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A Formal Total Synthesis of (±)-Kopsihainanine A Using a Raney-Cobalt Mediated Reductive Cyclization Route to Polyhydroquinolines

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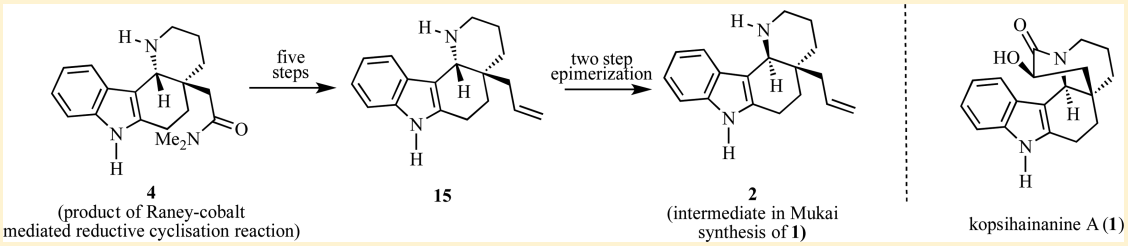
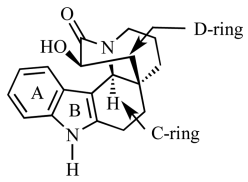
Supporting Information



ABSTRACT: Perhydroquinoline **4**, the product of a Raney-cobalt mediated reductive cyclization reaction, was readily converted into the *cis*-ring-fused perhydroquinoline **15** that could be epimerized to its *trans*-fused counterpart **2** on sequential treatment with iodosylbenzene then sodium borohydride. Tetracycle **2** is an advanced intermediate associated with a recently reported total synthesis of the alkaloid kopsihainanine A (**1**).

In 2011 Gao and co-workers reported[1] the isolation and structural elucidation of certain secondary metabolites produced by *Kopsia hainanensis*, an evergreen tree found in the Hainan Province of China and used in traditional medicine for treating dropsy, tonsillitis, rheumatoid arthritis, and pharyngitis. Extensive NMR analyses revealed that one of these metabolites was the monoterpene indole alkaloid kopsihainanine A (**1**) (Figure 1) that possesses an "un-



1

Figure 1. Structure of the alkaloid kopsihainanine A (**1**).

precedented 6/5/6/6/6 pentacyclic" framework. While this compound showed inhibitory activity against acetylcholine esterase (AChE) (IC_{50} 38.5 μM) further pharmacological evaluation was precluded because of the limited amount of material available from the natural source.

The novel, cage-like structure of kopsihainanine A (**1**) together with its tantalizing biological properties has served to make it an interesting synthetic target. In 2012 She and co-workers described[2] the first total synthesis of the racemic modification of this alkaloid. A key aspect of their work was the formation of an α,α-disubstituted carbazolone and the engagement of this in a reductive cyclization reaction that established the perhydroquinoline or CD-ring system of the target. An intramolecular *N*-alkylation reaction involving an angular γ-hydroxypropyl group located at the CD-ring junction then provided the required pentacyclic framework. In 2013 groups lead by Lupton[3] and Shao[4] detailed, in back-to-back papers, palladium-catalyzed and enantioselective decarboxylative allylation reactions of carbazolones that enabled them to establish total syntheses of the natural or (+)-form of alkaloid **1**. The following year the Zhu group reported[5] a total synthesis of (±)-kopsihainanine A using, as a key step, a novel dehydrative cyclization of a spirocyclic system that afforded the pentacyclic framework of the target compound in a remarkably direct manner. Mukai's total synthesis of (+)-kopsihainanine A[6] was similar to those of Lupton and Shao insofar as Stoltz's enantioselective asymmetric allylation reaction was again employed. In this instance, however, a δ-lactam served as the "substrate" for such a process, the product of which contained a pendant indole residue that could be engaged in a Bischler–Napieralski (BN) cyclization reaction. This afforded the tetracyclic ABCD-ring system of the target in which an angular allyl group was located at the *trans*-fused CD-ring junction. The latest synthesis of (+)-kopsihainanine A is due to Jia[7] and resembles that of Mukai in that an α,α-disbustituted δ-lactam bearing a pendant indole was subjected to a modified BN cyclization reaction.

Our recent synthetic studies on the application of tandem reductive cyclization reactions to the construction of polycyclic indole alkaloids[8] prompted us to examine modifications of these that might permit the assembly of the pentacyclic ring system of kopsihainanine A. Herein we report the successful application of this type of process to the synthesis of the racemic modification of compound **2** (Figure 2), an advanced

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intermediate in the Mukai synthesis of the title alkaloid and so representing a formal total synthesis of (±)-kopsihainanine A.

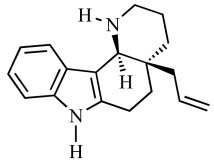

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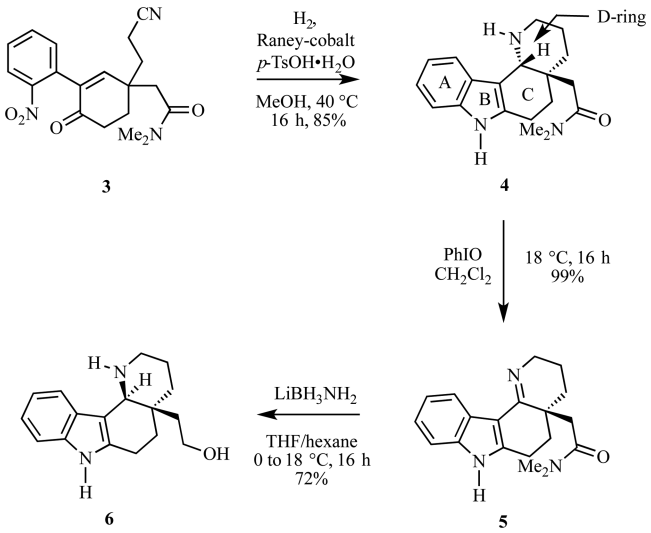
Figure 2. Amine **2**, an advanced intermediate in Mukai's synthesis of alkaloid **1** and the target of the present study.

