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# 1,6-DIHYDRO-3(2*H*)-PYRIDINONES AS SYNTHETIC INTERMEDIATES. A NOVEL TOTAL SYNTHESIS OF (±)-IBOGAMINE AND (±)-EPIIBOGAMINE

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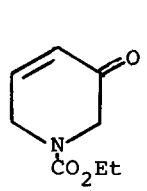
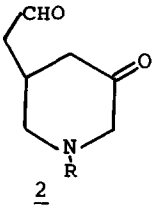
Summary: A new synthesis of (±)-ibogamine (4) and (±)-epiibogamine (5), involving the intramolecular Michael addition of the keto unsaturated ester (11), is described.

In the previous studies we have revealed that ethyl 1,6-dihydro-3(2*H*)-pyridinone-1-carboxylate (1) is a very potential synthon for many kinds of alkaloids and related compounds.[1] In the course of the studies, 5-(2-oxoethyl)-3-piperidinones (2) derived from 1 was found to be easily converted to the 2-azabicyclo-[2.2.2]octan-6-one system (3) under an acidic condition.[1c] As an application of this new method for the azabicyclooctane ring formation, we wish to report here a novel total synthesis of (±)-ibogamine and (±)-epiibogamine (4 and 5)[2] using an intramolecular Michael addition in the key step.

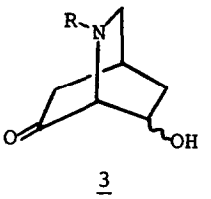


1



2

a R=$CO_2Et$
b R=Cbz



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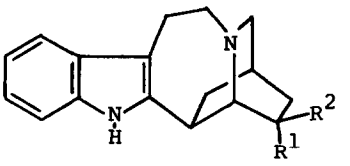
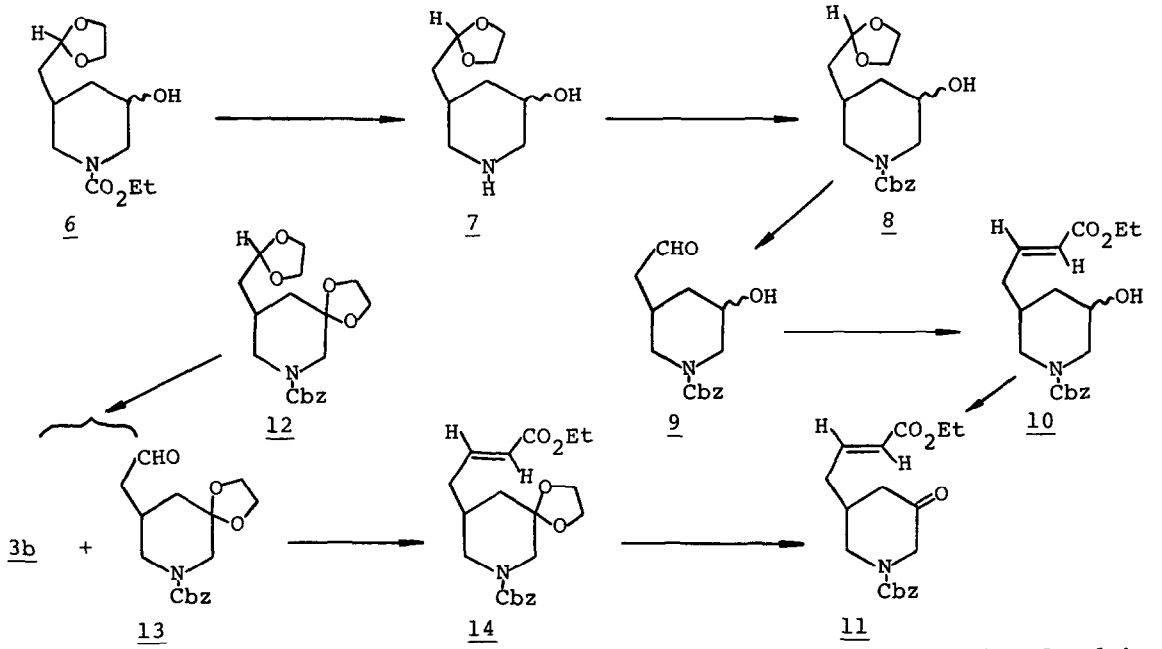


