Total Synthesis of Carbazomycins E and F

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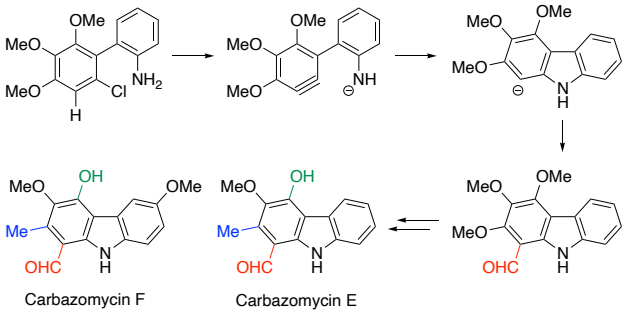
ABSTRACT: Total synthesis of carbazomycins E and F was achieved by double functionalization of an aryne intermediate generated from a 2-aminobiphenyl derivative. The tethered amino group underwent nucleophilic addition to the aryne intermediate to construct the carbazole skeleton. The resulting carbanion was formylated to give the multiply substituted carbazole. This formyl group caused several problems. For example, it was difficult to perform regioselective demethylation of the methoxy group proximal to the formyl group without protecting the carbazole nitrogen. In addition, the formyl group was unexpectedly reduced to give a methoxymethyl group under heating conditions with copper iodide and sodium methoxide. Oxidation of this compound in the presence of water was effective for obtaining the formylated carbazole, leading to the first total synthesis of carbazomycin F.



INTRODUCTION

Several synthetic studies on carbazole alkaloids have been conducted because of their structural diversity and biological activities.[1] Carbazomycins A–F are representative carbazole alkaloids with a fully substituted benzene moiety (Figure 1).[2] Carbazomycins A–D have methyl and methoxy substituents, and carbazomycins B and C possess a phenolic hydroxy group. Carbazomycins E (**1**) and F (**2**) bear a formyl group on the benzene ring, with all the substituents being different.[3] Owing to the variety of substituents, only one total synthesis of carbazomycin E has been previously reported,[4] and the total synthesis of carbazomycin F has not been reported. Recently, we achieved total synthesis of carbazomycins A–D on gram scales[5] using our original method to functionalize halogenated arenes.[6] We envisioned that the total synthesis of carbazomycins E and F can be also achieved with this method. Herein, we report the total synthesis of carbazomycins E and F.

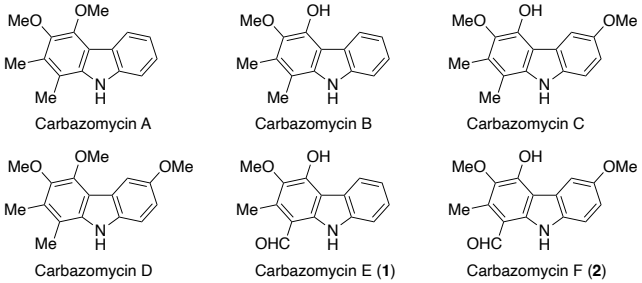
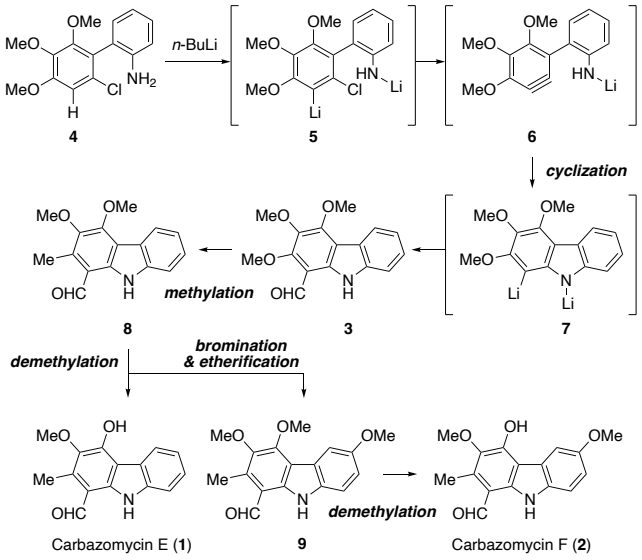


