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A NEW SYNTHETIC ROUTE TO THE 1-OXYGENATED CARBAZOLE ALKALOIDS, MUKONINE AND CLAUSINE E (CLAUZOLINE I)

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This paper is dedicated to the late Dr. John W. Daly

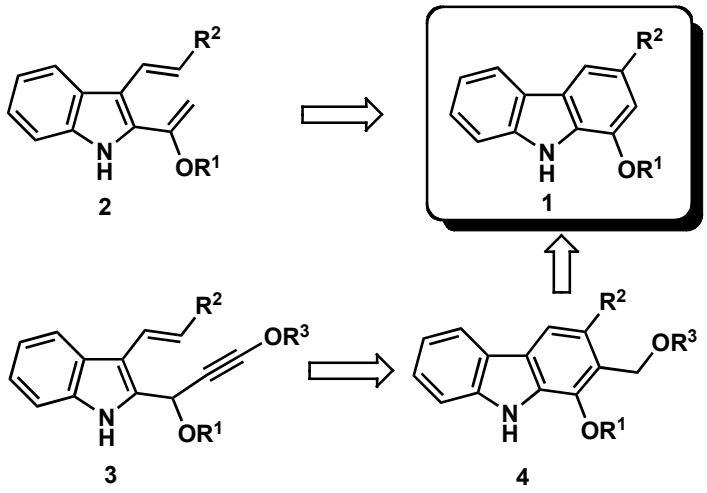
Abstract – A new synthesis of the 1-oxygenated 1,3-disubstituted carbazole alkaloids, mukonine (**1a**) and clausine (**1f**) is described. The construction of the carbazole framework is based on an allene-mediated electrocyclic reaction involving the indole 2,3-bond. The 1,3-disubstituted 1-oxygenated carbazoles **1a** and **1f** are derived from the 1,2,3-trisubstituted carbazole.

INTRODUCTION

Naturally occurring carbazole alkaloids display a wide variety of biological activities, such as antitumor, antibacterial, antimicrobial, and anti-inflammatory activities. An intensive effort has been directed toward their isolation, and total synthesis.[1] The search for the biologically active compounds of *Murraya* and *Clausena* led to the discovery of a broad variety of carbazole alkaloids, including the 1-oxygenated 3-substituted carbazoles and 2-oxygenated 3-substituted carbazoles. Among them, the simple 1-oxygenated 3-substituted carbazole alkaloids, mukonine (**1a**) and clausine E (clauzoline I: **1f**) have been isolated from *Murraya koenigii*[1a,2] and *Clausena excavata*[1,3,4] (and *anisata*), together with **1b**~**1e**, **1g,** and **1h** (Scheme 1). Several excellent synthetic routes for their preparation have been reported.[1,5]

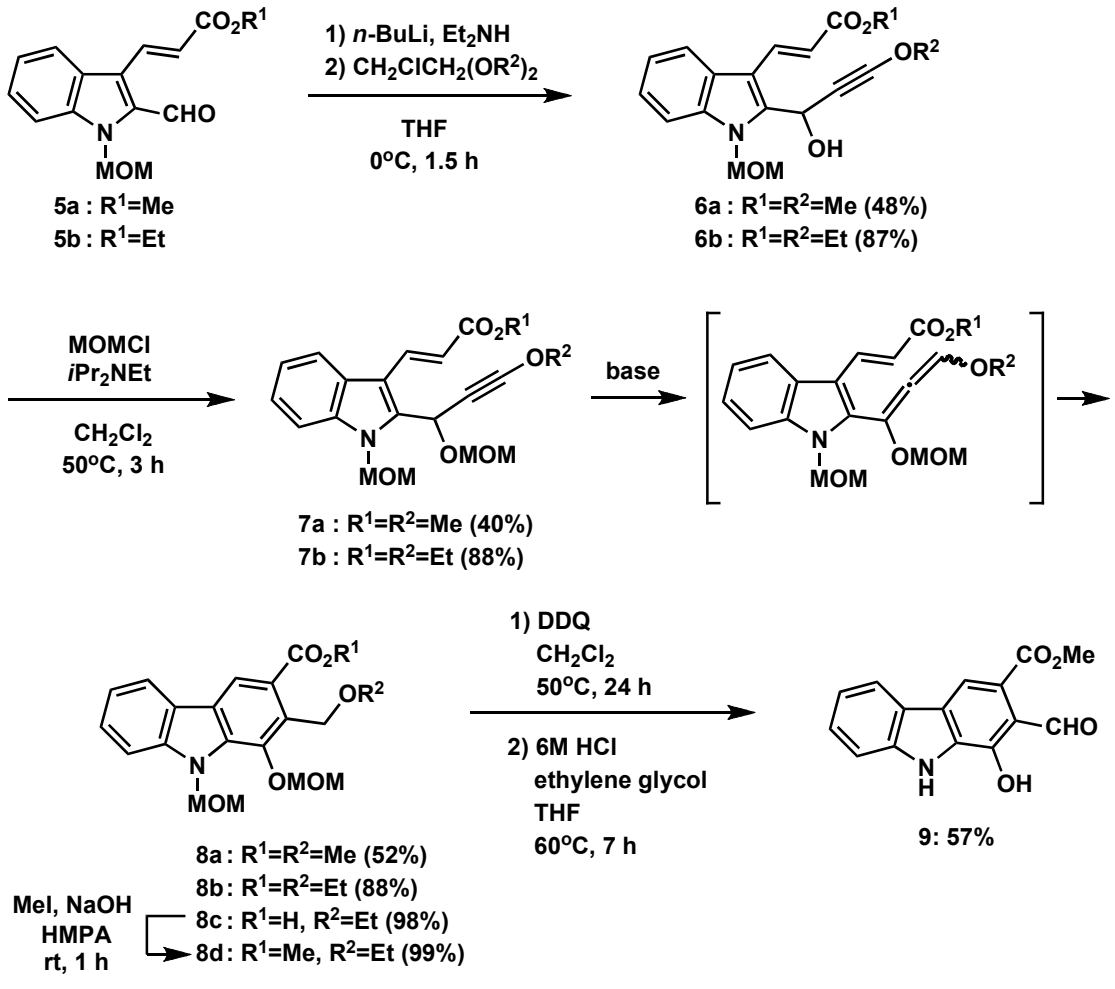
We have been working to develop the synthesis of a biologically active condensed heterocyclic compound based on a thermal electrocyclic reaction of either the 6π-electron system or the aza 6π-electron system.[6] Recently, the total synthesis of 3-oxygenated or 3,4-dioxygenated polyfunctionalized carbazole alkaloids was developed by an allene-mediated electrocyclic reaction involving the indole 2,3-bond.[7] Initially, we planned a short-step sequence toward a 1-oxyganated carbazole 1 based on a