In 2012, and as a pivotal step in a synthesis of the *Aspidosperma* alkaloid limaspermidine, we showed[8c] that compound **3** reacts with dihydrogen in the presence of Raney cobalt[9] (Scheme 1) to give, via a tandem reductive cyclization

Scheme 1. Synthesis of the *trans*-Ring-Fused Perhydroquinoline 6 from the *cis*-Ring-Fused Precursor 4



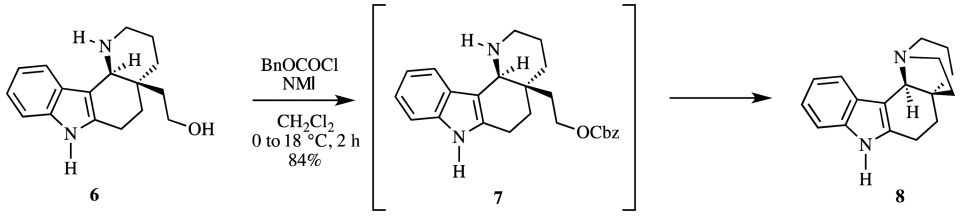
reaction, the pentacyclic product **4** (85%) in which there is *cis*-fusion between the associated C- and D-rings. This ring-junction stereochemistry was the only one ever observed in such processes—*viz.* the corresponding *trans*-ring fused isomer was never detected, even in trace amounts. Accordingly, and as was necessary if this chemistry were to be adapted to the synthesis of compounds such as kopsihainanine A, we sought to identify means by which to invert the configuration at the CD-ring junction carbon bearing nitrogen. Ultimately, this proved to be a straightforward matter and simply involved initial oxidation of amine **4** to the corresponding imine **5** (99%) using iodosylbenzene.[10] In a second step, exhaustive reduction of compound **5** with lithium amidoborohydride ($LiBH_3NH_2$)[11] proceeded smoothly to give the amino-alcohol **6** (72%) in which the associated C- and D-rings are now *trans*-fused to one another. The structures of compounds **5** and **6** follow from single-crystal X-ray analyses of each of them (see Experimental Section and Supporting Information (SI) for details).

The reaction sequence shown in Scheme 1 provides a very straightforward means for converting a *cis*-ring-fused polyhydroquinoline into the corresponding *trans*-form. This inversion of stereochemistry also resulted in the nonindolic nitrogen being brought into close proximity to the angular *β*-hydroxyethyl group. As a consequence, when efforts were made (Scheme 2) to protect this nitrogen as the corresponding benzylcarbamate (using benzyl chloroformate in the presence of *N*-methylimidazole, NMI), the carbonate **7** was formed instead and this then cyclized, in a 5-*exo*-tet process, to give the pentacyclic compound **8** in 84% yield. The formation of this product, the structure of which was confirmed by single-crystal X-ray analysis (see Experimental Section and SI for details), clearly indicates that transannular processes can interfere with the manipulation of an angularly located side chain contained within a *trans*-ring-fused perhydroquinoline. Accordingly, the necessary inversion of configuration at the ring-junction carbon bearing nitrogen within derivatives of the *cis*-ring fused perhydroquinoline **4** was postponed until the very end of the reaction sequence.

The reaction sequence leading to the *cis*-isomer of compound **2** (i.e. compound **15**) is shown in Scheme 3 and started with the reduction of amide **4** to the corresponding alcohol **9** (89%) using $LiEt_3BH$. The piperidine ring nitrogen within the latter compound could be selectively protected as the corresponding *tert*-butylcarbamate **10** (87%) under standard conditions, and this was then subjected to oxidation with pyridinium chlorochromate (PCC). Surprisingly, both the anticipated aldehyde **11** (49%) and its over oxidized counterpart **12** (21%) were obtained.[12] The cited yields of compounds **11** and **12** were determined through analysis of the relevant signals in the ^1H and ^{13}C NMR spectra of the mixture.

Since products **11** and **12** could not be readily separated from one another on a preparative scale, the mixture of the two was subject to a Wittig olefination reaction and the corresponding terminal olefins **13** (38%) and **14** (25%) were thus obtained. While these products could be separated chromatographically for the purposes of characterization, at the preparative scale it was operationally much more convenient to commit the mixture to the final step of the reaction sequence. Thus, treatment of these product olefins with trifluoroacetic acid resulted in cleavage of the associated Boc-groups and the formation of the corresponding free piperidines **15** (quant) and **16** (52%), respectively. These could be readily separated chromatographically.

Scheme 2. Transannular Cyclization of an Activated Form, 7, of Alcohol 6 Leading to 3°-Amine 8



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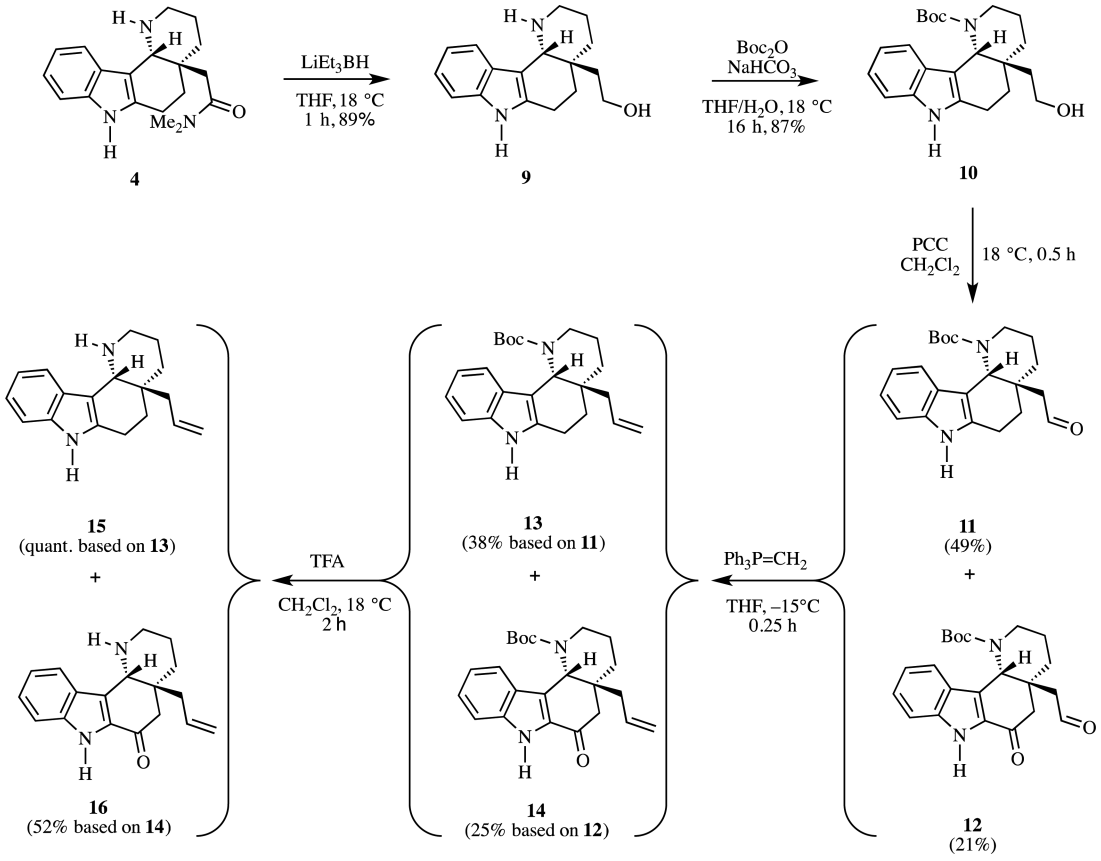
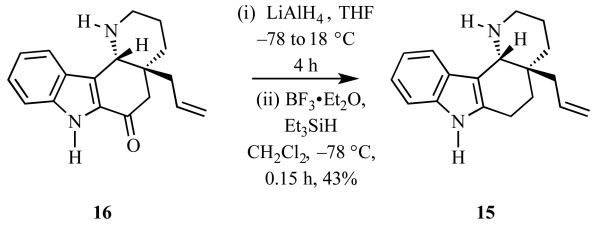
Scheme 3. Synthesis of Amine 15, the Epimer of Target 2, from the Reductive Cyclization Product 4