Figure 1. Structures of Carbazomycins A–F

Scheme 1. Synthetic Strategy toward Carbazomycins E and F



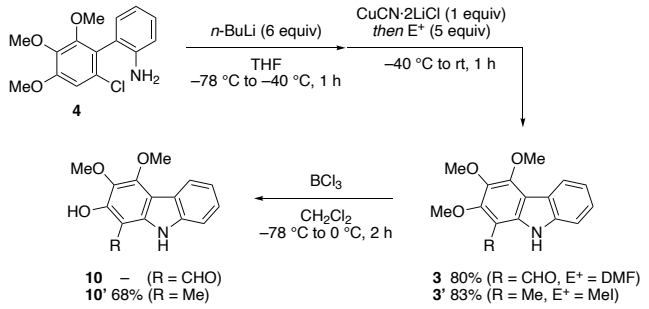
RESULTS AND DISCUSSION

Referring to our synthetic route for carbazomycins A–D,[5] we designed the synthetic strategy toward carbazomycins E and F (Scheme 1). We hypothesized that formylated carbazole **3** could be prepared using our method to synthesize multiply substituted carbazole from 2-aminobiphenyl **4**. The aryllithium species **5**, generated by deprotonation

with *n*-BuLi, is converted into aryne intermediate **6**. The tethered amino group undergoes nucleophilic addition to the aryne to construct the carbazole framework. The resulting dianion **7** reacts with a formylating reagent, producing carbazole **3**. Next, considering the structures of carbazomycins E (**1**) and F (**2**), we need to convert the methoxy group that is proximal to the formyl group into the methyl group to obtain methylcarbazole **8**. The methoxy group at the C4 position of methylcarbazole **8** should be regioselectively demethylated to give carbazomycin E (**1**), according to our previous report.[5] We also envisioned that carbazomycin F (**2**) could be synthesized using methylcarbazole **8** as the common synthetic intermediate. Introduction of the methoxy group provides methoxycarbazole **9**, and subsequent regioselective demethylation provides carbazomycin F (**2**).

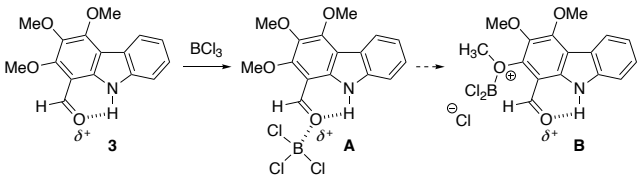
The synthesis commenced with the preparation of formylated carbazole **3** (Scheme 2). We prepared 2-aminobiphenyl **4** according to our previously reported method.[5] After adding 6 equivalents of *n*-BuLi, the resulting reaction mixture was treated with CuCN·2LiCl[7] followed by DMF to provide the desired carbazole **3** in 80% yield. We next examined the regioselective demethylation of the methoxy group proximal to the formyl group. In our previous synthesis of carbazomycins A–D, the desired phenol **10'** was obtained from methylated carbazole **3'** as the major product with BCl_3.[5a] The formylated carbazole **3** prepared in this work contains the formyl group at the *ortho*-position of the methoxy group we expected to react.[8] However, the reaction did not proceed with full recovery of the starting material. The desired phenol **10** was not obtained even when BBr_3 was used.

Scheme 2. Attempt to Synthesize Hydroxycarbazole through Carbazole Formation and Demethylation



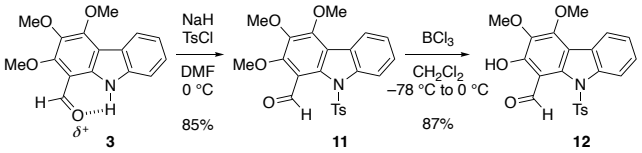
We attributed this result to the following reasons (Scheme 3). Demethylation using boron trihalide proceeds regioselectively at a methoxy group adjacent to carbonyl groups, through the coordination of boron trihalide with the carbonyl oxygen. However, the intramolecular interaction of the carbonyl oxygen and the hydrogen atom on the carbazole nitrogen hindered the formyl group from coordinating with the boron atom. Even if BCl_3 coordinated with the carbonyl oxygen to generate intermediate **A**, BCl_3 could not interact with the methoxy group to form intermediate **B**, which is the plausible intermediate in the demethylation.

