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SYNTHETIC STUDIES ON PASPALINE: LEWIS ACID-MEDIATED SEQUENTIAL CONSTRUCTION OF A-E RING SKELETON†

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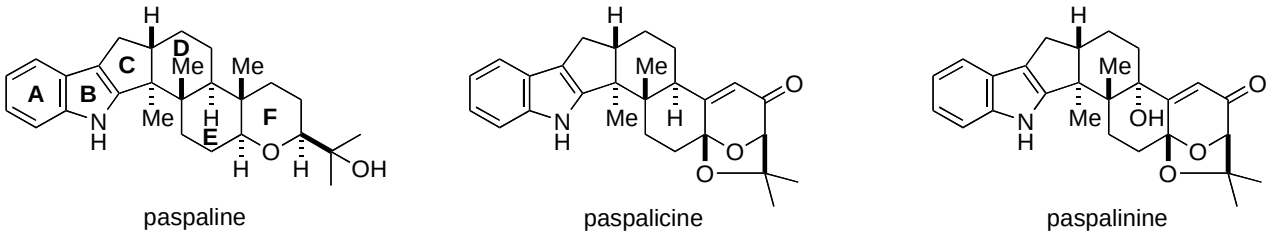
Abstract – The common pentacyclic skeleton of indole diterpene alkaloids, paspaline and its derivatives was constructed by a sequential reaction. The appropriate choice of the protecting group on the indole nitrogen was critical for the formation of bis(methylthio)allylic alcohol, which then underwent sulfonium ion formation and intramolecular electrophilic C-C-bond formation at the indole 3-position.

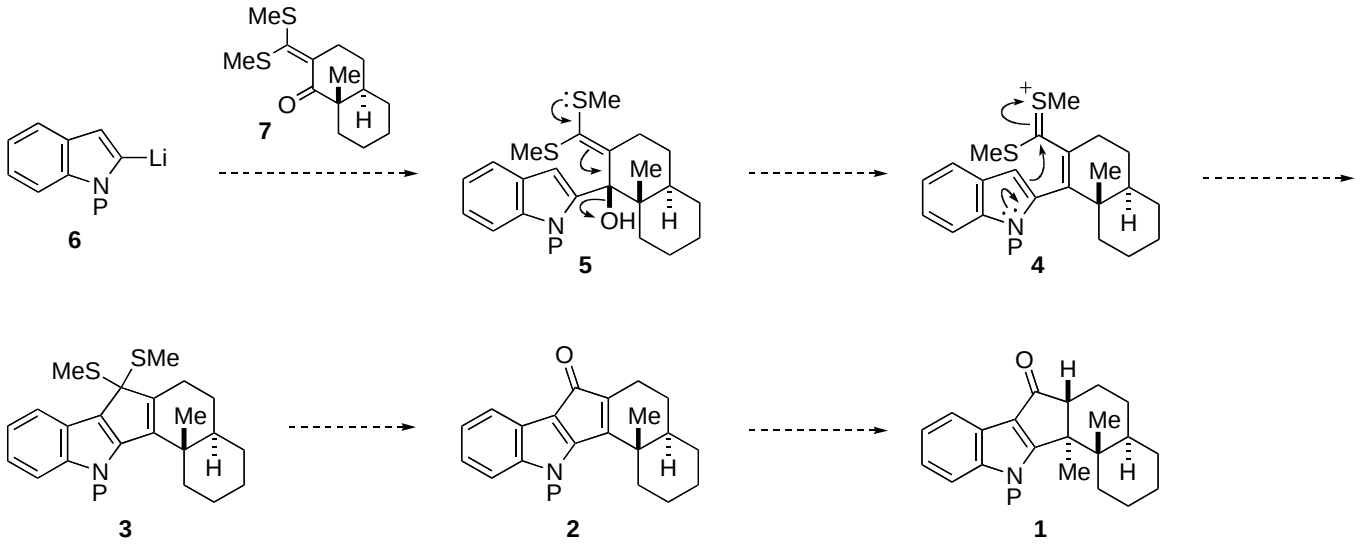
Since a number of indole alkaloids have potent bioactivities, synthetic studies on this class of natural products have been the subject of intense research in organic synthesis. Among them, a family of indole diterpenes containing paspaline,[1] paspalicine,[2] and paspalinine[3] has attracted a great deal of interest from the synthetic community because of their unique structure and significant bioactivity.[4] Despite numerous synthetic efforts, however, few efficient synthetic strategies are available for construction of the common pentacyclic A to E ring skeleton including an indole nucleus. To date, a limited number of total syntheses of these alkaloids have been reported.[5] In this paper, we described a novel strategy for construction of the core pentacyclic framework of these compounds.



