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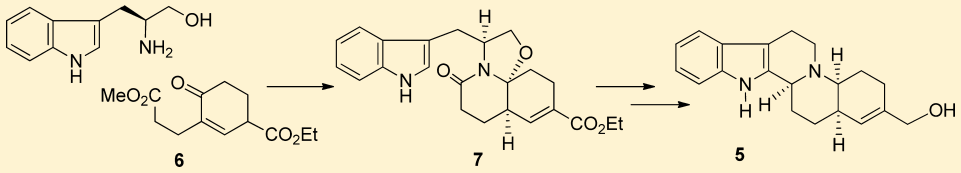
Stereoselective Total Synthesis of the Putative Structure of Nitraraine

Federica Arioli, Maria Pérez, Fabiana Subrizi, Núria Llor, Joan Bosch, and Mercedes Amat*

Laboratory of Organic Chemistry, Faculty of Pharmacy, and Institute of Biomedicine (IBUB), University of Barcelona, 08028-Barcelona, Spain

Supporting Information



ABSTRACT: After the structure originally proposed for nitraraine was shown to be incorrect by total synthesis, the alternative structure **5** was recently suggested for the alkaloid on biosynthetic grounds and by comparison with the ^{1}H NMR data of tangutorine. The unambiguous synthesis of **5** is reported from tryptophanol and ketodiester **6**, via oxazoloquinolone lactam **7**. However, the melting point and ^{1}H NMR data of **5** did not match those reported for the natural product.

Nitraraine[1] is an indole alkaloid isolated in 1985 from *Nitraria schoberi* L., collected in Kyzyl-Kum (Uzbekistan). On the basis of its mass-spectrometric fragmentation, spectroscopic UV, IR, and ^{1}H NMR data, chemical transformations and correlations, and degradation studies, the yohimbane-type structure **1** was assigned to nitraraine (Figure 1). Catalytic hydrogenation of nitraraine afforded dihydronitraraine (assigned as **2**), which had also been isolated from the same plant.[2] Some years later, two new alkaloids, *O*-acetylnitraraine[3] and nitraraidine,[4] were also isolated from *Nitraria* species, and their structures were assigned as **3** and **4**, respectively, mainly by chemical correlations with nitraraine and dihydronitraraine.

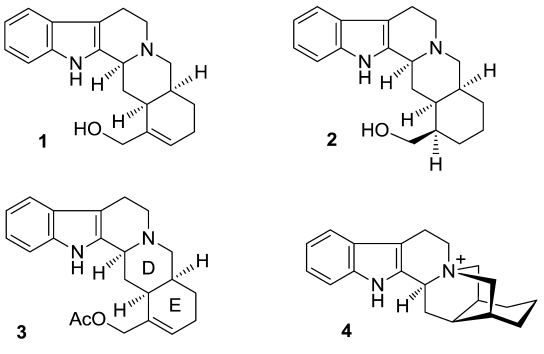


Figure 1. Structures proposed for nitraraine, dihydronitraraine, *O*-acetylnitraraine, and nitraraidine.

A pentacyclic alcohol with the structure **1** had previously been prepared[5] by $LiAlH_4$ reduction of apo-α-yohimbine. However, the data reported for this alcohol **1** (obtained as the hydrochloride) did not allow the proposed structure for nitraraine (isolated as the base) to be corroborated.

Later on, three different syntheses of pentacyclic alcohol **1**, either in enantiopure form[6,7] or as a racemate,[8] were reported. The melting point and ^{1}H NMR data of **1** were significantly different from those reported for nitraraine. Similarly, the melting point of synthetic **2** differed[6] from that of the alkaloid dihydronitraraine.[2] Consequently, a reasonable doubt arose about the correct structure of the alkaloids of the nitraraine family.

In 2011, Poupon et al. published[9] an excellent and comprehensive article that provides a detailed analysis of the data available for nitraraine and the above-mentioned nitraraine-related alkaloids, suggesting pentacyclic alcohol **5**, a structural isomer of **1**, as a possible structure for nitraraine. The proposal was based on biosynthetic considerations[10] and a comparison of the physical and spectroscopic data reported for these alkaloids with those of tangutorine[11] and its *O*-acetyl and dihydro derivatives (Figure 2).

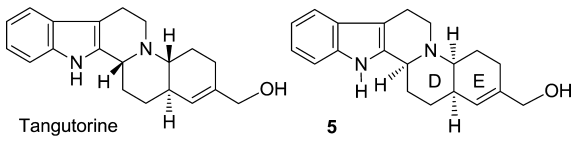


Figure 2. Structure of tangutorine and putative structure of nitraraine.

Both nitraraine and tangutorine are alkaloids isolated from *Nitraria* species (*Nitraria schoberi* and *Nitraria tangutorum*, respectively), which belong to the Nitrariaceae family, whereas yohimbine-type alkaloids have a monoterpenoid origin and are found in plants of the Rubiaceae, Loganiaceae, and Apocinaceae families. Moreover, the specific rotation reported for both

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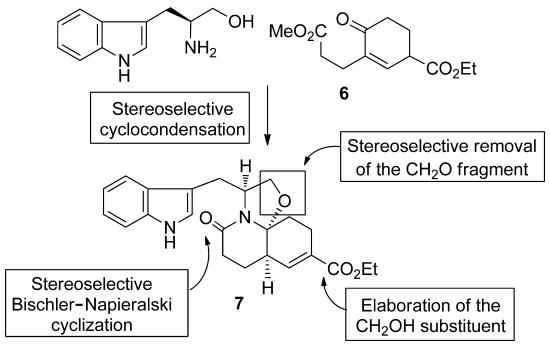
alkaloids is zero, which could be attributed to similar biosynthetic pathways that do not involve the monoterpene secologanin. On the other hand, nitraraine, tangutorine, and their *O*-acetyl derivatives each have an olefinic proton that resonates at a very similar chemical shift in their ^{1}H NMR spectra. Further, the melting point of these two alkaloids differs by only a few degrees Celsius. Another point of interest is that treatment of dihydronitraraine with *p*-TsCl provides the alkaloid nitraraidine, which is an *N*-quaternary hexacyclic salt, thus pointing to a *cis* D/E ring junction. Taking into account all the above, Poupon proposed the tangutorine diastereoisomer **5** as a plausible structure for nitraraine.

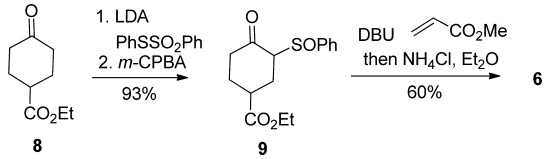
In this communication, we report the enantioselective total synthesis of **5**. In the context of our studies on the use of tryptophanol-derived lactams as enantiomeric scaffolds for the synthesis of indole alkaloids,[12] we visualized a synthetic route to this alcohol. Key steps to assemble the required pentacyclic skeleton would be a stereoselective cyclocondensation of (*S*)-tryptophanol with an appropriately substituted 6-oxocyclohexenepropionate derivative **6** and a Bischler−Napieralski cyclization of the resulting oxazoloquinolone lactam **7**[13] (Scheme 1). The synthesis would also require the subsequent removal of the hydroxymethyl substituent coming from tryptophanol and the reduction of the ester function.

