Studies on the Syntheses of Heterocyclic and Natural Products. Part 979 (1). Attempted Asymmetric Synthesis of Yohimbol by Photocyclization of the Enamide

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An asymmetric synthesis of yohimbane alkaloid has been attempted by the photolysis of the corresponding enamide (**3**) as a key reaction.

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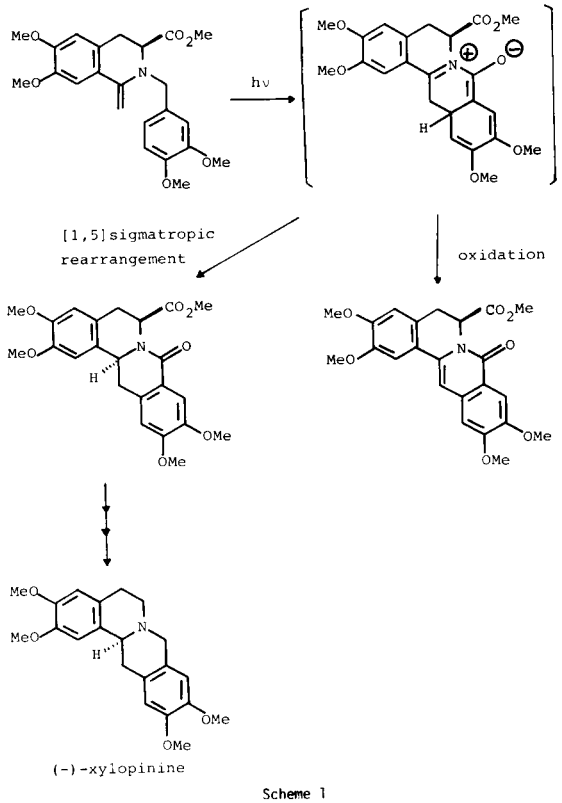
Recently we have developed a new asymmetric synthesis of protoberberine alkaloid, (-)-xylopinine, by photocyclization of an enamide as a key step (2), in which 1,3-asymmetric transfer was induced during the photolysis followed by [1,5] sigmatropic rearrangement shown in Scheme 1.

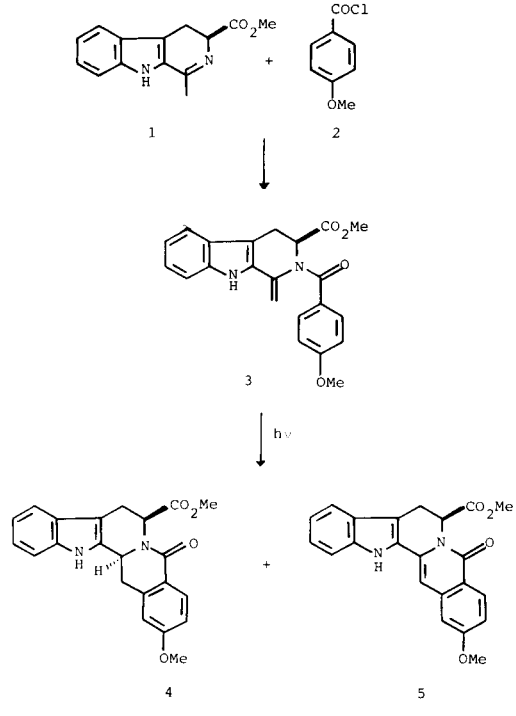


Scheme 1

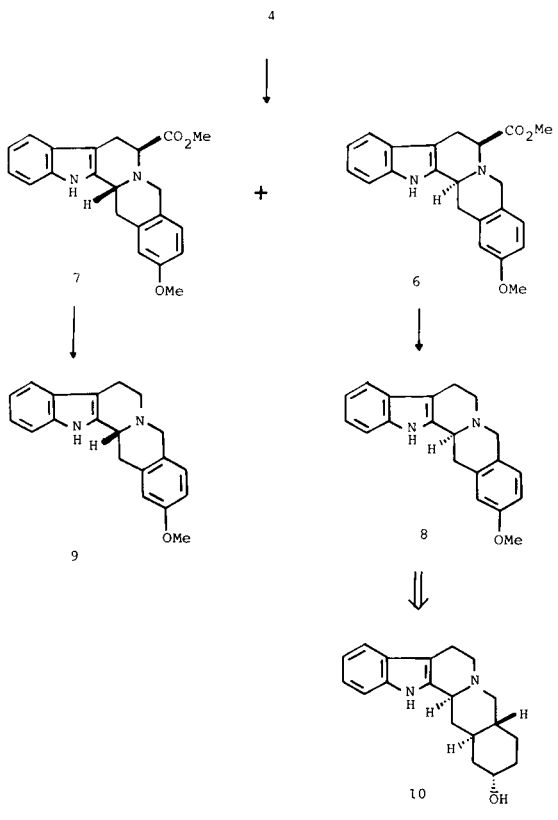
As an extension of our work on this asymmetric synthesis, we have investigated the synthesis of yohimbol (10) from L-tryptophan. Methyl 3,4-dihydro-1-methyl-β-carboline-3-carboxylate (**1**) as a starting material was prepared from L-tryptophan according to Previero's method (3).

