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FORMAL SYNTHESIS OF HAPALINDOLE O AND SYNTHETIC EFFORTS TOWARDS HAPALINDOLE K AND AMBIGUINE A

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Abstract – The formal synthesis of *D,L*-hapalindole O has been accomplished intercepting Natsume's total synthesis route. The intercepted substrate was synthesized in an overall 36% yield over ten-synthetic steps compared to Natsume's overall 1% yield over eighteen-synthetic steps. In addition, advanced substrates for the continuing progress towards hapalindole K and ambiguine A has been synthesized. All routes described herein employ a silyl ether-based strategy accessing the functionalized 6:5:6:6 ring system, that has previously been used in our laboratory to access the total synthesis of *D,L*-hapalindoles J and U.

INTRODUCTION

The Stigonemataceae family of blue-green algae, have been found to contain a large wealth of indole-containing secondary metabolites which differ in terms of their core structures and biological effects, but also possess a great homology in terms of their basics skeletal structures. Isolation chemists/biologists have successfully isolated and characterized families of compounds from this blue-green algae, such as the tri- and tetracyclic hapalindoles, fischerindoles, welwitindolinones and ambiguines, (Figure 1).[1] These families of natural products, while structurally different within their cores, possess many of the same key functionalities as well as bond connections. Each member of these families of natural alkaloids contain an indole ring from which the core structures are formed. For the tetracyclic hapalindoles, welwitindolinones and ambiguines, C3 and C4 are the structural branching points, whereas C2 and C3 are the structural branching points for the fischerindoles. All of the members of these families also contain a methyl-vinyl substituted quaternary carbon center along with either an isocyanate or isothiocyanate functionality, adjacent to the quaternary carbon center. With respect to the ambiguine and tri- and tetracyclic hapalindoles, most of the compounds within these families possess

little or no further functionality within this uppermost cyclohexane ring system, specifically about C14. Within these two families there are members that possess either a hydroxyl or chloride about C13, thus increasing the molecular complexity and intrigue about these unique natural products.[2]

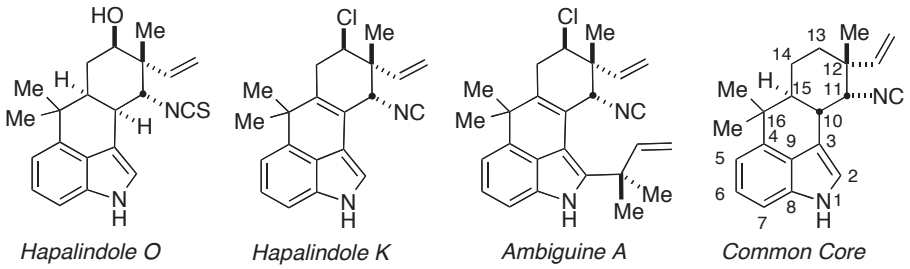
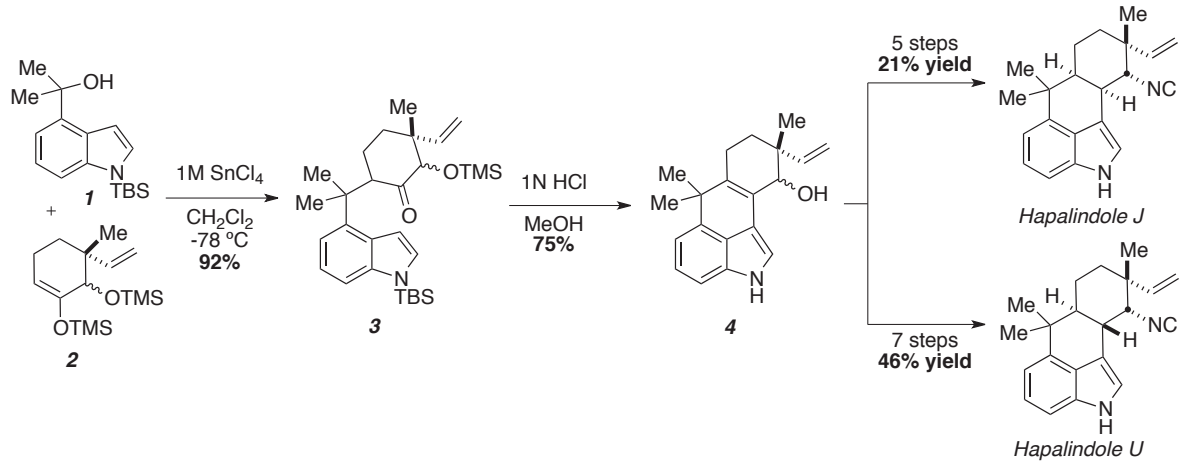


Figure 1. Hapalindole's O and K, Ambiguine A and Ring Notation.

