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Stereospecific Total Synthesis of the Indole Alkaloid Ervincidine. Establishment of the C-6 Hydroxyl Stereochemistry

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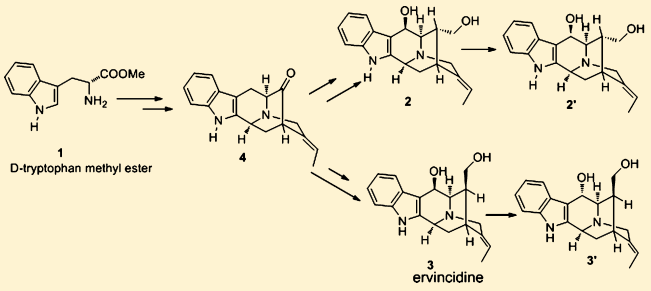
Supporting Information

ABSTRACT: The total synthesis of the indole alkaloid ervincidine (**3**) is reported. This research provides a general entry into C-6 hydroxy-substituted indole alkaloids with either an α or a β configuration. This study corrects the errors in Glasby's book (Glasby, J. S. *Encyclopedia of the Alkaloids*; Plenum Press: New York, 1975) and Lounasmaa et al.'s review (Lounasmaa, M.; Hanhinen, P.; Westersund, M. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 1999; Vol. 52, pp 103−195) as well as clarifies the work of Yunusov et al. (Malikov, V. M.; Sharipov, M. R.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1972**, *8*, 760−761. Rakhimov, D. A.; Sharipov, M. R.; Aripov, Kh. N.; Malikov, V. M.; Shakirov, T. T.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1970**, *6*, 724−725). It establishes the correct absolute configuration of the C-6 hydroxyl function in ervincidine. This serves as a structure proof and corrects the misassigned structure reported in the literature.



INTRODUCTION

Indole alkaloids are of prominence because of the similarity with tryptophan, which is an essential amino acid. The sarpagine alkaloids contain the common structural element of the parent pentacyclic sarpagan ring system[1,2] with established stereochemistry at C-3 (*S*), C-5 (*R*), and C-15 (*R*).[2] The alkaloid ervincidine (Figure 1) belongs to the sarpagine class and has been

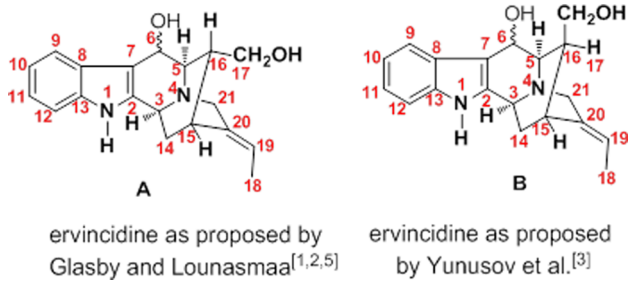


Figure 1. The indole alkaloid ervincidine.

isolated from the epigeal part of *Vinca erecta* Rgl. et Schmalh.[3,4] The structure of ervincidine has six stereocenters, four of which have the C-3 (*S*), C-5 (*R*), C-15 (*R*), and C-16 (*R*) configuration, and contains a double bond at C(19)−C(20), which is usually the thermodynamically less stable *E* configuration.

The stereochemistry of the alcohol function at the C-6 position was not assigned by Glasby and Lounasmaa[1,2,5] nor was the location of the hydroxylmethyl at the C-16 group unequivocally established. Yunusov et al.,[3,4] who isolated this alkaloid, had reported the structure of ervincidine as similar to that of the polyneuridine subclass with four stereocenters, C-3 (*S*), C-5 (*R*), C-15 (*R*), and the hydroxymethyl function in the β configuration at C-16 (*S*). However, the stereochemistry of the C-6 alcohol was not assigned in this report as well. As illustrated in Figure 1, in the proposed structure of ervincidine by Glasby[1] and Lounasmaa et al.,[5] the hydroxymethyl group at C-16 was assigned the α stereochemistry, while, according to Yunusov et al.,[4] the hydroxymethyl group at C-16 was proposed to have the β stereochemistry. The stereochemistry and the structure of ervincidine especially with regard to the C-6 and C-16 stereocenters stimulated interest in this alkaloid. The total synthesis of this natural product was also necessary because the only information known in the literature[3,4] was the optical rotation of the isolated indole alkaloid ervincidine (**3**), which was reported as +29.5° (*c* 0.6, MeOH) by Yunusov et al.[3,4] No unequivocal spectral information or elemental analysis had been reported. Additionally, the stability of the C-6 hydroxyl function had not been explored in the literature. The aim of this report was hence centered on the stereospecific total synthesis of the indole alkaloid ervincidine and correction of the stereochemical ambiguity reported in the literature.[2−5] Moreover, the design of a synthetic entry into the C-6 alcohol stereospecifically, as well as an assessment of the thermodynamic stability of the C-6 hydroxyl group, was of significant importance because indole alkaloids are usually isolated by an acidic/basic extraction