thermal electrocyclic reaction of 2,3-bisalkenylindole **2**[6] (Scheme 1). However, it was difficult to prepare the precursor **2**. Taking advantage of our recent efforts,[7] we applied this methodology for the syntheses of mukonine (**1a**) and clausine (**1f**).



	R^1	R^2
1a	Me	CO_2Me
1b	Me	CO_2H
1c	Me	CHO
1d	Me	CH_2OH
1e	Me	Me
1f	H	CO_2Me
1g	H	CHO
1h	H	Me

Scheme 1

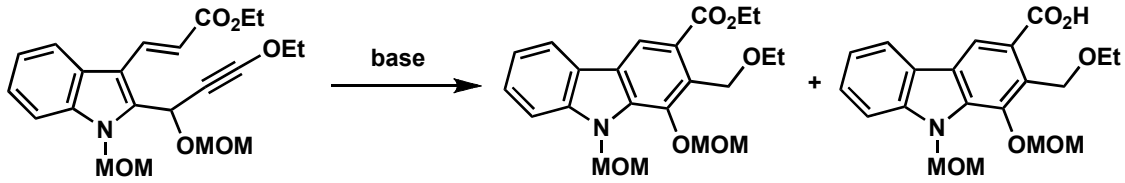


Scheme 2

RESULTS AND DISCUSSION

In the present paper, we describe a new synthesis of the 1-oxygenated 3-substituted carbazoles, mukonine (**1a**) and clausine (**1f**), based on an alle4ne-mediated electrocyclic reaction of the 6π-electron system involving the indole 2,3-bond (Scheme 2). We chose methyl 3-[2-formyl-*N*-(methoxymethyl)-indole-3-yl]acrylate (**5a**) and ethyl 3-[2-formyl-*N*-(methoxymethyl)indole-3-yl]acrylate (**5b**) as starting materials.[8] Nucleophilic addition reaction of **5a** and **5b** with lithium methoxyacetylide or ethoxyacetylide, (prepared from chloroacetaldehyde dimethyl acetal or chloroacetaldehyde diethyl acetal with lithium diethylamide in *in situ*),[9] gave the propargyl alcohol **6a** and **6b**, respectively. Subsequent treatment of **6a** and **6b** with chloromethyl methyl ether (MOMCl) in CH_2Cl_2 at 50 °C afforded the propargyl ether **7a** and **7b,** respectively. An allene-mediated electrocyclic reaction of the propargyl ether **7a** was carried out by tetrahydroammonium fluoride (TBAF) according to the reported procedure[7b] to give the 1,2,3-trisubstituted carbazole-3-methyl ester **8a** in somewhat low yield.

Table 1. Synthesis of 1,2,3-Trisubstituted Carbazoles by Allene-mediated Electrocyclic Reaction



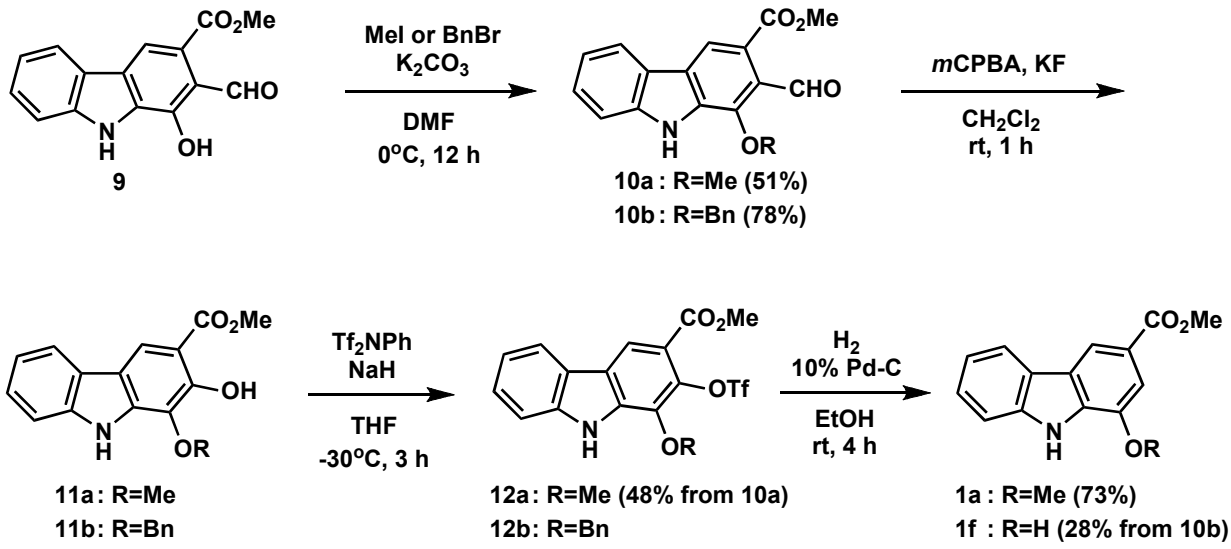
7b 8b 8c

run	base	base (eq.)	time (min)	yield (%) of 8b	yield (%) of 8c
1	TBAF	5	10	88	–
2	TBAF	5	15	76	9
3	TBAF	5	60	64	18
4	*t*-BuOK	5	60	–	98
5	*t*-BuOK	3	60	–	89

