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Facile synthesis of papaverine, (±) setigeridine, (±) setigerine, and related isoquinoline alkaloids

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ABSTRACT

A highly efficient and simple protocol for the synthesis of papaverine, (±) Setigeridine, (±) Setigeri ne, and related isoquinoline alkaloids like Dihydropapavaralidine, Papavaralidine and (±) Papavaranol by using copper mediated aerial Oxidative Amidation reaction conditions.

Key words: Isoquinoline alkaloids, Oxidative Amidation–Bischler–Napieralski Reaction, Dihydropapavaralidine, Papavaralidine, (±) Papavaranol, papaverine, (±) Setigerine and (±) Setigeridine.

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INTRODUCTION

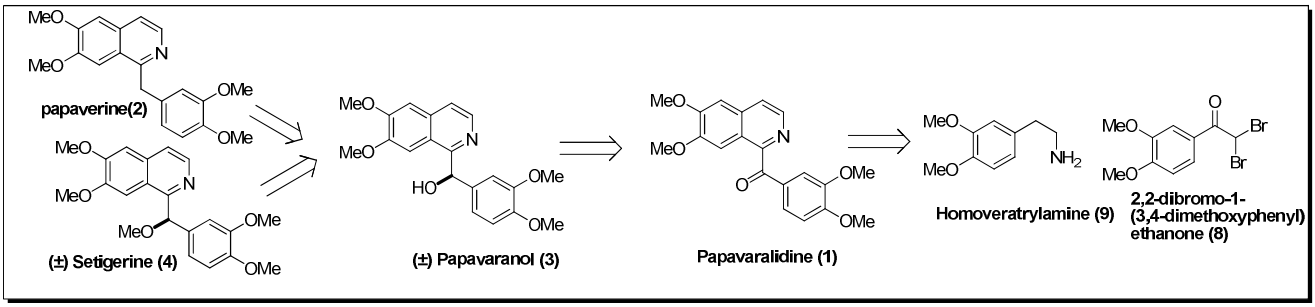
Isoquinoline nucleus is the heart of vital family of alkaloids. Alkaloids have been the source of much human interest and enthrallment both in terms of scientific research and intellectual usage. Habitually extremely reactive in small amounts, their effects on the human physiology is most incredible on the nervous system. Natural products that contain an Isoquinoline moiety frequently exhibit imperative biological activity. Apart from the Isoquinoline alkaloids, 1-Substituted isoquinoline alkaloids are the most imperative members of this isoquinoline alkaloid family[1,2], which are either naturally open alkaloids or intermediates in both organic synthesis and biosynthesis[3]. These Isoquinoline alkaloids are a large category of medicinally active alkaloids, whose properties are variable. Their properties include being antispasmodic, antimicrobial, antitumor, antifungal, anti-inflammatory, cholagogue, hepatoprotective, antiviral, amoebicidal, anti-oxidant and can act as enzyme inhibitors. Examples include protoberberines, aporphines, and papaverines. As a result, there is much interest in the synthesis of 1-Substituted Isoquinoline derivatives.[4]

Functionalized isoquinoline alkaloids have interesting biological activities and many of them exploited with benign therapeutic activity.[5] These alkaloids are rampant scaffolds that serve as essential building blocks for the synthesis of natural products[6] shown in figure **1**, such as Papavaralidine (**1a**), (±) Papavaranol (**3a**), papaverine (**2**), (±) Setigerine (**4**) and (±) Setigeridine (**5**). Previously, numerous novel naturally available papaverineisoquinolines (±) Setigerine (**4**) and (±)Setigeridine (**5**) have been isolated from Papaversetigerum DC.[7] Since (±)Setigeridine (**5**), (±) Setigerine (**4**) and a few of their derivatives are known to display diverse biochemical and pharmacological actions while being moderately non-toxic to human, making it extensively applicable[8] in terms of hepatoxicity and anti-malarial activity.[8,9] The modification of Setigerine (**4**)has been attractive in organic synthesis.[9]

Jan Jacobs *etal* demonstrated an improved synthetic route for the preparation of the new alkaloid (±) Setigerine (**4**) and some new 3,4-dihydro papaverine and papaverine derivatives are reported.[10] Hear in, we reported a facile and practical synthesis of naturally occurring papaverineisoquinoline alkaloids by way of copper mediated aerial Oxidative Amidation reaction.[11,12] From that we extended our ongoing research project on the total synthesis of biologically active natural products Papaverine (**2**), (±) Papaveranol (**3**), (±) Setigerine (**4**) and (±)Setigeridine (**5**).

