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

Sundari K. Rallapalli, † Ojas A. Namjoshi, † V. V. N. Phani Babu Tiruveedhula, † Jeffrey R. Deschamps, ‡ and James M. Cook,* ‡

†Department of Chemistry & Biochemistry, University of Wisconsin-Milwaukee, Milwaukee, Wisconsin 53201, United States
‡Center for Biomolecular Science and Engineering, Naval Research Laboratory, Code 6930, Washington, DC 20375, United States


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 system1 2 with established stereochemistry at C-3 (α), C-5 (R), and C-15 (R).2 The alkaloid ervindicidine (Figure 1), isolated from the epigal part of Vinca erecta Rgl. et Schmalh.,3 4 has the C-3 (α), 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 Lounasmaa2 3 5 nor was the location of the hydroxymethyl at the C-16 group unequivocally established. Yunusov et al.,3 4 who isolated this alkaloid, had reported the structure of ervindicidine 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 ervindicidine by Glasby1 and Lounasmaa et al.,2 3 the hydroxymethyl group at C-16 was assigned the α stereochemistry, while, according to Yunusov et al.,3 4 the hydroxymethyl group at C-16 was proposed to have the β stereochemistry. The stereochemistry and the structure of ervindicidine 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 literature3 4 was the optical rotation of the isolated indole alkaloid ervindicidine (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 ervindicidine and correction of the stereochemical ambiguity reported in the literature.2 3 4 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.

Figure 1. The indole alkaloid ervindicidine.
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). The aldehyde function of 5 was then reduced with sodium borohydride to provide the alcohol nor-nornacusine B (6), the spectral data of which are in complete agreement with that of the natural product. The C-17 functionalized alcohol was then protected as the triisopropylsilyl ether employing 2,6-lutidine as the base to provide the ether. 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 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 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. The stereochemistry of 2 was confirmed using single-crystal X-ray structural analysis.

The optical rotation of this diastereomer 2 was determined to be [α]D +79° (c 0.6, MeOH), which was not in agreement with the value reported in the literature. Hence, the diastereomer 2 was stirred in 0.2 N HCl at 0 °C. Examination by TLC (silica gel; CH2Cl2:MeOH 9:1) indicated a new component at a lower Rf 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., pentacyclic ketone 4 was treated with triphenylphosphonium bromide in benzene in the presence of potassium tert-butoxide to provide diene 10 in 90% yield (Scheme 2). 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, 9-BBN was chosen as the hydroboration agent. This was carried out under the standard conditions with the Kabalka borate work up procedure to prohibit Nb-oxidation. This was a key process because Nb-oxidation oftentimes complicates this oxidation with H2O2.
The synthesis of TIPS derivative 12 was executed analogous to the previous preparation 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 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 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 (\([\alpha]_D^{26} +29.00^\circ (c 0.6, \text{MeOH})\) was in excellent agreement with that reported in the literature (\([\alpha]_D^{26} +29.5^\circ (c 0.6, \text{MeOH})\)), 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. 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 with the C-6 carbonyl oxygen atom as well as the Nb 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 \([\alpha]_D^{26} +17.00^\circ (c 0.6, \text{MeOH})\) and was not in agreement with that reported in the literature for 3. It appears that 9-BBN complexed with the Nb-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 the 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 H2O2, as expected in this series. The IBX-mediated oxidation and the Luche reduction afforded the stereospecific total synthesis of ervincidine 3. Another...
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 book1 and Lounasmaa et al.’s review2 and clarifies the work of Yunusov et al. as well as providing the correct absolute configuration of the C-6 hydroxyl function in eviscindine 3,4.

**EXPERIMENTAL SECTION**

**IBX-Mediated Oxidation To Provide (6S,11S,11aR,E)-9-Ethylidene-11-(trisopropylsilyloxy)methyl-6,8,9,10,11,11a-hexahydro-6,10-methanoindolo[3,2-b]quinoliniz-12(5H)-one (8).** To a solution of trisopropylsilyl ether 7 (100 mg, 0.22 mmol) in EtOAc/DMSO (10 mL/5 mL) was added IBX (0.552 g, 3.88 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 NaNHCO3 (4 mL), followed by treatment with a saturated solution of aq Na2SO4 (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 (K2CO3). The solvent was removed under reduced pressure to provide the crude oil, which was purified by flash chromatography [silica gel, hexane:EtOAc:1 (1:1)] to provide the benzylic ketone 8 (87 mg, 85%).1 H NMR (300 MHz, CDCl3) δ 6.04 (s, 2H), 1.66 (d, 3H, J = 6.3 Hz), 1.82 (d, 1H, J = 6.3 Hz), 2.13 (t, 1H, J = 9.9 Hz), 2.86 (d, 1H, J = 7.7 Hz), 3.17 (s, 1H), 3.5 (m, 3H), 3.8 (dd, 1H, J = 9.6 Hz, J = 4.2 Hz), 4.2 (d, 1H, J = 8.4 Hz), 5.4 (q, 1H, J = 7.7 Hz), 7.14 (m, 3H), 8.07 (d, 1H, J = 7.2 Hz), 9.03 (br, 1H).13C NMR (75.5 MHz, CDCl3) δ 11.9, 12.9, 18.0, 29.7, 32.5, 42.6, 50.5, 54.8, 63.9, 64.9, 106.5, 111.6, 118.5, 121.6, 122.7, 123.6, 124.5, 123.6, 154.7, 192.0. HRMS (ESI) m/z calcd for C34H34NO18S (M + H)+ 637.2196; found: 637.2126. This material was used directly in a later step.