As shown in Scheme 4, ketone **16** could be converted into/"recycled" to congener **15** (43%) by successive treatment of the former compound with lithium aluminum hydride and then a mixture of boron trifluoride diethyl etherate and triethylsilane.[13] All the spectral data recorded on amine **15** matched those reported[14] by Shao and co-workers who prepared this compound during the course of their efforts to synthesize the alkaloid limaspermidine.

Scheme 4. "Recycling" of Ketone 16 through Reductive Deoxygenation–Formation of Compound 15



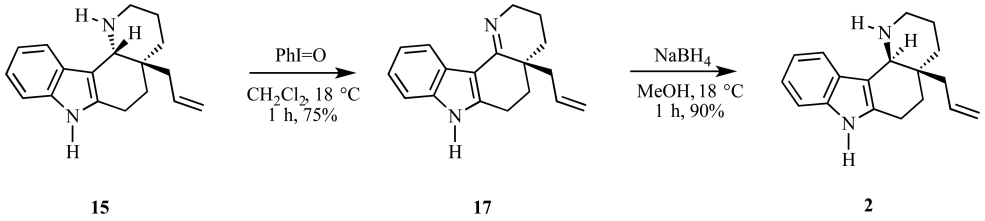
The completion of the synthesis of amine **2** proved to be a straightforward matter. Thus, as shown in Scheme 5, compound **15** was treated with iodosylbenzene so as to form imine **17** (75%) and the latter was then reduced with sodium borohydride. By such means target **2** was obtained in 90% yield (from **17**), and the spectral data acquired on this material proved an excellent match with those reported[6] by Mukai and co-workers.

While the reaction sequence leading to compound **2** is longer than that described by Mukai, it does highlight the capacity to produce both *cis*- and *trans*-ring-fused perhydroquinolines by generating the former systems using our Raney-cobalt-mediated reductive cyclization methodology and then epimerizing these to the latter using the redox "shunt" described here.

EXPERIMENTAL SECTION

General Protocols. Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$

Scheme 5. Conversion of the *cis*-Ring-Fused Perhydroquinoline 15 into Its *trans*-Isomer 2



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"triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. ^{1}H NMR data are presented as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. Infrared spectra (ν_{max}) were recorded on an FTIR spectrometer. Samples were analyzed as thin films on KBr plates. Low-resolution ESI mass spectra were recorded on a single quadrupole mass spectrometer interfaced with a liquid chromatograph, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (conc.)/water (37.5 g/7.5 g/37.5 g/720 mL), potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g/20 g/5 mL/300 mL), and *p*-anisaldehyde or vanillin/sulfuric acid (conc.)/ethanol (15 g/2.5 mL/250 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[16] with silica gel 60 (40−63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents, drying agents, and other inorganic salts were generally commercially available and were used as supplied. Tetrahydrofuran (THF), methanol, and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[17] Where necessary, reactions were performed under a nitrogen atmosphere.

Specific Chemical Transformations. *rac-2-(2,3,4,5,6,7-Hexahydro-4aH-pyrido[3,2-c]carbazol-4a-yl)-N,N-dimethylacetamide (**5**).* A magnetically stirred solution of amide **4**[8c] (200 mg, 0.64 mmol) in dry dichloromethane (5 mL) maintained under a nitrogen atmosphere was treated with freshly prepared iodosylbenzene (71 mg, 0.32 mmol). The resulting solution was stirred at 18 °C for 16 h and then filtered through a pad of diatomaceous earth, and the filtrate was concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1.5:8.5 v/v ammonia-saturated methanol/dichloromethane elution) to afford, after concentration of the relevant fractions (R_f = 0.3 in 1:9 v/v ammonia-saturated methanol/dichloromethane), compound **5** (196 mg, 99%) as a white, crystalline solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.95 (dd, J = 7.6 and 0.8 Hz, 1H), 7.31 (dd, J = 7.6 and 0.8 Hz, 1H), 7.20−7.05 (complex m, 2H), 3.86 (m, 1H), 3.69−3.58 (complex m, 1H), 3.14−3.03 (complex m, 1H), 2.91 (s, 3H), 2.89 (m, 1H), 2.84 (s, 3H), 2.80 (d, J = 15.9 Hz, 1H), 2.56 (ddd, J = 13.5, 5.3, and 1.6 Hz, 1H), 2.49 (d, J = 15.9 Hz, 1H), 2.27 (m, 1H), 1.94−1.84 (complex m, 2H), 1.78−1.69 (complex m, 1H), 1.55 (m, 1H) (signal due to NH group proton not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 173.0, 170.9, 145.5, 139.2, 126.4, 123.2, 121.6, 121.5, 112.3, 110.6, 39.3, 38.3, 36.4, 36.2, 35.9, 32.0, 21.5, 20.0 (one signal obscured or overlapping); IR υ_{max} 3246, 2929, 1622, 1471, 1454, 1395, 1330, 746 cm^{-1}; MS (ESI, +ve) m/z 310 [(M + H)$^+$, 100%]; HRMS (M + H)$^+$ calcd for $C_{19}H_{24}N_3O$ 310.1919, found 310.1919.

