Novel Syntheses of Murrayaquinone A and Furostifoline through 4-Oxygenated Carbazoles by Allene-Mediated Electrocyclic Reactions Starting from 2-Chloroindole-3-carbaldehyde

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The formal total synthesis of murrayaquinone A (1) and the total synthesis of furostifoline (5) were completed by the construction of 4-oxygenated 3-methylcarbazoles 7 based on a new type of electrocyclic reaction through 2-alkenyl-3-allenylindole intermediates 8 derived from the 2-alkenyl-3-propargylindoles 9, starting from 2-chloroindole-3-carbaldehyde (11). The *N*,*O*-bisbenzyloxymethyl group of 16c and 22 underwent a Birch reduction followed by treatment with Triton B to produce the known 4-hydroxy-3-methylcarbazole (7a) and 4-hydroxy-3-methylfuro[3,2-*a*]carbazole (7b) as precursors of murrayaquinone A (1) and furostifoline (5), respectively. The trifluoromethanesulfonyloxy-3-methylfuro[3,2-*a*]carbazole (24), prepared from 7b, was subjected to reductive cleavage to provide furostifoline (5).

Key words murrayaquinone A; carbazole-1,4-quinone; furostifoline; furo[3,2-*a*]carbazole; allene; electrocyclic reaction

The carbazole-1,4-quinone, murrayaquinone A (**1**) was first isolated from the root bark of *Murraya eucrestifolia* HAYATA (Rutaceae) collected in Taiwan together with three closely related alkaloids [murrayaquinones B—D (**2**—**4**)] by Furukawa and co-workers[1,2] from 1983 to 1985. The new tetracyclic furo[3,2-*a*]carbazole alkaloid, furostifoline (**5**), was isolated in 1990 by the same group[3] along with furo[3,2-*g*]carbazole, eustifoline D (**6**) from the same origin. Extracts of the leaves and bark of this tree have been used as a folk medicine for analgesia and local anaesthesia and for the treatment of eczema, rheumatism and dropsy.[2a] Among these alkaloids, murrayaquinone A (**1**) has been found to exhibit the cardiotonic activity on guinea pig papillary muscle.[4]

A wide variety of syntheses of murrayaquinone A (**1**) have been reported by twelve groups including our approach.[2c,4a,5,6] In addition, the syntheses of furostifoline (**5**) have been completed by three groups[7] as well as ourselves.[6] Among these works, total syntheses of both alkaloids have been achieved by the Knölker group using a convergent iron-mediated construction of the carbazole nucleus.[5g,7a] We have also been interested in the syntheses of both alkaloids in the course of our studies and have recently reported total syntheses of 3-oxygenated and 3,4-dioxygenated carbazole alkaloids based on the thermal electrocyclic reaction of the 3-alkenyl-2-allenylindole intermediate derived from 3-alkenyl-2-propargylindole.[8] We describe here the details of our preliminary report[6] describing the formal synthesis of murrayaquinone A (**1**) and the total synthesis of furostifoline (**5**). We envisaged that 4-oxygenated 3-methylcarbazoles **7a** and **7b** might be obtained by electrocyclic reactions through reverse 3-allenylindole intermediates **8a** and **8b**, which would be derived from 3-propargylindoles **9a** and **9b**, respectively. These precursors **9a** and **9b** would be provided from 2-chloroindole-3-carbaldehyde (**11**)[9] as a common starting material depicted in the retro-synthetic analysis (Chart 2).

For the synthesis of known 4-hydroxy-3-methylcarbazole (**7a**),[5d—f] we initially used phenylsulfonyl group as the *N*-protecting group of 2-chloroindole-3-carbaldehyde (**11**). Treatment of **11** with phenylsulfonyl chloride in the presence of Et_3N and dimethylaminopyridine (DMAP) in CH_2Cl_2 gave the *N*-phenylsulfonylindole **12a** in 20% yield. The cross-coupling reaction between **12a** and ethenyl tributylstannane in the presence of bis(triphenylphosphine)palladium(II) chloride [$Pd(PPh_3)_2Cl_2$] afforded the 2-ethenylindole **13a** (90%). Treatment of **13a** with ethynylmagnesium bromide followed by treatment of the resulting alcohol **14a** with chloromethyl methyl ether (MOMCl) produced the 2-ethenyl-3-propargylindole **15a** (72% from **13a**). An allene-mediated electrocyclic reaction of **15a** in the presence of potassium *tert*-butoxide (*t*-BuOK) in *tert*-butanol (*t*-BuOH) and THF (tetrahydrofuran) was carried out at 90 °C according to the previous reported method[8] for the reverse type of allene generation to give the *N*-deprotected 4-oxygenated 3-methylcarbazole **16a** in 35% yield.

Although all of the reactions proceeded, the yields of the two steps were poor; to improve them, two other protecting groups were examined. Treatment of **11** with chloromethyl methyl ether (MOMCl) [or benzyl chloromethyl ether (BOMCl)] in the presence of potassium carbonate in DMF (dimethylformamide) afforded the *N*-MOM-indole **12b** (93%) and the *N*-BOM-indole **12c** (99%). The cross-coupling reaction between **12b** (or **12c**) and ethenyl tributylstannane in the presence of $Pd(PPh_3)_2Cl_2$ gave the 2-ethenylindoles **13b** (97%) and **13c** (78%). The Grignard reaction of **13b** (or **13c**) with ethynylmagnesium bromide followed by