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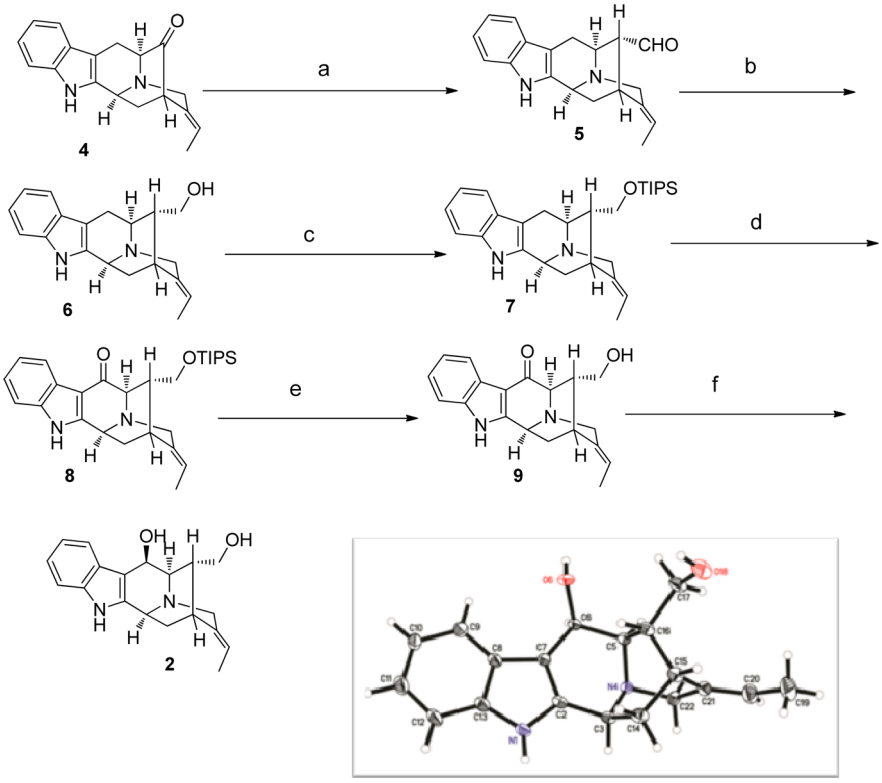
Scheme 1. General Approach to the Total Synthesis of the Ervincidine Diastereomer (Structural Assignment Proposed by Glasby and Lounasmaa et al.)[a1,2,5]



ORTEP view of crystal structure of **2**

[a]Reagents and conditions: (a) 1. $CH_3OCH_2PPh_3Cl$ (7.3 equiv), *t*-BuOK (7.9 equiv), benzene/THF; 2. 2 N aq HCl/THF, 55 °C, 90%. (b) $NaBH_4$ (1.4 equiv), EtOH, 0 °C, 8 h, 90%. (c) TIPSCl, 2,6-lutidine, CH_2Cl_2, 0 °C, 90%. (d) IBX, EtOAc:DMSO (2:1), 80 °C, 8 h, 85%. (e) TBAF·H_2O, THF, 0 °C to rt, 85%. (f) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH, −78 °C to rt, 90%.

process. In a retrosynthetic sense, the possible diastereomers **2** and **2′** as well as **3** and **3′** might be available via a common intermediate, pentacyclic ketone **4**. The chirality of **4** was to be employed to introduce the correct stereocenters in the target alkaloids **2**, **2′** or **3**, **3′**.

