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Total Synthesis of Hapalindoles J and U

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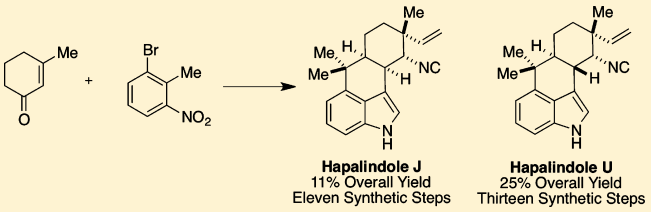
Supporting Information

ABSTRACT: The total synthesis of D,L-hapalindoles J and U has been accomplished. Hapalindole J was prepared in 11% overall yield over 11 synthetic steps and hapalindole U was prepared in 25% overall yield over 13 synthetic steps from commercially available materials. The route employs a novel silyl ether-based strategy for accessing the 6:5:6:6 ring system of the hapalindoles rapidly and in good yields.



INTRODUCTION

The hapalindoles were first isolated in 1984 by Moore and Patterson.[1,2] Since that time, the family has expanded to include 29 members, which comprise both tri- and tetracyclic variants (Figure 1). The tetracyclic hapalindoles differ structurally from

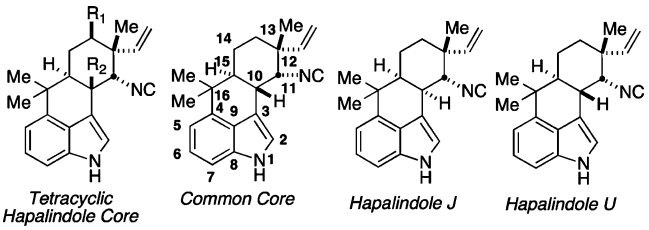


Figure 1. Tetracyclic hapalindoles J and U and ring notation.

their tricyclic counterparts only by the presence of their C4–C16 bond, with absolute configurations remaining otherwise mostly identical. Both hapalindole types contain a quaternary carbon center at C12 and an isonitrile or isothiocyanate at C11. Additionally, both structural types possess a hydrogen or alcohol at C10 (R_2) and a hydrogen or chlorine at C13 (R_1).

To date, a number of the hapalindoles have been conquered by total synthesis, most in racemic form with a few enantioselective reports. Of these syntheses, hapalindoles J and U (Figure 1), isolated in 1986 from the cultured cyanophyte *Hapalosiphon fontinalis*, have been reported both by Natsume (a racemic synthesis) and Baran (hapalindole U; enantioselectively), respectively. Natsume's total synthesis of hapalindole U was accomplished in 20 synthetic steps in an overall yield of 0.2%,[3] and Baran's elegant 9-step enantioselective effort from commercially available material gave 7% overall yield.[4] Natsume, in addition to hapalindole U, also reported the total synthesis of hapalindole J in 0.5% overall yield in 17 synthetic steps.[5] Our interest in these prenylated indole alkaloids is in large measure devoted to studying the biosynthesis of these agents, and to that end, we required an efficient and flexible synthetic strategy that would permit the construction of isotopically labeled putative biosynthetic pathway metabolites. Herein, we report our synthetic routes to D,L-hapalindoles J and U, which is readily amenable for analogues to be synthesized for biosynthetic studies.

We envisioned that hapalindoles J and U could arise from the oxidation of alcohol **1**, followed by reductive amination to afford the allylic amine, formylation of said amine, and subjection to dehydration conditions affording the desired isonitrile (Scheme 1). Tetracycle **1** could be accessed from the ring closure of tricycle **2**, which in turn could arise from the Lewis acid mediated coupling of TMS-enol ether **3** and functionalized indole **4**. Compound **3** could be accessed via alcohol protection and enolization of **6**, which could be formed through a Rubottom oxidation following vinyl cuprate addition to 3-methylcyclohexenone. Functionalized indole **4** could be accessed from 4-bromoindole (**5**).

RESULTS

Our route to α-hydroxy-ketone **6** began by subjecting commercially available 3-methylcyclohexenone (**7**) to Michael conditions utilizing vinyl Grignard, CuBr·Me_2S, TMEDA, and TMSCl to generate TMS-enol ether **8**, as shown in Scheme 2. Cleavage of the TMS-enol ether was accomplished with an acetic acid/water/THF mixture to furnish compound **9**. Subjecting **8** to Rubottom oxidation conditions, according to related literature precedent,[6] failed to give any α-hydroxy-ketone **6a**/**6b** but did afford **9** in 82% yield. For this reaction, the workup involved washing with aqueous saturated $NaHCO_3$ until the aqueous layer became colorless. It is thought that these conditions might not fully remove the copper from the TMS-enol ether species, ultimately contributing to the unsuccessful oxidation with *m*CPBA. Modification of the workup conditions (washing the crude material sequentially with a 0.1 M phosphate buffer at pH 7, followed by 1.0 M EDTA solution) completely removed the copper from the TMS-enol ether. Ensuing treatment of **8** with *m*CPBA,

