Synthesis and Absolute Configuration of (+)-Hapalindole Q

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Abstract: The versatility of brominated camphor derivatives as six-membered-ring chiral building blocks in the synthesis of compounds of mixed biogenesis has been demonstrated in an eight-step synthesis of (+)-hapalindole Q from (+)-(1*R*)-9-bromocamphor in an overall 8% yield which confirms the absolute stereochemistry to be 10*R*, 11*R*, 12*R*, 15*R*.

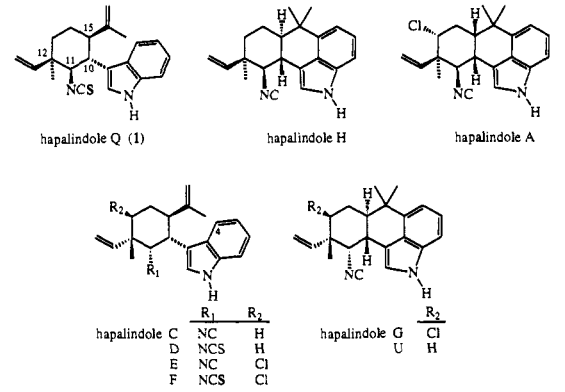
Introduction

Blue-green algae are sources of a bewildering array of structurally interesting secondary metabolites possessing a variety of biological activities.[1] Among these are the indoloterpenes of *Hapalosiphon fontinalis*,[2] metabolites of mixed biogenesis presumably arising from tryptophan and a monoterpene unit. A number of related metabolites have also been reported including other hapalindoles,[3] hapalonamides,[4] cyclopropane-containing hapalindolinones,[5] ambiguine isonitriles,[6] and Fischer indole L.[7] Although syntheses of racemic hapalindoles J, M, H, and U have been reported by Natsume,[8] there has yet to be published an enantiospecific synthesis of any member of this class. We now report an *8-step enantiospecific synthesis* of (+)-hapalindole Q ((+)-**1**; Chart I), from (+)-(1*R*)-9-bromocamphor which confirms the absolute stereochemistry proposed by Moore[9] and allows widespread absolute stereochemical assignment within this family.

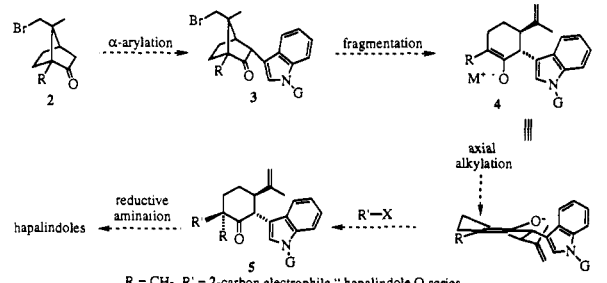
Strategy

We desired a general approach to both the tri- and tetracyclic metabolites in this series. Biogenetically, it is reasonable that the tetracycles arise via cationic cyclization of a precursor in the tricyclic series. Our approach follows this tenet, and hence we set as an initial goal the production of a tricyclic seco metabolite. Moore apparently reported such biogenetic cyclizations of the isopropenyl groups of hapalindoles C and E onto the C4 position of their respective indole rings.[9] However, this was an error in the manuscript,[10] and no such cyclizations have been observed in the natural product series. However, we have carried out similar

Chart I



Scheme I. Strategy for Construction of C10–C15 Trans-Substituted Hapalindoles



cyclizations onto furans,[11] albeit in low to moderate yields.[12] In any case, we feel that cyclization of an appropriately substituted intermediate will lead from the tricyclic to the tetracyclic series. A unified approach to two series of metabolites containing C10–C15 trans ring fusions is shown in Scheme I. α-Arylation of the 9-bromocamphor derivative **2** should lead to **3** with the 3-indolyl substituent in the thermodynamically favored endo position. Fragmentation of the C1–C7 bond of this substance leads to the enolate **4**. We speculated that alkylation of **4** would take place via a transition state in which the isopropenyl and indolyl groups occupy equatorial and pseudoequatorial orientations, respectively, and that the electrophile would enter axially producing the ketone **5**. Appropriate choice of starting camphor derivative and alkylating agent would allow entry into either the hapalindole C

(1) (a) Moore, R. E. In *Marine Natural Products, Chemical and Biological Perspectives*; Scheuer, P. J., Ed.; Academic Press: 1977; Vol. 1. (b) Periodic reviews of blue-green algae metabolite isolations are performed by: Faulkner, D. J. *Nat. Prod. Rep.* **1991**, *8*, 97. Also see previous installments in this series.

(2) Moore, R. E.; Cheuk, C.; Patterson, G. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 6456.

(3) Moore, R. E.; Cheuk, C.; Yang, X.-Q. G.; Patterson, G. M. L.; Bonjouklian, R.; Smitka, T. A.; Mynderse, J. A.; Foster, R. S.; Jones, N. D.; Swartzendruber, J. K.; Deeter, J. B. *J. Org. Chem.* **1987**, *52*, 1036.