**Synthesis of (6S,11S,11aR,E)-9-Ethylidene-11-(hydroxyethyl)-6,8,9,10,11,11a-hexahydro-6,10-methanoindolo[3,2-b]quinoliniz-12(5H)-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 30°C. 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 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 (Na2SO4). After removal of the solvent under reduced pressure, the residue was purified by flash chromatography [EtOAc:hexane (4:1)] to provide the target mono 9 (11 mg, 85%).1 H NMR (300 MHz, CDOD) δ 0.68 (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, 4H), 4.35 (dd, 1H, J = 9 Hz, J = 3 Hz), 5.55 (q, 1H, J = 7.5 Hz), 7.25 (m, 2H), 7.43 (d, 1H, J = 7 Hz), 7.08 (d, 1H, J = 8.4 Hz).13C NMR (75.5 MHz, CDOD) δ 11.6, 19.3, 29.2, 42.6, 50.4, 54.3, 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 C29H27N2O11 (M + H)+ 539.1823; found: 539.1794. This material was used directly in a later step.

**Preparation of (6S,11R,11aR,12R)-9-Ethylidene-11-(hydroxymethyl)-6,8,9,10,11,11a,12-octahydro-6,10-methanoindolo[3,2-b]quinoliniz-12(5H)-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 NaNHCO3 (4 mL), followed by treatment with a saturated solution of aq Na2SO4 (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 (K2CO3). 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, CDOD) δ 1.66 (d, 3H, J = 6 Hz), 1.9 (m, 1H), 2.36 (m, 1H), 3.6 (m, 3H), 4.0...
(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, CD3OD) $\delta$ 11.1, 34.4, 38.5, 50.1, 54.4, 67.4, 105.9, 106.2, 124.3, 128.6, 131.6, 131.7, 132.4, 135.7, 136.7, 145.1, 155.9, 190.2; HRMS (ESI) m/z calcd for C19H19N2O (M + H)$^+$: 291.1497; found: 291.1513. This material was employed directly in the next step.

Preparation of (65,115,116R,125S,-)-9-Ethylidene-11-(hydroxymethyl)-5,6,8,9,10,11,14,12-octahydro-6,10-methanoindolo[3,2-b]quinolinizin-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, 0.344 mmol) dropwise, at 0 °C. The reaction mixture was then cooled to 0 °C, and NaBO3·4H2O (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 CH2Cl2 (50 mL), washed with H2O (3 × 50 mL) as well as brine (50 mL), and dried (K2CO3). The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, CH2Cl2/MeOH; 9:1) to provide alcohol 3$′$ (75.5 MHz, CD3OD) $\delta$ 5.36 (d, 1H, $\nu$ = 4.8 Hz), 7.0 (m, 2H), 7.35 (s, 1H), 7.82 (d, 1H, $\nu$ = 6 Hz), 1.8 (m, 3H), 1.92 ($\nu$ = 2 Hz), 5.39 (q, 1H, $\nu$ = 6.6 Hz), 1.8 (m, 3H), 1.92 (m, 2H), 2.27 (m, 1H), 2.9 (s, 1H), 3.16 (dd, 1H, $\nu_{11}$ = 11.4 Hz, $\nu_{12}$ = 6 Hz), 3.61 (m, 3H), 3.8 (m, 1H), 4.2 (m, 1H), 5.3 (q, 1H, $\nu$ = 6.6 Hz), 5.36 (d, 1H, $\nu$ = 4.8 Hz), 7.0 (m, 2H), 7.35 (s, 1H), 7.82 (d, 1H, $\nu$ = 7.5 Hz); $^{13}$C NMR (75.5 MHz, CD3OD) $\delta$ 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, 190.2; HRMS (ESI) m/z calcd for C19H23N2O2 (M + H)$^+$: 298.1513. This material was employed directly in the next step.

**REFERENCES**

(16) ORTEP view of the crystal structure of 2. CCDC 942158 (2) and CCDC 965610 (9) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(18) Yin, W.; Ma, J.; Rivas, F. M.; Cook, J. M. Org. Lett. 2007, 9, 295–298.