Scheme 1. Paspaline and Its Derivatives

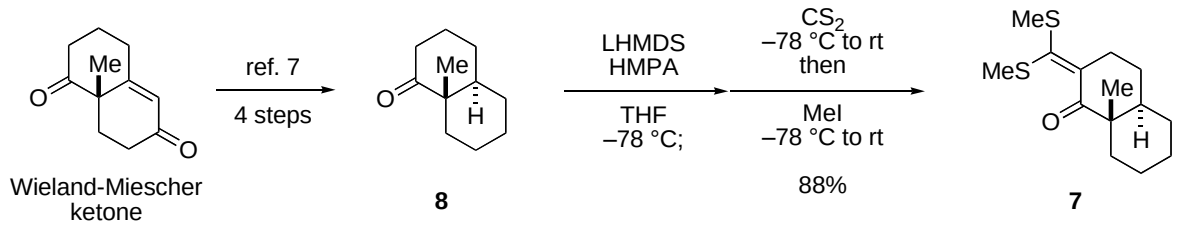
†This paper is dedicated to Professor Dr. Albert Padwa on the occasion of his 75th birthday.

Considering an introduction of the angular methyl group at the later stage of synthesis, we selected pentacyclic indole **2** as a model compound in this synthetic study (Scheme 2). For formation of the cyclopentenone ring, we planned to examine the intramolecular electrophilic aromatic substitution reaction of sulfonium ion **4**. Thus, sulfonium ion **4** would be generated by acidic treatment of bis(methylthio)allylic alcohol **5**, which was developed by Junjappa and Ila as an α,β-unsaturated acylium ion equivalent.[6] Bis(methylthio)allylic alcohol **5**, the precursor of sulfonium ion **4**, would be readily assembled by 1,2-addition of 2-lithioindole (**6**) to ketene dithioacetal **7**.



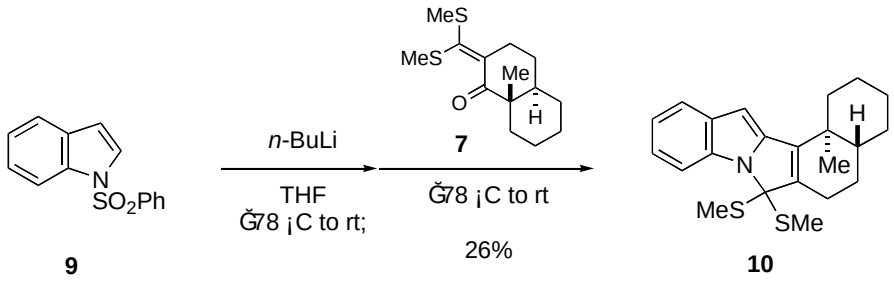
Scheme 2. Synthetic Strategy to Construct Pentacyclic Indole Skeleton using Ketene Dithioacetal

We set out the research by preparation of ketene dithioacetal **7** from decalone **8** according to Paquette's protocol[6b] (Scheme 3). Thus, ketone **8**, which was derived from Wieland-Miescher ketone by the known four-step sequence,[7] was converted to lithium enolate in the presence of excess base. The desired ketene dithioacetal **7** was obtained by successive treatment with carbon disulfide and iodomethane.



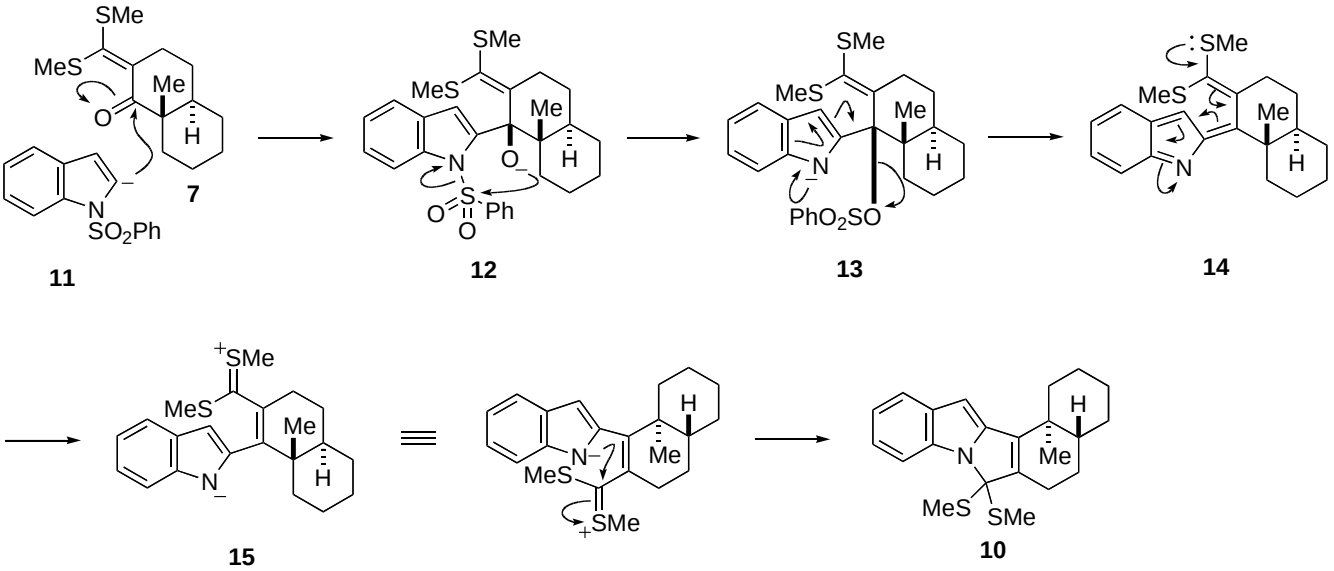
Scheme 3. Preparation of Ketene Dithioacetal **7**