Scheme 3. Rationale for the Unsuccessful Demethylation



To prohibit the undesired interaction, we considered introducing a protecting group on the carbazole nitrogen. Following a report on the demethylation of a similar substrate,[9] a tosyl group was introduced on the carbazole nitrogen (Scheme 4). Tosylated carbazole **11** was treated with BCl_3, and demethylation proceeded at the desired methoxy group.

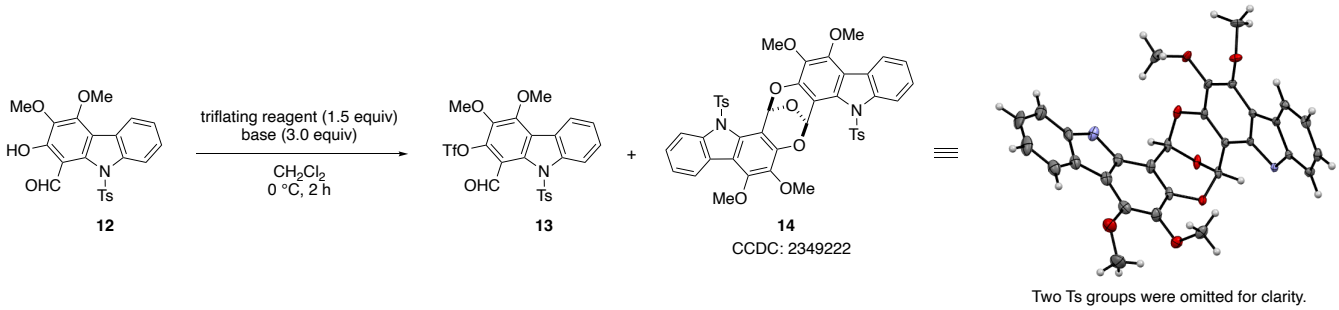
Scheme 4. Protection of the Carbazole Nitrogen Atom and Regioselective Demethylation of the Methoxy Group



For the introduction of a methyl group, we performed triflation of hydroxycarbazole **12** (Table 1). In our total synthesis of carbazomycins A–D, hydroxycarbazole was triflated using a combination of Et_3N and Tf_2O.[5] In this case, however, the desired triflate **13** was obtained in 27% yield under the same reaction conditions (entry 1). Instead, the undesired diacetal formation proceeded to give dimer **14**[10] as a major isomer. Based on the literature precedents regarding the diacetal formation of 2-acyl phenols,[11] a catalytic amount of Brønsted acid was used to activate carbonyl oxygen to generate the oxocarbenium ion. In this case, Tf_2O would react with the formyl group to form the oxocarbenium ion. To improve the yield of the desired triflate **13**, we examined several bases, but a substantial amount of the undesired dimer **14** was still produced. To circumvent the formation of the oxocarbenium ion, we used Comins' reagent,[12] which is a less reactive triflating reagent. As a result, the formation of the undesired dimer **14** was completely suppressed (entries 2 and 3). In addition, the desired triflate was obtained in quantitative yield using a combination of DMAP and Comins' reagent (entry 4).

Triflate **13** was then methylated with the formyl group intact using DABAL-Me_3,[13] an air-stable DABCO-$AlMe_3$ adduct, in the presence of palladium catalyst to give methylcarbazole **15** in 87% yield (Scheme 5). After the tosyl group was removed by NaOH in DMF at 60 °C, the resulting unprotected carbazole underwent demethylation of the methoxy group at the C4 position using a combination of NaOH and dodecanethiol at 130 °C[14] in the same reaction vessel to achieve the total synthesis of carbazomycin E (**1**) in 55% yield.

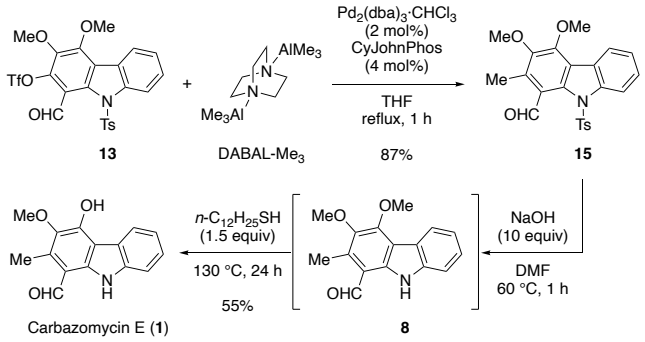
Table 1. Triflation of the Hydroxycarbazole[a]



entry	triflating reagent	base	triflate **13** (%)	dimer **14** (%)
1	Tf_2O	Et_3N	27[b]	62[b] (60[c])
2	Comins' reagent	Et_3N	24[b]	–[d]
3	Comins' reagent	*i*-Pr_2NEt	74[b]	–[d]
4[e]	Comins' reagent	DMAP	quant[c]	–[d]

