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A New Indole Alkaloid, 14α-Hydroxyrauniticine: Structure Revision and Partial Synthesis[1)]

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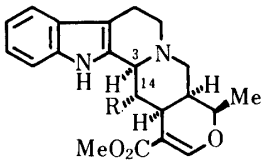
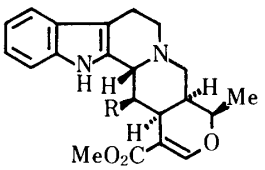
Oxidation of the enamine (**6**) with dibenzoyl peroxide followed by reduction with $NaBH_4$ gave the benzoate (**8**), which was converted to the *cis*-hydroxyl compound (**9**), while hydroboration–oxidation of **6** gave the *trans*-isomer (**11**). Treatment of a mixture of the enamines (**13** and **14**) with dibenzoyl peroxide/$NaBH_4$ gave the benzoates (**15** and **16**), which were converted to 14α-hydroxy-3-isorauniticine (**17**) and the acetal (**18**), respectively. Hydroboration–oxidation of **13** gave 14α-hydroxyrauniticine (**2**), which was found to be identical with the natural alkaloid whose structure had erroneously been proposed as 14β-hydroxy-3-isorauniticine (**4**).

Keywords——indole alkaloid; 14α-hydroxyrauniticine; structure revision; partial synthesis; *Uncaria attenuata*; enamine; hydroxylation; hydroboration

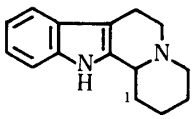
In 1980, a heteroyohimbine alkaloid having a 14-hydroxyl group was isolated from *Uncaria attenuata* and the structure was proposed as 14β-hydroxy-3-isorauniticine (**4**).[2)] We reported preliminarily[3)] on the development of general and stereoselective C-14 (C-1 in the case of **5**) hydroxylation methods using 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**5**)[4)] and the synthesis of the natural 14-hydroxylated heteroyohimbine alkaloid (**2**). At that time, the 270 MHz proton nuclear magnetic resonance (^{1}H-NMR) spectrum and other spectra were re-examined and the structure was revised to 14α-hydroxyrauniticine (**2**). We describe here the methods of hydroxylation at C-14 of indole alkaloids and the structure revision of the



1 : R=H, rauniticine
2 : R=OH



3 : R=H, 3-isorauniticine
4 : R=OH



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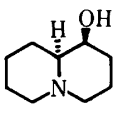

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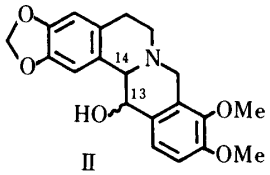


II

Chart 1

natural alkaloid in detail.

Introduction of a hydroxyl group at the β-position to a nitrogen has been reported by oxidation–reduction and hydroboration–oxidation methods *via* the corresponding enamine as follows: a) oxidation of 1,10-dehydroquinolizidine with dibenzoyl peroxide followed by reduction with $NaBH_4$ to give *cis*-(H-1/H-10)-1-benzoyloxyquinolizidine, which was hydrolyzed to *cis*-(H-1/H-10)-1-hydroxyquinolizidine (I),[5] b) hydroboration–oxidation of dihydroberberine to give 13-epiophiocarpine [II: *trans*-(H-13/H-14)] as a major product together with ophiocarpine [II: *cis*-(H-13/H-14)].[6]

Oxidation of the enamine (**6**) with dibenzoyl peroxide was reported to give **7** in the course of the synthesis of eburnamonine.[7] The desired compounds (**9** and **11**) were considered to be formed through reduction of the iminium part of **7** followed by removal of the benzoyl group. The enamine (**6**) was prepared from **5** *via* the 12b-dehydronium chloride by the reported method [i) *tert*-BuOCl, ii) HCl–MeOH, iii) aq. KOH–MeOH].[8-10]

The enamine (**6**) was oxidized with dibenzoyl peroxide in dioxane[7] followed by successive addition of MeOH, 1 N HCl and $NaBH_4$ to give the *cis*-(H-1/H-12b)-1-benzoyloxyindoloquinolizidine (**8**) in 57% yield. Compound **8** showed the following spectral data, which indicated the presence of the *trans*-quinolizidine skeleton (A: $R^1=H$, $R^2=OCOPh$); Bohlmann bands in the infrared (IR) spectrum,[11] the ^{1}H-NMR signal due to H-12b at δ 3.72 in an upfield position[12] and the carbon-13 nuclear magnetic resonance (^{13}C-NMR) signal at δ 21.5[13] assignable to C-7. The ^{1}H-NMR signals of H-12b and H-1 which appeared at δ 3.72 and 5.80 as broad singlets indicated *cis* arrangement of these protons and therefore, axial orientation of the benzoyloxy group. This assignment was further confirmed by the observed upfield shift of the ^{13}C-NMR signal of C-3 [**5** (δ 25.7)[14] → **8** (δ 21.0)] due to 1,3-diaxial interaction between the axial benzoyloxy group and C_3–H bond.

Treatment of **8** with NaOMe in MeOH gave the *cis*-(H-1/H-12b)-1-hydroxyindoloquinolizidine (**9**)[15] in 86% yield. The presence of Bohlmann bands in the IR spectrum and the characteristic chemical shifts of H-12b (δ 3.48) and C-7 (δ 20.9) in the ^{1}H- and ^{13}C-NMR spectra indicated that **9** possessed the same conformation as **8**. The changes of the shift values for D ring carbons of **9** from the skeletal compound (**5**) were consistent with those reported for cyclohexanes having an axial hydroxyl group [α(+37.8 ppm), β(+5.5), γ(−6.8)].[16] Acetylation of **9** gave the acetate (**10**, 97%), which was also in *trans*-quinolizidine form (A: $R^1=H$, $R^2=OAc$).