*rac-2-((4aR,11cS)-1,2,3,4,5,6,7,11c-Octahydro-4aH-pyrido[3,2-c]carbazol-4a-yl)ethan-1-ol (**6**).* A magnetically stirred mixture of diisopropylamine (723 μL, 5.16 mmol) in dry THF (3 mL) maintained under a nitrogen atmosphere at −78 °C was treated with *n*-butyllithium (3.2 mL of a 1.6 M solution in hexanes, 5.09 mmol). After 0.2 h the reaction mixture was warmed to 0 °C and stirred at this temperature for a further 0.2 h and then treated, in one portion, with the borane−ammonia complex (158 mg, 5.09 mmol). The resulting suspension was stirred at 0 °C for 0.25 h and then at 18 °C for the same period before being recooled to 0 °C and then treated, dropwise, with a solution of compound **5** (105 mg, 0.34 mmol) in dry THF (1 mL followed by a 1 mL rinse). The reaction mixture thus obtained was allowed to stir at 18 °C for 16 h and then cooled to 0 °C and quenched with HCl (5 mL of a 3 M aqueous solution). After 0.5 h the aqueous layer was separated and extracted with ethyl acetate (4 × 4 mL). Sufficient sodium hydroxide was added to the aqueous layer at 0 °C so as to achieve a pH > 7, and the resulting solution was then extracted with ethyl acetate (4 × 4 mL) and dichloromethane (4 × 4 mL). The combined organic layers were dried ($MgSO_4$), filtered, and then concentrated under reduced pressure. Subjection of the resulting pale-yellow oil to flash chromatography (silica, 1:9 v/v ammonia-saturated methanol/dichloromethane) afforded, after concentration of the relevant fractions (R_f = 0.5), compound **6** (66 mg, 72%) as a white, crystalline solid: mp = 180 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.70 (d, J = 8.2 Hz, 1H), 7.22 (d, J = 8.2 Hz, 1H), 6.97 (m, 1H), 6.90 (m, 1H), 3.86 (s, 1H), 3.73−3.57 (complex m, 2H), 3.25 (m, 1H), 2.90−2.80 (complex m, 2H), 2.70 (dd, J = 17.3 and 6.5 Hz, 1H), 2.00−1.79 (complex m, 4H), 1.60−1.45 (complex m, 3H), 1.25 (m, 2H) (signals due to NH and OH group protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 138.0, 134.9, 127.9, 121.0, 120.2, 119.4, 111.5, 110.2, 65.9, 59.6, 48.1, 36.8, 35.2, 33.9, 28.7, 22.9, 21.2; IR υ_{max} 3384, 3269, 2918, 2851, 1463, 1326, 1049, 740 cm^{-1}; MS (ESI, +ve) m/z 271 [(M + H)$^+$, 100%]; HRMS (M + H)$^+$ calcd for $C_{17}H_{23}N_2O$ 271.1810, found 271.1809.

*rac-(1R,4aR)-3,4,5,6,7,11c-Hexahydro-2H-1,4a-ethanopyrido[3,2-c]carbazole (**8**).* A magnetically stirred solution of compound **6** (44 mg, 0.16 mmol), triethylamine (100 μL), and NMI (28 mg, 0.18 mmol) in dichloromethane (3 mL) maintained at 0 °C under a nitrogen atmosphere was treated, dropwise, with benzyl chloroformate (26 μL, 0.18 mmol). The resulting mixture was allowed to warm to 18 °C over 2 h after which time it was concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:9 v/v ammonia-saturated methanol/dichloromethane elution) to afford, after concentration of the relevant fractions (R_f = 0.5 in 1.5:8.5 v/v ammonia-saturated methanol/dichloromethane), compound **8** (34 mg, 84%) as a white, crystalline solid: mp = 218 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.67 (d, J = 8.1 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 7.02 (m, 1H), 6.94 (m, 1H), 3.90 (s, 1H), 3.20−2.75 (complex m, 4H), 2.74−2.60 (complex m, 2H), 2.00 (m, 1H), 1.90−1.75 (complex m, 3H), 1.68 (m, 1H), 1.60−1.50 (complex m, 3H) (signal due to NH group proton not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 138.2, 136.6, 127.9, 121.8, 120.0, 119.5, 111.4, 109.0, 70.8, 56.6, 51.4, 43.9, 39.5, 31.2, 30.4, 21.3, 20.4; IR υ_{max} 2931, 2866, 2847, 1466, 1452, 1323, 1007, 867, 745 cm^{-1}; MS (ESI, +ve) m/z 253 [(M + H)$^+$, 100%]; HRMS (M + H)$^+$ calcd for $C_{17}H_{21}N_2$ 253.1705, found 253.1706.

*rac-2-((4aR,11cR)-1,2,3,4,5,6,7,11c-Octahydro-4aH-pyrido[3,2-c]carbazol-4a-yl)ethan-1-ol (**9**).* A magnetically stirred solution of amide **4** (1.00 g, 3.21 mmol) in dry THF (5 mL) maintained at 18 °C under a nitrogen atmosphere was treated, dropwise, with $LiEt_3BH$ (16 mL of a 1.0 M solution in THF, 16.03 mmol). After 1 h the reaction mixture was quenched with methanol (15 mL) and then concentrated under reduced pressure. Subjection of the yellow oil thus obtained to flash chromatography (silica, 2:8 v/v ammonia-saturated methanol/dichloromethane elution) afforded, after concentration of the relevant fractions (R_f = 0.3 in 1:9 v/v ammonia-saturated methanol/dichloromethane), compound **9** (770 mg, 89%) as a clear, yellow oil: ^{1}H NMR (400 MHz, CD_3OD) δ 7.53 (d, J = 7.9 Hz, 1H), 7.24 (d, J = 7.9 Hz, 1H), 7.01 (m, 1H), 6.97 (m, 1H), 3.70−3.60 (complex m, 3H), 2.95 (m, 1H), 2.84−2.66 (complex m, 3H), 2.50−2.39 (complex m, 1H), 1.80 (m, 1H), 1.74−1.60 (complex m, 3H), 1.55−1.41 (complex m, 2H), 1.33 (m, 1H) (signals due to the NH and OH group protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 138.1, 135.7, 128.4, 121.6, 119.7, 118.3, 111.5, 59.1, 57.4, 46.8, 40.9, 36.4, 35.4, 25.7, 22.9, 21.0 (one signal obscured or overlapping); IR υ_{max} 3400, 2935, 1623, 1467, 1433, 1329, 1265, 1037, 1011, 741, 702 cm^{-1}; MS (ESI, +ve) m/z 271 [(M + H)$^+$, 100%]; HRMS (M + H)$^+$ calcd for $C_{17}H_{23}N_2O$ 271.1810, found 271.1810.