RESULTS AND DISCUSSION

As illustrated in Scheme 1, ketone **4** was subjected to a Wittig reaction with methoxymethyl triphenylphosphonium chloride in the presence of anhydrous potassium *tert*-butoxide to provide a mixture of two isomeric enol ethers (not shown) at C-16. After a short wash column, the mixture of enol ethers was hydrolyzed under acidic conditions to provide vellosimine **5** in 90% yield (over two steps).[6−9] The aldehyde function of **5** was then reduced with sodium borohydride to provide the alcohol normacusine B (**6**), the spectral data of which are in complete agreement with that of the natural product.[7−10]

The C-17 functionalized alcohol was then protected as the triisopropylsilyl ether **7** employing 2,6-lutidine as the base to provide the ether.[7,8,10] Repeated attempts to oxidize the C-6 position of **7** with DDQ were unsuccessful. Finally, the oxidation at the C-6 position was successfully accomplished using IBX at 80 °C[11−14] to form the desired ketone **8**.

Deprotection of the silyl group was accomplished using TBAF/THF to provide the C-16 substituted alcohol **9**, as shown in Scheme 1. The selective reduction of the ketone **9** was carried out via a Luche reduction[15] using sodium borohydride in combination with cerium chloride heptahydrate to afford the final product **2**. Reduction occurred stereospecifically to give the β alcohol in **2** as a single diastereomer.[16] The stereochemistry of **2** was confirmed using single-crystal X-ray structural analysis.

The optical rotation of this diastereomer **2** was determined to be $[\alpha]_D^{26}$ +79° (*c* 0.6, MeOH), which was not in agreement with the value reported in the literature.[3−5] Hence, the diastereomer **2** was stirred in 0.2 N HCl at 0 °C. Examination by TLC (silica gel; CH_2Cl_2:MeOH 9:1) indicated a new component at a lower R_f value, which illustrated that complete epimerization of the alcohol function at C-6 to diastereomer **2′** had occurred. Unfortunately, the new material could not be isolated due to the small amount of the compound available. It appears that the C-6 α-hydroxyl group was, presumably, in the more stable α position in epimeric alcohol **2′** based on this preliminary experiment.

To achieve the synthesis of the diastereomer with the C-16 hydroxymethyl function in the β position as proposed by Yunusov et al.,[3,4] pentacyclic ketone **4** was treated with triphenylphosphonium bromide in benzene in the presence of potassium *t*-butoxide to afford diene **10** in 90% yield (Scheme 2).[17] To facilitate attack on diene **10** from the less hindered face of the exocyclic methylene function and prevent hydroboration of the C(19)−C(20) olefinic bond,[18] 9-BBN was chosen as the hydroborating agent. This was carried out under the standard conditions with the Kabalka borate work up procedure[19] to prohibit N_b-oxidation. This was a key process because N_b-oxidation oftentimes complicates this oxidation with H_2O_2.

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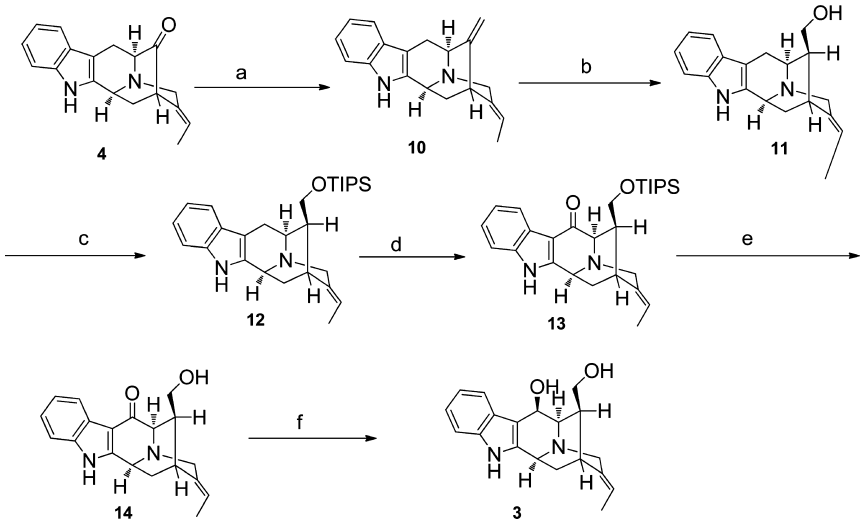
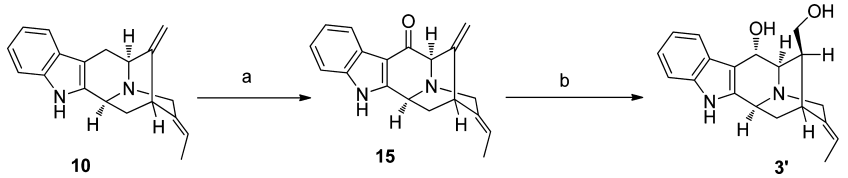
Scheme 2. General Approach to the Total Synthesis of the Ervincidine Diastereomer[a3,4]