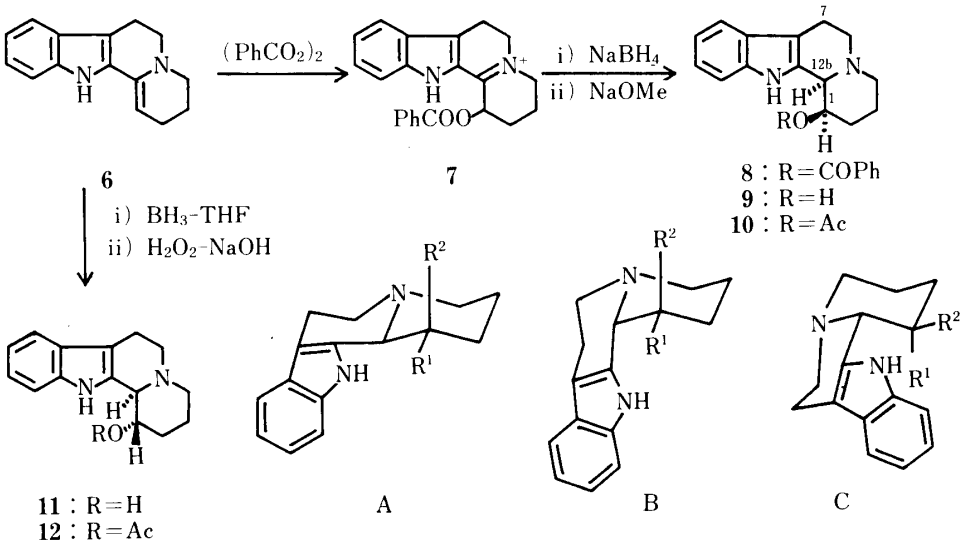


Chart 2

TABLE I. ^{13}C Chemical Shifts[a] of Indoloquinolizidines

Carbon	5[b]	8[c]	9[d]	10[e]	11[f]	12[g]
1	30.0	68.2	64.9	67.1	72.3	75.5
2	24.3	28.9	30.9	28.8	35.4	30.4
3	25.7	21.0[h]	20.1[h]	20.9[h]	24.5	23.3
4	55.8	54.5	54.4	54.7	56.1	54.7
6	53.5	53.9	52.6	53.9	54.4	52.6
7	21.6	21.5[h]	20.9[h]	21.2[h]	22.4	21.5
7a	108.1	110.0	107.6	110.0	108.4	109.5
7b	127.6	127.3	126.6	127.3	128.0	126.7
8	118.1	117.9	117.1	118.0	118.6	118.2
9	119.3	119.2	117.9	119.3	120.2	119.3
10	121.2	121.4	120.1	121.5	122.1	121.7
11	110.8	111.1	110.8	111.1	112.1	110.7
11a	136.1	136.3	136.0	136.3	137.6	135.8
12a	135.2	131.4	133.8	131.1	135.3	132.4
12b	60.3	62.7	63.7	62.7	67.0	62.2

a) The values are in ppm downfield from Me_4Si. The spectra were measured in $CDCl_3$ unless otherwise stated. *b*) Values from ref. 14. *c*) Benzoyl δ: 167.0 (CO), 130.0 (C-1), 129.7, 128.3 (C-2, C-3), 133.4 (C-4). *d*) In Me_2SO-d_6 solution. *e*) Acetyl δ: 171.6 (CO), 21.3. *f*) In CD_3OD solution at 50 °C. *g*) Acetyl δ: 169.4, 21.7. *h*) Values in any column may be interchanged.

The *trans*-isomer (**11**) corresponding to the natural alkaloid (**2**) was obtained by use of the hydroboration–oxidation method. Thus treatment of the enamine (**6**) with 1 M BH_3–THF (3 molar eq) in dry tetrahydrofuran (THF) at room temperature (RT) followed by oxidation with 3 N NaOH and 30% H_2O_2 at 45—50 °C gave the desired compound, *trans*-(H-1/H-12b)-1-hydroxyindoloquinolizidine (**11**, 23%), accompanied with **5** (55%). The presence of Bohlmann bands in the IR spectrum and characteristic chemical shifts of H-12b (δ 3.07) and C-7 (δ 22.4) in the ^1H- and ^{13}C-NMR spectra indicated that **11** possessed *trans*-quinolizidine form (A: $R^1=OH$, $R^2=H$). The hydroxyl group was demonstrated to be in an equatorial position by the coupling pattern of H-1 [δ: 3.73 (td, $J_{1,12b}=J_{1,2ax}=10$ Hz, $J_{1,2eq}=4.5$ Hz)]. Further evidence for the structure of **11** having an equatorial hydroxyl group was obtained by comparison of the ^{13}C-NMR shift values for D ring carbons of **11** with those of **5**, showing the substituent effects of an equatorial hydroxyl group [$\alpha(+43.2)$, $\beta(+7.9)$, $\gamma(-1.1)$].[16] Acetylation of **11** gave the acetate (**12**, 95%), which was demonstrated to be in *trans*-quinolizidine form (A: $R^1=OAc$, $R^2=H$).