*tert-Butyl rac-(4aR,11cR)-4a-(2-Hydroxyethyl)-2,3,4,4a,5,6,7,11c-octahydro-1H-pyrido[3,2-c]carbazole-1-carboxylate (**10**).* A magnetically stirred solution of compound **9** (423 mg, 1.57 mmol) in THF/water (18 mL of a 1:1 v/v mixture) maintained at 18 °C was treated with $NaHCO_3$ (657 mg, 7.82 mmol) and Boc_2O (1.03 g, 4.69 mmol). The ensuing and turbid mixture was stirred at 18 °C for 16 h and then diluted with water (30 mL) before being extracted with ethyl

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acetate (3 × 20 mL). The combined organic layers were washed with brine (1 × 40 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give compound **10** (504 mg, 87%) as a pale-yellow solid: mp = 207 °C. This material was used, without purification, in the next step of the reaction sequence.

A small sample of the above-mentioned pale-yellow solid was subjected to flash chromatography (silica, 1:9 v/v methanol/dichloromethane), and after concentration of the relevant fractions (R_f = 0.5) material suitable for spectroscopic characterization was obtained: ^{1}H NMR (400 MHz, CD_3OD) δ (mixture of rotamers) 7.25 (m, 1H), 7.19 (d, J = 7.2 Hz, 1H), 7.00 (m, 1H), 6.88 (m, 1H), 5.24 (s, 0.4H), 5.22 (s, 0.6H), 3.95 (m, 1H), 3.80−3.63 (complex m, 2H), 2.79 (m, 1H), 2.74−2.64 (complex m, 1H), 2.53−2.33 (complex m, 1H), 1.99−1.65 (complex m, 6H), 1.60 (s, approximately 4H), 1.57 (s, approximately 5H), 1.36−1.21 (complex m, 2H) (signals due to NH and OH group protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ (mixture of rotamers) 157.4(3), 157.3(7), 138.2, 136.2, 135.9, 127.7, 121.7, 119.8, 119.7, 118.9, 118.8, 111.7(2), 111.6(6), 108.1, 81.4, 81.0, 59.1, 57.0, 55.9, 40.7, 39.6, 39.4, 36.5, 33.8, 33.7, 29.0, 28.8, 27.2, 26.9, 22.4, 22.0, 20.3; IR υ_{max} 3280, 2924, 2857, 1661, 1456, 1425, 1365, 1172, 1150, 1015, 744 cm^{-1}; MS (ESI, +ve) m/z 763 [(2 M + Na)$^+$, 100%], 393 [(M + Na)$^+$, 55], 371 [(M + H)$^+$, 28]; HRMS (M + H)$^+$ calcd for $C_{22}H_{31}N_2O_3$ 371.2335, found 371.2335.

*tert-Butyl rac-(4aR,11cR)-4a-(2-Oxoethyl)-2,3,4,4a,5,6,7,11c-octahydro-1H-pyrido[3,2-c]carbazole-1-carboxylate (**11**) and tert-Butyl rac-(4aS,11cR)-6-Oxo-4a-(2-oxoethyl)-2,3,4,4a,5,6,7,11c-octahydro-1H-pyrido[3,2-c]carbazole-1-carboxylate (**12**).* A magnetically stirred solution of alcohol **10** (332 mg, 0.90 mmol) in dry dichloromethane (10 mL) maintained under a nitrogen atmosphere at 18 °C was treated with pyridinium chlorochromate (213 mg, 0.99 mmol). The ensuing deep-brown mixture was stirred for 0.5 h at 18 °C then filtered through a pad of diatomaceous earth, and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.5 in 7:3 v/v ethyl acetate/hexane), a *ca.* 7:3 mixture of compound **11** and its oxo-derivative **12** (232 mg, 70% combined yield) as a clear, bright-yellow oil. This material was used without further purification in the next step of the reaction sequence.

A small portion of this mixture was subjected to further flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution), and after concentration of the relevant fractions (R_f = 0.5 in 7:3 v/v ethyl acetate/hexane) a sample of compound **11** suitable for spectroscopic characterization was obtained as a light-yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (mixture of rotamers) 9.97 (s, 0.6H), 9.95 (s, 0.4H), 8.11 (s, 0.6H), 8.06 (s, 0.4H), 7.33 (m, 1H), 7.28 (m, 1H), 7.12 (m, 1H), 7.03 (m, 1H), 5.51 (s, 0.4H), 5.47 (s, 0.6H), 4.13 (m, 0.6H), 3.97 (m, 0.4H), 2.95−2.76 (complex m, 1H), 2.76−2.41 (complex m, 2H), 2.15−1.66 (complex m, 6H), 1.60 (s, approximately 4H), 1.55 (s, approximately 5H), 1.45−1.29 (complex m, 1H), 1.29−1.17 (complex m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (mixture of rotamers) 203.2, 202.6, 155.5, 155.3, 136.1, 134.0, 133.8, 126.3, 121.4, 121.3, 119.9, 119.6, 118.5, 110.5, 110.4, 108.0, 80.2, 79.7, 77.2, 55.0, 54.0, 49.4, 49.2, 38.1, 36.6, 36.5, 32.8, 32.6, 28.6, 28.5, 27.8, 27.5, 26.6, 20.8, 19.5, 19.4; IR υ_{max} 3389, 3320, 2971, 2930, 2865, 1717, 1682, 1664, 1457, 1422, 1365, 1278, 1169, 1152, 740 cm^{-1}; MS (ESI, +ve) m/z 423 [(M + CH_3OH + Na)$^+$, 100%] 391 [(M + Na)$^+$, 33]; HRMS (M + Na)$^+$ calcd for $C_{22}H_{28}N_2Na\ O_3$ 391.1998, found 391.1998.

A sample of compound **12** suitable for spectroscopic characterization could not be obtained.

*tert-Butyl rac-(4aR,11cR)-4a-Allyl-2,3,4,4a,5,6,7,11c-octahydro-1H-pyrido-[3,2-c]carbazole-1-carboxylate (**13**) and tert-Butyl rac-(4aS,11cR)-4a-Allyl-6-oxo-2,3,4,4a,5,6,7,11c-octahydro-1H-pyrido-[3,2-c]carbazole-1-carboxylate (**14**).* A magnetically stirred suspension of methyltriphenylphosphonium bromide (449 mg, 1.25 mmol) in dry THF (3 mL) maintained under a nitrogen atmosphere at −15 °C was treated with *n*-butyllithium (791 μL of a 1.51 M solution in hexanes, 1.19 mmol). The resulting suspension was stirred at −15 °C for 0.5 h and then treated, dropwise, with a solution of a *ca.* 7:3 mixture of compounds **11** and **12** (220 mg, 0.60 mmol) in dry THF (2 mL). The reaction mixture thus obtained was allowed to stir at −15 °C for 0.25 h then poured into NH_4Cl (10 mL of a saturated aqueous solution) and extracted with ethyl acetate (3 × 5 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure, and the residue thus obtained was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.5 in 4:6 v/v ethyl acetate/hexane), a *ca.* 3:2 mixture of compound **13** and its oxo-derivative **14** (139 mg, 63%) as a clear, yellow oil. This material was used without further purification in the next step of the reaction sequence.