Retro synthetic scheme

With anticipation that the oxidative amidation methodology could be used as a key step in the isoquinoline synthesis, we have designed a proficient retro synthetic route for the synthesis of (±) papaveranol (**3**), Papaverine (**2**)and (±) setigerine (**4**)as shown in the retrosynthetic approach (Scheme 1) and same approach applied for the synthesis of (±)Setigeridine (**5**). Papavaranol(**3**)on deoxygenation and by methylation produce respective Papaverine (**2**)and(±) Setigerine (**4**). Papavaranol(**3**)would be obtained by the reduction of papavaraldine (**1a**).Itcould efficiently be synthesized using modified Oxidative Amidation–Bischler–Napieralski Reaction from the corresponding key starting materiels 2,2-dibromo-1-(3,4-dimethoxyphenyl)ethanone (**8**) with Homoveratrylamine (**9**)under the reported conditions.



Scheme1

MATERIALS AND METHODS

All reagents were used as received from commercial sources without further purification or prepared as described in the literature. Reactions were stirred using Teflon-coated magnetic stirring bars. TLC plates were visualized by ultraviolet light or by treatment with a spray of Pancaldi reagent {$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O}. Chromatographic purification of products was carried out by flash column chromatography on silica gel (60-120mesh). Melting points were determined using an electro thermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1650 Fourier transform spectrometer. NMR spectra were measured in $CDCl_3$, acetone, DMSO-d_6 (all with TMS as internal standard) on a Varian Gemini 400 MHz FT NMR spectrometer magnetic resonance spectrometer. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t= triplet, q = quartet, m = multiplet. Mass spectra were recorded on an HP-5989A quadrapole mass spectrometer.

General Procedure for theSynthesis of *N*-(3,4-dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)-2-oxoacetamide (7a):

A mixture of 2,2-dibromo-1-(3,4-dimethoxyphenyl)ethanone**(8a)** (6.0 g, 0.0177mol) and Pyridine (4.21 g , 0.0532mol) in Toluene (30 mL, 5 vol) were stirred at 85-90 °C for 3-4 hrs. Then allowed to 25-30 °C and added water (6.0 mL, 1.0 vol) stirred for 15-20 minutes. Powdered Copper (I) Bromide (0.25 g, 0.018mmol), 2,2'-Bipyridyl (0.6 g, 0.1 w/w) and 2-(3,4-dimethoxyphenyl) ethanamine**(9)** (3.53 g, 0.0195mol) were then added into the reaction mixture and was stirred for about 8 hours at 85-90 °C in air (1atm) . After completion of the reaction (by TLC), cool the reaction mass to 25-35 °C and faltered the mass. Collected filtrate was concentrated under vaccum. The crude product was purified by column (silicagel, ethylacetate hexane mixture, 7:3), yielded the expected *N*-(3,4-dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)-2-oxoacetamide **(7a)** in5.03 g (76.0%) as a pale yellow color solid.

***N*-(3,4-dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)-2-oxoacetamide (7a):**Melting point: 78-79 °C; **IR (KBr)**:657, 766, 868, 1029, 1141, 1267, 1416, 1513, 1591, 1651, 2835, 2935, 3332; **^{1}H NMR (400 MHz, $CDCl_3$)**δ: 2.85 (t, 2H, *J*=7.2 Hz), 3.64 (q, 2H, *J*=6.0 Hz), 3.86 (s, 3H), 3.88 (s, 3H), 3.94 (s, 3H), 3.97 (s, 3H), 6.75 (s, 1H),

6.78-6.93 (m, 3H), 7.2 (b, NH), 7.86 (d, 1H, *J*=2.0 Hz), 8.23 (dd, 1H, *J*=8.8 Hz, 2.0 Hz); **^{13}C NMR (200 MHz, $CDCl_3$)**δ: 34.9, 40.5, 55.8, 55.9, 56.0, 110.0, 111.3, 111.8, 112.4, 120.5, 126.2, 127.1, 130.7, 147.6, 148.6, 148.9, 154.5, 162.1, 185.4; **MS:***m/z* (%) = 374.2 [M+1].

