Photocyclization of Enamides. XXXIV.[1] A Practical Total Synthesis of Aromatic Yohimboid Alkaloids, Oxogambirtannine and Naucleficine[2]

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Total synthesis of naucleficine (3a) was accomplished for the first time *via* an alkaloid, oxogambirtannine (3b), which was efficiently prepared by photocyclization of the *o*-methoxy-enamide 2b. The method is a practical one, suitable for large-scale preparation.

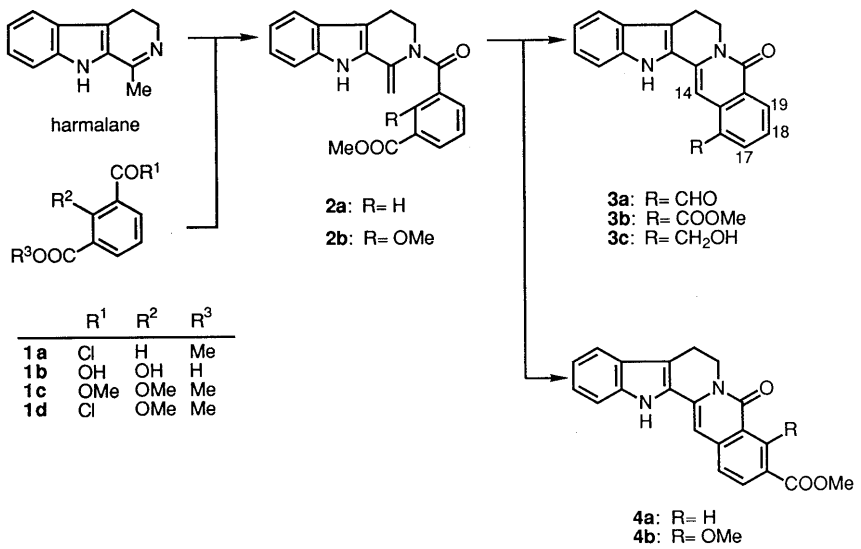
Keywords naucleficine; oxogambirtannine; alkaloid; total synthesis; photocyclization; enamide

Naucleficine (**3a**) was isolated as a minor alkaloid from the stems of *Nauclea officinalis* (Rubiaceae) which has been used as an anti-inflammatory and anti-bacterial herb in Chinese folk medicine.[3] Since its natural availability is low, large-scale chemical synthesis is desirable for the elucidation of its latent pharmacological activities and possibly also for its practical use. We now report in full detail an efficient and practical synthesis of naucleficine through a route involving enamide photocyclization,[4] which makes the alkaloid readily available by a convenient, practical method that is well suited to a multigram-scale synthesis.

As a preliminary experiment, we first investigated photocyclization of the enamide **2a**,[5] which was readily prepared by the acylation of harmalane with isophthalic monoacid chloride **1a**. The enamide **2a** was so unstable that it was, without purification, subjected to the following photocyclization. Irradiation of the crude enamide **2a** with a high-pressure mercury lamp through a Pyrex filter in either acetonitrile or benzene gave the photocyclized lactam **4a** in 80—81% yield as a sole product. The product **4a** exhibited a molecular ion peak at *m/z* 344 in the mass spectrum (MS) and showed proton nuclear magnetic resonance (^{1}H-NMR) signals due to an olefinic and aromatic protons at δ 7.15 (1H, s, 14-H) and 8.84 (1H, d, J=1.5 Hz, 19-H), respectively. These spectral data suggested its benzindoloquinolizine structure with a methoxycarbonyl group at the 18-position. Thus, photocyclization of the enamide **2a** was proved to proceed exclusively in the undesired direction at the *p*-position of the methoxycarbonyl group.

Previously, we have demonstrated that regioselective photocyclization[6] of an *o*-methoxy-substituted enamide proceeds regioselectively at the root of the *o*-methoxyl group and shown that the introduction of a methoxyl group into an *o*-position of the amido group effectively controls the direction of cyclization. Therefore, we prepared the *o*-methoxy-enamide **2b** and irradiated it in order to prepare the benzindoloquinolizine with a methoxycarbonyl group at the 16-position. The starting 2-methoxyisophthalic acid ester **1c** was prepared as follows. Oxidation of 2-hydroxy-3-methylbenzoic acid with lead dioxide gave 2-hydroxyisophthalic acid **1b** (68% yield), which was then alkylated with methyl iodide in the presence of potassium carbonate to give dimethyl 2-methoxy-isophthalate **1c** in 76% yield. Acylation of harmalane with the acid chloride **1d**, which was prepared by successive treatment of the ester **1c** with an equivalent amount of potassium hydroxide and then thionyl chloride, gave the desired enamide **2b** in good yield. This enamide **2b** was also unstable and was characterized only by ^{1}H-NMR [δ 5.01 and 5.86 (each 1H, br s, C=CH$_2$)]; without purification, it was subjected to irradiation in three different solvent systems [benzene, acetonitrile, and ether–methanol (40 : 1)] to afford a mixture of two photocyclized lactams **3b** and **4b**, which were readily isolated by column chromatography in the yields shown in Table I.