The present methods were applied to rauniticine (**1**). Dehydrogenation of **1** in the usual manner [i) *tert*-BuOCl, ii) HCl–MeOH, iii) aq. KOH–MeOH] gave precipitates (84%), which were composed of the enamines [**13** and **14** (1 : 1)] as shown by the spectral data (Experimental). The mixture of **13** and **14**, without further purification, was oxidized with dibenzoyl peroxide followed by reduction with $NaBH_4$ to give two benzoates [**15** (16%) and **16** (16%)]. Compound **15** showed the following spectral data, which indicated *trans*-quinolizidine conformation; Bohlmann bands in the IR spectrum, the ^1H-NMR signal due to H-3 at δ 3.55 in an upfield position and the ^{13}C-NMR signal due to C-6 at δ 21.5. The ^1H-NMR signals of H-3 and H-14 of **15**, which appeared at δ 3.55 and 6.93, respectively, as broad singlets, indicated *cis* arrangement of these protons and therefore, the axial orientation of the benzoyloxy group. The above observations suggested that the structure of **15** is either D ($R^1=$ OCOPh, $R^2=H$) or E ($R^1=H$, $R^2=$OCOPh). A large steric compression is expected in the latter because of the 1,3-diaxial C_{19}-Me and 14β-benzoyloxy group. The ^1H- and ^{13}C-NMR analyses confirmed that **15** existed in the structure D: the chemical shift of C-21 (δ 49.4) in **15** was similar to that (δ 49.8)[17] of 3-isorauniticine (**3**) [D ($R^1=R^2=H$)] rather than that

(δ 53.7)[13] of rauniticine (**1**) [E ($R^1=R^2=H$)]. In addition, the observation of the ^{1}H-NMR signal of H-21β as a triplet (δ 2.46, $J=11$ Hz) showed the diaxial arrangement of H-21β and H-20. The following data for the other benzoate (**16**) were similar to those of **15**, indicating its structure to be F: Bohlmann bands in the IR spectrum, the appearance of the ^{1}H-NMR signals of H-3 (δ 3.76) and H-14 (δ 5.98) as broad singlets and the ^{13}C-NMR signals of C-6 (δ 21.4) and C-21 (δ 49.4) in the expected positions. The observation of the signals of H-17 (δ 5.01, d, $J=4$ Hz), 17-OMe (δ 3.32, s) and the ^{13}C-NMR signals of C-16 (δ 42.7) and C-17 (δ 98.0) indicated the methyl acetal structure for the E ring of **16**. Furthermore, the large coupling of H-16 (δ 3.11, dd) with H-15 (δ 2.85, ddd, $J_{15,16}=13$ Hz, $J_{15,20}=4$ Hz, $J_{14,15}=2$ Hz) ascertained by spin–spin decoupling demonstrated the diaxial configuration of H-15 and H-16. The small coupling of H-17 with H-16 ($J=4$ Hz) supported *cis* configuration of these protons. Therefore, the benzoate (**16**) was characterized as the 16*R*, 17*S*-derivative [F (R = COPh)].

Treatment of **15** and **16** with NaOMe in MeOH at RT gave the hydroxyl derivatives [**17** (96%) and **18** (100%), respectively]. The spectral data (IR, ^{1}H- and ^{13}C-NMR) indicated that conformational change did not occur in the course of debenzoylation. In addition, further evidence for the structure of **17** was provided by the similarity of circular dichroism (CD) spectra between **17** and 3-isorauniticine (**3**).

The dehydrogenation method was modified for **1** so as to avoid acetal formation before attempting hydroxylation by hydroboration-oxidation. When dry dimethoxyethane (DME) was used as the solvent, instead of MeOH, the enamine (**13**) was obtained as the sole product (87%) on treatment with HCl.

Treatment of **13** with 1 M BH_3–THF in dry THF at RT followed by oxidation with 3 N