Scheme 1. Synthetic Strategy



The required δ-keto ester **6** was prepared in 56% overall yield from ethyl 4-oxocyclohexanecarboxylate **8**, via keto sulfoxide **9**, as outlined in Scheme 2.

Scheme 2. Preparation of the Starting δ-Keto Ester 6



The cyclocondensation reaction of (*S*)-tryptophanol with δ-keto ester **6** stereoselectively gave tricyclic lactam **7** in 71% yield.[14] Starting from **7**, the closure of the central C ring was satisfactorily accomplished under classical Bischler−Napieralski reaction conditions. Without purification, treatment of the resulting hexacyclic derivative with $LiAlH_4$ brought about both the reductive opening of the oxazolidine ring to stereoselectively give the required *cis*-decahydroquinoline ring junction and the reduction of the ester function, leading to the pentacyclic diol derivative **10** in 60% overall yield (Scheme 3). In contrast, a similar sequence from **7′** led to the indoloquinolizidine derivative **11**, arising from an initial α-amidoalkylation reaction on the indole ring[15] (Scheme 4).

The next stage of the synthesis was the removal of the hydroxymethyl substituent coming from tryptophanol, which required the selective protection of the allylic hydroxy group, but unfortunately, the insolubility of diol **10** precluded its manipulation. For this reason, the indole nitrogen of **7** was protected as a *p*-methoxybenzyl derivative, and the resulting lactam **12** was converted to **13** in 68% overall yield following the above Bischler−Napieralski cyclization−$LiAlH_4$ reduction sequence.

Once the allylic hydroxyl group was selectively protected with the bulky *tert*-butyldiphenylsilyl group, the removal of the hydroxymethyl substituent of **14** was performed in four steps: oxidation to aldehyde **15** using tetrapropylammonium perruthenate in the presence of *N*-methylmorpholine *N*-oxide as the co-oxidant (TPAP/NMO),[16] subsequent dehydration of the corresponding oxime **16** with Burgess reagent, and reductive decyanation of the resulting α-amino nitrile.

Finally, deprotection of the indole nitrogen of pentacycle **17** using TFA in the presence of PhSH as a carbocation scavenger, followed by desilylation of the alcohol function, gave the target pentacyclic alcohol **5**.

Our synthetic product **5** showed mass-spectral peaks with the same *m*/*z* as natural nitraraine.[1] However, the melting point (241−242 °C) of **5** and the chemical shift of the olefinic proton in its ^{1}H NMR spectrum (δ 5.86 in CF_3CO_2D) were different from those described for the alkaloid (mp 280−281 °C; δ 5.22 in CF_3CO_2H[17]) (Figure 3).

The above data made evident that the real structure of nitraraine and related alkaloids remains an unsolved question and that further synthetic efforts are needed to reach a definitive conclusion.

EXPERIMENTAL SECTION

Ethyl 4-Oxo-3-(phenylsulfonyl)cyclohexanecarboxylate (9). *First step:* LDA (4.41 mL, 8.82 mmol of a 2 M solution in THF/heptane/ethylbenzene) was added at −78 °C to a solution of commercial ethyl 4-oxocyclohexanecarboxylate (**8**; 1.5 g, 8.82 mmol) in dry THF (90 mL), and the solution was stirred for 30 min. Then, $PhSSO_2Ph$ (2.21 g, 8.82 mmol) in THF (10 mL) was added, and the resulting mixture was stirred at −78 °C for 40 min. The reaction was quenched with saturated aqueous NH_4Cl (50 mL), and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried, filtered, and concentrated to afford ethyl 4-oxo-3-(phenylthio)cyclohexanecarboxylate, which was used in the next step without purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 3H), 1.93−2.02 (m, 1H), 2.25−2.29 (m, 1H), 2.31−2.38 (m, 1H), 2.39−2.43 (m, 2H), 2.98−3.03 (m, 1H), 3.04−3.11 (m, 1H), 3.89 (td, *J* = 4.4, 0.8 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 7.29 (d, *J* = 7.2 Hz, 2H), 7.40 (dd, *J* = 8.8, 2.0 Hz, 2H), 7.56 (d, *J* = 6.8 Hz, 1H). *Second step*: A solution of *m*-CPBA (70%, 2.17 g, 8.82 mmol) in CH_2Cl_2 (20 mL) was added at −78 °C to a solution of the above phenylthio derivative (2.46 g, 8.82 mmol) in CH_2Cl_2 (180 mL). After 5 min, the reaction was quenched with the addition of saturated aqueous $Na_2S_2O_3$. The resulting mixture was extracted with CH_2Cl_2, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried, filtered, and concentrated. Flash chromatography of the residue (4:1 hexane−EtOAc) afforded the sulfonyl derivative **9** (2.38 g, 93% yield for the two steps) as a complex mixture of diastereoisomers. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{15}H_{19}O_4S$ 295.0999; Found 295.0999.

Methyl 3-(Ethoxycarbonyl)-6-oxocyclohexenepropionate (6). A solution of DBU (374 mg, 2.45 mmol) in DMF (5 mL) was added at −40 °C, under an inert atmosphere, to a solution of the above sulfonyl derivatives **9** (720 mg, 2.45 mmol) in DMF (15 mL),

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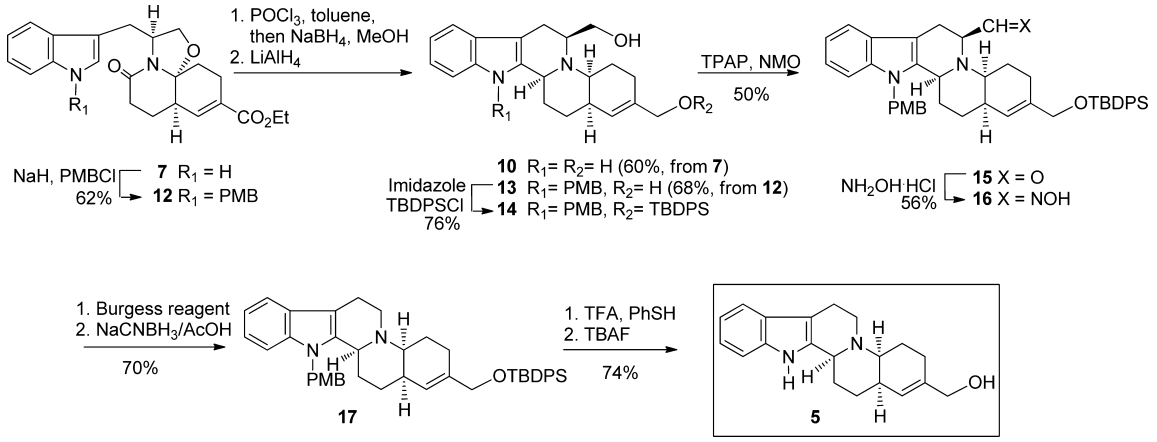
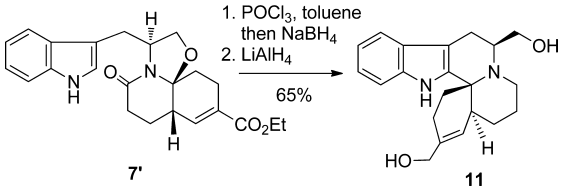
Scheme 3. Synthesis of 5, the Putative Structure of Nitraraine