Our laboratory recently published concise total syntheses of hapalindoles J and U.[3] Our conceptual approach to the syntheses of the tetracyclic hapalindoles involves the tin-mediate coupling of functionalized indole **1** to TMS-enol ether **2** to afford tricycle **3**. Treatment of **3** with methanolic HCl successfully allowed for ring closure to the corresponding allylic alcohol tetracycle **4** in good yields. Compound **4** was elaborated further into hapalindoles J and U. Employing similar substrates to that of indole (**1**) and TMS-enol ether (**2**), as well as the tin-mediated/methanolic HCl conditions, recent efforts have been directed towards the total syntheses the more complex and intriguing natural products hapalindole K and ambiguine A.

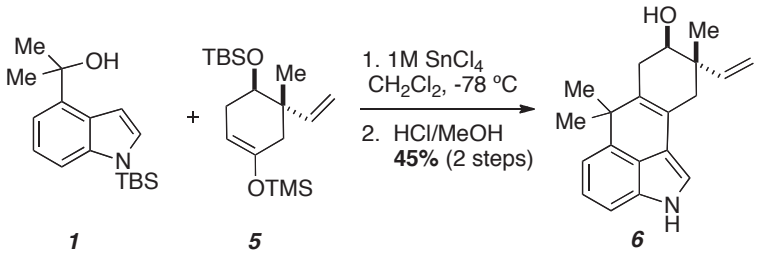


Scheme 1. Our current route to Hapalindoles J and U.

RESULTS AND DISCUSSION

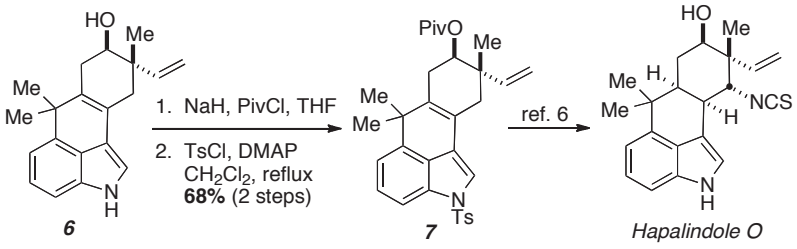
Our approach to hapalindole K began with the requisite functionalized indole (**1**) and TMS-enol ether (**5**) which were both prepared via our previously reported procedures.[3-5] The resulting ketone was

successfully elaborated into TMS-enol ether **5** with LHMDS and TMSCl in quantitative yields. Treating a solution of TMS-enol ether **5** and indole **1** in CH_2Cl_2 at -78 °C with a 1M tin(IV) chloride solution afforded the expected tricycle (similar to **3** in Scheme 1) and subsequently closed to the desired dehydrated tetracycle **6** with aqueous HCl in MeOH in 45% yield over two-steps (Scheme 2).



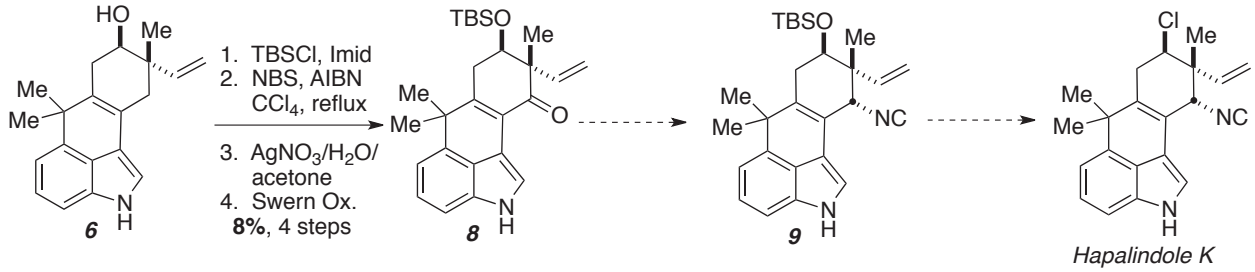
Scheme 2. Accessing the C13 hydroxyl tetracyclic ring system.

Prior to attempting to advance dehydrated tetracycle **6** on to hapalindole K it was realized that this compound could be used to intercept Natsume's total synthesis of hapalindole O.[6] To this end, pivaloyl protection of the secondary alcohol was accomplished with NaH and PivCl in THF to afford the corresponding Piv-protected dehydrated tetracycle in 88% yield (Scheme 3). Subsequent tosyl protection of the indole nitrogen with TsCl, DMAP (cat.) in CH_2Cl_2 at reflux furnished the desired O-Piv N-Ts protected dehydrated tetracycle **7** in 68% over two steps, which Natsume has taken onto hapalindole O in six-synthetic steps with an overall 23%. Natsume accessed compound **7** in an overall 1% yield over eighteen-steps, whereas we are able to access this same substance in an overall 26% yield over ten-synthetic steps. While our route discussed gives access to a *dl*-mixture of **7**, unlike the enantioselective route employed by Natsume, the enhanced yielded as well as greatly reduced step count inherent within our route is a valuable contribution to the synthesis of these complex alkaloids. It must be noted, that while our yields and step count are superior to that of Natsume's, the route currently employed is a modification of the strategy originally developed and implemented by Natsume. Accessing **5** in an asymmetric fashion is currently being pursued, which upon completion should allow for enantioselective access to **7** and other completed or in progress alkaloids within this diverse family.