[a]Reagents and conditions: (a) CH_3PPh_3Br (7.3 equiv), *t*-BuOK (7.9 equiv), benzene/THF, 90%. (b) 9-BBN (5 equiv), 0 °C to rt, 1.5 h; $NaBO_3 \cdot 4H_2O$, 0 °C to rt, 2 h, 70%. (c) TIPSCl, 2,6-lutidine, CH_2Cl_2, 90%. (d) IBX, EtOAc:DMSO (2:1), 80 °C, 8 h, 85%. (e) TBAF·H_2O, THF, 90%. (f) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 90%.

Scheme 3. Synthesis of the C-6 α Diastereomer 3′ of Ervincidine[a]



[a]Reagents and conditions: (a) IBX, EtOAc: DMSO (2:1), 80 °C, 8 h, 80%. (b) THF, 9-BBN (5 equiv), 0 °C to rt, 1.5 h; $NaBO_3 \cdot 4H_2O$, 0 °C to rt, 2 h, 70%.

The synthesis of TIPS derivative **12** was executed analogous to the previous preparation[20] from alcohol **11** in 90% yield. The oxidation of the C-6 benzylic position to the ketone in **13** was achieved by radical oxidation using IBX[11−14] at 80 °C in 85% yield.

As shown in Scheme 2, the silyl group from ketone **13** was removed by treatment with TBAF in THF to give **14** in 90% yield. The selective reduction of the ketone **14** was carried out by Luche reduction[15] to achieve the stereospecific synthesis of the natural product ervincidine **3** with a β-hydroxyl group at C-6 and the β-hydroxymethyl function at C-16 as a single diastereomer in 90% yield. The optical rotation of **3** {$[\alpha]_D^{26}$ +29.00° (*c* 0.6, MeOH)} was in excellent agreement with that reported in the literature[2−5] {$[\alpha]_D^{26}$ +29.5° (*c* 0.6, MeOH)}, which completed the stereospecific total synthesis of the natural product ervincidine **3** (Scheme 2). The structure and stereochemistry at the C-6 and C-16 positions in **3** were established unequivocally by NOESY and NOE NMR spectroscopy, including the absolute configuration of the hydroxyl group at C-6, which is reported in the Supporting Information.

The synthesis of the diastereomer with the opposite stereochemistry to that of ervincidine **3** at the C-6 position was also pursued (Scheme 3). Diene **10** was treated with IBX to give ketone **15** at the C-6 position in 80% yield. In order to shorten the synthetic route and also synthesize the other isomer, 9-BBN was chosen, which reduced the C-6 keto group to the α alcohol and also acted as a hydroborating agent at the C(16)−C(17) olefinic bond.[21,22] Since 9-BBN is a bulky hydroborating agent, it was proposed that the attack took place from the exo (top) face of the molecule. The boron could coordinate[10] with the C-6 carbonyl oxygen atom as well as the N_b nitrogen atom, leading to the formation of the α diastereomer **3′**. This process was executed, as shown in Scheme 3, in 70% yield. The optical rotation of **3′** was $[\alpha]_D^{26}$ +17.00° (*c* 0.6, MeOH) and was not in agreement with that reported in the literature for **3**.[3,4] It appears that 9-BBN complexed[10] with the N_b-nitrogen function and blocked the attack from the bottom face of the ketone so that excess 9-BBN could reduce the carbonyl group from the top face to give α alcohol **3′**.

