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ALTERNATE AND IMPROVED SYNTHESIS OF THE CACTUS ALKALOID ARIZONINE

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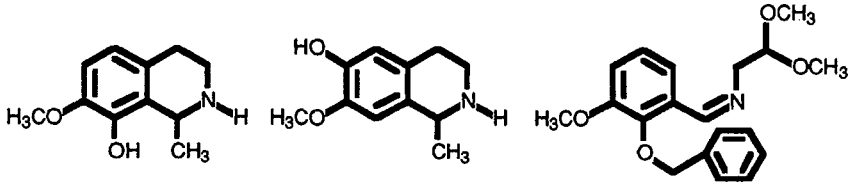
Abstract: An alternate and high-yield synthesis of the simple tetrahydroisoquinoline alkaloid arizonine, *via* the sodium cyanoborohydride mediated reductive amination of 2-benzyloxy-3-methoxyacetophenone with aminoacetaldehyde diethyl acetal, as the key step, is reported.

Cactaceae are the source from which most of the natural simple tetrahydroisoquinolines have been obtained. A recent investigation of the alkaloids of the giant cactus [*Carnegiea gigantea* (Engelm.) Br. & R., saguaro] resulted in the isolation of arizonine (**1**), the second known simple tetrahydroisoquinoline to display the rare 7,8-disubsitution pattern.[1] Later, compound **1** was also found in *Pachycereus pecten-aboriginum* together with its biogenetic isomer, the widespread salsoline (**2**).[2]

There are two reported syntheses of arizonine,[1] however, they proceed in very low yields. The shortest one,

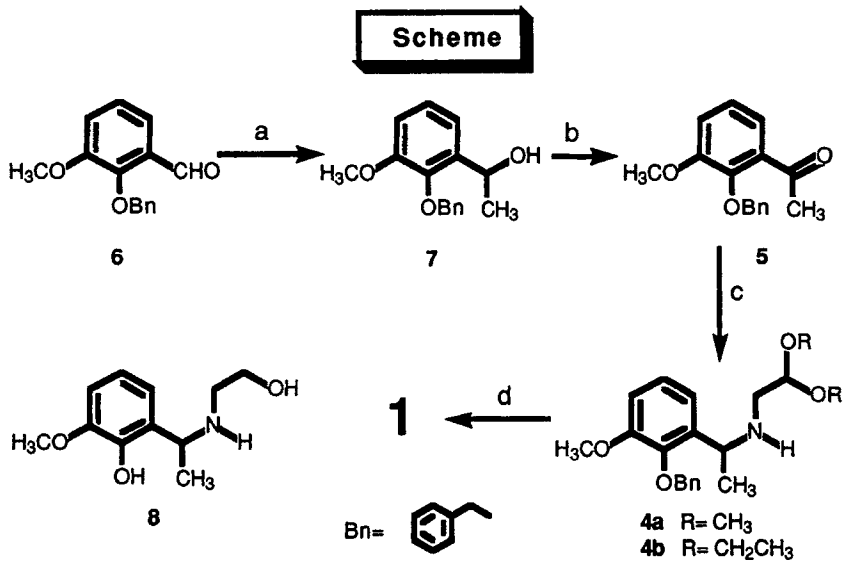
based on the Bobbitt[3] modification of the Pomeranz-Fritsch cyclization, gave at best less than 10% yield of **1** after four reaction steps. In the above synthetic scheme, introduction of the C-1 methyl group was carried out by addition of a Grignard reagent to Schiff base **3** producing the key intermediate **4a** (Scheme) which, after debenzylation and acid-catalyzed cyclization, was transformed into **1**.



1 **2** **3**

Since the processes of synthesis and transformation of **4a** constituted the main sources of the poor yield of the overall sequence, it was felt that if a better strategy for the elaboration of **4** and adequate cyclization conditions of it could be devised, an improved synthesis of **1** would be at hand. The approach reported here consists in the reductive amination of ketone **5** as an alternate route towards **4**, associated with milder cyclization conditions to increase the recovery of **1**.

