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Studies towards the synthesis of (±)-reserpine: Photocyclization mediated a novel and efficient synthesis of 11,18-dimethoxy-(20α)-18,19-didehydro-yohimban-17-one

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ABSTRACT

A short, highly efficient synthesis of advanced intermediates to reserpine **1** has been developed starting from enamide **8**. The enamide underwent photocyclization reaction using high pressure mercury lamp to afford the lactam **9** in excellent yield. Then lactam was reduced to the required amine **10**, which upon acidic hydrolysis gave the nonconjugate ketone product **11**, followed by reaction with sodium hydroxide resulted the desired conjugate ketone **12**. Epoxidation, and then ring opening of the epoxide **13** with methanol yielded the desired product **14**, which is key intermediate to the total synthesis of (±)-reserpine.

1. Introduction

Reserpine **1**, a naturally occurring alkaloid was initially isolated from *Rauwolfia serpentina* [1], and is regarded one of the most important medicinal agents existing in nature mainly due to its extensive use in the treatment of hypertension and mental disorder [2-5]. Reserpine is one of the most complex natural products [6-9], having six chiral centers and a pentacyclic motif (Figure 1) [10-19].

The chemical and pharmacological properties of reserpine have made it an interesting and challenging target for synthesis. The first total synthesis of reserpine was accomplished by Woodward and co-workers in 1956, and is considered a milestone in the field of organic synthesis [10,11,20]. Woodward and co-workers used the Diels-Alder reaction to generate the rings D and E starting from vinyl acrylic acid and quinone [10]. Following Woodward considerable attention has been taken by other research groups towards the synthesis of reserpine and various synthetic strategies have been developed and applied to the synthesis of reserpine. For example, Pearlman developed an intramolecular photoinduced [2+2] cyclization strategy using 1,4-dihydrobenzoic acid to generate the required Woodward ring E precursor [12].

Later Wender and co-workers established a new method to make D/E ring unit using methyl 1,2-dihydropyridine-1-carboxylate, and which underwent a Diels-Alder reaction and then Cope rearrangement to produce a *cis*-hydroisoquinoline intermediate [13,14,21].

Martin and associates developed a general protocol following an intramolecular Diels-Alder reaction to generate a hydroisoquinoline ring system which contains the trisubstituted D/E ring unit [15,16].

Stork and co-workers used enantiomerically pure 3-cyclohexenecarboxylic acid to produce a penta substituted carbocycle representing ring E via a stereocontrolled building of the required functionalities [17].

We have considered the enamide photocyclization approach to the total synthesis of (±)-reserpine, **1**. This approach is continuation of our previously established reductive photocyclization of enamides methodology; we have reported efficient synthesis of various natural alkaloids using this method [22,23]. We wanted to further explore this protocol towards the synthesis of structurally more complicated and medicinal important natural alkaloid, (±)-reserpine.

As described above, our aim is the enamidephotocyclization based construction of the key pentacyclic motif **14**. Herein we illustrate the synthesis of pentacyclic key intermediate **14** from naturally occurring harmaline, **2** [24].

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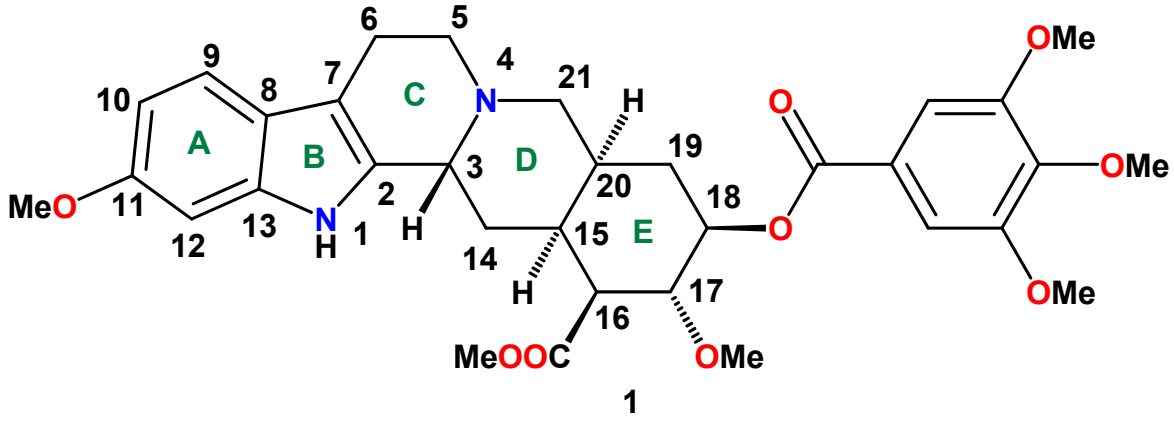


Figure 1. Reserpine, **1**.

