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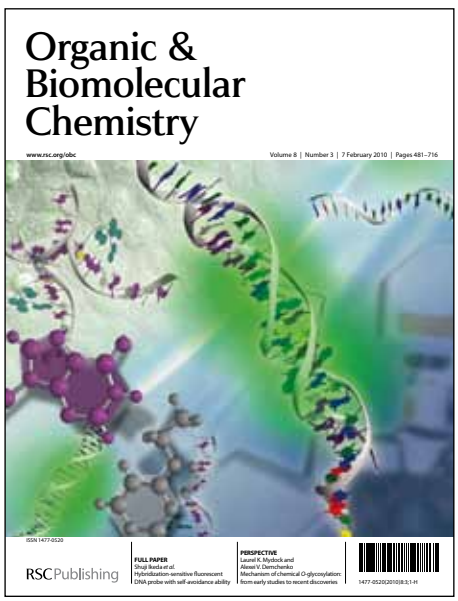

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PAPER

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An Efficient Au-Catalyzed Synthesis of Isomukonidine, Clausine L, Mukonidine, Glycosinine, Mukonal, and Clausine V from Propadienyl Methyl Ether

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Naturally occurring carbazole alkaloids such as isomukonidine, clausine L, mukonidine, glycosinine, mukonal, and clausine V have been synthesized through a gold-catalyzed cyclization reaction of 1-(indol-2-yl)-2-methoxy-2,3-allenols, which are readily available from indolecarbaldehydes and methoxypropadiene. Compared to the reported procedures, our approach is general, atom economic, highly selective, and the starting materials are easily available.

Introduction

Carbazole alkaloids have received considerable interest because of their existence in nature and unnatural compounds with promising biological activities. For example, many 2-oxygenated carbazole alkaloids have been isolated from different parts of *Murraya*, which grows in southern Asia. Some of these compounds (Fig. 1) show useful biological activities:[1] Mukonal was isolated from the stem bark of this plant by Bhattacharyya in 1984;[2] Wu and co-workers described the isolation of mukonidine and its *O*-methyl derivative (clausine L) from Chinese medicinal plant *Clausena excavate* during studies on antiplatelet aggregation activity in 1993.[3] Chakraborty et al. isolated mukonidine from the stem bark of *Murraya koenigii* in 1978,[4] however, the physical and spectroscopic data were not in full agreement with those of Wu's synthesized sample. Finally, the data of Knölker's synthetic mukonidine confirmed that the structure of Wu's mukonidine is correct;[5] Bhattacharyya et al. obtained clausine L from the stem bark of *Murraya koenigii* in 1994;[6] Lange et al. reported the isolation of *O*-methylmukonal from *Murraya siamensis* in 1990.[7a] Two years later, Bhattacharyya and co-workers also obtained *O*-methylmukonal from the root bark of a different natural source, *Glycosmis pentaphylla* collected in Thailand, and named glycosinine.[7b] Glycosinine was also isolated by Kongkathip and co-workers from the rhizomes and roots of *Claysena excavate*, and shows interesting anti-HIV activity;[7c] in 1999, Wu and co-workers reported the isolation of clausine V from the acetone extract of the root bark of *Clausena excavate.*[8]

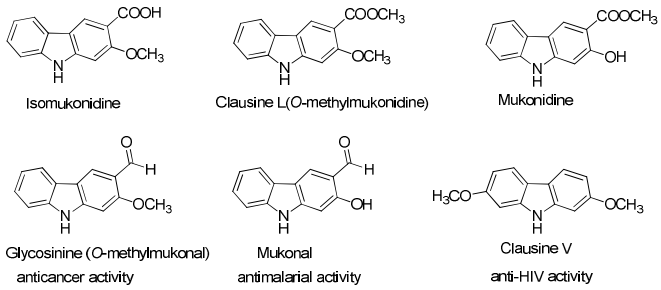

Fig. 1 Naturally occurring 2-oxygenated and 2,7-dioxgenated carbazole alkaloids

Knölker et al. reported the synthesis of mukonidine based on the oxidation of the tricarbonyl [η^4-4a,9a-dihydro-9*H*-carbazole] iron complex with *p*-chloranil (tetrachloro-1,4-benzoquinone) providing the desired product in very low yield (22%) together with the undesired 21% biaryl derivative;[9] the same group subsequently described a remarkable approach for the preparation of clausine L, mukonidine, glycosinine, and clausine V *via* palladium(Ⅱ)-catalyzed oxidative cyclization of *N, N*-diarylamines, which was prepared *via* Buchwald-Hartwig coupling of iodobenzene and 3-methoxy-4-methylaniline.[5a] However, large amounts of oxidants (2.5 equiv of $Cu(OAc)_2$, 2.2 equiv of DDQ, 25 equiv of MnO_2) and highly toxic reagent (5 equiv of KCN) limit large scale synthesis. In the same year, clausine L and mukonidine were synthesized by an improved palladium(Ⅱ)-catalyzed route *via* C-H activation of *N,N*-diarylamines, which was synthesized by palladium(0)-catalyzed Buchwald-Hartwig amination of iodobenzene and methyl 4-amino-2-methoxybenzoate.[5b] Even before the isolation of the naturally occurring clausine V, Hsieh and Litt reported the synthesis of this compound via Cadogan's reductive cyclization of 2-nitrobiphenyl derivative with triethyl phosphite.[10a] In