Scheme 4. Cyclization of Lactam 7′



Nitraraine (natural product, ref 1)	Compound **5**
mp: 280-281 °C	mp: 241-242 °C
^{1}H NMR (100 MHz)	^{1}H NMR (400 MHz)
In CF_3COOH	In CF_3COOD
=CH: multiplet, δ 5.22	=CH: broad singlet, δ 5.86

Figure 3. Melting point and ^{1}H NMR data of nitraraine and compound **5**.

and the resulting mixture was stirred for 20 min. A solution of methyl acrylate (211 mg, 2.45 mmol) in DMF (5 mL) was then added to the mixture, and the reaction was allowed to reach 10 °C over 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL), and the resulting mixture was extracted with Et_2O. The organic layer was dried and filtered, and the filtrate was stirred at room temperature for 20 h. After this time, the solvent was evaporated under reduced pressure. Flash chromatography of the residue (hexane to 9.5:0.5 hexane−EtOAc) afforded oxoester **6** (375 mg, 60%): IR (film) ν (cm^{-1}) 1678 (CO), 1736 (CO); ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.30 (t, J = 7.1 Hz, 3H, CH_3), 2.12−2.23 (m, 1H, H-4′), 2.30−2.41 (m, 2H, H-2, H-4′), 2.44−2.49 (m, 2H, H-3), 2.53−2.61 (m, 3H, H-2, H-5′), 3.36−3.42 (m, 1H, H-3′), 3.66 (s, 3H, OCH_3), 4.21 (q, J = 7.1 Hz, 2H, CH_2CH_3), 6.85 (d, J = 4.4 Hz, 1H, H-2′); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1 (CH_3), 25.4 (C-3), 25.7 (C-4′), 32.8 (C-5′), 36.6 (C-2), 42.0 (C-3′), 51.5 (OCH_3), 61.3 (CH_2CH_3), 132.6 (C-1′), 142.3 (C-2′), 171.8 (COO), 173.3 (COO), 197.8 (CO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{19}O_5$ 255.1227; Found 255.1228.

Ethyl (3*S*,7a*R*,11a*R*)-3-(3-Indolylmethyl)-5-oxo-2,3,5,6,7,7a,10,11-octahydrooxazolo[2,3-*j*]quinoline-9-carboxylate (7). Isobutyric acid (105 μL, 1.13 mmol) was added to a solution of tryptophanol (97 mg, 0.51 mmol) and oxoester **6** (100 mg, 0.39 mmol) in toluene (8 mL). The mixture was stirred at reflux for 24 h, with azeotropic elimination of water by a Dean−Stark system. The resulting mixture was cooled and concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$. The combined organic extracts were dried, filtered, and concentrated to give a foam. Crystallization from EtOAc gave lactam 7 (109 mg, 71%). Evaporation of the solvent afforded the (3*S*,7a*S*,11a*S*) diastereoisomer (7′; 19 mg, 17%). **Lactam 7**: $[\alpha]_D^{22}$ + 20.2 (*c* 1.0, $CHCl_3$); IR (film) ν (cm^{-1}) 1629 (NCO), 1714 (COO), 3303 (NH); ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.28 (t, J = 7.5 Hz, 3H, CH_3), 1.56−1.68 (m, 2H, H-7, H-11), 1.95 (dm, J = 14.0 Hz, 1H, H-7), 2.05−2.10 (m, 1H, H-11), 2.25−2.30 (m, 1H, H-7a), 2.33−2.39 (m, 1H, H-10), 2.43−2.52 (m, 2H, H-6, H-10), 2.63 (dd, J = 18.4, 6.4 Hz, 1H, H-6), 2.89 (dd, J = 14.0, 10.4 Hz, 1H, CH_2-ind), 3.62 (ddd, J = 14.0, 3.4, 0.8 Hz, 1H, CH_2-ind), 3.81 (dd, J = 8.8, 8.0 Hz, 1H, H-2), 4.01 (dd, J = 8.8, 8.0 Hz, 1H, H-2), 4.19 (q, J = 7.5 Hz, 2H, CH_2CH_3), 4.67 (dtd, J = 10.4, 8.0, 8.0, 3.4 Hz, 1H, H-3), 6.84 (dd, J = 5.0, 2.0 Hz, 1H, H-8), 7.01 (d, J = 2.4 Hz, 1H, ArH), 7.12 (td, J = 8.0, 1.2 Hz, 1H, ArH), 7.20 (td, J = 8.0, 1.2 Hz, 1H, ArH), 7.34 (d, J = 8.0 Hz, 1H, ArH), 7.89 (d, J = 8.0 Hz, 1H, ArH), 8.40 (s, 1H, NH ind); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2 (CH_3), 22.6 (C-10), 25.5 (C-7), 26.3 (C-11), 30.2 (CH_2-ind), 31.0 (C-6), 40.6 (C-7a), 56.2 (C-3), 60.6 (CH_2CH_3), 68.2 (C-2), 92.6 (C-11a), 111.1 (CHAr), 111.6 (CAr), 119.2 (CHAr), 119.5 (CHAr), 122.0 (CHAr), 122.1 (CHAr), 127.5 (CAr), 129.6 (C-9), 136.2 (CAr), 137.7 (C-8), 166.5 (CO_2), 169.4 (CO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{27}N_2O_4$ 395.1965; Found 395.1978. Anal. Calcd for $C_{23}H_{26}N_2O_4 \cdot {}^1/_2\ H_2O$: C 68.47; H 6.74, N 6.94. Found: C 68.42; H 6.60; N 6.59. **Lactam 7′**: $[\alpha]_D^{22}$ − 40.8 (*c* 0.8, $CHCl_3$); IR (film) ν (cm^{-1}) 1628 (NCO), 1706 (COO), 3297 (NH); ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.28 (t, J = 7.2 Hz, 3H, CH_3), 1.53−1.63 (m, 2H, H-7, H-11), 2.02 (dd, J = 14.0, 6.0 Hz, 1H, H-7), 2.11−2.20 (m, 1H, H-11), 2.31−2.39 (m, 2H, H-7a, H-10), 2.48−2.51 (m, 3H, H-6, H-10), 2.76 (dd, J = 14.0, 9.6 Hz, 1H, CH_2-ind), 3.79 (dd, J = 14.0, 2.0 Hz, 1H, CH_2-ind), 3.97 (m, 2H, H-2), 4.18 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.42 (m, 1H, H-3), 6.90 (dd, J = 5.0, 2.4 Hz, 1H, H-8), 7.04 (d, J = 2.4 Hz, 1H, ArH), 7.13 (td, J = 7.5, 1.2 Hz, 1H, ArH), 7.20 (td, J = 7.5, 1.2 Hz, 1H, ArH), 7.36 (d, J = 7.5 Hz, 1H, ArH), 7.80 (d, J = 7.5 Hz, 1H, ArH), 8.07 (s, 1H, NH ind); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2 (CH_3), 22.8 (C-10), 25.7 (C-7), 26.3 (C-11), 26.6 (CH_2-ind), 30.1 (C-6), 39.8 (C-7a), 56.5 (C-3), 60.6 (CH_2CH_3), 67.4 (C-2), 92.7 (C-11a), 111.0 (CHAr), 112.4 (CAr), 119.3 (CHAr), 119.6 (CHAr), 122.2 (CHAr), 122.3 (CHAr), 127.7 (CAr), 129.2 (C-9), 136.1 (CAr), 138.8 (C-8), 166.6 (CO_2), 168.1 (CO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{27}N_2O_4$ 395.1965; Found 395.1971.