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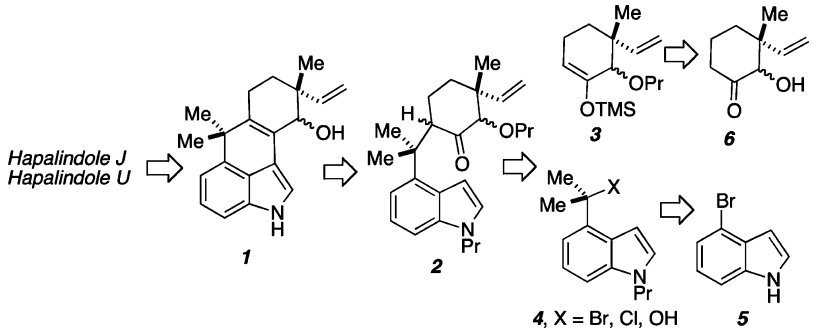
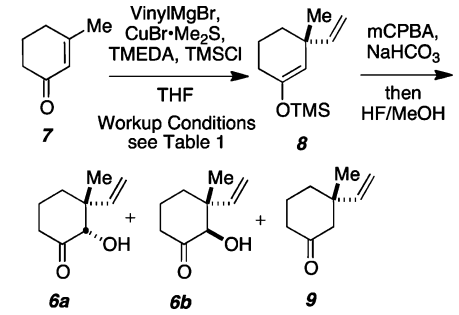
Scheme 1. Retrosynthetic Analysis for Hapalindoles J and U



Scheme 2. Accessing 6a,b via a Rubottom Oxidation

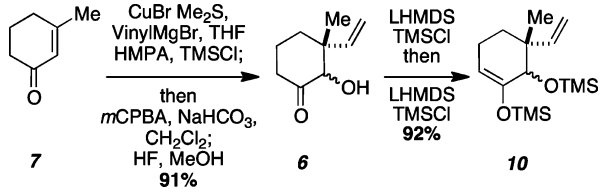


Conditions	Result of 6a:6b:9
$NaHCO_{3(aq)}$	9 (82%)
PO_4^{3-} Buffer/EDTA	6a/6b (89%, 3:1)
PO_4^{3-} Buffer/EDTA (>200 mg)	9 (95%)

followed by TMS cleavage with HF in MeOH, gave a 3:1 diastereomeric mixture of α-hydroxy-ketones **6a**:**6b**. Unfortunately, it was found that the phosphate buffer and EDTA quench conditions only worked reproducibly on scales of up to 200 mg. On larger scales these conditions preferentially cleaved the TMS-enol ether to afford ketone **9**, and further modifications failed to circumvent this result.

Attention was then directed toward modifying the cuprate addition (Scheme 3). Slowly adding CuBr·Me_2S in HMPA to

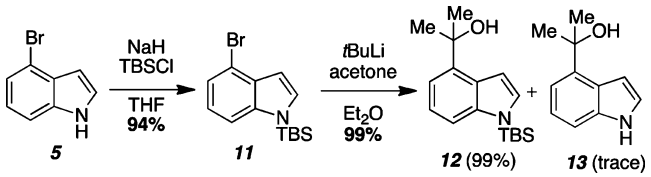
Scheme 3. Multigram Route Accessing 6



vinylmagnesium bromide at −78 °C over 5 min, followed by TMSCl and **7** in THF (1 M) over 30 min, gave the desired TMS-enol ether in excellent yields. Subjecting this substance to Rubottom oxidation conditions then afforded **6** in 91% in one pot (3:1 ratio as in Scheme 2). TMS protection of the secondary alcohol was accomplished with LHMDS and TMSCl; sequential treatment with more LHMDS/TMSCl in one pot then furnished the desired TMS-enol ether **10** in 92%. This route gives multiple grams of product **10**, starting from **7**. Surprisingly, treatment of **6** with more than 2.0 equiv of LHMDS/TMSCl or excess TMSOTf failed to give **10** directly.

Our route to **12** began by converting 2-bromo-6-nitrotoluene (not shown) to indole **5** (also commercially available), in high yield.[7] Treatment of **5** with NaH and TBSCl furnished the *N*-TBS-protected indole **11** (Scheme 4). Subjecting **11** to

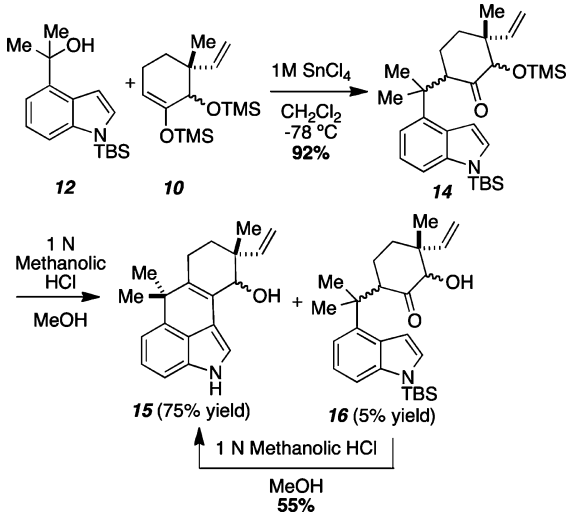
Scheme 4. Synthesis of Various Functionalized Indoles



lithium−halogen exchange conditions followed by addition of acetone furnished **12** in 99% yield with trace amounts of **13** obtained.