Scheme 3. Formal synthesis of Hapalindole O.

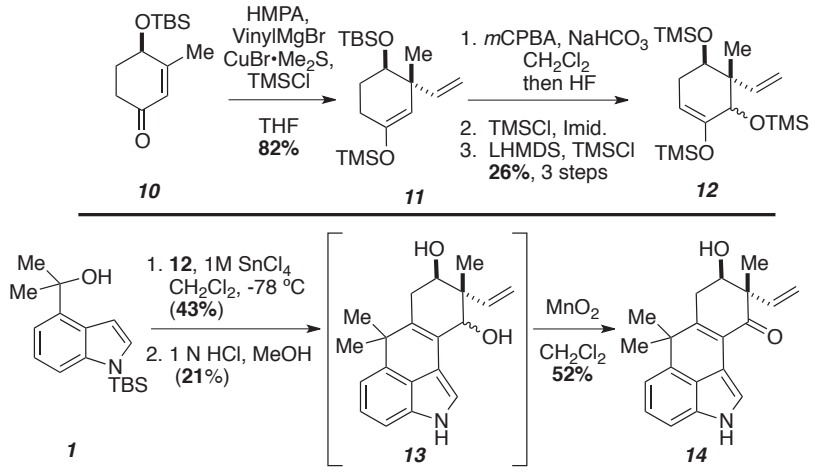
Re-directing our efforts back towards accessing the chloride-containing hapalindole K, compound **6** was treated with TBSCl, imidazole in DMF to furnish the corresponding O-TBS protected tetracycle (Scheme 4). Employing modified conditions used by Natsume,[7] allylic radical bromination with subsequent $AgNO_3$ in H_2O/acetone treatment provided the corresponding allylic alcohol that was subjected to Swern oxidation conditions delivering compound **8** in 8% yield over four-steps. It is envisioned that compound **8** can be elaborated to compound **9** in the same fashion as compound **4** was elaborated into hapalindoles J and U via reductive amination, coupling with formic acid followed by dehydration with Burgess reagent.[3,8] Compound **9** can then be elaborated into hapalindole K via TBS deprotection followed by installation of the chlorine atom with net retention of stereochemistry.



Scheme 4. Initial efforts of advancing **6** onto the total synthesis of Hapalindole K.

While the conditions delineated in Scheme 4 does give access to the requisite allylic alcohol, the low yield presents a potentially crippling bottle-neck towards accessing hapalindole K. Noting the success in employing the TMS variant of the α-hydroxyketone of **2** (Scheme 1) towards the total synthesis of hapalindole J and U, efforts were redirected towards accessing a similar system, but with the required C13 alcohol, or protected-alcohol, installed.

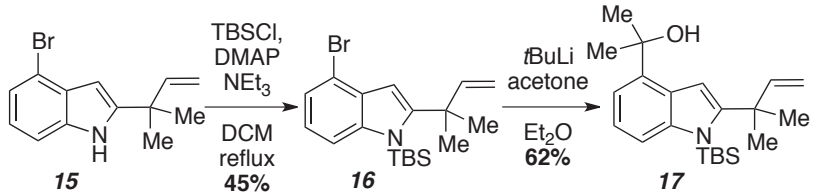
Slowly adding CuBr•Me_2S in HMPA to vinylmagnesium bromide at –78 °C over 5 min, followed by TMSCl and enone **10** in THF (1M) over 30 min, gave the desired TMS-enol ether **11** in 82% yield (Scheme 5). Elaboration of **11** into **12** was successfully completed by subjecting **11** to Rubottom oxidation, TMSCl, imidazole in DMF followed by LHMDS and TMSCl providing **12** in 26% yield over three steps. Treating a solution of **12** and indole **1** in CH_2Cl_2 at –78 °C with a 1M tin(IV) chloride solution afforded the expected tricycle (similar to **3** in Scheme 1) which subsequently cyclized to the desired tetracyclic allylic alcohol **13** through the agency of 1N methanolic HCl in 9% crude-yield over two-steps. Subjecting compound **13** to allylic oxidation conditions with MnO_2 furnished **14** in 52% yield. It can be envisioned that **14** could be elaborated onto hapalindole K in a similar fashion as described in Scheme 4.



Scheme 5. Alternative approach toward Hapalindole K.