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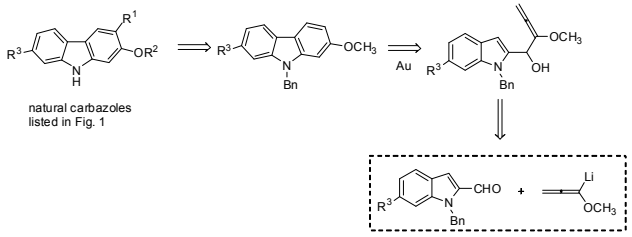
analogy to Heish and Litt's procedure, clausine V was also prepared by Keuethe and Childers. The difference is that the 2-nitrobiphenyl derivative was synthesized by Suzuki-Miyaura cross-coupling of the 4-methoxy-2-nitrobenzenediazonium tetrafluoroborate salt with 4-methoxyphenylboronic acid.[10b] However, this approach was not environmental-friendly due to the employment of large amounts of organophosphorous reagents yielding two equivalents of phosphorous oxide. Thus, a general and efficient route to these compounds is still desirable. In 2009, we have described an approach to the carbazole skeleton through a Pt-catalyzed cyclization of 1-(indol-2-yl)-2,3-allenols.[11] Two years later, we developed an Au-catalyzed route to 2-oxygenated carbazoles, which was applied to the synthesis of naturally occurring carbazole alkaloids such as siamenol, clausine-N, clausine-C, clauszoline-K, and clausine-M.[12] Herein, we wish to report further application of this methodology to the general synthesis of isomukonidine, clausine L, mukonidine, glycosinine, mukonal, and clausine V.

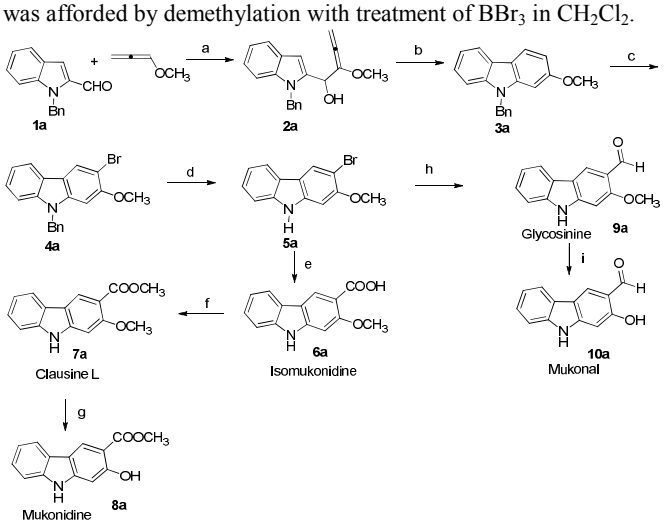
Results and discussion

By retrosynthetic analysis of these carbazoles, the gold-catalyzed cyclization of indoly-2,3-allenols would be the key step for synthesis of these natural carbazoles. Firstly, we considered that using readily available methoxypropadiene[13] and indole-2-carbaldehyde as the starting materials for the synthesis of indoly-2,3-allenols.[12] Then, regioselective bromination at C-3 with *N*-bromosuccinimide, debenzylation, and necessary final transformations would afford these natural carbazoles listed in Fig.1 (Scheme 1).



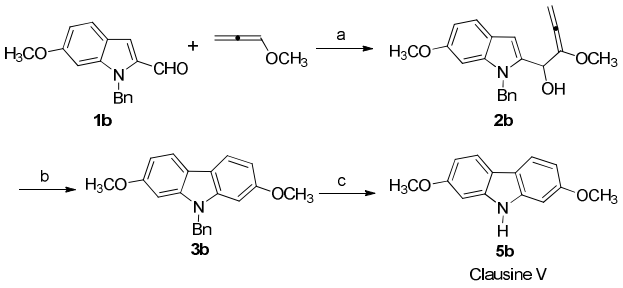
Scheme 1 Retrosynthetic analysis of carbazoles listed in Fig. 1

