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Photocyclization of Enamides. XXVI.[1] Photochemical Synthesis of Yohimban, Epiyohimban, and Alloyohimban, Basic Skeletal Structures of Yohimbine- and Reserpine-Type Alkaloids[2]

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Photocyclization of two enamides (**2a** and **2b**) has provided a new entry for the construction of three yohimbans, yohimban (**5a**), epiyohimban (**5b**), and alloyohimban (**5c**), which are basic structures of yohimbine- and reserpine-type alkaloids.

Keywords——yohimban; epiyohimban; alloyohimban; yohimbine; reserpine; enamide; photocyclization

Since the yohimbine family[3] of indole alkaloids, such as yohimbine and reserpine, includes medicinally and structurally important bases, many synthetic studies have been carried out in attempts to find new biologically active compounds. Hydrobenz[*g*]indolo[2,3-*a*]quinolizine is a basic skeletal structure commonly found in the yohimbine family of indole alkaloids. The stereochemistry of this ring system[4] divides the alkaloids into four groups, that is, the yohimban, epiyohimban, alloyohimban, and epialloyohimban groups. Methodologically, most of the reported syntheses[5] of these yohimban ring systems have involved the construction of the C-ring as their final step. We have applied enamide photocyclization to the synthesis of yohimban ring systems and have succeeded in establishing two novel approaches which involve the construction of the D-ring as the final step. In this paper, we report the details of our photochemical synthesis of three yohimbans.

Yohimban Synthesis by Non-oxidative Photocyclization of an *N*-(Cyclohex-1-enecarbonyl)-enamine-Type Enamide

As shown in the photochemical synthesis[6] of benzindolo- and indolopyridoquinolizines related to several heteroyohimbine alkaloids, the photocyclization of some *N*-aroylenamine-type enamides can give the aromatized lactams even under non-oxidative conditions.[6,7]

We first attempted to develop a versatile photochemical synthesis of yohimbans by applying non-oxidative photocyclization[8] of an *N*-(cyclohex-1-enecarbonyl)enamine-type enamide (**2a**). The enamide (**2a**) was prepared by acylation of harmalane (**1**) with cyclohex-1-enecarbonyl chloride.[9] Photocyclization of the enamide (**2a**) proceeded very smoothly to afford the unstable lactam (**3**) in good yield; this product showed two spots on thin-layer chromatography (TLC), suggesting the formation of two stereoisomers with respect to the D/E-ring junction. Though the stereostructure of **3** could not be directly established from the spectral data, it was confirmed by the following chemical conversion into the desired yohimbans. Catalytic hydrogenation of **3** in the presence of platinum dioxide afforded a mixture of three saturated lactams (**4a**, **4b**, and **4c**) in a 2 : 1 : 2 ratio; these were separated by chromatography and characterized as stereoisomeric yohimban-21-ones from spectral evidence. All three lactams (**4a**, **4b**, and **4c**) showed an identical molecular ion peak at *m/z* 294 in their mass spectra (MS) and exhibited similar infrared (IR) absorptions at 3450 (NH) and

1620 (NCO) cm^{-1}. The proton nuclear magnetic resonance (^{1}H-NMR) spectra of two lactams (**4a** and **4c**) showed 3-H signals at δ 5.14 and 5.19, respectively (both as dd, J=8, 2 Hz), but the corresponding signal appeared at δ 5.82 (m) in the third lactam (**4b**). Then, these yohimban-21-ones (**4a**, **4b**, and **4c**) were reduced with lithium aluminum hydride to afford the corresponding amines (**5a**, **5b**, and **5c**, respectively) in almost the same yield of 85%. Similar reduction of a mixture of the three yohimban-21-ones (**4a**, **4b**, and **4c**) with lithium aluminum hydride afforded a mixture of three amines (**5a**, **5b**, and **5c**) in a 2 : 1 : 2 ratio with the combined yield of 27—35% from harmalane (**1**). Another reduction sequence of the photocyclized lactam (**3**), that is, lithium aluminum hydride reduction followed by sodium borohydride reduction of the resulting unstable enamine, resulted in the formation of two amines (**5a** and **5c**) in a 3 : 2 ratio with the combined yield of 27% from harmalane (**1**). The amines (**5a**, **5b**, and **5c**) obtained by the above two procedures were unambiguously identified as follows. Yohimban (**5a**) was identified by comparison with an authentic sample prepared by the known procedure[10] from (±)-yohimbinone which was kindly given by Professor Cs.