(4) Moore, R. E.; Yang, X.-Q. G.; Patterson, G. M. L.; Bonjouklian, R.; Smitka, T. A. *Phytochemistry* **1989**, *28*, 1565.

(5) Schwartz, R. E.; Hirsch, C. F.; Springer, J. P.; Pettibone, D. J.; Zink, D. L. *J. Org. Chem.* **1987**, *52*, 3704.

(6) Smitka, T. A.; Bonjouklian, R.; Doolin, L.; Jones, N. D.; Deeter, J. B.; Yoshida, W. Y.; Prinsep, M. R.; Moore, R. E.; Patterson, G. M. L. *J. Org. Chem.* **1992**, *57*, 857.

(7) Park, A.; Moore, R. E.; Patterson, G. M. L. *Tetrahedron Lett.*, in press.

(8) (a) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1989**, *30*, 1815. (b) Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6331. (c) Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6343. (d) Muratake, H.; Kumagami, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6351.

(9) Bonjouklian, R.; Moore, R. E.; Patterson, G. M. L. *J. Org. Chem.* **1988**, *53*, 5866.

(10) The error in the manuscript concerns the structures of compounds **18** and **19** in Scheme II. These should instead be formulated as the corresponding secondary amines arising via complete hydrolysis of the isonitriles (private communication with Prof. Dick Moore).

(11) (a) Vaillancourt, V.; Richou, O.; Faulkner, D. J.; Albizati, K. F. *J. Org. Chem.* **1989**, *54*, 4729. (b) Vaillancourt, V.; Agharahimi, M. R.; Sundram, U. N.; Richou, O.; Faulkner, D. J.; Albizati, K. F. *J. Org. Chem.* **1991**, *56*, 378.

(12) Subsequent to publication of the original manuscripts, we have found that the addition of propylene oxide to the reaction mixture as an acid scavenger increases the yields of these processes substantially.

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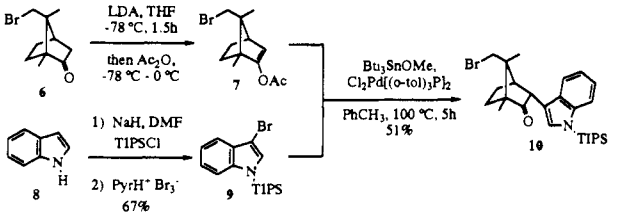
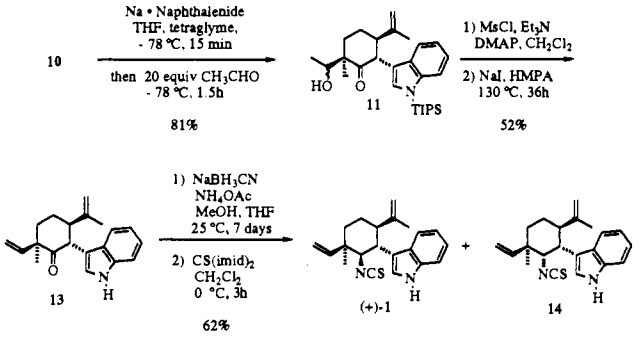
Scheme II. Arylation of (+)-9-Bromocamphor



Scheme III. Conversion of **10** to (+)-Hapalindole Q

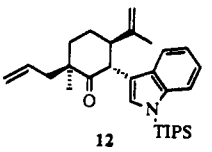


or Q stereochemical series. Reductive amination or a reduction–Mitsunobu inversion sequence performed on **5** would provide an amine which could be converted to the isonitrile or isothiocyanate functionalities in the later stages of a relatively short and efficient pathway.

Results

We have studied the coupling of aromatic moieties to camphor as a general strategy for the construction of compounds of mixed biogenesis containing monoterpene substructures. Using this strategy, a general approach to both the tricyclic and tetracyclic hapalindoles requires the coupling of an appropriately substituted indole fragment to the 3-position of substituted camphor derivatives. Specifically, the synthetic strategy requires the coupling of the C3 position of indole to the C3 position of 9-bromocamphor in an endo orientation. Our first attempts utilized the arylation method recently described[13] which involved an α-halo ketone displacement by aryl cuprates. This was unsuccessful due to the known[14] thermal instability of 3-indolyl cuprate reagents. A second method of camphor α-arylation was uncovered and features a $Cl_2Pd[(o\text{-tol})_3P]_2$-catalyzed reaction of the protected 3-bromoindole **9** with the tin enolate of 9-bromocamphor, which was generated in situ from the enol acetate **7** (Scheme **II**).[15] This resulted in a 51% yield of the desired endo camphor derivative **10**. Up to 10% of the undesired exo isomer was also obtained. Other catalysts were also examined, and $Pd(PPh_3)_4$, $Cl_2Pd(PhCN)_2$, $Cl_2Pd(PPh_3)_2$, and tris(dibenzylideneacetone)dipalladium(0) were all found to be ineffective for the coupling reaction.