Treating a solution of TMS-enol ether **10** and indole **12** in CH_2Cl_2 at −78 °C with a 1 M tin(IV) chloride solution afforded tricycle **14** (Scheme 5). Similar tricycles, with the

Scheme 5. Accessing Allylic Alcohol Tetracycle 15



exception of the α-trimethylsiloxy group, have been closed to their corresponding tetracycles with BF_3·Et_2O with *N*-alkyl indoles.[8] Treating tricycle **14** with BF_3·Et_2O in CH_2Cl_2 failed to give any of the desired tetracycle **15**, but rather only the TBS-deprotected analogue of **16**. Given the lability of *O*/*N*-TBS residues to acidic conditions, several acid-mediated conditions were screened.[9] Treating tricycle **14** with 1 N methanolic HCl (9 equiv) in MeOH afforded the desired tetracycle **15** in 75% yields and tricycle **16** in 5% yields. Tricycle **16** could be converted into tetracycle **15** via treatment with an excess of 1 N

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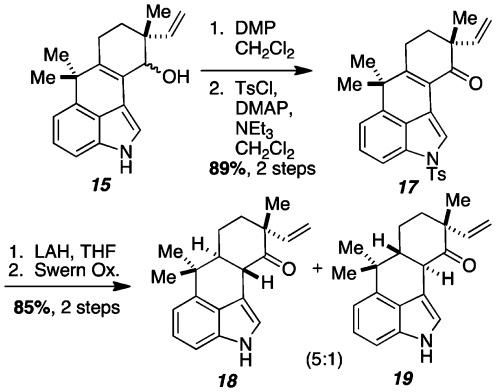
methanolic HCl (40 equiv) in MeOH in 55% yield; the remaining 45% suffering decomposition. The desired allylic hydroxy-tetracycle **15** is thereby accessed in 54% yield over six synthetic steps from commercially available materials.

Oxidation of **15** with Dess–Martin periodionane in CH_2Cl_2 gave the corresponding ketone, which was subsequently treated with TsCl, NEt_3, and catalytic DMAP at reflux to furnish compound **17** in 89% yield over the two synthetic steps (Scheme 6). Treating **17** with LAH in THF over 12 h afforded

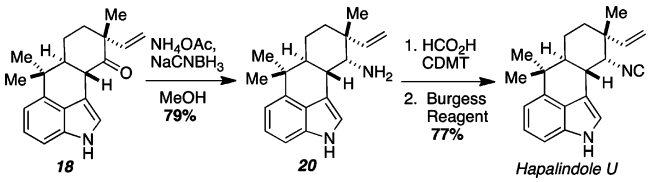
Scheme 6. Elaboration of 15 into Ketone 18



the reduced *cis*-decalin system in a 3:1 ratio favoring the desired isomer, which was then subjected to Swern oxidation conditions to afford *trans*-decalins **18** and **19** (5:1 ratio) in 85% yield. Purification of the oxidized mixture provided the desired isomer **18**, as well as undesired **19**, in 71% and 14% respective yields over two steps from **17**. Isomer **18** was structurally confirmed via ^{1}H NMR comparison to the same intermediate within Baran's hapalindole U route.[4]

Reductive amination of **18** with ammonium acetate and $NaCNBH_3$ in MeOH gave the desired substance **20** in 79% yield, with only a 10% yield of the undesired diastereomer (Scheme 7). Formamide assembly was accomplished by

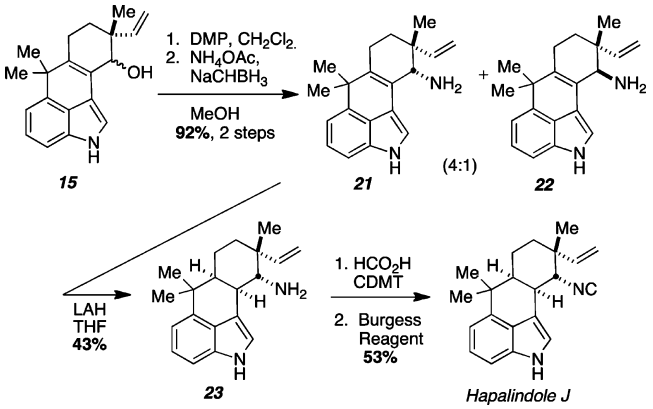
Scheme 7. Accessing Hapalindole U



treating **20** with formic acid, 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), catalytic DMAP, and *N*-methyl-morpholine in CH_2Cl_2.[4] The resulting intermediate (not shown) was subsequently dehydrated with Burgess reagent in benzene to afford hapalindole U in 77% yield from **20** (Scheme 7). Comparison of the ^{1}H and ^{13}C NMR obtained to Baran's and Natasume's spectra of the natural and synthetic product confirmed the total synthesis of hapalindole U.[3−5]