Addition of 1-methoypropadienyllithium to the 1-benzyl-1*H*-indole-2-carbaldehyde **1a**, afforded the required methoxy-substituted allenol **2a**, which was used without further purification in the next step. Luckily, 9-benzyl-2-methoxy-9*H*-carbazole was formed exclusively in 77% yield from **1a** to **3a** with a catalytic amount of gold (Ⅰ) chloride. Regioselective electrophilic bromination at C-3 with *N*-bromosuccinimide, provided 9-benzyl-3-bromo-2-methoxy-9*H*-carbazole **4a** in 93% yield. Then, debenzylation by treatment with potassium *tert*-butoxide in dimethylsulfoxide under oxygen atmosphere provided the carbazole **5a** in 81% yield.[14] Gladly, isomukonidine was synthesized by deprotonation of **5a** with potassium hydride, Br-Li exchange with *n*-BuLi, and carboxylation with gaseous carbon dioxide in a moderate yield (50%). Clausine L was obtained by methylation of **6a** functionality with MeI in 90% yield with $NaHCO_3$ as base. Then, removal of the methyl group in clausine L by treatment with BBr_3 in CH_2Cl_2 led to mukonidine. For the synthesis of glycosinine, deprotonation of **5a** with potassium hydride, bromide-lithium exchange and addition of dimethylformamide afforded glycosinine in 60% yield. Mukonal was afforded by demethylation with treatment of BBr_3 in CH_2Cl_2.



Scheme 2 AuCl-catalyzed synthesis of Isomukonidine, Clausine L, Mukonidine, Glycosinline, Mukonal: a) *n*-BuLi, -40 °C, THF; b) AuCl, toluene, rt, 77% (fron **1a** to **3a**) ; c) NBS, CCl_4, rt, 30 min, 93%; d) *t*-BuOK,DMSO/THF, O_2 (1 atm), rt, 81%; e) (1) KH, THF, rt, (2) *n*-BuLi, -78 °C, CO_2, 50%; f) MeI, $NaHCO_3$, DMF, 90%; g) BBr_3 (4.0 equiv), CH_2Cl_2, -78 °C~-20 °C, 65%; h) (1) KH, THF, rt, (2) *n*-BuLi, -30 °C, DMF, 60%; i) BBr_3 (4.0equiv), CH_2Cl_2, -78 °C~-20 °C, 86%.

A similar approach may also be used for the synthesis of allenol **2b**, which undergoes a smoothly AuCl-catalyzed cyclization under the standard reaction conditions to afford exclusively carbazole **3b** in 74% yield from **1b** to **3b**. Then, clausine V was obtained by deprotection of the *N*-benzyl group with potassium *tert*-butoxide in dimethylsulfoxide under oxygen atmosphere (Scheme 3).



Scheme 3 AuCl-catalyzed synthesis of Clausine V: a) *n*-BuLi, -40 °C, THF; b) AuCl, toluene, rt, 74% (from **1b** to **3b**); c) *t*-BuOK,DMSO/THF, O_2 (1 atm), rt, 83%;

Total yields of naturally occurring carbazole alkaloids from the readily available methoxypropadiene are: isomukonidine (5 steps with 29% overall yield), clausine L (6 steps with 26% overall yield), mukonidine (7 steps with 17% overall yield), glycosinine (5 steps with 34% overall yield), mukonal (6 steps with 30% overall yield), clausine V (3 steps with 61% overall yield). The spectroscopic data of our synthetic compounds are in full agreement with those reported for the corresponding natural products.

Conclusions

In conclusion, we have realized the highly efficient synthesis of isomukonidine, clausine L, mukonidine, glycosinine, mukonal, and clausine V via AuCl-catalyzed cyclization of indoly-2,3-

allenols **2a** and **2b** from the easily available indolecarbaldehydes and methoxypropadiene with an excellent regioselectivity. Due to the easy availability of the starting materials, excellent selectivity, smooth reaction conditions, these routes will have a wide range of application in organic synthesis and industrial production. Further studies including biological activity studies of the derivatives are being carried out in our laboratory.

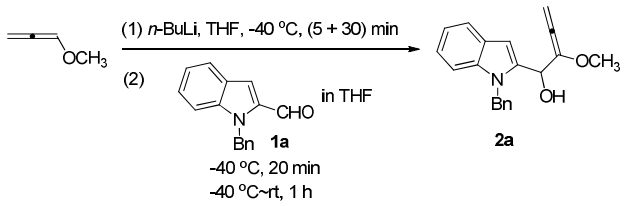
Acknowledgements

Financial support from the National Basic Research Program of China (2009CB825300) and the National Natural Science Foundation for China (21232006) is greatly appreciated. S. Ma. is a Qiu shi Ajunct professor at Zhejiang University. We thank Ms. Nan Wang in our group for reproducing the results of **9a** (glycosinine) and **10a** (mukonal) in Scheme 2.

Experimental Section

General information：^{1}H and ^{13}C NMR spectra were recorded with a Bruker AM 300 MHz spectrometer. IR spectra were recorded with a Perkin–Elmer 983G instrument. Elemental analyses were measured with a Carlo-Erba EA1110 elementary analysis instrument. Mass spectrometry was performed with a HP 5989A system. High-resolution mass spectrometry was determined with a Finnigan MAT 8430 or Bruker APEXIII instrument. Toluene, THF, Et_2O, and CH_2Cl_2 were distilled from Na/benzophenone before use. KH and dimethylformamide were purchased from Acros, BBr_3 (1.0 M in CH_2Cl_2) was purchased from TCI. Unless otherwise indicated, chemicals and solvents were purchased from commercial suppliers.