Methyl 3,4-dihydro-1-methyl-β-carboline-3-carboxylate (**1**) $[\alpha]_D^{18}$ - 269° (c = 0.45, methanol), on treatment with 4-methoxybenzoyl chloride (**2**) in the presence of triethylamine in benzene afforded the enamide (**3**). Irradiation of a solution of the enamide in dry benzene (4) with Ushio 400 W high pressure mercury lamp equipped with Pyrex filter at ambient temperature for 4 hours yielded the 21-oxoyohimbane (**4**) and the oxidized product (**5**) in 11% and 15% yield, respectively. Treatment of **4** with phosphoryl chloride afforded the quaternary salt which without isolation was reduced with sodium borohydride in methanol to furnish the amines (**6** and **7**) in 13% and 13% yield, respectively. Though the structure of the former compound was assigned to be **6** based on its spectral data, which was consistent with those of reported one (**4**), the optical rotation [$[\alpha]_D^{20}$ - 20° (c = 0.7, chloroform)] of **6** was much lower than that of the literature (5).

Since it has been known that the racemization of 3,4-di-



Scheme II - 1



Scheme II - 2

hydro-β-carboline bearing alkoxycarbonyl group at the C_3-position would readily occur (6), this insufficient asymmetric induction might be explained that the racemization at the C_3-position would take place before the formation of the enamide (**3**). Finally, removal of carboxylate ester unit at the C_5-position from **6** was investigated to complete the synthesis of yohimbol (**10**) in an optically active form. Although Yamada has not succeeded in the conversion on **6** into **8** (5), we could accomplish it by adoption of Rapoport's procedure (7). Thus, the ester was hydrolyzed with potassium hydroxide in aqueous methanol to give the acid, which was then treated with phosphoryl chloride and subsequently with sodium borohydride to afford **8** in 1.7% yield. Since the conversion of **8** into yohimbol (**10**) has already been reported (5), this synthesis constitutes the formal synthesis of the optically active **10**.

Moreover, the isomer (**7**) was converted into (3*R*)-(+)-isomer (**9**), which showed the positive optical rotation as expected.

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were measured on a Hitachi 260-10 spectrophotometer, nmr spectra with a JEOL JNM-FX100 spectrometer using tetramethylsilane as an internal standard with chemical shift (δ) expressed in ppm downfield from TMS. Mass spectra were taken with a JEOL-D300 spectrometer.

Methyl 2-(4-Methoxybenzoyl)-2,3,4,9-tetrahydro-1-methylene-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (**3**).

To a stirred solution of the β-carboline (**1**) (1.12 g) and triethylamine (1.4 g) in dry benzene (50 ml) was added a solution of 4-methoxybenzoyl chloride (780 mg) in dry benzene (10 ml) at room temperature in a current of nitrogen and the resulting mixture was then warmed at 50° for 2 hours. After insoluble material had been filtered off, the filtrate was concentrated to afford the unstable enamide (**3**) (5.1 g, 100%); ir: 3490 cm^{-1} (NH), 1740 cm^{-1} (C=O), 1650 cm^{-1} (C=O), 1580 cm^{-1} (C=C); nmr (deuteriochloroform): δ 3.60 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.36 (d, J = 3.2 Hz, 1H, olefinic), 5.00 (d, J = 3.2 Hz), 5.75 (m, 1H, C_3-H), 6.75 (d, J = 9.0 Hz, 2H, aromatic), 6.92 - 7.36 (m, 4H, aromatic), 7.48 (d, J = 9.0 Hz, 2H, aromatic), 8.42 (s, 1H, NH). This compound is not enough stable to obtain a satisfactory elemental analysis.

Photolysis of the Enamide (**3**).

A solution of the enamide (**3**) (5.1 g) in dry benzene (700 ml) was irradiated at 10-20° with an Ushio 400 W high pressure mercury lamp equipped with a Pyrex filter for 4 hours. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel and eluted with benzene-acetone (98:2 v/v) to give dehydrolactam, whose recrystallization from methanol afforded **5** (258 mg, 15%) as yellowish needles, mp 256-257°; ir 3495 cm^{-1} (NH), 1740 cm^{-1} (C=O), 1640 cm^{-1} (C=O); nmr (deuteriochloroform-deuteriodimethylsulfoxide): δ 3.46 (d, J = 6.0 Hz, 2H, CH_2), 3.70 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.25 (m, 1H, C_5-H), 6.8-7.5 (m, 6H, aromatic), 8.30 (d, J = 8.0 Hz, 1H, C_{19}-H), 8.82 (s, 1H, NH); ms: m/e 374 (M^+); $[\alpha]_D^{20}$ - 0.54° [c = 1.06, chloroform-dimethylsulfoxide (4:1 v/v)].