Then, we attempted to introduce an indole unit at the carbonyl group of **7**. Unfortunately, however, the reaction between 2-lithiated *N*-phenylsulfonylindole (**9**) and ketone **7** resulted in formation of a totally unexpected product **10** in low yield (Scheme 4). The structure of product **10** was established by extensive NMR analysis.[8]



Scheme 4. Unexpected Formation of Pentacyclic Compound **10**

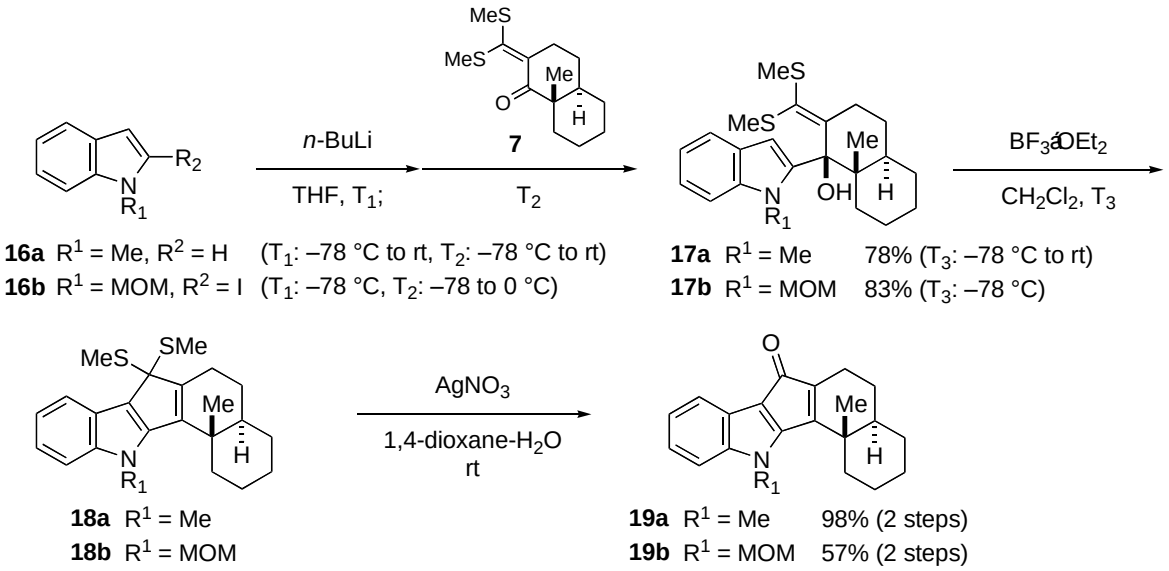
The plausible reaction mechanism for the formation of **10** is depicted in Scheme 5. After 1,2-addition of 2-lithioindole **11** to ketene dithioacetal **7**, intramolecular migration of the phenylsulfonyl group to the proximal lithium alkoxide took place to provide sulfonate **13**. Then, elimination of sulfonate and cyclization of the resulting zwitter ion **15** led to the pentacyclic product **10**.



Scheme 5. Plausible Mechanism of the Unexpected Cyclization

At this point we considered that a more robust protective group on the indole nitrogen should be necessary to circumvent the undesired reaction. With these considerations, we examined the reaction using *N*-methylindole[9] (**16a**) (Scheme 6). Thus, 1,2-addition of 2-lithio-*N*-methylindole to **7** proceeded smoothly to give tertiary alcohol **17a** as a single isomer.[10] Upon treatment with trifluoroborane etherate, the tertiary alcohol **17a** underwent the expected cyclization reaction at the indole 3-position quite

smoothly at –78 °C to furnish the desired pentacyclic compound **18a**. Finally, removal of the dithioacetal with aqueous silver nitrate provided enone **19a** in high overall yield (75% from **16a**). The structure of **19a** was unambiguously identified by X-ray crystallography[11] (Figure 1). The three-step sequence was also able to convert MOM-protected indole **16b**[12] to the corresponding pentacyclic compound **19b** in moderate yield.[13]