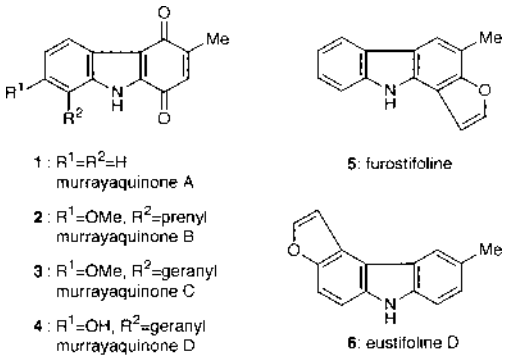

Chart 1

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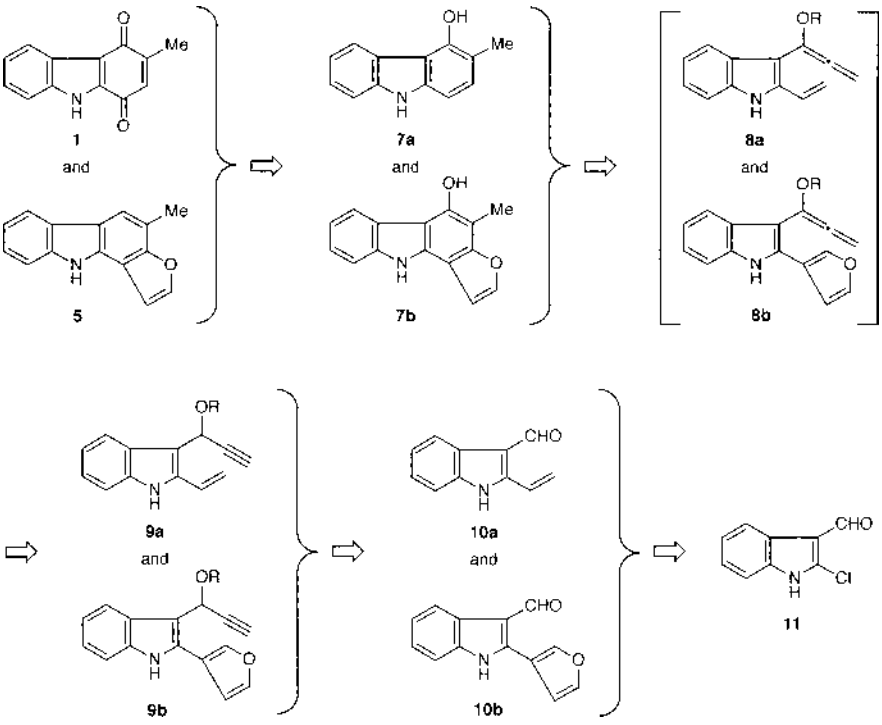
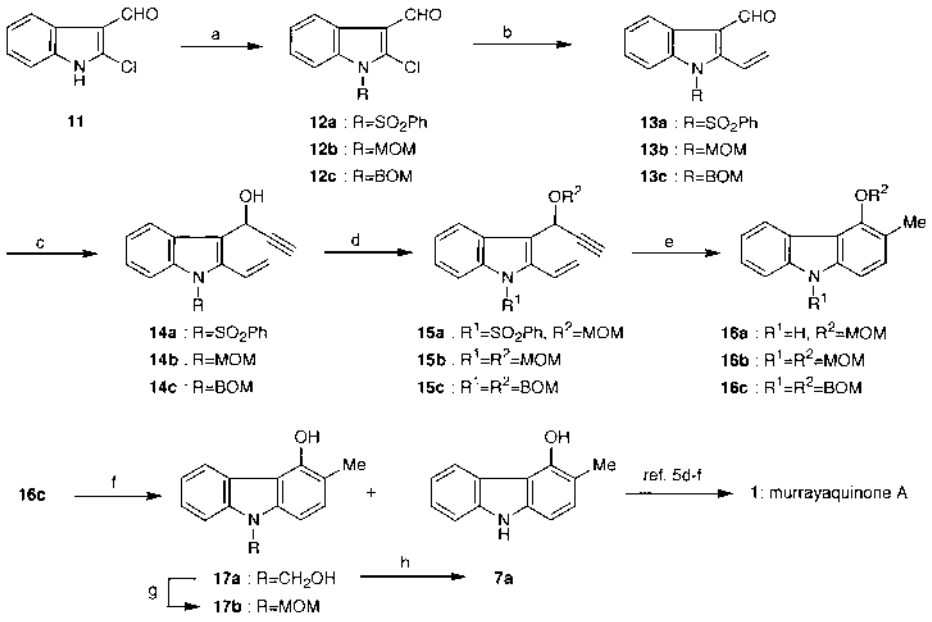


Chart 2

treatment of the resulting alcohol **14b** (or **14c**) with MOMCl (or BOMCl) produced the 2-alkenyl-3-propargylindoles **15b** (90% from **13b**) and **15c** (56% from **13c**). The 3-propargylindole **15b** (or **15c**) was subjected to an electrocyclic reaction under similar conditions to yield the expected carbazoles **16b** (58%) and **16c** (81%). Two types of 4-oxygenated 3-methylcarbazole **16b** and **16c** were obtained in 47% and 34% yields from **11**, respectively. Next, the deprotection of *N*-MOM-4-MOMoxy-3-methylcarbazole (**16b**) was examined under several acidic conditions or with sodium iodide and TMSCl (chlorotrimethylsilane). However, the expected 4-hydroxy-3-methylcarbazole (**7a**) was not obtained. In particular, it was difficult to remove the *N*-MOM group of **16b**. In contrast, deprotection of *N*,*O*-bis-BOM group of **16c** was investigated by hydrogenolysis or under Birch conditions to give a separable mixture of 4-hydroxy-3-methylcarbazole (**7a**) (22%) and *N*- or *O*-hydroxymethyl-4-hydroxy-3-methylcarbazole (**17a**) (75%) under Birch conditions, respectively. It is unclear at this time whether the structure of **17a** is *N*-hydroxymethylcarbazole (**17a**) or *O*-hydroxymethylcarbazole (**16a**). When the carbazole **17a** was treated with 0.5 M HCl in methanol to remove the *N*- or *O*-hydroxymethyl group of **17a**, **17a** was converted into the *N*- or *O*-MOM-carbazole **17b**. This carbazole **17b** was not identical to the formerly synthesized 4-MOMoxy-3-methylcarbazole (**16a**) based on a comparison of ^{1}H-NMR spectra. Accordingly, the structure of **17a** was determined to be *N*-hydroxymethyl-4-hydroxy-3-methylcarbazole. The removal of the *N*-hydroxymethyl group of **17a** successfully proceeded by heating with Triton B in an aqueous THF according to the Anderson procedure[10] to yield **7a** (71%) (Chart 3). The synthetic 4-hydroxy-3-methylcarbazole (**7a**) was identical in all respects to the precursor of murrayaquinone A (**1**), as reported previously.[5d—f] This constitutes the formal total synthesis of murrayaquinone A (**1**).

