A New Indole Alkaloid, 14z-Hydroxyrauniticine: Structure Revision and Partial Synthesis

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Oxidation of the enamine (6) with dibenzoyl peroxide followed by reduction with NaBH₄ gave the benzoate (8), which was converted to the cis-hydroxyl compound (9), while hydroboronation–oxidation of 6 gave the trans-isomer (11). Treatment of a mixture of the enamines (13 and 14) with dibenzoyl peroxide/NaBH₄ gave the benzoates (15 and 16), which were converted to 14z-hydroxy-3-isorauniticine (17) and the acetal (18), respectively. Hydroboronation–oxidation of 13 gave 14z-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—inole alkaloid; 14z-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). We reported preliminarily 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-az]quinolizine (5) and the synthesis of the natural 14-hydroxylated heteroyohimbine alkaloid (2). At that time, the 270 MHz proton nuclear magnetic resonance (¹H-NMR) spectrum and other spectra were re-examined and the structure was revised to 14z-hydroxyrauniticine (2). We describe here the methods of hydroxylation at C-14 of indole alkaloids and the structure revision of the
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 NaBH₄ to give cis-(H-1/H-10)-1-benzyloxyquinolizidine, which was hydrolyzed to cis-(H-1/H-10)-1-hydroxyquinolizidine (I), 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)].

Oxidation of the enamine (6) with dibenzoyl peroxide was reported to give 7 in the course of the synthesis of eburnamonine. 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-dehydromonom chloride by the reported method [i] tert-BuOCl, ii) HCl–MeOH, iii) aq. KOH–MeOH. The enamine (6) was oxidized with dibenzoyl peroxide in dioxane by successive addition of MeOH, 1 N HCl and NaBH₄ to give the cis-(H-1/H-12b)-1-benzyloxyindoloquinolizidine (8) in 57% yield. Compound 8 showed the following spectral data, which indicated the presence of the trans-quinolizidine skeleton (A: R² = H, R² = OCOPh); Bohlmann bands in the infrared (IR) spectrum, the ¹H-NMR signal due to H-12b at δ 3.72 in an upfield position and the carbon-13 nuclear magnetic resonance (¹³C-NMR) signal at δ 21.5 (assignable to C-7. The ¹H-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 benzoxyl group. This assignment was further confirmed by the observed upfield shift of the ¹³C-NMR signal of C-3 [5 (δ 25.7) → 8 (δ 21.0)] due to 1,3-diaxial interaction between the axial benzoxyl group and C-H bond.

Treatment of 8 with NaOMe in MeOH gave the cis-(H-1/H-12b)-1-hydroxyindoloquinolizidine (9) 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 ¹H- and ¹³C-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)]. Acetylation of 9 gave the acetate (10, 97%), which was also in trans-quinolizidine form (A: R¹ = H, R² = OAc).

![Chart 2](image-url)
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 mm BH$_3$-THF (3 molar eq) in dry tetrahydrofuran (THF) at room temperature (RT) followed by oxidation with 3 N NaOH and 30% H$_2$O$_2$ 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 $^1$H- 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 = 12.8 Hz = 6 Hz), J = 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 [α (5.43), β(7.9), γ (1.1)]. 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 dibenzoxy 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 $^1$H-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 $^1$H-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 benzoxyl 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$_9$-Me and 14$\beta$-benzoxyl group. The $^1$H- 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) of 3-isorauniticine (3) [D (R$^1$ = R$^2$ = H)] rather than that.
(δ 53.7) of rauniticine (1) [E (R¹ = R² = H)]. In addition, the observation of the ¹H-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 ¹H-NMR signals of H-3 (δ 3.76) and H-14 (δ 5.98) as broad singlets and the ¹³C-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 ¹³C-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, J₁₅,₁₆ = 13 Hz, J₁₅,₂₀ = 4 Hz, J₁₄,₁₅ = 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 16R, 17S-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, ¹H- and ¹³C-NMR) indicated that conformational change did not occur in the course of debenzylation. 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 BH₃·THF in dry THF at RT followed by oxidation with 3 N

![Chart 3](image-url)
TABLE II. $^{13}$C Chemical Shifts$^a$ of Heteroyohimbines

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$^a$ The values are in ppm downfield from Me$_3$Si. 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.

