A NOVEL TOTAL SYNTHESIS OF (±)-AJMALICINE

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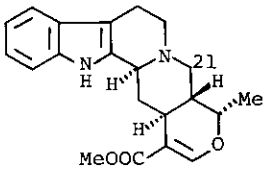
Abstract——A common key intermediate (9) for the synthesis of (±)-ajmalicine was prepared in 11 steps from harmalane (2) with 30% overall yield.

Ajmalicine (1) is a pharmacologically important member of heteroyohimbine alkaloids and has found clinical use, being effective as an adrenergic blocking agent both alone and in combination therapy with reserpine.[1] As part of our general project toward the development of practical and general synthetic routes for the monoterpenoid alkaloids such as ipecac and corynantheine-heteroyohimbine alkaloids,[2] we have now succeeded in the development of an efficient synthesis of (±)-ajmalicine (1) by the stereoselective preparation of a key intermediate,[3-5] α-methyl-δ-lactone (9) via the route involving incorporation of a furan ring into a monoterpene unit of the alkaloid. The key steps in our synthesis are i) construction of the basic structure of the alkaloid by reductive photocyclization[6] of enamide, ii) stereoselective introduction of an electrophile into the α-position of the lactam carbonyl group, and iii) chemoselective reduction of the lactam carbonyl group.

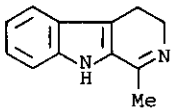
Reductive photocyclization[6] of the enamide (3) having a furan ring, which was readily prepared from harmalane (2) and 2-furoyl chloride, in acetonitrile-methanol (9:1) proceeded smoothly to give the furanoquinolizine (4a) in 94% yield [ν(Nujol) 3250, 1635, and 1615; δ($CDCl_3$) 6.44(dd, J=2.5, 1.5 Hz, 2-H), 5.12(t, J=2.5 Hz, 1-H), 4.85(d, J=10 Hz, 3a-H), 4.82(br dd, J=12, 3 Hz, 12b-H), and 1.54(br q, J=13 Hz, 13-Hax)]. The lactam (4a) was metalated with 6 equiv. of lithium diisopropylamide (-30°C, THF, 40 min) and then treated with 6 equiv. of acetic anhydride (-30°C, 1 h) to give a mixture of two diacetates (4b and 4c)

in a 1:1 ratio in 85 % yield which was separated by p.l.c. on silica gel and characterized by their spectral data [(4b): $\nu(CHCl_3)$ 1710, 1690, and 1640; $\delta(CDCl_3)$ 2.84(s, NAc) and 2.46(s, Ac); (4c): $\nu(CHCl_3)$ 1770, 1690, and 1650; $\delta(CDCl_3)$ 5.50 and 5.25(each d, J=2.5 Hz, $C=CH_2$), 2.86(s, NAc), and 2.24(s, OAc)]. Treatment of respective acetates (4b and 4c) with 15%H_2SO_4 afforded the hemiacetal (5) as a 1:1 epimeric mixture in quantitative yield which was also obtained by the same reaction of a crude mixture of two acetates (4b and 4c), prepared by acetylation of the lactam (4a). As in the case of the synthetic route developed by our group,[2] oxidation of the hydroxyl group in the hemiacetal (5) with dimethyl sulfoxide-acetic anhydride followed by reductive cleavage of the resulting keto-γ-lactone (6) with zinc powder in acetic acid and then esterification of the acid (7a) with diazomethane afforded the desired acetyl ester (7b) homogeneously in 80% overall yield, [$\nu(CHCl_3)$ 3475, 1730-1710, and 1630; $\delta(CDCl_3)$ 3.71(s, COOMe) and 2.46(s, Ac)]. Upon comparison with their i.r. and n.m.r. spectra, this acetyl ester (7b) is found to be identical with the known compound, prepared by Massiot et al.,[7] who however gave no comment on the usefulness of this compound for the synthesis of heteroyohimbine alkaloids such as ajmalicine.

In order to synthesize a key intermediate (9) for the synthesis of (±)-ajmalicine, the chemoselective conversion of the lactam (7b), which contains three different types of carbonyl groups, into the amine (7d) was then investigated. The best and convenient conversion was achieved by a new chemoselective reduction as follows. Treatment of the lactam (7b) with Lawesson's reagent[8] in toluene at 100°C gave chemoselectively the thiolactam (7c) in 92% yield which was then subjected to desulfurization with W-2 Raney nickel in methanol to lead to the formation of the unstable vinylogous amide (8)[$\nu(CHCl_3)$ 3480, 1730, and 1580; $\delta(CDCl_3)$ 7.40(s, 4-H), 3.58(s, COOMe), and 2.13(s, Ac)]. This vinylogous amide (8) was then reduced with sodium cyanoborohydride in methanol containing hydrogen chloride[9] to give the aminoacetyl ester (7d) [$\nu(CHCl_3)$ 3490, 2850, 2810, 2770, 1730, and 1710; $\delta(CDCl_3)$ 3.71(s, COOMe) and 2.26(s, Ac)] in 50% yield from 7c, which was identical with the sample of a key intermediate for the synthesis of not only ajmalicine[3,5] but also corynantheine group of alkaloids.[10] Stereoselective conversion of 7d into the desired α-methyl-δ-lactone (9) was uneventfully accomplished in a quantitative yield according to the route estab-