1. Synthesis of 1-(1-benzyl-1*H*-indol-2-yl)-2-methoxybuta-2,3-dien-1-ol (2a)

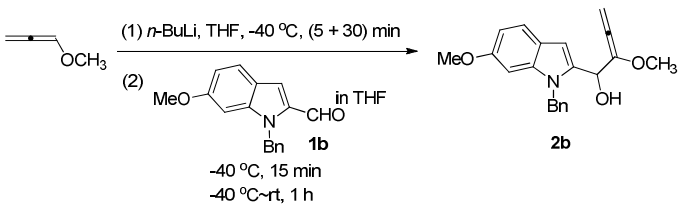


Typical procedure Ⅰ: To a solution of 1-methoxypropa-1,2-diene (180.1 mg, 2.57 mmol) in THF (13 mL) was added dropwise *n*-BuLi (1.0 mL, 2.5 M in hexane, 2.5 mmol) at -40 ˚C with stirring under a nitrogen atmosphere within 5 min. After being stirred for 30 min at -40 ˚C, a solution of 1-benzyl-1*H*-indole-2-carbaldehyde (470.1 mg, 2.0 mmol) in THF (3 mL) was added dropwise at this temperature within 20 min. Then the mixture was allowed to warm up to room temperature, after 1 h, the reaction was complete as monitored by TLC. The mixture was quenched with a saturated aqueous solution of NH_4Cl (10 mL), and extracted with diethyl ether (20 mL×3). The combined organic layer was washed with water and dried over anhydrous K_2CO_3. After filtration and evaporation, the crude product **2a** was then submitted to the next step without further purification.

2. Synthesis of 9-benzyl-2-methoxy-9*H*-carbazole (3a)

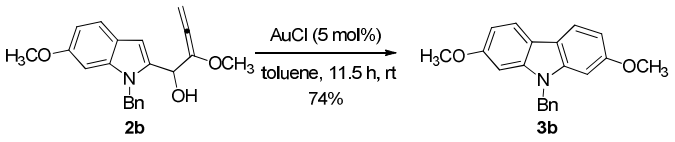
Typical procedure Ⅱ: To a dry Schlenk tube were added sequentially AuCl (23.0 mg, 0.1 mmol), **2a** (prepared in the previous step) and toluene (20 mL) under nitrogen atmosphere. After stirring for 12 h at rt, the reaction was complete as monitored by TLC. Filtration, evaporation and column chromatography on silica gel (petroleum ether/ethyl acetate = 40/1) afforded **3a** (443.2 mg, 77%, from **1a** to **3a**): solid; m.p. 143-144 °C (*n*-hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06-7.88 (m, 2H, ArH), 7.38-7.04 (m, 8H, ArH), 6.90-6.72 (m, 2H, ArH), 5.38 (s, 2H, CH_2), 3.81 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 142.0, 140.7, 137.0, 128.7, 127.4, 126.4, 124.5, 123.2, 121.1, 119.5, 119.3, 116.9, 108.6, 107.5, 93.4, 55.6, 46.5; IR (KBr) ν (cm^{-1}) 3086, 3060, 3031, 3009, 2962, 2936, 2833, 1625, 1603, 1575, 1496, 1464, 1451, 1358, 1334, 1248, 1200, 1173, 1119, 1055, 1033; MS (70 ev, EI) *m/z* (%) 288 (M^++1, 21.55), 287 (M^+, 100); Elemental analysis calcd for $C_{20}H_{17}NO$: C, 83.59; H, 5.96; N, 4.87; Found: C, 83.50, H, 5.92; N, 4.92.

3. Synthesis of 1-(1-benzyl-6-methoxy-1*H*-indol-2-yl)-2-methoxybuta-2,3-dien-1-ol (2b)



Following typical procedure Ⅰ: The reaction of 1-methoxypropa-1,2-diene (382.0 mg, 5.46 mmol)/THF (20 mL), *n*-BuLi (2.0 mL, 2.5 M in hexane, 5 mmol), and 1-benzyl-6-methoxy-1*H*-indole-2-carbaldehyde (1069.0 mg, 4 mmol)/THF (5 mL) afforded **2b**, the crude product **2b** was then submitted to the next step without further purification.