NaOH and 30% H$_2$O$_2$ at 45—50°C gave the hydroxyl derivative (2, 6%) together with rauniticine (1, 48%) and 3-isorauniticine (3, 12%). The spectral data (IR, $^1$H-NMR, CD) of the hydroxyl derivative (2) were identical with those of the natural alkaloid. The 270 MHz $^1$H-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 $^1$H-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 \textit{trans}-quinolizidine ring structure together with the above partial structure. Evidently only the stereostructure E (R: = OH, R': = H) meets the requirements, and the natural alkaloid was thus shown to be 14x-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.\(^{19}\)

Furthermore, the conformational change observed on acetylation of the alkaloid (2) was of great interest. Acetylation with acetic anhydride (Ac₂O) in pyridine in the presence of 4-dimethylaminopyridine (DMAP) afforded 14α-acetoxyrauniticine (19, 90%). The absence of Bohllmann bands in the IR spectrum, and characteristic chemical shifts of H-3 (δ 4.37) and C-6 (δ 17.6) in H- and 13C-NMR spectra showed that the acetate (19) possessed the cis-quinolizidine conformation G. The 1H-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 C₁₅–C₁₂, C₈–C₉ and C₁₅–C₁₆ bonds with C₃₁–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 (J₁₈,₁₉ = 7 Hz, J₁₉,₂₀ = 5 Hz) in 14α-hydroxyrauniticine (2), like that (J₁₈,₁₉ = 7 Hz, J₁₉,₂₀ = 6 Hz)\(^{19}\) of rauniticine (1), was different from that (J₁₈,₁₉ = 6.5 Hz, J₁₉,₂₀ = 1 Hz) of the acetate (19) or that (J₁₈,₁₉ = 6 Hz, J₁₉,₂₀ = 1 Hz)\(^{19}\) of 3-isorauniticine (3). This kind of structure has been proposed for rauniticine methiodide H\(^{20}\) and a small contribution of this conformation was considered even for rauniticine (1) on the basis of by H- and 13C-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. 1H-NMR spectra were recorded on JEOL JM4H-100 (100 MHz) and FX-270 (270 MHz) spectrometers with tetramethylsilane as an internal standard in CDCl₃ unless otherwise stated. 13C-NMR spectra were measured with a JEOL FX-270 (67.8 MHz) spectrometer in CDCl₃ 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 Al₂O₃, Brockmann (activity II → III). Organic solution were dried with anhydrous Na₂SO₄. Abbreviations used are: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), shoulder (sh).

\textit{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), NaBH₄ (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 NaBH₄ and the mixture was concentrated. The residue was basified with 2 N Na₂CO₃ and extracted with CH₂Cl₂. The extract was washed with water, dried and concentrated. The residue was chromatographed on Al₂O₃ (10 g). Elution with CH₃Cl followed by crystallization from MeOH gave the benzoate (8, 133 mg), and the mother liquor (100 mg) was subjected to SiO₂ (5 g) chromatography with CH₂Cl₂–CHCl₃–EtOAc. Eluates with EtOAc gave 8 (65 mg); total yield 198 mg (57%). mp 178 → 179 °C (MeOH). UV \( \lambda_{max} \) nm (log ε): 225 (4.71), 274 (3.98), 280 (3.98), 290 (3.87). IR (KBr): 2840, 2800, 2720 (Bohllmann bands), 1685. MS m/z (%): 346 (M⁺, 13), 241 (57), 224 (100). 1H-NMR (100 MHz): \( \delta \): 3.72 (1H, brs, H-12b), 3.80 (1H, brs, H-11), 4.70 → 5.2 (7H, m), 7.0 → 7.2 (7H, m), 7.90 (2H, dd, \( J = 8, 2 \) Hz), 8.28 (1H, brs, NH). Anal. Caled for C₂₄H₂₅N₂O₄: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.22; H, 6.42; N, 8.10.

