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Biomimetic Collective Total Synthesis of Bioactive Carbazole Alkaloids Indizoline, Mafaicheenamine A, Claulamine A, Claulansine A, and the Proposed Claulamine E

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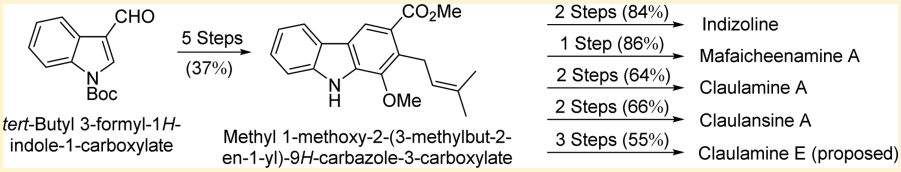
Supporting Information



ABSTRACT: The common precursor 1-methoxy-2-prenyl-3-carbomethoxycarbazole was synthesized from dimethyl indolylmethylenesuccinate in four steps. Well-planned reductive and/or oxidative transformations and intramolecular cyclizations were performed on a pivotal common precursor to accomplish collective first total synthesis of titled natural products and proposed claulamine E. Burgess reagent induced formation of kinetically controlled product claulamine A, and intramolecular cyclizations to form bicyclic claulansine A were the key reactions. An alternatively attempted synthesis failed to provide the structural isomer of proposed claulamine E.

Carbazoles are an important class of alkaloids, and a large number of them have been isolated from plant, animal, microbial, and marine origin.[1−3] Carbazoles display a wide range of biological activities and also find applications in electroluminescent materials owing to their electrical and thermal properties.[1−6] Indizoline, mafaicheenamine A, claulamine A, claulansine A, and claulamine E have been recently isolated from *Clausena lansium*, and they exhibit potent anti-inflammatory, neuroprotective, and antitumor activities against human cancer cell lines (Figure 1).[7−11] In the synthesis of carbazoles, regioselective installation of appropriate substituents on the eight different available sites in the aromatic ring systems is a challenging task.[1−3,12] Total synthesis of bioactive natural products has very successfully completed ample significant achievements. A collective total synthesis of bioactive natural products is of contemporary interest from the point of view of strategic flexibility and dedicated SAR studies.[13−20] The synthesis of structurally interesting and biologically important selected target compounds, however, merits further investigation. On the basis of retrosynthetic analysis, we reasoned that the combination of readily available *N*-boc-protected-3-formylindole, dimethyl maleate, and prenyl bromide would constitute diversity-oriented convergent access to these important carbazole-based natural products. In the continuation of our studies on cyclic anhydrides and their conversion to bioactive natural products,[16,21−25] we herein report the collective total synthesis of target compounds (Schemes 1−3).

The Wittig adduct dimethyl (*E*)-2-((1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)methylene)succinate (**1**)[16] upon treatment with NaHMDS/prenyl bromide delivered expected monoprenylated product **2** in 71% yield. Diester **2** on selective base-induced hydrolysis of the more reactive saturated ester moiety exclusively provided desired carboxylic acid **3** in 89% yield (Scheme 1). Both the *N*-boc-deprotection and regioselective ester hydrolysis took place in one pot. The witnessed in situ *N*-boc-deprotection under basic conditions was plausibly due to the conjugation of the nitrogen lone pair with the $\alpha,\beta,\gamma,\delta$-unsaturated ester moiety. Acid **3** on triphosgene induced intramolecular acylation followed by *O*-methylation of the formed phenol **4**, resulting in the suitably trisubstituted requisite carbazole **5** in 58% yield over two steps. An appropriately designed 20-carbon-bearing versatile single precursor **5** can then be neatly tailored to each of the five target compounds via various reductive and/or oxidative regio- and stereoselective intramolecular cyclization pathways.

The potential precursor carbazole **5** on DIBAL-H reduction of carbomethoxy unit provided alcohol **6** in 88% yield, which upon PCC oxidation furnished the first natural product indizoline (**7**) in 95% yield (Scheme 2). The two-step transformation of natural sample of indizoline (**7**) to yet another natural product, claulansine G (**8**), is known but in very low overall yield,[9] plausibly due to the poor stability and inherent polymerization issues. The prenyl group bearing carbazole **6** upon treatment with *m*-CPBA at −10 °C resulted in the expected epoxide **9** in 72% yield in 15 min. Epoxide **9** was highly prone to further intramolecular ring closure, and hence, it was characterized without purification. Isolated epoxide **9**, upon simple stirring in acetone at room temperature, underwent regioselective intramolecular cyclization with a cleavage of the oxirane moiety to provide desired product **10**

