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INTRODUCTION OF HYDROXYL GROUP AT C-14 OF INDOLE ALKALOIDS: THE PARTIAL SYNTHESIS OF 14α-HYDROXYRAUNITICINE[1)]

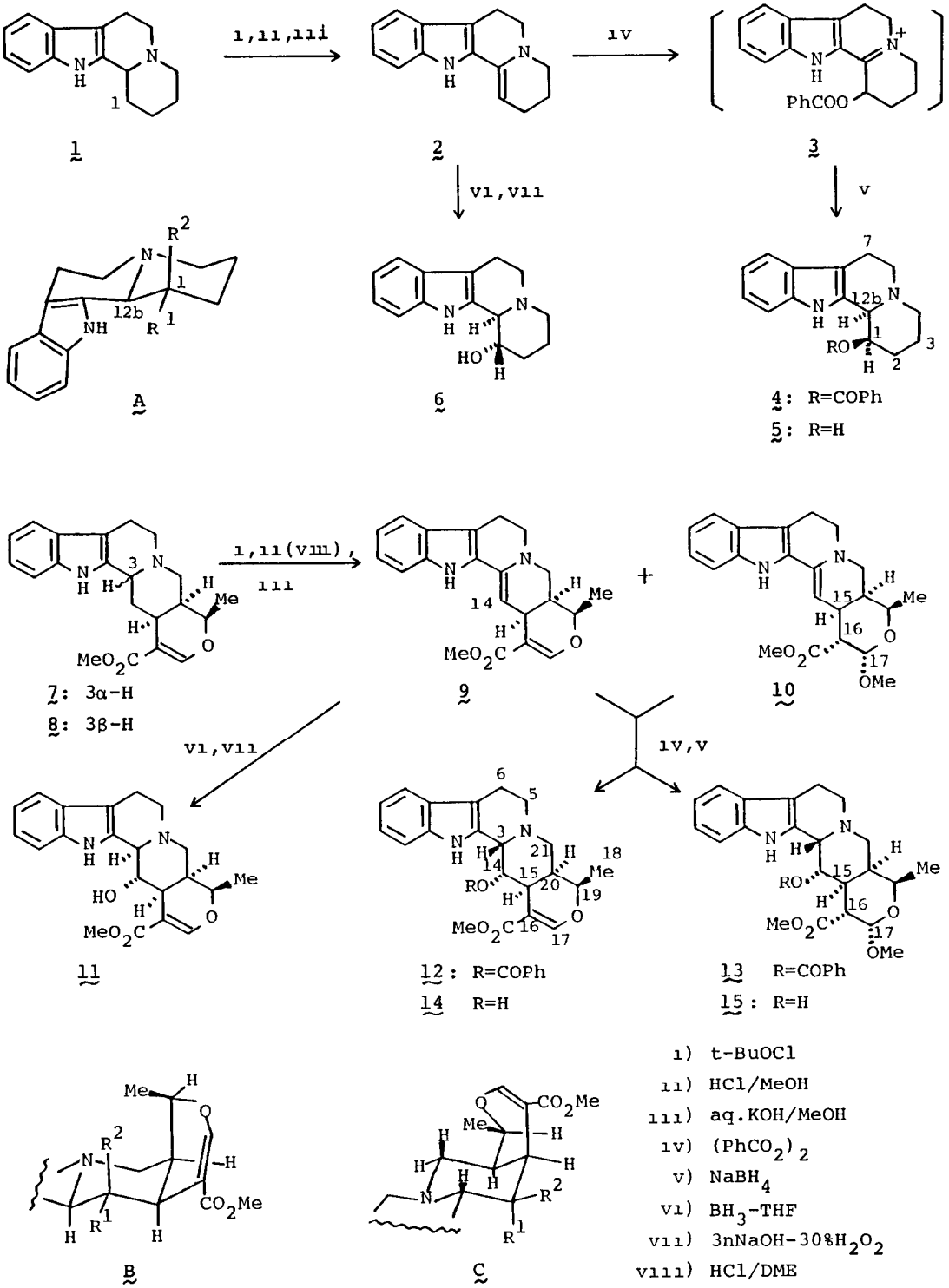
Etsuji Yamanaka, Etsuko Maruta, Satoe Kasamatsu, Norio Aimi and Shin-ichiro Sakai*
Faculty of Pharmaceutical Sciences, Chiba University,
1-33 Yayoi, Chiba, 260, Japan
Dhavadee Ponglux, Sumphan Wongseripipatana and Tanomjit Supavita
Faculty of Pharmaceutical Sciences, Chulalongkorn University,
Bangkok 5, Thailand