2. Experimental

2.1. Instrumentation

Chromatography: Flash chromatography was performed on silica gel (Merck Kieselgel 60, 230-400 mesh) unless otherwise stated. TLC was performed on aluminium-backed silica plates ($60F_{254}$, 0.2 mm). The photochemical reactions were carried out using a high pressure (100 W) mercury lamp model number EL-60. All the commercially available reagents were used as obtained from Wako Chemical Co. Japan. All the solvents were used as obtained, except THF and Et_2O were dried over Na in benzophenone. IR spectra were recorded on a Jasco A-302 IR spectrophotometer. ^{1}H-NMR spectra were recorded on Bruker NMR 400 or 500 MHz spectrometer and chemical shifts were calculated with reference to $CDCl_3$ (δ 7.25 ppm). Mass spectra were recorded on a Varian MAT 312 double focusing spectrometer, connected to an IBM-AT compatible PC computer system.

2.2. Synthesis

2.2.1. 11-Methoxy-2,3,4,9-tetrahydro-2-(benzoyl)-1-methylen-1H-pyrido[3,4]-indole (4)

Benzoyl chloride (310 mg, 2.20 mmol) was added dropwise to ice-cooled, stirred solution of harmaline **2** (220 mg, 1.03 mmol) and triethylamine (600 mg, 5.93 mmol) in anhydrous benzene (70 mL). After being stirred at room temperature for 30 minutes, the reaction mixture was filtered to remove triethylamine hydrochloride. The filtrate was evaporated to give the unstable enamide **4** (315 mg, 96%) as a brown gum, which was used for irradiation without purification (Scheme 1).

2.2.2. Benzo[g]indolo[2,3-a]quinolizin-5-(7H)-one-8,13-dihydro-11-methoxy (5)

Sodium borohydride (350 mg, 9.26 mmol) and methanol (45 mL) were added successively to a stirred solution of the enamide **4** (315 mg, 0.989 mmol) in acetonitrile (150 mL) at room temperature. When the added sodium borohydride had dissolved, the resulting solution was cooled to 0-5 °C and irradiated for 6 hours. The reaction mixture was filtered and evaporated under reduced pressure. 10 % Sodium bicarbonate was added and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated to give a solid, which was recrystallized from methanol to give a lactam **5** as light yellow crystals (Scheme 1). Yield: 295 mg, 93%. M.p.: 187-188 °C. IR (ν_{max}, thin film, cm^{-1}): 1630 (C=C), 1609 (N*CO*). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 8.40 (1H, d, *J* = 9 Hz, 9-H), 8.21(1H, s, N-H), 6.62 (1H, m, 19-H), 7.57-7.42 (3H, m, 16, 17, and 18-H), 6.87 (1H, s, 12-H), 6.80 (1H, d, *J* = 9 Hz, 10-H), 6.55 (1H, s, 14-H), 4.50 (2H, m, 5-H_2), 3.85 (3H, s, OMe), 3.07 (2H, m, 6-H_2). MS (*m/z*, EI): 316. HRMS calcd. for $C_{20}H_{16}N_2O_2$ (M^+): 316.1212, Found: 316.1214.