Synthesis of 3,4-dihydro Dihydropapaveraldine (6a):*N*-(3,4-dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)-2-oxoacetamide (7) (3.5 g , 0.0093mol) and 48% boron trifluorideetherate (17.5 mL, 5vol) was taken in the RB flask under nitrogen atmosphere and the mixture was heated at 80-85 °C for 12 h under nitrogen atmosphere. The mixture was then cooled to 0 °C and quenched into saturated sodium bicarbonate solution (35 mL, 10 vol) below 10°C. The product was then extracted with DCM (35 mL, 10 vol). The organic layer was washed with 10% sodium bicarbonate solution (17.5 mL, 5 vol) and dried over anhydrous sodium sulphate. The organic layer was distilled off under vaccum, added hexane(17.5 mL, 5 vol) and filtered the product to provide 2.93 g (88.0%) 3,4-dihydro Dihydropapaveraldine of as a brown color solid.

3,4-dihydro Dihydropapaveraldine (6a): Melting point: 188-190 °C; **IR (KBr)**: 631, 866, 1024, 1134, 1269, 1278, 1361, 1460, 1515, 1583, 1660, 2833, 2969;**^{1}H NMR (400 MHz, $CDCl_3$)**δ: 2.82 (t, 2H, *J*=8.0 Hz), 3.78 (s, 3H), 3.92 (b, 2H), 3.93 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 6.75 (s, 1H), 6.88 (d, 1H, *J*=8.4 Hz), 6.91 (s, 1H), 7.60 (dd, 1H, *J*=8.4 Hz ,1.6 Hz), 7.67 (d, 1H, *J*= 1.6 Hz);**^{13}C NMR (200 MHz, $CDCl_3$)** δ: 25.3, 47.1, 55.9, 56.0, 109.6, 109.9, 110.4, 111.2, 119.4, 126.4, 128.5, 130.9, 147.5, 149.0, 151.5, 154.0, 164.5, 192.6; **MS**: *m/z* (%) = 356.2 [M+1].

Synthesis of Papavaraldine (1a): To a stirred 3,4-dihydro Dihydropapaveraldine**(6)** (2.6 g,0.073mol) in DCM (30 mL, 5 vol), 1,8-diazabicyclo undec-7-ene (DBU) (3.34 g,0.021mol) was added and the mixture was stirred at 25 °C for 12 h. The mixture was concentrated in vaccum and the obtained residue was purified by column chromatography (silicagel, ethylacetate hexane mixture, 7:3) to give **(3)**2.31 g (90 %) in as a Yellow color solid.

Papavaraldine (1a): Melting point: 203-205 °C; **IR (KBr)**: 631, 860, 1024, 1140, 1269, 1324, 1512, 1584, 1656, 2836, 2934, 3070, 3403; **^{1}H NMR (400 MHz, $CDCl_3$)**δ: 3.95 (s, 3H), 3.96 (s, 6H), 4.0 (s, 3H), 6.87 (d, 1H, *J*=8.4 Hz), 7.14 (s, 1H), 7.43 (dd, 1H, *J*=8.4 Hz, 1.6 Hz), 7.54 (s, 1H), 7.65 (d, 1H, *J*=5.2 Hz), 7.71 (d, 1H, *J*=2.0 Hz), 8.45 (d, 1H, *J*=5.2 Hz); **^{13}C NMR (400 MHz, $CDCl_3$)**δ: 56.0, 56.1, 104.1, 104.8, 109.9, 112.0, 121.2, 122.8, 126.8, 129.9, 133.9, 140.0,149.0, 151.0, 153.2, 153.7, 153.8, 193.9; **MS**: *m/z* (%) = 354.4 [M+1].

Synthesis of (±) Papavaranol (3a): Charged papaveraldine**(7)** (2.0g, 0.0056mol) in methanol (4mL, 2vol) and cooled 0-10 °C. Then sodium borohydride(0.1g, 0.0028mol) was charged slowly into the reaction mass at 0-10 °C. Allowed the r.m to 25-30 °C and stirred for 1h at 25-30 °C. After completion of thereaction by TLC, reaction mass is quenched with water (20mL, 10vol) and extracted with ethyl acetate (20mL, 10vol). The organic layer was concentrated in vaccum, added heptane (10mL, 5vol)and filtered the product to afford(±) papavaranol **(3)** as Pale yellow color solid in 86 % (1.72 g) yield.