The main product **3b** exhibited a molecular ion peak at



	R^1	R^2	R^3
1a	Cl	H	Me
1b	OH	OH	H
1c	OMe	OMe	Me
1d	Cl	OMe	Me

Chart 1

TABLE I. Photocyclization of the Enamide **2b**

Solvent	Yield (%)[a]	
	3b	**4b**
MeCN	53	26
C_6H_6	58	19
Et_2O–MeOH (40 : 1)	56	19

a) Yield from harmalane.

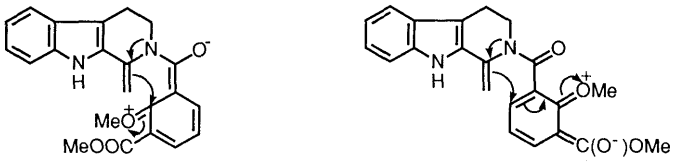


Fig. 1. Two Intermediates

m/z 344 in the MS and ^{1}H-NMR signals at δ 4.00 (3H, s, OMe), 8.03 (1H, s, 14-H), 7.45 (1H, t, J=8 Hz, 18-H), 8.37 (1H, dd, J=8, 1.5 Hz, 17-H), and 8.70 (1H, br d, J=8 Hz, 19-H), establishing the structure of **3b** bearing an ester group at the 16-position. This lactam **3b** corresponds to the known alkaloid oxogambirtannine,[7] which had been already synthesized by several groups,[5,8] though most of the syntheses would not be suitable for large-scale practical synthesis, except Martin's synthesis.[8d] Recently, oxogambirtannine **3b** has been reported[9] to act as an immunostimulator in lung infection induced by *L. monocytogenes*. The minor product **4b** was also characterized from the spectral data [*m/z* 374 (M^+), δ 3.94 and 4.10 (each 3H, s, OMe, COOMe), 6.61 (1H, s, 14-H), 7.97 (1H, d, J=8 Hz, 17-H), and 7.26 (1H, d, J=8 Hz, 16-H)], which firmly established the 18,19-disubstituted benz[*g*]indolo[2,3-*a*]-quinolizine structure. Although the ratio of the desired lactam **3b** was slightly improved by using either ether or benzene as a solvent for irradiation, it is quite exceptional to have observed that photocyclization of the *o*-methoxyenamide **2b** showed low regioselectivity in the direction of cyclization. This result can be explained as follows[6]; in the case of the enamide having an electron-attracting group such as a methoxycarbonyl group in addition to a methoxyl group at the *o*-position, the *o*-methoxyl group would contribute to the resonance with not only the amide carbonyl but also the *o*-methoxycarbonyl group, resulting in the formation of two intermediates, A and B in Fig. 1.

Thus, the photocyclization would proceed to afford a mixture of two lactams **3b** (major) and **4b** (minor) as a result of the preferential contribution of an excited from A over the other form B.

Since direct conversion of the ester **3b** to the aldehyde **3a** by partial reduction with diisobutylaluminum hydride was unsuccessful, we investigated a two-step conversion *via* the corresponding alcohol **3c**. Reduction of the ester **3b** with sodium borohydride at refluxing temperature in a mixture of methanol–tetrahydrofuran (THF) (7 : 1) for 10 h quantitatively afforded the alcohol **3c**, which gave spectral data identical with those of the authentic alcohol,[3] derived from naucleficine by Mao's group. Finally, oxidation of the alcohol **3c** with manganese dioxide in chloroform afforded the desired aldehyde **3a** in 66% yield. This was found by direct comparison to be identical with an authentic sample of the natural alkaloid,[3] naucleficine, provided by Professor Mao. Thus, we have completed the first total synthesis of naucleficine in four steps from harmalane, in a total yield of 38%.