As shown in Table 1, the propargyl ether **7b** was subjected to a similar reaction using TBAF to yield the cyclized carbazoles **8b** in moderate to good yields, together with the carbazole-3-carboxylic acid **8c** (run 1-3). On the other hand, the same reaction of **7b** using *t*-BuOk[7] gave the exclusively carbazole-3-carboxylic acid **8c** through a cyclization followed by a hydrolysis of the ester **8c** (run 4, 5). The carbazole-3-carboxylic acid **8c** was treated with MeI in the presence of hexamethylphosphoramide (HMPA) to proceed to the carbazole-3-methyl ester **8d**. Oxidation of the alkoxymethyl group at the 2-position of carbazoles **8a** and **8d** with dichlorodicyanoquinone (DDQ) in CH_2Cl_2 provided the 2-formyl-1-hydroxycarbazole **9**, derived from both compounds. The allover yield (42%) of 1-oxygenated

carbazole **9** from **5b** was greater than that of the methyl ester series **5a** (5%).

For the synthesis of **1a** and **1f** (Scheme 3), alkylation of the 1-hydroxycarbazole **9** was carried out by MeI or benzyl bromide in the presence of K_2CO_3 at 0 °C to yield 1-methoxycarbazole **10a** and 1-benzyloxycarbazole **10b**, respectively. Baeyer-Villiger reaction of **10a** and **10b** with *m*-chloroperbenzoic acid (*m*CPBA) in the presence of potassium fluoride (KF)[10] in CH_2Cl_2 afforded 2-hydroxycarbazoles **11a** and **11b**, respectively. Subsequent treatment of **11a** and **11b** with *N*-phenyl bistrifluoromethanesulfonylamide (Tf_2NPh) in the presence of NaH gave triflates **12a** and **12b**, which were subjected to hydrogenolysis[11] with 10% Pd-C and hydrogen gas to produce mukonine (**1a**) and clausine E (**1f**) along with debenzylation. The spectral and physical data of the obtained mukonine (**1a**) and clausine E (**1f**) were identified by comparison with those reported previously.[12]



Scheme 3

CONCLUSION

In summary, 1,3-disubstituted 1-oxygenated carbazole alkaloids, mukonine (**1a**) and clausine E (**1f**) were newly synthesized by the construction of 1,2,3-trisubstituted 1-oxygenated carbazoles **8a** and **8c** based on an allene-mediated electrocyclic reaction involving the indole 2,3-bond, followed by removal of the alkoxymethyl group at the 2-position of **8a** and **8c** in four-steps. Although this synthetic route is a long process, this scheme can be applied to a synthesis of the other carbazole alkaloids **1b**-**1e**, **1g**, and **1h**. In addition, we demonstrated that 2,3-disubstituted 2-oxygenated carbazole alkaloids such as mukonal and mukonidine[1,3,5] can be derived from 1,2,3-trisubstituted carbazole **9**.

EXPERIMENTAL

All melting points were measured with a Yanagimoto micro-melting point apparatus MP-500D and are uncorrected. IR spectra were recorded with ATR method using a Shimadzu FTIR-8000 spectrophotometer and Technologies DuraScop. ^{1}H-NMR and ^{13}C-NMR spectra were taken with a JEOL AL-300 instrument

using tetramethylsilane as an internal standard. Mass spectra (MS) were determined with a Shimadzu QP5050 (EI) and JMS-700 (CI with isobutane) spectrometers by direct inlet system, respectively. Solvents were distilled by normal methods (THF dried over sodium benzophenone ketyl, CH_2Cl_2 dried over CaH_2, DMF dried over CaH_2). Silica gel $60PF_{254}$ (60-100 mesh, Merck Art 7744) was used for column chromatography.

Methyl 3-[2-formyl-*N*-(methoxymethyl)indol-3-yl]acrylate (5a)

A stirred mixture of 3-iodoindole (1 g, 3.17 mmol), methyl acrylate (0.57 mL, 6.3 mmol), Et_3N (0.87 mL, 6.3 mmol), PPh_3 (26 mg, 0.1 mmol), and $Pd(OAc)_2$ (13.5 mg, 0.06 mmol) in DMF (45 mL) were heated at 100 ^oC for 1 h under Ar. After being cooled to ambient temperature, the reaction mixture was diluted with water, and the mixture was extracted with EtOAc. The EtOAc was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 20 g) using EtOAc-hexane (1:4 v/v) as an eluent to give the *N*-MOM-indole **5a**[8] (734 mg, 85%). mp 104-106 ^oC (EtOAc); IR (ATR) ν : 1697, 1647 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 3.32 (3H, s), 3.86 (3H, s), 6.01 (2H, s), 6.69 (1H, d, *J*=16.0 Hz), 7.35 (1H, t, *J*=7.3 Hz), 7.52 (1H, t, *J*=7.3 Hz), 7.61 (1H, d, *J*=7.3 Hz), 8.01 (1H, d, *J*=7.3 Hz), 8.32 (1H, d, *J*=16.0 Hz), 10.38 (1H, s); MS *m/z*: 273 (M^+).