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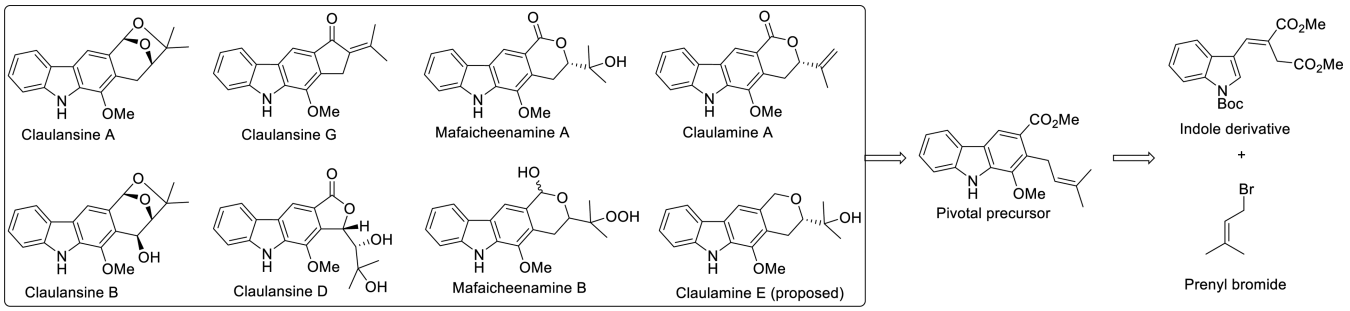
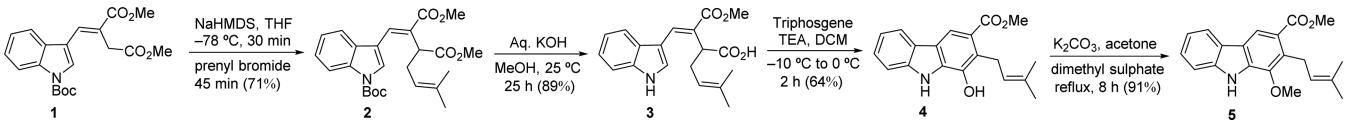
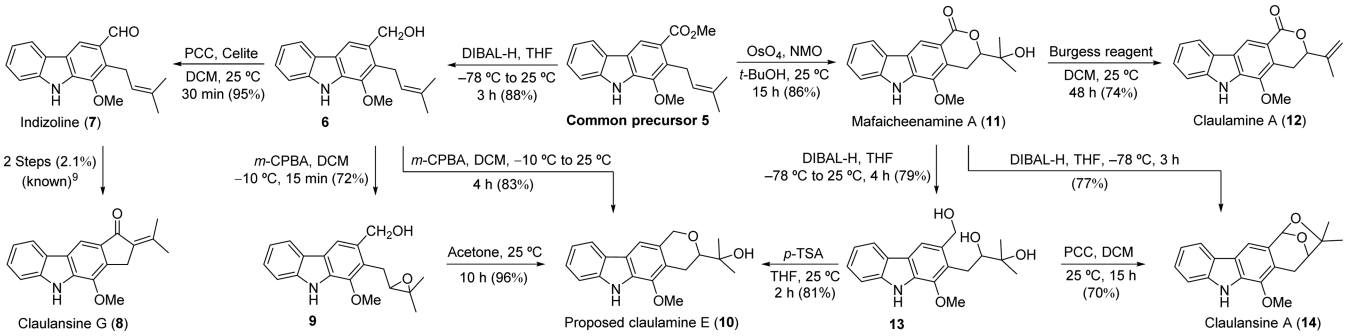


Figure 1. Representative bioactive carbazole alkaloids and their concise retrosynthetic analysis.

Scheme 1. Facile Synthesis of Common Precursor 1-Methoxy-2-prenyl-3-carbomethoxycarbazole



Scheme 2. Concise and Efficient Collective Total Synthesis of Bioactive Carbazole Alkaloids



in 96% yield. The above-mentioned *m*-CPBA epoxidation of carbazole **6** at room temperature directly furnished planned product **10** in 83% yield. Unfortunately, the obtained analytical and spectral data for compound **10** was not in agreement with reported data for the natural product claulamine E (Table 1). Finally, the structural assignment of synthetic product **10** was unequivocally confirmed by X-ray crystallography. Hence, what we have accomplished is the total synthesis of the structure initially proposed as claulamine E (**10**), and an appropriate revision in structural assignment for the natural product is therefore recommended. In principle, several regioisomeric unknown structures are possible, and the X-ray crystallographic analysis of the natural product would be most appropriate for the proper structural assignment.

Common precursor carbazole **5** upon osmium tetraoxide-induced *cis*-dihydroxylation directly delivered natural product mafaicheenamine A (**11**) in 86% yield via an anticipated in situ regioselective lactonization (Scheme 2). The reactions of mafaicheenamine A (**11**) with $SOCl_2/P_2O_5/POCl_3$ were not selective and resulted in a mixture of products. However, the reaction of mafaicheenamine A (**11**) with the Burgess reagent[26] was completely selective and provided the kinetically controlled desired natural product claulamine A (**12**) in 74% yield. We propose that both the steric bulk and higher reactivity of Burgess reagent are responsible for the exclusive formation of kinetically controlled product **12**. Mafaicheenamine A (**11**) upon DIBAL-H reduction at −78 to 25 °C formed corresponding triol **13** in 79% yield in 4 h. In a cascade reaction, triol **13** upon treatment with PCC directly yielded yet another natural product, claulansine A (**14**), in 70% yield. Mechanistically, the stepwise selective oxidation of the primary alcohol to the corresponding aldehyde, an in situ cyclic *trans*-hemiacetal formation with the secondary alcohol and an