(2a*R*,6a*S*,8*S*,14b*S*)-4,8-Bis(hydroxymethyl)-2,2a,5,6,6a,8,9,14b-octahydro-1*H*-benz[*f*]indolo[2,3-*a*]quinolizine (10). $POCl_3$ (1.12 mL, 12.16 mmol) was added to a solution of lactam 7 (600 mg, 1.52 mmol) in toluene (20 mL), and the solution was stirred at 100 °C for 1.5 h. The solvent was evaporated, and dry methanol (30 mL) was added to the residue. $NaBH_4$ (173 mg, 4.57 mmol) was slowly added at 0 °C to the solution, and the mixture was stirred, allowing it to reach room temperature (about 1.5 h). The reaction was quenched by addition of saturated aqueous $NaHCO_3$. The methanol was evaporated, and the aqueous solution was extracted

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with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated. $LiAlH_4$ (866 mg, 23 mmol) was added to a solution of the resulting residue in anhydrous THF (25 mL), and the mixture was stirred at reflux for 3 h. The reaction was quenched at 0 °C with water (866 μL), and 10% aqueous NaOH (866 μL) and then water (2.5 mL) were added. The resulting suspension was dried with $MgSO_4$, filtered, and concentrated. Flash chromatography of the resulting oil (9:1 CH_2Cl_2−MeOH) afforded pentacyclic compound **10** as a light yellow foam (308 mg, 60%): IR (film) ν (cm^{-1}) 3402 (OH, NH); ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.14 (qd, J = 12.8, 4.8 Hz, 1H, H-6), 1.40 (qd, J = 13.2, 4.8 Hz, 1H, H-2), 1.67 (m, 2H, H-2, H-6), 1.78 (dd, J = 17.2, 4.0 Hz, 1H, H-5), 1.91 (m, 1H, H-5), 2.12 (m, 1H, H-1), 2.35 (m, 2H, H-1, H-2a), 2.80 (dd, J = 8.8, 1.6 Hz, 2H, H-9), 3.27 (dq, J = 12.8, 2.4 Hz, 1H, H-6a), 3.51 (m, 1H, H-8), 3.82 (s, 2H, CH_2OH), 3.86 (dd, J = 11.6, 6.4 Hz, 1H, CH_2OH), 4.04 (dd, J = 11.6, 7.6 Hz, 1H, CH_2OH), 4.27 (brs, 1H, H-14b), 5.55 (d, J = 4.0 Hz, 1H, H-3), 6.99 (td, J = 7.6, 0.8 Hz, 1H, ArH), 7.06 (td, J = 8.0, 1.2 Hz, 1H, ArH), 7.33 (d, J = 8.0 Hz, 1H, ArH), 7.37 (d, J = 7.6 Hz, 1H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.2 (C-6), 25.1 (C-2), 26.5 (C-9), 27.1 (C-1), 27.3 (C-5), 37.6 (C-2a), 53.8 (C-14b), 55.9 (C-6a), 62.9 (C-8), 64.3 (CH_2OH), 66.7 (CH_2OH), 108.5 (CAr), 112.0 (CHAr), 118.3 (CHAr), 119.7 (CHAr), 121.7 (CHAr), 127.1 (C-3), 128.9 (CAr), 137.5 and 137.8 (2CAr, C-4); HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{21}H_{27}N_2O_2$ 339.2067; Found 339.2064.

(9*S*,4a*S*,15b*R*)-3,9-Bis(hydroxymethyl)-1,2,4a,5,6,7,9,10-octahydrobenz[*i*]indolo[2,3-*a*]quinolizine (11). Operating as in the above cyclization of lactam **7**, from the minor isomer **7′** (180 mg, 0.35 mmol) in toluene (5.0 mL) and $POCl_3$ (257 μL, 2.79 mmol), then $NaBH_4$ (40 mg, 1.05 mmol) in anhydrous methanol (7.0 mL), and finally $LiAlH_4$ (200 mg, 5.25 mmol) in THF (6 mL), compound **11** (77 mg, 65%) was obtained after column chromatography (9:1 CH_2Cl_2−MeOH): IR (film) ν (cm^{-1}) 3405 (OH, NH); ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.40 (dm, J = 12.4 Hz, 1H, H-6), 1.51 (dt, J = 14.4, 4.4 Hz, 1H, H-5), 1.58 (dm, J = 12.4 Hz, 1H, H-5), 1.60 (m, 1H, H-6), 1.79 (m, 1H, H-1), 2.01 (dm, J = 16.0 Hz, 1H, H-2), 2.25 (dm, J = 16.0 Hz, 1H, H-2), 2.30 (ddd, J = 13.2, 4.4, 2.8 Hz, 1H, H-1), 2.38 (td, J = 12.0, 2.4 Hz, 1H, H-7), 2.51 (dd, J = 15.6, 4.0 Hz, 1H, H-10), 2.63 (dd, J = 15.6, 10.4 Hz, 1H, H-10), 2.73 (m, 1H, H-7), 2.84 (brs, 1H, H-4a), 3.64 (d, J = 5.2 Hz, 1H, CH_2OH), 3.75−3.79 (m, 2H, H-9, CH_2OH), 4.12 (s, 2H, CH_2OH), 7.10 (td, J = 7.2, 0.8 Hz, 1H, ArH), 7.16 (td, J = 7.2, 0.8 Hz, 1H, ArH), 7.33 (d, J = 7.6 Hz, 1H, ArH), 7.46 (d, J = 7.6 Hz, 1H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.3 (C-10), 21.1 (C-6), 22.6 (C-2), 27.4 (C-5), 34.6 (C-1), 38.7 (C-4a, C-7), 54.0 (C-9), 56.5 (C-15b), 61.2 (CH_2OH), 66.5 (CH_2OH), 107.1 (CAr), 110.9 (CHAr), 118.0 (CHAr), 119.5 (CHAr), 121.5 (CHAr), 125.0 (C-4), 127.4 (CAr), 135.4 (CAr), 137.9 (CAr), 138.5 (C-3); HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{21}H_{27}N_2O_2$ 339.2067; Found 339.2066.