Experimental

The ^{1}H-NMR spectra were measured with JEOL PMX-60 (60 MHz) and Varian XL-200 (200 MHz) instruments for solutions in deuteriochloroform (with tetramethylsilane as an internal reference), and the infrared (IR) spectra were measured with a Hitachi 270-30 machine for solutions in chloroform unless otherwise stated. MS were taken with a Hitachi M-80 spectrometer. All melting points were determined with a Kofler-type hot-stage apparatus and are uncorrected. Extracts from the reaction mixture were washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. 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); during irradiation, the solutions were kept at 0—5 °C, whilst being stirred and bubbled through with nitrogen. Thin layer chromatography (TLC) was performed on pre-coated Silica gel 60F-254 plates (0.25 mm thick, Merck) and preparative TLC (p-TLC) on pre-coated Silica gel 60F-254 plates (0.5 mm thick, Merck), and spots were detected by ultraviolet (UV) irradiation of the plate at 254 and 300 nm or by exposure to iodine vapor. Short column chromatography (SCC) was undertaken on a short glass filter with Silica gel 60F-254 (Merck) under reduced pressure using an aspirator.

Methyl 3,14,15,16,17,18,19,20-Octadehydro-21-oxoyohimban-18-carboxylate (4a) A mixture of the isophthalic acid monopotassium salt (523 mg) and thionyl chloride (5.4 ml) in benzene (11 ml) was refluxed for 1.5 h. The cooled reaction mixture was filtered and the filtrate was concentrated to give an oil. Benzene was added and then evaporated to give the acid chloride **1a**. A solution of the crude acid chloride **1a** in benzene (20 ml) was added to a solution of harmalane (368 mg) and triethylamine (0.4 ml) in benzene (20 ml) with stirring at 0 °C. After being stirred at room temperature for 1 h, the reaction mixture was filtered. The filtrate was diluted with either benzene or acetonitrile (300 ml) and the resulting solution was irradiated for 1 h. The solvent was evaporated off under reduced pressure and the resulting residue was triturated with acetonitrile to give a solid, which was recrystallized from methylene dichloride to give the lactam **4a** as yellow crystals, mp > 280 °C, in 80—81% yield. IR (Nujol): 3250 (NH), 1710 (COOMe), 1650 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz, dimethylsulfoxide (DMSO)-d_6) δ: 8.84 (1H, d, J=1.5 Hz, 19-H), 8.20 (1H, dd, J=8, 1.5 Hz, 17-H), 7.74 (1H, d, J=8 Hz, 16-H), 7.15 (1H, s, 14-H), 4.45 (2H, t, J=7 Hz, 5-H_2), 3.94 (3H, s, COOMe), 3.14 (2H, t, J=7 Hz, 6-H_2). High-resolution MS *m/z*: Calcd for $C_{21}H_{16}N_2O_3$ (M^+) 344.116. Found: 344.115. *Anal.* Calcd for $C_{21}H_{16}N_2O_3 \cdot 1/5CH_2Cl_2$: C, 70.47; H, 4.58; N, 7.75. Found: C, 70.34; H, 4.49; N, 7.97.

Dimethyl 2-Methoxyisophthalate (1c) According to the literature,[10] 2-hydroxyisophthalic acid (**1b**) was prepared by oxidation of 2-hydroxy-3-methylbenzoic acid with lead dioxide. A mixture of methyl iodide (4 ml), anhydrous potassium carbonate (1 g), and the acid **1b** (355 mg) in anhydrous acetone (10 ml) was heated at 40—50 °C for 4—5 h, then allowed to cool. Potassium carbonate was filtered off and the filtrate was concentrated to give a residue, which was extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a residue, which was distilled to afford the diester **1c** (163 mg, 76%) as a colorless oil, bp 160—170 °C (4—5 mmHg). IR: 1730 (COOMe) cm^{-1}. ^{1}H-NMR (60 MHz) δ: 7.83 (2H, d, J=8 Hz, 4- and 6-H), 7.12 (1H, dd, J=10, 8 Hz, 5-H), 3.90 (9H, s, COOMe × 2 and OMe). High-resolution MS *m/z*: Calcd for $C_{11}H_{12}O_5$ (M^+) 224.068. Found: 224.069.

2,3,4,9-Tetrahydro-2-(2-methoxy-3-methoxycarbonylbenzoyl)-1-methylene-1*H*-pyrido[3,4-*b*]indole (2b) A mixture of the diester **1c** (1.2 g) and potassium hydroxide (370 mg) in methanol (17.3 ml) was refluxed for 3.5 h. Evaporation of the solvent gave a residue, which was washed with hexane–ether (1 : 1) to afford the colorless potassium salt. Treatment of the salt with thionyl chloride as described for **4a** and usual work-up gave the acid chloride **1d**. A solution of the acid chloride **1d** in benzene (40 ml) was added to a solution of harmalane (720 mg) and triethylamine (580 mg) in benzene (250 ml) with stirring at 0 °C. After being stirred at room temperature for 1 h, the reaction mixture was filtered. The filtrate was

concentrated to give the unstable enamide **2b** (1.18 g, 80%) as a yellow oil, which was irradiated without purification. ^{1}H-NMR (60 MHz) δ: 5.86 and 5.01 (each 1H, br s, C=CH_2), 3.80 (6H, s, OMe and COOMe).