Thus, the known 2-benzyloxy-3-methoxybenzaldehyde (**6**) was reacted with ethereal methylmagnesium bromide to cleanly afford 94% of benzyl alcohol **7**, which was readily oxidized with pyridinium chlorochromate supported on alumina[4] in refluxing dichloromethane, to give the required acetophenone **5** in 93% yield.



Reagents and Reaction Conditions: a. MeMgBr, Et_2O, 0°C--> RT, 94%; b. PCC/Al_2O_3, NaAcO, CH_2Cl_2, reflux, 93%; c. $H_2NCH_2CH(OCH_2CH_3)_2$, glacial AcOH, $NaCNBH_3$, $MgSO_4$, MeOH, reflux 9 h, 93%; d. 1. 4N HCl, overnight, 2. 10% Pd/C, H_2, 89%.

The crucial next step, reductive amination of **5** with aminoacetaldehyde diethyl acetal, was initially undertaken by attempting condensation of the amine with the ketone in refluxing benzene under acid catalysis and azeotropic removal of water. This proved unsuccessful, probably because of the sluggishness with which aromatic ketones undergo this condensation[5] and the retardatory effect on the reaction rate produced by the electron donating *ortho*-benzyloxy group.

Better results, but still far from optimum, were obtained when an excess of the amine hydrochloride was used and the imminium intermediate was reduced *in situ* with sodium cyanoborohydride, as reported by Borch *et al.*[6] Finally, by

analogy with the work of Williams *et al.*[7] and the results of Nichols *et al.*,[8] cyanoborohydride reduction of a mixture of ketone **5** in refluxing absolute methanol with a fivefold excess of the amine and 4.5 equivalents of glacial acetic acid afforded the secondary amine **4b** in 86% yield. Further improvement, leading to a 93% recovery of **4b** was obtained when calcined magnesium sulfate[9] was added to the reaction mixture, as a dehydrating agent.

Debenzylation and cyclization of **4b** were achieved in "one-pot" by stirring overnight the amine in 4N aqueous hydrochloric acid, followed by catalytic hydrogenation with palladized charcoal as catalyst; by avoiding the isolation of the readily oxidizable phenolic intermediate, this procedure afforded the hydrochloride of **1** in 89% yield.

Choice of cyclization conditions was arrived at after carefully controlled experiences employing different acid concentrations; it was observed that concentrations of hydrochloric acid above 5N caused extensive decomposition of the reaction product, leading to the formation of colored impurities which made very difficult the chromatographic purification of **1**.

The final compound was characterized by comparison of its ^{1}H NMR spectrum and the melting point of its salicylate with published data,[1] resulting in a complete agreement. Additionally, small quantities of aminoalcohol **8**, were isolated. Aminoalcohols are known to be the major side products of the above cyclization reaction.[3]

In conclusion, appropriate selection of the synthetic steps and reaction conditions allowed a facile, direct and improved elaboration of **1**.

EXPERIMENTAL

Infrared spectra were measured with a Beckman Acculab 8 spectrometer, melting points were determined on an Ernst Leitz hot-stage apparatus and NMR spectra were recorded on a Bruker WP 80 SY spectrometer in $CDCl_3$, unless otherwise stated. The ^1H NMR spectra were measured at 80.13 MHz, employing Me_4Si as an internal standard, chemical shifts are expressed in δ, while J and $w_{1/2}$ values are given in hertz. The ^{13}C NMR spectra were determined at 20.15 MHz and the chemical shift values are given in parts per million downfield from Me_4Si. High and low resolution mass spectral data were obtained from CERIDE (Santa Fe) and chromatographic separations were performed using a Chromatotron,® employing increasing amounts of EtOAc in hexane as solvent, unless otherwise noted.