(±) Papavaranol (3a): Melting point: 135-137 °C; **IR (KBr)**:1017, 1161, 1237, 1403, 1509, 1620, 2839, 2941, 3343, 3855;**^{1}H NMR (400 MHz, $CDCl_3$)**δ: 3.76(s, 3H), 3.80(s, 3H), 3.82(s, 3H), 3.99(s, 3H), 6.14(s, 1H), 6.82(m, 2H), 6.90(dd, 1H, *J*=8.4 Hz, 2.0 Hz), 7.07(s, 1H), 7.12(s, 1H), 7.51(d, 1H *J*=5.2 Hz,), 8.40(d, 1H *J*=6.0 Hz); **^{13}C NMR (400 MHz, $CDCl_3$)**δ: 55.7, 55.8, 55.9, 56.0, 72.5, 103.2, 105.2, 110.5, 110.9, 119.7, 120.1, 119.7, 120.1, 120.9, 133.5, 136.1, 138.8, 148.7, 149.3, 149.8, 152.6, 156.5;**MS**: *m/z* (%) = 356.3 [M+1].

Synthesis of Papaverine (2): A mixture of 10% Pd/C catalyst (0.1 g) and Papaveranol**(3)** (1.0g, 0.0027mol) were charged into a hydrogenator containing Methanol (10.0 mL, 10 vol) and Acetic acid (2.0 mL, 2.0 vol) solution mixture. This was hydrogenated with hydrogen pressure (10 psi) at 25 to 35 °C until consumption of the hydrogen gas slowed down. The catalyst was then filtered off, the solution was concentrated and the residue was treated with 10% sodium carbonate solution (20 mL, 20 vol) and filtered off the solid. The crude product was further purified by column chromatography (silicagel, hexane–EtOAc, 8:2) yielded 0.89 g (66 %) Papaverine (2) as an Off-white color solid.

Papaverine (2): Melting point: 146-148 °C; **IR (KBr):** 1018,1116,1140, 1231, 1349, 1421, 1464, 1515, 1583, 1614, 1667, 2838, 2936, 3078; **^{1}H NMR (400 MHz, $CDCl_3$)**δ: 3.88(s, 3H), 3.93(s, 3H), 4.02(s, 3H), 4.07(s, 3H), 4.48 (s, 2H), 6.95 (d, 2H, *J*=8.8 Hz), 7.36 (s, 1H), 7.93–7.99 (m,2H), 8.48 (d, 1H, *J*=5.2Hz); **^{13}C NMR (400 MHz, $CDCl_3$)**δ: 46.2, 55.5, 56.0, 61.2, 61.6, 100.3, 103.7, 113.7, 116.5, 123.7, 129.1, 129.7, 133.2, 139.5, 144.2, 146.7, 154.0, 154.5; **MS**: *m/z* (%) = 340.3 [M+1].

Synthesis of (±) Setigerine (4): Charged Sodium hydride (0.13g, 0.0054mol) into a round bottom flask with THF (6.5mL, 5vol) and stirred under nitrogen atmosphere. Then cooled to 0-5 °C and added a solution of (±) papavaranol**(3)** (1.3g, 0.0036mol) in THF (6.5mL, 5vol) drop wise into the reaction mass. Added methyl iodide (0.61g, 0.0043mol) at 0-5 °C drop wise and allowed the reaction mixture to 25-30 °C. Then stirred reaction mass at 25-30 °C and the reaction was monitored by TLC after 2-3 hrs. Cooled the reaction mass to 0-10 °C and Quenched with methanol (2.6mL, 2vol), followed by added water (26mL, 20 vol) and stirred well for 30min. Product was extracted with DCM (6.5mL, 5vol) twice and the organic layer distilled under vaccum. The crude compound was purified by flash column chromatography (silicagel, hexane–EtOAc, 7:3) yielded 0.89 g (66 %) (±) setigerine**(4)** as an Off-white color solid.