Anal. Calcd. for $C_{22}H_{18}N_2O_4 \cdot 0.5H_2O$: C, 68.92; H, 4.99; N, 7.30. Found: C, 69.06; H, 4.76; N, 7.20.

Further elution with benzene-acetone (97:3 v/v) gave the lactam which was recrystallized from methanol to afford **4** (190 mg, 11%) as yellowish needles, mp 190°; ir: 1730 cm^{-1} (C=O), 1640 cm^{-1} (C=O); nmr (deuteriochloroform): δ 3.24 (d, J = 5.0 Hz, 2H, C_6-H_2), 3.61 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 5.17 (s, 1H, C_3-H), 5.52 (m, 1H, C_5-H), 6.7-7.5 (m, 6H, aromatic), 8.30 (d, J = 8.0 Hz, 1H, C_{19}-H), 8.29 (s, 1H, NH); ms: m/e 376 (M^+); $[\alpha]_D^{20}$ + 2.65° (c = 1.13, chloroform).

Anal. Calcd. for $C_{22}H_{20}N_2O_4 \cdot 0.75H_2O$: C, 67.76; H, 5.56; N, 7.19. Found: C, 67.80; H, 5.25; N, 7.07.

(3*S*,5*S*)-(-)-Methyl 15,16,17,18,19,20-Hexadehydro-17-methoxyyohimbane-5-carboxylate (**6**) and (3*R*,5*S*)-(+)-isomer (**7**).

A mixture of the lactam (**5**) (1.49 g) and phosphoryl chloride (35 ml) was heated at 60° for 2 hours in a current of nitrogen and then evaporated. The residue was dissolved in methanol (40 ml) under nitrogen and sodium borohydride (350 mg) was added in small portions with stirring at 0°. After being stirred at ambient temperature for 2 hours, the solution was evaporated and the residue was extracted with methylene chloride. The organic layer was washed with water, dried and evaporated to give the residue, which was subjected to column chromatography on silica gel. Elution with benzene afforded the ester, which was recrystallized from methanol to give **6** (300 mg, 13%) as yellowish needles, mp 183° [lit (5), 185°]; ir: 2900-2700 cm^{-1} (Bohlmann bands); nmr (deuteriochloroform): δ 3.20 (m, 4H, C_6-H_2 and C_{14}-H_2), 3.80 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.64 - 7.56 (m, 7H, aromatic), 7.84 (s, 1H, NH); ms: m/e 362 (M^+); $[\alpha]_D^{20}$ -20° (c = 0.7, chloroform) [lit (4), -149.5°].

Further elution with benzene-acetone (99:1 v/v) afforded the isomer, which was recrystallized from methanol to yield **7** (300 mg, 13%) as yellowish needles, mp 181°; ir: 1710 cm^{-1} (C=O); nmr (deuteriochloroform): δ 3.60 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 6.65-7.55 (m, 7H, aromatic), 7.91 (s, 1H, NH); ms: m/e 362 (M^+); $[\alpha]_D^{20}$ + 35° (c = 1.06, chloroform).

(3*S*)-(-)-15,16,17,18,19,20-Hexahydro-17-methoxyyohimbane (**8**).

A solution of the ester (**6**) (400 mg) and potassium hydroxide (228 mg) in methanol (2 ml) and water (0.42 ml) was heated at 60° for 24 hours. After removal of the solvent, the residue was dissolved in methanol and

treated with hydrogen chloride in methanol to prepare its hydrochloride. The solvent was evaporated and the residue was dissolved into phosphoryl chloride (4.8 ml). The mixture was warmed at 90° for 10 minutes and then evaporated. The residue was dissolved in methanol (10 ml) under nitrogen, to a solution of which sodium borohydride (450 mg) was added in small portions with stirring at 0°. After being stirred at ambient temperature for 2 hours, the solvent was evaporated and the residue was extracted with chloroform. The extract was washed with water, dried, and evaporated to give the residue, which was subjected to column chromatography on silica gel. Elution with benzene-acetone (98:2 v/v) afforded the yohimbane, which was recrystallized from methanol to give **8** (5.6 mg, 1.7%) as colorless needles, mp 219° [lit (4), 235°]; $[\alpha]_D^{20}$ −40° (c = 0.03, methanol) [lit (4), −235°].

(3*R*)-(+)-15,16,17,18,19,20-Hexahydro-17-methoxyyohimbane (**9**).

The decarbomethoxylation of **7** (250 mg) was carried out as described above to give **9** (4 mg, 1.9%); nmr (deuteriochloroform): δ 3.79 (s, 3H, OCH_3), 6.64 - 7.58 (m, 7H, aromatic), 7.90 (s, 1H, NH); ms: m/e 304 (M^+); $[\alpha]_D^{20}$ + 30° (c = 0.25, methanol).

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