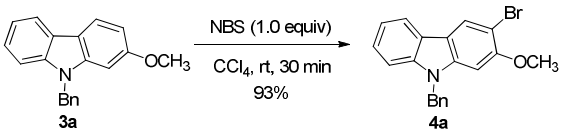
4. Synthesis of 9-benzyl-2,7-dimethoxy-9*H*-carbazole (3b)



Following typical procedure Ⅱ. The reaction of AuCl (53.5 mg, 0.23 mmol) and **2b** (prepared in the previous step) in toluene (20 mL) at rt for 11.5 h afforded **3b** (943.7 mg, 74%) (petroleum ether/ethyl acetate = 30/1~20/1): solid; m.p. 146-147 °C (*n*-hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 8.4 Hz, 2H, ArH), 7.31-7.20 (m, 3H, ArH), 7.18-7.08 (m, 2H, ArH), 6.88-6.74 (m, 4H, ArH), 5.37 (s, 2H, CH_2), 3.84 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 142.1, 136.9, 128.8, 127.4, 126.4, 120.1, 117.1, 107.1, 93.6, 55.6, 46.5; IR (KBr) ν

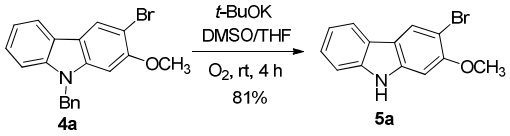
(cm^{-1}) 3087, 3063, 3027, 2999, 2953, 2937, 2833, 1601, 1575, 1484, 1470, 1453, 1358, 1332, 1257, 1241, 1195, 1167, 1120, 1051, 1026; MS (70 ev, EI) *m/z* (%) 318 (M^++1, 24.01), 317 (M^+, 100); Elemental analysis calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41; Found: C, 79.54, H, 6.09; N, 4.53.

5. Synthesis of 9-benzyl-3-bromo-2-methoxy-9*H*-carbazole (4a)



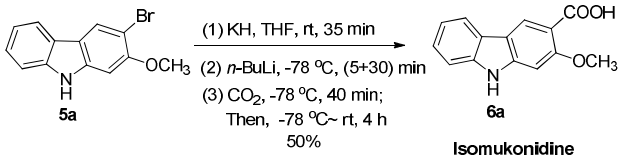
A suspension of **3a** (715.1 mg, 2.49 mmol) and NBS (447.6 mg, 2.51 mmol) in CCl_4 (25 mL) was stirred at rt for 30 min. The reaction was complete as monitored by TLC. Evaporation and column chromatography on silica gel (petroleum ether/ethyl acetate = 40/l) afforded **4a** (848.5 mg, 93%): solid; m.p. 140-141 °C (*n*-hexane/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H, ArH), 7.93 (d, *J* = 7.2 Hz, 1H, ArH), 7.37-7.00 (m, 8H, ArH), 6.70 (s, 1H, ArH), 5.32 (s, 2H, CH_2), 3.82 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 140.7, 140.6, 136.5, 128.8, 127.5, 126.2, 125.0, 124.5, 122.1, 119.7, 119.6, 117.5, 108.8, 103.2, 92.5, 56.3, 46.5; IR (KBr) ν (cm^{-1}) 3061, 3028, 3004, 2929, 1630, 1601, 1494, 1463, 1454, 1421, 1353, 1314, 1256, 1194, 1174, 1123, 1043, 1028; MS (70 ev, EI) *m/z* (%) 367 (M^+(^{81}Br), 69.63), 365 (M^+(^{79}Br), 70.80), 91 (100); Elemental analysis calcd for $C_{20}H_{16}BrNO$: C, 65.59; H, 4.40; N, 3.82; Found: C, 65.54; H, 4.36; N, 3.84.

6. Synthesis of 3-bromo-2-methoxy-9*H*-carbazole (5a)



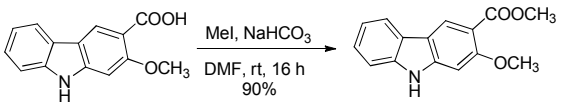
A solution of **4a** (909.4 mg, 2.48 mmol) and *t*-BuOK (2780.4 mg, 24.8 mmol) in THF (15 mL) and DMSO (15 mL) with a O_2 balloon was stirred at rt. After 4 h, the reaction was complete as monitored by TLC. The resulting mixture was diluted with 20 mL of ethyl acetate, and quenched with water (10 mL). The aqueous layer was extracted with ethyl acetate (20 mL×3), the combined organic layer was washed with water (10 mL×2) and dried over anhydrous Na_2SO_4. After filtration and evaporation, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/l~5/1~2/1) afforded **5a** (556.0 mg, 81%), solid; m.p. 190-191 °C (*n*-hexane/ethyl acetate); ^{1}H NMR (300 MHz, acetone-d_6) δ 10.39 (bs, 1H, NH), 8.32 (s, 1H, ArH), 8.09 (d, *J* = 7.8 Hz, 1H, ArH), 7.51 (d, *J* = 7.8 Hz, 1H, ArH), 7.37 (t, *J* = 7.7 Hz, 1H, ArH), 7.29-7.10 (m, 2H, ArH), 3.99 (s, 3H, CH_3); ^{13}C NMR (75 MHz, acetone-d_6) δ 156.1, 142.1, 141.9, 126.5, 125.8, 124.0, 121.1, 120.9, 119.4, 112.4, 104.2, 96.2, 57.4; IR (KBr) ν (cm^{-1}) 3412, 3017, 2981, 2943, 1607, 1573, 1481, 1461, 1444, 1369, 1310, 1252, 1230, 1195, 1165, 1037, 1025; MS (70 ev, EI) *m/z* (%) 277 (M^+(^{81}Br), 96.66), 275 (M^+(^{79}Br), 100); Elemental analysis calcd for $C_{13}H_{10}BrNO$: C, 56.55; H, 3.65; N, 5.07; Found: C, 56.71; H, 3.68; N, 5.05.