2.2.3. 11-Methoxy-16,17,19,20- tetrahydroyohimban-21-one (6)

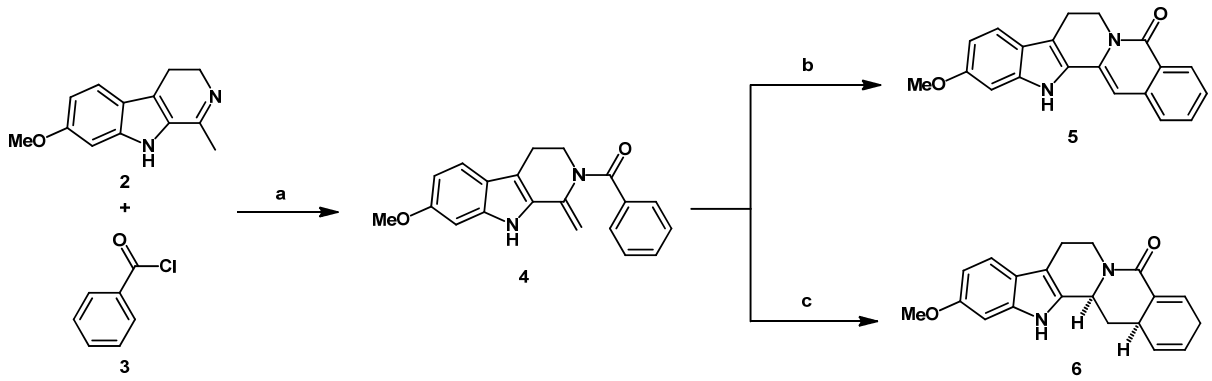
The title compound **6** was synthesized following the above procedure used for compound **5** except irradiation time was 1 hour instead of 6 hours (starting enamide disappeared on TLC), lactam **6** was obtained as light yellow crystals (Scheme 1). M.p.: 247-249 °C. Yield: 290 mg, 93%. IR (ν_{max}, thin film, cm^{-1}): 3316 (NH), 1682 and 1632 (C=C), 1592 (NCO). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 10.8 (1H, s, NH), 7.26 (1H, d, *J* = 8.5 Hz, 9-H), 6.81 (1H, d, *J* = 8.5 Hz, 10-H), 6.73 (1H, br s, 12-H), 6.62 (1H, m, 19-H), 5.72 (1H, m, 16-H), 5.36 (1H, m, 17-H), 4.82 (1H, brdd, *J* = 12 and 4 Hz, 3-H), 3.73 (3H, s, OCH_3), 3.15 (1H, m, 15-H), 2.89-2.70 (6H, m, 18-H_2, 6-H_2, and 5-H_2), 2.58 (1H, ddd, *J* = 12, 4, and 3.5 Hz, 14-Heq), 1.32 (1H, q, *J* = 12 Hz, 14-Hax). MS (*m/z*, EI): 320; HRMS calcd. for $C_{20}H_{20}N_2O_2$ (M^+) 320.1525, Found: 320.1521.

2.2.4. 11-Methoxy-2,3,4,9-tetrahydro-2-(4-methoxybenzoyl)-1-methylen-1H-pyrido[3,4]-indole (8)

4-Methoxybenzoyl chloride (450 mg, 2.64 mmol) was added dropwise to ice-cooled, stirred solution of harmaline, **2**, (220 mg, 1.03 mmol) and triethylamine (600 mg, 5.93 mmol) in anhydrous benzene (70 mL). After being stirred at room temperature for 45 minutes, the reaction mixture was filtered to remove triethylamine hydrochloride. The filtrate was evaporated to give the unstable enamide, **8**, (350 mg, 98%) as a brown gum, which was used for irradiation without further purification (Scheme 2).

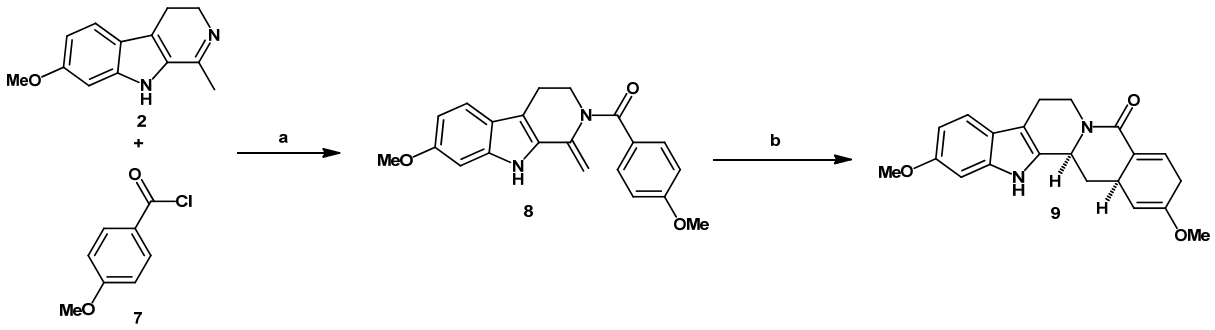
2.2.5. 11,17-Dimethoxy-16,17,19,20-tetrahydroxy-yohimban-21-one (9)