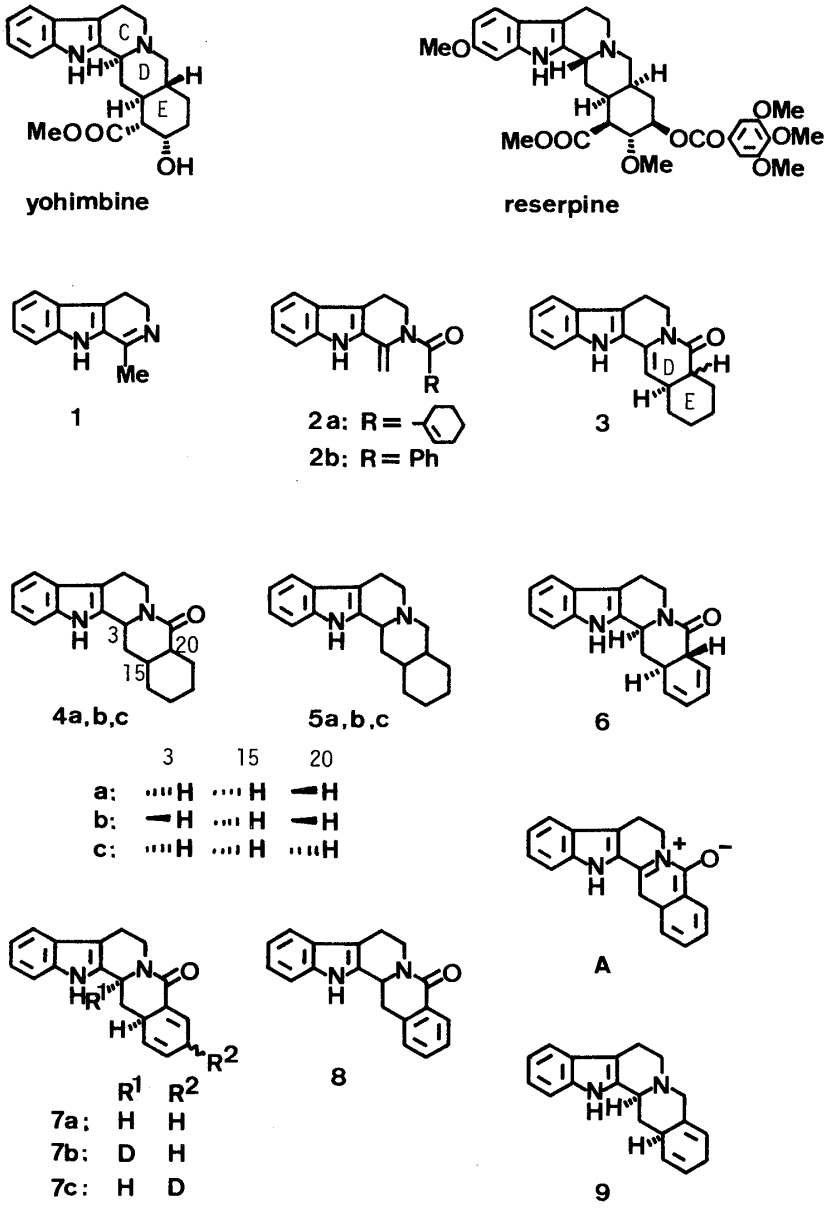

Fig. 1

Szántay. Epiyohimban (**5b**) and alloyohimban (**5c**) were identified by comparisons of their IR spectra with those of authentic samples.[11,12] The ^{1}H-NMR spectrum of epiyohimban (**5b**) showed a characteristic 3-H signal at δ 4.56 (m) which appeared at lower field than that in the C/D-*trans* quinolizidines, as reported for many other C/D-*cis* isomers.[13]

Thus, we have synthesized three stereoisomeric yohimbans (**5a**, **5b**, and **5c**) in 4 steps from harmalane (**1**) in 27—35% overall yield without isolation of intermediates.