The intermediate **10** underwent fragmentation of the C1–C7 bond by treatment with sodium naphthalenide at −78 °C (Scheme III).[16] The resulting enolate was directly alkylated with acetaldehyde resulting in an 81% yield of products (**11**), which were isomeric only at the carbinol center which would subsequently be removed. At this point we did not know the stereochemistry at the quaternary carbon. This would have to await completion of the pathway. We also found that alkylation of the enolate with allyl bromide gave a single product (**12**) in high yield, which,



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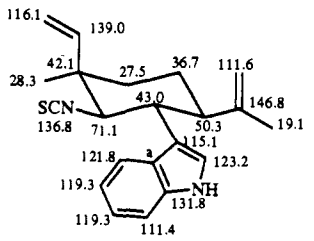
by analogy, probably possesses the same relative stereochemistry as the aldol adduct. This stereospecific transformation of the bicyclo[2.2.1] ring system to a cyclohexanone possessing a chiral quaternary α-carbon is clearly the highlight of the strategy and generates substituents in the proper arrangement to generate the tri- and tetracyclic ring systems of several *Hapalosiphon* metabolites. Mesylation of **11** under standard conditions provided a mixture of two isomeric mesylates in 86% yield. Attempts at elimination using DBU, DBN, or DABCO were unsuccessful. Elimination was achieved by an iodide ion promoted thermal elimination[17] to give the ketone **13** as a single stereoisomer in 60% yield. In order to confirm that the diastereomeric mixture **11** is isomeric only at the carbinol carbon, the alcohols were separated and each was subjected to the same mesylation and elimination conditions, which yielded the same product (**13**) in both instances. Reductive amination employing ammonium acetate and sodium cyanoborohydride was followed by treatment with 1,1′-thiocarbonyldiimidazole, which provided a 62% yield of (+)-hapalindole Q ((+)-**1**) together with 19% of epimer **14**. The ^{1}H NMR spectrum of synthetic (+)-**1** ($[\alpha]^{25}_D = +30°$ (c = 1.26, CH_2Cl_2))[18] was identical to that of an authentic sample[19] of naturally occurring (+)-**1**.

The ^{13}C NMR spectrum of **1** had not been reported, and we were concerned that we could not observe all of the carbons in $CDCl_3$ and that other signals were quite broad. Further, the proton NMR spectrum of (+)-**1** showed three broad peaks for three protons which figure prominently in the structural assignment. Wishing to clarify the situation, we undertook a detailed spectroscopic study of **1**. It is reasonable that the problem with the broad peaks in the ^{1}H NMR spectrum is related to the absence (via extensive broadening) of several peaks in the ^{13}C NMR spectrum and this might be due to a dynamic process which is relatively slow on the NMR time scale.[20] This was confirmed by taking the spectra at 60 °C, which resolved problems with both spectra. The high-temperature ^{1}H NMR spectrum showed a doublet (J = 11 Hz) at 3.88 ppm, a sharp triplet (J = 11 Hz) at 3.18 ppm, and a broad triplet (J = 10 Hz) at 2.75 ppm for the three previously broad signals. These are assigned to the six-membered-ring methine hydrogens at C11, C10 and C15, respectively. At room temperature the ^{13}C NMR spectrum showed signals for only 14 of the 21 carbons and also showed very broad resonances for other carbon signals. Again, these signals sharpened at 60 °C, and we could finally observe 20 of the 21 carbons. Further carbon–proton correlation studies at 60 °C allowed assignment of all carbon signals, shown in structure **15**. These full spectroscopic assignments should aid biosynthetic studies and allow further assignments in this and related metabolite families.

Conclusion

An eight-step sequence for the synthesis of (+)-hapalindole Q from (+)-(1*R*)-9-bromocamphor has been accomplished in an

(13) Vaillancourt, V.; Albizati, K. *J. Org. Chem.* **1992**, *57*, 3627.
(14) Wenkert, E.; Angell, E. C.; Ferreira, V. F.; Michelotti, E. L.; Piettre, S. R.; Sheu, J.-H.; Swindell, C. S. *J. Org. Chem.* **1986**, *51*, 2343.
(15) (a) Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *J. Chem. Soc., Chem. Commun.* **1983**, 344. (b) Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 242. Further references to the use of 3-halo- and 3-triflate-substituted indoles in palladium cross-coupling reactions include: Gribble, G. W.; Conway, S. C. *Synth. Commun.* **1992**, *22*, 2129. Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657. Harrington, P. J.; Hegedus, L. S.; McDaniel, K. F. *J. Am. Chem. Soc.* **1987**, *109*, 4335. Merlic, C. A.; Semmelhack, M. *J. Organomet. Chem.* **1990**, *391*, C23.
(16) Fragmentation was achieved in the same manner as previously reported in ref 11a and b.
(17) Mehta, G.; Padma, S. *J. Am. Chem. Soc.* **1987**, *109*, 2212.
(18) Reported value[3] $[\alpha]^{25}_D = +24.1°$ (c = 1.1, CH_2Cl_2).
(19) Spectral data kindly provided by Prof. R. E. Moore.
(20) It is noteworthy that the epimeric compound **14** shows no such broadening in any of its room temperature spectra.