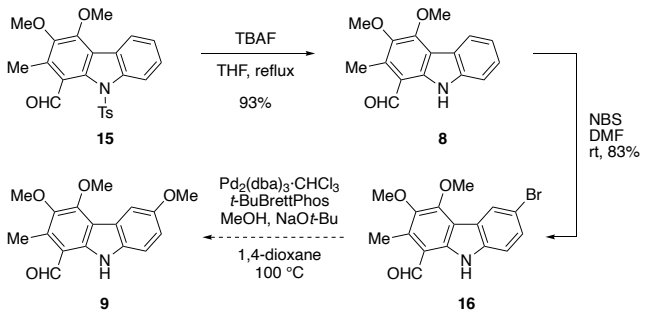
[a]Reaction conditions: hydroxycarbazole (**12**; 1.0 equiv), triflating reagent (1.5 equiv), base (3.0 equiv), CH_2Cl_2, 0 °C, 2 h. [b]The yield was determined from the ^1H NMR spectrum of the crude product using 1,1,2,2-tetrachloroethane as an internal standard. [c]Isolated yield. [d]Not observed. [e]Reaction time: 15 min.

Scheme 5. Total Synthesis of Carbazomycin E



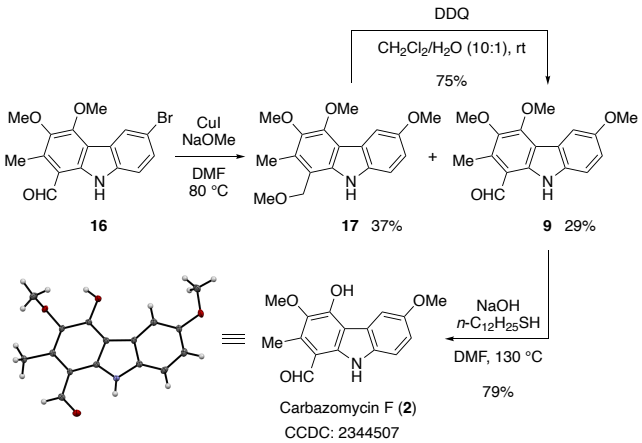
We next set out to synthesize carbazomycin F (Scheme 6). Because the bromination of tosylated methylcarbazole **15** resulted in low conversion, we removed the tosyl group[15] and then brominated methylcarbazole **8**. We attempted to introduce a methoxy group onto bromocarbazole **16** using a palladium catalyst,[16] but the reaction gave a complex mixture, and the starting material was mainly recovered.

Scheme 6. Synthesis of Bromocarbazole and Attempt to Introduce the Methoxy Group



We employed Ullmann coupling instead,[17] obtaining the desired carbazole **9** in 29% yield, but unexpectedly, methoxymethylcarbazole **17** was generated in 37% yield as a major product (Scheme 7). This carbazole **17**, involving the *para*-methoxybenzyl (PMB) substructure, was oxidized with DDQ in CH_2Cl_2/H_2O,[4,18] leading to the desired carbazole **9** in 75% yield. Finally, we performed the regioselective demethylation, and the first total synthesis of carbazomycin F (**2**) was achieved.

Scheme 7. Total Synthesis of Carbazomycin F



CONCLUSIONS

In summary, we accomplished the total synthesis of carbazomycins E and F. The aryne intermediate generated from the 2-aminobiphenyl underwent nucleophilic addition of the tethered amino group to construct the carbazole framework. Further functional group manipulation produced carbazomycin E. However, the unexpected reduc-

tion of the formyl group occurred during the installation of another methoxy group in the synthesis of carbazomycin F. The undesired carbazole bearing the PMB moiety was oxidized and demethylated to provide carbazomycin F.