(±) Setigerine (4): Melting point: 147-149 °C; IR (KBr):1025, 1140, 1269, 1417, 1512, 1606, 2072, 2932, 3053, 3444, 3853; **^{1}H NMR (400 MHz, $CDCl_3$)**δ: 3.47(s, 3H), 3.79(s, 3H), 3.82(s, 3H), 3.88(s, 3H), 3.99(s, 3H), 5.85(s, 1H), 6.78(d, 1H *J*=8.4 Hz), 6.96(dd, 1H *J*=8.4 Hz, 1.6 Hz), 7.04-7.18(m, 2H), 7.47(d, 1H *J*=5.6 Hz), 7.71(s, 1H), 8.40(d, 1H *J*=5.6 Hz); **^{13}C NMR (400 MHz, $CDCl_3$)**δ: 55.7, 55.8, 55.9, 57.2, 86.9, 104.3, 105.0, 109.5, 110.5, 118.5, 119.6, 121.9, 133.3, 133.9, 140.4, 148.1, 148.7, 149.4, 152.3,156.9;**MS**: *m/z* (%) = 370.3 [M+1]; **HRMS**: Found mass: 369.1637, Calc. Mass:370.1654[M+1], Anal Calcd for $C_{21}H_{24}NO_5$[M+H].

Synthesis of 2-(benzo[*d*][1,3]dioxol-5-yl)-*N*-(3,4-dimethoxyphenethyl)-2-oxoacetamide (7b):
This product was prepared in a similar manner for the preparation of **7b** using 1-(benzo[*d*][1,3]dioxol-5-yl)-2,2-dibromoethanone **(8b**;5.0g, 0.0156 mol) and Homo veratrylamine (**9**; 3.1 g, 0.0171 mol) to give an white crystalline solid which was purified by column chromatography (silicagel, hexane-AcOEt, 6:4) to give **7b**:4.33 g, 78% yield.

2-(benzo[*d*][1,3]dioxol-5-yl)-*N*-(3,4-dimethoxyphenethyl)-2-oxoacetamide (7b):Melting point: 101-103 °C; **IR (KBr):** 795, 924, 1031, 1232,1263, 1444, 1503, 1645, 2941, 3402; **^{1}H NMR (400 MHz, $CDCl_3$)**δ: 2.85 (t, 2H, *J*=6.8 Hz), 3.62 (q, 2H, *J*=6.8 Hz), 3.87 (s, 3H), 6.74-6.88 (m, 4H), 7.2 (b, NH), 7.76 (d, 1H, *J*=1.2 Hz), 8.15 (dd, 1H, *J*=8.4 Hz, 1.6 Hz); **^{13}C NMR (400 MHz, $CDCl_3$)**δ: 35.0, 40.6, 55.8, 55.9, 101.9, 108.1, 110.2, 111.4, 111.8, 120.6, 127.8, 129.0, 130.8, 147.8, 147.9, 149.1, 153.1, 162.0, 185.3;**MS:***m/z* (%) = 358.1 [M+1].

Synthesis of benzo[*d*][1,3]dioxol-5-yl(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)methanone (6b):This product was prepared in a similar manner for the preparation of **6a** using 2-(benzo[d][1,3]dioxol-5-yl)-N-(3,4-dimethoxyphenethyl)-2-oxoacetamide (7**b;** 2.0 g, 0.0056 mol) to give **6b** as green color solid 1.71g, 90% yield.

Benzo[d][1,3]dioxol-5-yl(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)methanone (6b):
Melting point: 149-151 °C; **IR (KBr)**: 792, 927, 1037, 1107, 1239, 1443, 1658, 2833, 2924;**^{1}H NMR (400 MHz, $CDCl_3$)**δ: 2.81 (t, 2H, *J*=7.6 Hz), 3.78 (s, 3H), 3.90 (b, 2H), 3.93 (s, 3H), 3.93 (s, 3H), 6.05 (s, 1H), 6.74 (s, 1H), 6.85 (d, 1H, *J*=7.6 Hz), 6.89 (s, 1H), 7.53 (d, 1H, *J*=1.2 Hz). 7.62 (dd, 1H, *J*=8.4 Hz ,2.0 Hz); **^{13}C NMR (400 MHz, $CDCl_3$)**δ: 25.3, 47.1, 55.9, 56.0, 101.9, 107.9, 109.3, 109.5, 110.4, 119.2, 127.7, 130.1, 131.0, 147.5, 148.0, 151.6, 152.5, 164.5, 192.1; **MS**: *m/z* (%) = 340.1[M+1].

Synthesis ofbenzo[*d*][1,3]dioxol-5-yl(6,7-dimethoxyisoquinolin-1-yl)methanone (1b):
This product was prepared in a similar manner for the preparation of **1a** using benzo[*d*][1,3]dioxol-5-yl(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)methanone **(6b;** 1.5 g, 0.0044 mmol) to give 1b as yellow color solid 1.2 g, 80% yield.