Table 1. NMR Data of Natural and Proposed Claulamine E in Acetone-d_6

natural[11]		proposed **10**	
^{1}H (400 MHz)	^{13}C (100 MHz)	^{1}H (500 MHz)	^{13}C (125 MHz)
1.32 (s, 3H)	19.7	1.28 (s, 3H)	24.2
1.36 (s, 3H)	27.6	1.29 (s, 3H)	25.7
3.29 (dd, 1H)	31.3	2.80–2.90 (m, 1H)	26.4
3.39 (dd, 1H)	61.4	3.10 (dd, 1H)	60.4
	66.5	3.44 (br s, 1H)	70.0
3.55 (dd, 1H)	75.7	3.49 (dd, 1H)	72.0
3.92 (s, 3H)	79.6	3.96 (s, 3H)	82.7
4.60 (d, 1H)	111.9	4.92 (d, 1H)	111.7
4.84 (d, 1H)	115.7	5.05 (d, 1H)	112.0
7.15 (dd, 1H)	119.7	7.14 (t, 1H)	119.7
7.35 (dd, 1H)	120.7	7.36 (t, 1H)	120.9
7.51 (d, 1H)	123.4	7.50 (d, 1H)	124.35
7.66 (s, 1H)	124.4	7.55 (s, 1H)	124.43
8.03 (d, 1H)	126.1	8.02 (d, 1H)	124.7
10.39 (br s, 1H)	128.1	10.31 (br s, 1H)	126.5
	133.6		127.8
	134.6		132.8
	141.1		141.5
	144.4		143.9

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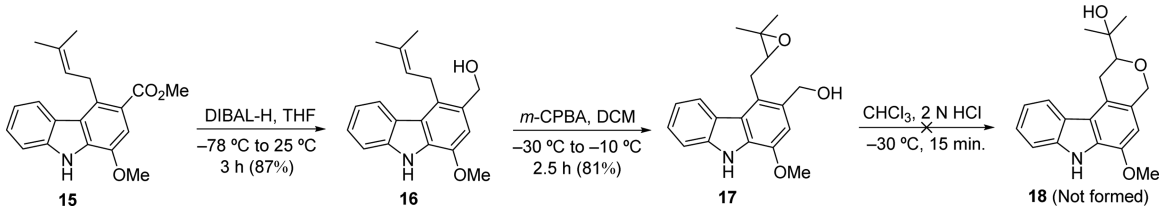
Scheme 3. Synthesis of Regioisomer of the Proposed Claulamine E



associated instantaneous diastereoselective intramolecular dehydrative ring closure utilizing the tertiary alcohol, took place to form desired product **14** in one pot. Similarly, an osmium tetraoxide induced *cis*-dihydroxylation of indizoline (**7**) at room temperature also directly furnished claulansine A (**14**) in good yield. The temperature-controlled DIBAL-H reduction of mafaicheenamine A (**11**) at −78 °C also directly delivered claulansine A (**14**) in 77% yield in 3 h. During the DIBAL-H reductions, the intermediate lactol was fairly stable at −78 °C and further underwent a concomitant diastereoselectve intramolecular dehydrative cyclization to provide claulansine A (**14**). Either the DIBAL-H reduction of **11** directly forms the *trans*-hemiacetal intermediate or the formed *cis*-hemiacetal could be rearranged to the *trans*-hemiacetal via ring−chain tautomerism, making the formation of corresponding desired acetal **14** feasible. Triol **13** upon treatment with *p*-TSA again provided proposed claulamine E (**10**) in 81% yield via protonation of benzylic alcohol followed by regioselective intramolecular dehydrative cyclization. The obtained analytical and spectral data for all target compounds except for claulamine E were in complete agreement with reported data.[7−11,27]

To address the inconsistencies between the structure of proposed claulamine E and compound **10**, we propose a revised structure for claulamine E. On the basis of structural features of all the carbazoles depicted in Figure 1, we presumed that the assigned positions of the -OMe group and the cyclic benzyl ether unit in the proposed claulamine E are accurate. Therefore, alternatively, the prenyl moiety could be at the para position of the methoxy group. Accordingly, we planned the synthesis of corresponding isomeric compound **18** as a potential revised structure of claulamine E (Scheme 3). Thus, desired precursor **15** was synthesized using known literature procedures.[28] Compound **15** upon DIBAL-H reduction resulted in benzylic alcohol **16** in 87% yield, which upon treatment with *m*-CPBA delivered compound **17** in 81% yield. Epoxide **17** remained unreacted in refluxing acetone, whereas it decomposed in the presence of 2 N HCl in chloroform at −30 °C. Unfortunately, epoxide **17** failed to undergo intramolecular cyclization to provide desired regioisomeric product **18**.

In summary, we have demonstrated concise and efficient access to accomplish a biogenetic collective total synthesis of carbazole alkaloids from readily available simple starting materials. The involved different types of intramolecular cyclizations with the generation of new carbon−oxygen bonds selectively leading to those natural products are noteworthy from the point of view of both basic chemistry and applications. More specifically, a remarkable cascade reaction has been demonstrated in the synthesis of claulansine A by taking advantage of the reactivity difference in three different types of alcohol units. We have accomplished an efficient total synthesis of the proposed structure of claulamine E, and regioisomeric revision in the structural assignment of the natural product is necessary. Sharpless asymmetric dihydroxylation reactions will provide access to the enantiomerically pure target compounds and their antipodes. The present approach provides an avenue to natural and unnatural carbazoles for SAR studies.

EXPERIMENTAL SECTION

General Description. Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 200, 400, and 500 MHz NMR spectrometers using TMS as an internal standard. The ^{13}C NMR spectra were recorded on 200 NMR (50 MHz), 400 NMR (100 MHz), and 500 NMR (125 MHz) spectrometers. Mass spectra were taken on an MS-TOF mass spectrometer. HRMS (ESI) were taken on an Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. The IR spectra were recorded on an FT-IR spectrometer. Commercially available starting materials and reagents were used.

