (CH_2), 42.8 (CH), 31.1 (CH_2). ESI-MS (M^+): 238.3.

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