CONCLUSION

In conclusion, the stereospecific total synthesis of ervincidine **3** has been accomplished from commercially available D-(+)-tryptophan methyl ester **1**, which served as both the chiral auxiliary and the starting material. Moreover, this synthesis unequivocally sets the correct stereochemistry of the hydroxyl group at C-6 in a stereospecific fashion, as well as the β-C-16 hydroxymethyl group. The stereospecific conversion of D-(+)-tryptophan methyl ester **1** into the key template pentacyclic ketone **4** occurred via the asymmetric Pictet−Spengler reaction (600 g scale), Dieckmann cyclization, and palladium-mediated enolate cross-coupling reaction, which were the key steps to synthesize these indole alkaloids. The Kabalka sodium borate process worked much better than H_2O_2, as expected in this series. The IBX-mediated oxidation and the Luche reduction afforded the stereospecific total synthesis of ervincidine **3**. Another

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important study was the epimerization of the C-6 alcohol with 0.2 N HCl, which indicated that care must be employed in the isolation of these alkaloids that contain a benzylic hydroxyl group. The research process developed here also provides a general entry into C-6 hydroxy-substituted indole alkaloids with either the α or the β configuration. The structures of the diastereomers were also unequivocally assigned by employing X-ray analysis on **2** and detailed high-resolution, NOESY and NOE studies and then compared to those on **2**. This research corrects the errors in Glasby's book[1] and Lounasmaa et al.'s review[5] and clarifies the work of Yunusov et al. as well as providing the correct absolute configuration of the C-6 hydroxyl function in ervincidine **3**.[3,4]

EXPERIMENTAL SECTION

IBX-Mediated Oxidation To Provide (6*S*,11*S*,11*aR*,*E*)-9-Ethylidene-11-((triisopropylsilyl)oxy)methyl)-6,8,9,10,11,11*a*-hexahydro-6,10-methanoindolo[3,2-*b*]quinolizin-12(5*H*)-one (8).[11−14] To a solution of triisopropylsilyl ether **7** (100 mg, 0.22 mmol) in EtOAc/DMSO (10 mL/5 mL) was added IBX (0.552 g, 0.88 mmol) in one portion at rt. The mixture that resulted was heated and stirred at 80 °C overnight, and the reaction progress was monitored by TLC (silica gel, EtOAc). The reaction mixture was cooled to 0 °C and quenched with a saturated solution of aq $NaHCO_3$ (4 mL), followed by treatment with a saturated solution of aq $Na_2S_2O_3$ (5 mL). After this, the mixture was stirred for an additional 10 min at 0 °C. The aq layer was extracted with additional amounts of EtOAc (3 × 10 mL), and the combined organic layers were washed with brine (10 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to provide the crude oil, which was purified by flash chromatography [silica gel, hexane:EtOAc (1:1)] to provide the benzylic ketone **8** (87 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 21H), 1.66 (d, 3H, J = 6.3 Hz), 1.82 (d, 1H, J = 6.3 Hz), 2.13 (t, 2H, J = 9.9 Hz), 2.86 (d, 1H, J = 7 Hz), 3.17 (s, 1H), 3.5 (m, 3H), 3.8 (dd, 1H, J_1 = 9.6 Hz, J_2 = 4.2 Hz), 4.2 (d, 1H, J = 8.4 Hz), 5.4 (q, 1H, J = 7 Hz), 7.14 (m, 3H), 8.07 (d, 1H, J = 7.2 Hz), 9.03 (br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.9, 12.9, 18.0, 29.7, 32.5, 42.6, 50.5, 54.8, 63.9, 64.6, 106.5, 111.6, 118.5, 121.6, 122.7, 123.6, 124.5, 132.3, 136.1, 154.7, 192.0; HRMS (ESI) m/z calcd for $C_{28}H_{41}N_2O_2Si$ (M + H)$^+$ 465.2937; found: 465.2950.

Synthesis of (6*S*,11*R*,11*aR*,*E*)-9-Ethylidene-11-(hydroxymethyl)-6,8,9,10,11,11*a*-hexahydro-6,10-methanoindolo[3,2-*b*]quinolizin-12(5*H*)-one (9). A solution of benzylic ketone **8** (20 mg, 0.043 mmol) was stirred in THF (1 mL) in a 5 mL round-bottom flask. At 0 °C, excess TBAF hydrate was then added to the mixture, and it was allowed to warm to rt. The reaction mixture was stirred for 2 h until analysis of the mixture by TLC indicated the absence of starting material. The reaction was quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL), washed with brine, and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the residue was purified by flash chromatography [EtOAc:hexane (4:1)] to provide the target monol **9** (11 mg, 85%). ^{1}H NMR (300 MHz, CD_3OD) δ 1.68 (d, 3H, J = 6 Hz), 1.87 (d, 1H, J = 12 Hz), 2.12 (br, 1H), 2.28 (t, 1H, J = 12 Hz), 2.84 (d, 1H, J = 6 Hz), 3.25 (s, 1H), 3.66 (m, 5H), 4.35 (dd, 1H, J_1 = 9 Hz, J_2 = 3 Hz), 5.55 (q, 1H, J = 7.5 Hz), 7.25 (m, 2H), 7.43 (d, 1H, J = 7 Hz), 7.98 (d, 1H, J = 8.4 Hz); ^{13}C NMR (75.5 MHz, CD_3OD) δ 11.6, 19.3, 29.2, 42.6, 50.2, 54.4, 63.2, 64.3, 105.4, 111.6, 117.9, 120.5, 122.2, 123.2, 124.3, 133.3, 136.8, 156.4, 193.7; HRMS (ESI) m/z calcd for $C_{19}H_{21}N_2O_2$ (M + H)$^+$: 309.1603; found: 309.1588. This material was used directly in a later step.