Dimethyl (*E*)-2-((1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)-methylene)-3-(3-methylbut-2-en-1-yl)succinate (2). To a stirred solution of compound **1** (10.00 g, 26.66 mmol) in dry THF (70 mL) was dropwise added a solution of NaHMDS in THF (1 M, 53.3 mL, 53.33 mmol) at −78 °C under an argon atmosphere. The reaction mixture was stirred for 30 min, and prenyl bromide (4.64 mL, 40.21 mmol) was added dropwise. It was further stirred for 45 min at −78 °C, and the reaction was quenched with saturated aqueous NH_4Cl. Solvent was removed in vacuo, and the obtained residue was dissolved in EtOAc (300 mL). The organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60−120 mesh) column chromatographic purification of the obtained residue using ethyl acetate−petroleum ether (1:9) as an eluent yielded pure **2** as a thick oil (8.38 g, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.58 (s, 3H), 1.59 (s, 3H), 1.68 (s, 9H), 2.47−2.57 (m, 1H), 2.83−2.93 (m, 1H), 3.68 (s, 3H), 3.82 (s, 3H), 3.89 (dd, J = 8 and 8 Hz, 1H), 5.06 (t, J = 8 Hz, 1H), 7.28 (t, J = 8 Hz, 1H), 7.36 (t, J = 8 Hz, 1H), 7.67 (d, J = 8 Hz, 1H), 7.81 (s, 1H), 7.93 (s, 1H), 8.14 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.7, 25.6, 28.0, 28.4, 44.5, 51.8, 51.9, 84.3, 115.1, 115.3, 119.0, 121.1, 123.0, 124.8, 125.0, 129.9, 130.6, 131.7, 133.6, 134.9, 149.2, 166.9, 172.9; ESIMS (m/z) 464 $[M + Na]^+$; HRMS (ESI) calcd for $C_{25}H_{31}O_6NNa$ 464.2044, found 464.2036; IR ($CHCl_3$) ν_{max} 1736, 1636 cm^{-1}.

(*E*)-2-(1-(1*H*-Indol-3-yl)-3-methoxy-3-oxoprop-1-en-2-yl)-5-methylhex-4-enoic Acid (3). To a solution of compound **2** (7.50 g, 17.00 mmol) in MeOH−H_2O (3:1, 40 mL) was added KOH (2.09 g, 37.41 mmol) at 25 °C, and the reaction mixture was stirred for 25 h. The reaction mixture was concentrated in vacuo, and the obtained residue was acidified by 2 N HCl and extracted with ethyl acetate (70 mL × 3). The combined extract was washed with water and brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo, and the obtained residue was purified by silica gel (60−120 mesh) column chromatography using ethyl acetate−petroleum ether (8:2) as an eluent to yield acid **3** as a white solid (4.94 g, 89%). Mp 188−190 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.50 (s, 6H), 2.07−2.55 (m, 1H), 2.60−2.80 (m, 1H), 3.71 (s, 3H), 3.93 (dd, J = 10 and 6 Hz, 1H), 5.06 (t, J = 8 Hz, 1H), 7.05−7.25 (m, 2H), 7.46 (d, J = 8 Hz, 1H), 7.69 (d, J = 8 Hz, 1H), 7.78 (d, J = 2 Hz, 1H), 7.97 (s, 1H), 11.77 (br s, 1H), 12.16 (br s, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 17.6, 25.6, 28.3, 44.0, 51.5, 109.8, 112.1, 118.0, 120.3, 122.2, 122.4, 124.9, 126.7, 127.5, 131.9, 132.4, 135.8, 167.3, 174.0; ESIMS (m/z) 350 $[M + Na]^+$; HRMS (ESI) calcd for $C_{19}H_{21}O_4NNa$ 350.1363, found 350.1357; IR (nujol) ν_{max} 3372, 1704, 1613 cm^{-1}.

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Methyl 1-Hydroxy-2-(3-methylbut-2-en-1-yl)-9*H*-carbazole-3-carboxylate (4). To a solution of compound **3** (4.00 g, 12.23 mmol) in DCM (25 mL) at −10 °C were added triethylamine (1.70 mL, 12.23 mmol) and triphosgene (5.43 g, 18.34 mmol), and the reaction mixture was stirred at −10 to 0 °C for 2 h. The reaction mixture was concentrated in vacuo, and the obtained residue was dissolved in ethyl acetate (150 mL). The organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60−120 mesh) column chromatographic purification of the obtained residue using ethyl acetate−petroleum ether (3:7) as an eluent provided product **4** as a gummy solid (2.42 g, 64%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.80 (s, 3H), 1.91 (s, 3H), 4.00 (br s, 5H), 5.40 (t, J = 8 Hz, 1H), 5.98 (s, 1H), 7.22−7.30 (m, 1H), 7.40−7.48 (m, 2H), 8.07 (d, J = 8 Hz, 1H), 8.34 (br s, 1H), 8.56 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.9, 25.7, 26.5, 52.0, 111.1, 116.7, 120.0, 120.5, 121.7, 122.2, 122.4, 123.65, 123.74, 126.1, 132.1, 134.8, 139.8, 140.5, 169.3; ESIMS (m/z) 332 [M + Na]$^+$; HRMS (ESI) calcd for $C_{19}H_{19}O_3NNa$ 332.1257, found 332.1270; IR ($CHCl_3$) ν_{max} 3362, 1701, 1646 cm^{-1}.