Scheme 6. Successful Construction of Pentacyclic Carbon Framework

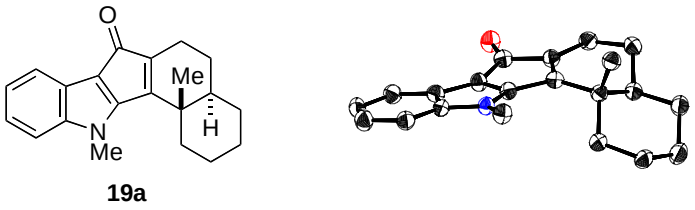


Figure 1. ORTEP Drawing of the Molecular Structure of Compound **19a** with Thermal Ellipsoids at 30% Probability Levels. Hydrogen Atoms are Omitted for Clarity.

In conclusion, we have established a synthetic strategy for construction of the pentacyclic indole skeleton, starting from 1,2-addition of 2-lithioindole to β,β-bis(methylthio)enone and the subsequent one-pot sequential reaction including acid-mediated generation of sulfonium ion and intramolecular electrophilic aromatic substitution at the indole 3-position. This strategy would provide rapid access to a cyclopentenone ring fused to indole, which is a common structure motif in the indole diterpene hybrid molecules. Further synthetic studies towards natural products are currently under investigation.

EXPERIMENTAL

General

All moisture or air sensitive reactions were carried out under a positive atmosphere of argon in dried glassware. Materials were obtained from commercial suppliers and used without further purification unless otherwise mentioned. Anhydrous THF, Et_2O, and CH_2Cl_2 were purchased from Kanto Chemical Co. Inc. Anhydrous toluene, MeCN, acetone, DMF, and DMSO were purchased from Wako Pure Chemical Industries. Flash column chromatography was performed on Silica Gel 60N (Kanto, spherical neutral, 40-50 μm) using the indicated solvent. Preparative TLC was performed on Merck 60 F_{254} glass plates precoated with a 0.50 mm thickness of silica gel. Analytical TLC was performed on Merck 60 F_{254} glass plates precoated with a 0.25 mm thickness of silica gel. IR spectra were measured on SHIMADZU FTIR-8300 spectrometer. NMR spectra were recorded on a Varian Gemini 2000 spectrometer, a JNM-AL400 spectrometer and a GX500 spectrometer with tetramethylsilane or chloroform as an internal standard. Mass spectra were recorded on a JEOL JMS-DX-303 or a JMS-AX-500 spectrometers.

***rac*-(4a*R*,8a*S*)-2-(Bis(methylthio)methylene)-8a-methyloctahydronaphthalen-1(2*H*)-one (7).**

A flame-dried 10-mL two-necked round-bottomed flask equipped with a magnetic stirring bar was charged with **8** (50.5 mg, 304 μmol) and dry THF (0.7 mL) under argon atmosphere. To the solution were added LHMDS in THF (1.60 M, 400 μL, 640 μmol) and HMPA (120 μL, 691 μmol) at –78 °C, respectively. The resulting orange solution was stirred at –78 °C for 1 h, and carbon disulfide (40.0 μL, 665 μmol) was added to the solution at –78 °C. The resulting red solution was stirred at –78 °C for 1.5 h, after which time TLC (hexanes-EtOAc = 5:1) indicated complete consumption of **8**. To the solution was added MeI (90.0 μL, 1.45 mmol) at –78 °C. The resulting mixture was stirred at –78 °C for 20 min and was then warmed to rt. The reaction mixture was stirred for 1 h, after which time the excess reagent was quenched by saturated aqueous ammonium chloride, and the resulting mixture was extracted with Et_2O three times. The combined organic extracts were washed twice with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (hexanes- EtOAc = 20:1) to afford **7** (71.7 mg, 265 μmol, 88%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.37–3.29 (m, 1H), 2.28 (s, 3H), 2.24 (s, 3H), 1.73–1.06 (m, 12H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.5, 143.6, 138.0, 48.8, 45.0, 33.7, 32.5, 28.0, 27.9, 25.9, 21.2, 17.7, 17.0, 14.0; IR (neat, cm^{-1}): 2924, 2856, 1695, 1452, 1435, 1267, 1258, 1016, 868; LRMS-EI (*m/z*) 270 (M^+); HRMS-EI (*m/z*) calcd. for $C_{14}H_{22}OS_2$, 270.1111; found, 270.1110.

Compound 10.