Summary: Stereoselective hydroxylation at C-1 of the indoloquinolizidine (1) to the hydroxyl derivatives (5 and 6) and the partial synthesis of 14α-hydroxyrauniticine (11) from rauniticine (7) are described.

In 1980 a 14-hydroxylated heteroyohimbine alkaloid was isolated from *Uncaria attenuata*[2)] and the structure was elucidated as 14β-hydroxy-3-iso-rauniticine. Recently, however, the structure was revised to 14α-hydroxy-rauniticine (11).[3)] The present communication describes the stereoselective formation of the natural alkaloid from rauniticine (7).

First, model experiments were carried out to establish the methods of the stereoselective hydroxylation at C-14 (C-1 in the case of 1). The enamine (2)[4)] was treated with dibenzoyl peroxide[5)] followed by successive addition of MeOH, n-HCl (1.5 eq), and $NaBH_4$ (2mol eq) to give the *cis*-1-benzoyloxyindoloquinolizidine (4) [57%; mp 178-179°C(MeOH); m/z(%): 346(M^+, 13), 224(100)].[6)] The spectral data of 4 showed the *trans*-quinolizidine structure (A: R^1=H, R^2=OCOPh): Bohlmann bands in the IR spectrum, ^{1}H-NMR signal due to H-12b at δ3.72 in upfield position,[7)] and ^{13}C-NMR signal at δ21.5[8)] assignable to C-7 (Table). The ^{1}H-NMR signals of H-12b and H-1 (δ5.80) were observed as broad singlets respectively indicating their *cis* arrangement. The benzoyloxy group was axial as evidenced by the observed upfield shift of C-3[1(δ25.7)[9)] ⟶ 4(δ21.0)] due to γ-*gauche* effect. Treatment of 4 with NaOMe in MeOH gave the *cis*-1-hydroxyindoloquinolizidine (5)[10)] [86%, mp 209-211°C(MeOH), m/z(%): 242(M^+,76); ^{1}H-NMR δ: 4.13(br s,H-1)].

The *trans*-isomer (6) corresponding to the natural alkaloid (11) was obtained by use of hydroboration-oxidation method. Thus treatment of the enamine (2) with BH_3-THF (3mol eq) in dry THF at room temperature followed by oxidation with 3n-NaOH/30%H_2O_2 at 45-50°C[11)] gave 6 [23%; mp 201-203°C ($CHCl_3$), m/z(%): 242(M^+,100)] together with 1 (55%). The hydroxyl group of



1 2 3 A 6 4: R=COPh 5: R=H

7: 3α-H 8: 3β-H 9 10 11 12: R=COPh 14 R=H 13 R=COPh 15: R=H

B C

Table. Characteristic Chemical Shifts for *trans*-Indoloquinolizidines[a]

Compound	4	5	6	7	8	11	12	13	14	15
H-3(12b)[b]	3.72[c]	3.48[c]	3.07	3.48[d]	3.12[d]	3.21	3.55	3.76	3.37	3.62
C-6(7)[b]	21.5	20.9[e]	22.4[f]	21.1[g]	21.7[h]	21.8	21.5	21.4	21.5	21.5

[a] The values are in ppm downfield from Me_4Si. [b] Numbering system in parentheses is for compounds (4,5 and 6) [c] At 100 MHz [d] Value from ref 7 [e] In Me_2SO-d_6 solution [f] In CD_3OD solution [g] Value from ref 8 [h] Value from ref. 13

6 (A: R^1=OH, R^2=H) was equatorial as evidenced by the coupling pattern of H-1[δ3.73(td, J=10 and 4.5 Hz)].