Yohimban Synthesis by Reductive Photocyclization of an *N*-Benzoylenamine-Type Enamide

Recently, we have established reductive photocyclization of enamide[8,14] as a useful synthetic tool for the preparation of heterocyclic compounds and we now applied this method to yohimban synthesis, aiming at the development of a stereoselective synthetic method for the yohimbine family of indole alkaloids.

Although non-oxidative photocyclization of the readily available enamide (**2b**) was found to give the aromatized lactam as reported previously,[6,7] its reductive photocyclization proceeded as expected to give a mixture of two hydrogenated lactams (**6** and **7a**) in addition to a small amount of the lactam (**8**)[15] in ratios that depended on the hydride reagent and the solvent system employed as shown in Table I.

TABLE I. Results of Reductive Photocyclization of the Enamide (**2b**)

Hydride	Solvent	Yield (%)		
		6	**7a**	**8**
$NaBH_4$	C_6H_6–MeOH	7	21	20
$NaBH_4$	Et_2O–MeOH	17	32	5
$NaBH_4$	MeCN–MeOH	—	98	—
$LiBH_4$	C_6H_6–THF	—	5	13

The lactam (**7a**) having an unconjugated diene structure was obtained in quantitative yield by photocyclization using sodium borohydride as the hydride reagent in a solvent system of acetonitrile–methanol (10 : 1), while its isomeric lactam (**6**) was obtained as a mixture with **7a** and **8** in a solvent system of benzene– or ether–methanol. The structures of these two hydrogenated lactams (**6** and **7a**) were established from the following spectral data. Both lactams (**6** and **7a**) showed an identical molecular ion peak at *m/z* 290 in their MS, two mass units larger than that of the parent enamide (**2b**). The lactam (**6**) exhibited an IR absorption at 1620 cm^{-1} due to a lactam carbonyl group and ^{1}H-NMR signals of four olefinic protons at δ 6.43 (br d, J=9 Hz, 19-H), 6.12 (2H, m, 17- and 18-H), and 5.88 (br d, J=9 Hz, 16-H) and of an angular proton at δ 2.61 (br dd, J=20, 12 Hz, 15-H), suggesting the *syn–trans*[16] structure, which is in agreement with the result of chemical conversion to yohimban (**5a**) as described later. The other lactam (**7a**) exhibited an IR absorption at 1605 cm^{-1} due to an α,β-unsaturated lactam carbonyl group and ^{1}H-NMR signals of three olefinic protons at δ 7.00 (s-like, 19-H), 5.78 (br d, J=10 Hz, 17-H), and 5.64 (br dd, J=10, 2 Hz, 16-H), of which the 19-H signal appeared at low field due to the anisotropy of the lactam carbonyl group.

In order to establish the mechanism of the reductive photocyclization of the enamide (**2b**), affording the two hydrogenated lactams (**6** and **7a**), we investigated the reaction by using deuterated reagent and solvent. When sodium borodeuteride was used in acetonitrile–methanol as the solvent, we obtained the lactam (**7b**), which was deuterated exclusively at the 3-position, in 93% yield. On the other hand, when acetonitrile–methanol-*d* (CH_3OD) was used as the solvent and sodium borohydride as the reducing agent, we obtained the lactam (**7c**), which was deuterated at the 18-position, in 93% yield. Both lactams (**7b** and **7c**) were characterized from their spectral data. From these results, the reaction mechanism can be

explained as follows: in the photocyclized intermediate (A) of the enamide (**2b**), a hydride ion attacks the iminium moiety and a proton from the solvent methanol attacks the dienolate moiety, as in the cases of other enamides.[14,17]