Noting that both strategies that have been investigated in gaining access to compounds **8** (C13 alcohol TBS protected) and **14** (C13 free-alcohol) proceed in low overall yield (5.8% overall yield over nine-steps and 1.5% overall yield over eleven steps, respectively), several points must be addressed. The radical bromination strategy used in Scheme 4 gave a one-time best yield of 11%, wherein most yields ranged from 4-7%, and the strategy used in Scheme **5**, specifically the ring closure step, was found to be highly scale-dependent (25 mg max scale for methanolic HCl treatment). Efforts are being taken to overcome the scale dependence within the silyl chemistry route (Scheme 5).

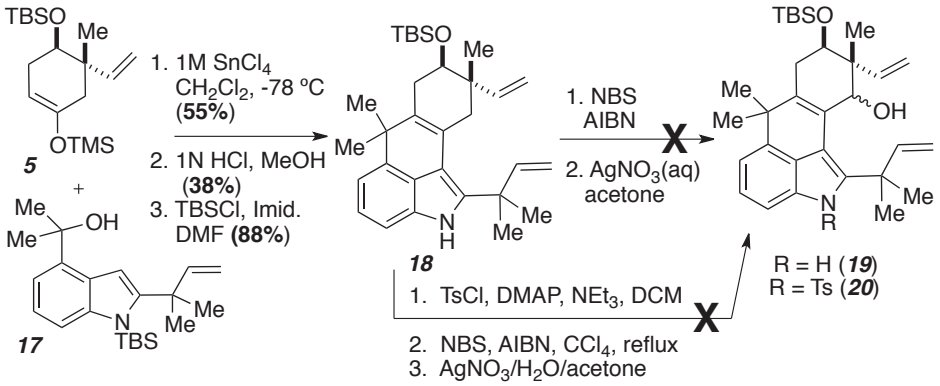
Concurrently, work towards ambiguine A was being undertaken along similar lines. Rather than attempting a late-stage reverse prenylation on functionalized tetracycles, it was decided to introduce the reverse prenyl group at an earlier stage. To this end, 4-bromo-indole was elaborated into **15** in 78% over three-steps.[9] Treating **15** with TBSCl, NEt_3, DMAP (cat) in CH_2Cl_2 at reflux furnished **16** in 45% yield, which was subsequently subjected to lithium-halogen exchange conditions affording **17** in 62% (Scheme 6).



Scheme 6. Synthesis of Functionalized Indole **17**.

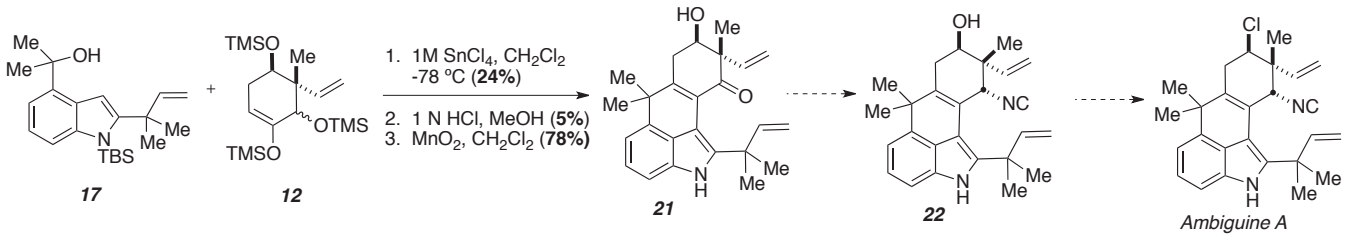
Treating a solution of TMS-enol ether **5** and indole **17** in CH_2Cl_2 at -78 °C with a 1M tin(IV) chloride solution afforded the expected tricycle (similar to 3 in Scheme 1) that subsequently cyclized to the desired tetracycle **18** with 1 N HCl in MeOH followed by TBS protection of the secondary alcohol in 18% yield

over three-steps (Scheme 7). All attempted radical bromination conditions on **18** failed to afford any of the desired allylic bromide. Considering that the free indolic N-H present could be adversely affecting the radical bromination, tosyl protection of the indole was performed in 60% yield. Subjecting the *N*-tosylated analog of **18** to a variety of radical bromination conditions, unfortunately still failed to afford any of the desired allylic oxidation product.



Scheme 7. Attempted allylic radical oxidations.

Given our inability to identify conditions to effect the allylic oxidation, efforts were directed towards employing a strategy patterned after that outlined in Scheme 5. Treating a solution of TMS-enol ether **12** and indole **17** in CH_2Cl_2 at -78 °C with a 1M tin(IV) chloride solution afforded the expected tricycle (similar to 3 in Scheme 1) that was subsequently cyclized to the desired tetracyclic allylic alcohol with 1N methanolic HCl followed by allylic oxidation with MnO_2 to afford **21** in low overall yield (Scheme 8).



Scheme 8. Efforts towards Ambiguine A from **12** via Silyl-Strategy.