Ethyl 3-[2-formyl-*N*-(methoxymethyl)indol-3-yl]acrylate (5b)

The same procedure as above was carried out using 3-iodoindole (1 g, 3.17 mmol) and ethyl acrylate (697 μL, 6.4 mmol) to give the *N*-MOM-indole **5b** (830 mg, 91%). mp 83-85^oC (EtOAc); IR (ATR) ν : 1709, 1631 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 1.38 (3H, t, *J*=7.1 Hz), 3.31 (3H, s), 4.32 (2H, q, *J*=7.1 Hz), 6.01 (2H, s), 6.68 (1H, d, *J*=15.8 Hz), 7.43 (1H, t, *J*=7.3 Hz), 7.51 (1H, t, *J*=7.3 Hz), 7.54 (1H, d, *J*=7.3 Hz), 8.02 (1H, d, *J*=7.3 Hz), 8.31 (1H, d, *J*=15.8 Hz), 10.38 (1H, s); MS *m/z*: 287 (M^+).

Methyl 3-[2-(1-hydroxy-3-methoxyprop-2-yn-1-yl)-*N*-(methoxymethyl)indol-3-yl]acrylate (6a)

Et_2NH (3.59 mL, 34.69 mmol) was added to a solution of *n*-BuLi (2.59 mol/L in hexane, 12.1 mL, 31.22 mmol) in THF (27 mL) under cooling with ice-water. After stirring at the same temperature for 10 min, chloroacetaldehyde dimethyl acetal (1.19 mL, 10.41 mmol) was added to the reaction mixture at the same temperature for further 1.5 h. A solution of *N*-MOM-indole **5a** (474 mg, 1.73 mmol) in THF (15 mL) was added to the reaction mixture at same temperature for further 1.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, and then extracted with EtOAc. The EtOAc was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 15 g) using EtOAc-hexane (3:7 v/v) as an eluent to give the oily propargyl alcohol **6a** (274 mg, 48%). IR (ATR) ν : 2271, 1712 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 3.35 (3H, s), 3.64 (1H, d, *J*=7.5 Hz), 3.82 (3H, s), 3.91 (3H, s), 5.63 (1H, d, *J*=11.0 Hz), 6.09 (1H, d, *J*=7.5 Hz), 6.13

(1H, d, *J*=11.0 Hz), 6.57 (1H, d, *J*=15.8 Hz), 7.27 (1H, t, *J*=7.2 Hz), 7.34 (1H, t, *J*=7.2 Hz), 7.52 (1H, d, *J*=7.2 Hz), 7.93 (1H, d, *J*=7.2 Hz), 8.09 (1H, d, *J*=15.8 Hz), MS *m/z*: 329 (M^+). HR-MS *m/z*: 329.1270 (Calcd for $C_{18}H_{19}NO_5$: 329.1263)

Ethyl 3-[2-(3-ethoxy-1-hydroxyprop-2-yn-1-yl)-*N*-(methoxymethyl)indol-3-yl]acrylate (6b)

The same procedure as above was carried out using *N*-MOM-indole **5b** (753 mg, 2.62 mmol) and chloroacetaldehyde diethyl acetal (3.34 mL, 22.57 mmol) to give the oily propargyl alcohol **6b** (817 mg, 87%). IR (ATR) ν : 2264, 1697 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 1.33 (3H, t, *J*=7.1 Hz), 1.35 (3H, t, *J*=7.1 Hz), 3.33 (3H, s), 3.90 (1H, d, *J*=5.9 Hz), 4.12 (2H, q, *J*=7.1 Hz), 4.25 (2H, q, *J*=7.1 Hz), 5.65 (1H, d, *J*=11.0 Hz), 6.09 (1H, d, *J*=11.0 Hz), 6.11 (1H, d, *J*=5.9 Hz), 6.52 (1H, d, *J*=16.0 Hz), 7.25 (1H, t, *J*=7.6 Hz), 7.31 (1H, t, *J*=7.6 Hz), 7.51 (1H, d, *J*=7.6 Hz), 7.92 (1H, d, *J*=7.6 Hz), 8.08 (1H, d, *J*=16.0 Hz), MS *m/z*: 357 (M^+). HR-MS *m/z*: 357.1585 (Calcd for $C_{20}H_{23}NO_5$: 357.1576).

Methyl 3-{2-[3-methoxy-1-(methoxymethyloxy)prop-2-yn-1-yl]-*N*-(methoxymethyl)indol-3-yl} acrylate (7a)

A solution of propargyl alcohol **6a** (548 mg, 1.66 mmol), MOMCl (0.76 mL, 9.98 mmol), and *i*-Pr_2NEt (2.29 mL, 13.31 mmol) in CH_2Cl_2 (15 mL) were heated at 50 ^{o}C for 3 h. After being cooled to ambient temperature, the reaction mixture was quenched with water, and then was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 15 g) using EtOAc-hexane (3:7 v/v) as an eluent to give the oily propargyl ether **7a** (264 mg, 40%). IR (ATR) ν : 2268, 1709 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 3.34 (3H, s), 3.39 (3H, s), 3.82 (3H, s), 3.90 (3H, s), 4.58 (1H, d, *J*=6.6 Hz), 4.93 (1H, d, *J*=6.6 Hz), 5.75 (2H, s), 6.07 (1H, s), 6.55 (1H, d, *J*=15.8 Hz), 7.26 (1H, td, *J*=7.0, 1.2 Hz), 7.32 (1H, td, *J*=7.0, 1.2 Hz), 7.58 (1H, dd, *J*=7.0, 1.2 Hz), 7.92 (1H, dd, *J*=7.0, 1.2 Hz), 8.10 (1H, d, *J*=15.8 Hz), MS *m/z*: 373 (M^+). HR-MS *m/z*: 373.1550 (Calcd for $C_{20}H_{23}NO_6$: 373.1525).