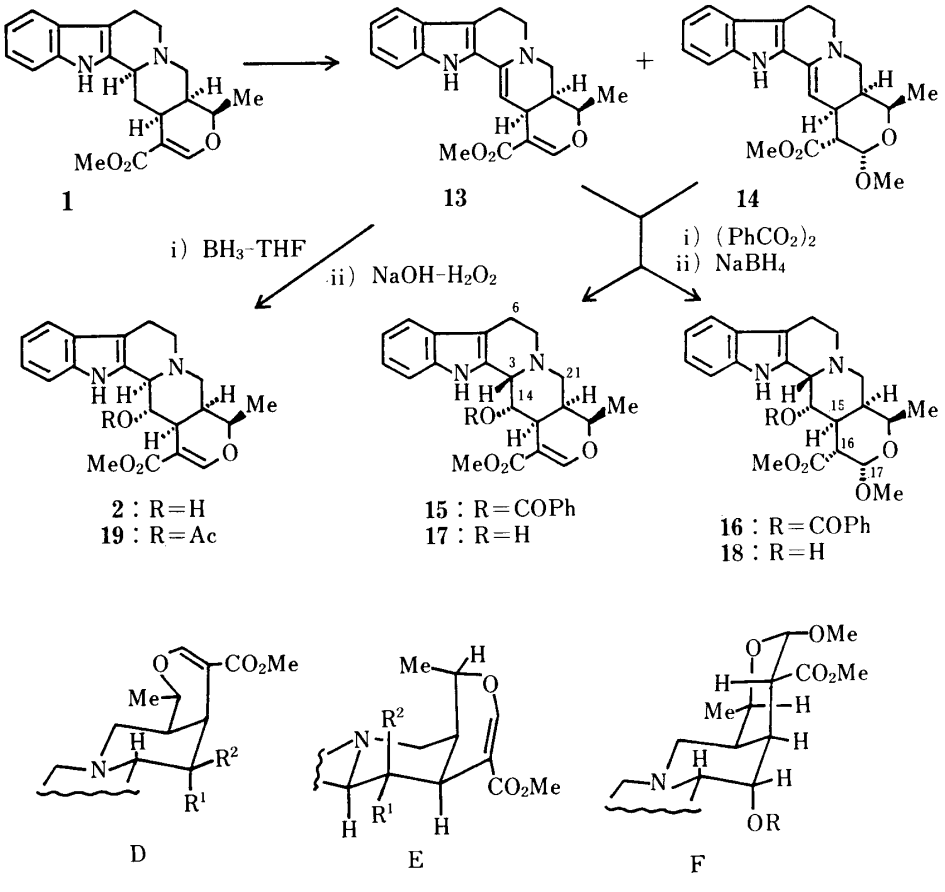


Chart 3

TABLE II. ^{13}C Chemical Shifts[a] of Heteroyohimbines

Carbon	3[b]	15[c]	16[d]	17	18[e]	1[f]	2	19[g]
2	134.5	131.0	128.1	131.6	131.4	134.3	134.4	129.9
3	55.0	58.8	58.9	59.0	59.1	58.0	65.2	57.8
5	53.4	54.1	54.4	52.8	53.4	52.8	53.0	51.9
6	21.7	21.5	21.4	21.5	21.5	21.1	21.8	17.6
7	105.9	110.3	110.5	110.6	110.9	107.1	107.8	108.0
8	127.1	127.2	127.2	127.1	127.2	127.0	126.5	127.3
9	117.9	117.7	117.8	117.9	117.9	117.7	117.7	118.1
10	119.2	119.1	119.2	119.3	119.3	119.1	118.8	119.4
11	121.3	121.4	121.4	121.7	121.5	121.0	121.1	121.7
12	110.8	111.3	111.3	111.1	111.2	110.6	111.0	110.7
13	136.1	136.4	136.4	136.5	136.7	135.8	135.8	135.9
14	31.2	67.3	64.8	66.1	64.9	32.5	74.0	69.4
15	31.6	37.1	35.3	38.6	36.3	29.5	37.7	35.3
16	108.1	103.5	42.7	104.5	42.7	107.7	105.1	103.7
17	157.3	158.1	98.0	157.8	98.0	154.3	156.8	157.2
18	17.3	17.4	17.6	17.5	17.6	19.1	19.4	17.7
19	75.6	75.7	68.2	75.6	67.3	76.4	76.4	75.7
20	37.1	33.5	34.6	32.8	33.3	34.2	35.0	33.9
21	49.8	49.4	49.4	49.8	50.0	53.7	55.3	42.2
C=O	167.9	166.4	170.4	167.7	171.4	168.0	171.9	170.2
OMe	51.1	51.4	52.2	51.3	52.1	51.0	52.1	51.0

a) The values are in ppm downfield from Me_4Si. The spectra were measured in $CDCl_3$. *b*) Values from ref. 17. *c*) Benzoyl δ: 167.4 (C=O), 129.9 (C-1), 129.9, 128.2 (C-2, C-3), 132.9 (C-4). *d*) Benzoyl δ: 166.3 (C=O), 130.5 (C-1), 129.9, 128.1 (C-2, C-3), 133.0 (C-4); Acetal δ: 55.0 (OMe). *e*) Acetal δ: 54.9. *f*) Values from ref. 13. *g*) Measured at 55 °C. Acetyl δ: 168.7 (C=O), 21.5.

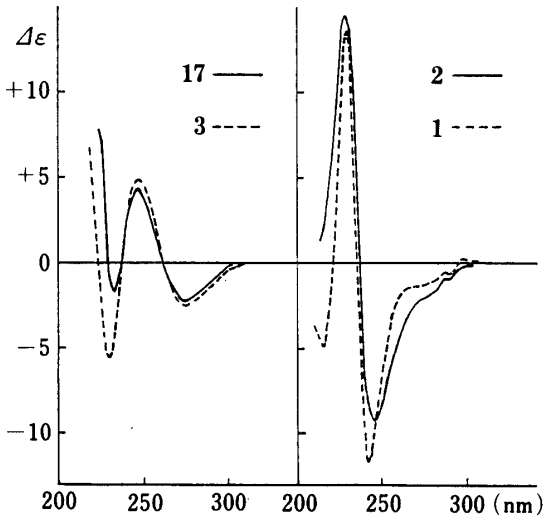
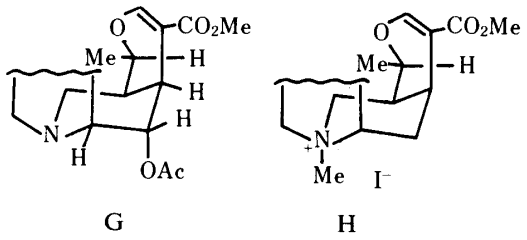


Fig. 1. CD Spectra (in MeOH)



G H

Chart 4

NaOH and 30% H_2O_2 at 45—50 °C gave the hydroxyl derivative (**2**, 6%) together with rauniticine (**1**, 48%) and 3-isorauniticine (**3**, 12%). The spectral data (IR, ^1H-NMR, CD) of the hydroxyl derivative (**2**) were identical with those of the natural alkaloid. The 270 MHz ^1H-NMR spectrum showed the presence of a triplet signal at δ 3.86, which was assigned to H-14; the corresponding signal in the 100 MHz ^1H-NMR spectrum had been observed as a doublet.[2] The coupling constants ($J_{3,14} = J_{14,15} = 9$ Hz) indicated a *trans*-diaxial arrangement of H-14 to both H-3 and H-15 and thus the equatorial orientation of 14-hydroxyl group was

revealed. The natural alkaloid (**2**) has the *trans*-quinolizidine ring structure[2] together with the above partial structure. Evidently only the stereostructure E (R^1=OH, R^2=H) meets the requirements, and the natural alkaloid was thus shown to be 14α-hydroxyrauniticine (**2**) instead of 14β-hydroxy-3-isorauniticine (**4**) as formerly proposed. This assignment was further supported by the facts that the alkaloid (**2**) and rauniticine (**1**) have similar chemical shift values of C-21 [**2** (δ 55.3) and **1** (δ 53.7)] and superimposable CD spectra.[18]