A small sample of the above-mentioned mixture was subjected to further flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.6 in 2:3 v/v ethyl acetate/hexane) afforded compound **13** as a clear, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (mixture of rotamers) 8.08 (s, 0.6H), 8.00 (s, 0.4H), 7.38 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.11 (m, 1H), 7.03 (m, 1H), 6.01−5.79 (complex m, 1H), 5.36 (s, 0.4H), 5.24 (s, 0.6H), 5.18−5.09 (complex m, 2H), 4.11 (broad d, J = 13.2 Hz, 0.6H), 3.93 (broad d, J = 13.3 Hz, 0.4H), 2.84−2.71 (complex m, 1H), 2.71−2.60 (complex m, 1H), 2.55−2.15 (complex m, 3H), 1.85−1.65 (complex m, 5H), 1.61 (s, approximately 4H), 1.57 (s, approximately 5H), 1.38−1.23 (complex m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (mixture of rotamers) 155.6, 155.4, 136.2(2), 136.1(7), 134.5, 134.4, 134.3, 126.6, 126.5, 121.1, 121.0, 119.6, 119.4, 118.7, 117.9(4), 117.8(5), 110.4, 110.3, 108.9, 108.8, 79.8, 79.3, 77.2, 55.0, 53.9, 40.6, 39.5, 38.3, 36.2(4), 36.1(9), 32.2, 28.7, 28.6, 28.3, 26.0, 25.6, 21.1, 20.7, 19.5(8), 19.5(5); IR υ_{max} 3403, 3314, 2975, 2931, 2856, 1686, 1663, 1462, 1426, 1365, 1170, 1152, 1141, 913, 739 cm^{-1}; MS (ESI, +ve) m/z 389 [(M + Na)$^+$, 100%]; HRMS (M + Na)$^+$ calcd for $C_{23}H_{30}N_2NaNO_2$ 389.2205, found 389.2209.

Concentration of fraction B (R_f = 0.5 in 2:3 v/v ethyl acetate/hexane) afforded compound **14** as a clear, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (mixture of rotamers) 9.74 (s, 0.6H), 9.69 (s, 0.4H), 7.59−7.43 (complex m, 2H), 7.35 (m, 1H), 7.11 (m, 1H), 5.99−5.84 (complex m, 1H), 5.88 (s, 0.4H), 5.71 (s, 0.6H), 5.25−5.13 (complex m, 2H), 4.19 (d, J = 13.4 Hz, 0.6H), 4.01 (d, J = 13.4 Hz, 0.4H), 2.83 (m, J = 16.6 Hz, 0.6H), 2.81 (d, J = 16.6 Hz, 0.4H), 2.60−2.45 (complex m, 3H), 2.42−2.29 (complex m, 1H), 1.87−1.71 (complex m, 2H), 1.62 (s, approximately 4H), 1.57 (s, approximately 5H), 1.50−1.39 (complex m, 1H), 1.35−1.22 (complex m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (mixture of rotamers) 189.9, 155.3, 155.2, 138.4, 133.5, 133.3, 130.5, 127.0, 126.8, 125.7, 125.5, 125.1, 121.5, 121.3, 120.9, 119.3, 119.1, 112.9, 112.8, 80.5, 80.1, 77.2, 55.1, 53.9, 48.8, 48.7, 43.2, 43.0, 40.0(2), 39.9(6), 38.7, 28.6(4), 28.5(6), 28.4(9), 28.4(6), 20.8, 20.4; IR υ_{max} 3273, 2976, 2934, 2865, 1689, 1660, 1474, 1419, 1365, 1251, 1173, 1144, 1137, 962, 743 cm^{-1}; MS (ESI, +ve) m/z 403 [(M + Na)$^+$, 100%]; HRMS (M + Na)$^+$ calcd for $C_{23}H_{28}N_2NaO_3$ 403.1998, found 403.1993.

*rac-(4aR,11cR)-4a-Allyl-2,3,4,4a,5,6,7,11c-octahydro-1H-pyrido-[3,2-c]carbazole (**15**) and rac-(4aS,11cR)-4a-Allyl-1,2,3,4,4a,5,7,11c-octahydro-6H-pyrido[3,2-c]carbazol-6-one (**16**).* A magnetically stirred and *ca.* 3:2 mixture of compound **13** and its oxo-derivative **14** (46 mg) in dichloromethane (5 mL) maintained at 22 °C was treated, dropwise, with trifluoroacetic acid (1 mL, 7.2 mmol). The resulting solution was stirred at 18 °C for 2 h after which time sufficient ammonia-saturated methanol was added so as to achieve a pH > 7. The ensuing mixture was concentrated under reduced pressure, and the residue thus obtained was subjected to flash chromatography (silica, 0.5:9.5 to 1:4 v/v ammonia-saturated methanol/ethyl acetate gradient elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.3 in 1:9 v/v ammonia-saturated methanol/ethyl acetate) afforded compound **15**[14] (20 mg, quant.) as a clear, colorless oil: ^{1}H NMR (400 MHz, CD_3OD) δ 7.62 (d, J = 7.5 Hz, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.12 (m, 1H), 7.07 (m, 1H), 5.97−5.80 (complex m, 1H), 5.12 (dd, J = 10.1 and 1.9 Hz, 1H), 4.98 (dd, J = 16.6 and 1.8 Hz, 1H), 4.30 (s, 1H), 3.26 (d, J = 12.8 Hz, 1H), 3.12 (m, 1H), 3.00−2.80 (complex m, 2H), 2.40 (m, 1H), 2.20 (m, 1H),

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2.02 (m, 1H), 1.92−1.78 (complex m, 4H), 1.70−1.60 (complex m, 1H) (signals due to NH group protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 138.1, 136.3, 135.3, 128.0, 122.0, 120.0, 118.4, 118.2, 111.7, 109.5, 56.9, 46.4, 42.7, 36.2, 35.6, 25.5, 21.9, 20.6; IR υ_{max} 3221, 2928, 2848, 1655, 1636, 1618, 1585, 1455, 1329, 1303, 910, 743 cm^{-1}; MS (ESI, +ve) m/z 267 [(M + H)$^+$, 100%]; HRMS (M + H)$^+$ calcd for $C_{18}H_{23}N_2$ 267.1861, found 267.1862.