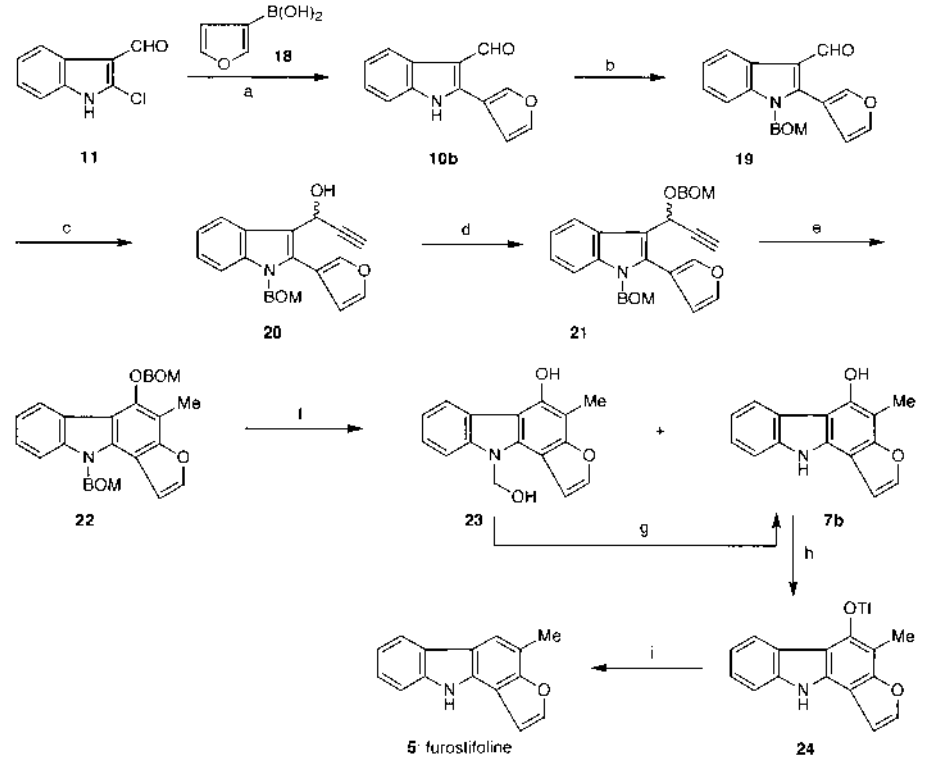
We then turned to the synthesis of 4-oxygenated-3-methylfuro[3,2-*a*]carbazole **7b** as a precursor of furostifoline (**5**). The cross-coupling reaction of **11** with furan-3-boronic acid (**18**)[11] was carried out in the presence of palladium(II) acetate and triphenylphosphine in DMF to obtain the 2-(3-furyl)indole **10b** (84%). After protection of the indole nitrogen atom of **10b** with BOMCl in the presence of potassium carbonate in DMF, the subsequent Grignard reaction of **19** with ethynylmagnesium bromide gave alcohol **20** (97%). Alcohol **20** was treated with BOMCl and sodium hydride in THF to yield the 2-(3-furyl)-3-propargylindole **21**, which was subjected to a thermal electrocyclic reaction in the presence of *t*-BuOK in *t*-BuOH at 90 °C to produce the 4-oxygenated tetracyclic furocarbazole **22** (61% yield from **20**). Birch reduction of **22** for the deprotection of *N*,*O*-bis-BOM groups gave a separable mixture of the desired 4-hydroxy-3-methylfuro[3,2-*a*]carbazole **7b** (51%) and 4-hydroxy-*N*-(hydroxymethyl)-3-methylfuro[3,2-*a*]carbazole **23** (41%). Compound **23** was similarly converted to **7b** by treatment with Triton B[10] (93%). Finally, treatment of the phenol **7b** with trifluoromethanesulfonic anhydride (Tf_2O) and pyridine afforded the triflate **24**, which was subjected to a reductive cleavage of the 4-trifluoromethanesulfonyloxy group of **24** with palladium(II) acetate and triphenylphosphine in the presence of formic acid and triethylamine in DMF at 60 °C according to Ortar's procedure[12] to produce furostifoline (**5**) (99%) (Chart 4). The synthetic 3-methylfuro[3,2-*a*]carbazole (**5**) was identical in all respects to natural[1b] and synthetic products.[7]

Thus, new synthetic routes to the carbazole-1,4-quinone, murrayaquinone A (**1**) and the tetracyclic furo[3,2-*a*]carbazole, furostifoline (**5**) have been established by the construction of the 4-oxygenated-3-methylcarbazole nucleus **7** based on a new type of allene-mediated electrocyclic reaction involving the indole 2,3-bond.