Furthermore, the conformational change observed on acetylation of the alkaloid (**2**) was of great interest. Acetylation with acetic anhydride (Ac_2O) in pyridine in the presence of 4-dimethylaminopyridine (DMAP) afforded 14α-acetoxyrauniticine (**19**, 90%). The absence of Bohlmann bands in the IR spectrum, and characteristic chemical shifts of H-3 (δ 4.37) and C-6 (δ 17.6) in ^{1}H- and ^{13}C-NMR spectra showed that the acetate (**19**) possessed the *cis*-quinolizidine conformation G. The ^{1}H-NMR signals of H-3 and H-14, which appeared at δ 4.37 and 6.59 as broad singlets, suggested a *trans*-diequatorial arrangement of these protons and therefore, the axial orientation of the acetoxy group. Further evidence for this assignment was provided by the upfield shift of C-21 (δ 42.2) due to 1,3-diaxial interaction of the C_3–C_2, C_5–C_6 and C_{15}–C_{16} bonds with C_{21}-H. The upfield shift of H-17 [**2** (δ 7.73)→**19** (δ 7.20)] was considered to be caused by the shielding effect due to the indole ring. In addition, the coupling pattern of H-19 ($J_{18,19}$=7 Hz, $J_{19,20}$=5 Hz) in 14α-hydroxyrauniticine (**2**), like that ($J_{18,19}$=7 Hz, $J_{19,20}$=6 Hz)[19] of rauniticine (**1**), was different from that ($J_{18,19}$=6.5 Hz, $J_{19,20}$=1 Hz) of the acetate (**19**) or that ($J_{18,19}$=6 Hz, $J_{19,20}$=1 Hz)[19] of 3-isorauniticine (**3**). This kind of structure has been proposed for rauniticine methoiodide H[20] and a small contribution of this conformation was considered even for rauniticine (**1**) on the basis of by ^{1}H- and ^{13}C-NMR analyses,[19,13] while similar conformation was found for the free base of the acetate (**19**).

Experimental

All melting points were measured on a Yamato MP-21 apparatus and are uncorrected. IR spectra were measured with a Hitachi 260 spectrometer, and ultraviolet (UV) spectra were measured in MeOH with a Hitachi 340 spectrometer. ^{1}H-NMR spectra were recorded on JEOL JNM4H-100 (100 MHz) and FX-270 (270 MHz) spectrometers with tetramethylsilane as an internal standard in $CDCl_3$ unless otherwise stated. ^{13}C-NMR spectra were measured with a JEOL FX-270 (67.8 MHz) spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Mass spectra (MS) were taken with Hitachi RMU 7M and 60 spectrometers. CD spectra were measured with a JASCO J-500A in MeOH. Thin layer chromatography was performed on Merck precoated Silica gel 60F-254 plates. Column chromatography utilized Merck Silica gel 60 (70—230 and 230—400 mesh) and Merck Al_2O_3, Brockmann (activity II—III). Organic solution were dried with anhydrous Na_2SO_4. Abbreviations used are: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), shoulder (sh).

***cis*-(H-1/H-12b)-1-Benzoyloxy-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (8)**——A solution of dibenzoyl peroxide (278 mg, 1.15 mmol) in dry dioxane (3 ml) was added dropwise over 5 min to a solution of the enamine (**6**, 224 mg, 1 mmol) and *p*-hydroquinone (22 mg, 0.2 mmol) in dry dioxane (3 ml) at 12—13 °C, and the mixture was stirred for 30 min at room temperature. After addition of MeOH (6 ml) and 1 N HCl (1.5 ml), $NaBH_4$ (76 mg, 2 mmol) was added in an ice bath, and the mixture was stirred for 1 h. Acetic acid (AcOH) was added to decompose the excess $NaBH_4$ and the mixture was concentrated. The residue was basified with 2 N Na_2CO_3 and extracted with CH_2Cl_2. The extract was washed with water, dried and concentrated. The residue was chromatographed on Al_2O_3 (10 g). Elution with CH_2Cl_2 followed by crystallization from MeOH gave the benzoate (**8**, 133 mg), and the mother liquor (100 mg) was subjected to SiO_2 (5 g) chromatography with CH_2Cl_2–$CHCl_3$–EtOAc. Eluates with EtOAc gave **8** (65 mg); total yield 198 mg (57%). mp 178—179 °C (MeOH). UV λ_{max} nm (log ε): 225 (4.71), 274 (sh, 3.98), 280 (3.98), 290 (3.87). IR (KBr): 2840, 2800, 2720 (Bohlmann bands), 1685. MS *m/z* (%): 346 (M^+, 13), 241 (57), 224 (100). ^{1}H-NMR (100 MHz) δ: 3.72 (1H, br s, H-12b), 5.80 (1H, br s, H-1), 7.0—7.5 (7H, m), 7.90 (2H, dd, J=8, 2 Hz), 8.28 (1H, br s, NH). *Anal.* Calcd for $C_{22}H_{22}N_2O_2$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.22; H, 6.42; N, 8.10.