Methyl 1-Methoxy-2-(3-methylbut-2-en-1-yl)-9*H*-carbazole-3-carboxylate (5). To a stirred solution of compound **4** (2.00 g, 6.47 mmol) in dry acetone (20 mL) were added K_2CO_3 (893 mg, 6.47 mmol) and dimethyl sulfate (494 μL, 5.17 mmol) at 25 °C, and the reaction mixture was refluxed for 8 h. The reaction mixture was allowed to reach room temperature and concentrated in vacuo. The obtained residue was dissolved in ethyl acetate (100 mL), and the organic layer was washed with water and brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo, and silica gel (60−120 mesh) column chromatographic purification of the obtained residue using ethyl acetate−petroleum ether (2:8) as eluent yielded pure product **5** as a white solid (1.91 g, 91%). Mp 130−132 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.71 (s, 3H), 1.84 (s, 3H), 3.94 (s, 2H), 3.96 (s, 6H), 5.27 (t, J = 8 Hz, 1H), 7.28 (t, J = 8 Hz, 1H), 7.40−7.50 (m, 2H), 8.07 (d, J = 8 Hz, 1H), 8.38 (br s, 1H), 8.49 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.1, 25.7, 25.9, 51.9, 61.1, 111.0, 120.1, 120.3, 120.5, 122.5, 122.6, 123.9, 124.1, 126.3, 131.3, 133.3, 135.5, 139.8, 143.2, 168.7; ESIMS (m/z) 346 [M + Na]$^+$; HRMS (ESI) calcd for $C_{20}H_{21}O_3NNa$ 346.1414, found 346.1409; IR ($CHCl_3$) ν_{max} 3468, 1706, 1608 cm^{-1}.

(1-Methoxy-2-(3-methylbut-2-en-1-yl)-9*H*-carbazol-3-yl)-methanol (6). To a stirred solution of compound **5** (120 mg, 0.37 mmol) in THF (5 mL) was added a solution of DIBAL-H in toluene (1 M, 1.11 mL, 1.11 mmol) at −78 °C under an argon atmosphere. The reaction mixture was stirred at −78 to 25 °C for 3 h. The reaction was quenched by saturated sodium−potassium tartarate solution and stirred for 1 h. The reaction mixture was concentrated in vacuo, and the obtained residue was dissolved in diethyl ether (30 mL). The organic layer was washed with water and brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo, and silica gel (60−120 mesh) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (3:7) as an eluent furnished pure product **6** as a white solid (96 mg, 88%). Mp 142−144 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.73 (s, 3H), 1.87 (s, 3H), 3.67 (d, J = 6 Hz, 2H), 3.97 (s, 3H), 4.83 (s, 2H), 5.15−5.27 (m, 1H), 7.24 (t, J = 8 Hz, 1H), 7.35−7.50 (m, 2H), 7.87 (s, 1H), 8.03 (d, J = 6 Hz, 1H), 8.20 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.0, 25.1, 25.7, 61.1, 64.2, 110.9, 116.8, 119.7, 120.3, 123.3, 123.9, 124.0, 125.7, 130.0, 131.9, 132.1, 132.8, 139.6, 143.2; ESIMS (m/z) 318 [M + Na]$^+$; HRMS (ESI) calcd for $C_{19}H_{21}O_2NNa$ 318.1465, found 318.1477; IR ($CHCl_3$) ν_{max} 3451 cm^{-1}.

1-Methoxy-2-(3-methylbut-2-en-1-yl)-9*H*-carbazole-3-carbaldehyde (Indizoline, 7).[7] To a mixture of compound **6** (70 mg, 0.237 mmol) and Celite (100 mg) in DCM (10 mL) was added PCC (102 mg, 0.47 mmol) at 25 °C under an argon atmosphere, and the reaction mixture was stirred for 30 min at the same temperature. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. Direct silica gel (60−120 mesh) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (2:8) as an eluent furnished aldehyde **7** as a gummy solid (66 mg, 95%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.70 (s, 3H), 1.85 (s, 3H), 3.95 (s, 2H), 3.97 (s, 3H), 5.24 (t, J = 8 Hz, 1H), 7.30 (t, J = 8 Hz, 1H), 7.40−7.52 (m, 2H), 8.08 (d, J = 8 Hz, 1H), 8.44 (s, 1H), 8.52 (br s, 1H), 10.29 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.1, 24.1, 25.7, 61.4, 111.2, 120.7, 120.8, 121.1, 123.3, 123.8, 124.0, 126.7, 127.8, 132.0, 134.0, 136.9, 139.8, 142.8, 191.9; ESIMS (m/z) 294 [M + H]$^+$; HRMS (ESI) calcd for $C_{19}H_{19}O_2NNa$ 316.1308, found 316.1304; IR ($CHCl_3$) ν_{max} 3302, 1725, 1659 cm^{-1}.