Ethyl 3-{2-[3-ethoxy-1-(methoxymethyloxy)prop-2-yn-1-yl]-*N*-(methoxymethyl)indol-3-yl}acrylate (7b)

The same procedure as above was carried out using propargyl alcohol **6b** (595 mg, 1.67 mmol) to give the oily propargyl ether **7b** (590 mg, 88%). IR (ATR) ν : 2264, 1716 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 1.35 (3H×2, t, *J*=7.1 Hz), 3.34 (3H, s), 3.39, (3H, s), 4.13 (2H, q, *J*=7.1 Hz), 4.28 (2H, q, *J*=7.1 Hz), 4.58 (1H, d, *J*=7.0 Hz), 4.94 (1H, d, *J*=7.0 Hz), 5.77 (2H, d, *J*=1.8 Hz), 6.09 (1H, s), 6.55 (1H, d, *J*=16.0 Hz), 7.26 (1H, t, *J*=7.6 Hz), 7.32 (1H, t, *J*=7.6 Hz), 7.58 (1H, d, *J*=7.6 Hz), 7.94 (1H, d, *J*=7.6 Hz), 8.10 (1H, d, *J*=16.0 Hz), MS *m/z*: 401 (M^+). HR-MS *m/z*: 401.1811 (Calcd for $C_{22}H_{27}NO_6$: 401.1838).

Methyl 2-(methoxymethyl)-*N*-(methoxymethyl)-1-(methoxymethyloxy)carbazole-3- carboxylate (8a)
TBAF (1M in THF, 3.29 mL, 3.29 mmol) was added to a solution of the propargyl ether **7a** (246 mg, 0.66 mmol) in THF (10 mL), and then heated at 90 ^{o}C for 10 min. After being cooled to an ambient temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, and then extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 10 g) using EtOAc-hexane (3:7 v/v) as an eluent to give the 2-methoxymethylcarbazole **8a** (128 mg, 52%). mp 58-60 ^{o}C (Et_2O-hexane); IR (ATR) ν : 1720 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 3.30 (3H, s), 3.48 (3H, s), 3.60 (3H, s), 3.97, (3H, s), 4.97 (2H, s), 5.26 (2H, s), 6.07 (2H, s), 7.32 (1H, t, *J*=7.7 Hz), 7.52 (1H, t, *J*=7.7 Hz), 7.60 (1H, d, *J*=7.7 Hz), 8.08 (1H, d, *J*=7.7 Hz), 8.49 (1H, s), MS *m/z*: 373 (M^+). HR-MS *m/z*: 373.1543 (Calcd for $C_{20}H_{23}NO_6$: 373.1525).

Ethyl 2-(ethoxymethyl)-*N*-(methoxymethyl)-1-(methoxy-methyloxy)carbazole-3-carboxylate (8b)
The same procedure as above was carried out using propargyl ether **7b** (600 mg, 1.49 mmol) to give the 2-ethoxymethylcarbazole **8b** (525 mg, 88%). mp 56-57 ^{o}C (Et_2O-hexane); IR (ATR) ν : 1712 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 1.25 (3H, t, *J*=7.0 Hz), 1.45 (3H, t, *J*=7.1 Hz), 3.28 (3H, s), 3.60, (3H, s), 3.64 (2H, q, *J*=7.0 Hz), 4.43 (2H, q, *J*=7.1 Hz), 5.00 (2H, s), 5.26 (2H, s), 6.05 (2H, s), 7.30 (1H, t, *J*=7.2 Hz), 7.50 (1H, t, *J*=7.2 Hz), 7.58 (1H, d, *J*=7.2 Hz), 8.07 (1H, d, *J*=7.2 Hz), 8.43 (1H, s), MS *m/z*: 401 (M^+). HR-MS *m/z*: 401.1824 (Calcd for $C_{22}H_{27}NO_6$: 401.1838).

2-(Ethoxymethyl)-*N*-(methoxymethyl)-1-(methoxymethyloxy)carbazole-3-carboxylic acid (8c)
A solution of propargyl ether **7b** (57 mg, 0.15 mmol) in THF (3 mL) was added to a solution of *t*-BuOK (86 mg, 0.76 mmol) in *t*-BuOH (3 mL), and then heated at 90 ^{o}C for 1 h. After being cooled to an ambient temperature, the reaction mixture was adjusted to pH 5 with AcOH, and then extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was recrystallized from $CHCl_3$-hexane to give the carbazole-3-carboxylic acid **8c** (52 mg, 98%). mp 138-139 ^{o}C ($CHCl_3$-hexane) IR (ATR) ν : 2924, 1682 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 1.33 (3H, t, *J*=7.1 Hz), 3.32 (3H, s), 3.61, (3H, s), 3.79 (2H, q, *J*=7.1 Hz), 4.99 (2H, s), 5.25 (2H, s), 6.03 (2H, s), 7.34 (1H, t, *J*=7.1 Hz), 7.54 (1H, t, *J*=7.1 Hz), 7.60 (1H, d, *J*=7.1 Hz), 8.10 (1H, d, *J*=7.1 Hz), 8.62 (1H, s), MS *m/z*: 373 (M^+). HR-MS *m/z*: 373.1509 (Calcd for $C_{20}H_{23}NO_6$: 373.1525).