Sodium borohydride (525 mg, 13.9 mmol) and methanol (50 mL) were added successively to a stirred solution of the enamide, **8**, (350 mg, 1.00 mmol) in acetonitrile (150 mL) at room temperature and resulting solution was cooled to -5 °C and irradiated for 1 hour (starting enamide disappeared on TLC). The reaction mixture was filtered and evaporated under reduced pressure. 10 % sodium bicarbonate was added, shaken well and extracted with ethyl acetate.



a) Et_3N (6 eq.), anhydrous benzene, 0-5 °C, 30 min., 97%.
b) $NaBH_4$ (9 eq.), CH_3CN:MeOH (9:1), 0-5 °C, irradiation using high pressure mercury lamp, 6 h, 92%.
c) $NaBH_4$ (9 eq.), CH_3CN:MeOH (9:1), 0-5 °C, irradiation using high pressure mercury lamp, 1 h, 90%.

Scheme 1



a) Et_3N (5 eq.), anhydrous benzene, 0-5 °C, 30 min., 98%.
b) $NaBH_4$ (14 eq.), CH_3CN:MeOH (9:1), 0-5 °C, irradiation using high pressure mercury lamp, 1 h, 98%.

Scheme 2

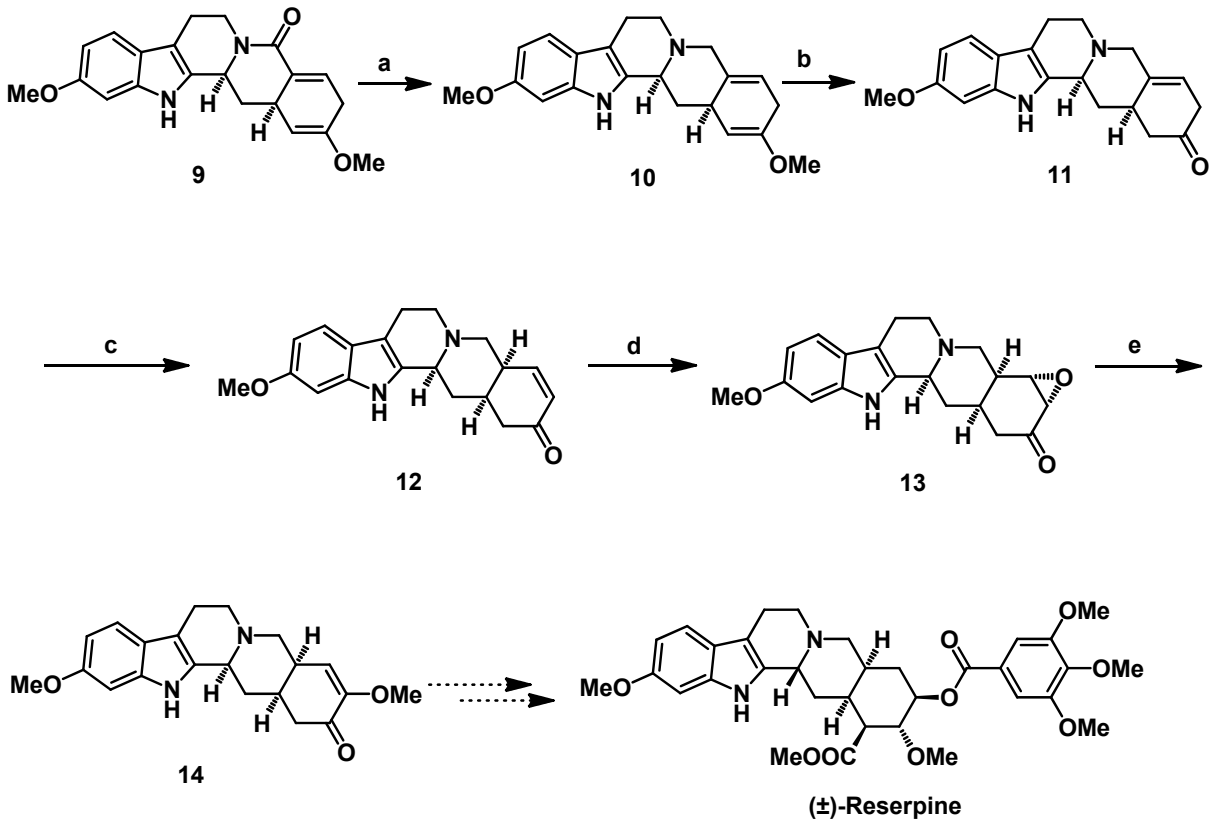
The organic layer was dried over sodium sulfate and evaporated to give a solid, which was recrystallized from methanol to give a lactam, **9**, as light yellow crystals (Scheme 2). Yield: 342 mg, 98%. M.p.: 265-266 °C. IR (ν_{max}, thin film, cm^{-1}): 3317 (NH), 1694 and 1656 (C=C), 1595 (N*CO*). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 10.7 (1H, s, NH), 7.34 (1H, d, *J*=8.5 Hz, 9-H), 6.86 (1H, d, 2.0 Hz, 12-H), 6.77 (1H, dd, *J* = 8.5 and 2.0 Hz, 10-H), 6.63 (1H, m, 19-H), 4.91 (1H, brdd, *J* = 12 and 4 Hz, 3-H), 4.66 (1H, s, 16-H), 3.75 (3H, s, OMe*) (*Methoxy attached to the aromatic ring A), 3.52 (3H, s, OMe), 2.59-2.49 (6H, m, 18-H_2, 6-H_2, and 5-H_2), 3.15 (1H, m, 15-H), 2.37 (1H, ddd, *J* = 12.5, 4, and 3.5 Hz, 14-Heq), 1.22-1.18 (1H, m, 14-Hax). MS (*m/z,* EI): 350; HRMS calcd. for $C_{21}H_{22}N_2O_3$ (M+): 350.1630, Found: 350.1627.