***cis*-(H-1/H-12b)-1-Hydroxy-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (9)**——A 1 N NaOMe solution (1.7 ml, MeOH) was added to a solution of the benzoate (**8**, 200 mg) in dry MeOH (9 ml) and the mixture was refluxed for 1 h under argon. The mixture was concentrated after addition of AcOH (0.05 ml), and the residue was basified with 2 N Na_2CO_3 then extracted with $CHCl_3$. The extract was washed with water, dried and concentrated to give the residue, which was chromatographed on Al_2O_3 (4 g). Elution with CH_2Cl_2 gave methyl benzoate and the eluates with

CH_2Cl_2 and EtOAc gave **9** (122 mg, 87%). mp 204—206 °C (benzene). An analytical sample was recrystallized from MeOH. mp 209—211 °C. UV λ_{max} nm (log ε): 224 (4.57), 274 (sh, 3.86), 282 (3.87), 290 (3.79). IR (KBr): 2820—2720 (Bohlmann bands). MS *m/z* (%): 242 (M^+, 76), 241 (82), 197 (67), 170 (82), 169 (100). ^{1}H-NMR (100 MHz, 40 °C) δ: 3.48 (1H, br s, H-12b), 4.13 (1H, br s, H-1), 7.00—7.46 (4H, m), 8.04 (1H, br s, NH). *Anal.* Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.29; H, 7.48; N, 11.55.

***cis*-(H-1/H-12b)-1-Acetoxy-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (10)**——A mixture of **9** (50 mg), Ac_2O (0.3 ml) and pyridine (0.5 ml) was stirred at room temperature overnight. The mixture was concentrated and the residue was basified with aq. $NaHCO_3$, then extracted with $CHCl_3$. The extract was washed with water, dried and concentrated to give the residue, which was purified by Al_2O_3 (1 g) column chromatography with CH_2Cl_2 and EtOAc to give the acetate (**10**, 57 mg, 97%). mp 141—142 °C (benzene). UV λ_{max} nm (log ε): 225 (4.57), 274 (sh, 3.86), 281 (3.88), 290 (3.80). IR (KBr): 2850, 2810, 2750 (Bohlmann bands), 1705. MS *m/z* (%): 284 (M^+, 42), 283 (45), 241 (75), 224 (100). ^{1}H-NMR (100 MHz) δ: 1.91 (3H, s, CH_3CO), 3.56 (1H, br s, H-12b), 5.64 (1H, br s, H-1), 7.00—7.56 (4H, m), 8.08 (1H, br s, NH). *Anal.* Calcd for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.90; H, 7.09; N, 9.73.

***trans*-(H-1/H-12b)-1-Hydroxy-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (11)**——A BH_3–THF solution (1 M, 9 ml) was added to a solution of the enamine (**6**, 660 mg) in dry THF (8 ml) in an ice bath under argon, and the mixture was stirred at room temperature for 3 h. After addition of water (0.9 ml), 3 N NaOH (2.9 ml) and 30% H_2O_2 (2.9 ml) were added under ice cooling and the mixture was stirred for 5 h at 45—50 °C. Next 2 N Na_2CO_3 was added to the mixture and the whole was extracted with $CHCl_3$. The extract was shaken well with 5% $NaHSO_3$,[21] and then basified with 2 N Na_2CO_3 followed by further shaking. The organic layer was washed with brine, dried and concentrated. The residue was chromatographed on SiO_2 (27 g). Elution with $CHCl_3$/EtOAc (1 : 1)–EtOAc gave a mixture of **5** and **11**, which was subjected to Al_2O_3 (60 g) chromatography. Elution with CH_2Cl_2 gave **5** (363 mg, 55%, mp 148—151 °C) and then **11** (164 mg, 23%), successively. mp 201—203 °C ($CHCl_3$). IR (KBr): 2820, 2790, 2740 (Bohlmann bands). MS *m/z* (%): 242 (M^+, 100), 241 (82), 197 (49), 170 (69), 169 (75). ^{1}H-NMR (270 MHz) δ: 3.07 (H-12b), 3.73 (1H, td, *J* = 10, 4.5 Hz, H-1), 7.0—7.5 (4H, m), 9.09 (1H, br s, NH). *Anal.* Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.42; H, 7.46; N, 11.59.

***trans*-(H-1/H-12b)-1-Acetoxy-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (12)**——A mixture of **11** (50 mg) and Ac_2O (0.24 ml) in pyridine (0.6 ml) was allowed to stand overnight, and then concentrated. The residue was basified with 2 N Na_2CO_3, and extracted with $CHCl_3$. The extract was dried and concentrated. The residue was purified by Al_2O_3 (1.5 g) short column chromatography with CH_2Cl_2 to give the acetate (**12**, 56 mg, 95%). mp 130—131 °C (EtOH). IR (KBr): 2850, 2800, 2750 (Bohlmann bands), 1720. MS *m/z* (%): 284 (M^+, 13), 283 (30), 241 (58), 224 (100), 223 (46). ^{1}H-NMR (100 MHz) δ: 2.22 (3H, s, CH_3CO), 3.47 (1H, d, *J* = 10 Hz, H-12b), 4.78 (1H, td, *J* = 10, 4 Hz, H-1), 7.0—7.5 (4H, m), 8.04 (1H, br s, NH). *Anal.* Calcd for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.67; H, 7.06; N, 9.79.