A flame-dried 30-mL two-necked round-bottomed flask equipped with a magnetic stirring bar was charged with **9** (121 mg, 468 μmol) and dry THF (2.0 mL) under argon atmosphere. The flask was cooled to –78 °C. To the flask was added *n*-BuLi (1.54 M in *n*-hexane, 150 μL, 231 μmol). The resulting mixture

was stirred at –78 °C for 17 min and warmed to 0 °C for 20 min. The resulting yellow solution was cooled to –78 °C for 25 min and to the mixture was added a solution of **7** (22.0 mg, 81.3 μmol) in THF (2.0 mL). The resulting mixture was stirred at –78 °C for 5 min, then warmed to rt for 20 min, after which time TLC (hexanes-CH_2Cl_2 = 1:1) indicated complete consumption of **7**. To the flask was added saturated aqueous ammonium chloride. The mixture was extracted with Et_2O three times. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by preparative TLC (hexanes-CH_2Cl_2 = 4:1) to afford **10** (10.1 mg, 21.1 μmol, 26%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, 1H, *J* = 8.4 Hz), 7.56 (d, 1H, *J* = 8.0 Hz) 7.17 (ddd, 1H, *J* = 8.4, 7.2, 1.2 Hz), 7.08 (ddd, 1H, *J* = 8.0, 7.2, 0.8 Hz), 6.16 (s, 1H), 2.62–2.52 (m, 1H), 2.49–2.36 (m, 1H), 2.28–2.22 (m, 1H), 1.86–1.78 (m, 1H), 1.73–1.31 (m, 15H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 142.8, 140.0, 133.3, 133.2. 121.5, 121.4, 120.0, 110.7, 93.2, 78.1, 44.4, 37.2, 35.7, 30.3, 27.8, 26.7, 25.2, 22.0, 21.6, 19.0, 12.0; IR (neat, cm^{-1}): 2928, 2855, 1448, 1335, 1304, 1217, 1150, 746; LRMS-EI (*m/z*) 369 (M^+); HRMS-EI (*m/z*) calcd. for $C_{22}H_{27}NS_2$, 369.1585; found, 368.1516.

***rac*-(1*R*,4a*R*,8a*S*)-2-(Bis(methylthio)methylene)-8a-methyl-1-(1-methyl-1*H*-indol-2-yl)-decahydro-naphthalen-1-ol (17a)**

A flame-dried 50-mL two-necked round-bottomed flask equipped with a magnetic stirring bar was charged with **16a** (129 mg, 983 μmol) and dry THF (4.0 mL) under argon atmosphere. The flask was cooled to –78 °C. To the flask was added *n*-BuLi (1.54 M in *n*-hexane, 530 μL, 816 μmol). The resulting mixture was stirred at –78 °C for 5 min and warmed to rt for 15 min. The resulting white suspension was cooled to –78 °C for 10 min and to the mixture was added **7** (101 mg, 375 μmol). The resulting mixture was stirred at –78 °C for 5 min, then warmed to rt for 10 min, after which time TLC (hexanes-CH_2Cl_2 = 1:1) indicated complete consumption of **7**. To the flask was added saturated aqueous ammonium chloride. The mixture was extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford crude **17a** (235 mg) as a yellow oil. The residue was purified by silica gel column chromatography (hexanes-CH_2Cl_2 = 7:3) to provide **17a** (118 mg, 294 μmol, 78%, yield is based on **7**) as a yellow amorphous. Physical data of pure **17a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, 1H, *J* = 8.4 Hz), 7.31 (d, 1H, *J* = 8.4 Hz), 7.18 (ddd, 1H, *J* = 8.4, 7.2, 1.2 Hz), 7.07 (dd, 1H, *J* = 8.4, 7.2 Hz), 6.51 (s, 1H), 6.44 (s, 1H), 3.98 (s, 3H), 3.34 (ddd, 1H, *J* = 16.8, 6.8, 2.4 Hz), 2.41 (ddd, 1H, *J* = 16.8, 11.6, 7.2 Hz), 2.26 (s, 3H), 2.18–2.05 (m, 1H), 2.03 (s, 3H), 1.95–1.81 (m, 1H), 1.63–1.28 (m, 7H), 1.27–0.97 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 141.5, 137.5, 126.73, 126.68, 121.1, 120.0, 119.2, 108.9, 103.3, 84.3, 45.2, 36.9, 32.9, 32.7, 32.0, 29.5, 28.3, 25.7, 22.0, 16.8, 16.3, 14.9; IR (neat, cm^{-1}): 3360, 2926, 2862, 1464, 1350, 1327, 1312, 1234, 1217, 748; LRMS-EI (*m/z*) 401 (M^+); HRMS-EI (*m/z*) calcd. for

$C_{23}H_{31}NOS_2$, 401.1847; found, 401.1838.