Reagents: (a) $PhSO_2Cl$, Et_3N, DMAP, CH_2Cl_2 (MOMCl or BOMCl, K_2CO_3, DMF), (b) CH_2=CH-$SnBu_3$, $PdCl_2(PPh_3)_2$, Et_4NCl, DMF, 80°C; (c) HC≡CMgBr, THF, rt; (d) MOMCl, *i*-Pr_2NEt, CH_2Cl_2 (BOMCl, NaH, THF); (e) *t*-BuOK, *t*-BuOH, THF, 90°C; (f) Na, liq. NH_3, -78°C; (g) 0.5 M HCl, MeOH, ethylene glycol, THF, rt, (h) Triton B, THF, H_2O.

Chart 3



Reagents: (a) $Pd(OAc)_2$, PPh_3, DMF, 100°C; (b) BOMCl, K_2CO_3, DMF, rt, (c) HC≡CMgBr, THF, rt; (d) BOMCl, NaH, THF, 0°C; (e) *t*-BuOK, *t*-BuOH, THF, 90°C; (f) Na, liq. NH_3, -78°C; (g) Triton B, THF, H_2O, reflux; (h) Tf_2O, Py, CH_2Cl_2; (i) $Pd(OAc)_2$, PPh_3, HCOOH, Et_3N, DMF, 60°C.

Chart 4

Experimental

All air-sensitive reactions were conducted in flame-dried glassware under an nitrogen atmosphere unless otherwise stated. THF was freshly distilled from benzophenone ketyl. DMF, triethylamine and ethyl diisopropylamine were freshly distilled after drying over CaH_2. Dichloromethane was freshly distilled after drying over P_2O_5. Silica gel (70—230 mesh, Merck Art. 7734) was used for column chromatography. Melting points were measured by a Yanagimoto MP-500D micro melting points apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8500 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were taken with a JEOL-AL 300 using tetramethylsilane as an internal standard. All mass spectra were obtained using Shimadzu 9020DF and QP5050 spectrometers equipped with an electrospray ionization source at 70 eV.

2-Chloro-*N*-(phenylsulfonyl)indole-3-carbaldehyde (12a) Phenylsulfonyl chloride (818 μl, 3.35 mmol) was added to the stirred mixture of 2-chloroindole **11** (500 mg, 2.79 mmol), Et_3N (482 μl, 3.07 mmol) and DMAP (340 mg, 2.79 mmol) in CH_2Cl_2 (5 ml) under cooling with ice. The mixture was stirred at room temperature for 12 h, which was quenched with water, then extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (1 : 9) as an eluent to give the *N*-(phenylsulfonyl)indole **12a** (174 mg, 20%). mp 166—167 °C (EtOAc). IR (KBr) cm^{-1}: 1677, 1388. ^{1}H-NMR ($CDCl_3$) δ: 7.43—8.53 (9H, m), 10.30 (1H, s). MS *m/z*: 321 (M^++2), 319 (M^+). *Anal.* Calcd for $C_{15}H_{10}ClNO_3S$: C, 56.34; H, 3.15; N, 4.38. Found: C, 56.46; H, 3.34; N, 4.28.

2-Chloro-*N*-(methoxymethyl)indole-3-carbaldehyde (12b) MOMCl (0.21 ml, 2.79 mmol) was added to a stirred mixture of 2-chloroindole **11** (100 mg, 0.56 mmol) and K_2CO_3 (385 mg, 2.79 mmol) in DMF (5 ml) under cooling with ice. The mixture was stirred at room temperature for 12 h, which was quenched with water, then extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (1 : 9) as an eluent to give the *N*-(methoxymethyl)indole **12b** (116 mg, 93%). mp 232—233.5 °C ($CHCl_3$). IR (KBr) cm^{-1}: 1639. ^{1}H-NMR ($CDCl_3$) δ: 3.43 (3H, s), 5.63 (2H, s), 7.23—7.57 (4H, m), 10.18 (1H, s). MS *m/z*: 225 (M^++2), 223 (M^+). *Anal.* Calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26. Found: C, 60.11; H, 4.58; N, 6.06.

***N*-(Benzyloxymethyl)-2-chloroindole-3-carbaldehyde (12c)** The same procedure as above was carried out using **11** with BOMCl to give the oily *N*-(benzyloxymethyl)indole **12c** (99%). IR (neat) cm^{-1}: 1653. ^{1}H-NMR ($CDCl_3$) δ: 4.51 (2H, s), 5.38 (2H, s), 7.24—7.37 (9H, m), 10.16 (1H, s). MS *m/z*: 301 (M^++2), 299 (M^+). HR-MS *m/z*: 299.0713 (Calcd for $C_{17}H_{14}ClNO_2$: 299.0722).

2-Ethenyl-*N*-(phenylsulfonyl)indole-3-carbaldehyde (13a) Tributyl(vinyl)tin (59 μl, 0.203 mmol) was added to a stirred mixture of the 2-chloroindole **12a** (30 mg, 0.135 mmol), Et_4NCl (22 mg, 0.135 mmol) and $PdCl_2(PPh_3)_2$ (2.8 mg, 4.05 mmol) in DMF (1 ml) under argon. The mixture was heated at 80 °C for 2 h, then cooled to an ambient temperature and quenched with an aqueous 30% KF solution (50 ml). The mixture was stirred at room temperature for 30 min and filtered through a Celite pad. The filtrate was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (3 : 17) as an eluent to give the 2-ethenylindole **13a** (38 mg, 90%). mp 133—134 °C (EtOAc). IR (KBr) cm^{-1}: 1643, 1383. ^{1}H-NMR ($CDCl_3$) δ: 5.59 (1H, dd, *J*=1.5, 17 Hz), 5.94 (1H, dd, *J*=1.5, 11 Hz), 7.26—8.31 (10H, m), 9.99 (1H, s). MS *m/z*: 311 (M^+). *Anal.* Calcd for $C_{17}H_{13}NO_3S$: C, 65.58; H, 4.21; N, 4.50. Found: C, 65.71; H, 4.36; N, 4.44.