(2-((3,3-Dimethyloxiran-2-yl)methyl)-1-methoxy-9*H*-carbazol-3-yl)methanol (9). To a solution of compound **6** (60 mg, 0.203 mmol) in DCM (5 mL) was added *m*-CPBA (34.98 mg, 0.203 mmol) at −10 °C under an argon atmosphere, and the reaction mixture was stirred for 15 min. The reaction was quenched with a saturated solution of $NaHCO_3$ at 0 °C. The reaction mixture was extracted with DCM (15 mL), and the organic layer was immediately concentrated in vacuo to obtain epoxide **9** as a white solid (43 mg, 72%), which was immediately characterized without any purification for stability issues. ^{1}H NMR (acetone-d_6, 400 MHz) δ 1.29 (s, 3H), 1.47 (s, 3H), 2.99 (dd, J = 20 and 4 Hz, 2H), 3.34 (dd, J = 12 and 4 Hz, 1H), 3.95−4.10 (br s, 1H), 4.01 (s, 3H), 4.80 (d, J = 4 Hz, 2H), 7.17 (t, J = 8 Hz, 1H), 7.37 (t, J = 8 Hz, 1H), 7.52 (d, J = 8 Hz, 1H), 7.91 (s, 1H), 8.07 (d, J = 8 Hz, 1H), 10.41 (br s, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 19.4, 25.0, 26.5, 59.9, 61.1, 64.1, 65.4, 112.1, 117.2, 119.9, 120.9, 124.55, 124.57, 126.4, 127.5, 133.4, 133.9, 141.4, 144.9; HRMS (ESI) calcd for $C_{19}H_{21}O_3NNa$ 334.1414, found 334.1410; IR ($CHCl_3$) ν_{max} 3453 cm^{-1}.

2-(5-Methoxy-1,3,4,6-tetrahydropyrano[4,3-*b*]carbazol-3-yl)propan-2-ol (Proposed Claulamine E, 10).[11] *Method A.* To a solution of compound **6** (60 mg, 0.203 mmol) in DCM (5 mL) was added *m*-CPBA (34.98 mg, 0.203 mmol) at −10 °C under an argon atmosphere, and the reaction mixture was stirred for 4 h at 25 °C. The reaction was quenched with a saturated solution of $NaHCO_3$ at 25 °C. The reaction mixture was extracted with DCM (10 mL × 2), and the combined organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60−120 mesh) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (2:8) as an eluent furnished product **10** as a white solid (53 mg, 83%).

Method B. The solution of compound **9** (20 mg, 0.064 mmol) in acetone (1 mL) was stirred at 25 °C for 10 h. The reaction mixture was concentrated in vacuo, and silica gel (60−120 mesh) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (2:8) as an eluent furnished product **10** as a white solid (19 mg, 96%).

Method C. A mixture of compound **13** (50 mg, 0.15 mmol) and *p*-TSA (52 mg, 0.30 mmol) in THF (5 mL) was stirred at 25 °C for 2 h. The reaction mixture was concentrated in vacuo, and the obtained residue was dissolved in ethyl acetate (20 mL). The organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60−120 mesh) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (2:8) as an eluent furnished product **10** as a white solid (38 mg, 81%). Mp 160−162 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 1.28 (s, 3H), 1.29 (s, 3H), 2.80−2.90 (m, 1H), 3.10 (dd, J = 15 and 5 Hz, 1H), 3.44 (br s, 1H), 3.49 (dd, J = 10 and 5 Hz, 1H), 3.96 (s, 3H), 4.92 (d, J = 15 Hz, 1H), 5.05 (d, J = 15 Hz, 1H), 7.14 (t, J = 10 Hz, 1H), 7.36 (t, J = 10 Hz, 1H), 7.50 (d, J = 10 Hz, 1H), 7.55 (s, 1H), 8.02 (d, J = 10 Hz, 1H), 10.31 (br s, 1H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 24.2, 25.7, 26.4, 60.4, 70.0, 72.0, 82.7, 111.7, 112.0, 119.7, 120.9, 124.35, 124.43, 124.7, 126.5, 127.8, 132.8, 141.5, 143.9; ESIMS (m/z) 334 [M + Na]$^+$; HRMS (ESI) calcd for $C_{19}H_{21}O_3NNa$ 334.1414, found 334.1409; IR ($CHCl_3$) ν_{max} 3685, 3468 cm^{-1}.

3-(2-Hydroxypropan-2-yl)-5-methoxy-4,6-dihydropyrano-[4,3-*b*]carbazol-1(3*H*)-one (Mafaicheenamine A, 11).[8] To a stirred solution of compound **5** (500 mg, 1.54 mmol) in *t*-BuOH (15 mL) were added OsO_4 in *t*-BuOH (1 M, 308 μL, 0.308 mmol) and 50% aqueous NMO solution (540 μL) at 25 °C, and the reaction mixture was stirred for 15 h. The reaction was quenched with a saturated solution of $NaHSO_3$ and stirred at 25 °C for the next 1 h. The reaction mixture was extracted with ethyl acetate (3 × 10 mL),

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and the combined organic layer was washed with water and brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo, and silica gel (60−120 mesh) column chromatographic purification of the obtained residue using ethyl acetate−petroleum ether (8:2) as eluent yielded pure product **11** as a colorless solid (435 mg, 86%). Mp 236−238 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 1.38 (s, 6H), 3.04 (dd, J = 15 and 15 Hz, 1H), 3.46 (dd, J = 15 and 5 Hz, 1H), 3.92 (br s, 1H), 4.00 (s, 3H), 4.30 (dd, J = 10 and 5 Hz, 1H), 7.27 (t, J = 10 Hz, 1H), 7.46 (t, J = 10 Hz, 1H), 7.59 (d, J = 10 Hz, 1H), 8.23 (d, J = 10 Hz, 1H), 8.60 (s, 1H), 10.86 (br s, 1H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 23.3, 25.5, 26.9, 61.4, 71.3, 85.2, 112.5, 118.1, 119.9, 121.0, 121.5, 124.5, 124.9, 127.5, 129.6, 137.5, 141.7, 142.1, 166.3; ESIMS (m/z) 326 [M + H]$^+$; HRMS (ESI) calcd for $C_{19}H_{20}O_4N$ 326.1387, found 326.1383; IR ($CHCl_3$) ν_{max} 3687, 3462, 1707, 1614 cm^{-1}.