The following reduction sequence of the two hydrogenated lactams (**6** and **7a**) provided a new stereoselective synthetic route to yohimbans. Catalytic hydrogenation of the lactam (**6**) on platinum dioxide afforded the saturated lactam (**4a**, 88%), while **7a** afforded a mixture of two lactams (**4a**, 46% and **4c**, 41%). These saturated lactams (**4a** and **4c**) were identical respectively with the authentic samples of yohimban-21-one (**4a**) and alloyohimban-21-one (**4c**), prepared above, and were further reduced with lithium aluminum hydride to afford yohimban (**5a**) and alloyohimban (**5c**), respectively, in 85% yields; these products were identical with the authentic samples prepared above.

Thus, we succeeded in developing a simple four-step synthesis of yohimban (**5a**) and alloyohimban (**5c**) from harmalane (**1**) in overall yields of 38 and 34%, respectively. This synthesis is superior to those previously reported[5] in terms of yield and number of steps. Alternatively, yohimban (**5a**) and alloyohimban (**5c**) were also synthesized *via* reduction of the unconjugated lactam (**7a**) with lithium aluminum hydride followed by catalytic hydrogenation of the resulting amine (**9**) on platinum dioxide in overall yields of 9 and 11% from harmalane (**1**), respectively. Accordingly, both non-oxidative and reductive photocyclizations of enamides have been developed to provide these yohimbans with a generally high level of chemical efficiency.

Further efforts are now being directed at the total synthesis of yohimbine, reserpine, and related alkaloids, which will be reported in subsequent papers.

Experimental

The ^{1}H-NMR spectra were measured with JEOL PMX-60 (60 MHz), Varian NEVA NV-21 (90 MHz), and Varian XL-200 (200 MHz) instruments for solutions in deuteriochloroform unless otherwise stated (with tetramethylsilane as an internal reference), and the IR spectra were measured with a Hitachi 215 machine for solutions in chloroform. MS were taken with JEOL JMS-01SG and Hitachi M-80 spectrometers. All melting points were determined with a Kofler-type hot-stage apparatus. Extracts from the reaction mixture were washed with water and dried over anhydrous sodium sulfate. The photochemical reactions were carried out by irradiation with a high-pressure (100 or 300 W) mercury lamp through a Pyrex filter (Eikosha, Osaka, Japan, PIH-100 or PIH-300).

Preparation of the Enamide (2a) and Its Non-oxidative Photocyclization——A solution of freshly prepared cyclohex-1-enecarbonyl chloride[9] (145 mg) in anhydrous benzene (10 ml) was added dropwise to an ice-cooled, stirred solution of a mixture of harmalane (**1**) (184 mg) and triethylamine (151 mg) in anhydrous benzene (60 ml). The mixture was stirred at room temperature for 3 h, and triethylamine hydrochloride formed was filtered off. The filtrate was diluted with anhydrous benzene (50 ml) and then irradiated at room temperature for 14 h. The solvent was removed under reduced pressure to give a yellow oil, which showed two major spots on TLC due to a mixture of two labile stereoisomeric lactams (**3**). The mixture was used, without purification, in the reduction described later.