As encountered with the related substrate in Scheme 5, the methanolic HCl ring closure step was found to be highly scale-dependent and constitutes the subject of current investigation. Nonetheless, compound **21**, containing the requisite reverse-prenyl unit, is a promising candidate for the further elaboration into several members of the ambiguine family of indole alkaloids and is being pursued in these laboratories in that context.

In summary, the formal synthesis of hapalindole O has been accomplished, intercepting Natsume's route

via compound **7** and constitutes a much shorter and higher-yielding entry to this alkaloid requiring over ten-synthetic steps in 36% overall yield compared to Natsume's route that required eighteen-synthetic steps in 1% overall yield over from commercially available materials. With respect to hapalindole K, the advanced tetracycles **8** and **14** have been accessed but will require further improvements in the yields. Work towards the total synthesis of ambiguine A, has resulted in the successful assembly of the C2 reverse-prenylated compound **21**. Optimization of the ring-closing steps in both the hapalindole K and ambiguine A routes are currently under investigation to allow access to the natural products as well as for preparing substrates for our recent biosynthetic studies on this family of alkaloids.

EXPERIMENTAL

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

Racemic-(8*R*,9*S*)-6,6,9-trimethyl-9-vinyl-2,6,7,8,9,10-hexa-hydronaphtho[1,2,3-*cd*]indol-8-ol (6):
To a solution of **1** (250 mg, 0.86 mmol, 1.0 eq.) and **5** (527 mg, 1.55 mmol, 1.8 eq.) in DCM (10 mL) at -78 °C was added a solution of 1 M tin(IV) chloride in DCM (1.12 mL, 1.12 mmol, 1.3 eq.) and left to stir at the same temperature. The reaction was poured onto a saturated aqueous $NaHCO_3$ 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 a silica plug and used without futher purification. To crude material was added MeOH (10 mL) followed by 1 M HCl (7 mL, 7.74 mmol, 9.0 eq.) and left to stir for 5 h. The reaction was poured onto a 1:1 (v:v) 2 N NaOH:DCM (30 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 in 45% yield over two-steps.
^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.78 (bs, 1H), 7.23 (t, 7.8, 6.7 Hz, 1H), 7.10 (d, 8.0 Hz, 1H), 7.02 (d, 7.3 Hz, 1H), 6.84 (s, 1H), 5.90 (dd, 10.6, 7.1 Hz, 1H), 5.22 (dd, 5.2, 11.5 Hz, 2H), 3.81 (m, 1H), 2.74 (dd, 5.1,

17.4 Hz, 1H), 2.54 (d, 16.9 Hz, 1H), 2.39 (d, 16.9 Hz, 1H), 2.05 (s, 1H), 1.76 (d, 3.9 Hz, 1H), 1.48 (s, 3H), 1.45 (s, 3H), 1.10 (s, 3H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 154.6, 149.3, 143.1, 139.0, 133.6, 127.2, 123.2, 115.6, 108.3, 106.7, 84.3, 47.6, 43.2, 38.4, 37.6, 37.2, 30.8, 18.1; **HMRS (ESI-APCI)**: [M+H] calcd for $C_{20}H_{24}NO$, 294.1813; found, 294.1852.

Racemic-(8*R*,9*S*)-6,6,9-trimethyl-2-tosyl-9-vinyl-2,6,7,8,9,10-hexahydronaphtho[1,2,3-*cd*]indol-8-yl pivalate (7): To a solution of NaH (10 mg, 0.24 mmol, 1.1 eq.) in THF (3 mL) was added compound **6** (65 mg, 0.22 mmol, 1.0 eq.) and left to stir. After 45 min PivCl (40 mg, 0.33 mmol, 1.5 eq.) was added and left to stir for 4 h. The reaction was quenched with saturated aqueous NH_4Cl, dried and concentrated to afford the product in quantitative yields. The material was taken up in CH_2Cl_2, to which DMAP (cat.) was added and refluxed for 6 h. The material was concentrated and purified via flash silica gel chromatography (1:4 EtOAc:hexane) to afford product in 68% yield over two-steps.
All ^{1}H and ^{13}C NMR Spectra and MS data matched Spectra and data reported by Natsume.