The above hydroxylation methods were applied to raunticine (7). Dehydrogenation of 7 in the usual manner[12] [i)t-BuOCl ii)HCl-MeOH iii) aq.KOH-MeOH] gave precipitates (84%) which were composed of the enamines 9 and 10 (1:1)[m/z(%): 382($M^+$of 10,41), 350($M^+$of 9,39)]. More conveniently, 9 was obtained as the sole product[87%; m/z(%): 350(M^+,100), ^{1}H-NMR δ 1.45 (3H,d,J=7Hz,H-18), 3.75(3H,s,OMe), 4.16(1H,qd,J=7,1.5Hz,H-19), 5.48(1H,d, J=5.5Hz,H-14)] when dry DME, instead of MeOH, was used as the solvent for HCl treatment. Hydroboration-oxidation of 9 as in the case of 2 gave the hydroxyl compound (11)[6%, ^{1}H-NMR δ: 1.42(3H,d,J=7Hz,H-18), 3.21(1H,d, J=9Hz,H-3), 3.79(3H,s,OMe), 3.86(1H,t,J=9Hz,H-14), 4.47(1H,qd,J=7,5Hz,H-19), 6.01(1H,br s,OH), 7.73(1H,s,H-17), 9.33(1H,br s,NH)] together with raunticine (7,48%) and 3-isoraunticine (8,12%). The spectral data (IR, MS, ^{1}H-NMR, CD) of the synthetic hydroxyl compound (11) were identical with those of the natural alkaloid, 14α-hydroxyraunticine.

The *cis*-isomer (14) was obtained by the method using dibenzoyl peroxide. The mixture of the enamines (9 and 10) was treated with $(PhCO_2)_2/NaBH_4$ to give two benzoates 12[16%; m/z(%): 472(M^+,7), 350(100)] and 13[16%; m/z (%): 504(M^+,6), 382(63)]. The structure of 12 (C: R^1=OCOPh, R^2=H) was confirmed as follows. ^{1}H-NMR signals of H-3 and H-14 (δ6.93) appeared as broad singlets indicating their *cis* arrangement. The triplet signal of H-21β (δ2.46, J=11Hz) supported the diaxial arrangement of H-21β and H-20. Chemical shift of C-21 (δ49.4) of 12 was similar to that (δ49.8)[13] of 3-isoraunticine[8(C: R^1=R^2=H)] and different from that (δ53.7)[8] of raunticine[7(B: R^1=R^2=H]. The compound (13) was characterized as the 16*R*,17*S*-3-isoraunticine methyl acetal derivative as follows. ^{1}H-NMR signals of H-3 (br s) and H-14 (δ5.98, br s), and ^{13}C-NMR signal of C-21 (δ49.4) were observed in the expected positions. The diaxial arrangement of H-15 and H-16 ($J_{15,16}$=13 Hz) and *cis* configuration of H-16 and H-17 ($J_{16,17}$=4 Hz) were also proved.

Treatment of 12 and 13 with NaOMe gave the hydroxyl derivatives 14 and 15, respectively[14: 96%; m/z(%): 368(M^+,52), 350(100); ^{1}H-NMR δ: 1.37(3H,d, J=7Hz,H-18), 3.37(1H,br s,H-3), 3.76(3H,s,OMe), 4.11(1H,qd,J=7,2Hz,H-19), 5.13(1H,d,J=2.5Hz,H-14), 7.65(1H,d,J=2Hz,H-17), 8.17(1H,br s,NH). 15: 100%; m/z(%): 400(M^+,100); ^{1}H-NMR δ: 1.18(3H,d,J=7Hz,H-18), 2.59(1H,t,J=12Hz,H-21β),

3.36(3H,s,17-OMe), 3.62(1H,br s,H-3), 3.79(3H,s,OMe), 4.04(1H,qd,J=7,2.5Hz, H-19), 4.26(1H,br s,H-14), 5.00(1H,d,J=4Hz,H-17),8.48(1H,br s,NH)].

Application of the present hydroxylation methods to other indole alkaloids is in progress.

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