2-Ethenyl-*N*-(methoxymethyl)indole-3-carbaldehyde (13b) The same procedure as above was carried out using **12b** to give the oily 2-ethenylindole **13b** (97%). IR (neat) cm^{-1}: 1697. ^{1}H-NMR ($CDCl_3$) δ: 3.33 (3H, s), 5.49 (2H, s), 5.90 (1H, dd, *J*=1.5, 17 Hz), 5.93 (1H, dd, *J*=1.5, 12 Hz), 7.02 (1H, dd, *J*=12, 17 Hz), 7.26—7.38 (2H, m), 7.48 (1H, d, *J*=7 Hz), 8.39 (1H, d, *J*=7 Hz), 10.13 (1H, s). MS *m/z*: 215 (M^+). HR-MS *m/z*: 215.0946 (Calcd for $C_{13}H_{13}NO_2$: 215.0958).

***N*-(Benzyloxymethyl)-2-ethenylindole-3-carbaldehyde (13c)** The same procedure as above was carried out using **12c** (650 mg, 2.17 mmol) to give the oily 2-ethenylindole **13c** (494 mg, 78%). IR (neat) cm^{-1}: 1693. ^{1}H-NMR ($CDCl_3$) δ: 4.52 (2H, s), 5.59 (2H, s), 5.90 (1H, dd, *J*=1.5, 12 Hz), 5.91 (1H, dd, *J*=1.5, 17 Hz), 6.79 (1H, dd, *J*=12, 17 Hz), 7.24—7.40 (9H, m), 10.12 (1H, s). MS *m/z*: 291 (M^+). HR-MS *m/z*: 291.1259 (Calcd for $C_{19}H_{17}NO_2$: 291.1266).

2-Ethenyl-3-(1-hydroxyprop-2-yn-1-yl)-*N*-(phenylsulfonyl)indole (14a) A solution of ethynylmagnesium bromide (0.5 in THF, 4 ml, 2.09 mmol) was added to a stirred solution of 2-ethenylindole **13a** (100 mg, 0.32 mmol) in dried THF (5 ml) under cooling with ice. After stirring at the same temperature for 2 h, the reaction mixture was quenched with an aqueous NH_4Cl (saturated) solution, then extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (3 : 7) as an eluent to give the oily propargyl alcohol **14a** (109 mg, 99%). IR (neat) cm^{-1}: 3294, 2117. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (1H, br s), 2.53 (1H, d, *J*=2 Hz), 5.12—6.89 (4H, m), 6.66—8.33 (9H, m). MS *m/z*: 337 (M^+). HR-MS *m/z*: 337.0773 (Calcd for $C_{19}H_{15}NO_3S$: 337.0765).

2-Ethenyl-3-(1-hydroxyprop-2-yn-1-yl)-*N*-(methoxymethyl)indole (14b) The same procedure as above was carried out using **13b** (372 mg, 1.42 mmol) to give the oily propargyl alcohol **14b** (337 mg, 98%). IR (neat) cm^{-1}: 3296, 2094. ^{1}H-NMR ($CDCl_3$) δ: 2.24 (1H, d, *J*=5 Hz), 2.65 (1H, d, *J*=2.5 Hz), 3.30 (3H, s), 5.44 (2H, s), 5.71 (1H, dd, *J*=1.5, 11 Hz), 5.78 (1H, dd, *J*=1.5, 17 Hz), 5.81—5.82 (1H, m), 6.87 (1H, dd, *J*=11, 17 Hz), 7.02 (1H, d, *J*=9 Hz), 7.26 (1H, t, *J*=9 Hz), 7.45 (1H, d, *J*=8 Hz), 8.09 (1H, t, *J*=8 Hz). MS *m/z*: 241 (M^+). HR-MS *m/z*: 241.1103 (Calcd for $C_{15}H_{15}NO_2$: 241.1098).

***N*-(Benzyloxymethyl)-2-ethenyl-3-(1-hydroxyprop-2-yn-1-yl)indole (14c)** The same procedure as above was carried out using **13c** (480 mg, 1.65 mmol) to give the oily propargyl alcohol **14c** (439 mg, 84%). IR (neat) cm^{-1}: 3294, 2114. ^{1}H-NMR ($CDCl_3$) δ: 2.28 (1H, d, *J*=5 Hz), 2.65 (1H, d, *J*=2.5 Hz), 4.49 (2H, s), 5.54 (2H, s), 5.68 (1H, dd, *J*=2, 11 Hz), 5.77 (1H, dd, *J*=2, 17 Hz), 5.80 (1H, dd, *J*=2.5, 5 Hz), 6.87 (1H, dd, *J*=11, 17 Hz), 7.24—7.36 (8H, m), 8.07 (1H, d, *J*=7 Hz). MS *m/z*: 317 (M^+). HR-MS *m/z*: 317.1416 (Calcd for $C_{21}H_{19}NO_2$: 317.1426).

2-Ethenyl-3-[1-(methoxymethyloxy)prop-2-yn-1-yl]-*N*-(phenylsulfonyl)indole (15a) A stirred solution of the propargyl alcohol **14a** (100 mg, 0.30 mmol), MOMCl (0.14 ml, 1.77 mmol), and iso-Pr_2NEt (0.41 ml, 2.36 mmol) in CH_2Cl_2 (5 ml) was heated at 45 °C for 12 h. The solution was treated with water, and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (3 : 7) as an eluent to give the oily *O*-MOM-ether **15a** (81 mg, 72%). ^{1}H-NMR ($CDCl_3$) δ: 2.68 (1H, d, *J*=2 Hz), 3.84 (3H, s), 4.58 (1H, d, *J*=7 Hz), 5.03 (1H, d, *J*=7 Hz), 5.33—6.00 (4H, m), 6.66—8.33 (9H, m). MS *m/z*: 381 (M^+). HR-MS *m/z*: 381.1035 (Calcd for $C_{21}H_{19}NO_4S$: 381.1052).