Benzo[*d*][1,3]dioxol-5-yl(6,7-dimethoxyisoquinolin-1-yl)methanone (1b):Melting point: 197-199 °C; **IR (KBr)**: 853, 927, 1037, 1260, 1331, 1448, 1504, 1640, 2948; **^{1}H NMR (400 MHz, $CDCl_3$)** δ: 3.96 (s, 3H), 4.0 (s, 3H), 6.0 (s, 2H), 6.84 (d, 1H, *J*=8.8 Hz), 7.13 (s, 1H), 6.49-7.55 (m, 3H), 7.64 (d, 1H, *J*=5.6 Hz), 8.45 (d, 1H, *J*=5.2 Hz); **^{13}C NMR (400 MHz, $CDCl_3$)**δ: 56.0, 56.1, 101.8, 104.0, 104.8, 107.9, 110.1, 121.3, 122.8, 128.1, 131.5, 133.9, 140.0, 147.9, 151.0, 152.2, 153.2, 153.5, 193.4; **HRMS**: Found mass:338.1003; Calc.Mass: 338.1028 [M+1], Anal Calcd for $C_{19}H_{16}NO_5$[M+H].

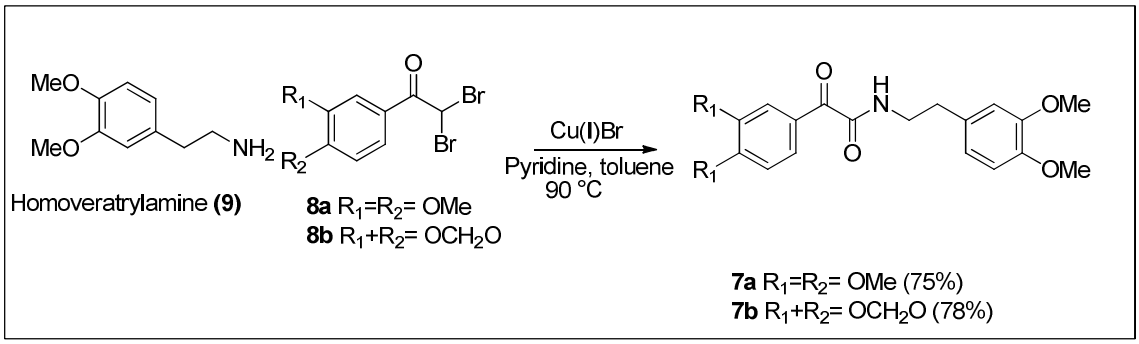
Syntesis of (±)benzo[*d*][1,3]dioxol-5-yl(6,7-dimethoxyisoquinolin-1-yl)methanol (3b):
This product was prepared in a similar manner for the preparation of **1a** using benzo[*d*][1,3]dioxol-5-yl(6,7-dimethoxyisoquinolin-1-yl)methanone(**1b;** 1.0 g, 0.0029 mol) to give **3b** as light yellow color solid 800 mg, 80% yield.

(±) Benzo[*d*][1,3]dioxol-5-yl(6,7-dimethoxyisoquinolin-1-yl)methanol (3b) :Melting point: 196-198 °C; **IR (KBr)**: 735, 909, 1041, 1265, 1508, 2253, 3054;**^{1}H NMR (400 MHz, $CDCl_3$)**δ: 3.75(s, 3H), 3.92(s, 3H), 5.80(d, 2H *J*=11.2 Hz,), 6.03(s, 1H), 6.34 (b, 1H), 6.57(s, 1H), 6.68(d, 1H *J*=7.6 Hz,), 6.87(d, 1H *J*=8.0 Hz,), 7.0(d, 2H *J*=13.6 Hz,), 7.43(d, 1H *J*=5.6 Hz,), 8.31(d, 1H *J*=6.0 Hz); **^{13}C NMR (400 MHz, $CDCl_3$)**δ: 55.8, 55.9, 72.4,101.0, 103.1, 105.2, 107.7, 108.0, 119.8, 120.8, 119.7, 121.4, 133.5, 137.6, 138.8, 147.2, 148.0, 149.8, 152.6, 156.3;**HRMS**: Found mass: 340.1175; Found. Mass:340.1185[M+1], Anal Calcd for $C_{19}H_{18}NO_5$[M+H].