General Procedure for Reductive Photocyclization of the Enamide (2b)——Either sodium borohydride or lithium borohydride (0.008 mol) and either methanol or tetrahydrofuran (30 ml) were successively added at room temperature to a stirred solution of the enamide (**2b**)[6] (0.001 mol) in either benzene, ether, or acetonitrile (300 ml) in the photochemical reaction vessel. After the added hydride agent had dissolved, the resulting solution was cooled to 5—10 °C and irradiated for 1 h. When benzene–methanol, ether–methanol, and benzene–tetrahydrofuran were used as the solvent system, water was added carefully to the cooled reaction mixture, and the organic layer was separated. The aqueous layer was extracted with benzene. The combined extracts were washed, dried, and evaporated to give a yellow viscous oil, which was purified by preparative TLC (p-TLC)[18] on silica gel to afford the lactams (**6**, **7a**, and **8**) in the yields shown in the table. On the other hand, when acetonitrile–methanol was used as the solvent system, evaporation of the solvent at room temperature and addition of water to the residue resulted in the formation of a pale-yellow solid which was recrystallized from methanol to afford the lactam (**7a**) as a sole product. 16,17,18,19-Tetradehydroyohimban-21-one (**6**); mp 208—210 °C (colorless crystals from methanol). IR: 3480 (NH), 1620 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) ($CDCl_3$–CD_3OD) δ: 6.43 (1H, br d, J=9 Hz, 19-H), 6.12 (2H, m, 17- and 18-H), 5.88 (1H, br d, J=9 Hz, 16-H), 5.14 (1H, m, 5-H_{eq}), 4.90 (1H, br dd, J=12, 5 Hz, 3-H), 2.78 (1H, br d, J=12 Hz, 14-H_{eq}), 2.61 (1H, br dd, J=20, 12 Hz, 15-H), 1.80 (1H, q, J=12 Hz, 14-H_{ax}). MS m/z: 290 (M^+). *Anal.* Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.66; H, 6.22; N, 9.49. 16,17,19,20-Tetradehydroyohimban-21-one (**7a**): mp 212—213 °C (colorless crystals from methanol). IR: 3480 (NH), 1680, 1635 (C=C), 1605 (NCO) cm^{-1}.

^{1}H-NMR (200 MHz) δ: 8.36 (1H, s, NH), 7.00 (1H, s-like, 19-H), 5.78 (1H, br d, J=10 Hz, 17-H), 5.64 (1H, br dd, J=10, 2 Hz, 16-H), 5.21 (1H, m, 5-H_{eq}), 4.93 (1H, br dd, J=12, 4 Hz, 3-H), 3.16 (1H, m, $W_{1/2}$=29 Hz, 15-H), 3.02—2.72 (5H, m, 18- and 6-H_2 and 5-H_{ax}), 2.58 (1H, dt, J=12.5, 4 Hz, 14-H_{eq}), 1.69 (1H, q, J=12.5 Hz, 14-H_{ax}). MS m/z: 290 (M^+). *Anal.* Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.77; H, 6.31; N, 9.58. 15,16,17,18, 19,20-Hexadehydroyohimban-21-one (**8**): mp 255—256 °C (dec.) (colorless needles from methanol) (lit.[15] 240—243 °C (dec.)). IR: 3475 (NH), 1635 (NCO), 1600 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 8.17 (1H, m, 19-H), 5.30—4.67 (2H, m, 3- and 5-H_{eq}). MS m/z: 288 (M^+).

Yohimban-21-one (4a), Epiyohimban-21-one (4b), and Alloyohimban-21-one (4c)——(a) From the Lactam (**3**): The unstable lactam (**3**), which was prepared from harmalane (**1**) (184 mg) by acylation and irradiation as described above, was subjected to catalytic hydrogenation over platinum dioxide (30 mg) in anhydrous methanol (50 ml) under a hydrogen atmosphere for 8 h. The catalyst was filtered off, and evaporation of the solvent from the filtrate gave a residue, which was purified by p-TLC on silica gel to afford three yohimban-21-ones (**4a**, **4b**, and **4c**). Yohimban-21-one (**4a**) (38 mg, 13%): mp 265 °C (dec.) (from methanol) (lit.[5c] 200—202 °C). IR (Nujol): 3450 (NH) and 1620 (NCO) cm^{-1}. ^{1}H-NMR (90 MHz) δ: 5.14 (1H, dd, J=8, 2 Hz, 3-H). MS m/z: 294 (M^+). *Anal.* Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.56; H, 7.44; N, 9.58. Epiyohimban-21-one (**4b**) (18 mg, 6%) as a yellow amorphous solid. IR (Nujol): 3450 (NH) and 1620 (NCO) cm^{-1}. ^{1}H-NMR (90 MHz) δ: 5.82 (1H, m, 3-H). High-resolution MS m/z: 294.1732 Calcd for $C_{19}H_{22}N_2O$ (M^+). Found: 294.1725. Alloyohimban-21-one (**4c**)[5c] (36 mg, 12%) as a yellow amorphous solid. IR (Nujol): 3450 (NH), 1620 (NCO) cm^{-1}. ^{1}H-NMR (90 MHz) δ: 5.19 (1H, dd, J=8, 2 Hz, 3-H). High-resolution MS m/z: 294.1732 Calcd for $C_{19}H_{22}N_2O$ (M^+). Found: 294.1741.