14α-Benzoyloxy-3-isorauniticine (15) and (16*R*,17*S*)-14α-Benzoyloxy-3-isorauniticine Methyl Acetal (16)——A solution of *tert*-BuOCl (42 mg) in dry CCl_4 (2 ml) was added dropwise over 10 min to a solution of rauniticine (**1**, 100 mg) and Et_3N (0.04 ml) in dry CH_2Cl_2 (5 ml) in an ice bath. The mixture was stirred for 30 min, then washed with water, dried and concentrated. The residue was dissolved in dry MeOH (2 ml), dry MeOH (1 ml) containing HCl gas was added, and then the mixture was allowed to stand for 1 h. The mixture was concentrated to give the 3-dehydronium chloride, which was dissolved in MeOH (1 ml) and water (0.5 ml). Then 20% KOH (0.5 ml) was added to give a mixture of **13** and **14** (1 : 1) as a precipitate. UV $\lambda_{max}^{EtOH+OH^-}$ nm: 228, 296 (sh), 307, 319. $\lambda_{max}^{EtOH+H^+}$ nm: 243, 355. MS *m/z* (%): 382 (M^+ of **14**, 41), 350 (M^+ of **13**, 39). ^{1}H-NMR (100 MHz) δ: 1.25 (1.5H, d, *J* = 7 Hz), 1.43 (1.5H, d, *J* = 7 Hz), 3.33 (1.5H, s, OMe), 3.75 (3H, s, OMe), 4.17 (1H, m, H-19), 4.93 (0.5H, d, *J* = 4 Hz, H-17), 5.22 (0.5H, d, *J* = 6 Hz, H-14), 5.50 (0.5H, d, *J* = 6 Hz, H-14), 6.95—7.55 (4.5H, m), 8.30 (1H, br s, NH).

A solution of dibenzoyl peroxide (73 mg, 1.5 eq) in dry dioxane (1 ml) was added dropwise over 5 min at room temperature to a solution of a mixture of the enamines (**13** and **14**, 70 mg) and *p*-hydroquinone (4 mg) in dry dioxane (1 ml), and the mixture was stirred for 30 min. MeOH (2 ml), 1 N HCl (0.2 ml) and $NaBH_4$ (15 mg) were added successively to the mixture in an ice bath, and the whole was stirred for 30 min. The reaction mixture was concentrated below 40 °C and the residue was basified with 2 N Na_2CO_3, and then extracted with $CHCl_3$. The extract was dried and concentrated to give the residue, which was chromatographed on Al_2O_3 (2 g). Elution with CH_2Cl_2 gave a mixture of **15** and **16** (55 mg), which was separated by flash column chromatography[21] with hexane–EtOAc (7 : 3). The less polar benzoate (**15**, 15 mg, 16%). IR ($CHCl_3$): 2850, 2820, 2780 (Bohlmann bands), 1710, 1625. MS *m/z* (%): 472 (M^+, 7), 350 (100). ^{1}H-NMR (270 MHz) δ: 1.43 (3H, d, *J* = 6.5 Hz, H-18), 2.46 (1H, t, *J* = 11 Hz, H-21β), 3.55 (1H, br s, H-3), 3.80 (3H, s, OMe), 4.16 (1H, qd, *J* = 6.5, 2 Hz, H-19), 6.93 (1H, br s, H-14), 7.0—7.5 (7H, m), 7.68 (1H, d, *J* = 1.5 Hz, H-17), 7.90 (2H, d, *J* = 7.3 Hz), 8.36 (1H, br s, NH). High-resolution (HR)-MS Calcd for $C_{28}H_{28}N_2O_5$: 472.1997. Found: 472.2014 (M^+). The more polar benzoate (**16**, 16 mg, 16%). IR ($CHCl_3$): 2820, 2780 (Bohlmann bands), 1740, 1710. MS *m/z* (%): 504 (M^+, 6), 382 (63), 251 (96), 223 (100). ^{1}H-NMR (270 MHz) δ: 1.27 (3H, d, *J* = 6.8 Hz, H-18), 2.85 (1H, ddd, *J* = 13, 4, 2 Hz, H-15), 3.11 (1H, dd, *J* = 13, 4.3 Hz, H-16), 3.32 (3H, s, 17-OMe), 3.76 (1H, br s, H-3), 3.83 (3H, s, OMe), 4.15 (1H, qd, *J* = 6.8, 2.5 Hz, H-19), 5.01 (1H, d, *J* = 4.3 Hz, H-17), 5.98 (1H, br s, H-14), 7.0—7.5 (7H, m), 7.91 (2H, d, *J* = 7.3 Hz), 8.31 (1H, br s, NH). HR-MS Calcd for $C_{29}H_{32}N_2O_6$: 504.2258. Found: 504.2236 (M^+).

Debenzoylation of 15 and 16——A mixture of **15** (12 mg) or **16** (12 mg) in dry MeOH (1 ml) in the presence of 1 N NaOMe solution (0.1 ml) was stirred for 3 h at room temperature under argon. A few drops of AcOH were added and the mixture was concentrated, then basified with 2 N Na_2CO_3 and extracted with $CHCl_3$. The extract was washed with water, dried and concentrated. The residue was chromatographed on SiO_2 (0.5 g) with CH_2Cl_2–$CHCl_3$–EtOAc. Elution with EtOAc gave the hydroxyl compound.

14α-Hydroxy-3-isorauniticine (**17**, 9 mg, 96%). IR ($CHCl_3$): 2830, 2780 (Bohlmann bands), 1695, 1620. MS *m/z* (%): 368 (M^+, 52), 350 (100). ^{1}H-NMR (270 MHz) δ: 1.37 (3H, d, *J*=7 Hz, H-18), 3.37 (1H, br s, H-3), 3.76 (3H, s, OMe), 4.11 (1H, qd, *J*=7, 2 Hz, H-19), 5.13 (1H, d, *J*=2.5 Hz, H-14), 7.0—7.5 (4H, m), 7.65 (1H, d, *J*=2 Hz, H-17), 8.17 (1H, br s, NH). HR-MS Calcd for $C_{21}H_{24}N_2O_4$: 368.1734. Found: 368.1729.