Accessing hapalindole J was accomplished via compound **15** as shown in Scheme 8. Oxidation of allylic alcohol **15** with DMP in CH_2Cl_2 followed by reductive amination with ammonium acetate and $NaCNBH_3$ in MeOH afforded allylic amines **21** and **22** (4:1 ratio) in 92% yield. Purification of the mixture provided the desired isomer **21**, as well as undesired **22**, in 74% and 18% yields, respectively, over the two steps

Scheme 8. Elaboration of 15 into Hapalindole J



from **15**. Isomers **21** and **22** were structurally confirmed via ^{1}H NMR comparison to the same intermediates within Natsume's hapalindole J route.[3,5]

Subjecting allylic amine **21** to reduction conditions with LAH in THF allowed for a face-selective reduction of the tetra-substituted alkene giving access to **23** in 43% yield. Coupling formic acid to **23** was accomplished with CDMT, catalytic DMAP, and *N*-methyl-morpholine in CH_2Cl_2 affording the resulting formamide compound (not shown). Treating the incipient formamide with Burgess reagent in benzene afforded hapalindole J in 53% yield from **23**. Comparison of the ^{1}H and ^{13}C NMR spectra obtained to Natsume's total synthesis spectra confirmed the total synthesis of hapalindole J.[3,5]

■ DISCUSSION

In summary, the total syntheses of D,L-hapalindoles J and U have been accomplished in 11% over 11 synthetic steps and 25% yield over 13 synthetic steps, respectively. The route delineated gaining access to hapalindole J, in this body of work, is six steps shorter, as well as 22-fold higher-yielding, than the route Natsume employed in accessing the compound previously, and to date no other total syntheses have been reported.

From the perspective of the two previous syntheses of hapalindole U, Natsume's racemic synthesis of over 20 steps, with an overall 0.2% yield,[3] and the beautiful enantioselective effort by Baran over nine steps, with an overall 7.5% yield,[4] our work constitutes an efficient approach to the natural product. Although our strategy is similar to that of Natsume's route, it requires eight fewer steps and gives an 80-fold greater yield, mostly due to the greatly enhanced efficiency of accessing the functionalized tetracycle core. Current efforts are being directed toward harnessing this approach to make isotopically labeled biosynthetic intermediates that we are presently investigating in the context of the biogenesis of these substances.

■ EXPERIMENTAL SECTION

^{1}H and ^{13}C spectra were obtained using 300 MHz spectrometer. The chemical shifts are given in parts per million (ppm) relative to TMS at δ 0.00 ppm or to residual $CDCl_3$ δ 7.26 ppm for proton spectra and relative to $CDCl_3$ at δ 77.23 ppm for carbon spectra. IR spectra were recorded on an FT-IR spectrometer as thin films. Mass spectra were obtained using a high/low-resolution magnetic sector mass spectrometer. All melting points are uncorrected. Flash column chromatography was performed with silica gel grade 60 (230–400 mesh). Unless otherwise noted, materials were obtained from commercially available sources and used without further purification.

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Dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), toluene (PhMe), *N*,*N*-dimethylformamide (DMF), acetonitrile (CH_3CN), triethylamine (Et_3N), and methanol (MeOH) were all degassed with argon and passed through a solvent purification system containing alumina or molecular sieves.

***rac*-2-Hydroxy-3-methyl-3-vinylcyclohexanone (6a:6b).** To a 500 mL RBF was added vinylmagnesium bromide (1 M in THF, 106 mL, 105.78 mmol, 1.5 equiv) and cooled to −78 °C to which a solution of CuBr·Me_2S (1.8 g, 7.05 mmol, 0.1 equiv) in HMPA (30 mL, 0.25 M to the CuBr) was added over 10 min and left to stir at the same temperature. After 30 min, a solution of compound (**7**) (8 mL, 70.52 mmol, 1.0 equiv) and TMSCl (18 mL, 141 mmol, 2.0 equiv) in THF (70 mL, 1 M to **7**) was added over 30 min and left to stir at the same temperature. After 3 h NEt_3 (40 mL) was added and allowed to warm to rt, diluted with hexane, washed with H_2O (2 × 100 mL) and once with aqueous NH_4Cl, dried over anhydrous $MgSO_4$, and concentrated to afford crude TMS-enol ether. The product was used without further purification. The crude material (8.55 g, 40.64 mmol, 1.0 equiv) and $NaHCO_3$ (4.1 g, 48.77 mmol, 1.2 equiv) was added to DCM (200 mL) and cooled to 0 °C. A solution of purified *m*CPBA (8.4 g, 48.77 mmol, 1.2 equiv) in DCM (80 mL) was added dropwise via addition funnel, and when complete, the reaction was warmed to rt and stirred for 3 h. The reaction was filtered through a pad of Celite and the filtrate concentrated. The resultant slurry was taken up in pentane and filtered through a pad of Celite to remove the solids and the filtrate was concentrated. The crude material was dissolved in MeOH (100 mL) to which 48% aq HF (2.95 mL, 81.28 mmol, 2.0 equiv) was added and left to stir for 2 h. Neutralization of the reaction was accomplished by adding saturated $NaHCO_3$ followed by H_2O and then EtOAc (300 mL) and extraction with additional EtOAc (200 mL). The organic layers were combined over anhydrous Na_2SO_4, dried and concentrated to give crude product. The crude material was purified by flash silica gel chromatography (1:2 EtOAc/hexane) to afford a yellow oil (3:1 ratio of diastereomers). Mixture of both diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01 (dd) and 5.72 (dd) a total of 1H, 5.14 (m, 2H), 4.07 (dd) and 3.98 (dd) a total of 1 H), 3.60 (d) and 3.51 (d) a total of 1 H), 2.58−2.35 (m) and 2.05−1.66 (m) a total of 6H), 1.32 (s) and 0.91 (s) a total of 3 H; ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.8, 145.1, 138.3, 115.8, 112.3, 81.9, 80.5, 60.3, 53.4, 47.6, 47.1, 38.7, 36.3, 34.8, 26.3, 22.1, 21.9, 15.7; IR (NaCl film) 1635, 3253 cm^{-1}; HMRS (ESI-APCI) [M] calcd for $C_9H_{14}O_2$, 154.10; found, 154.1041.