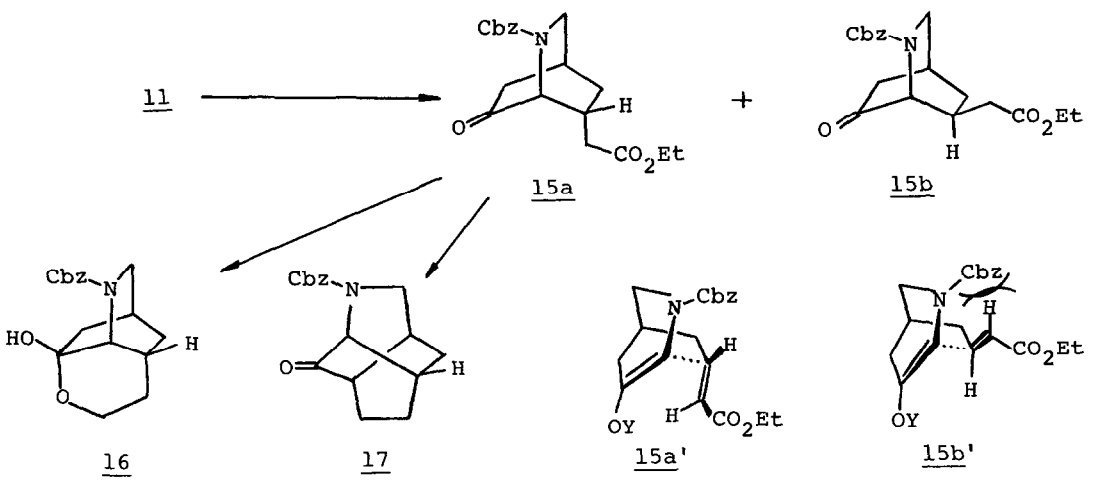
4 $R^1$=H, $R^2$=Et
5 $R^1$=Et, $R^2$=H

Ethyl 5-(2-ethylenedioxyethyl)-3-hydroxypiperidine-1-carboxylate[1c] (6) was subjected to an alkaline hydrolysis to provide the amine (7), which was treated with carbobenzoxy chloride in a usual manner to give the benzyl urethane (8) in overall 90% yield. The aldehyde (9) [$\nu^3$ 2720, 1720; $\delta^3$ 9.58(1H,t,*J*=1)], obtained by the reaction of 8 with 1% hydrochloric acid in acetone, was condensed with the ylid of triethyl phosphonoacetate in benzene at 0° to afford the unsaturated ester (10) [85% yield from 8; δ 5.77(1H,d,*J*=15), 6.6-7.0(1H,m)]. The Jones oxidation of 10 gave the ketone (11) [ν 1705, 1695, 1650; δ 5.80(1H,d,*J*=16), 6.4-7.0 (1H,m)] in 70% yield. The same keto ester (11) was also obtained in the different route but less effectively. A mild hydrolysis of the diketal (12)[1c] yielded the aldehyde (13) in 68% yield along with the overreaction product (3b; 16%). The modified Wittig reaction of 13, followed by deketalization furnished 11 *via*

14 in 57% yield.

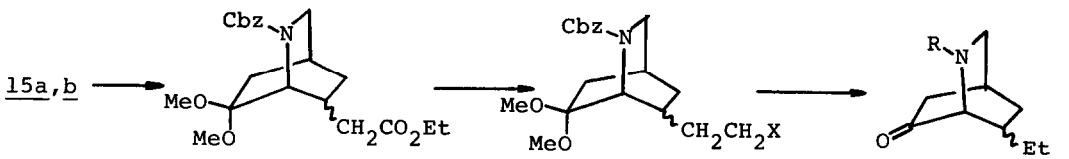


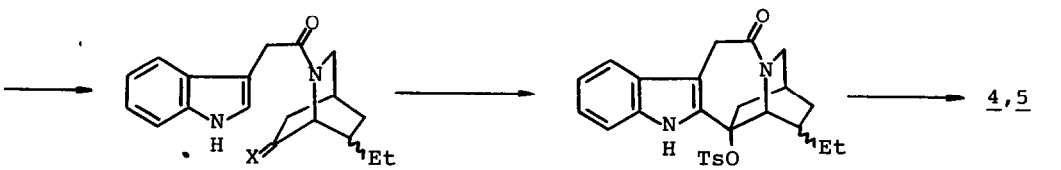
On treatment of 11 with potassium carbonate in ethanol under reflux for 1 hr the intramolecular Michael reaction proceeded smoothly to afford two isomers, 15a[73% yield; ν 1730, 1685; δ 1.21(3H,t,*J*=7), 3.44(2H,broad s), 4.06(2H,q,*J*=7), 4.21(1H,d,*J*=3), 5.07(2H,s), 7.25(5H,s); *m/e* 345($M^+$)] and 15b[15% yield; ν 1730, 1685; δ 1.20(3H,t,*J*=7), 3.38(2H,broad s), 4.03(2H,q,*J*=7), 4.23(1H,broad s), 5.07 (2H,s), 7.24(5H,s); *m/e* 345($M^+$)].[4] The same cyclization with sodium hydride in dioxane under reflux for 45 min resulted in somewhat increasing the yield of 15b (26%) together with 51% yield of 15a. The stereochemistry of the products was confirmed by the fact that the main product (15a) was transformed to the hemi-