\textit{cis-(H-1/H-12b)-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 Na₂CO₃, then extracted with CHCl₃. The extract was washed with water, dried and concentrated to give the residue, which was chromatographed on Al₂O₃ (4 g). Elution with CH₃Cl gave methyl benzoate and the eluates with
CH₂Cl₂ and EtOAc gave 9 (122 mg, 87%). mp 204–206 °C (benzene). An analytical sample was recrystallized from MeOH. mp 209–211 °C. UV \( \lambda_{max} \) nm (log ε): 224 (4.57), 274 (sh, 3.86), 282 (3.87), 290 (3.79). IR (KBr): 2820–2720 (Böhmann bands). MS \( m/z \) (%): 242 (M⁺, 76), 241 (82), 197 (67), 170 (82), 169 (100). \(^1\)H-NMR (100 MHz, 40°C) \( \delta \): 3.48 (1H, brs, H-12b), 4.13 (1H, brs, H-11), 7.00–7.46 (4H, m), 8.04 (1H, brs, NH). Anal. Calcd for C₁₅H₁₄N₂O₃: 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-2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (10) — A mixture of 9 (50 mg), Ac₂O (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. NaHCO₃, then extracted with CHCl₃. The extract was washed with water, dried, and concentrated to give the residue, which was purified by Al₂O₃ (1 g) column chromatography with CH₂Cl₂ and EtOAc to give the acetate (10, 57 mg, 97%). mp 141–142 °C (benzene). UV \( \lambda_{max} \) nm (log ε): 225 (4.57), 274 (sh, 3.86), 281 (3.88), 290 (3.80). IR (KBr): 2850, 2810, 2750 (Böhmann bands), 1705. MS \( m/z \) (%): 284 (M⁺, 42), 283 (45), 241 (75), 224 (100). \(^1\)H-NMR (100 MHz) \( \delta \): 1.91 (3H, s, CH₃CO), 3.56 (1H, brs, H-12b), 5.64 (1H, brs, H-1), 7.00–7.56 (4H, m), 8.08 (1H, brs, NH). Anal. Calcd for C₁₃H₁₂N₂O₃: 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-2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (11) — A BH₃·THF solution (1 ml, 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% H₂O₂ (2.9 ml) were added under ice cooling and the mixture was stirred for 5 h at 45–50 °C. Next 2 N Na₂CO₃ was added to the mixture and the whole was extracted with CHCl₃. The extract was shaken well with 5% NaHCO₃, then basified with 2 N Na₂CO₃ followed by further shaking. The organic layer was washed with brine, dried and concentrated. The residue was chromatographed on Silicagel (27 g). Elution with CHCl₃/EtOAc (1:1)–EtOAc gave a mixture of 5 and 11, which was subjected to Al₂O₃ (60 g) chromatography. Elution with CH₂Cl₂ gave 5 (363 mg, 55%), mp 148–151 °C and then 11 (164 mg, 23%), successively. mp 201–203 °C (CHCl₃), IR (KBr): 2820, 2790, 2740 (Böhmann bands). MS \( m/z \) (%): 242 (M⁺, 100), 241 (82), 197 (49), 170 (69), 169 (75). \(^1\)H-NMR (270 MHz) \( \delta \): 3.07 (H-12b), 3.73 (1H, td, J = 10, 4.5 Hz, H-1), 7.0–7.5 (4H, m), 9.09 (1H, brs, NH). Anal. Calcd for C₁₃H₁₁N₂O₂: C, 74.42; H, 7.46; N, 11.59.

trans-(H-1/H-12b)-1-Acetoxy-2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (12) — A mixture of 11 (50 mg) and Ac₂O (0.24 ml) in pyridine (0.6 ml) was allowed to stand overnight, and then concentrated. The residue was basified with 2 N Na₂CO₃, and extracted with CHCl₃. The extract was dried and concentrated. The residue was purified by Al₂O₃ (1.5 g) short column chromatography with CH₂Cl₂ to give the acetate (12, 56 mg, 95%). mp 130–131 °C (EtOH). IR (KBr): 2850, 2800, 2750 (Böhmann bands), 1720. MS \( m/z \) (%): 284 (M⁺, 13), 283 (30), 241 (58), 224 (100), 223 (46). \(^1\)H-NMR (100 MHz) \( \delta \): 2.22 (3H, s, CH₃CO), 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, brs, NH). Anal. Calcd for C₁₃H₁₂N₂O₃: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.67; H, 7.06; N, 9.79.