Ethyl (3*S*,7a*R*,11a*R*)-3-[1-(4-Methoxybenzyl)-3-indolylmethyl]-5-oxo-2,3,5,6,7,7a,10,11-octahydrooxazolo[2,3-*j*]-quinoline-9-carboxylate (12). Lactam **7** (195 mg, 0.49 mmol) was added at 0 °C under a nitrogen atmosphere to a suspension of NaH (60% dispersion in mineral oil, 18 mg, 0.74 mmol) in dry DMF (5 mL), and the resulting mixture was stirred for 30 min. 4-Methoxybenzyl chloride (80 μL, 0.59 mmol) was added, and the stirring was continued at 0 °C for 1 h. After neutralization with saturated aqueous NH_4Cl, the mixture was extracted three times with Et_2O. The combined organic extracts were washed with brine, dried, filtered, and concentrated. Flash chromatography of the residue (4:1 hexane−EtOAc) provided lactam **12** (170 mg, 67%): IR (film) ν (cm^{-1}) 1643 (NCO), 1707 (COO); ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.28 (t, J = 6.8 Hz, 3H, CH_3), 1.53−1.57 (m, 2H, H-7, H-11), 1.84 (dd, J = 14.0, 5.6 Hz, 1H, H-11), 2.04−2.10 (m, 1H, H-7), 2.25−2.29 (m, 1H, H-7a), 2.29−2.34 (m, 1H, H-10), 2.39 (m, 1H, H-10), 2.46 (ddd, J = 18.8, 11.6, 7.2 Hz, 1H, H-6), 2.62 (dd, J = 18.8, 5.2 Hz, 1H, H-6), 2.93 (dd, J = 14.4, 4.0 Hz, 1H, CH_2-ind), 3.56 (dd, J = 14.4, 3.2 Hz, 1H, CH_2-ind), 3.77 (s, 3H, CH_3O), 3.79 (t, J = 8.8 Hz, 1H, CH_2O), 4.00 (t, J = 8.8 Hz, 1H, CH_2O), 4.18 (q, J = 6.8 Hz, 2H, CH_2CH_3), 4.64 (ddd, J = 11.2, 8.0, 3.2 Hz, 1H, H-3), 5.20 (s, 2H, NCH_2), 6.83 (d, J = 8.4 Hz, 3H, H-8, ArH), 6.93 (s, 1H, H-2 ind), 7.06 (d, J = 8.4 Hz, 2H, ArH), 7.12 (t, J = 7.2 Hz, 1H, ArH), 7.19 (t, J = 7.2 Hz, 1H, ArH), 7.28 (d, J = 8.0 Hz, 1H, ArH), 7.78 (d, J = 8.0 Hz, 1H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2 (CH_3), 22.6 (C-10), 25.6 (C-7), 26.2 (C-11), 29.9 (CH_2-ind), 30.9 (C-6), 40.6 (C-7a), 49.3 (NCH_2), 55.2 (CH_3O), 56.3 (C-3), 60.5 (CH_3CH_2), 68.0 (CH_2O), 92.6 (C-11a), 109.6 (CHAr), 110.8 (CAr), 114.1 (CHAr), 119.3 (CHAr), 119.5 (CHAr), 121.9 (CHAr), 126.0 (CHAr), 128.2 (CHAr), 129.4 (CAr), 129.6 (CAr), 130.0 (C-9), 136.5 (CAr), 137.7 (C-8), 159.1 (CAr), 166.5 (CO_2), 169.3 (CO); HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{31}H_{35}N_2O_5$ 515.2540; Found 515.2545.

(2a*R*,6a*S*,8*S*,14b*S*)-4,8-Bis(hydroxymethyl)-14-(4-methoxybenzyl)-2,2a,5,6,6a,8,9,14b-octahydro-1*H*-benz[*f*]indolo[2,3-*a*]quinolizine (13). Operating as in the preparation of compound **10**, from lactam **12** (2.04 g, 4.66 mmol) in toluene (58 mL) and $POCl_3$ (3.4 mL, 37.3 mmol), then $NaBH_4$ (540 mg, 14 mmol) in anhydrous methanol (92 mL), and finally $LiAlH_4$ (1.77 g, 46.6 mmol) in THF (90 mL), pentacyclic diol **13** (1.45 g, 68%) was obtained after purification by column chromatography (99:1 CH_2Cl_2−MeOH): mp: 119−122 °C; $[\alpha]_D^{22}$ − 34.0 (*c* 0.4, $CHCl_3$); IR (film) ν (cm^{-1}) 3428 (OH); ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.26−1.41 (m, 2H, H-2, H-6), 1.60−1.70 (m, 2H, H-2, H-6), 1.81 (dd, J = 14.4, 3.2 Hz, 1H, H-5), 1.87−2.02 (m, 2H, H-1, H-5), 2.19−2.25 (m, 1H, H-1), 2.39 (m, 1H, H-2a), 2.78−2.82 (m, 2H, H-9), 3.31 (ddd, J = 12.0, 5.2, 3.2 Hz, 1H, H-6a), 3.53 (tt, J = 8.8, 6.4 Hz, 1H, H-8), 3.75 (s, 3H, CH_3O), 3.75−3.81 (dd, J = 11.2, 5.2 Hz, 1H, CH_2OH), 3.90 (s, 2H, CH_2OH), 3.87−3.95 (dd, J = 12.0, 5.2 Hz, 1H, CH_2OH), 4.22 (t, J = 5.2 Hz, 1H, H-14b), 5.25 (d, J = 17.2 Hz, 1H, NCH_2), 5.43 (d, J = 17.2 Hz, 1H, NCH_2), 5.48 (d, J = 3.2 Hz, 1H, H-3), 6.78 (d, J = 8.4 Hz, 2H, ArH), 6.83 (d, J = 8.4 Hz, 2H, ArH), 7.11 (td, J = 7.2, 1.2 Hz, 1H, ArH), 7.15 (td, J = 6.8, 1.2 Hz, 1H, ArH), 7.23 (d, J = 8.0 Hz, 1H, ArH), 7.47 (d, J = 6.8 Hz, 1H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.8 (C-6), 25.0 (C-2), 25.2 (C-9), 26.2 (C-5), 27.1 (C-1), 36.2 (C-2a), 47.5 (NCH_2), 53.0 (C-6a), 54.5 (C-14b), 55.2 (CH_3O), 61.0 (C-8), 62.5 (CH_2OH), 66.6 (CH_2OH), 109.3 (CHAr), 110.0 (CAr), 114.2 (CHAr), 117.8 (CHAr), 119.4 (CHAr), 121.5 (CHAr), 126.4 (C-3), 126.6 (CHAr), 126.9, 130.1, and 136.9 (C-4, 2CAr), 137.9 (CAr), 158.7 (CAr); HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{29}H_{35}N_2O_3$ 459.2642; Found 459.2628.