Photocyclization of the Enamide 2b According to the irradiation procedure described for **2a**, a solution of the unstable crude enamide **2b** (143 mg) was irradiated for 1.5 h in the solvents shown in Table I. Evaporation of the solvent and purification of the crude product by SCC (methanol : methylene dichloride = 3 : 97) gave oxogambirtannine (**3b**), mp 206—209 °C (lit.[8b] 201—205 °C) (yellow crystals from methanol) and methyl 3,14,15,16,17,18,19,20-octadehydro-19-methoxy-21-oxoyohimban-18-carboxylate (**4b**), mp 251—257 °C (pale yellow crystals from hexane–methanol) in the yields shown in Table I. **3b** showed IR, MS, and NMR spectra identical with those of an authentic sample.[7] **3b**: IR: 1700 (COOMe), 1640 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 8.94 (1H, br s, NH), 8.70 (1H, br d, J=8 Hz, 19-H), 8.37 (1H, dd, J=8, 1.5 Hz, 17-H), 8.03 (1H, s, 14-H), 7.45 (1H, t, J=8 Hz, 18-H), 4.55 (2H, t, J=8 Hz, 5-H_2), 4.00 (3H, s, COOMe), 3.16 (2H, t, J=8 Hz, 6-H_2). High-resolution MS m/z: Calcd for $C_{21}H_{16}N_2O_3$ (M^+) 344.116. Found: 344.117. *Anal.* Calcd for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.14. Found: C, 73.31; H, 4.49; N, 8.35. **4b**: IR: 1720 (COOMe), 1650 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 8.45 (1H, br s, NH), 7.97 (1H, d, J=8 Hz, 17-H), 7.26 (1H, d, J=8 Hz, 16-H), 6.61 (1H, s, 14-H), 4.52 (2H, t, J=6.5 Hz, 5-H_2), 4.10 and 3.96 (each 3H, s, COOMe and OMe), 3.16 (2H, t, J=6.5 Hz, 6-H_2). High-resolution MS m/z: Calcd for $C_{22}H_{18}N_2O_4$ (M^+) 374.127. Found: 374.127. *Anal.* Calcd for $C_{22}H_{18}N_2O_4 \cdot 1/2H_2O$: C, 68.92; H, 5.00; N, 7.31. Found: C, 68.99; H, 4.65; N, 7.60.

3,14,15,16,17,18,19,20-Octadehydro-21-oxoyohimban-16-methanol (3c) A solution of the ester **3b** (51 mg) and sodium borohydride (300 mg) in a mixture of methanol–THF (7 : 1) (23 ml) was refluxed for 10 h. Evaporation of the solvent gave a residue, which was dissolved in water (100 ml). The solution was acidified by the addition of 10% hydrochloric acid and cooled. The separated crystals were collected by filtration and recrystallized from water–methanol to give the alcohol (**3c**, 46.5 mg, 99%) as colorless crystals, mp 263—266 °C (lit.[3] 280—283 °C (dec.)), which showed MS and IR spectra identical with those of the authentic alcohol.[3] IR (Nujol): 3200 (NH and OH), 1640 (NCO) cm^{-1}. High-resolution MS m/z: Calcd for $C_{20}H_{16}N_2O_2$ (M^+) 316.121. Found: 316.120.

Naucleficine (3a) A mixture of the alcohol **3c** (30 mg) and manganese dioxide (95 mg) in a mixture of chloroform–THF (3 : 1) was refluxed with stirring for 30 min. Manganese dioxide was filtered off and the filtrate was concentrated to give a residue. Purification of the residue by p-TLC (hexane : AcOEt = 1 : 1) afforded the starting alcohol **3c** (8.3 mg) and naucleficine (**3a**) (19.6 mg, 66%), mp 284—290 °C (orange crystals from methylene dichloride–methanol), which was identical with an authentic sample[3] provided by Professor Mao, upon direct comparison of their MS, IR, and NMR spectra. IR (Nujol): 3350 (NH), 1680 (CHO), 1640 (NCO) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 12.80 (1H, s, CHO), 8.86 (1H, br s, NH), 8.75 (1H, br d, J=8 Hz, 19-H), 8.22 (1H, s, 14-H), 8.10 (1H, dd, J=8, 1.5 Hz, 17-H), 4.58 (2H, t, J=7 Hz, 5-H_2), 3.19 (2H, t, J=7 Hz, 6-H_2). High-resolution MS m/z: Calcd for $C_{20}H_{14}N_2O_2$ (M^+) 314.106. Found: 314.106.

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