5-Methoxy-3-(prop-1-en-2-yl)-4,6-dihydropyrano[4,3-*b*]-carbazol-1(3*H*)-one (Claulamine A, 12).[9] To a stirred solution of compound **11** (50 mg, 0.153 mmol) in dry DCM (5 mL) was added Burgess reagent (72.82 mg, 0.306 mmol) at 25 °C under argon atmosphere, and the reaction mixture was stirred for 48 h. The reaction mixture was diluted with EtOAc (20 mL), and the organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (60−120 mesh) column chromatographic purification of the obtained residue using ethyl acetate−petroleum ether (3:7) as an eluent yielded pure **12** as a white solid (35 mg, 74%). Mp 170−174 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.95 (s, 3H), 3.14 (dd, J = 18 and 6 Hz, 1H), 3.38 (dd, J = 16 and 4 Hz, 1H), 3.99 (s, 3H), 4.96 (dd, J = 12 and 4 Hz, 1H), 5.07 (s, 1H), 5.21 (s, 1H), 7.27−7.35 (m, 1H), 7.43−7.55 (m, 2H), 8.08 (d, J = 8 Hz, 1H), 8.56 (br s, 1H), 8.71 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.4, 26.9, 61.2, 81.0, 111.2, 113.9, 117.2, 120.0, 120.8, 120.9, 123.7, 124.4, 126.9, 127.7, 136.2, 139.8, 140.6, 142.1, 166.5; ESIMS (m/z) 308 [M + H]$^+$; HRMS (ESI) calcd for $C_{19}H_{18}O_3N$ 308.1281, found 308.1275; IR ($CHCl_3$) ν_{max} 3460, 1709, 1615 cm^{-1}.

1-(3-(Hydroxymethyl)-1-methoxy-9*H*-carbazol-2-yl)-3-methylbutane-2,3-diol (13). To a stirred solution of compound **11** (80 mg, 0.246 mmol) in THF (8 mL) was added a solution of DIBAL-H in toluene (1 M, 984 μL, 0.984 mmol) at −78 °C under an argon atmosphere. The reaction mixture was stirred at −78 to 25 °C for 4 h. The reaction was quenched by saturated sodium−potassium tartarate solution and stirred for 1 h. The reaction mixture was concentrated in vacuo, and the obtained residue was stirred with diethyl ether (25 mL). The organic layer was washed with water and brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo, and silica gel (60−120 mesh) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (7:3) as an eluent furnished pure product **13** as a gummy solid (64 mg, 79%). ^{1}H NMR (CD_3OD, 500 MHz) δ 1.32 (s, 3H), 1.33 (s, 3H), 2.84 (dd, J = 15 and 10 Hz, 1H), 3.30 (dd, J = 10 and 5 Hz, 1H), 3.71 (dd, J = 10 and 5 Hz, 1H), 4.00 (s, 3H), 4.67 (d, J = 15 Hz, 1H), 4.90 (d, J = 15 Hz, 1H), 7.13 (t, J = 10 Hz, 1H), 7.34 (t, J = 10 Hz, 1H), 7.47 (d, J = 10 Hz, 1H), 7.78 (s, 1H), 7.99 (d, J = 10 Hz, 1H), 10.68 (br s, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 25.5, 25.6, 29.8, 60.8, 64.8, 74.3, 79.8, 112.2, 118.2, 120.1, 121.0, 124.9, 125.0, 126.7, 129.5, 132.9, 134.4, 142.0, 145.4; ESIMS (m/z) 352 [M + Na]$^+$; HRMS (ESI) calcd for $C_{19}H_{23}O_4NNa$ 352.1519, found 352.1513; IR ($CHCl_3$) ν_{max} 3438, 1660 cm^{-1}.

6-Methoxy-3,3-dimethyl-3,4,5,7-tetrahydro-1*H*-1,4-epoxyoxepino[4,3-*b*]carbazole (Claulansine A, 14).[10] *Method A.* To a stirred solution of compound **11** (60 mg, 0.184 mmol) in THF (6 mL) was added a solution of DIBAL-H in toluene (1 M, 553 μL, 0.553 mmol) at −78 °C under an argon atmosphere. The reaction mixture was stirred at −78 °C for 3 h. The reaction was quenched by saturated sodium−potassium tartarate solution and stirred for 1 h. The reaction mixture was concentrated in vacuo, and the obtained residue was dissolved in diethyl ether (25 mL). The organic layer was washed with water and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed silica gel (60−120 mesh) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (3:7) as an eluent provided product **14** as a white solid (44 mg, 77%).