(2a*R*,6a*S*,8*S*,14b*S*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-8-(hydroxymethyl)-14-(4-methoxybenzyl)-2,2a,5,6,6a,8,9,14b-octahydro-1*H*-benz[*f*]indolo[2,3-*a*]quinolizine (14). Imidazole (32 mg, 0.48 mmol) and *tert*-butyldiphenylsilyl chloride (191 μL, 0.72 mmol) were added at 0 °C to a solution of diol **13** (220 mg, 0.48 mmol) in CH_2Cl_2 (25 mL). The solution was stirred for 15 min at this temperature. Then, saturated aqueous NH_4Cl was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (99:1 CH_2Cl_2−MeOH) of the residue afforded alcohol **14** as a yellow foam (254 mg, 76%): IR (film) ν (cm^{-1}) 3428 (OH), 1109 (OSi); ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.02 [s, 9H, C(CH_3)$_3$], 1.26−1.37 (m, 2H, H-2, H-6), 1.60−1.66 (m, 2H, H-2, H-6), 1.80−1.83 (m, 2H, H-5), 1.93−2.04 (m, 1H, H-1), 2.25−2.29 (m, 1H, H-1), 2.39 (m, 1H, H-2a), 2.79−2.82 (m, 2H, H-9), 3.31 (dm, J = 12.0 Hz, 1H, H-6a), 3.53−3.57 (m, 1H, H-8), 3.73 (s, 3H, CH_3O), 3.81 (dd, J = 10.8, 4.8 Hz, 1H, CH_2OH), 3.94 (s, 2H, CH_2OSi), 3.91−3.96 (m, 1H, CH_2OH), 4.26 (m, 1H, H-14b), 5.27 (d, J = 17.6 Hz, 1H, NCH_2), 5.45 (d, J = 17.6 Hz, 1H, NCH_2), 5.48 (m, 1H, H-3), 6.79 (d, J = 8.4 Hz, 2H, ArH), 6.84 (d, J = 8.4 Hz, 2H, ArH), 7.11 (td, J = 7.6, 1.2 Hz, 1H, ArH), 7.16 (td, J = 8.0, 1.2 Hz, 1H, ArH), 7.24 (d, J = 7.2 Hz, 1H, ArH), 7.31−7.41 (m, 6H, ArH), 7.47 (d, J = 6.8 Hz, 1H, ArH), 7.60−7.64 (m, 4H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.2 [*C*(CH_3)$_3$], 24.7 and 24.8 (C-6, C-2), 25.2 (C-9), 26.1 (C-5), 26.8 [C(CH_3)$_3$], 27.1 (C-1), 36.3 (C-2a), 47.5 (NCH_2), 53.0 (C-6a), 54.6 (C-14b), 55.2 (CH_3O), 61.3 (C-8), 62.4 (CH_2OH), 67.1 (CH_2OSi), 109.3 (CHAr), 110.0 (CAr), 114.2 (CHAr), 117.8 (CHAr), 119.4 (CHAr), 121.5 (CHAr), 125.1 (C-3), 126.6 (CHAr), 126.9 (CAr), 130.1 (CAr), 133.7 (CAr), 133.7 (CAr), 136.2 (C-4, CAr), 137.9 (CAr), 158.7 (CAr); HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{45}H_{53}N_2O_3Si$ 697.3820; Found 697.3807.

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(2a*R*,6a*S*,8*S*,14b*S*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-8-formyl-14-(4-methoxybenzyl)-2,2a,5,6,6a,8,9,14b-octahydro-1*H*-benz[*f*]indolo[2,3-*a*]quinolizine (15). 4 Å powdered sieves (376 mg) and NMO (115 mg, 0.96 mmol) were added at room temperature under an inert atmosphere to a solution of alcohol **14** (190 mg, 0.27 mmol) in CH_3CN (6 mL). Tetrapropylammonium perruthenate (19 mg, 0.054 mmol) was then added in one portion, and the resulting mixture was stirred at room temperature for 30 min. The solvent was evaporated, and the dark residue was dissolved in CH_2Cl_2. The solution was filtered through a short pad of silica using CH_2Cl_2 as the eluent. The filtrate was concentrated to give aldehyde **15** (95 mg, 50%), which was used in the next step without purification: IR (film) ν (cm^{-1}) 1656 (CHO), 1110 (OSi); ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.03 [s, 9H, $C(CH_3)_3$], 1.49 (qd, J = 12.8, 4.0 Hz, 1H, H-1), 1.65−1.79 (m, 3H, H-2, H-6), 1.83 (dm, J = 12.8 Hz, 1H, H-1), 1.93−1.96 (m, 2H, H-5), 2.14 (m, 1H, H-6), 2.47 (s, 1H, H-2a), 3.04 (ddd, J = 15.2, 5.6, 2.0 Hz, 1H, H-9), 3.23 (d, J = 15.2 Hz, 1H, H-9), 3.73 (m, 1H, H-6a), 3.74 (s, 3H, CH_3O), 3.97 (m, 1H, H-8), 4.08 (s, 2H, CH_2OSi), 4.18 (d, J = 10.8 Hz, 1H, H-14b), 5.14 (d, J = 16.8 Hz, 1H, NCH_2), 5.23 (d, J = 16.8 Hz, 1H, NCH_2), 5.27 (s, 1H, H-3), 6.78 (d, J = 8.8 Hz, 2H, ArH), 6.87 (d, J = 8.8 Hz, 2H, ArH), 7.03 (m, 1H, ArH), 7.06−7.09 (m, 2H, ArH), 7.24−7.34 (m, 6H, ArH), 7.51 (m, 1H, ArH), 7.64−7.68 (m, 4H, ArH), 9.66 (s, 1H, CHO); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.2 [$C(CH_3)_3$], 21.3 (C-5), 23.3 (C-9), 26.8 [$C(CH_3)_3$, C-6], 29.4 (C-1), 30.6 (C-2), 35.9 (C-2a), 47.2 (NCH_2), 55.2 (CH_3O), 55.3 (C-6a), 55.6 (C-14b), 59.8 (C-8), 67.6 (CH_2OSi), 107.1 (CAr), 110.0 (CHAr), 114.1 (CHAr), 117.9 (CHAr), 119.4 (CHAr), 121.4 (CHAr), 124.3 (C-3), 126.7 (CAr), 127.0 (CHAr), 127.5 (CHAr), 129.5 (CHAr), 135.4 (CAr), 135.5 (CAr), 137.1 (CAr), 137.8 (C-4), 137.9 (CAr), 158.7 (CAr), 205.6 (CHO); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{45}H_{51}N_2O_3Si$ 695.3663; Found 695.3636.