***rac*-Dithioacetal compound (18a).**

A flame-dried 50-mL two-necked round-bottomed flask equipped with a magnetic stirring bar was charged with **17a** (27.5 mg, 68.5 μmol) and dry CH_2Cl_2 (3.0 mL) under argon atmosphere. To the solution was added boron trifluoride etherate (35.0 μL, 284 μmol) dropwise at –78 °C. The resulting mixture was stirred at –78 °C for 10 min, then warmed to rt for 15 min, after which time TLC (hexanes-CH_2Cl_2 = 1:1) indicated complete consumption of **17a**. The excess reagent was quenched with saturated aqueous ammonium chloride, and the mixture was extracted with CH_2Cl_2 three times. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and filtered. The filtrate was concentrated under reduced pressure to afford crude **18a** (27.1 mg) as an orange oil, which was used for the next reaction without further purification. Physical data of pure **18a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75–7.66 (m, 1H), 7.35–7.27 (m, 1H), 7.21–7.08 (m, 2H), 3.94 (s, 3H), 2.63–2.35 (m, 3H), 1.95–1.15 (m, 19H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2, 146.4, 141.7, 141.3, 122.7, 121.6, 120.13, 120.07, 118.2, 110.0, 58.6, 46.3, 37.5, 36.0, 34.5, 28.3, 26.6, 25.6, 24.0, 21.9, 18.3, 13.3, 13.0; IR (neat, cm^{-1}): 2922, 2856, 1701, 1612, 1582, 1470, 1431, 1271, 1217, 1161, 1040, 791, 754; LRMS-EI (*m/z*) 383 (M^+); HRMS-EI (*m/z*) calcd. for $C_{23}H_{29}NS_2$, 383.1741; found, 383.1736.

***rac*-Pentacyclic indole (19a).**

A 50-mL round-bottomed flask equipped with a magnetic stirring bar was charged with crude **18a** (27.1 mg) and $AgNO_3$ (110 mg, 648 μmol). To the flask was added 1,4-dioxane-H_2O (2:1 = 6.0 mL). The reaction mixture was stirred for 20 min, after which time TLC (CH_2Cl_2) indicated complete consumption of **18a**. The reaction was quenched with H_2O and the aqueous layer was extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude product, which was purified by preparative TLC (CH_2Cl_2) to afford pure **19a** (20.0 mg, 65.5 μmol, 96% over 2 steps) as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, 1H, *J* = 8.0 Hz), 7.17 (d, 1H, *J* = 8.4 Hz), 7.14 (ddd, 1H, *J* = 8.0, 7.2, 1.2 Hz), 7.04 (ddd, 1H, *J* = 8.4, 7.2, 1.2 Hz), 3.86 (s, 3H), 2.38–2.28 (m, 1H), 2.22–2.07 (m, 2H), 1.83–1.75 (m, 1H), 1.73–1.57 (m, 2H), 1.55–1.30 (m, 7H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.5, 161.5, 150.8, 142.2, 141.9, 137.4, 123.4, 122.7, 120.8, 118.8, 110.7, 46.0, 35.64, 35.59, 34.6, 28.0, 26.4, 24.8, 22.2, 21.5, 16.5; IR (neat, cm^{-1}): 2930, 2858, 1693, 1611, 1472, 1456, 1408, 1042, 746; LRMS-EI (*m/z*) 305 (M^+); HRMS-EI (*m/z*) calcd. for $C_{21}H_{23}NO$, 305.1780; found, 305.1783.

***rac*-(1*R*,4a*R*,8a*S*)-2-(Bis(methylthio)methylene)-1-(1-(methoxymethyl)-1*H*-indol-2-yl)-8a-methyldeca-hydronaphthalen-1-ol (17b).**

A flame-dried 30-mL two-necked round-bottomed flask equipped with a magnetic stirring bar was charged with **16b** (171 mg, 595 μmol) and dry THF (6.0 mL) under argon atmosphere. The flask was