Racemic-(8*R*,9*S*)-8-((*tert*-butyldimethylsilyl)oxy)-6,6,9-trimethyl-9-vinyl-6,7,8,9-tetrahydronaphtho-[1,2,3-*cd*]indol-10(2*H*)-one (8): To a solution of **6** (200 mg, 0.68 mmol, 1.0 eq.) in DMF (10 mL) was added imidazole (93 mg, 1.36 mmol, 2.0 eq.) and TBSCl (154 mg, 1.02 mmol, 1.5 eq.) and left to stir for 13 h. The reaction was diluted with brine (100 mL) and extracted with hexane (100 mL x 2). The organic layers were combined, dried and concentrated to afford crude product that was used without further purification. To CCl_4 (4 mL) was added the crude material followed by NBS (132 mg, 0.74 mmol, 1.09 eq.) and AIBN (26 mg, 0.16 mmol, 0.23 eq.) and brought to reflux. After 45 min the reaction was cooled to 0 °C to which aqueous $NaHCO_3$ was added and extracted with DCM (3 x 6 mL). The organic layers were combined, washed with water and brine, dried and concentrated. The crude material was added to acetone (4 mL) to which $AgNO_3$ (185 mg, 1.09 mmol, 1.6 eq.) in H_2O (4 mL) was added and left to stir for 12 h. The reaction was quenched with aqueous $NaHCO_3$ and extracted with DCM (10 mL x 2). 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. The material was subjected to Swern oxidation conditions to afford product **8** in an overall 8% yield over four-steps.
^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.78 (bs, 1H), 7.23 (t, 7.8, 6.7 Hz, 1H), 7.10 (d, 8.0 Hz, 1H), 7.02 (d, 7.3 Hz, 1H), 6.84 (s, 1H), 5.90 (dd, 10.6, 7.1 Hz, 1H), 5.22 (dd, 5.2, 11.5 Hz, 2H), 3.81 (m, 1H), 2.74 (dd, 5.1, 17.4 Hz, 1H), 1.76 (d, 3.9 Hz, 1H), 1.48 (s, 3H), 1.45 (s, 3H), 1.10 (s, 3H), 0.93 (s, 9H), 0.11 (s, 6H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 199.7, 157.3, 146.2, 144.8, 137.5, 133.5, 125.1, 123.2, 120.8, 111.9, 111.7, 108.4, 108.0, 84.2, 51.7, 42.8, 34.5, 31.5, 25.1, 24.5, 24.4, 22.1, -1.1; **HMRS(ESI-APCI)**: [M+H] calcd

for $C_{26}H_{36}NO_2Si$, 422.2471; found, 422.2515.

Compound (12): Vinyl Grignard (1 M in THF, 25 mL, 25 mmol, 1.5 eq.) was cooled to -78 °C to which a pre-mixed solution of CuBr•Me_2S (129 mg, 0.5 mmol, 0.1 eq.) in HMPA (0.25 M) was added over 5 min and left to stir at the same temperature. After 30 min, a pre-mixed solution of TMSCl (1.27 mL, 10 mmol, 2.0 eq.) and **10** (1.2 g, 5.0 mmol, 1.0 eq.) in THF (1 M, 5.0 mL) was added over 30 min and left to stir at the same temperature for 3 h. TEA (10 mL) was added and the reaction was warmed to rt and diluted with hexane. The mixture was washed with water (100 mL x 2), once with a saturated NH_4Cl (100 mL), dried and concentrated to give product in 82% yields. The product was used without further purification.

Compound **11** (500 mg, 1.47 mmol, 1.0 eq.) was added to DCM (0.2 M, 7 mL) and cooled to 0 °C, at which time $NaHCO_3$ (148 mg, 1.76 mmol, 1.2 eq.) was added. To this solution freshly purified *m*CPBA (303 mg, 1.76 mmol, 1.2 eq.) in DCM (0.6 M, 3 mL) was added at the same temperature. Upon addition of the *m*CPBA the reaction was allowed to warm to rt and left to stir. After 2 h the reaction was filtered through a pad of celite, concentrated, taken up in pentane, filter through another pad of celite and concentrated once more. The crude greenish-yellow oil was dissolved into MeOH (15 mL) to which HF (48% in H_2O, 0.11 mL, 2.94 mmol, 2.0 eq.) is added. After 1 h $NaHCO_{3(s)}$ was added, followed by H_2O and then diluted with EtOAc. The aqueous layer was extracted several times with EtOAc, the organic layer combined, washed with H_2O and brine, dried and concentrated. The crude material was purified via flash silica gel chromatography (1:4 EtOAc:hexane) to afford a diastereomeric mixture of products.

To a solution of diol (200 mg, 1.18 mmol, 1.0 eq.) in DMF (15 mL) was added imidazole (121 mg, 1.77 mmol, 1.5 eq.) and TMSCl (0.30 mL, 2.36 mmol, 2.0 eq.) and stirred for 12 h. The reaction was diluted with brine (150 mL) and extracted with hexane (100 mL x 2), dried and concentrated. The crude material was taken up in THF (11 mL) was cooled to -78 °C to which LHMDS (1 M in THF, 1.24 mL, 1.24 mmol, 1.05 eq.) was added. The solution was warmed to 0 °C after 15 min and left to equilibrate. After 20 min TMSCl (0.19 mL, 1.53 mmol, 1.3 eq.) was added and left to stir for 1 h at the same temperature, then warmed to rt. The reaction was quenched with the addition of brine (50 mL), extracted with hexane, dried, concentrated and then re-subjected to the same conditions (LHMDS and TMSCl). The crude oil was used without further purification as diastereomeric mixture of products in an overall 26% crude-yield over three-steps due to stability of the material.