Concentration of fraction B (R_f = 0.6 in 1:9 v/v ammonia-saturated methanol/ethyl acetate) afforded compound **16** (7 mg, 52%) as a clear, colorless oil: ^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (d, J = 7.4 Hz, 1H), 7.45 (d, J = 7.4 Hz, 1H), 7.34 (m, 1H), 7.14 (m, 1H), 5.85−5.67 (complex m, 1H), 5.01 (d, J = 9.6 Hz, 1H), 4.84 (d, J = 13.3 Hz, 1H), 4.06 (s, 1H), 3.30 (partially obscured d, J = 12.3 Hz, 1H), 3.04 (m, 1H), 2.79 (d, 1H), 2.20 (d, J = 16.8 Hz, 1H), 2.17−2.09 (complex m, 1H), 2.08−1.98 (complex m, 1H), 1.76−1.60 (complex m, 4H) (signals due to NH group protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 192.9, 140.2, 134.4, 131.9, 128.3, 127.8, 126.6, 122.2, 121.6, 119.0, 113.8, 56.5, 46.4, 44.7, 43.5, 41.9, 35.2, 23.0; IR υ_{max} 3271, 2928, 2852, 1649, 1473, 1331, 1254, 1237, 917, 745 cm^{-1}; MS (ESI, +ve) m/z 281 [(M + H)$^+$, 100%]; HRMS (M + H)$^+$ calcd for $C_{18}H_{21}N_2O$ 281.1654, found 281.1658.

Reductive Deoxygenation of Ketone 16: Formation of Compound 15. A magnetically stirred solution of compound **16** (23 mg, 0.08 mmol) in dry THF (2 mL) maintained at −78 °C under a nitrogen atmosphere was treated with $LiAlH_4$ (164 μL of a 1 M solution in THF, 0.16 mmol). The ensuing mixture was stirred at this temperature for 2 h and then allowed to warm to 18 °C, stirred again for a further 2 h before being cooled to 0 °C, and quenched with water (4 mL) (***CAUTION***: hydrogen gas may be generated). The resulting suspension was filtered through a pad of diatomaceous earth, and the filtrate was concentrated under reduced pressure. The residue thus obtained was taken up in dry dichloromethane (2 mL), and the solution so-formed cooled to −78 °C then was treated with boron trifluoride diethyl etherate (12 μL, 0.10 mmol) followed by triethylsilane (1 mL, 6.3 mmol). The resulting mixture was stirred at −78 °C for 0.15 h, warmed to 0 °C, quenched with $NaHCO_3$ (4 mL of a saturated aqueous solution), left to stir for 0.15 h, and then warmed to 18 °C and stirred again at this temperature for an additional 0.33 h before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:9 v/v ammonia-saturated methanol/dichloromethane elution) to afford, after concentration of the relevant fractions (R_f = 0.5), compound **15** (9 mg, 43%) as a clear, pale-yellow oil. The ^{1}H and ^{13}C NMR spectral data acquired on this material were identical, in all respects, with those derived from compound **15** prepared as described above.

*rac-4a-Allyl-3,4,4a,5,6,7-hexahydro-2H-pyrido[3,2-c]carbazole (**17**).* A magnetically stirred solution of compound **15** (23 mg, 0.09 mmol) in dry dichloromethane (3 mL) maintained at 18 °C under a nitrogen atmosphere was treated with freshly prepared iodosylbenzene (95 mg, 0.43 mmol). The ensuing mixture was stirred at 18 °C for 1 h and then filtered through a pad of diatomaceous earth, and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:4 v/v ammonia-saturated methanol/dichloromethane elution) to afford, after concentration of the relevant fractions (R_f = 0.4 in 1.5:8.5 v/v ammonia-saturated methanol/dichloromethane), compound **17** (17 mg, 75%) as a clear, pale-yellow oil: ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 (m, 1H), 7.51 (m, 1H), 7.36 (m, 2H), 6.03−5.80 (complex m, 1H), 5.30 (d, J = 6.6 Hz, 1H), 5.27 (d, J = 10.4 Hz, 1H), 3.92 (dd, J = 15.5 and 6.7 Hz, 1H), 3.81−3.68 (complex m, 1H), 3.27 (partially obscured m, 1H), 3.07 (dd, J = 18.6 and 6.0 Hz, 1H), 2.63 (dd, J = 14.7 and 7.7 Hz, 1H), 2.51 (dd, J = 14.7 and 7.5 Hz, 1H), 2.26−2.17 (complex m, 2H), 2.16−1.96 (complex m, 3H), 1.66 (m, 1H) (signal due to NH group proton not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 178.0, 155.4, 139.2, 132.9, 125.8, 124.6, 124.2, 120.8, 120.5, 113.8, 105.7, 45.2, 39.9, 38.7, 34.1, 28.7, 21.0, 17.3; IR υ_{max} 2923, 2848, 1617, 1472, 1331, 1261, 1193, 1035, 1009, 921, 796, 749 cm^{-1}; MS (ESI, +ve) m/z 265 [(M + H)$^+$, 100%]; HRMS (M + H)$^+$ calcd for $C_{18}H_{21}N_2$ 265.1705, found 265.1706.

*rac-(4aR,11cS)-4a-Allyl-2,3,4,4a,5,6,7,11c-octahydro-1H-pyrido-[3,2-c]carbazole (**2**).* A magnetically stirred solution of compound **17** (10 mg, 0.04 mmol) in methanol (3 mL) maintained at 18 °C was treated with finely ground sodium borohydride (3 mg, 0.08 mmol). After the sodium borohydride had completely dissolved (0.17 h), the clear solution was concentrated under reduced pressure and the residue thus obtained was subjected to flash chromatography (silica, 1:9 v/v methanol/dichloromethane elution). Concentration of the relevant fractions (R_f = 0.5 in 1:9 v/v methanol/dichloromethane) gave compound **2** (9 mg, 90%) as a wax: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.8 Hz, 1H), 7.78 (broad s, 1H), 7.07 (m, 1H), 7.02 (m, 1H), 5.98−5.73 (complex m, 1H), 5.07 (m, 2H), 3.96 (s, 1H), 3.31 (dd, J = 12.9 and 4.9 Hz, 1H), 2.92 (m, 1H), 2.81 (m, 1H), 2.64 (m, 1H), 2.43 (dd, J = 14.6 and 7.3 Hz, 1H), 2.05−1.90 (complex m, 2H), 1.90−1.59 (complex m, 4H), 1.59−1.36 (complex m, 2H), 1.32−1.18 (complex m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ see Table 1 of the SI; IR υ_{max} 3394, 3261, 2923, 2853, 1637, 1636, 1455, 1327, 1243, 1142, 1112, 909, 739 cm^{-1}; MS (ESI, +ve) m/z 267 [(M + H)$^+$, 100%]; HRMS (M + H)$^+$ calcd for $C_{18}H_{23}N_2$ 267.1861, found 267.1869.