2.2.6. 11,17-Dimethoxy-16,17,19,20- tetrahydro-yohimban (10)

A solution of the lactam **9** (350 mg, 1.00 mmol) in anhydrous THF (35 mL) was added dropwise to an ice-cooled, stirred solution of lithium aluminium hydride (525 mg, 13.8 mmol) in anhydrous ether (35 mL) under argon. After being refluxed for 2 h, the reaction mixture was allowed to cool and sufficient amount of ethyl acetate was added dropwise by keeping the reaction mixture in the ice-cooled water in order to decompose the LAH completely. After filtration the reaction mixture was extracted with ethyl acetate. The extract was dried and evaporated to give the amine **10** as pale yellow crystals (Scheme 3). M.p.: 198-200 °C. Yield: 324 mg, 96 %. IR (ν_{max}, thin film, cm^{-1}): 3359 (NH), 1699 and 1651 (C=C). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 10.2 (1H, s, NH), 7.32 (1H, d, *J* = 8.5 Hz, 9-H), 6.83 (1H, d, 2.0 Hz, 12-H), 6.71 (1H, dd, *J* = 8.5, 2.0 Hz, 10-H), 5.42 (1H, br s, 19-H), 4.48 (1H, brs, 16-H), 3.77 (3H, s, OMe), 3.58 (3H, s, OMe), 3.60 (1H, br, dd, *J* =12 and 2.5 Hz, 3-H), 3.40 and 3.0 (2H, Abq, *J* = 12 Hz, 21-H_2), 3.59 (1H, m, 15-H), 2.79-2.67 (6H, m, 18-H_2, 6-H_2, and 5-H_2), 2.50 (1 H, ddd, *J* = 12, 4.5 and 2.5 Hz, 14-Heq), and 1.40 (1H,q, *J* = 12 Hz, 14-Hax). MS (*m/z,* EI): 336; HRMS calcd. for $C_{21}H_{24}N_2O_2$ (M+): 336.1838, Found: 336.1837.