Preparation of (6*S*,11*R*,11*aR*,12*R*,*E*)-9-Ethylidene-11-(hydroxymethyl)-5,6,8,9,10,11,11*a*,12-octahydro-6,10-methanoindolo[3,2-*b*]quinolizin-12-ol (2). A solution of alcohol **9** (15 mg, 0.049 mmol) was stirred in MeOH (1 mL) in a 5 mL flask. At −78 °C, $CeCl_3{\cdot}7H_20$ (19 mg, 0.054 mmol) and $NaBH_4$ (2 mg, 0.049 mmol) were added to the mixture, and it was allowed to warm to rt. The reaction mixture was stirred for 3 h until analysis of the mixture by TLC (silica gel) indicated the absence of starting material. The reaction was quenched with aq NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL), washed with brine, and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the residue was purified by flash chromatography [CH_2Cl_2:MeOH (90:10)] to provide the target diol **2** (13 mg, 90%); R_f 0.75 (silica gel, CH_2Cl_2/MeOH, 9:1); $[\alpha]_D^{25}$ +79° (c 0.6 MeOH); [lit.[3−5] $[\alpha]_D^{22}$ = +29.5° (c 0.6 in CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 1.67 (d, 3H, J = 6.6 Hz), 1.80 (td, 1H, J_1 = 12.6 Hz, J_2 = 6 Hz), 2.13 (m, 1H), 2.2 (m, 1H), 2.7 (t, 1H, J = 6.6 Hz), 3.01 (s, 1H), 3.5 (m, 3H), 3.6 (m, 2H), 4.10 (d, 1H, J = 8 Hz), 5.23 (d, 1H, J = 6 Hz), 5.47 (q, 1H, J = 6.6 Hz), 7.04 (m, 2H), 7.3 (d, 1H, J = 7.8 Hz), 7.78 (d, 1H, J = 7.8 Hz); ^{13}C NMR (75.5 MHz, CD_3OD) δ 11.6, 27.2, 32.5, 39.2, 50.2, 55.6, 59.7, 63.8, 65.9, 102.3, 110.6, 116.9, 118.6, 119.2, 120.8, 126.5, 135.2, 136.9, 138.5; HRMS (ESI) m/z calcd for $C_{19}H_{23}N_2O_2$ (M + H)$^+$: 311.1760; found: 311.1758.

Preparation of (6*S*,11*S*,11*aR*,*E*)-9-Ethylidene-11-((triisopropylsilyl)oxy)methyl)-6,8,9,10,11,11*a*-hexahydro-6,10-methanoindolo[3,2-*b*]quinolizin-12(5*H*)-one (13). The synthesis of ketone **13** from TIPS derivative **12** was carried out analogous to the preparation of **8** from **7** in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, 21H, J = 2.7*Hz*), 1.66 (d, 3H, J = 7 Hz), 1.81 (t, 1H, J = 11 Hz), 2.06 (dd, 1H, J_1 = 9.9 Hz, J_2 = 3.3 Hz), 2.25 (m, 1H), 3.35 (d, 1H, J = 2 Hz), 3.47 (t, 1H, J = 11 Hz), 3.74 (d, 2H, J = 2.4 Hz), 3.78 (s, 1H), 3.84 (dd, 1H, J_1 = 10.2 Hz, J_2 = 4.8 Hz), 4.14 (dd, 1H, J_1 = 10.5 Hz, J_2 = 4.5 Hz), 5.32 (q, 1H, J = 6.9 Hz), 7.27 (m, 3H), 8.13 (d, 1H, J = 6.9 Hz), 8.9 (br, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.9, 12.7, 17.9, 25.9, 27.8, 38.5, 50.1, 55.5, 59.9, 63.5, 108.6, 111.3, 114.3, 121.8, 122.8, 123.5, 123.9, 135.7, 139.2, 155.3, 191.5; HRMS (ESI) m/z calcd for $C_{28}H_{41}N_2O_2Si$ (M + H)$^+$: 465.2937; found: 465.2914. This material was employed directly in the next step.