Methyl 2-(ethoxymethyl)-*N*-(methoxymethyl)-1-(methoxymethyloxy)carbazole-3-carboxylate (8d)
25% aqueous NaOH (1.1 mL, 6.74 mmol) solution was added to a solution of the carbazole-3-carboxylic acid **8c** (629 mg, 1.68 mmol) in HMPA (15 mL) at rt, and then stirred at same temperature for 30 min. MeI (0.84 mL, 13.48 mmol) was added to a reaction mixture, and then stirred at the same temperature for

further 1 h. The reaction mixture was adjusted to pH 5 with AcOH, and then extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 20 g) using EtOAc-hexane (1:4 v/v) as an eluent to give the oily 2-ethoxymethylcarbazole **8d** (647 mg, 99%). IR (ATR) ν : 1726 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 1.25 (3H, t, *J*=7.0 Hz), 3.29 (3H, s), 3.60 (3H, s), 3.65 (2H, q, *J*=7.0 Hz), 3.96, (3H, s), 5.00 (2H, s), 5.26 (2H, s), 6.05 (2H, s), 7.30 (1H, t, *J*=7.5 Hz), 7.50 (1H, t, *J*=7.5 Hz), 7.58 (1H, d, *J*=7.5 Hz), 8.06 (1H, d, *J*=7.5 Hz), 8.44 (1H, s), MS *m/z*: 387 (M^+). HR-MS *m/z*: 387.1702 (Calcd for $C_{21}H_{25}NO_6$: 387.1682).

Methyl 2-formyl-1-hydroxycarbazole-3-carboxylate (9)

A solution of 2-methoxymethylcarbazole **8a** (100 mg, 0.27 mmol), DDQ (122 mg, 0.54 mmol), and $LiClO_4$ (28 mg, 0.27 mmol) in CH_2Cl_2/H_2O (18:1) (10 mL) were heated at 60 ^{o}C for 24 h. After being cooled to ambient temperature, the reaction mixture was filtered though Celite pad. The filtrate was extracted with CH_2Cl_2. The organic layer was washed water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was used without purification. 6 M HCl (0.5 mL) and ethylene glycol (0.5 mL) were added to a solution of the residue in THF (4 mL), and then heated at 60^{o}C for 7 h. After being cooled to ambient temperature, the reaction mixture was added water and then extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 5 g) using EtOAc-hexane (3:17 v/v) as an eluent to give the 2-formylcarbazole **9** (32 mg, 46%). mp 204-205 ^{o}C (Et_2O-hexane); IR (ATR) ν : 3355, 1682, 1647 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 4.01 (3H, s), 7.31-7.36 (1H, m), 7.55 (2H, br d, *J*=4.0 Hz), 8.11 (1H, d, *J*=7.3 Hz), 8.34 (1H, s), 8.85 (1H, br s), 10.84 (1H, s), 13.22 (1H, s), MS *m/z*: 269 (M^+). HR-MS *m/z*: 269.0697 (Calcd for $C_{15}H_{11}NO_4$: 269.0688).

Methyl 2-formyl-1-hydroxycarbazole-3-carboxylate (9)

The same procedure as above was carried out using 2-ethoxymethylcarbazole **8d** (200 mg, 0.52 mmol) to give the 2-formylcarbazole **9** (79 mg, 57%).

Methyl 2-formyl-1-methoxycarbazole-3-carboxylate (10a)

A mixture of 2-formylcarbazole **9** (39 mg, 0.14 mmol), MeI (9 μL, 0.14 mmol), and K_2CO_3 (20 mg, 0.14 mmol) in DMF (5 mL) was stirred at rt for 12 h. The reaction mixture was quenched with aqueous NH_4Cl solution, and then extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 5 g) using EtOAc-hexane (1:4 v/v) as an eluent to give the 1-methoxycarbazole **10a** (21 mg, 51%). mp 204-205 ^{o}C (EtOAc-hexane); IR (ATR) ν : 3240, 1682 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 3.99 (3H, s),

4.10 (3H, s), 7.30-7.36 (1H, m), 7.53-7.55 (2H, m), 8.11 (1H, d, *J*=7.3 Hz), 8.42 (1H, s), 8.67 (1H, br s), 10.59 (1H, s), MS *m/z*: 283 (M^+). HR-MS *m/z*: 283.0849 (Calcd for $C_{16}H_{13}NO_4$: 283.0845).

Methyl 1-benzyloxy-2-formylcarbazole-3-carboxylate (10b)

The same procedure as above was carried out using 2-formylcarbazole **9** (57 mg, 0.21 mmol) and benzyl bromide (25 μL, 0.21 mmol) to give the 1-benzyloxycarbazole **10b** (59 mg, 78%). mp 128-129 ^oC (Et_2O-hexane); IR (ATR) ν : 3545, 1678 cm^{-1}; ^1H-NMR ($CDCl_3$) δ : 3.98 (3H, s), 5.23 (2H, s), 7.28 (1H, t, *J*=7.5 Hz), 7.35-7.50 (7H, m), 8.05 (1H, d, *J*=7.5 Hz), 8.30 (1H, br s), 8.39 (1H, s), 10.49 (1H, s), MS *m/z*: 359 (M^+). HR-MS *m/z*: (Calcd for $C_{22}H_{17}NO_4$: 359.1158).