***rac*-3-Methyl-2-((trimethylsilyl)oxy)-3-vinylcyclohexanone (10).** To a RBF were added THF (26 mL) and compound (**6a**/**b**) (407 mg, 2.64 mmol, 1.0 equiv) and cooled to −78 °C. LHMDS (1 M in THF, 2.9 mL, 2.9 mmol, 1.1 equiv) was added and left to stir at the same temperature for 20 min, then brought to 0 °C. After 45 min, TMSCl (0.44 mL, 3.4 mmol, 1.3 equiv) was added and stirred for an addition 45 min. LHMDS (1 M in THF, 0.56 mL, 0.56 mmol, 1.1 equiv) was added and left to stir at the same temperature. After 1 h, TMSCl (0.08 mL, 0.612 mmol, 1.2 equiv) was added, stirred for an addition 45 min, and quenched with brine. The solution was poured onto 1:1 (v:v) brine/hexane, extracted with hexanes, dried over anhydrous Na_2SO_4, and concentrated to give crude product. The crude material was purified by a silica plug to afford a light yellow oil. The material was not thermally stable for long durations, so upon formation it was carried on to the next reaction (as such, no ^{13}C could be obtained as decomposed was observed). Mixture of both diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02−5.77 (1H), 5.06−4.95 (2H), 4.83−4.80 (1H), 3.54 and 3.42 a total of 1 H, 2.08−1.14 (6H), 0.99 and 0.97 a total of 3 H, 0.22−0.08 (18 H); IR (NaCl film) 3253 cm^{-1}.

***N*-TBS-4-bromo-indole (11).** To a solution of THF (600 mL) and NaH (2.46 g, 61.4 mmol, 1.1 equiv) was added 4-bromoindole (7 mL, 55.81 mmol, 1.0 equiv). After 1 h TBSCl (10.1 g, 66.97 mmol, 1.2 equiv) was added and left to stir for 2 h. The reaction was quenched with aqueous NH_4Cl and extracted with hexanes (×3). The organic layers were combined, washed with water and brine, dried, and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc/hexane) to afford an opaque color oil in 94% yield (16.3 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.482 (d, 8.3 Hz, 1H), 7.296 (d, 7.6 Hz, 1H), 7.239 (d, 3.3 Hz, 1H), 7.025 (t, 7.8, 8.1 Hz, 1H), 6.692 (d, 4.1 Hz, 1H), 1.277 (s, 1H), 0.935 (s, 9H), 0.617 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4, 132.2, 131.8, 122.9, 122.5, 114.7, 113.2, 105.3, 26.5, 19.7, 3.7; HMRS (ESI-APCI) [M] calcd for $C_{14}H_{39}NO_4SSi$, 310.06; found, 310.0619.

4-(2-Hydroxy-2-propyl)-*N*-TBS-indole (12). Compound (**11**) (1.0 g, 3.22 mmol, 1 equiv) was taken up in Et_2O (60 mL) and cooled to −78 °C. To the cooled solution was added *t*BuLi (3.79 mL, 6.44 mmol, 2 equiv) slowly and left to stir for 15 min to which a solution of acetone (0.24 mL, 3.22 mmol, 1 equiv) in Et_2O (15 mL) was added. After 45 min the reaction was quenched with aqueous NH_4Cl and extracted with hexanes (x2). The organic layers were combined, washed with water and brine, dried, and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc/hexane) to afford product as an oil in 99% yield (923 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.452 (d, 7.8 Hz, 1H), 7.205 (d, 3.3 Hz, 1H), 7.176−7.088 (m, 2H), 6.965 (d, 3.3 Hz, 1H), 1.992 (s, 1H), 1.763 (s, 6H), 0.946 (s, 9H), 0.603 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 139.1, 128.9, 122.4, 121.6, 113.2, 110.1, 101.5, 75.0, 32.8, 30.2, 25.2, −0.8; IR (NaCl film) 3256 cm^{-1}; HMRS (ESI-APCI) [M+ Na^+] calcd for $C_{17}H_{27}NNaOSi$, 312.48; found, 312.4821.

