A SIMPLE SYNTHESIS OF YOHIMBAN, ALLOYOHIMBAN, AND ALLOYOHIMBONE BY REDUCTIVE PHOTOCYCLIZATION OF ENAMIDES

Takeaki Naito, Yukiko Tada, Yoshino Nishiguchi, and Ichiya Ninomiya*
Kobe Women's College of Pharmacy
Motoyamakita, Higashinada, Kobe 658, Japan

Abstract ------- A simple synthesis of yohimban (6a) and alloyohimban (6b), and alloyohimbone (10) was achieved by reductive photocyclization of the enamides (1a) and (1b) in the presence of sodium borohydride respectively.

Previously, we have reported the synthesis of three yohimbans by applying non-oxidative photocyclization of the unstable enamide which was prepared from harmalan and 1-cyclohexene-1-carbonyl chloride.[1] The present investigation was undertaken in order to synthesize yohimban and yohimbone stereoselectively by applying reductive photocyclization of enamides which had recently been discovered by our group.[2]

Reductive photocyclization[2] of the enamide (1a), which was readily prepared from harmalan and benzoyl chloride, proceeded smoothly to give a mixture of two hydrogenated lactams (2)[3] and (3a)[4] in addition to small amount of the aromatic lactam (4)[5] in the ratios depending on the hydride reagent and the solvent system employed as shown in the table. As clear from the table, the hydrogenated lactam (3a) having an unconjugated diene structure was exclusively obtained in an excellent yield by reductive photocyclization using sodium borohydride as the hydride and a mixture of acetonitrile-methanol (20 : 1) as the solvent system. Catalytic hydrogenation of the lactams (2) and (3a) on platinum dioxide afforded the saturated lactam (5a) (88 %) and a mixture of the lactams (5a)(46 %) and (5b)(41 %) respectively, each of which was identified with the authentic samples of yohimban-21-one[1] and alloyohimban-21-one[1] respectively.

The saturated lactams (5a) and (5b) were reduced with lithium aluminum hydride to afford yohimban (6a) and alloyohimban (6b) in 85 % yields,which were identical with the authentic samples[1]respectively.

Thus, we succeeded in a simple four-step synthesis of yohimban (6a) and alloyohimban (6b) from harmalan in overall yields of 38 and 34 % respectively.

Alternatively, yohimban (6a) and alloyohimban (6b) were also synthesized via the route of reduction with lithium aluminum hydride of the unconjugated lactam (3a) followed by catalytic hydrogenation of the resulting amine (7a) on platinum dioxide in overall yield of 11 % from the lactam (3a) as shown in the figure.

Reductive photocyclization[2] of the para-methoxy substituted enamide (1b), prepared from harmalan and p-methoxybenzoyl chloride, in an acetonitrile-methanol solution in the presence of sodium borohydride gave the unconjugated lactam (3b)[6] as a sole product in 90 % yield.

Reduction of the lactam (3b) with a large amount of lithium aluminum hydride gave two amines (7b)[7] and (8b)[8] in 73 and 5 % yields respectively, of which the latter (8b) was identical with the authentic sample[9] upon comparison with their melting points and spectral data.

Hydrolysis of the enol-amine (7b) with hydrochloric acid gave the unconjugated enone (9a)[10] which was readily isomerized into the conjugated enone (9b)[11] upon treatment with silica gel in 90 % yield from (7b). Catalytic hydrogenation of both enones (9a) and (9b) on platinum dioxide afforded alloyohimbone (10) in 97-98 % yields, which was identical with the authentic sample derived from alloyohimbinone upon acidic decarboxylation.[12]

Thus, we also succeeded in a stereoselective synthesis of alloyohimbone (10) from harmalan in five steps and in overall yield of 59 %.

Since it is now established that reductive photocyclization of enamides provided a versatile intermediates (3a) and (3b) for the synthesis of yohimbine, total synthetic work of natural alkaloid is now under progress.

ACKNOWLEDGEMENT

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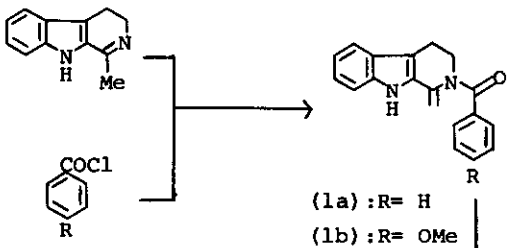
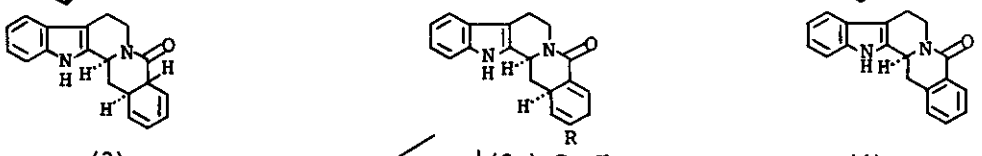


(1a) : R= H
(1b) : R= OMe

Table

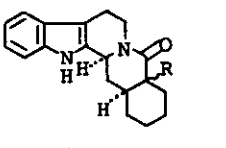
Hydride	Solvent	Yields(%) (2)	(3a)	(4)
$NaBH_4$	C_6H_6-MeOH	7	21	20
$NaBH_4$	Et_2O-MeOH	17	32	5
$NaBH_4$	MeCN-MeOH	--	98	--
$LiBH_4$	C_6H_6-THF	--	5	13