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[a]not observed

overall 8% yield and confirms the absolute stereochemistry to be 10*R*, 11*R*, 12*R*, 15*R*. This demonstrates the versatility of camphor as a six-membered-ring chiral building block in the synthesis of compounds of mixed biogenesis. Full ^1H and ^{13}C spectroscopic structural assignments of **1** have been made, exposing the occurrence of a slow dynamic NMR process which had previously made full assignment difficult. Work in this area is continuing and will be reported in due course.

Experimental Section

General Methods. ^1H NMR data were measured at 300 MHz and ^{13}C data at 75 MHz. The residual singlet at δ 7.26 and the triplet centered at δ 77.0 were used as internal standards for ^1H and ^{13}C spectra, respectively. Infrared spectroscopic samples were prepared as neat oils (liquids) or as KBr pellets (solids). All electron-impact high-resolution mass spectral (HRMS) data were measured at 70 eV. Optical rotations were measured at the designated concentrations at 25 °C on a Perkin Elmer Model 241MC polarimeter. All experiments were carried out under an atmosphere of dry argon or nitrogen in flame-dried flasks fitted with addition funnels of the pressure-equalizing type. THF and diethyl ether were freshly distilled from sodium/benzophenone ketyl and were transferred via syringes. Alkyllithium reagents were obtained from the Aldrich Chemical Company as standard solutions. High-performance liquid chromatography (HPLC) was performed on either a Varian 5000 liquid chromatograph or a semipreparative component system obtained from the Rainin Instrument Corporation. HPLC separations were performed on 250 × 20 mm 8-μm silica Magnum semipreparative columns obtained from the Rainin Instrument Corporation.

***N*-(Triisopropylsilyl)indole.** A solution of 4.68 g (40 mmol) of indole (**8**) in 10 mL of DMF was added dropwise to a solution of 1.20 g (50 mmol) of sodium hydride in 50 mL of DMF at 0 °C under argon. When H_2 evolution had ceased, 9 mL (42 mmol) of triisopropylsilyl chloride was added and stirring was continued overnight. The reaction mixture was partitioned between pentane and water. The aqueous phase was extracted three times with pentane. The combined organic layers were washed twice with water and once with brine, dried over Na_2SO_4, and condensed. The crude product was chromatographed on silica, eluting with hexanes to yield 8.16 g (75%) of the protected indole: ^1H NMR ($CDCl_3$) δ 7.76 (d, J = 7 Hz, 1 H), 7.63 (d, J = 8 Hz, 1 H), 7.36 (d, J = 3 Hz, 1 H), 7.24 (overlapping multiplets, 2 H), 6.74 (d, J = 3 Hz, 1 H), 1.82 (septet, J = 7 Hz, 3 H), 1.26 (d, J = 7 Hz, 18 H); ^{13}C NMR ($CDCl_3$) δ 140.8, 131.4, 131.0, 121.3, 120.5, 119.8, 113.8, 104.8, 18.1, 12.8; IR (neat) 2941, 2860, 1509, 1457, 1445, 1267, 1134, 1006, 972, 880, 735 cm^{-1}. HRMS m/z calcd for $C_{17}H_{27}NSi$, 273.1912; found, 273.1911.

3-Bromo-*N*-(triisopropylsilyl)indole (9). To a solution of 5.56 g (20 mmol) of *N*-TIPS-indole in 30 mL of dry pyridine at 0 °C under argon was added dropwise a solution of 6.40 g (20.4 mmol) of pyridinium bromide perbromide in 30 mL of dry pyridine. When addition was complete, the reaction was poured into cold pentane. The aqueous layer was extracted three times with pentane. The combined organic layers were washed three times with cold water, dried over Na_2SO_4, and condensed. The crude product was chromatographed on alumina, eluting with hexanes to yield 6.27 g (89%) of the brominated indole **9**: mp 62–64 °C; ^1H NMR ($CDCl_3$) δ 7.56 (quartet, J = 3 Hz, 1 H), 7.47 (quartet, J = 3 Hz, 1 H), 7.23 (s, 1 H), 7.19 (quartet, J = 3 Hz, 2 H), 1.68 (septet, J = 7 Hz, 3 H), 1.14 (d, J = 7 Hz, 18 H); ^{13}C NMR ($CDCl_3$) δ 140.1, 130.0, 129.7, 122.5, 120.5, 119.1, 114.1, 93.6, 18.0, 12.8; IR 2943, 2859, 1436, 1274, 1133, 1006, 731, 513 cm^{-1}. HRMS m/z calcd for $C_{17}H_{26}BrNSi$, 351.1018; found, 351.1022. Anal. Calcd for $C_{17}H_{26}BrNSi$: C, 57.94; H, 7.44; N, 3.97. Found: C, 58.04; H, 7.49; N, 3.92.