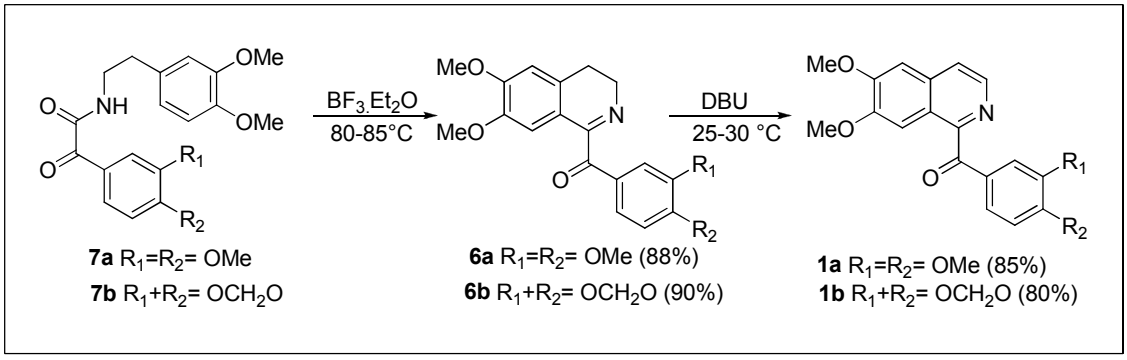
Synthesis of (±) Setigeridine (5): This product was prepared in a similar manner for the preparation of **5** using benzo[d][1,3]dioxol-5-yl(6,7-dimethoxyisoquinolin-1-yl)methanol **(3b**;500 mg, 0.0014 mol) to give **5** as a colorless oily liquid after purification by column chromatography (Silicagel; Hexane-EtOAc, 4:6) to give **5:** 312 mg, 60% yield, colorless oily liquid.
(±) Setigeridine (5):IR (KBr):1038, 1101, 1253, 1480, 1505, 1621, 2221, 2927, 3639; **^{1}H NMR (400 MHz, $CDCl_3$)**δ: 3.46(s, 3H), 3.88(s, 3H), 3.99(s, 3H), 5.81(s, 2H), 5.88-5.89(t, 1H *J*=1.6 Hz), 6.72(d, 1H *J*=8.4 Hz), 6.92-6.95(m, 2H), 7.04(s, 1H), 7.47(d, 1H *J*=5.6 Hz), 7.70(s, 1H), 8.40(d, 1H *J*=6.0 Hz); **^{13}C NMR (400 MHz, $CDCl_3$)**δ: 55.8, 55.9, 57.3, 87.0, 100.8, 104.3, 105.0, 106.9, 107.7, 119.5, 119.7, 121.9, 134.0, 134.7, 140.3, 146.6, 147.5, 149.4, 152.4,156.8;**HRMS:**Found mass: 354.1336; Calc. Mass:354.1341[M+1], Anal Calcd for $C_{20}H_{20}NO_5$[M+H].

RESULTS AND DISCUSSION

The starting materials, α-keto amide analogues **7a** and **7b**, were prepared by coupling of 2-aryl dibromoethanone derivatives **8a**and **8b** with Homoveratrylamine (**9**) under copper mediated aerial oxidative amidation reaction conditions.[11,12] Under these reaction conditions, α-keto amide anologues**7a**&**7b** were isolated with 76 & 78 % corresponding yields. However, corresponding benzamides were formed less than 5 % under these conditions. (Scheme 2)



Scheme 2



(Scheme 3)

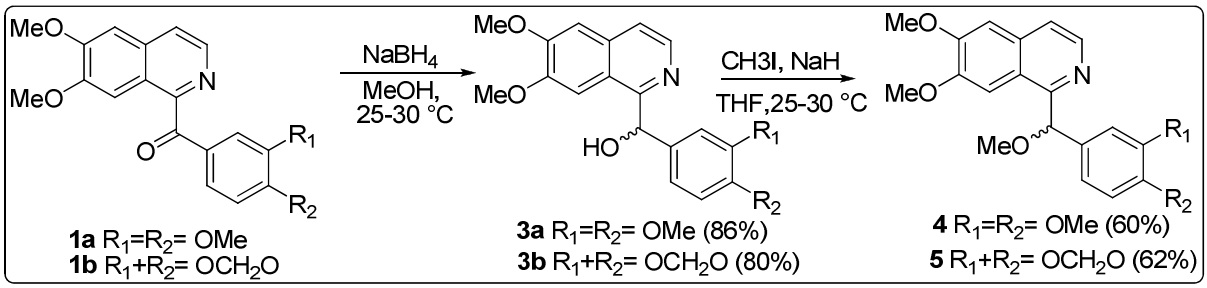
Essential 3,4-Dihydroisoquinolines **6a** and **6b** were synthesized respectively in 88 & 90% yields from α-keto amides **7a** and **7b***via* the Bischler–Napieralskicyclodehydration reaction involving a cyclization with 48% boron trifluorideetherate at 80–85 °C for 10-12 h (Scheme 3). The aromatization of 3,4-dihydro isoquinolines**6a** and **6b**, obtained via oxidative amidationBischler–Napieralski approach, was then carried out. The aromatization of 3,4-