cooled to –78 °C. To the flask was added *n*-BuLi (1.54 M in *n*-hexane, 424 μL, 655 μmol). The resulting mixture was stirred at –78 °C for 10 min and to the mixture was added a solution of **7** (193 mg, 714 μmol) in THF (2.0 mL). The resulting mixture was stirred at –78 °C for 5 min, then warmed to 0 °C for 20 min, after which time TLC (hexanes-CH_2Cl_2 = 1:1) indicated complete consumption of **16b**. To the flask was added water. The mixture was extracted with EtOAc three times. The combined organic extracts were dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford crude **17b** as yellow oil. The residue was purified by recrystallization (hexanes-EtOAc) to afford **17b** (213 mg, 494 μmol, 83%) as a white amorphous. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, 1H, *J* = 7.2 Hz), 7.47 (d, 1H, *J* = 7.2 Hz), 7.25–7.15 (m, 1H), 7.10 (dd, 1H, *J* = 7.2, 7.2 Hz), 6.64 (s, 1H), 6.35 (s, 1H), 6.18 (d, 1H, *J* = 10.0 Hz), 5.50 (d, 1H, *J* = 10.0 Hz), 3.40 (ddd, 1H, *J* = 18.4, 7.6, 2.4 Hz), 3.32 (s, 3H), 2.56 (ddd, 1H, *J* = 19.2, 10.8, 8.4 Hz), 2.27 (s, 3H), 1.96–1.73 (m, 5H), 1.63–0.80 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 142.6, 138.0, 128.7, 127.1, 121.8, 120.2, 120.1, 109.7, 105.1, 83.8, 75.9, 56.0, 44.1, 35.6, 33.1, 31.3, 29.7, 27.1, 25.4, 22.0, 17.2, 16.1, 15.4; IR (neat, cm^{-1}): 3358, 2922, 2858, 1458, 1346, 1302, 1169, 1065, 910, 754, 735; LRMS-FAB (*m/z*) 431 (M^+); HRMS-FAB (*m/z*) calcd. for $C_{24}H_{33}NO_2S_2$, 431.1953; found, 431.1952.

***rac*-Dithioacetal compound (18b).**

A flame-dried 30-mL two-necked round-bottomed flask equipped with a magnetic stirring bar was charged with **17b** (20.6 mg, 47.8 μmol) and dry CH_2Cl_2 (5.0 mL) under argon atmosphere. To the solution was added boron trifluoride etherate (30.0 μL, 243 μmol) dropwise at –78 °C. After 4 h, the reaction was quenched with MeOH/CH_2Cl_2 (1:10, 5.0 mL) and the resulting mixture was let warm to room temperature. Water was then added to the resulting mixture and the mixture was extracted twice with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude product, which was purified by preparative TLC (CH_2Cl_2-hexanes = 2:3) to afford pure **18b** (13.1 mg, 31.7 μmol, 66%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77–7.70 (m, 1H), 7.49–7.42 (m, 1H), 7.22–7.13 (m, 2H), 5.63 (d, 1H, *J* = 10.8 Hz), 5.60 (d, 1H, *J* = 10.8 Hz), 3.27 (s, 3H), 2.63–2.53 (m, 1H), 2.52–2.41 (m, 1H), 2.34–2.26 (m, 1H), 1.82–1.76 (m, 4H) 1.73–1.31 (m, 12H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4, 145.9, 142.4, 141.7, 123.8, 123.2, 121.0, 121.0, 118.4, 110.8, 76.1, 58.2, 55.5, 46.2, 37.2, 36.3, 28.4, 26.6, 25.5, 23.8, 21.9, 18.2, 13.1, 12.7; IR (neat, cm^{-1}): 2924, 2856, 1448, 1377, 1340, 1186, 1105, 1076, 961, 916, 743; LRMS-EI (*m/z*) 413 (M^+); HRMS-EI (*m/z*) calcd. for $C_{24}H_{31}NOS_2$, 413.1847; found, 413.1857.

***rac*-Pentacyclic indole (19b).**

A 10-mL round-bottomed flask equipped with a magnetic stirring bar was charged with **18b** (13.1 mg, 31.7 μmol) and $AgNO_3$ (16.2 mg, 95.1 μmol). To the flask was added 1,4-dioxane-H_2O (1:1 = 1.0 mL). The reaction mixture was stirred for 1.5 h, after which time TLC (hexanes-EtOAc = 4:1) indicated

complete consumption of **18b**. The reaction was quenched with H_2O and the aqueous layer was extracted with EtOAc three times. The combined organic extracts were dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude product, which was purified by preparative TLC (hexanes-EtOAc = 4:1) to afford pure **19b** (9.2 mg, 27 μmol, 86%, 57% over 2 steps) as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, 1H, *J* = 8.0 Hz), 7.34 (d, 1H, *J* = 8.0 Hz), 7.16 (ddd, 1H, *J* = 8.0, 7.2, 1.2 Hz), 7.07 (ddd, 1H, *J* = 8.0, 7.2, 1.0 Hz), 5.53 (d, 1H, *J* = 11.2 Hz), 5.48 (d, 1H, *J* = 11.2 Hz), 3.36 (s, 3H), 2.39–2.28 (m, 1H), 2.24–2.05 (m, 2H), 1.83–1.75 (m, 1H), 1.73–1.59 (m, 2H), 1.52–1.29 (m, 7H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.3, 160.6, 151.9, 142.2, 136.6, 123.7, 122.7, 121.6, 119.0, 111.7, 111.3, 76.1, 56.1, 45.9, 36.1, 35.8, 28.2, 26.5, 24.8, 22.1, 21.6, 16.9; IR (neat, cm^{-1}): 2929, 2858, 1699, 1454, 1427, 1391, 1114, 1082, 1036, 748; LRMS-EI (*m/z*) 335 (M^+); HRMS-EI (*m/z*) calcd. for $C_{22}H_{25}NO_2$, 335.1885; found, 335.1880.