7. Synthesis of 2-methoxy-9*H*-carbazole-3-carboxylic acid (Isomukonidine)



To a suspension of freshly washed and dried potassium hydride (321.0 mg, 25%, 2.0 mmol) in THF (25 mL) was added **5a** (275.6 mg, 1.0 mmol). After being stirred for 35 min at rt, the resulting mixture was cooled to -78 °C, *n*-BuLi (0.44 mL, 2.5 M in hexane, 1.1 mmol) was added within 5 min. After being stirred at -78 °C for additional 30 min, CO_2 (dried by passing through concentrated H_2SO_4) was bubbled through the mixture for 40 min. The resulting mixture was then allowed warm up to room temperature. After 4 h, the reaction was complete as monitored by TLC. The mixture was diluted with 30 mL of ethyl acetate, acidified with dilute hydrochloric acid (aq. 10%) to PH < 4, extracted with ethyl acetate (20 mL×3), washed with water (10 mL), and dried over anhydrous Na_2SO_4. After filtration and evaporation, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1/1~1/2 for the first round, dichloromethane/ethyl acetate = 3/1 for the second round (impure part)) to give isomukonidine **6a** (combined weight: 121.3 mg, 50%): solid; m.p. 224-226 °C (*n*-hexane/ethyl acetate) (lit.[5a]: 226 °C (decomp.)); ^{1}H NMR (300 MHz, acetone-d_6) δ 10.88 (bs, 1H, COOH), 10.65 (bs, 1H, NH), 8.81 (s, 1H, ArH), 8.20 (d, *J* = 8.1 Hz, 1H, ArH), 7.56 (d, *J* = 8.1 Hz, 1H, ArH), 7.43 (t, *J* = 7.5 Hz, 1H, ArH), 7.33-7.24 (m, 2H, ArH), 4.17 (s, 3H, CH_3); ^{13}C NMR (75 MHz, acetone-d_6) δ 167.4, 159.7, 145.9, 142.4, 127.2, 127.0, 124.8, 121.7, 121.5, 119.0, 112.7, 112.6, 95.5, 58.0; IR (KBr) ν (cm^{-1}) 3240, 1706, 1626, 1609, 1577, 1495, 1460, 1439, 1402, 1343, 1327, 1224, 1163, 1028; MS (70 ev, EI) *m/z* (%) 242 (M^++ 1, 15.98), 241 (M^+, 100).

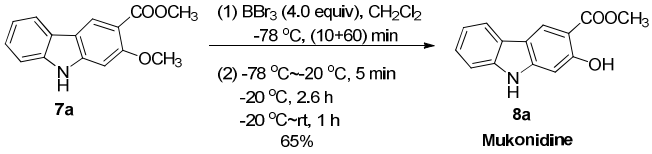
8. Synthesis of methyl 2-methoxy-9*H*-carbazole-3-carboxylate (Clausine L)



To a Schlenk tube was added **6a** (159.8 mg, 0.66 mmol), $NaHCO_3$ (201.9 mg, 2.4 mmol), DMF (12 mL), and MeI (0.17 mL, d=2.28 g/mL, 2.7 mmol) sequentially. After being stirred for 16 h, the reaction was complete as monitored by TLC. The resulting mixture was quenched with water (20 mL). The aqueous layer was extracted with ethyl acetate (20 mL×3), the combined organic layer was washed with water (5 mL×2) and dried over anhydrous Na_2SO_4. After filtration and evaporation, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1/1) to give Clausine L **7a** (151.7 mg, 90%): solid; m.p. 174-175 °C (*n*-hexane/ethyl acetate) (lit.[5a]: 172-173

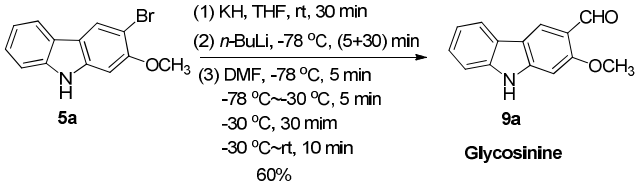
°C); δ 10.52 (bs, 1H, NH), 8.61 (s, 1H, ArH), 8.13 (d, *J* = 7.8 Hz, 1H, ArH), 7.53 (d, *J* = 8.1 Hz, 1H, ArH), 7.40 (t, *J* = 7.4 Hz, 1H, ArH), 7.24 (t, *J* = 7.2 Hz, 1H, ArH), 7.18 (s, 1H, ArH), 3.94 (s, 3H, CH_3), 3.90 (s, 3H, CH_3); ^{13}C NMR (75 MHz, acetone-d_6) δ 168.2, 160.5, 145.4, 142.2, 126.7, 125.7, 124.9, 121.4, 121.2, 117.7, 114.4, 112.5, 95.5, 57.1, 52.5; IR (KBr) ν (cm^{-1}) 3271, 3005, 2980, 2954, 1704, 1634, 1609, 1580, 1463, 1428, 1393, 1349, 1314, 1279, 1247, 1203, 1165, 1086, 1036; MS (70 ev, EI) *m/z* (%) 256 (M^+ + 1, 17.35), 255 (M^+, 98.43), 224 (100);