Mixture of diastereomers: **^{1}HNMR:** (300 MHz, $CDCl_3$) δ 6.02-5.77 (1H), 5.06-4.95 (2H), 4.83-4.80 (1H), 3.84-3.30 (2H), 2.08-1.14 (2H), 0.87 and 0.86 a total of 3 H, 0.31-0.01 (27 H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ Unable to acquire due to instability of the material; **HMRS (ESI-APCI)**: [M+H] calcd for $C_{18}H_{39}O_3Si_3$, 387.2162; found, 387.2207.

Racemic-(8*R*,9*S*)-8-hydroxy-6,6,9-trimethyl-9-vinyl-6,7,8,9-tetrahydronaphtho[1,2,3-*cd*]indol-10(2*H*)-one (14): To a solution of **1** (300 mg, 1.04 mmol, 1.0 eq.) and **12** (724 mg, 1.87 mmol, 1.8 eq.) in DCM (10 mL) at -78 °C was added a solution of 1 M tin(IV) chloride in DCM (1.35 mL, 1.35 mmol, 1.3 eq.) and left to stir at the same temperature. The reaction was poured onto a saturated aqueous $NaHCO_3$ 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. The resulting tricycle was taken up in MeOH (11 mL) followed by 1 N methanolic HCl (1 N HCl in MeOH, 9.4 mL, 9.4 mmol, 9.0 eq.) and left to stir for 5 h. The reaction was poured onto a 1:1 (v:v) 2 N NaOH:DCM (20 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 the expect allylic alcohol.

To a solution of the allylic alcohol (29 mg, 0.09 mmol, 1.0 eq.) in CH_2Cl_2 (1 mL) was added MnO_2 (39 mg, 0.45 mmol, 5 eq.). After 48 h the reaction was filtered through a pad of celite, which was washed with CH_2Cl_2 (4 x 10 mL), dried and concentrated. The crude material was purifed via flash silica gel chromatography (1:4 EtOAc:hexane) to afford product **14** in 52% yield.

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.81 (bs, 1H), 7.22 (t, 7.9, 6.6 Hz, 1H), 7.08 (d, 7.9 Hz, 1H), 7.03 (d, 7.2 Hz, 1H), 6.79 (s, 1H), 6.05 (dd, 10.5, 16.3 Hz, 1H), 5.21 (dd, 10.4, 16.1 Hz, 2H), 3.92 (dd, 1.0, 11.5 Hz, 1H), 2.11 (s, 1H), 2.07-1.92 (m, 2H), 1.49 (s, 3H), 1.42 (s, 3H), 1.18 (s, 3H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 199.2, 158.1, 145.4, 145.1, 138.0, 133.4, 125.3, 123.5, 121.3, 112.0, 111.5, 107.8, 107.6, 82.8, 51.7, 42.8, 34.9, 24.7, 24.5, 22.8; **HMRS (ESI-APCI)**: [M+H] calcd for $C_{20}H_{22}NO_2$, 308.1606; found, 308.1651.

2-(1-(*tert*-Butyldimethylsilyl)-2-(2-methylbut-3-en-2-yl)-1*H*-indol-4-yl)propan-2-ol (17): To a solution of THF (300 mL) and NaH (133 mg, 3.3 mmol, 1.1 eq.) was added **15** (800 mg, 3.03 mmol, 1.0 eq.). After 1 h TBSCl (548 g, 3.64 mmol, 1.2 eq.) was added and left to stir for 2 h. The reaction was quenched with aqueous NH_4Cl and extracted with hexanes (x3). 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 **16** in 45% yield.

Compound **16** (400 mg, 1.06 mmol, 1eq.) was taken up in Et_2O (20 mL) and cooled to -78 °C. To the cooled solution was added *t*BuLi (1.25 mL, 2.12 mmol, 2 eq.) slowly and left to stir for 15 min to which a solution of acetone (0.08 mL, 1.06 mmol, 1 eq.) in Et_2O (5 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 **17** in 62% yield.

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.23-7.14 (m, 3H), 6.69 (s, 1H), 6.09 (dd, 17.4, 10.6 Hz, 1H), 5.08 (dd, 21.7, 10.6 Hz, 2H) 3.74, 2.06 (s, 1H), 1.78 (s, 6H), 1.56 (s, 6H), 0.94 (s, 9H), 0.62 (s, 6H); **^{13}CNMR:** (75 MHz, $CDCl_3$) δ 146.4, 145.9, 140.5, 123.9, 120.9, 115.1, 112.7, 108.4, 99.7, 73.8, 38.8, 31.8, 28.6, 26.4, -0.09; **HMRS (ESI-APCI)**: [M+H] calcd for $C_{22}H_{36}NOSi$, 358.2521; found, 358.2566.