(+)-(1*R*,3*R*,7*R*)-*endo*- and -exo-7-(Bromomethyl)-1,7-dimethyl-3-[3-(*N*-(triisopropylsilyl)indolyl)]bicyclo[2.2.1]heptan-2-one (10-*exo* and 10-*endo*). A stirred solution of 3.65 g (13.4 mmol) of 9-bromocamphor enol acetate (**7**),[21] 3.88 mL (13.4 mmol) of tributyltin methoxide, 3.14 g (8.9 mmol) of 3-bromo-*N*-(triisopropylsilyl)indole (**9**), 0.071 g (1 mole %) of $Cl_2Pd[(o\text{-tol})_3P]_2$, and 10 mL of toluene was heated to 100 °C for 5 h. The solution was then cooled to room temperature and chromatographed through a short silica column, eluting with hexane–EtOAc (90:10). The crude reaction product was rechromatographed on silica, eluting with hexane–EtOAc (98:2) to yield 2.26 g (4.59 mmol, 51%) of the desired endo indolated camphor derivative (**10-*endo***): $[\alpha]^{25}_D$ = +164 (c = 0.497, $CHCl_3$); mp 55–58 °C; ^1H NMR ($CDCl_3$) δ 7.55 (dd, J = 7, 2 Hz, 1 H), 7.49 (d, J = 8 Hz, 1 H), 7.15 (m, J = 1, 7 Hz, 2 H), 7.05 (s, 1 H), 4.02 (d, J = 4 Hz, 1 H), 3.69 (d, J = 10 Hz, 1 H), 3.33 (d, J = 10 Hz, 1 H), 2.95 (t, J = 4 Hz, 1 H), 1.68 (septet, J = 8 Hz, 3 H), 1.5–1.8 (overlapping multiplets, 2 H), 1.40 (m, 1 H), 1.24 (s, 3 H), 1.1–1.3 (overlapping multiplets, 1 H), 1.14 (d, J = 4 Hz, 9 H), 1.11 (d, J = 4 Hz, 9 H), 1.07 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 217.5, 141.4, 130.5, 129.0, 121.7, 119.5, 118.7, 114.0, 113.1, 59.1, 50.1, 47.7, 46.0, 40.1, 30.0, 20.7, 18.0, 16.7, 12.7, 10.0; IR (thin film) 2950, 2859, 1739, 1443, 1340, 1006, 957, 879, 731, 654, 513 cm^{-1}. HRMS m/z calcd for $C_{27}H_{40}BrNOSi$, 501.2062; found, 501.2055. Anal. Calcd for $C_{27}H_{40}BrNOSi$: C, 64.5; H, 8.02; N, 2.79. Found: C, 64.39; H, 7.90; N, 2.71. Up to 10% of the undesired exo isomer was also obtained (**10-*exo***): ^1H NMR ($CDCl_3$) δ 7.74 (m, 1 H), 7.48 (m, 1 H), 7.16 (m, 2 H), 7.13 (s, 1 H), 3.62 (d, J = 10 Hz, 1 H), 3.58 (s, 1 H), 3.19 (d, J = 10 Hz, 1 H), 3.02 (d, J = 4 Hz, 1 H), 2.15 (m, 1 H), 1.7–1.9 (overlapping multiplets, 3 H), 1.69 (septet, J = 7 Hz, 3 H), 1.15 (d, J = 7 Hz, 9 H), 1.12 (d, J = 7 Hz, 9 H), 1.05 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 217.1, 141.1, 130.6, 127.9, 121.6, 119.6, 119.5, 115.4, 113.8, 58.0, 51.4, 51.3, 45.8, 40.9, 29.4, 28.2, 18.0, 17.8, 12.7, 9.7; IR 2954, 2860, 2737, 1442, 1135, 1010, 878, 734 cm^{-1}. HRMS m/z calcd for $C_{27}H_{40}BrNOSi$, 501.2062; found 501.2069. Anal. Calcd for $C_{27}H_{40}BrNOSi$: C, 64.52; H, 8.02; N, 2.79. Found: C, 64.32; H, 7.91; N, 2.62.