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REFERENCES AND NOTES

1. T. Fehr and W. Acklin, *Helv. Chim. Acta*, 1966, **49**, 1907.
2. J. P. Springer and J. Clardy, *Tetrahedron Lett.*, 1980, **21**, 231.
3. W. Acklin, F. Weibel, and D. Arigoni, *Chimia*, 1977, **31**, 63.
4. (a) P. F. Dowd, R. J. Cole, and R. F. Vesonder, *J. Antibiot.*, 1988, **41**, 1868; (b) K. Nozawa, S. Nakajima, and K. Kawai, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2607.
5. Total synthesis of paspaline: (a) A. B. Smith, III and R. Mewshaw, *J. Am. Chem. Soc.*, 1985, **107**, 1769; (b) R. E. Mewshaw, M. D. Taylor, and A. B. Smith, III, *J. Org. Chem.*, 1989, **54**, 3449; (c) A. B. Smith, III and T. L. Leenay, *J. Am. Chem. Soc.*, 1989, **111**, 5761. Total synthesis of paspalicine and paspalinine: (d) A. B. Smith, III, J. Kingery-Wood, T. L. Leenay, E. G. Nolen, and T. Sunazuka, *J. Am. Chem. Soc.*, 1992, **114**, 1438. Total synthesis of penitrem D: (e) A. B. Smith, III, N. Kanoh, H. Ishiyama, and R. A. Hartz, *J. Am. Chem. Soc.*, 2000, **122**, 11254.
6. (a) H. Junjappa, G. Singh, M. L. Purkayastha, and H. Ila, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1289;

(b) L. A. Paquette, A. G. Schaefer, and J. P. Springer, *Tetrahedron*, 1987, **43**, 5567; (c) H. Ila, A. K. Yadav, S. Peruncheralathan, and H. Junjappa, *J. Org. Chem.*, 2007, **72**, 1388. For a review, see: (d) H. Junjappa, H. Ila, and C. V. Asokan, *Tetrahedron*, 1990, **46**, 5423.

7. (a) R. E. Mewshaw, M. D. Taylor, and A. B. Smith, III, *J. Org. Chem.*, 1989, **54**, 3449; (b) A. B. Smith, III, L. Krti, A. H. Davulcu, and Y. S. Cho, *Org. Proc. Res. Dev.*, 2007, **11**, 19.
8. NMR analysis including ^{1}H, ^{13}C, DEPT, COSY, HMQC, HMBC, and NOESY indicated that the ring formation took place at the indole nitrogen instead of the 3-position.
9. S. Roy, A. Eastman, and G. W. Gribble, *Tetrahedron*, 2006, **62**, 7838.
10. We tentatively assigned the stereochemistry according to the following reports, see: (a) B. J. M. Jansen, R. M. Peperzak, and A. de Groot, *Recl. Trav. Chim. Pays-Bas*, 1987, **106**, 489; (b) B. J. M. Jansen, R. M. Peperzak, and A. de Groot, *Recl. Trav. Chim. Pays-Bas*, 1987, **106**, 549.
11. *Crystal data* for **19a** $C_{12}H_{23}NO$: MW = 305.40, orthorhombic, a = 7.7989(4), b = 16.8310(7), c = 24.1167(12) Å, β = 90 °, V = 3165.6(3) Å^3, T = 173 K, space group Pnaa (no. 56), Z = 8, μ(MoKα) = 0.78 cm^{-1}, D_{calc} = 1.282 g/cm^{-3}. A total of 28499 reflections were measured, of which 3599 (R_{int} = 0.110) reflections were used for analysis. The structure was refined to a goodness of fit (GOF) of 1.129 and the final residuals were R = 0.066 and wR = 0.151. Crystallographic data of **19a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-829556. Copies of the date can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB1 1EZ, UK (fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk).
12. C. A. Merlic, Y. You, D. M. McInnes, A. L. Zechman, M. M. Miller, and Q. Deng, *Tetrahedron*, 2001, **57**, 5199.
13. In the case of reaction using **17b**, we observed generation of a number of side products including a compound in which the MOM group was transformed to a MTM group under the Lewis acid mediated reaction conditions. A several attempts to introduce the angular methyl group by Michael addition conditions (e.g., Me_2CuLi with TMSCl in THF)[14] were unsuccessful.
14. E. J. Corey and N. W. Boaz, *Tetrahedron Lett.*, 1985, **26**, 6019.