Preparation of (6*S*,11*S*,11*aR*,*E*)-9-Ethylidene-11-(hydroxymethyl)-6,8,9,10,11,11*a*-hexahydro-6,10-methanoindolo[3,2-*b*]quinolizin-12(5*H*)-one (14). The synthesis of monol **14** from TIPS derivative **13** was carried out analogous to the preparation of **9** from **8** in 90% yield. ^{1}H NMR (300 MHz, CD_3OD) δ 1.68 (td, 3H, J_1 = 6.6 Hz, J_2 = 3.9 Hz), 2.06 (m, 4H), 2.26 (m, 1H), 3.3 (m, 1H), 3.67 (dd, 1H, J_1 = 11 Hz, J_2 = 5 Hz), 3.77 (m, 3H), 4.28 (dd, 1H, J_1 = 11 Hz, J_2 = 5 Hz), 5.4 (q, 1H, J = 6 Hz), 7.27 (m, 2H), 7.47 (m, 1H), 8.01 (m, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 11.5, 24.8, 27.6, 38.1, 49.5, 54.6, 58.3, 63.2, 107.6, 111.6, 114.4, 120.6, 122.4, 123.3, 123.5, 136.7, 138.2, 156.3, 191.8; HRMS (ESI) m/z calcd for $C_{19}H_{21}N_2O_2$ (M + H)$^+$: 309.1603; found: 309.1588. This material was employed directly in the next step.

Preparation of Ervincidine [(6*S*,11*S*,11*aR*,12*R*,*E*)-9-ethylidene-11-(hydroxymethyl)-5,6,8,9,10,11,11a,12-octahydro-6,10-methanoindolo[3,2-*b*]quinolizin-12-ol (3)]. The synthesis of **3** from **14** was carried out analogous to the preparation of **2** from **9** in 90% yield. R_f 0.71 (silica gel, CH_2Cl_2/MeOH, 9:1); $[\alpha]_D^{25}$ +29.0° (c 0.6 in MeOH); [lit.[3−5] $[\alpha]_D^{22}$ = +29.5° (c 0.6 in CH_3OH)]; ^{1}H NMR (300 MHz, CD_3OD) δ 1.70 (d, 3H, J = 6.9 Hz), 1.94 (m, 2H), 2.26 (m, 1H), 2.9 (q, 1H, J = 2.4 Hz), 3.14 (dd, 1H, J_1 = 11.4 Hz, J_2 = 6 Hz), 3.61 (dd, 1H, J_1 = 10 Hz, J_2 = 5.4 Hz), 3.6 (s, 3H), 3.8 (m, 1H), 4.2 (dd, 1H, J_1 = 8.4 Hz, J_2 = 4 Hz), 5.4 (m, 2H), 7.0 (t, 1H, J = 7 Hz), 7.08 (t, 1H, J = 7 Hz), 7.32 (d, 1H, J = 8.1 Hz), 7.76 (d, 1H, J = 7.8 Hz); ^{13}C NMR (75.5 MHz, CD_3OD) δ 11.5, 26.3, 28.1, 42.5, 50.1, 55.7, 58.7, 61.0, 67.3, 110.2, 110.6, 114.2, 118.6, 119.7, 120.8, 125.0, 136.2, 136.9, 138.9; HRMS (ESI) m/z calcd for $C_{19}H_{23}N_2O_2$ (M + H)$^+$: 311.1760; found: 311.1773. The optical rotation and mass spectrum were in excellent agreement with the natural product.[3,4]