2-Ethenyl-*N*-(methoxymethyl)-3-[1-(methoxymethyloxy)prop-2-yn-1-yl]indole (15b) The same procedure as above was carried out using **14b** (215 mg, 0.89 mmol) to give the oily *O*-MOM-ether **15b** (229 mg, 90%). ^{1}H-NMR ($CDCl_3$) δ: 2.54 (1H, d, *J*=2 Hz), 3.28 (3H, s), 3.38 (3H, s), 4.56 (1H, d, *J*=7 Hz), 4.59 (1H, d, *J*=7 Hz), 5.41 (2H, s), 5.50—6.00 (3H, m), 6.77 (1H, dd, *J*=11, 17 Hz), 6.59—7.59 (3H, m), 7.74—8.17 (1H, m). MS *m/z*: 285 (M^+). HR-MS *m/z*: 285.1365 (Calcd for $C_{17}H_{19}NO_3$: 285.1344).

***N*-(Benzyloxymethyl)-3-[1-(benzyloxymethyloxy)prop-2-yn-1-yl]-2-ethenylindole (15c)** A solution of the propargyl alcohol **14c** (100 mg, 0.315 mmol) in dried THF (3 ml) was added to a stirred suspension of 60% NaH (15 mg, 0.379 mmol) in dried THF (2 ml) under cooling with ice. After stirring at the same temperature for 30 min, BOMCl (53 μl, 0.379 mmol) was added to the reaction mixture. The mixture was stirred at the same temperature for 1 h, then quenched with water and extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (3 : 7) as an eluent to give the oily *O*-BOM–ether **15c** (75 mg, 56%). IR (neat) cm^{-1}: 2115. ^{1}H-NMR ($CDCl_3$) δ: 2.59 (1H, d, *J*=2.5 Hz), 4.51 (2H, s), 4.64 (2H, s), 4.77 (1H, d, *J*=7 Hz), 5.08 (1H, d, *J*=7 Hz), 5.55 (2H, s), 5.63 (1H, dd, *J*=1.5, 11 Hz), 5.80 (1H, dd, *J*=1.5, 17 Hz), 5.80 (1H, dd, *J*=2.5 Hz), 6.87 (1H, dd, *J*=11, 17 Hz), 7.17—7.39 (13H, m), 7.99 (1H, d, *J*=7 Hz). MS *m/z*: 437 (M^+). HR-MS *m/z*: 437.1991 (Calcd for $C_{29}H_{27}NO_3$: 437.1987).

4-(Methoxymethyloxy)-3-methylcarbazole (16a) A solution of the MOM-ether **15a** (80 mg, 0.21 mmol) in THF (1.5 ml) was added to a stirred solution of *t*-BuOK (71 mg, 0.63 mmol) in *t*-BuOH (3.5 ml) at an ambient temperature. The mixture was refluxed at 90 °C for 2 h and cooled to room temperature, then quenched with an aqueous NH_4Cl (saturated) solution, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–hexane (1 : 9) as an eluent to give the oily carbazole **16a** (20 mg, 35%). IR (neat) cm^{-1}: 3410. ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s), 3.59 (3H, s), 5.24 (2H, s), 7.03 (1H, d, *J*=8 Hz), 7.13—7.36 (4H, m), 7.96 (1H, br s), 8.13 (1H, d, *J*=7.7 Hz). MS

m/z: 241 (M^+). HR-MS *m/z*: 241.1103 (Calcd for $C_{15}H_{15}NO_2$: 241.1088).

***N*-(Methoxymethyl)-4-(methoxymethyloxy)-3-methylcarbazole (16b)** The same procedure as above was carried out using **15b** (150 mg, 0.53 mmol) to give the oily carbazole **16b** (87 mg, 58%). ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s), 3.27 (3H, s), 3.60 (3H, s), 5.24 (2H, s), 5.52 (2H, s), 7.02—7.36 (5H, m), 8.13 (1H, d, J=8 Hz). MS *m/z*: 285 (M^+). HR-MS *m/z*: 285.1365 (Calcd for $C_{17}H_{19}NO_3$: 285.1379).

***N*-(Benzyloxymethyl)-4-(benzyloxymethyloxy)-3-methylcarbazole (16c)** The same procedure as above was carried out using **15c** (2.1 g, 4.80 mmol) to give the carbazole **16c** (1.7 g, 81%). mp 70—71 °C (Et_2O–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s), 4.47 (2H, s), 4.93 (2H, s), 5.44 (2H, s), 5.75 (2H, s), 7.19—7.50 (15H, m), 8.26 (1H, d, J=8 Hz). MS *m/z*: 437 (M^+). *Anal.* Calcd for $C_{29}H_{27}NO_3$: C, 79.61; H, 6.22; N, 3.20. Found: C, 79.76; H, 6.38; N, 3.05.