(+)-(2*R*,5*R*,6*R*)-2-(1-Hydroxyethyl)-5-isopropenyl-2-methyl-6-[3-(*N*-(triisopropylsilyl)indolyl)]cyclohexanone (11). A solution of 750 mg (1.5 mmol) of **10** in 3 mL of dry THF was cooled to –78 °C under argon. The cooled solution was then titrated with ca. 15 mL (6 mmol) of a freshly prepared 0.4 M sodium naphthalenide –0.4 M tetraethylene glycol dimethyl ether solution in THF until a deep-green color persisted. The solution was allowed to stir an additional 20 min at –78 °C and then 1.68 mL (30 mmol) of freshly distilled acetaldehyde was syringed in dropwise. The solution was stirred at –78 °C for 1.5 h and then quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted three times with ether. The combined organic layers were washed two times with saturated aqueous $NaHCO_3$ and once with brine, dried with Na_2SO_4 and condensed. The crude product was chromatographed on silica, eluting first with hexanes and then with hexane–EtOAc (90:10) to yield 570 mg (1.22 mmol, 81%) of a mixture of the desired alcohols. The alcohols were separated by HPLC, eluting with hexane–EtOAc (80:20) for the purpose of identification. Major alcohol (**11a**): $[\alpha]^{25}_D$ = +60° (c = 0.539, $CHCl_3$); mp 58–60 °C; ^1H NMR ($CDCl_3$) δ 7.46 (m, 2 H), 7.08 (overlapping multiplets, 2 H), 7.03 (s, 1 H), 4.66 (s, 1 H), 4.60 (overlapping multiplets, 2 H), 4.34 (d, J = 11 Hz, 1 H), 2.98 (dt, J = 11, 4 Hz, 1 H), 2.20–1.88 (overlapping multiplets, 3 H), 1.68 (septet, J = 7 Hz, 3 H), 1.60–1.82 (overlapping multiplets, 2 H), 1.58 (s, 3 H), 1.22 (d, J = 6 Hz, 3 H), 1.15 (d, J = 7 Hz, 9 H), 1.13 (d, J = 7 Hz, 9 H), 1.06 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 213.1, 146.8, 140.9, 131.1, 129.9, 120.9, 119.1, 113.6, 111.9, 70.4, 53.1, 51.5, 48.1, 35.6, 26.9, 18.5, 18.0, 17.5, 16.3, 12.7; IR (neat) 3492, 3063, 3040, 2941, 2866, 1707, 1640, 1605, 1447, 1379, 1161, 1142, 878, 732 cm^{-1}. HRMS m/z calcd for $C_{29}H_{45}NO_2Si$, 467.3219; found, 467.3224. Anal. Calcd for $C_{29}H_{45}NO_2Si$: C, 74.46; H, 9.70; N, 2.99. Found: C, 74.23; H, 9.66; N, 3.02. Minor alcohol (**11b**): $[\alpha]^{25}_D$ = +89.4 (c = 0.865, $CHCl_3$); mp 148–150 °C; ^1H NMR ($CDCl_3$) δ 7.46 (d, J = 8 Hz, 1 H), 7.35 (d, J = 8 Hz, 1 H), 7.08 (quintet, J = 7 Hz, 2 H), 6.99 (s, 1 H), 4.59 (s, 1 H), 4.53 (s, 1 H), 4.43–4.47 (overlapping multiplets, 1 H), 4.00 (d, J = 12 Hz, 1 H), 2.94 (td, J = 11, 5 Hz, 1 H), 2.42 (dt, J = 14, 4 Hz, 1 H), 2.10–2.26 (m, 1 H), 1.94 (broad s, 1 H), 1.78–1.90 (m, 2 H), 1.67 (septet, J = 8 Hz, 3 H), 1.56 (s, 3 H), 1.17 (overlapping multiplets, 3 H), 1.14 (d, J = 7 Hz, 9 H), 1.13 (d, J = 8 Hz, 9 H), 1.07 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 212.7, 146.6, 141.0, 130.9, 130.1, 120.9, 119.2, 118.7, 113.9, 112.0, 68.8, 53.9, 52.0, 49.6, 34.0, 26.4, 18.6, 18.3, 18.1, 17.1, 12.8; IR (neat) 3497, 2941, 2865, 1697, 1442, 1161, 1142, 1008, 950, 880, 733

(21) Joshi, G. C.; Chambers, W. D.; Warnhoff, E. W. *Tetrahedron Lett.* **1967**, 3613.

cm^{-1}. HRMS m/z calcd for (M + H) $C_{29}H_{45}NO_2Si$, 468.3297; found, 468.3302. Anal. Calcd for $C_{29}H_{45}NO_2Si$: C, 74.46; H, 9.70; N, 2.99. Found: C, 74.22; H, 9.57; N, 3.06.