14z-Benzoyloxy-3-isoarunicine (15) and (16R,175S)-14z-Benzoyloxy-3-isoarunicine Methyl Acetate (16) — A solution of tert-ButOCl (42 mg) in dry CCl₄ (2 ml) was added dropwise over 10 min to a solution of raunikine (1, 100 mg) and Et₂N (0.04 ml) in dry CH₂Cl₂ (5 ml) in an ice bath. The mixture was stirred for 30 min, then washed with water, dried, and concentrated. The residue was basified with 2 N Na₂CO₃ and then extracted with CHCl₃. The extract was dried and concentrated to give the residue, which was chromatographed on Al₂O₃ (2 g). Elution with CH₂Cl₂ gave a mixture of 15 and 16 (55 mg), which was separated by flash column chromatography with hexane–EtOAc (7:3). The less polar benzoate (15, 15 mg, 16%). IR (CHCl₃): 2850, 2820, 2780 (Böhmann bands), 1710, 1625. MS \( m/z \) (%): 427 (M⁺, 7), 350 (100). \(^1\)H-NMR (270 MHz) \( \delta \): 1.43 (3H, d, J = 6.5 Hz, H-18), 2.46 (1H, t, J = 11 Hz, H-21b), 3.55 (1H, brs, H-3), 3.80 (3H, s, OMe), 4.16 (1H, qd, J = 6.5, 2 Hz, H-19), 6.93 (1H, brs, 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, brs, NH). High-resolution (HR)-MS Calcd for C₁₃H₉₂N₂O₄: 472.1997. Found: 472.2014 (M⁺). The more polar benzoate (16, 16 mg, 16%). IR (CHCl₃): 2820, 2780 (Böhmann bands), 1740, 1710. MS \( m/z \) (%): 504 (M⁺, 6), 382 (63), 251 (96), 223 (100). \(^1\)H-NMR (270 MHz) \( \delta \): 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, brs, 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, brs, H-14), 7.0–7.5 (7H, m), 7.91 (2H, d, J = 7.3 Hz), 8.31 (1H, brs, NH). HR-MS Calcd for C₁₃H₁₂N₂O₄: 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 Na₂CO₃ and extracted with CHCl₃. The extract was washed with water, dried and concentrated. The residue was chromatographed on SiO₂ (0.5 g) with CH₂Cl₂–CHCl₃–EtOAc. Elution with EtOAc gave the hydroxyl compound.

14α-Hydroxy-3-isoaconitic (17, 9 mg, 96%). IR (CHCl₃): 2830, 2780 (Bohmann bands), 1695, 1620. MS m/z (%): 368 (M⁺, 52), 350 (100). ¹H-NMR (270 MHz): δ: 1.37 (3H, d, J = 7 Hz, H-18), 3.37 (1H, brs, H-3), 3.76 (3H, s, OMe), 4.11 (1H, dq, 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, brs, NH). HR-MS Calcd for C₁₃H₁₈N₂O₅: 368.1734. Found: 368.1729.

(16R,17S)-14α-Hydroxy-3-isoaconitic methyl acetal (18, 10 mg, 100%). IR (CHCl₃): 2830, 2780 (Bohmann bands), 1725. MS m/z (%): 400 (M⁺, 100), 399 (56), 171 (85). ¹H-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, brs, H-3), 3.79 (3H, s, OMe), 4.04 (1H, dq, J = 6.6, 2.6 Hz, H-19), 4.26 (1H, brs, H-14), 5.00 (1H, d, J = 4.3 Hz, H-17), 7.0–7.5 (4H, m), 8.48 (1H, brs, NH). HR-MS Calcd for C₁₃H₂₀N₂O₇: 400.07. Found: 400.2013.

