FIRST TOTAL SYNTHESIS OF (±)-HIRSUTEINE

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Abstract——First total synthesis of (±)-hirsuteine, 3β-epimer of corynantheine, was achieved via the route involving retro Michael and the subsequent Michael reaction of the furo[3,2-c]pyridone (2b).

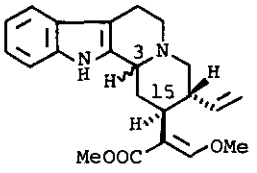
The design and development of general strategies for the synthesis of the monoterpenoid alkaloids have been one of major focuses of research in our laboratory, and we have recently succeeded in a facile synthesis of ipecac and heteroyohimbine alkaloids with the 3α-H (3,15-syn) stereochemistry.[1-3] We now describe another general strategy for the synthesis of corynantheine-heteroyohimbine alkaloids[4] with the 3β-H (3,15-anti) stereochemistry by the first total synthesis of (±)-hirsuteine (the 3β-epimer of corynantheine). The overall strategy is based on the elimination-addition reaction of furopyridone which consists of retro Michael reaction of the furo[3,2-c]pyridone and the subsequent Michael reaction of the resulting α,β-unsaturated lactam.

Stereoselective construction of the basic skeletal structure (2a) of the desired indoloquinolizine alkaloids was accomplished by the well known[5] reductive photocyclization of the enamide (1), which was prepared from harmalane and 3-furoic acid, by the analogous procedure given previously in emetine synthesis.[3] Catalytic hydrogenation of (2a) in the presence of platinum dioxide afforded quantitatively the tetrahydrofuropyridone (2b) which was subjected to elimination reaction by treatment with lithium diisopropylamide (LDA) in tetrahydrofuran at -78°C to give the α,β-unsaturated lactam (3a)[6] in 71% yield. We then investigated the Michael reaction of (3a) with two donors, 2-lithioacetamide (4) and 2-lithioacetate (5) inspite of the fact[7] that an analogous acceptor (3b) is reluctant to the Michael reaction. The Michael reaction with the former donor

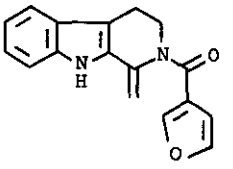
(4) proceeded smoothly to give the desired anti adducts (6a) and (6b) in a 1:1 ratio in 80% yield, whereas the same reaction with the latter donor (5) gave the adducts (7a)[8] and (7b)[8] in only 2% combined yield. However, a one-pot Michael reaction[3] between the furopyridone (2b) and 2-lithioacetate (5)(5 eq.) proceeded very smoothly at the temperature (-78°C at the start and then raised up to 10°C at the end) to afford a 1:1 mixture of trans- and cis-anti adducts (7a) and (7b) in 53% yield. Anti-stereochemistry of the adducts (7a) and (7b) obtained in the above one-pot Michael reaction would be explained by assuming chelation between the carbanion formed in situ at the 3a-position of (2b) and 2-lithioacetate (5) in a transition state (A). Stereochemistries of the adducts (6a), (6b), (7a), and (7b) were deduced by comparison of their nmr spectra with those of analogous compounds previously reported.[3] Thus, we succeeded in a simple preparation of the desired 3,15-anti-disubstituted indoloquinolizines (7a) and (7b), the former of which was then converted into the final alkaloid as follows.

Treatment of the trans-anti alcohol (7a) with o-nitrophenylselenocyanate-tributylphosphine[4,9] followed by oxidation of the resulting alkylarylselenide (7c) with hydrogen peroxide afforded the trans-anti olefin (8a)[10] in 59% yield from (7a). Similarly, the cis-anti alcohol (7b) was converted into the cis-anti olefin (8b)[10] which can be used as a key intermediate for the synthesis of epiallo-corynantheine types of alkaloids.[11] Chemoselective reduction of the lactam carbonyl group in the lactam (8a) with aluminum hydride[12] followed by formylation of the resulting amine (8c)[13] with ethyl formate in the presence of LDA at -40°C gave the formyl ester (9a)[14] in 45% yield. Finally, treatment of (9a) with methanol saturated with hydrogen chloride[15] followed by methylation with diazomethane afforded (±)-hirsuteine along with the corresponding acetal (9b) in 52 and 21% yields respectively, the former of which was identical with the natural alkaloid[16,17] upon comparisons of their ir, nmr, and mass spectra, and Rf values. Thus we succeeded in the first total synthesis of (±)-hirsuteine.[4] Since hirsuteine had already been converted into hirsutine,[17] the present work also completes a formal total synthesis of this alkaloid.

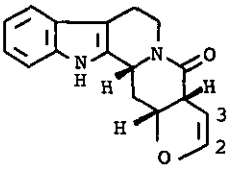
Coupled with the previous synthesis[2] of the normal series of alkaloid having 3,15-syn structure from 2-furoic acid, the present synthesis of (±)-hirsuteine having 3,15-anti structure from 3-furoic acid would provide a new general synthetic strategy widely applicable to both 3,15-syn and anti types of alkaloids simply by the selection of either 2- or 3-furoic acid as a starting material.



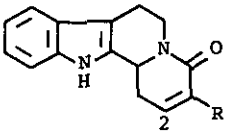
3α-H ; Corynantheine
3β-H ; Hirsuteine



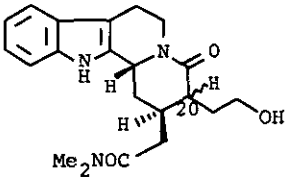
(1)



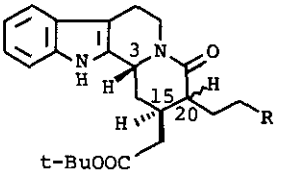
(2a)
(2b); 2,3-dihydro



(3a); R=$(CH_2)_2OH$
(3b); R=Et



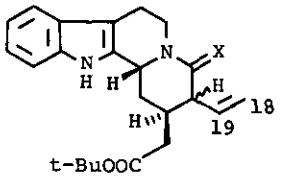
(6a); 20β-H
(6b); 20α-H



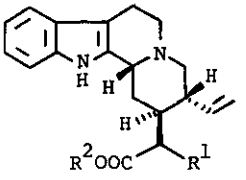
(7a); 20β-H, R=OH
(7b); 20α-H, R=OH
(7c); 20β-H,
R=$SeC_6H_4(o\text{-}NO_2)$

(4) $LiCH_2CONMe_2$

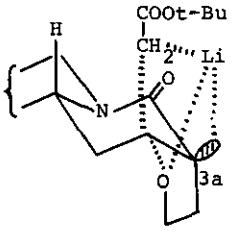
(5) $LiCH_2COOt\text{-}Bu$



(8a); 20β-H, X=O
(8b); 20α-H, X=O
(8c); 20β-H, X=H_2



(9a); R^1=CHO, R^2=t-Bu
(9b); R^1=$CH(OMe)_2$, R^2=Me



(A)

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(7b):Ir($CHCl_3$)cm^{-1}:3490, 3350, 1720, and 1618. Nmr($CDCl_3$) δ:4.93(1H, dd, J=9 and 5Hz, 3-H) and 2.09(1H, br t, J=9Hz, 14-Hax)

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(8b):Nmr($CDCl_3$) δ:5.49(1H, ddd, J=17, 11, and 8Hz, 19-H), 5.42-5.24(2H, m, 18-H_2), and 3.14(1H, dd, J=8 and 3Hz, 20-H)

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