(+)-(2*R*,5*R*,*R*)-5-Isopropenyl-2-(1-((methylsulfonyl)oxy)ethyl)-2-methyl-6-[3-(*N*-(triisopropylsilyl)indolyl)]cyclohexanone (Mesylate of 11). A solution of 1.05 mL (7.5 mmol) of triethylamine and 0.05 g of 4-(dimethylamino)pyridine (DMAP) was cooled to 0 °C. To this was added a solution of 0.35 g (0.75 mmol) of the alcohol **11** in 3 mL of dry CH_2Cl_2 followed by addition of 0.29 mL of methanesulfonyl chloride. The resulting mixture was allowed to warm to room temperature and stirred for an additional 4 h. The reaction was then quenched with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted three times with ether. The combined organic layers were washed twice with saturated aqueous $NaHCO_3$ and once with brine, dried over Na_2SO_4, and condensed. The crude product was chromatographed on silica, eluting with hexane–EtOAc (85:15) to yield 0.35 g (0.65 mmol, 86%) of the desired mesylates. Major mesylate: $[\alpha]^{25}_D = +61.4°$ ($c = 0.728$, $CHCl_3$); ^{1}H NMR ($CDCl_3$) ∂ 7.40–7.54 (m, 2 H), 7.07 (m, 2 H), 6.98 (s, 1 H), 5.80 (quartet, $J = 6$ Hz, 1 H), 4.4–4.5 (overlapping multiplets, 3 H), 2.89 (m, 1 H), 2.80 (s, 3 H), 2.09 (m, 2 H), 1.78 (m, 2 H), 1.67 (septet, $J = 7$ Hz, 3 H), 1.57 (s, 3 H), 1.10–1.15 (overlapping multiplets, 24 H); ^{13}C NMR ($CDCl_3$) ∂ 209.6, 145.7, 141.2, 130.8, 130.6, 120.8, 119.5, 119.1, 113.8, 113.2, 112.4, 80.0, 53.7, 52.8, 48.5, 39.0, 36.1, 26.8, 18.5, 18.0, 17.0, 16.0, 12.7; IR (thin film) 2439, 2864, 1709, 1447, 1329, 1166, 1010, 961, 886, 730 cm^{-1}. HRMS m/z calcd for $C_{30}H_{47}NO_4SSi$, 545.2995; found, 545.3003. Anal. Calcd for $C_{30}H_{47}NO_4SSi$: C, 66.01; H, 8.68; N, 2.57. Found: C, 66.29; H, 8.79; N, 2.61. Minor mesylate: $[\alpha]^{25}_D = +110°$ ($c = 1.22$, $CHCl_3$); mp 146–148 °C; ^{1}H NMR ($CDCl_3$) ∂ 7.45 (d, $J = 7$ Hz, 1 H), 7.32 (d, $J = 7$ Hz, 1 H), 7.08 (quintet, $J = 7$ Hz, 2 H), 6.97 (s, 1 H), 5.53 (quartet, $J = 6$ Hz, 1 H), 4.56 (s, 1 H), 4.51 (s, 1 H), 3.96 (d, $J = 12$ Hz, 1 H), 3.03 (s, 3 H), 2.93 (dt, $J = 11$, 5 Hz, 1 H), 2.20–2.42 (overlapping multiplets, 3 H), 1.80–1.92 (m, 1 H), 1.67 (septet, $J = 8$ Hz, 3 H), 1.56 (s, 3 H), 1.40 (d, $J = 6$ Hz, 3 H), 1.10–1.16 (overlapping multiplets, 21 H); ^{13}C NMR ($CDCl_3$) ∂ 209.9, 146.1, 141.0, 130.6, 130.3, 121.1, 119.3, 118.6, 113.9, 112.7, 112.4, 79.0, 53.3, 52.1, 50.0, 38.8, 34.1, 26.0, 18.5, 18.1, 17.4, 16.6, 12.8; IR (thin film) 2936, 2859, 1703, 1443, 1344, 1168, 907, 781, 731, 527 cm^{-1}. HRMS m/z calcd for $C_{30}H_{47}SO_4NSi$, 545.2995; found, 545.3000.

(+)-(2*R*,5*R*,6*R*)-5-Isopropenyl-2-methyl-6-(3-indolyl)-2-vinylcyclohexanone (13). A solution of 0.223 g (0.409 mmol) of the mesylates in 1 mL of ether was added to a solution of 0.012 g (0.082 mmol) of NaI in 5 mL of HMPA under argon. The resulting solution was heated to 130 °C for 36 h. The mixture was then partitioned between ether and water. The aqueous layer was extracted three times with ether. The combined organic layers were washed twice with saturated aqueous $NaHCO_3$ and once with brine, dried over Na_2SO_4, and condensed. The crude product was chromatographed on silica, eluting with hexane–EtOAc (85:15) to yield 72.5 mg (0.25 mmol, 60%) of the desired eliminated product: $[\alpha]^{25}_D = +146.1°$ ($c = 0.72$, $CHCl_3$); mp 173–174 °C; ^{1}H NMR ($CDCl_3$) ∂ 8.17 (s, 1 H), 7.37 (d, $J = 8$ Hz, 1 H), 7.05–7.25 (overlapping multiplets, 3 H), 6.63 (d, $J = 2$ Hz, 1 H), 6.22 (dd, $J = 18$, 11 Hz, 1 H), 5.39 (d, $J = 11$ Hz, 1 H), 5.24 (d, $J = 18$ Hz, 1 H), 4.64 (s, 1 H), 4.56 (s, 1 H), 4.30 (d, $J = 12$ Hz, 1 H), 2.96 (dt, $J = 12$, 4 Hz, 1 H), 2.15–2.35 (m, 2 H), 1.80–1.95 (m, 2 H), 1.56 (s, 3 H), 1.29 (s, 3 H); ^{13}C NMR ($CDCl_3$) ∂ 211.4, 146.6, 143.0, 136.0, 127.4, 123.6, 121.2, 118.9, 118.6, 116.0, 111.9, 111.4, 110.9, 53.2, 52.2, 48.4, 39.1, 28.5, 24.9, 18.2; IR 3345, 3062, 2957, 2921, 1696, 1450, 1098, 907, 886, 731 cm^{-1}. HRMS m/z calcd for $C_{20}H_{23}NO$, 293.1179; found, 293.1781. Anal. Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.79; H, 7.84; N, 4.78.