Methyl 1-methoxy-2-(trifluoromethanesulfonyloxy)carbazole-3-carboxylate (12a)

A solution of 1-methoxycarbazole **10a** (47 mg, 0.17 mmol), *m*CPBA (382 mg, 1.66 mmol), and KF (193 mg, 3.32 mmol) in CH_2Cl_2 (10 mL) was stirred at rt for 1 h. The reaction mixture was purified by column chromatography (silica gel 5 g) using EtOAc-hexane (3:17 v/v) as an eluent to give crude 2-hydroxycarbazole **11a**. A solution of 2-hydroxycarnazole in THF (3 mL) was added to a suspension of 60%NaH (11 mg, 0.28 mmol) in THF (3 mL) at -30 ^oC. After stirred at the same temperature for 0.5 h, the reaction mixture which was added Tf_2NPh (47 mg, 0.13 mmol), was stirred at the same temperature for further 3 h. The reaction mixture was quenched with aqueous NH_4Cl solution, and then extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 3 g) using EtOAc-hexane (3:17 v/v) as an eluent to give the oily triflate **12a** (32 mg, 48%). IR (ATR) ν : 3320, 1709, 1358, 1120 cm^{-1}; ^1H-NMR ($CDCl_3$) δ : 4.00 (3H, s), 4.09 (3H, s), 7.31-7.37 (1H, m), 7.52 (2H, br d, *J*=3.7 Hz), 8.10 (1H, d, *J*=7.7 Hz), 8.56 (1H, s), 8.58 (1H, br s), MS *m/z*: 403 (M^+). HR-MS *m/z*: 403.0318 (Calcd for $C_{16}H_{12}F_3NO_6S$: 403.0337).

Mukonine (1a)

A suspension of triflate **11a** (28 mg, 0.069 mmol) and 10%Pd-C (30 mg) in EtOH (2 mL) was stirred at rt for 6 h under hydrogen atmosphere. The reaction mixture was filtrated through Celite pad, and the Celite pad was washed EtOAc. The combined filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 3 g) using EtOAc-hexane (3:17 v/v) as an eluent to give the mukonine (**1a**) (13 mg, 73%). mp 197-198 ℃ (Et_2O-hexane) (Lit.,[5a] mp 197-198 ^oC, Lit.,[11a] mp 195 ^oC and Lit.,[11b] mp 201 ^oC) ; IR (ATR) ν : 3316, 1693 cm^{-1}; ^1H-NMR ($CDCl_3$) δ : 3.92 (3H, s), 4.07 (3H, s), 7.26 (1H, t, *J*=7.8 Hz), 7.45 (1H, t, *J*=7.8 Hz), 7.58 (1H, s), 7.63 (1H, d, *J*=7.8 Hz), 8.21 (1H, d, *J*=7.8 Hz), 8.47 (1H, s), 10.78 (1H, br s), MS *m/z*: 255 (M^+). HR-MS *m/z*: 255.0876 (Calcd for $C_{15}H_{13}NO_3$:

255.0895).

Clausine E (1f)

A solution of 1-benzyloxycarbazole **10b** (79 mg, 0.22 mmol), *m*CPBA (509 mg, 2.20 mmol), and KF (255 mg, 4.40 mmol) in CH_2Cl_2 (5 mL) was stirred at rt for 1 h. The reaction mixture was purified by column chromatography (silica gel 5 g) using EtOAc-hexane (1:19 v/v) as an eluent to give crude 2-hydroxycarbazole **11b**. A solution of 2-hydroxycarbazole **11b** in THF (3 mL) was added to a suspension of 60%NaH (18 mg, 0.44 mmol) in THF (3 mL) at -30 ^oC. After stirred at the same temperature for 0.5 h, the reaction mixture which was added Tf_2NPh (79 mg, 0.22 mmol), was stirred at the same temperature for further 3 h. The reaction mixture was quenched with aqueous NH_4Cl solution, and then extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 3 g) using EtOAc-hexane (1:9 v/v) as an eluent to give the crude triflate **12b**. A suspension of the crude triflate **12b** and 10%Pd-C (50 mg) in EtOH (2 mL) was stirred at rt for 6 h under hydrogen atmosphere. The reaction mixture was filtrated through Celite pad, and the Celite pad was washed with EtOAc. The combined filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel 3 g) using EtOAc-hexane (3:7 v/v) as an eluent to give the clausine E (**1f**) (15 mg, 28%). mp 190-191 ^oC (Et_2O-hexane) (Lit.,[3a] mp 218-220 ^oC and Lit.,[11b] mp 203 ^oC) ; IR (ATR) ν : 3347, 1655, 1631, 1601 cm^{-1}; ^{1}H-NMR (acetone-d_6) δ : 3.88 (3H, s), 7.23 (1H, td, *J*=7.4, 1.1 Hz), 7.43 (1H, td, *J*=7.4, 1.1 Hz), 7.56 (1H, d, *J*=1.1 Hz), 7.61 (1H, dd, *J*=7.4, 1.1 Hz), 8.18 (1H, dd, *J*=7.4, 1.1 Hz), 8.38 (1H, d, *J*=1.1 Hz), 9.07 (1H, s), 10.64 (1H, br s), MS *m/z*: 241 (M^+). HR-MS *m/z*: 241.0756 (Calcd for $C_{14}H_{11}NO_3$: 241.0739).

REFERENCES

1. (a) D. P. Chakraborty, *Prog. Chem. Org. Nat. Prod.*, ed. by W. Herz, H. Grisebach, and G. W. Kirby, Springer, Wien, 1977, Vol. 34, p. 299; (b) P. Bhattacharyya and D. P. Chakraborty, *Prog. Chem. Org. Nat. Prod.*, ed. by W. Herz, H. Grisebach, and G. W. Kirby, Springer, Wien, 1987, Vol. 52, p. 159; (c) D. P. Chakraborty and S. Roy, *Prog. Chem. Org. Nat. Prod.*, ed. by W. Herz, H. Grisebach, and G. W. Kirby, Springer, Wien, 1991, Vol. 57, p. 71; (d) D. P. Chakraborty, *The Alkaloids,* ed. by G. A. Cordell, Academic Press, New York, 1993, Vol. 44, p. 257; (e) H.-J. Knölker, *Chem. Soc. Rev.*, 1999, **28**, 151; (f) H.-J. Knölker and K. R. Reddy, *Chem. Rev.*, 2002, **102**, 4303; (g) H.-J. Knölker, *Top. Curr. Chem.,* 2005, **244**, 115.
2. (a) B. K. Chowdhury and D. P. Chakraborty, *Chem. Ind.,* (London), 1969, 549; (b) B. K. Chowdhury and D. P. Chakraborty, *Phytochemistry,* 1971, **10**, 481; (c) D. P. Chakraborty, P. Bhattacharyya, S. Roy, S. P. Bhattacharyya, and A. K. Biswas, *Phytochemistry,* 1978, **17**, 834.
3. (a) T.-S. Wu, S.-C. Huang, P.-L. Wu, and C.-M. Teng, *Phytochemistry,* 1996, **43**, 133; (b) T.-S. Wu,

S.-C. Huang, P.-L. Wu, and C.-S. Kuoh, *Phytochemistry*, 1999, **52**, 523.