(2a*R*,6a*S*,8*S*,14b*S*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-8-[(hydroxyimino)methyl]-14-(4-methoxybenzyl)-2,2a,5,6,6a,8,9,14b-octahydro-1*H*-benz[*f*]indolo[2,3-*a*]quinolizine (16). $NH_2OH{\cdot}HCl$ (42 mg, 0.59 mmol) was added to a solution of aldehyde **15** (75 mg, 0.11 mmol) in pyridine (250 μL) and ethanol (250 μL). The mixture was heated at reflux for 2 h, and then the solvent was removed under reduced pressure. Aqueous H_2SO_4 (0.2 N, 2 mL) was added, and the mixture was stirred for 10 min and extracted with EtOAc. The organic extracts were washed with 2 N aqueous NaOH, dried, filtered, and concentrated to afford oximes **16** (44 mg, 56%): *Major isomer*: IR (film) ν (cm^{-1}) 1110 (OSi); ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.02 [s, 9H, $C(CH_3)_3$], 1.48−1.52 (m, 2H, H-2, H-5), 1.64−1.67 (m, 3H, H-1, H-2, H-6), 1.91 (m, 1H, H-5), 2.00 (m, 1H, H-1), 2.32 (d, J = 14.0 Hz, 1H, H-6), 2.46 (m, 1H, H-2a), 2.79 (d, J = 15.2 Hz, 1H, H-9), 3.06 (brs, 1H, H-6a), 3.16 (ddd, J = 15.2, 5.2, 2.0 Hz, 1H, H-9), 3.68 (d, J = 10.4 Hz, 1H, H-14b), 3.75 (s, 3H, CH_3O), 4.08 (s, 2H, CH_2OSi), 4.15 (m, 1H, H-8), 5.17 (d, J = 17.2 Hz, 1H, NCH_2), 5.29 (m, 1H, H-3), 5.30 (d, J = 17.2 Hz, 1H, NCH_2), 6.80 (d, J = 8.4 Hz, 2H, ArH), 6.88 (d, J = 8.4 Hz, 2H, ArH), 7.09 (d, J = 4.8 Hz, 2H, ArH), 7.28−7.36 (m, 7H, ArH), 7.33 (m, 1H, *CH*NOH), 7.48 (m, 1H, ArH), 7.64−7.68 (m, 4H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.3 [$C(CH_3)_3$], 21.2 (C-2), 26.6 (C-9), 26.8 [$C(CH_3)_3$, C-6], 29.7 (C-1), 29.7 (C-5), 36.0 (C-2a), 47.4 (NCH_2), 50.0 (C-8), 55.2 (CH_3O), 55.4 (C-6a), 55.6 (C-14b), 67.5 (CH_2OSi), 107.0 (CAr), 109.8 (CHAr), 114.1 (CHAr), 118.0 (CHAr), 119.3 (CHAr), 121.4 (CHAr), 124.2 (C-3), 127.0 (CHAr), 127.2 (CHAr), 127.5 (CHAr), 127.6 (CHAr), 129.5 (CHAr), 129.7 (CAr), 133.9 (CAr), 134.0 (CAr), 135.4 (CHAr), 135.5 (CHAr), 136.7 (CAr), 137.5 (C-4), 138.3 (CAr), 151.2 (*CH*NOH), 158.8 (CAr); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{45}H_{52}N_3O_3Si$ 710.3772; Found 710.3762. *Minor isomer*: ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC, selected resonances) δ 1.02 [s, 9H, $C(CH_3)_3$], 2.35 (dm, J = 14.0 Hz, 1H, H-6), 2.43 (m, 1H, H-2a), 2.89 (d, J = 15.2 Hz, 1H, H-9), 2.96 (brs, 1H, H-6a), 3.10 (m, 1H, H-9), 3.65 (d, J = 10.4 Hz, 1H, H-14b), 3.75 (s, 3H, CH_3O), 4.08 (s, 2H, CH_2OSi), 4.82 (m, 1H, H-8), 5.18 (d, J = 17.2 Hz, 1H, NCH_2), 5.27 (m, 1H, H-3), 5.33 (d, J = 17.2 Hz, 1H, NCH_2), 6.76 (m, 1H, *CH*NOH), 6.78 (d, J = 8.4 Hz, 2H, ArH), 6.87 (d, J = 8.4 Hz, 2H, ArH), 7.09 (s, 1H, ArH), 7.28−7.36 (m, 7H, ArH), 7.48 (m, 1H, ArH), 7.64−7.68 (m, 4H, ArH).

(2a*R*,6a*S*,14b*S*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-14-(4-methoxybenzyl)-2,2a,5,6,6a,8,9,14b-octahydro-1*H*-benz[*f*]-indolo[2,3-*a*]quinolizine (17). *First step:* Burgess reagent was added in three portions (3 × 30 mg) to a solution of oximes **16** (88 mg, 0.12 mmol) in CH_2Cl_2 (1.25 mL) over a period of 2 h. The resulting solution was stirred at room temperature for 2 h. Water was then added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated to afford the corresponding cyano derivative, which was used in the next step without purification. *Second step*: AcOH (17 μL) was added to a solution of $NaBH_3CN$ (28 mg, 0.45 mmol) in CH_3CN (120 μL), and the solution was stirred at room temperature for 30 min. Then, a solution of the above cyano compound (88 mg, 0.075 mmol) in CH_3CN (115 μL) was added, and the resulting mixture was stirred at room temperature for 9 h. CH_2Cl_2 and 4 N aqueous NaOH were then added, and the mixture was extracted with CH_2Cl_2. The organic extracts were washed with brine, dried, filtered, and concentrated. Flash chromatography of the residue (9:1 hexane−EtOAc) afforded compound **17** (35 mg, 70%, two steps): IR (film) ν (cm^{-1}) 1111 (OSi); ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.06 [s, 9H, $C(CH_3)_3$], 1.56 (td, J = 11.6, 4.8 Hz, 1H, H-1), 1.62−1.72 (m, 3H, H-2, H-6), 1.88−1.92 (m, 2H, H-1, H-5), 2.11 (t, J = 14.8 Hz, 1H, H-5), 2.22−2.28 (m, 2H, H-6, H-8), 2.48 (brs, 1H, H-2a), 2.70−2.76 (m, 2H, H-6a, H-9), 2.88 (m, 1H, H-9), 3.40−3.47 (m, 2H, H-8, H-14b), 3.77 (s, 3H, CH_3O), 4.11 (s, 2H, CH_2OSi), 5.18 (d, J = 17.2 Hz, 1H, NCH_2), 5.30 (d, J = 17.2 Hz, 1H, NCH_2), 5.33 (m, 1H, H-3), 6.80 (d, J = 8.8 Hz, 2H, ArH), 6.88 (d, J = 8.8 Hz, 2H, ArH), 7.06−7.10 (m, 3H, ArH), 7.29−7.37 (m, 7H, ArH), 7.51−7.53 (m, 1H, ArH), 7.48 (m, 1H, ArH), 7.67−7.70 (m, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.3 [$C(CH_3)_3$], 21.3 (C-5), 23.1 (C-9), 26.8 [$C(CH_3)_3$], 27.1 (C-6), 28.5 (C-1), 30.2 (C-2), 36.0 (C-2a), 46.3 (C-8), 47.6 (NCH_2), 55.2 (CH_3O), 58.6 (C-6a), 59.9 (C-14b), 67.5 (CH_2OSi), 109.7 (CHAr), 114.0 (CHAr), 118.0 (CHAr), 119.2 (CHAr), 121.1 (CHAr), 124.6 (C-3), 127.0 (CHAr), 127.1 (CHAr), 127.5 (CHAr), 129.0 (CAr), 129.5 (CHAr), 129.5 (CHAr), 129.9 (CAr), 133.9 (CAr), 134.0 (CAr), 135.4 (CHAr), 135.5 (CHAr), 137.7 (CAr), 137.9 (C-4), 138.1 (CAr), 158.6 (CAr); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{44}H_{51}N_2O_2Si$ 667.3714; Found 667.3711.