Method B. To a solution of compound **13** (30 mg, 0.091 mmol) in DCM (5 mL) was added PCC (39.13 mg, 0.182 mmol) at 25 °C, and the reaction mixture was stirred for 15 h. The reaction mixture was filtered and concentrated in vacuo. Silica gel (60−120 mesh) column chromatographic purification of the obtained residue using ethyl acetate−petroleum ether (3:7) as an eluent provided product **14** as a white solid (20 mg, 70%). Mp 180−182 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.15 (s, 3H), 1.27 (s, 3H), 3.01 (d, J = 16 Hz, 1H), 3.22 (dd, J = 16 and 4 Hz, 1H), 3.91 (s, 3H), 4.49 (s, 1H), 6.10 (s, 1H), 7.14 (t, J = 8 Hz, 1H), 7.36 (t, J = 8 Hz, 1H), 7.49 (d, J = 8 Hz, 1H), 7.61 (s, 1H), 8.02 (d, J = 8 Hz, 1H), 11.33 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 23.7, 25.6, 29.4, 59.8, 79.2, 79.9, 100.4, 111.3, 111.8, 118.8, 119.9, 120.2, 122.2, 122.9, 125.4, 130.1, 132.4, 139.9, 142.5; ESIMS (m/z) 310 [M + H]$^+$; HRMS (ESI) calcd for $C_{19}H_{20}O_3N$ 310.1438, found 310.1433; IR ($CHCl_3$) ν_{max} 3417, 1603 cm^{-1}.

(1-Methoxy-4-(3-methylbut-2-en-1-yl)-9*H*-carbazol-3-yl)-methanol (16). To a stirred solution of compound **15** (100 mg, 0.30 mmol) in THF (5 mL) was added a solution of DIBAL-H in toluene (1 M, 900 μL, 0.90 mmol) at −78 °C under an argon atmosphere, and the reaction mixture was stirred at −78 to 25 °C for 3 h. The reaction was quenched by saturated sodium−potassium tartarate solution and stirred for 1 h. The reaction mixture was concentrated in vacuo, and the obtained residue was dissolved in diethyl ether (30 mL). The organic layer was washed with water and brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo, and silica gel (60−120 mesh) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (3:7) as an eluent furnished pure product **16** as a gummy solid (80 mg, 87%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.71 (s, 3H), 1.94 (s, 3H), 4.00 (s, 2H), 4.01 (s, 3H), 4.85 (s, 2H), 5.33 (t, J = 8 Hz, 1H), 6.96 (s, 1H), 7.25 (t, J = 8 Hz, 1H), 7.43 (t, J = 8 Hz, 1H), 7.49 (d, J = 8 Hz, 1H), 8.13 (d, J = 8 Hz, 1H), 8.38 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.3, 25.7, 28.1, 55.6, 64.0, 107.7, 110.9, 119.5, 122.8, 123.0, 123.2, 123.7, 125.3, 127.8, 129.7, 129.9, 132.5, 139.6, 143.6; ESIMS (m/z) 318 [M + Na]$^+$; HRMS (ESI) calcd for $C_{19}H_{21}O_2NNa$ 318.1465, found 318.1466; IR ($CHCl_3$) ν_{max} 3595, 3468 cm^{-1}.

(4-((3,3-Dimethyloxiran-2-yl)methyl)-1-methoxy-9*H*-carbazol-3-yl)methanol (17). To a solution of compound **16** (70 mg, 0.237 mmol) in DCM (5 mL) was added *m*-CPBA (40 mg, 0.237 mmol) at −30 °C under an argon atmosphere, and the reaction mixture was stirred for 2.5 h below −10 °C. The reaction was quenched with saturated solution of $NaHCO_3$ at 25 °C. The reaction mixture was extracted with DCM (10 mL × 2), and the combined organic layer was washed with water and brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by silica gel (60−120 mesh) column chromatographic purification of the resulting residue using ethyl acetate−petroleum ether (3:7) as an eluent furnished product **17** as a white solid (60 mg, 81%). Mp 166−168 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 1.29 (s, 3H), 1.56 (s, 3H), 3.11 (dd, J = 5 and 5 Hz, 1H), 3.27 (dd, J = 15 and 10 Hz, 1H), 3.84 (dd, J = 15 and 5 Hz, 1H), 3.86 (br s, 1H), 4.00 (s, 3H), 4.68 (d, J = 10 Hz, 1H), 4.82 (d, J = 10 Hz, 1H), 7.06 (s, 1H), 7.20 (t, J = 10 Hz, 1H), 7.40 (t, J = 10 Hz, 1H), 7.62 (d, J = 10 Hz, 1H), 8.27 (d, J = 10 Hz, 1H), 10.45 (br s, 1H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 19.5, 25.1, 29.1, 56.0, 60.6, 63.5, 64.8, 109.0, 112.4, 119.9, 123.1, 123.6, 124.3, 124.8, 125.9, 131.0, 132.9, 141.4, 145.1; ESIMS (m/z) 334 [M + Na]$^+$; HRMS (ESI) calcd for $C_{19}H_{21}O_3NNa$ 334.1414, found 334.1412; IR ($CHCl_3$) ν_{max} 3424, 1640 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00702.

X-ray crystallographic data for compound **10** (CIF)

^{1}H NMR, ^{13}C NMR, and DEPT spectra of all compounds and 2D NMR spectra of compounds **10** and **17** (PDF)

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Notes

The authors declare no competing financial interest.

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