(b) From the Lactams (**6** and **7a**): According to the catalytic hydrogenation procedure described for **3**, the conjugated diene-lactam (**6**) (30 mg) was hydrogenated over platinum dioxide (10 mg) in methanol (9 ml) for 18 h to afford yohimban-21-one (**4a**) (27 mg, 88%) (colorless crystals from methanol), mp 265—266 °C, which was identical with the authentic sample prepared in (a) upon comparison of their *Rf* values and IR spectra. Similarly, catalytic hydrogenation of the unconjugated diene-lactam (**7a**) (65 mg) afforded a mixture of yohimban-21-one (**4a**) (30 mg, 46%) and alloyohimban-21-one (**4c**) (27 mg, 41%), which were isolated by p-TLC on silica gel, and were identical with the respective authentic samples prepared in (a) upon comparison of their *Rf* values and IR spectra.

Yohimban (5a), Epiyohimban (5b), and Alloyohimban (5c)——(a) From Yohimban-21-ones (**4a**, 4b, and **4c**): Lithium aluminum hydride (10 mg) was added carefully to a solution of a yohimban-21-one (**4a**, **4b** or **4c**) (21 mg) in anhydrous tetrahydrofuran (5 ml) and the mixture was refluxed for 2 h. After usual work-up, yohimban-21-one (**4a**), epiyohimban-21-one (**4b**), or alloyohimban-21-one (**4c**) afforded yohimban (**5a**), epiyohimban (**5b**), or alloyohimban (**5c**), respectively, in a yield of *ca.* 85% (16—18 mg) in each case. Similarly, a mixture of the three yohimban-21-ones (**4a**, **4b**, and **4c**) (114 mg), which was derived from harmalane (**1**) (71.5 mg) as described above, was reduced with lithium aluminum hydride and purification of the crude amines by p-TLC on silica gel afforded yohimban (**5a**) (37 mg, 34%), epiyohimban (**5b**) (18.5 mg, 17%), and alloyohimban (**5c**) (37 mg, 34%). Yohimban (**5a**): mp 177—178 °C (from methanol) (lit.[19] 181.5—183 °C). IR (Nujol): 3450 (NH) cm^{-1}. High-resolution MS m/z: 280.1940 Calcd for $C_{19}H_{24}N_2$(M^+). Found: 280.1954. Epiyohimban (**5b**): mp 220—221 °C (from methanol) (lit.[11] 220—221 °C). IR (Nujol): 3450 (NH) cm^{-1}. ^{1}H-NMR (90 MHz) δ: 4.56 (1H, m, 3-H) (lit.[13b,c] 4.45 (m)). High-resolution MS m/z: 280.1940 Calcd for $C_{19}H_{24}N_2$ (M^+). Found: 280.1922. Alloyohimban (**5c**): mp 145—148 °C (from methanol) (lit.[12a] 147—149 °C). IR: 3470 (NH) cm^{-1}. MS m/z: 280 (M^+).

(b) From the Lactam (**3**): Successive reductions of the photocyclized unstable lactam (**3**), prepared from harmalane (**1**) (47.5 mg) as described above, with lithium aluminum hydride (20 mg) in tetrahydrofuran, followed by sodium borohydride (20 mg) of the resulting enamine in methanol (7 ml) gave the crude amines, which were purified by p-TLC on silica gel to afford yohimban (**5a**) (12 mg, 16%) and alloyohimban (**5c**) (8 mg, 11%). These yohimbans (**5a** and **5c**) were identical with the authentic samples prepared in (a) upon comparison of the *Rf* values and IR spectra.