4-Hydroxy-*N*-(hydroxymethyl)-3-methylcarbazole (17a) and 4-Hydroxy-3-methylcarbazole (7a) A solution of the carbazole **16c** (100 mg, 0.23 mmol) in THF (3 ml) was added to a liquid NH_3 at −78 °C. A piece of Na (54 mg, 2.33 mmol) was added to the mixture. After stirring at the same temperature for 30 min, the mixture was quenched with NH_4Cl and then the temperature was raised to room temperature. The resultant mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (3 : 17) as an eluent to give the *N*-hydroxymethylcarbazole **17a** (39 mg, 75%) and the carbazole **7a** (10 mg, 22%). **17a**: mp 122—125 °C (EtOAc–hexane). IR (KBr) cm^{-1}: 3368. ^{1}H-NMR ($CDCl_3$) δ: 2.41 (3H, s), 2.87 (1H, t, J=6.6 Hz, exchangeable with D_2O), 5.26 (1H, br s), 5.82 (2H, d, J=6.6 Hz), 7.03 (1H, d, J=8 Hz), 7.20—7.34 (2H, m), 7.41—7.50 (2H, m), 8.28 (1H, d, J=8 Hz). MS *m/z*: 227 (M^+). *Anal.* Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.13; H, 5.84; N, 6.01. **7a**: mp 160—163 °C (EtOAc–hexane) (lit.,[5f] mp 161—163 °C). IR (KBr) cm^{-1}: 3380, 1611. ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s), 5.21 (1H, br s), 6.93 (1H, d, J=8 Hz), 7.16 (1H, d, J=8 Hz), 7.20—7.26 (1H, m), 7.37—7.39 (2H, m), 7.94 (1H, br s), 8.26 (1H, d, J=8 Hz). ^{13}C-NMR ($CDCl_3$) δ: 149.7, 140.0, 139.2, 128.5, 125.0, 122.6, 122.3, 119.5, 112.0, 111.9, 110.0, 102.8, 14.8. MS *m/z*: 197 (M^+). *Anal.* Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.31; H, 5.78; N, 6.94.

4-Hydroxy-3-methylcarbazole (7a) from 4-Hydroxy-*N*-(hydroxymethyl)-3-methylcarbazole (17a) Triton B (40% in water, 1 drop with a pipet) was added to a stirred solution of *N*-hydroxymethylcarbazole **17a** (12 mg, 0.0528 mmol) in THF (2 ml) and H_2O (1 ml). The mixture was heated at 100 °C for 20 min, cooled to an ambient temperature, diluted with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (1 : 4) as an eluent to give the carbazole **7a** (8 mg, 71%).

4-Hydroxy-*N*-(methoxymethyl)-3-methylcarbazole (17b) A solution of *N*-hydroxymethylcarbazole **17a** (12 mg, 0.0528 mmol), ethylene glycol (0.5 ml), and 0.5 M HCl (2 ml) in THF (2 ml) was stirred at room temperature for 30 min. The mixture was basified with an aqueous Na_2CO_3 (saturated) solution, and then the resulting mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC using EtOAc–hexane (1 : 4) as an eluent to give the oily *N*-MOM-carbazole **17b** (13 mg, 75%). ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s), 3.59 (3H, s), 5.24 (2H, s), 7.03 (1H, d, J=8 Hz), 7.13—7.36 (4H, m), 8.13 (1H, d, J=7.7 Hz). MS *m/z*: 241 (M^+). HR-MS *m/z*: 241.1103 (Calcd for $C_{15}H_{15}NO_2$: 331.1123).

2-(3-Furyl)indole-3-carbaldehyde (10b) A stirred mixture of 2-chloroindole **11** (995 mg, 5.56 mmol), furan-3-boronic acid (**18**) (1.12 g, 10 mmol), Et_3N (2.3 ml, 16.7 mmol), PPh_3 (mg, 0.34 mmol), and $Pd(OAc)_2$ (38 mg, 0.17 mmol) in DMF (10 ml) was heated at 100 °C for 5 h. After cooling to an ambient temperature, the mixture was quenched with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc–hexane (3 : 7) as an eluent to give the 2-furylindole **10b** (982 mg, 84%). mp 255—258 °C ($CHCl_3$). IR (KBr) cm^{-1}: 3157, 1632. ^{1}H-NMR (acetone-d_6) δ: 6.77 (1H, dd, J=0.7, 1.8 Hz), 7.26—7.50 (3H, m), 7.62 (1H, t, J=1.8 Hz), 8.02 (1H, d, J=0.7 Hz), 8.34 (1H, m), 8.66 (1H, br s), 10.22 (1H, s). MS *m/z*: 211 (M^+). *Anal.* Calcd for $C_{13}H_9NO_2$: C, 73.92; H, 4.29; N, 6.63. Found: C, 74.25; H, 4.40; N, 6.49.

***N*-(Benzyloxymethyl)-2-(3-furyl)indole-3-carbaldehyde (19)** The same procedure as the synthesis of **12c** from **11** was carried out using **10b** (288 mg, 1.36 mmol) to give the oily *N*-BOM-indole **19** (442 mg, 98%). IR (neat) cm^{-1}: 1651. ^{1}H-NMR ($CDCl_3$) δ: 4.56 (2H, s), 5.54 (2H, s), 6.76 (1H, dd, J=0.7, 1.8 Hz), 7.26—7.48 (8H, m), 7.62 (1H, t, J=1.8 Hz), 7.84 (1H, d, J=0.7 Hz), 8.41—8.44 (1H, m), 9.98 (1H, s). MS *m/z*: 331 (M^+). HR-MS *m/z*: 331.1208 (Calcd for $C_{21}H_{17}NO_3$: 331.1219).

***N*-(Benzyloxymethyl)-2-(3-furyl)-3-(1-hydroxyprop-2-yn-1-yl)indole (20)** The same procedure as the synthesis of **13c** from **12c** was carried out using **19** (276 mg, 0.83 mmol) to give the oily alcohol **20** (295 mg, 99%). IR (neat) cm^{-1}: 3288, 2106. ^{1}H-NMR ($CDCl_3$) δ: 2.20 (1H, d, J=4.8 Hz), 2.65 (1H, d, J=2.6 Hz), 4.52 (2H, s), 5.50 (2H, s), 5.65 (1H, dd, J=2.6, 4.8 Hz), 6.72 (1H, dd, J=0.7, 1.8 Hz), 7.22—7.45 (8H, m), 7.57 (1H, t, J=1.8 Hz), 7.77 (1H, d, J=0.7 Hz), 8.10—8.13 (1H, m). MS *m/z*: 357 (M^+). HR-MS *m/z*: 357.1365 (Calcd for $C_{23}H_{19}NO_3$: 357.1384).