α-Methyl-(2-benzyloxy-3-methoxy)-benzyl alcohol (7): An ethereal methyl magnesium bromide solution (2.17 mL, 2.17 mmol), diluted in Et_2O (10 mL), was added dropwise under nitrogen to a stirred ethereal (7 mL) solution of **6** (500 mg, 2.07 mmol), cooled in an ice-water bath. After addition was complete, the reaction mixture was further stirred for 30 min at room temperature, then saturated aqueous NH_4Cl solution (10 mL) was added and the organic material was extracted with Et_2O (3 x 30 mL); the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), concentrated *in vacuo* and chromatographed to afford **7** (501 mg, 1.94 mmol,

94%) as a colorless oil. IR ν 3400, 3060, 2960, 1580, 1480, 1270, 1070, 920, 850, 790, 760 and 700 cm^{-1}; ^1H NMR δ 1.40 (d, 3H, J= 6.4), 2.04 (br d, 1H, J= 6.4), 3.90 (s, 3H), 5.08 (s, 2H) and 6.76-7.50 (m, 8H); ^{13}C NMR δ 23.49, 55.54, 64.89, 74.56, 111.28, 117.77, 124.04, 127.76, 127.97, 128.13, 137.38, 139.40, 144.34 and 152.15.

2-Benzyloxy-3-methoxy acetophenone (5): Alcohol 7 (500 mg, 1.94 mmol) was dissolved in dry CH_2Cl_2, to which anhydrous sodium acetate (318 mg, 3.88 mmol) and PCC supported on alumina (4.79 g, 2 equiv.) were added portionwise. The reaction mixture was stirred under reflux until the starting material dissapeared, the suspension was poured over Celite contained in a Büchner funnel and filtered under vacuum; the solids were repeatedly washed with CH_2Cl_2, the combined filtrates were concentrated, eluted with CH_2Cl_2 through a short plug of silica gel and chromatographed, yielding 5 (461 mg, 1.80 mmol, 93%) as an oil. IR ν 3080, 2960, 1690, 1590, 1490, 1280, 1060, 990, 800, 770, 750 and 710 cm^{-1}; ^1H NMR δ 2.52 (s, 3H), 3.90 (s, 3H), 5.07 (s, 2H) and 6.99-7.49 (m, 8H); ^{13}C NMR δ 30.93, 55.75, 75.46, 115.54, 120.42, 123.77, 127.81, 128.08, 134.40, 136.79, 146.78, 152.79 and 199.98; MS, m/e(%): 256(M^+, 7), 238(5), 214(9), 213(8), 151(18), 92(20), 91(100) and 65(21); found for M^+, m/e 256.1100 ($C_{16}H_{16}O_3$ requires m/e 256.1099).

α-Methyl-(2-benzyloxy-3-methoxy)- benzylaminoacetaldehyde diethyl acetal (4b): Acetophenone 5 (410 mg, 1.60 mmol), aminoacetaldehyde diethyl acetal (1.10 mL, 8.0 mmol) and glacial AcOH (0.41 mL, 7.21 mmol) were mixed with stirring in anhydrous MeOH (8 mL) under a nitrogen atmosphere. Calcined $MgSO_4$ (250 mg) and $NaCNBH_3$ (98 mg, 1.60 mmol) were added portionwise to the above solution and the reaction mixture was refluxed for 9 h. The reaction was

quenched with 1N KOH (10 mL) and the product was extracted with EtOAc (3 x 40 mL). The EtOAc extracts were washed with brine (10 mL), dried (Na_2SO_4) and the solvent was removed under reduced pressure to give an oil which was chromatographed, affording **4b** (557 mg, 1.49 mmol, 93%); IR ν 3080, 2980, 2920, 2880, 1590, 1480, 1380, 1270, 1130, 1070, 790, 760, 740 and 700 cm^{-1}; ^1H NMR δ 1.15 (t, 3H, J= 7), 1.16 (t, 3H, J= 7), 1.27 (d, 3H, J= 4.8), 2.51 (d, 2H, J= 5.6), 3.49 (q, 2H, J= 7), 3.58 (q, 2H, J= 7), 3.88 (s, 3H), 4.17 (q, 1H, J= 4.8), 4.52 (t, 1H, J= 5.6), 5.01 (s, 2H), 6.73-7.14 (m, 3H) and 7.26-7.55 (m, 5H); ^{13}C NMR δ 15.04, 22.91, 49.74, 51.07, 55.43, 61.59, 61.97, 74.46, 102.04, 110.54, 118.25, 123.93, 127.49, 127.76, 128.02, 137.70, 139.03, 145.40 and 152.36; MS m/e (%): 373(M^+, 2), 368(2), 329(4), 270(20), 257(9), 241(76), 209(13), 150(13), 137(18), 103(23), 91(100) and 75(22); found for M^+, m/e 373.2260 ($C_{22}H_{31}O_4N$ requires m/e 373.2253). Addition of 25% EtOH to the eluant allowed the recovery of unreacted aminoacetaldehyde diethyl acetal (565 mg).