(+)-Hapalindole Q ((+)-1). A solution of 17 mg (0.058 mmol) of ketone **13**, 180 mg (2.33 mmol) of NH_4OAc, and 78 mg (0.58 mmol) of $NaBH_3CN$ in 4 mL of MeOH and 1 mL of THF was stirred at room temperature for 7 days. The MeOH and THF were evaporated, and the residue was partitioned between ether and saturated aqueous $NaHCO_3$. The aqueous layer was extracted three times with ether. The combined organic layers were washed once with brine, dried, and condensed. The residue was then taken up into 1 mL of CH_2Cl_2, and the resulting solution was cooled to 0 °C. To this was added 11 mg (0.062 mmol) of 1,1′-thiocarbonyldiimidazole. The solution was allowed to warm to room temperature and stirred for an additional 4 h. The solvent was evaporated, and the residue was chromatographed on silica, eluting with hexane–CH_2Cl_2 (60:40) to yield 3.7 mg (20%) of epihapalindole Q (**14**): ^{1}H NMR ($CDCl_3$) ∂ 8.11 (broad s, NH, 1 H), 7.45 (d, $J = 8$ Hz, 1 H), 7.38 (d, $J = 8$ Hz, 1 H), 7.20 (dt, $J = 7$, 1 Hz, 1 H), 7.03–7.14 (overlapping m, 2 H), 6.01 (dd, $J = 18$, 11 Hz, 1 H), 5.38 (d, $J = 11$ Hz, 1 H), 5.29 (d, $J = 18$ Hz, 1 H), 4.81 (s, 1 H), 4.64 (s, 1 H), 3.95 (d, $J = 2$ Hz, 1 H), 3.52 (dd, $J = 12$, 2 Hz, 1 H), 2.81 (dt, $J = 11$ Hz, 4 H), 1.6–1.88 (overlapping m, 4 H), 1.47 (s, 3 H), 1.16 (s, 3 H); ^{13}C NMR ($CDCl_3$) ∂ 147.4, 142.8, 135.7, 126.6, 124.8, 123.8, 122.0, 119.5, 117.5, 115.0, 114.4, 112.2, 111.4, 68.6, 43.7, 41.7, 37.7, 31.4, 28.7, 28.5, 18.6; IR (neat) 3410, 3060, 2921, 2126, 2088 (broad), 1452, 1091, 913, 881, 735 cm^{-1}. HRMS m/z calcd for $C_{21}H_{24}N_2S$, 336.1660; found 336.1662. Further elution with the same solvent system provided 11.8 mg (0.035 mmol, 62%) of (+)-hapalindole Q ((+)-**1**) spectroscopically identical to the natural material: $[\alpha]^{25}_D = +30.4°$ ($c = 1.26$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) ∂ 8.00 (broad s, 1 H), 7.67 (d, $J = 8$ Hz, 1 H), 7.35 (d, $J = 8$ Hz, 1 H), 7.19 (t, $J = 7$ Hz, 1 H), 7.12 (t, $J = 7$ Hz, 1 H), 7.00 (d, $J = 2$ Hz, 1 H), 6.25 (dd, $J = 18$, 11 Hz, 1 H), 5.40 (d, $J = 11$ Hz, 1 H), 5.30 (d, $J = 18$ Hz, 1 H), 4.53 (s, 1 H), 4.46 (s, 1 H), 3.88 (broad s, 1 H), 3.15 (broad t, $J = 10$ Hz, 1 H), 2.79 (broad s, 1 H), 2.01 (d, $J = 13$ Hz, 1 H), 1.83 (m, 1 H), 1.60 (d, $J = 13$ Hz, 2 H), 1.52 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR ($CDCl_3$, 60 °C) ∂ 146.8, 139.0, 136.8, 131.8, 123.4, 121.8, 119.3 (two overlapping signals), 116.1, 115.1, 111.6, 111.4, 71.1, 50.3, 43.0, 42.1, 36.7, 28.3, 27.5, 19.1; IR (neat) 3421, 3074, 2956, 2923, 2178, 2092, 1634, 1451, 1326, 1091, 887, 737 cm^{-1}. HRMS m/z calcd for $C_{21}H_{24}N_2S$, 336.1660; found, 336.1664. Anal. Calcd for $C_{21}H_{24}N_2S$: C, 74.96; H, 7.19; N, 8.33. Found: C, 74.64; H, 7.05; N, 7.94.

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