2.2.7. 11-Methoxy-19,20-didehydroyohimban-17-one (11)

10% Hydrochloric acid (18 mL) was added to a solution of the amine 10 (250 mg, 0.744 mmol) in methanol (15 mL). After being stirred at room temperature under argon atmosphere for 1 h, the reaction mixture was evaporated. Water (5 mL) was added to the residue and the mixture was made alkaline by the addition of saturated aqueous sodium hydrogen carbonate, and then extracted with dichloromethane. The organic layer was washed, dried, and evaporated to give a dark brownish solid, which was triturated with ether to obtain the nonconjugated enone, **11**, as light brown solid which was further purified by recrystallization from methanol to afford colorless crystals (Scheme 3). M.p.: 178-181 °C. Yield: 235 mg, 98%. IR (ν_{max}, thin film, cm^{-1}): 3369 (NH). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 10.5 (1H, s, NH), 7.40 (1H, d, *J* = 8.5 Hz, 9-H), 6.91 (1H, d, *J* = 2.0 Hz, 12-H), 6.82 (1H, dd, *J* = 8.5, 2.0 Hz, 10-H), 5.71 (1H, s-like, 19-H), 3.80 (3H, s, OMe), 3.46 and 3.42 (2H, ABq, *J* = 12 Hz, 21-H_2),



a) $LiAlH_4$ (14 eq.), 2 h reflux, 96%.
b) 10% HCl, MeOH, 1 h, RT, 98%.
c) NaOH (4 eq.), MeOH, 0-5 °C, 90 min, 98%.
d) 35% H_2O_2, NaOH, 0-5 °C, 90 min, 86%.
e) Conc. H_2SO_4, MeOH, reflux, 6 h, 86%.

Scheme 3

3.37-3.25 (2H, m, 18-H_2), 3.13 (1H, brd, *J* = 12 Hz, 3-H), 2.79 (1H, brd, *J* = 13 and 3.5 Hz, 16-H), 2.62-2.54 (4H, m, 6-H_2, and 5-H_2), 2.51 (1H, dd, *J* = 15 and 5 Hz, 16-H), 2.35 (1H, ddd, *J* =12, 4.5, and 2.5 Hz, 14-Heq), 2.27-2.20 (1H, m, 15-H), and 2.18 (1H, q, *J* = 12 Hz, 14-Hax). MS m/z (EI) 322; HRMS calcd. for $C_{20}H_{22}N_2O_2$ (M+): 322.1681, Found: 322.1681.

2.2.8. 11-Methoxy-(20α) 18,19-didehydroyohimban-17-one (12)

A solution of sodium hydroxide (100 mg, 2.50 mmol) in methanol (1 mL) was added to an ice-cooled, stirred solution of the enone, **11**, (200 mg, 0.621 mmol) in a mixture of methanol:methylene dichloride (4:1) (20 mL) under argon stream. After being stirred under ice-cooling for 1 and half hours, the reaction mixture was diluted with water and extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a solid, which was recrystallized from methanol to afford the *cis*-enone, **12**, as colorless crystals (Scheme 3). M.p.: 188-190 °C. Yield: 196 mg, 98%. IR (ν_{max}, thin film, cm^{-1}): 3374 (NH), 1662 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.75 (1H, s, NH), 7.41 (1H, d, *J* = 8.3 Hz, 9-H), 6.87 (1H, d, 2.2 Hz, 12-H), 6.78 (1H, dd, *J* = 8.3, 2.2 Hz, 10-H), 6.43 (1H, dt, *J* =10.1 and 1.9 Hz, 19-H), 5.98 (1H, dd, *J* =10.1 and 2.3 Hz, 18-H), 3.79 (3H, s, OMe), 3.22-3.16 (2H, m, 21-H_2), 3.42 (1H, brd, *J* = 12 Hz, 3-H), 2.91 (1H, brs, 20-H), 2.86 (1H, brd, *J* = 13 and 3.5 Hz, 16-H), 2.82 (1H, dt, *J* = 12 and 5.5 Hz, 14-Heq), 2.67 (1H, dd, *J* = 15 and 5 Hz, 16-H), 2.57-2.48 (4H, m, 6-H_2, and 5-H_2), 2.29-2.22 (1H, m, 15-H), 2.08 (1H, ddd, *J* = 12.5, 11.8 and 10.5 Hz, 14-Hax). MS (*m/z*, EI): 322; HRMS calcd. for $C_{20}H_{22}N_2O_2$ (M+): 322.1681, Found: 322.1678.