8-Hydroxy-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline, arizonine (**1**): Cold 4N HCl (2 mL) was added under nitrogen to an ice-cooled and stirred ethereal (0.5 mL) solution of benzylamine **4b** (100 mg, 0.278 mmol). After 30 min, the Et_2O was removed under vacuum and the remaining solution was further stirred overnight at room temperature. Then, 10% Pd/C (55 mg) was added and the reaction was stirred under hydrogen (1 atm) for 24 h. The catalyst was separated from the liquid phase containing **1** by centrifugation and exhaustively washed with distilled water (3 x 2 mL). The aqueous solution was concentrated under vacuum and chromatographed, employing an EtOH-$CHCl_3$ mixture (30:70), to obtain the hydrochloride of **8** (4 mg, 0.02 mmol, 7%), IR ν 3400, 2940, 2830, 1600, 1490, 1270, 1240, 1080, 1020, 840, 790, 750 and 700 cm^{-1}; ^1H NMR (D_2O) δ 1.47 (d, 3H, J= 6.4), 2.70-2.84 (m, 2H), 3.70-3.90 (m, 2H), 3.86 (s, 3H), 3.97 (q, 1H, J= 6.4), 4.89

(bs, 3H $w_{1/2}$= 15) and 6.51-6.82 (m, 3H); irradiation at δ: 1.47 collapsed the δ: 3.97 quartet into a singlet; irradiation at δ: 2.78 produced a singlet at δ: 3.80 from the δ: 3.70-3.90 multiplet; ^{13}C NMR (D_2O) δ 21.74, 48.89, 55.54, 58.14, 60.53, 110.33, 118.46, 119.95, 126.54, 146.15 and 147.74; this was followed by arizonine hydrochloride (1, 57 mg, 0.248 mmol, 89%); mp: 215°C, dec. (recryst. from $CHCl_3$-MeOH); IR ν 3500 - 2550, 1590, 1440, 1380, 1290, 1250, 1100, 1060 and 810 cm^{-1}; ^1H NMR (D_2O) δ 1.54 (d, 3H, J= 7.2), 2.78-3.00 (m, 2H), 3.28-3.50 (m, 2H), 3.80 (s, 3H), 4.70 (q, 1H, J= 7.2), 6.58 and 6.92 (AB quartet, 2H, J= 8); irradiation at δ: 2.80 transformed the 3.28-3.50 multiplet into a singlet resonating at δ: 3.37; irradiation at δ: 4.70 produced a singlet at δ: 1.54; ^{13}C NMR (D_2O) δ 16.01, 23.03, 35.73, 46.31, 55.50, 111.19, 119.38, 119.86, 122.78, 140.74 and 144.89. The hydrochloride (30 mg) was dissolved in 2N ammonia (8 mL) and the free base [^1H NMR δ 1.65 (d, 3H, J= 7.2), 2.80-3.13 (m, 2H), 3.25-3.45 (m, 2H), 3.85 (s, 3H), 4.71 (q, 1H, J= 7.2), 5.49 (bs, 2H, $w_{1/2}$= 5) and 6.60 and 6.75 (AB quartet, 2H, J= 8)] was extracted with CH_2Cl_2 (3 x 10 mL), the combined extracts were dried over Na_2SO_4, concentrated *in vacuo* and dissolved in Et_2O (2 mL), to which a saturated ethereal solution of salicylic acid was added dropwise. The salicylate soon formed as a white solid, it was separated by centrifugation, washed with cold Et_2O and dried, mp: 209-211°C (lit:[1] 208-210°C).

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