(16*R*,17*S*)-14α-Hydroxy-3-isorauniticine methyl acetal (**18**, 10 mg, 100%). IR ($CHCl_3$): 2830, 2780 (Bohlmann bands), 1725. MS *m/z* (%): 400 (M^+, 100), 399 (56), 171 (85). ^{1}H-NMR (270 MHz) δ: 1.18 (3H, d, *J*=6.6 Hz, H-18), 2.59 (1H, t, *J*=12 Hz, 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*=6.6, 2.6 Hz, H-19), 4.26 (1H, br s, H-14), 5.00 (1H, d, *J*=4.3 Hz, H-17), 7.0—7.5 (4H, m), 8.48 (1H, br s, NH). HR-MS Calcd for $C_{22}H_{28}N_2O_5$: 400.2007. Found: 400.2013.

Hydroboration–Oxidation of 13——A solution of *tert*-BuOCl (66 mg, 1.4 eq) in dry CCl_4 (2 ml) was added dropwise over 5 min to a solution of rauniticine (**1**, 150 mg) and Et_3N (0.06 ml) in dry CH_2Cl_2 (6 ml) in an ice bath and the mixture was stirred for 30 min. The mixture was washed with water, dried and concentrated to give the residue which was dissolved in dry DME (2 ml). To this solution, dry DME (1 ml) containing HCl gas was added and the mixture was stirred for 1 h. The mixture was concentrated to give the residue which was dissolved in MeOH (1 ml) and water (0.5 ml). Then 20% KOH (1 ml) was added to the solution followed by water (3 ml) to give 3,14-dehydrorauniticine (**13**, 130 mg, 87%) as a precipitate. MS *m/z* (%): 350 (M^+, 100). ^{1}H-NMR (270 MHz) δ: 1.45 (3H, d, *J*=7 Hz, H-18), 3.75 (3H, s, OMe), 4.16 (1H, qd, *J*=7, 1.6 Hz, H-19), 5.48 (1H, d, *J*=5.6 Hz, H-14), 7.0—7.5 (5H, m), 8.13 (1H, br s, NH).

A 1 M BH_3–THF solution (1 ml) was added dropwise over 3 min to a solution of **13** (120 mg) in dry THF (1 ml) in an ice bath and the mixture was stirred for 2 h at room temperature. Under ice cooling, water (0.05 ml) was added, then 3 N NaOH (0.35 ml) and 30% H_2O_2 (0.35 ml) were added and the mixture was stirred at 45—50 °C overnight. The mixture was basified with 2 N Na_2CO_3 and extracted with $CHCl_3$. The extract was shaken well with 5% $NaHSO_3$,[21] and then basified with 2 N Na_2CO_3 followed by further shaking. The organic layer was washed with brine, dried and concentrated. The residue was subjected to flash chromatography with hexane–EtOAc. Elution with hexane–EtOAc (7:3) gave 14α-hydroxyrauniticine (**2**, 7 mg, 6%). IR ($CHCl_3$): 2850, 2810, 2750 (Bohlmann bands), 1665, 1620. MS *m/z* (%): 368 (M^+, 100), 350 (64). ^{1}H-NMR (270 MHz) δ: 1.42 (3H, d, *J*=7 Hz, H-18), 3.21 (1H, d, *J*=9 Hz, H-3), 3.79 (3H, s, OMe), 3.86 (1H, t, *J*=9 Hz, H-14), 4.47 (1H, qd, *J*=7, 5 Hz, H-19), 6.01 (1H, br s, OH), 7.0—7.5 (4H, m), 7.73 (1H, s, H-17), 9.33 (1H, br s, NH). HR-MS Calcd for $C_{21}H_{24}N_2O_4$: 368.1733. Found: 368.1721.

Elution with hexane–EtOAc (1:1) and EtOAc followed by crystallization of the product from MeOH gave rauniticine (**1**, 46 mg, mp 221—223 °C). The mother liquor was subjected to flash chromatography[21] with MeOH–$CHCl_3$. Elution with 1% MeOH–$CHCl_3$ gave 3-isorauniticine (**3**, 15 mg, 12%) and elution with 4% MeOH–$CHCl_3$ gave rauniticine (**1**, 12 mg: total yield 48%).

14α-Acetoxyrauniticine (19)——A mixture of 14α-hydroxyrauniticine (**2**, 8 mg), dry pyridine (0.3 ml), Ac_2O (0.2 ml) and DMAP (3 mg) was stirred at room temperature under argon overnight. The mixture was concentrated under an N_2 stream. The residue was basified with 2 N Na_2CO_3 and extracted with $CHCl_3$. The extract was washed with brine, dried and concentrated. The residue was chromatographed on SiO_2 (1 g) and elution with 1% MeOH–$CHCl_3$ gave 14α-acetoxyrauniticine (**19**, 8 mg). Further purification of **19** was done by Al_2O_3 (0.3 g) chromatography and elution with CH_2Cl_2 gave **19** (8 mg, 90%). IR ($CHCl_3$): 1730, 1690, 1620. MS *m/z* (%): 410 (M^+, 5), 350 (100). ^{1}H-NMR (270 MHz) δ: 1.39 (3H, d, *J*=6.5 Hz, H-18), 2.20 (3H, s, MeCO), 3.61 (3H, s, OMe), 4.12 (1H, qd, *J*=6.5, 1 Hz, H-19), 4.37 (1H, br s, H-3), 6.59 (1H, br s, H-14), 7.0—7.5 [5H, m; 7.20 (br s, H-17)]. HR-MS Calcd for $C_{23}H_{26}N_2O_5$: 410.1839. Found: 410.1833.

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