(c) From the Lactam (**7a**): According to the reduction procedure described for **4a**, reduction of the lactam (**7a**) (100 mg) with an excess of lithium aluminum hydride gave 16,17,19,20-tetradehydroyohimban (**9**) (33 mg, 35%), mp 161—164 °C (from methanol). IR: 3480 (NH) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 5.62 (3H, m, 19-, 17-, and 16-H), 3.53 (1H, br d, J=12 Hz, 3-H), 3.40 and 3.06 (each 1H, ABq, J=12.5 Hz, 21-H_2), 2.25 (1H, br d, J=12 Hz, 14-H_{eq}), 1.50 (1H, q, J=12 Hz, 14-H_{ax}). MS m/z: 276 (M^+). *Anal.* Calcd for $C_{19}H_{20}N_2 \cdot 1/8$ MeOH: C, 81.92; H, 7.37; N, 9.99. Found: C, 82.07; H, 7.61; N, 9.72. Catalytic hydrogenation of the amine (**9**) (33 mg) over platinum dioxide (15 mg) in anhydrous ethanol (9 ml) under a hydrogen atmosphere followed by purification of the crude product by p-TLC on silica gel afforded yohimban (**5a**) (9 mg, 27%) and alloyohimban (**5c**) (11 mg, 33%), which were identical with the authentic samples prepared in (a) and (b) upon comparison of their *Rf* values and IR spectra.

Reductive Photocyclization of the Enamide (2b) Using Deuterated Agent——(a) Using Sodium Borodeuteride: According to the photochemical procedure described for **2b** in acetonitrile–methanol, irradiation of the enamide (**2b**) (96 mg) in acetonitrile (100 ml)–methanol (10 ml) using sodium borodeuteride (100 mg) as a reducing agent was performed. Recrystallization of the crude solid product from methanol afforded the lactam (**7b**) (90 mg, 93%) as colorless crystals. This product was found to be deuterated at the 3-position. mp 177—180 °C. ^{1}H-NMR (200 MHz) δ: 8.39 (1H, s, NH), 7.03 (1H, s-like, 19-H), 5.80 (1H, br d, J=10 Hz, 17-H), 5.67 (1H, br dd, J=10, 2 Hz, 16-H), 5.25 (1H, m, 5-H_{eq}), 3.18 (1H, m, 15-H), 3.05—2.72 (together 5H, m, 18- and 6-H_2 and 5-H_{ax}), 2.60 (1H, dd, J=12.5, 3 Hz,

14-H_{eq}), 1.71 (1H, t, J=12.5 Hz, 14-H_{ax}). MS m/z: 291 (M^+).

(b) In Acetonitrile–Methanol-*d*: According to the photochemical procedure described for **2b** in acetonitrile–methanol, irradiation of the enamide (**2b**) (96 mg) in acetonitrile (100 ml)–methanol-*d* (10 ml) in the presence of sodium borohydride (100 mg) was performed, and purification of the crude product by p-TLC on silica gel afforded the lactam (**7c**) (90 mg, 93%) as colorless crystals. This product was found to be deuterated at the 18-position. mp 181—184 °C (from methanol). ^{1}H-NMR (200 MHz) δ: 8.11 (1H, s, NH), 7.02 (1H, s-like, 19-H), 5.80 (1H, br d, J=10 Hz, 17-H), 5.68 (1H, br d, J=10 Hz, 16-H), 5.24 (1H, m, 5-H_{eq}), 4.96 (1H, br dd, J=12.5, 4 Hz, 3-H), 3.18 (1H, m, $W_{1/2}$=26 Hz, 15-H), 3.04—2.70 (together 4H, m, 6-H_2, 18-H_{ax} and 5-H_{ax}), 2.58 (1H, dt, J=12.5, 4 Hz, 14-H_{eq}), 1.71 (1H, q, J=12.5 Hz, 14-H_{ax}). MS m/z: 291 (M^+).

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