Synthesis of (6*S*,11*aR*,*E*)-9-Ethylidene-11-methylene-6,8,9,10,11,11*a*-hexahydro-6,10-methanoindolo[3,2-*b*]quinolizin-12(5*H*)-one (15). To a solution of diene **10** (100 mg, 0.36 mmol) in EtOAc/DMSO (5 mL/2.5 mL) was added IBX (0.9 g, 1.44 mmol) in one portion at rt. The mixture was heated and stirred at 80 °C overnight, and the reaction progress was monitored by TLC (silica gel, EtOAc). The reaction mixture was cooled to 0 °C and quenched with a saturated solution of aq $NaHCO_3$ (4 mL), followed by treatment with a saturated solution of aq $Na_2S_2O_3$ (5 mL). After this, the mixture was stirred for an additional 10 min at 0 °C. The aq layer was extracted with additional amounts of EtOAc (3 × 10 mL), and the combined organic layers were washed with brine (10 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to provide the crude oil, which was purified by chromatography [silica gel, hexane:EtOAc (3:1)] to provide the benzylic ketone **15** (84 mg, 80%). ^{1}H NMR (300 MHz, CD_3OD) 1.66 (d, 3H, J = 6 Hz), 1.9 (m, 1H), 2.36 (m, 1H), 3.6 (m, 3H), 4.0

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(m, 1H), 4.9 (d, 1H, J = 2 Hz), 5.0 (d, 1H, J = 2 Hz), 5.39 (q, 1H, J = 6.8 Hz), 7.27 (m, 2H), 7.4 (m, 1H), 7.6 (m, 2H), 8.0 (m, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 11.1, 34.4, 38.5, 50.1, 54.4, 67.4, 105.9, 106.2, 124.3, 128.5, 128. 6, 131.6, 131.7, 132.4, 135.7, 136.7, 145.1, 155.9, 190.2; HRMS (ESI) m/z calcd for $C_{19}H_{19}N_2O$ $(M + H)^+$: 291.1497; found: 291.1513. This material was employed directly in the next step.

Preparation of (6*S*,11*S*,11*aR*,12*S*,*E*)-9-Ethylidene-11-(hydroxymethyl)-5,6,8,9,10,11,11*a*,12-octahydro-6,10-methanoindolo[3,2-*b*]quinolizin-12-ol (3′). To a solution of olefin **15** (100 mg, 0.344 mmol) in THF (10 mL) was added 9-BBN (0.5 M in THF, 3.44 mL, 1.72 mmol) dropwise, at 0 °C. The solution was allowed to warm to rt and stirred for 1.5 h. The reaction mixture was then cooled to 0 °C, and $NaBO_3{\cdot}4H_2O$ (0.795 g, 5.16 mmol) was added, and the reaction temperature was allowed to warm to rt. The mixture that resulted was stirred for 2 h at rt, diluted with CH_2Cl_2 (50 mL), washed with H_2O (3 × 50 mL) as well as brine (50 mL), and dried (K_2CO_3). The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, CH_2Cl_2/MeOH; 9:1) to provide alcohol **3′** (74 mg, 70% yield). R_f 0.73 (silica gel, CH_2Cl_2/CH_3OH, 9:1); $[\alpha]_D^{25}$ = +17.0° (c 0.6 in CH_3OH); [lit.[3−5] $[\alpha]_D^{22}$ = +29.5° (c 0.6 in CH_3OH)]; ^{1}H NMR (300 MHz, CD_3OD) δ 1.70 (d, 3H, J = 6 Hz), 1.8 (m, 3H), 1.92 (m, 2H), 2.27 (m, 1H), 2.9 (s, 1H), 3.16 (dd, 1H, J_1 = 11.4 Hz, J_2 = 6 Hz), 3.61 (m, 3H), 3.8 (m, 1H), 4.2 (m, 1H), 5.3 (q, 1H, J = 6.6 Hz), 5.36 (d, 1H, J = 4.8 Hz), 7.0 (m, 2H), 7.35 (s, 1H), 7.82 (d, 1H, J = 7.5 Hz); ^{13}C NMR (75.5 MHz, CD_3OD) δ 11.5, 26.3, 28.2, 42.6, 50.1, 55.7, 58.7, 61.1, 67.4, 110.2, 110.6, 114.1, 118.6, 119.7, 120.8, 125.1, 136.3, 136.9, 139.1; HRMS (ESI) m/z calcd for $C_{19}H_{23}N_2O_2$ $(M + H)^+$: 311.1760; found: 311.1748

■ ASSOCIATED CONTENT

Supporting Information

Spectral data for all new compounds including X-ray data for **9** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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