Racemic-(8*R*,9*S*)-8-((*tert*-butyldimethylsilyl)oxy)-6,6,9-trimethyl-1-(2-methylbut-3-en-2-yl)-9-vinyl-2,6,7,8,9,10-hexahydronaphtho[1,2,3-*cd*]indole (18): To a solution of **17** (300 mg, 0.84 mmol, 1.0 eq.) and **5** (514 mg, 1.51 mmol, 1.8 eq.) in DCM (10 mL) at -78 °C was added a solution of 1 M tin(IV) chloride in DCM (1.09 mL, 1.09 mmol, 1.3 eq.) and left to stir at the same temperature. The reaction was poured onto a saturated aqueous $NaHCO_3$ 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).

The tricycle (200 mg, 0.46 mmol, 1.0 eq.) was taken up in MeOH (5 mL) followed by 1 N methanolic HCl (1 N HCl in MeOH, 4.14 mL, 4.14 mmol, 9.0 eq.) and left to stir for 5 h. The reaction was poured onto a 1:1 (v:v) 2 N NaOH:DCM (15 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.

To a solution of tetracyle (50 mg, 0.14 mmol, 1.0 eq.) in DMF (2 mL) was added imidazole (14 mg, 0.21 mmol, 1.5 eq.) and TMSCl (42 mL, 0.28 mmol, 2.0 eq.) and stirred for 12 h. The reaction was diluted with brine (150 mL) and extracted with hexane (100 mL x 2), dried and concentrated to afford crude material. The crude material was purified via flash silica gel chromatography (1:4 EtOAc:hexane) to afford product **18**.

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.98 (bs, 1H), 7.15-7.09 (m, 2H), 7.00 (d, 17.1 Hz, 1H), 6.21 (dd, 10.3, 17.5 Hz, 1H), 5.92 (dd, 10.7, 17.3 Hz, 1H), 5.28 (d, 17.2 Hz, 1H), 5.18 (d, 10.2 Hz, 1H), 5.16 (d, 10.7 Hz, 1H), 5.15 (d, 17.6 Hz, 1H), 3.74 (m, 1H), 1.61-1.48 (m, 4H), 1.46 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.12 (s, 3H); **HMRS (ESI-APCI)**: [M+H] calcd for $C_{31}H_{46}NOSi$, 476.3304; found, 476.3349.

Racemic-(8*R*,9*S*)-8-hydroxy-6,6,9-trimethyl-1-(2-methylbut-3-en-2-yl)-9-vinyl-6,7,8,9-tetrahydronaphtho[1,2,3-*cd*]indol-10(2*H*)-one (21): To a solution of **17** (350 mg, 0.98 mmol, 1.0 eq.) and **12** (681 mg, 1.76 mmol, 1.8 eq.) in DCM (10 mL) at -78 °C was added a solution of 1 M tin(IV) chloride in DCM (1.27 mL, 1.27 mmol, 1.3 eq.) and left to stir at the same temperature. The reaction was poured onto a saturated aqueous $NaHCO_3$ 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 the respective tricycle in 24 % yield.

To the tricycle (100 mg, 0.19 mmol, 1.0 eq.) was added MeOH (2 mL) followed by 1 N methanolic HCl (1 N HCl in MeOH, 1.71 mL, 1.71 mmol, 9.0 eq.) and left to stir for 5 h. The reaction was poured onto a 1:1 (v:v) 2 N NaOH:DCM (6 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 the allylic alcohol tetracycle product in 5% yield.

To a solution of the allylic alcohol (10 mg, 0.03 mmol, 1.0 eq.) in CH_2Cl_2 (0.7 mL) was added MnO_2 (13 mg, 0.15 mmol, 5 eq.). After 48 h the reaction was filtered through a pad of celite, which was washed with CH_2Cl_2 (4 x 10 mL), dried and concentrated. The crude material was purified via flash silica gel chromatography (1:4 EtOAc:hexane) to afford product **21** in 78% yield.

^{1}HNMR: (300 MHz, $CDCl_3$) δ 7.99 (bs, 1H), 7.14-7.10 (m, 2H), 6.99 (d, 17.1 Hz, 1H), 6.20 (dd, 10.2, 17.6 Hz, 1H), 5.95 (dd, 10.8, 17.5 Hz, 1H), 5.25 (d, 17.4 Hz, 1H), 5.20 (d, 10.4 Hz, 1H), 5.15 (d, 10.8 Hz, 1H), 5.12 (d, 17.4 Hz, 1H), 3.84 (m, 1H), 2.75 (s, 1H), 1.61-1.50 (m, 2H), 1.57 (s, 3H), 1.53 (s, 3H), 1.49 (s, 3H), 1.29 (s, 3H), 1.08 (s, 3H); **HMRS (ESI-APCI)**: [M+H] calcd for $C_{25}H_{30}NO_2$, 376.2232; found, 376.2276.

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