***rac*-6-(2-(1-(*tert*-butyldimethylsilyl)-1*H*-indol-4-yl)propan-2-yl)-3-methyl-2-((trimethylsilyl)oxy)-3-vinylcyclohexanone (14).** To a solution of 12 (76 mg, 0.26 mmol, 1.0 equiv) and 285 (141 mg, 0.47 mmol, 1.8 equiv) in DCM (3 mL) at −78 °C was added a solution of 1 M tin(IV) chloride in DCM (0.34 mL, 0.34 mmol, 1.3 equiv) and left to stir at the same temperature. The reaction was poured onto a saturated $NaHCO_3$ solution 15 min later and extracted with DCM. The organic layers were combined, washed with H_2O and brine, dried, and concentrated to afford crude material. The crude material was purified via flash silica gel chromatography (10% EtOAc in hexane) to afford product as an oil in 92% yield (119 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.35 (m, 1H), 7.16−7.15 (m, 1H), 7.09−7.07 (m, 2H), 6.78−6.77 (m, 1H), 5.72−5.62 (m, 1H), 5.09−5.00 (m, 2H), 4.07−4.01 (m, 1H), 3.50−3.33 (m, 1H), 1.65−1.26 (m, 10H), 0.95 (s, 9H), 0.89−0.88 (m, 3H), 0.59 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1, 146.5, 144.2, 139.7, 130.1, 122.5, 120.1, 114.4, 112.4, 102.3, 98.7, 61.4, 39.5, 32.6, 31.47, 30.2, 26.4, 24.6, 20.1, 19.0, 4.1, −0.9; IR (NaCl film) 1635, 1205 cm^{-1}; HMRS (ESI-APCI) [M+ Na^+] calcd for $C_{29}H_{47}NNaO_2Si_2$, 520.30; found, 520.2976.

***rac*-(9*R*)-6,6,9-Trimethyl-9-vinyl-2,6,7,8,9,10-hexahydronaphtho[1,2,3-*cd*]indol-10-ol (15).** To compound **14** (75 mg, 0.15 mmol, 1.0 equiv) was added MeOH (2 mL) followed by 3 N methanolic HCl (3 N HCl in MeOH, 0.5 mL, 1.51 mmol, 9.0 equiv) and left to stir for 5 h. The reaction was poured onto a 1:1 (v:v) 2 N NaOH/DCM (10 mL) and stirred for 1 h and extracted with DCM. The organic layers were combined, washed with water and brine, dried over $MgSO_4$, and concentrated. The crude material was purified by flash silica gel chromatography (1:4 EtOAc/hexane) to afford product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (bs, 1H), 7.3−76.9 (m, 3H), 6.7 (s, 1H), 5.78 (dd, 18 Hz, 1H), 5.21−4.92 (m, 2H), 4.81−4.65 (m, 1H), 2.51−2.19 (m, 4H), 1.62−1,53 (m, 1H), 1.39 (s, 6H), 1.06−0.76 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 150.6, 146.3, 131.2, 134.5, 127.0, 125.3, 111.8, 108.2, 106.4, 74.8, 48.3, 40.1, 38.2, 36.7, 32.1, 29.3, 21.4, 19.1; IR (NaCl, neat) 3210; HMRS (ESI-APCI) [M + H] calcd for $C_{20}H_{24}NO$, 294.19; found, 294.1946.

***rac*-(*R*)-6,6,9-Trimethyl-2-tosyl-9-vinyl-6,7,8,9-tetrahydronaphtho[1,2,3-*cd*]indol-10(2*H*)-one (17).** To DCM (2 mL) were added compound **15** (55 mg, 0.19 mmol, 1.0 equiv) and DMP (157 mg, 0.37 mmol, 2.0 equiv) and left to stir for 2 h. The reaction was quenched with aqueous NaS_2O_3 (4 mL) and left to stir for 45 min, washed with aqueous $NaHCO_3$ (×2), once with aqueous NaS_2O_3, water, and brine, dried over $MgSO_4$, and concentrated. The crude material was dissolved in DCM (2 mL) to which TsCl (145 mg, 0.76 mmol, 4 equiv) and DMAP (5 mg, 0.04 mmol, 0.2 equiv) were added and brought to reflux. After 12 h the reaction was quenched with saturated NH_4Cl and extracted with DCM. The organic layers were combined, washed with H_2O and brine, dried, and concentrated. The crude material was purified via flash silica gel chromatography

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(1:8 EtOAc/hexane) to afford product as an amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (t, 2.1 Hz, 1H), 7.49−7.29 (m, 4H), 7.05−7.02 (m, 2H), 6.99 (s, 1H), 6.31 (dd, 10.5, 16.3 Hz, 1H), 5.11 (dd, 10.4, 16.1 Hz, 1H), 3.92 (dd, 1.0, 11.5 Hz, 1H), 2.43 (s, 3H), 1.92−2.11 (m, 4H), 1.49 (s, 3H), 1.42 (s, 3H), 1.18 (s, 3H); HMRS (ESI-APCI) [M + H] calcd for $C_{27}H_{28}NO_3S$, 446.18; found, 446.1825.