***N*-(Benzyloxymethyl)-3-[1-(benzyloxymethyloxy)prop-2-yn-1-yl]-2-(3-furyl)indole (21)** The same procedure as the synthesis of **15c** from **14c** was carried out using **20** (431 mg, 1.20 mmol) to give the *O*-BOM ether **21**. Compound **21** was used in the next step without further purification.

***N*-(Benzyloxymethyl)-4-(benzyloxymethyloxy)-3-methylfuro[3,2-*a*]carbazole (22)** The same procedure as the synthesis of **16c** from **15c** was carried out using **21** to give the carbazole **22** (350 mg, 61% from **20**). mp 79—81 °C (Et_2O–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.63 (3H, s), 4.53 (2H, s), 4.96 (2H, s), 5.45 (2H, s), 5.95 (2H, s), 7.14 (1H, d, J=2.2 Hz), 7.23—7.48 (13H, m), 7.72 (1H, d, J=2.2 Hz), 8.29 (1H, d, J=7 Hz). MS *m/z*: 477 (M^+). *Anal.* Calcd for $C_{31}H_{27}NO_4$: C, 77.97; H, 5.70; N, 2.93. Found: C, 78.11; H, 5.91; N, 2.75.

4-Hydroxy-*N*-hydroxymethyl-3-methylfuro[3,2-*a*]carbazole (23) and 4-Hydroxy-3-methylfuro[3,2-*a*]carbazole (7b) The same procedure as the synthesis of **17a** and **7a** from **16c** was carried out using **22** (114 mg, 0.24 mmol) to give the *N*-hydroxymethylcarbazole **23** (26 mg, 41%) and the carbazole **7b** (29 mg, 51%). **23**: mp 142—145 °C (Et_2O–hexane). IR (KBr) cm^{-1}: 3309. ^{1}H-NMR ($CDCl_3$) δ: 2.54 (3H, s), 2.46 (1H, t, J=7 Hz), 5.26 (1H, s), 6.02 (2H, d, J=7 Hz), 7.14 (1H, d, J=1.8 Hz), 7.31 (1H, t, J=8 Hz), 7.43 (1H, t, J=8 Hz), 7.54 (1H, d, J=8 Hz), 7.69 (1H, d, J=1.8 Hz), 8.34 (1H, d, J=8 Hz). MS *m/z*: 267 (M^+). *Anal.* Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.93; H, 4.86; N, 5.28. **7b**: mp 170—173 °C (Et_2O–hexane). IR (KBr) cm^{-1}: 3421. ^{1}H-NMR ($CDCl_3$) δ: 2.53 (3H, s), 5.28 (1H, br s), 6.92 (1H, d, J=2.2 Hz), 7.27 (1H, t, J=8 Hz), 7.37 (1H, t, J=8 Hz), 7.47 (1H, d, J=8 Hz), 7.63 (1H, d, J=2.2 Hz), 8.29 (1H, br s), 8.30 (1H, d, J=8 Hz). MS *m/z*: 237 (M^+). *Anal.* Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 76.16; H, 4.90; N, 5.71.

4-Hydroxy-3-methylfuro[3,2-*a*]carbazole (7b) from 23 The same procedure as the synthesis of **7a** from **17a** was carried out using **23** (6 mg, 0.024 mmol) to give the carbazole **7b** (5 mg, 93%).

3-Methyl-4-(trifluoromethanesulfonyloxy)furo[3,2-*a*]carbazole (24) Tf_2O (7.4 μl, 0.0443 mmol) was added to a stirred solution of the 4-hydroxycarbazole **7b** (7 mg, 0.0295 mmol) and pyridine (7.2 μl, 0.0885 mmol) in CH_2Cl_2 (1 ml) under cooling with ice. After stirring at room temperature for 10 min, the solution was treated with water, and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (3 : 17) as an eluent to give the triflate **24** (10 mg, 92%). mp 138—140 °C (Et_2O–hexane). IR (KBr) cm^{-1}: 3446, 1383, 1134. ^{1}H-NMR ($CDCl_3$) δ: 2.67 (3H, s), 7.01 (1H, d, J=2.2 Hz), 7.26—7.47 (3H, m), 7.80 (1H, d, J=2.2 Hz), 8.32 (1H, d, J=8 Hz), 8.47 (1H, br s). MS *m/z*: 369 (M^+). *Anal.* Calcd for $C_{16}H_{10}F_3NO_4S$: C, 52.03; H, 2.73; N, 3.79. Found: C, 52.32; H, 2.98; N, 3.71.

Furostifoline (5) HCOOH (22 μl, 0.54 mmol) was added to the mixture of the triflate **24** (10 mg, 0.027 mmol), Et_3N (34 μl, 0.234 mmol), PPh_3 (0.28 mg, 0.0011 mmol) and $Pd(OAc)_2$ (0.12 mg, 0.00054 mmol) in DMF (3 ml) under argon. The mixture was heated at 60 °C for 12 h. After cooling to an ambient temperature, the solution was treated with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (1 : 9) as an eluent to give furostifoline (**5**) (6 mg, 99%). mp 173—175 °C (Et_2O–hexane) (lit.,[3] mp 174—175 °C). IR (KBr) cm^{-1}: 3408, 1456. ^{1}H-NMR ($CDCl_3$) δ: 2.68 (3H, s), 7.00 (1H, d, J=2.2 Hz), 7.26 (1H, dt, J=1.1, 8.1 Hz), 7.38 (1H, dt, J=1.1, 8.1 Hz), 7.49 (1H, br d, J=8.1 Hz), 7.73 (1H, d, J=2.2 Hz), 7.78 (1H, br s), 8.06 (1H, br d, J=8.1 Hz), 8.26 (1H, br s). MS *m/z*: 221 (M^+). *Anal.* Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.59; H, 5.32; N, 6.11.

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