Hydroboration–Oxidation of 13—A solution of tert-ButOCl (66 mg, 1.4 eq) in dry CCl₄ (2 ml) was added dropwise over 5 min to a solution of rauninic acid (1, 150 mg) and Et₃N (0.06 ml) in dry CH₂Cl₂ (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-dehydro-rauninic acid (13, 130 mg, 87%) as a precipitate. MS m/z (%): 350 (M⁺, 100). ¹H-NMR (270 MHz): δ: 1.45 (3H, d, J = 7 Hz, H-18), 3.75 (3H, s, OMe), 4.16 (1H, dq, 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, brs, NH).

A 1 M BH₃·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 3N NaOH (0.35 ml) and 30% H₂O₂ (0.35 ml) were added and the mixture was stirred at 45–50°C overnight. The mixture was basified with 2 N Na₂CO₃ and extracted with CHCl₃. The extract was shaken well with 5% NaHSO₄,1 then and basified with 2 N Na₂CO₃ 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-hydroxyrauninic acid (2, 7 mg, 6%). IR (CHCl₃): 2850, 2810, 2750 (Bohmann bands), 1665, 1620. MS m/z (%): 368 (M⁺, 100), 350 (64). ¹H-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, dq, J = 7, 5.5 Hz, H-19), 6.01 (1H, brs, OH), 7.0–7.5 (4H, m), 7.73 (1H, s, H-17), 9.33 (1H, brs, NH). HR-MS Calcd for C₁₃H₂₁N₂O₅: 368.1733. Found: 368.1821.

Elution with hexane–EtOAc (1:1) and EtOAc followed by crystallization of the product from MeOH gave rauninic acid (1, 46 mg, mp 221–223°C). The mother liquor was subjected to flash chromatography with MeOH–CHCl₃. Elution with 1% MeOH–CHCl₃ gave 3-isoaconitic acid (3, 15 mg, 12%) and elution with 4% MeOH–CHCl₃ gave rauninic acid (1, 12 mg: total yield 48%).

14α-Acetoxyrauninic acid (19)—A mixture of 14α-hydroxyrauninic acid (2, 8 mg), dry pyridine (0.3 ml), Ac₂O (0.2 ml) and DMAP (3 mg) was stirred at room temperature under argon overnight. The mixture was concentrated under an N₂ stream. The residue was basified with 2 N Na₂CO₃ and extracted with CHCl₃. The extract was washed with brine, dried and concentrated. The residue was chromatographed on SiO₂ (1 g) and elution with 1% MeOH–CHCl₃ gave 14α-acetoxyrauninic acid (19, 8 mg). Further purification of 19 was done by Al₂O₃ (0.3 g) chromatography and elution with CH₂Cl₂ gave 19 (8 mg, 90%). IR (CHCl₃): 1730, 1690, 1620. MS m/z (%): 410 (M⁺, 5), 350 (100). ¹H-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, dq, J = 6.5, 1Hz, H-19), 4.37 (1H, brs, H-3), 6.59 (1H, brs, H-14), 7.0–7.5 (5H, m; 7.20 (brs, H-17)). HR-MS Calcd for C₁₉H₂₅N₃O₇: 410.1839. Found: 410.1833.

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References and Notes

1) A contribution from a cooperative project between Chulalongkorn University and Chiba University promoted by the Asian Research Committee of Chiba University.
15) Though preparation of the hydroxyl derivatives (9 and 11) from 1-indole-3-ylethyl)-3-oxidopyridinium was reported [W. R. Ashcroft and J. A. Joule, Heterocycles, 16, 1883 (1981)], no physical data were given.
18) Measurement of the CD spectrum was carried out again for the carefully purified natural alkaloid and we found that the data reported in the previous paper (ref. 2) should be corrected as follows; \( \Delta \text{e}_{290} = -1.1, \Delta \text{e}_{275} = -2.0 \text{ (sh.)} \), \( \Delta \text{e}_{264} = -9.3, \Delta \text{e}_{236} = 0, \Delta \text{e}_{228} = +14.6, \Delta \text{e}_{212} = 0 \).
21) For regeneration of free amines from possible reaction products, N-oxides.