acetal (16) [mp 85-87°; ν(KBr) 3350, 1675] and the 2-azatwistanone (17; ν 1745, 1680) in a few-steps sequence. Neither of the isomers (15a and b) isomerized to each other under the same conditions as that for the cyclization, leading the assumption that the ratio of two products would be reflected by relative stability of the trasition state (15a' and 15b').

Ketalization (methyl orthoformate, *p*-TsOH, methanol, reflux) of 15a gave 18a in 97% yield, which was reduced ($LiAlH_4$, ether, 0°) to the alchohol (19a; 92% yield). Mesylation ($MeSO_2Cl$, $Et_3N$, $C_6H_6$, r.t.) of 19a to 20a and the subsequent reduction with zinc-sodium iodide in boiling 1,2-dimethoxyethane[5] gave 21a in 82% yield from 19a. Although the benzyl group in 21a resisted hydrogenolysis, the ketone (22a) obtained from 21a (1%HCl in acetone, reflux, quantitatively) underwent easily hydrogenolysis over 5% palladium on carbon in methanol to give the labile amino ketone (23a), which was immediately condensed with β-indolylacetyl chloride in dichloromethane to yield the amide (24a) in 93% yield from 22a. The dimethyl ketal (25a; 82% yield) was treated with *p*-toluenesulfonic acid in boiling benzene for a short time to give the pentacyclic tosylate (26a)[6] [79% yield; mp 176-178°; ν 3440, 1630, 1597, 1360, 1175; δ 0.77(3H,t,*J*=7), 2.39(3H,s), 3.75(2H, s), 4.79(1H,d,*J*=3), 7.0-7.6(8H), 8.04(1H,broad s); *m/e* 292($M^+$-TsOH)]. An efficient one-step synthesis of (±)-epiibogamine (5) from 26a was able to be accomplished with a lithium aluminum hydride-aluminum chloride complex. Namely, treatment of 26a with a large excess of $AlH_2Cl$[7] (prepared *in situ* from a 1:1 mixture of $LiAlH_4$ and $AlCl_3$) in tetrahydrofuran at room temperature furnished 5 [86% yield; mp 197-199°; ν 3450, 1460; δ 0.93(3H,t,*J*=7), 6.9-7.3(3H), 7.3-7.5 (1H), 7.95(1H,broad s); High MS *m/e* $M^+$: 280.193 (calcd for $C_{19}H_{24}N_2$: 280.194); *m/e* 280($M^+$,base), 156, 124].



On the other hand, the minor isomer (15b) was also utilized for the synthesis of (±)-ibogamine (4) [mp 117-120°; ν 3460, 1460; δ 0.90(3H,t,*J*=7), 7.0-7.3(3H), 7.3-7.5(1H), 7.60(1H,broad s); High MS *m/e* $M^+$: 280.194 (calcd for $C_{19}H_{24}N_2$: 280.194); *m/e* 280($M^+$), 136(base)] in the same manner as above: 15b → 18b(94%) → 19b(92%) → 20b(91%) → 21b(85%) → 22b(quant) → 23b → 24b(50% from 22b) → 25b → 26b(40% from 24b) → 4(74%). The synthetic products (4 and 5) are proved to be identical with natural ibogamine and epiibogamine, respectively, by means of spectral comparison.

Thus, as one of the continuous studies on various alkaloids syntheses using a common synthon, ethyl 1,6-dihydro-3(2*H*)-pyridinone-1-carboxylate (1), we have achieved total synthesis of (±)-ibogamine and (±)-epiibogamine *via* an efficient intramolecular Michael cyclization step.

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3. Unless otherwise stated, IR and PMR spectra were measured in $CHCl_3$ and $CDCl_3$ solutions, respectively.
4. Under the acidic condition similar to that for 3, the unsaturated ester (11) was found to remain unchanged.
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6. Nagata and co-workers[2c] had synthesized (±)-epiibogamine and (±)-ibogamine from 26a and b in low yields by the several-steps sequence.
7. H.O. House,"Modern Synthetic Reactions," second edition, W.A. Benjamin, Inc., California, 1972, p 48.

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