9. Synthesis of methyl 2-hydroxy-9*H*-carbazole-3-carboxylate (Mukonidine)



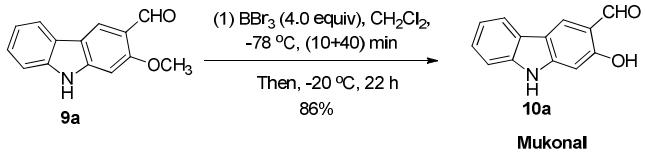
To a solution of **7a** (144.1 mg, 0.57 mmol) in CH_2Cl_2 (10 mL) was added a solution of BBr_3 (2.2 mL, 1.0 M in CH_2Cl_2, 2.2 mmol) at -78 °C within 10 min under N_2. The mixture was stirred at -78 °C (1 h), -20 °C (2.6 h), and room temperature (1 h), the reaction was complete as monitored by TLC. The mixture then was quenched with 15 mL of a saturated aqueous solution of $NaHCO_3$ at 0 °C, the aqueous layer was extracted with ethyl acetate (20 mL×3). The organic layer was washed with water and dried over anhydrous Na_2SO_4. After filtration and evaporation, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3/1) to give Mukonidine **8a** (88.9 mg, 65%): solid; m.p. 192-193 °C (*n*-hexane/ethyl acetate) (lit.[5a]: 189 °C); ^{1}H NMR (300 MHz, acetone-d_6) δ 11.13 (s, 1H, OH), 10.54 (bs, 1H, NH), 8.64 (s, 1H, ArH), 8.11 (d, *J* = 7.8 Hz, 1H, ArH), 7.50 (d, *J* = 8.1 Hz, 1H, ArH), 7.40 (t, *J* = 7.5 Hz, 1H, ArH), 7.24 (t, *J* = 7.2 Hz, 1H, ArH), 6.97 (s, 1H, ArH), 4.03 (s, 3H, CH_3) ; ^{13}C NMR (75 MHz, acetone-d_6) δ 172.9, 162.3, 147.3, 142.6, 127.2, 125.0, 124.1, 121.6, 121.3, 118.5, 112.5, 106.6, 98.4, 53.3; IR (KBr) ν (cm^{-1}) 3355, 2951, 1647, 1631, 1466, 1434, 1374, 1330, 1261, 1239, 1167, 1095; MS (70 ev, EI) *m/z* (%) 242 (M^+ + 1, 8.02), 241 (M^+, 52.69), 209 (100);

10. Synthesis of 2-methoxy-9*H*-carbazole-3-carbaldehyde (Glycosinine)



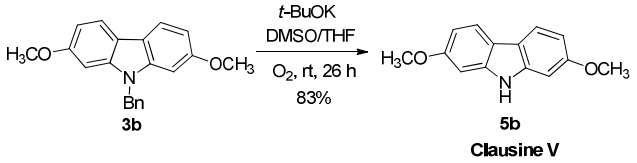
To a suspension of freshly washed and dried potassium hydride (321.6 mg, 25%, 2.0 mmol) in THF (25 mL) was added **5a** (275.5 mg, 1.0 mmol). After being stirred for additional 30 min at rt, the mixture was cooled to -78 °C, *n*-BuLi (0.44 mL, 2.5 M in hexane, 1.1 mmol) was added to the mixture within 5 min. After being stirred at -78 °C for 30 min, a mixture of anhydrous DMF (0.39 mL, d = 0.9445 g/mL, 5.0 mmol)/THF (2 mL) was added dropwise for 5 min. The mixture was stirred at -30 °C (0.5 h), and room temperature (10 min). The resulting mixture was quenched with water (10 mL) at 0 °C and extracted with ethyl acetate (20 mL×3). The organic layer was washed with dilute hydrochloric acid (5%), and dried over anhydrous Na_2SO_4. After filtration and evaporation, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1~3/1 for the first round, petroleum ether/ethyl acetate = 5/1~3/1 for the second round (impure part)) to give Glycosinine **9a** (combined weight: 133.8 mg, 60%): solid; m.p. 192-194 °C (*n*-hexane/ethyl acetate), (lit.[5a] 196-198 °C); ^{1}H NMR (300 MHz, acetone-d_6) δ 10.64 (bs, 1H, NH), 10.47 (s, 1H, CHO), 8.52 (s, 1H, ArH), 8.14 (d, *J* = 7.8 Hz, 1H, ArH), 7.51 (d, *J* = 8.1 Hz, 1H, ArH), 7.38 (t, *J* = 7.8 Hz, 1H, ArH), 7.23 (t, *J* = 7.5 Hz, 1H, ArH), 7.16 (s, 1H, ArH), 4.02 (s, 3H, CH_3); ^{13}C NMR (75 MHz, acetone-d_6) δ 189.4, 163.2, 147.2, 142.4, 127.2, 125.2, 122.2, 121.8, 121.5, 120.4, 118.8, 112.7, 94.6, 57.1; IR (KBr) ν (cm^{-1}) 3408, 3310, 2865, 1666, 1601, 1579, 1463, 1435, 1328, 1259, 1243, 1201, 1157, 1034; MS (70 ev, EI) *m/z* (%) 226 (M^+ + 1, 15.14), 225 (M^+, 100).