2.2.9. 11-Methoxy-(18α, 19α, 20α)-18,19-epoxy-yohimban-17-one (13)

Hydrogen peroxide (35%, 8 mL) and 10 % methanolic sodium hydroxide solution (2.5 mL) were successively added to a solution of the conjugated enone, **12**, (200 mg, 0.621) in methanol (8 mL) and methylene dichloride (2 mL) with stirring under ice cooling in argon atmosphere. Stirring was continued at 0 °C for one and half hours. Water was added to the reaction mixture, which was extracted with methylene dichloride. The extract was washed with brine, dried, and evaporated to give a brownish solid, which was recrystallized from ethanol to afford on the epoxyketone **13** as white crystals (Scheme 3). M.p.: 203-205 °C. Yield: 180 mg, 86 %. IR (ν_{max}, thin film, cm^{-1}): 1712 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.65 (1H, s, NH), 7.42 (1H, d, *J* = 8.1 Hz, 9-H), 6.93 (1H, d, *J* = 2.1 Hz, 12-H), 6.85 (1H, dd, *J* = 8.1, 2.1 Hz, 10-H), 3.80 (3H, s, OMe), 3.53 (1H, brd, *J* = 12 Hz, 3-H), 3.31 (1H,dd, *J* = 3.2 and 1.6 Hz, 19-H), 3.43 (1H, dd, *J* = 3.6 Hz, 18-H), 2.97-2.85 (6H, m, 5-H_2, 6-H_2 and 21-H_2), 2.81 (1H, brd, *J* = 13 and 3.5 Hz, 16-H), 2.66 (1H, brd, *J* = 12.9 Hz, 14-Heq), 2.65 (1H, q, *J* = 11.2 Hz, 14-Hax). 2.54 (1H, dd, *J* = 15 Hz and 5 Hz, 16-H), 2.51 (1H, brs, 20-H), 2.25 (1H, brd, *J* = 11.7 Hz, 15-H). MS (*m/z*, EI): 338; HRMS calcd. for $C_{20}H_{22}N_2O_3$ (M+): 338.1630, Found: 338.1625.

2.2.10. 11,18-Dimethoxy- (20α)-18,19-didehydro-yohimban-17-one (14)

Concentrated sulfuric acid (0.02 mL) was added to a solution of the epoxy ketone, **13**, (30 mg, 0.089 mmol) in methanol (5 mL). The resulting solution was refluxed for 6 hours under argon atmosphere. During the course of the reaction, concentrated sulfuric acid (0.5 mL) was added dropwise to the reaction mixture. After the temperature of the reaction mixture reached to room temperature, the solution was made alkaline by the addition of sodium bicarbonate; the reaction mixture was extracted with methylene dichloride. The extract was washed, dried and evaporated to give a residue, which was further purified by recrystallization from methanol to afforded 18-methoxyenone, **14**, as light yellow crystals (Scheme 3). M.p.:149-153 °C. Yield: 27 mg, 86 %. IR (ν_{max}, thin film, cm^{-1}): 3350 (NH), 1681 (C=C-CO), 1628 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.76 (1H, s, NH), 7.46 (1H, d, *J* = 8.2 Hz, 9-H), 6.91 (1H, d, *J* = 2.0 Hz, 12-H), 6.81 (1H, dd, *J* = 8.2 and 2.0 Hz, 10-H), 5.34 (1H, brs, 19-H), 3.80 (3H, s, OMe), 3.66 (3H, s, OMe), 3.34 (1H, brd, *J* = 12 Hz, 3-H), 3.12-3.01 (2H, m, 21-H_2), 2.73 (1H, brs, 20-H), 2.59-2.49 (2H, m 16-H_2), 2.43-2.35 (4H, m, 6-H_2, and 5-H_2),2.30 (1H, dt, *J* = 11.5 and 2.9 Hz, 14-Heq), 2.27-2.18 (5H, m, 6-H_2, and 5-H_2, 15-H), 2.07 (1H, q, 11.6 Hz, 14-H ax). MS (*m/z*, EI): 352; HRMS calcd. for $C_{20}H_{22}N_2O_3$ (M+): 352.1787, Found: 352.1782.