Crystallographic Studies. *Crystallographic Data. Compound **5**.* $C_{19}H_{23}N_3O{\cdot}CH_3OH$, M = 341.45, T = 200 K, monoclinic, space group $P2_1/c$, Z = 4, a = 8.3982(1) Å, b = 10.5143(2) Å, c = 20.8016(4) Å; β = 94.8955(10)°; V = 1830.11(5) Å^3, D_x = 1.239 g cm^{-3}, 4173 unique data ($2\theta_{max}$ = 54.8°), R = 0.040 [for 3240 reflections with $I > 2.0\sigma(I)$]; Rw = 0.103 (all data), S = 0.96.

*Compound **6**.* $C_{17}H_{22}N_2O$, M = 270.37, T = 200 K, orthorhombic, space group $Pca2_1$, Z = 4, a = 23.7420(5) Å, b = 7.5924(1) Å, c = 7.8870(2) Å; V = 1421.70(5) Å^3, D_x = 1.263 g cm^{-3}, 1740 unique data ($2\theta_{max}$ = 55°), R = 0.030 [for 1582 reflections with $I > 2.0\sigma(I)$]; Rw = 0.074 (all data), S = 0.99.

*Compound **8**.* $C_{17}H_{20}N_2$, M = 252.36, T = 200 K, monoclinic, space group $P2_1/c$, Z = 4, a = 11.2237(3) Å, b = 10.5952(3) Å, c = 11.5492(2) Å; β = 90.1718(15)°; V = 1373.39(6) Å^3, D_x = 1.220 g cm^{-3}, 3137 unique data ($2\theta_{max}$ = 55°), R = 0.044 [for 2482 reflections with $I > 2.0\sigma(I)$]; Rw = 0.112 (all data), S = 0.98.

Structure Determination. Images were measured on a CCD diffractometer (Mo Kα, graphite monochromator, λ = 0.71073 Å), and data were extracted using the DENZO package.[18] Structure solution was by direct methods (SIR92).[19] The structures of compounds **5**, **6**, and **8** were refined using the CRYSTALS program package.[20] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC Nos. 1482202, 1482203, and 1482204). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01400.

ORTEPs derived from the single-crystal X-ray analyses of compounds **5**, **6**, and **8**; ^{1}H and ^{13}C NMR spectra of compounds **2**, **5**, **6**, **8**−**11**, and **13**−**17** (PDF)

Crystallographic data (CIF, CIF, CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Chen, J.; Chen, J.-J.; Yao, X.; Gao, K. *Org. Biomol. Chem.* **2011**, *9*, 5334.
(2) Jing, P.; Yang, Z.; Zhao, C.; Zheng, H.; Fang, B.; Xie, X.; She, X. *Chem. - Eur. J.* **2012**, *18*, 6729.
(3) (a) Gartshore, C. J.; Lupton, D. W. *Angew. Chem., Int. Ed.* **2013**, *52*, 4113. (b) Gartshore, C. J.; Lupton, D. W. *Aust. J. Chem.* **2013**, *66*, 882.
(4) Li, Z.; Zhang, S.; Wu, S.; Shen, X.; Zou, L.; Wang, F.; Li, X.; Peng, F.; Zhang, H.; Shao, Z. *Angew. Chem., Int. Ed.* **2013**, *52*, 4117.
(5) Wagniéres, O.; Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2014**, *136*, 15102.
(6) Mizutani, M.; Yasuda, S.; Mukai, C. *Chem. Commun.* **2014**, *50*, 5782.
(7) Chen, Z.; Zhou, S.; Jia, Y. *J. Org. Chem.* **2015**, *80*, 12545.
(8) See, for example: (a) Ma, X.; Vo, Y.; Banwell, M. G.; Willis, A. C. *Asian J. Org. Chem.* **2012**, *1*, 160. (b) Reekie, T. A.; Banwell, M. G.; Willis, A. C. *J. Org. Chem.* **2012**, *77*, 10773. (c) Tan, S. H.; Banwell, M. G.; Willis, A. C.; Reekie, T. A. *Org. Lett.* **2012**, *14*, 5621. (d) White, L. V.; Banwell, M. G. *J. Org. Chem.* **2016**, *81*, 1617. (e) Tang, F.; Banwell, M. G.; Willis, A. C. *J. Org. Chem.* **2016**, *81*, 2950. (f) Tang, F.; Banwell, M. G.; Willis, A. C. *J. Org. Chem.* **2016**, DOI: 10.1021/acs.joc.6b01424.
(9) Banwell, M. G.; Jones, M. T.; Reekie, T. A.; Schwartz, B. D.; Tan, S. H.; White, L. V. *Org. Biomol. Chem.* **2014**, *12*, 7433.
(10) Larsen, J.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1213.
(11) Pasumansky, L.; Goralski, C. T.; Singaram, B. *Org. Process Res. Dev.* **2006**, *10*, 959.
(12) We have successfully exploited this unusual oxidation reaction in the synthesis of certain of the uleine alkaloids; see refs 8e and 8f.
(13) For a related reduction sequence, see: Frei, R.; Staedler, D.; Raja, A.; Franke, R.; Sasse, F.; Gerber-Lemaire, S.; Waser, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 13373.
(14) Zhang, S.-X.; Shen, X.-L.; Li, Z.-Q.; Zou, L.-W.; Wang, F.-Q.; Zhang, H.-B.; Shao, Z.-H. *J. Org. Chem.* **2013**, *78*, 11444.
(15) For a closely related reduction, see: Desmaeele, D.; d'Angelo, J. *J. Org. Chem.* **1994**, *59*, 2292.
(16) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(17) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
(18) DENZO–SMN. Otwinowski, Z.; Minor, W. Processing of X-ray diffraction data collected in oscillation mode. In *Methods in Enzymology*, Vol. *276*: *Macromolecular Crystallography, Part A*; Carter, C. W., Jr., Sweet, R. M., Eds.; Academic Press: New York, 1997; pp 307–326.
(19) SIR92. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435.
(20) Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

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