***rac*-(6a*S*,9*R*,10a*S*)-6,6,9-Trimethyl-9-vinyl-6,6a,7,8,9,10a-hexahydronaphtho[1,2,3-*cd*]indol-10(2*H*)-one (18).** To a solution of compound **17** (175 mg, 0.39 mmol, 1.0 equiv) in THF (5 mL) was added LAH (30 mg, 0.79 mmol, 2.0 equiv) and left to stir at rt. After 14 h Rochelle's salt (10 mL) was added and left to stir for an additional 2 h, and the mixture was extracted with DCM. The organic layers were combined, washed with H_2O and brine, dried, and concentrated. To oxalyl chloride (0.04 mL, 0.47 mmol, 1.2 equiv) in DCM (1 mL) was added DMSO (0.07 mL, 0.94 mmol, 2.4 equiv) at −78 °C and left to stir for 25 min at the same temperature, to which crude alcohol in DCM (1 mL) was added at the same the temperature. Triethyl amine (0.27 mL, 1.95 mol, 5.0 equiv) was added 20 min later and allowed to warm to rt. The reaction was diluted with H_2O and extracted with hexane. The organic layers were combined, washed with H_2O and brine, dried, and concentrated. The crude material was purified via flash silica gel chromatography (1:3 EtOAc/hexane) to afford product as a white crystalline solid (mp 141−151 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (bs, 1H), 7.49 (t, 1.9 Hz, 1H), 7.20−7.15 (m, 2H), 7.03 (s, 1H), 6.21 (dd, 10.7, 17.2 Hz, 1H), 5.15 (dd, 10.7, 17.3 Hz, 1H), 3.92 (dd, 1.0, 11.5 Hz, 1H) 1.92−2.11 (m, 5H), 1.51 (s, 3H), 1.48 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.2, 142.8, 139.7, 133.6, 125.3, 122.4, 121.0, 112.3, 112.2, 108.6, 107.9, 51.6, 50.3, 44.1, 38.0, 37.5, 24.7, 24.1, 23.0, 21.3; IR (NaCl, neat) 3402, 3050, 1672; HMRS-FAB [M + H]$^+$ calcd for $C_{20}H_{24}NO$, 294.18; found, 294.1847.

***rac*-(6a*S*,9*R*,10*R*,10a*S*)-6,6,9-Trimethyl-9-vinyl-2,6,6a,7,8,9,10,10a-octahydronaphtho[1,2,3-*cd*]indol-10-amine (20).** Compound (**18**) (100 mg, 0.34 mmol, 1.0 equiv) was dissolved in THF (0.8 mL, 0.5 M) and added to a solution of ammonium acetate (1.05 g, 13.6 mmol, 40 equiv), $NaCNBH_3$ (214 mg, 3.4 mmol, 10 equiv) in MeOH (4 mL) and left to stir for 48 h at rt. The reaction was quenched with aqueous $NaHCO_3$ and extracted with Et_2O (×3). The organic layers were combined and washed with 1 N HCl, and the organic and aqueous layers were separated. The aqueous layer was brought to above pH 8 with 2 N NaOH and extracted with EtOAc. The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The crude material was filtered through a silica plug, used without further purification to afford product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (bs, 1H), 7.25−6.98 (m, 3H), 6.87 (s, 1H), 6.01 (dd, 10.5, 16.9 Hz, 1H), 5.06 (dd, 10.6, 15.9 Hz, 2H), 3.01 (s, 1H), 2.89 (bs, 1H), 2.21−2.05 (m, 2H), 1.82−1.53 (m, 2H), 1.49 (s, 3H), 1.39 (s, 3H), 0.98 (s, 3H); HRMS-FAB [M + H]$^+$ calcd for $C_{20}H_{27}N_2$, 295.21; found, 295.2175.

***rac*-Hapalindole U.** Compound **20** (22 mg, 0.07 mmol, 1.0 equiv) was dissolved in DCM (1.0 mL), to which was added sequentially formic acid (0.006 mL, 0.15 mmol, 2.0 equiv), 2-chloro-4,6-dimethoxy-1,3,5-triazine (26 mg, 0.15 mmol, 2.2 equiv), DMAP (0.5 mg, 0.004 mmol, 0.06 equiv), and *N*-methyl morpholine (0.002 mL, 0.15 mmol, 2.2 equiv). The mixture was stirred for 2 h, diluted with DCM ,and poured onto saturated $NaHCO_3$. The aqueous layer was extracted with DCM (×5). The organic layers were combined, washed with 1 N HCl and brine, dried over anhydrous $MgSO_4$, and concentrated. The crude material was dissolved in benzene (0.01 M), and Burgess reagent (67 mg, 0.28 mmol, 4.0 equiv) was added at ambient temperature. Upon completion of the reaction, as determined by TLC, the solvent was removed in vacuo, and the crude material was purified by flash silica gel chromatography (1:3 EtOAc/hexane) to afford hapalindole U as a white crystalline solid (mp 239−241 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (bs, 1H), 7.19−7.18 (m, 2H), 7.04−7.03 (m, 1H), 6.90 (bt, 1H), 6.05 (dd, 10.8, 17.3 Hz, 1H), 5.19 (dd, 10.9, 17.4 Hz, 2H), 4.11 (bd, 1H), 3.29−3.26 (m, 1H), 2.07−1.93 (m, 3H), 1.70−1.66 (m, 2H), 1.49 (s, 3H), 1.45 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 145.7, 141.1, 133.9, 125.8, 122.8, 116.0, 113.1, 113.0, 112.6, 108.2, 63.1, 43.2, 39.6, 37.4, 33.7, 30.0, 25.4, 24.4, 21.6, 21.0; IR (NaCl neat) 2143, 1642; HRMS-FAB [M + Na]$^+$ calcd for $C_{21}H_{24}NaN_2$, 327.18; found, 327.1846.