3. Results and discussion

We began our studies with the photocyclization of enamide **4**, elected as a model substrate (Scheme 1), which was synthesized in high yield from harmaline, **2**, and benzoyl chloride, **3**, in the presence of triethylamine. A number of photocyclization reaction conditions were optimized, and it was observed that in photocyclization step, the duration of irradiation is extremely important. Initially, irradiation of enamide, **4**, using high pressure mercury lamp at 0-5 °C for 6 hours in the presence of sodium borohydride and acetonitrile:methanol (9:1) afforded only the undesired lactam, **5**, in 92% yield. However, to our delight enamide, **4**, produced the required lactam, **6**, in good yield under the same reaction condition as described above except when the 6 hours irradiation was replaced by 1 hour irradiation. However it was observed that starting material was disappeared in 1 hour time during the formation of **5** or **6**.

3.1. Synthesis of lactam, 9

To target the required lactam **9**, harmaline, **2**, was treated with *p*-anisoyl chloride, **7**, in the presence of triethylamine and benzene, this produced the expected enamide, **8**, in good yield (98%). Then following our previous photocyclization conditions optimized on model enamide, **4**, afforded the required lactam, **9**, in good yield (98%) (Scheme 2).

3.2. Transformation of lactam, 9, to advanced intermediate 14

Then lactam, **9**, was reduced with lithium aluminum hydride in diethyl ether upon refluxing for 2 hours under the argon atmosphere to give the corresponding amine, **10**, (Scheme 3). The amine, **10**, bearing enol-ether functionality in the ring E, was treated with 10% hydrochloric acid at room temperature for one hour to produce the corresponding α, β-unsaturated ketone, **11**. The compound **11** exhibited IR spectrum absorption band at 1712 cm^{-1} due to the presence of un-conjugated ketone, and ^{1}H-NMR signal at δ 5.71 ppm (s-like, 19-H) of olefinic proton.

The nonconjugated enone, **11**, was treated with sodium hydroxide in methanol:methylene dichloride (4:1) at 0-5 °C for one and half hour to isomerize the double bond to the conjugated position to obtain the conjugated enone, **12**. The IR absorption at 1662 cm^{-1} (conjugated C=O), and ^{1}H NMR signals of two olefinic protons at δ 6.43 ppm (dt, *J* = 10.1 and 1.9 Hz, 19-H), 5.98 (dd, *J* = 10.1 and 2.3 Hz, 18-H) confirms the presence of a D/E-*cis* junction in enone, **12**. The spectroscopic data is consistent with our previous reports on similar systems [23].

We considered the epoxidation of enone, **12**, to build the oxygen functionality at C-18. Reaction of α, β-unsaturated 17-ketone, **12**, with H_2O_2 and sodium hydroxide in the presence of methanol:methylene dichloride (4:1) at 0-5 °C for one and half hours gave the 18/19-α-epoxide, **13**, in 86% yield. IR absorption at 1712 cm^{-1} for (saturated C=O) and ^{1}H NMR signals at δ 3.31 ppm (dd, *J* = 3.2 and 1.6 Hz, 19-H) and 3.43 (dd, *J* = 3.6 Hz, 18-H) supported the structure of compound **13**. The α-epoxy ketone, **13**, was observed due to the convex α-face epoxidation [23]. The epoxide **13** was allowed to react with conc. sulfuric acid (a few drops) in methanol and refluxing for 6 hours in an argon atmosphere, the required 18-methoxy enone, **14**, was obtained in 86% yield. The structure of the key product **14** was established from the following spectral data; IR absorption at 1681 cm^{-1} (for the conjugated enone) and ^{1}H NMR signal of olefinic proton at δ 5.34 ppm (brs, 19-H).

4. Conclusion

From the viewpoint of simple procedure, mild reaction conditions, and high yields, the present route provides a practical method for synthesis of 11,18-dimethoxy-(20α)-18,19-didehydro-yohimban-17-one, **14**, a key intermediate to the total synthesis of (±)-reserpine **1**, The synthetic studies towards the conversion of this key intermediate **14** to (±)-reserpine are in progress in our laboratory and will be published later.

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