4. (a) C. Ito, S. Katsuno, H. Ohta, M. Omura, I. Kajiura, and H. Furukawa, *Chem. Pharm. Bull.*, 1997, **45**, 48; (b) C. Ito, S. Katsuno, M. Itoigawa, N. Ruangrungsi, T. Mukainaka, M. Okuda, Y. Kitagawa, H. Tokuda, H. Nishino, and H. Furukawa, *J. Nat. Prod.*, 2000, **63**, 125.
5. (a) A. Zempoalteca and J. Tamariz, *Heterocycles*, 2002, **57**, 259; (b) H.-J. Knölker and M. Wolpert, *Tetrahedron*, 2003, **59**, 5317; (c) A. Kuwahara, K. Nakano, and K. Nozaki, *J. Org. Chem.*, 2005, **70**, 413; (d) L.-C. Campeau, M. Parisien, A. Jean, and K. Fagnou, *J. Am. Chem. Soc.*, 2006, **128**, 581; (e) Z. Liu and R. C. Larock, *Tetrahedron*, 2007, **63**, 347; (f) B. Liegault, D. Lee, M. P. Huestis, D. R. Stuart, and K. Fagnou, *J. Org. Chem.*, 2008, **73**, 5022.
6. (a) S. Hibino and E. Sugino, In *Advances in Nitrogen Heterocycles*, ed. by C. J. Moody, JAI Press, Greenwich, CT, 1995, Vol. 5, p. 699; (b) T. Kawasaki and M. Sakamoto, *J. Indian Chem. Soc.*, 1994, **71**, 443; (c) T. Choshi, *Yakugaku Zasshi*, 2001, **121**, 487; (d) T. Choshi, T. Kumemura, J. Nobuhiro, and S. Hibino, *Tetrahedron Lett.*, 2008, **49**, 3725 and related references cited therein.
7. (a) T. Choshi, T. Sada, H. Fujimoto, C. Nagayama, E. Sugino, and S. Hibino, *Tetrahedron Lett.*, 1996, **37**, 2593; (b) T. Choshi, H. Fujimoto, E. Sugino, and S. Hibino, *Heterocycles*, 1996, **43**, 1847; (c) T. Choshi, T. Sada, H. Fujimoto, C. Nagayama, E. Sugino, and S. Hibino, *J. Org. Chem.*, 1997, **62**, 2535; (d) H. Hagiwara, T. Choshi, H. Fujimoto, E. Sugino, and S. Hibino, *Chem. Pharm. Bull.*, 1998, **46**, 1948; (e) H. Hagiwara, T. Choshi, H. Fujimoto, E. Sugino, and S. Hibino, *Tetrahedron*, 2000, **56**, 5807; (f) H. Hagiwara, T. Choshi, H. J. Nobuhiro, H. Fujimoto, and S. Hibino, *Chem. Pharm. Bull.*, 2001, **49**, 881; (g) M. Hirayama, T. Choshi, T. Kumemura, S. Tohyama, J. Nobuhiro, and S. Hibino, *Heterocycles*, 2004, **63**, 1765; (h) J. Nobuhiro, M. Hirayama, T. Choshi, K. Kamoshita, S. Maruyama, Y. Sukenaga, T. Ishizu, H. Fujioka, and S. Hibino, *Heterocycles*, 2006, **70**, 491; (i) S. Tohyama, T. Choshi, K. Matsumoto, A. Yamabuki, K. Ikegata, J. Nobuhiro, and S. Hibino, *Tetrahedron Lett.*, 2005, **46**, 5263; (j) A. Yamabuki, H. Fujinawa, T. Choshi, S. Tohyama, K. Matsumoto, K. Ohmura, J. Nobuhiro, and S. Hibino, *Tetrahedron Lett.*, 2006, **47**, 5859.
8. K. Ohmura, T. Choshi, S. Watanabe, Y. Satoh, J. Nobuhiro, and S. Hibino, *Chem. Pharm. Bull.*, 2008, **56**, 237.
9. S. Raucher and B. L. Bray, *J. Org. Chem.*, 1987, **52**, 2332.
10. (a) E. Lee-Ruff and F. J. Ablenas, *Can. J. Chem.*, 1987, **65**, 1663; (b) B.-P. Ying, B. G. Trogden, D. T. Kohlman, S.-X. Liang, and Y.-C. Xu, *Org. Lett.*, 2004, **6**, 1523.
11. J. P. Horwitz, V. K. Iyer, H. B. Vardhan, J. Corombos, and S. C. Brooks, *J. Med. Chem.*, 1986, **29**, 692.
12. (a) D. P. Chakraborty, P. Bhattacharyya, S. Roy, S. P. Bhattacharyya, and A. K. Biswas, *Phytochemistry*, 1978, **17**, 834; (b) G. Bringmann, S. Tasler, H. Endress, and K. Peters, and E.-M. Peters, *Synthesis*, 1998, 1501.