11. Synthesis of 2-hydroxy-9*H*-carbazole-3-carbaldehyde (Mukonal)



To a solution of **9a** (113.1 mg, 0.5 mmol) in CH_2Cl_2 (10 mL) was added a solution of BBr_3 (2.0 mL, 1.0 M in CH_2Cl_2, 2.0 mmol) at -78 °C within 10 min under N_2. The mixture was stirred at -78 °C (40 min) and -20 °C (22 h). The reaction was complete as monitored by TLC. The resulting mixture was quenched with 20 mL of a saturated aqueous solution of $NaHCO_3$ at -20 °C, then diluted with 30 mL of ethyl acetate. The aqueous layer was extracted with ethyl acetate (20 mL×3). The organic layer was washed with water and dried over anhydrous Na_2SO_4. After filtration and evaporation, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to give Mukonal **10a** (90.7 mg, 86%): solid; m.p. 239-240 °C (*n*-hexane/ethyl acetate) (lit.[2] 238 °C); ^{1}H NMR (300 MHz, acetone-d_6) δ 11.52 (s, 1H, OH), 10.75 (bs, 1H, NH), 10.03 (s, 1H, CHO), 8.48 (s, 1H, ArH), 8.12 (d, *J* = 7.5 Hz, 1H, ArH), 7.54 (d, *J* = 8.4 Hz, 1H, ArH), 7.43 (t, *J* = 7.5 Hz, 1H, ArH), 7.27 (t, *J* = 7.5 Hz, 1H, ArH), 6.94 (s, 1H, ArH); ^{13}C NMR (75 MHz, acetone-d_6) δ 197.4, 162.7, 147.8, 142.7, 129.3, 127.5, 125.0, 122.0, 121.4, 119.3, 117.0, 112.8, 98.1; IR (KBr) ν (cm^{-1}) 3375, 2961, 2941, 2855, 1640, 1610, 1477, 1455, 1363, 1326, 1249, 1205, 1167; MS (70 ev, EI) *m/z* (%) 212 (M^+ + 1, 14.33), 211 (M^+, 100).

12. Synthesis of 2,7-dimethoxy-9*H*-carbazole (5b) (Clausine V)



A solution of **3b** (325.5 mg, 1.03 mmol) and *t*-BuOK (1124.6 mg, 10 mmol) in THF (12.5 mL) and DMSO (12.5 mL) with a O_2 balloon was stirred at rt for 26 h, the reaction was complete as monitored by TLC. The mixture was diluted with 20 mL of ethyl acetate, the reaction was quenched with water(10 mL). The aqueous layer was extracted with ethyl acetate (20 mL×3), the combined organic layer was washed with water (20 mL×2) and dried over anhydrous Na_2SO_4. After filtration and evaporation, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 2/1~1/1, it shoud be noted that the column packed with silica gel was eluted with a mixture of petroleum ether and triethylamine (100:1) before loading the sample) afforded clausine V **5b** (193.6 mg, 83%), solid; m.p. 279-280 °C (*n*-hexane/ethyl acetate) (lit.[10a] 272-274 °C); ^{1}H NMR (300 MHz, acetone-d_6) δ 10.11 (bs, 1H, NH), 7.89 (d, J = 8.4 Hz, 2H, ArH), 7.02 (d, J = 2.2 Hz, 2H, ArH), 6.80 (dd, J_1 = 8.6 Hz, J_2 = 2.2 Hz, 2H, ArH), 3.88 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, acetone-d_6) δ 159.9, 143.1, 121.4, 118.8, 109.2, 96.4, 56.5; IR (KBr) ν (cm^{-1}) 3383, 2836, 1609, 1573, 1504, 1456, 1323, 1265, 1233, 1198, 1160, 1120, 1027; MS (70 ev, EI) *m/z* (%) 228 (M^++ 1, 15.75), 227 (M^+, 100).

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