D,L-(10*S*)-6,6,9-Trimethyl-9-vinyl-2,6,7,8,9,10-hexahydronaphtho[1,2,3-*cd*]indol-10-amine (21). To DCM (2 mL) were added compound **15** (55 mg, 0.19 mmol, 1.0 equiv) and DMP (157 mg, 0.37 mmol, 2.0 equiv) and left to stir for 2 h. The reaction was quenched with aqueous NaS_2O_3 (4 mL) and left to stir for 45 min, washed with aqueous $NaHCO_3$ (×2), once with aqueous NaS_2O_3, water, and brine, dried over $MgSO_4$ and concentrated. The crude material was dissolved in THF (0.5 mL, 0.5 M) and added to a solution of ammonium acetate (586 mg, 7.6 mmol, 40 equiv) and $NaCNBH_3$ (119 mg, 1.9 mmol, 10 equiv) in MeOH (70 mL) and left to stir for 48 h at rt. The reaction was quenched with aqueous $NaHCO_3$ and extracted with Et_2O (×3). The organic layers were combined and washed with 1 N HCl, and the organic and aqueous layers were separated. The aqueous layer was brought to above pH 8 with 2 N NaOH and extracted with EtOAc. The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The crude material was filtered through a silica plug and was used without further purification, to afford product as a crystalline solid in 66% yield (total yield 73% including compound **22**). ^{1}H NMR (300 MHz, $CDCl_3$) δ7.5−7.2 (m, 3H), 6.7 (s, 1H), 5.78 (dd, 18 Hz, 1H), 5.29−4.87 (m, 2H), 4.92 (br s, 2H), 4.65 (d, 1H), 2.51−2.19 (m, 4H), 1.62 (s, 1H), 1.39 (s, 6H), 1.06 (s, 3H); HMRS-FAB [M + H]$^+$ calcd for $C_{20}H_{24}N_2$, 293.20; found, 293.2017.

D,L-Hapalindole J. Compound **23** (22 mg, 0.07 mmol, 1.0 equiv) was dissolved in DCM (1.0 mL), to which was added sequentially formic acid (0.006 mL, 0.15 mmol, 2.0 equiv), 2-chloro-4,6-dimethoxy-1,3,5-triazine (26 mg, 0.15 mmol, 2.2 equiv), DMAP (0.5 mg, 0.004 mmol, 0.06 equiv), and *N*-methyl morpholine (0.002 mL, 0.15 mmol, 2.2 equiv). The mixture was stirred for 2 h, diluted with DCM, and poured onto saturated $NaHCO_3$. The aqueous layer was extracted with DCM (×5). The organic layers were combined, washed with 1 N HCl and brine, dried over anhydrous $MgSO_4$, and concentrated. The crude material was dissolved in benzene (0.01 M), and Burgess reagent (68 mg, 0.29 mmol, 4.0 equiv) was added at ambient temperature. Upon completion of the reaction, as determined by TLC, the solvent was removed in vacuo and the crude material was purified by flash silica gel chromatography (1:4 EtOAc/hexane) to afford hapalindole J as a white crystalline solid (mp 182−184 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (bs, 1H), 7.22−7.14 (m, 2H), 7.03−7.02 (m, 1H), 6.91 (bt, 1H), 6.05 (dd, 10.7, 17.4 Hz, 1H), 5.19 (d, 10.9, 17.2 Hz, 2H), 4.11 (bd, 1H), 3.31−3.25 (m, 1H), 2.069−1.94 (m, 3H), 1.69−1.67 (m, 2H), 1.50 (s, 3H), 1.45 (s, 3H), 1.21 (s, 3H); ^{13}C NMR 155.9, 146.1, 141.0, 134.0, 124.2, 123.1, 116.5, 113.1, 112.9, 108.1, 62.2, 43.6, 39.1, 37.9, 33.1, 30.1, 25.2, 24.8, 21.1; IR (NaCl, neat) 2150, 1642; HRMS-FAB [M + Na]$^+$ calcd for $C_{21}H_{24}NaN_2$, 327.18; found, 327.1846.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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