Dihydroisoquinolines **6a** and **6b**, were attempted by means of a regioselective base-catalyzed air oxidation by using 1,8-diazabicycloundec-7-ene (DBU), and the 1-benzoyl isoquinolinesPapavaralidine (**1a**) and benzo[*d*][1,3]dioxol-5-yl(6,7-dimethoxyisoquinolin-1-yl)methanone (**1b**) were isolated with excellent yields 85 & 80 % respectively.

The successful implementation of the Oxidative Amidation–Bischler–Napieralski Reaction sequence to skeletally diverse 1-benzoyl isoquinoline alkaloid systems(**1a,1b**) encouraged us to explore the synthesis of biologically active natural products Papaverine (**2**), (±) Papaveranol (**3**), (±) Setigerine (**4**) and (±)Setigeridine (**5**).

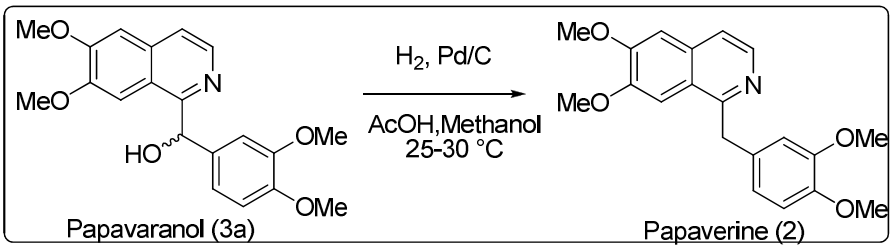
The (±) Papavaranol (**3a**) and (±) benzo[*d*][1,3]dioxol-5-yl(6,7-dimethoxyisoquinolin-1-yl)methanol (**3b**) class of natural products readily accessed by the sodium borohydride reduction (scheme 4). Reduction of 1-benzoyl isoquinolines (**1a,1b**) cleanly provided the (±) Papavaranol (**3a**) and (±) benzo[*d*][1,3]dioxol-5-yl(6,7-dimethoxyisoquinolin-1-yl)methanol (**3b**) with an yield of 86 % and 80 % correspondingly. Further, (±) Papavaranol (**3a**) and (±) benzo [d][1,3] dioxol-5-yl(6,7-dimethoxyisoquinolin-1-yl)methanol (**3b**) on treatment with Methyl iodide and Potassium tertiary butoxide in DMF leads to the formation of (±)setigerine (**4**)and (±)Setigeridine (**5**)in 60 % and 62 % yields.

The (±) setigerine (**4**)was isolated as off-white color solid, with melting point 147-149 °C and (±)Setigeridine (**5**)isolated as colorless oily liquid. Both the compounds were well characterized by spectral and analytical data, and is in well agreement with the analytical data reported in the literature (Scheme 4).[13]



Scheme 4

Consequently, we had taken up the synthesis of Papaverine (**2**)from Papavaranol (**3a**) (Scheme 5). Deoxygenation of the benzylic position in papavaranol (**3a**) with a mixture of 10% Pd/C catalyst and a solution of Methanol glacial acetic acid mixture under hydrogen pressure (10 psi) at 25 to 35 °C until consumption of the hydrogen gas slowed down. Then the regular workup and purification afforded **2** with 78 % yield as off-white color solid with melting point 146-148 °C, which is well supported by literature value.[14]



Scheme 5

In summary, based on the Oxidative Amidation-Bischler–Napieralski Reaction and subsequent reduction, developed a facile approach for preparing Papaverine (**2**), (±) Setigerine (**4**), (±) Setigeridine (**5**) and related isoquinoline alkaloids with excellent yields.

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