(1)



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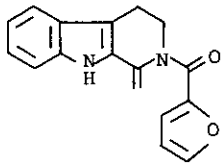

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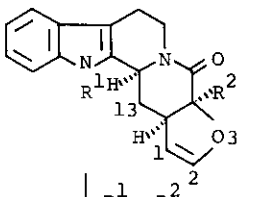
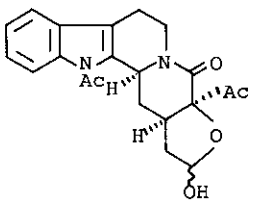
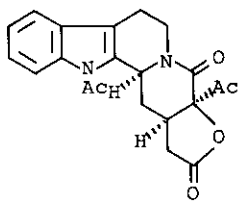


	R^1	R^2
(4a)	H	H
(4b)	Ac	Ac
(4c)	Ac	$-C(OAc)=CH_2$



(5)



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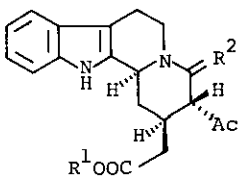
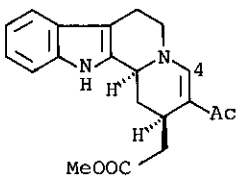
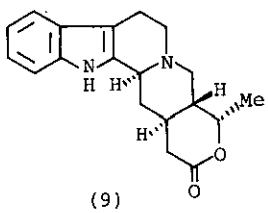


	R^1	R^2
(7a)	H	O
(7b)	Me	O
(7c)	Me	S
(7d)	Me	H_2



(8)



(9)

lished by van Tamelen's group.[3] The synthetic lactone (9) could not be distinguished from an authentic sample given by Professors Winterfeldt[4] and Massiot[5] upon comparisons with their Rf values in t.l.c., i.r. and n.m.r. spectra. The overall yield of the lactone (9) from harmalane (2) was 30% in 11 steps.

Thus, we have succeeded in a new stereoselective synthesis of an important key intermediate (9) which had been already converted into (±)-ajmalicine.[3-5] Since we prepared an acetyl ester (7d) stereoselectively *via* its dehydro derivative (8) as shown above, our synthetic method described here would provide a synthesis of cathenamine (20,21-dehydroajmalicine) which has been recently attracted much attention by alkaloid chemists in view of the biosynthetically importance as an intermediate of corynantheine-heteroyohimbine group of alkaloids.[11]

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REFERENCES

1. N. Neuss, 'Indole and Biogenetically Related Alkaloids,' eds. by J. D. Phillipson and M. H. Zenk, Academic Press., London, 1980, pp. 298-301.
2. T. Naito, N. Kojima, O. Miyata, and I. Ninomiya, J. Chem. Soc., Chem. Commun., 1985, 1611.
3. E. E. van Tamelen, C. Placeway, G. P. Schiemenz, and I. G. Wright, J. Am. Chem. Soc., 1969, 91, 7359.
4. E. Winterfeldt, A. J. Gaskell, T. Korth, H.-E. Radunz, and M. Walkowiak, Chem. Ber., 1969, 102, 3558.
5. G. Massiot and T. Mulamba, J. Chem. Soc., Chem. Commun., 1984, 715.
6. T. Naito, Y. Tada, Y. Nishiguchi, and I. Ninomiya, J. Chem. Soc., Perkin Trans. 1, 1985, 487.
7. G. Massiot, T. Mulamba, and J. Lévy, Bull. Soc. Chim. Fr., 1982, II-241.
8. M. P. Cava and M. I. Levinson, Tetrahedron, 1985, 41, 5061.
9. R. J. Sundberg, C. P. Walters, and J. D. Bloom, J. Org. Chem., 1981, 46, 3730.
10. E. E. van Tamelen and I. G. Wright, J. Am. Chem. Soc., 1969, 91, 7349.
11. R. B. Herbert, 'The Chemistry of Heterocyclic Compounds,' eds. by A. Weissberger and E. C. Taylor, John Wiley and Sons, Inc., New York, 1983, Vol. 25 (Indoles, Part 4), pp. 63-146.

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