(2a*R*,6a*S*,14b*S*)-4-(Hydroxymethyl)-2,2a,5,6,6a,8,9,14b-octahydro-1*H*-benz[*f*]indolo[2,3-*a*]quinolizine (5). *First step:* Thiophenol (125 μL, 2.25 mmol) and cold TFA (1.40 mL) were added at 0 °C to compound **17** (30 mg, 0.045 mmol), and the mixture was stirred for 2 h. The solution was poured into a cold saturated solution of $NaHCO_3$, and the resulting mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated. Flash chromatography (4:1 hexane−EtOAc) afforded the deprotected indole derivative (22 mg, 90%): ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.01 [s, 9H, $C(CH_3)_3$], 1.57−1.69 (m, 2H, H-1), 1.82 (m, 3H, H-2, H-5, H-6), 2.05 (m, 1H, H-5), 2.28 (m, 2H, H-6, H-8), 2.55 (brs, 1H, H-2a), 2.65 (brs, 1H, H-6a), 2.70 (d, J = 15.2 Hz, 1H, H-9), 2.82 (m, 1H, H-9), 3.35 (brd, J = 10.4 Hz, 1H, H-14b), 3.47 (dd, J = 11.2, 4.0 Hz, 1H, H-8), 4.02 (d, J = 13.2 Hz, 1H, CH_2OSi), 4.09 (d, J = 13.2 Hz, 1H, CH_2OSi), 5.38 (m, 1H, H-3), 7.07−7.20 (m, 6H, ArH), 7.27−7.32 (m, 4H, ArH), 7.62−7.67 (m, 4H, ArH), 7.69 (brs, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.3 [$C(CH_3)_3$], 20.8 (C-5), 22.6 (C-9), 26.8 [$C(CH_3)_3$], 26.9 and 27.1 (C-6, C-1), 30.1 (C-2), 36.3 (C-2a), 47.4 (C-8), 58.0 (C-6a), 59.8 (C-14b), 67.3 (CH_2OSi), 108.7 (CAr), 110.7 (CHAr), 118.0 (CHAr), 119.3 (CHAr), 121.1 (CHAr), 123.9 (C-3), 127.4 (CHAr), 127.5 (CHAr), 129.4 (CHAr), 129.5 (CHAr), 133.8 (CAr), 134.0 (CAr), 135.4 (CHAr), 135.5 (CHAr), 136.0 (CAr), 137.9 (C-4). *Second step:* TBAF (55 μL, 0.055 mmol) was added at 0 °C to a solution of the above deprotected indole derivative (15 mg, 0.028 mmol) in THF (2.8 mL). The mixture was stirred for 4 h, and then concentrated under reduced pressure. Flash chromatography of the residue afforded pentacyclic alcohol **5** (7 mg, 85%): mp: 241−242 °C; ^1H NMR (500 MHz, CD_3OD, *g*-HSQC) δ 1.33 (m, 1H, H-1), 1.56−1.64 (m, 1H, H-2), 1.72 (td, J = 14.0, 6.0 Hz, 1H, H-6), 1.86−1.96 (m, 2H, H-1, H-5), 2.16−2.22 (m, 2H, H-2,

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H-5), 2.40 (dm, J = 14.0 Hz, 1H, H-6), 2.46 (m, 1H, H-8), 2.62 (brs, 1H, H-2a), 2.77 (dd, J = 16.0, 4.0 Hz, 1H, H-9), 2.82 (brs, 1H, H-6a), 2.93 (dm, J = 16.0 Hz, 1H, H-9), 3.56 (brs, 1H, H-14b), 3.68 (m, 1H, H-8), 3.92 (s, 2H, CH_2OH), 5.39 (brs, 1H, H-3), 6.95 (td, J = 8.0, 1.5 Hz, 1H, ArH), 7.03 (td, J = 8.0, 1.5 Hz, 1H, ArH), 7.27 (d, J = 7.5 Hz, 1H, ArH), 7.37 (d, J = 7.5 Hz, 1H, ArH); when the spectrum was recorded in CF_3CO_2D (400 MHz), the olefinic proton appeared at δ 5.86 as a broad singlet; ^{13}C NMR (125.0 MHz, CD_3OD) δ 22.1 (C-5), 22.5 (C-9), 26.9 and 27.3 (C-2, C-6), 30.7 (C-1), 37.3 (C-2a), 48.8 (C-8), 60.8 (C-6a), 62.4 (C-14b), 67.7 (CH_2OH), 108.2 (CAr), 111.9 (CHAr), 118.6 (CHAr), 119.8 (CHAr), 122.0 (CHAr), 127.2 (C-3), 128.3 (CAr), 136.0 (CAr), 138.1 (CAr), 139.9 (C-4); m/z (%) 308 (91, M^+), 307 (100, $[M - 1]^+$), 291 (44), 277 (17), 223 (15), 197 (24), 184 (36), 171 (29), 170 (58), 169 (68), 156 (21), 144 (31); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{25}N_2O$ 309.1961; Found 309.1954.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of compounds **5**, **7**, **7′**, and **10**−**17**, and a table with mass-spectral fragmentations of natural nitraraine and compound **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: amat@ub.edu.

Notes

The authors declare no competing financial interest.

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