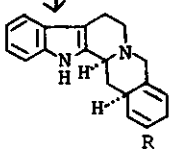
(2)

(3a) : R= H
(3b) : R= OMe

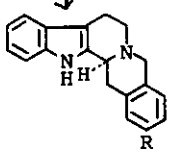
(4)



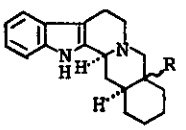
(5a) : R= —H
(5b) : R= ····H



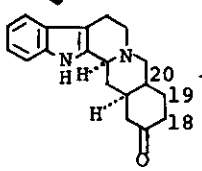
(7a) : R= H
(7b) : R= OMe



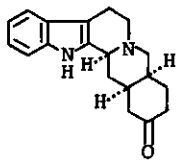
(8a) : R= H
(8b) : R= OMe



(6a) : R= —H (yohimban)
(6b) : R= ····H (alloyohimban)



(9a) : $\Delta^{19,20}$
(9b) : $\Delta^{18,19}$



(10) (alloyohimbone)

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3 MS m/z: 290(M^+). IR($CHCl_3$) cm^{-1}: 3480 and 1620. NMR($CDCl_3$+CD_3OD) δ: 6.43 (1H, br.d, J=9Hz, 19-H), 6.12(2H, m, 17- and 18-H), 5.88(1H, br.d, J=9Hz, 16-H), 5.14 (1H, m, 5eq-H), 4.90(1H, br.dd, J=12 and 5Hz, 3-H), 2.78(1H, br.d, J=12Hz, 14eq-H), 2.61(1H, br.dd, J=20 and 12Hz, 15-H), and 1.80(1H, q, J=12Hz, 14ax-H).

4 MS m/z: 290(M^+). IR($CHCl_3$) cm^{-1}: 3480, 1680, 1635, and 1605. NMR($CDCl_3$) δ: 7.00 (1H, s-like, 19-H), 5.78(1H, br.d, J=10Hz, 17-H), 5.64(1H, br.dd, J=10 and 2Hz, 16-H), 5.21(1H, m, 5eq-H), 4.93(1H, br.dd, J=12 and 4Hz, 3-H), 3.16(1H, m, 15-H), 2.58(1H, dt, J=12.5 and 4Hz, 14eq-H), and 1.69(1H, q, J=12.5Hz, 14ax-H).

5 IR($CHCl_3$) cm^{-1}: 3475, 1635, and 1600. NMR($CDCl_3$) δ: 8.17(1H, m, 19-H), and 5.30-4.67(2H, m, 3- and 5eq-H).

6 MS m/z: 320(M^+). IR($CHCl_3$) cm^{-1}: 3455, 1690, 1655, and 1610. NMR($CDCl_3$) δ: 6.94 (1H, m, 19-H), 5.18(1H, m, 5eq-H), 4.95(1H, br.dd, J=12 and 4Hz, 3-H), 4.56(1H, s-like, 16-H), 3.58(3H, s, OMe), 3.35(1H, m, 15-H), 2.56(1H, ddd, J=12, 4, and 3.5Hz, 14eq-H), and 1.69(1H, q, J=12Hz, 14ax-H).

7 MS m/z: 306(M^+). IR($CHCl_3$) cm^{-1}: 3480, 2940, 2850, 2750, 1660, and 1610. NMR($CDCl_3$) δ: 5.59(1H, m, 19-H), 4.56(1H, br.d, J=3Hz, 16-H), 3.56(3H, s, OMe), 3.52(1H, br.dd, J=12 and 2.5Hz, 3-H), 3.44 and 3.07(2H, ABq, J=12Hz, 21-H_2), 2.26(1H, ddd, J=12, 4.5, and 2.5Hz, 14eq-H), and 1.49(1H, q, J=12Hz, 14ax-H).

8 IR($CHCl_3$) cm^{-1}: 3475 and 1605. NMR($CDCl_3$) δ: 4.03(1H, d, J=15Hz, 21-H), and 3.75(3H, s, OMe). m.p. 161-162° (lit.[9] 168-169°).

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10 IR($CHCl_3$) cm^{-1}: 3480 and 1720. NMR($CDCl_3$) δ: 5.43(1H, s-like, 19-H), 3.54 and 3.07(2H, ABq, J=12.5Hz, 21-H_2), 3.40(1H, br.d, J=12Hz, 3-H), 2.30(1H, ddd, J=12, 5, and 3Hz, 14eq-H), and 1.54(1H, q, J=12Hz, 14ax-H).

11 IR($CHCl_3$) cm^{-1}: 3475 and 1660. NMR($CDCl_3$) δ: 6.89(1H, dt, J=10 and 1.8Hz,19-H), 6.00(1H, dd, J=10 and 2.5Hz, 18-H), 3.25(1H, br.d, J=11Hz, 3-H), 1.86(1H, dt, J=12.5 and 5Hz, 14eq-H), and 1.72(1H, ddd, J=13, 12.5, and 11Hz, 14ax-H).

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