EXPERIMENTAL SECTION

General Information. All reactions were conducted in a flame-dried glassware under an inert atmosphere of argon, unless otherwise stated. All workup and purification procedures were carried out with reagent-grade solvents in air. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Flash column chromatography was performed on high-efficiency irregular silica (25–40 μm, Santai Science Inc.). Anhydrous THF (>99.5%, water content: <10 ppm) was purchased from Kanto Chemical Co., Inc. and anhydrous CH_2Cl_2 (>99.5%, water content: <1 ppm) was purchased from Kanto Chemical Co., Inc. Anhydrous THF and CH_2Cl_2 were further dried by passing through a solvent purification system (Glass Contour) prior to use. *n*-BuLi (1.6 M in *n*-hexane) was purchased from Kanto Chemical Co., Inc. (Product number: 04937-25). A methanol solution of sodium methoxide (28%) was purchased from Fujifilm Wako Pure Chemical Co. (Product number: 197-02463). Analytical thin layer chromatography was performed on Fujifilm Wako 70 F_{254} glass plates precoated with a 0.25 mm thickness of silica gel. Melting points (Mp) were measured on a Yanaco MP-J3 and are uncorrected. Infrared (IR) spectra were recorded on a Bruker Alpha with an ATR attachment (Ge) and are reported in wavenumbers (cm^{-1}). ^1H NMR (400 MHz) and $^{13}C\{^1H\}$ NMR (100 MHz) spectra were obtained on a JEOL ECZ400 spectrometer. Chemical shifts for ^1H NMR are reported in parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 ppm, pyridine-d_4: δ 8.71 ppm) and coupling constants are given in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, m = multiplet, and br = broad. Chemical shifts for $^{13}C\{^1H\}$ NMR are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm, pyridine-d_5: δ 135.50 ppm). High-resolution mass spectroscopy (HRMS) was performed on a JEOL JMS-T100LP AccuTOF LC-Plus [electrospray ionization (ESI)] with a JEOL MS-5414DART attachment.

Preparation of a THF Solution of CuCN·2LiCl.[7] Commercially available LiCl (2.123 g, 50.0 mmol) was flame-dried for 15 min in a 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar. After cooling to room temperature, anhydrous CuCN (2.239 g, 25.0 mmol) and THF (25 mL) was added to the Schlenk tube, and the mixture was stirred at room temperature for 1 h to provide a THF solution of CuCN·2LiCl (1.0 M in THF).

Total Synthesis of Carbazomycin E.

*2,3,4-Trimethoxy-9H-carbazole-1-carbaldehyde (**3**).*

A flame-dried 500-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with 2-aminobiphenyl **4**[5a] (2.725 g, 9.28 mmol, 1.0 equiv) and THF (92 mL). The solution was cooled to −78 °C, and *n*-BuLi (1.56 M in hexane, 35.6 mL, 55.6 mmol, 6.0 equiv) was added dropwise to the Schlenk tube. After stirring at −40 °C for 1 h, the reaction mixture was treated with CuCN·2LiCl (1.0 M in THF, 9.3 mL, 9.3 mmol, 1.0 equiv) followed by DMF (3.6 mL, 46 mmol, 5.0 equiv). The resulting mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with saturated aqueous ammonium chloride (100 mL). After being partitioned, the aqueous layer was extracted with EtOAc (50 mL). The combined organic extracts were washed with saturated aqueous ammonium chloride (60 mL) three times and brine (100 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 9:1 to 4:1, gradient), to provide the title compound as a yellow solid (2.129 g, 7.46 mmol, 80%). R_f = 0.40 (hexane/diethyl ether = 1:1); mp 109–111 °C; IR (ATR, cm^{-1}): 3388, 2939, 2850, 1654, 1586, 1491, 1454, 1419, 1350, 1314, 1292, 1236, 1171, 1075, 1043, 988, 954, 817, 749; ^1H NMR (400 MHz, $CDCl_3$): δ 10.43 (s, 1H), 10.39 (br s, 1H), 8.21 (d, 1H, *J* = 7.6 Hz), 7.47 (d, 1H, *J* = 7.6 Hz), 7.40 (ddd, 1H, *J* = 7.6, 7.6, 1.2 Hz), 7.27 (ddd, 1H, *J* = 7.6, 7.6, 1.2 Hz), 4.30 (s, 3H), 4.14 (s, 3H), 3.94 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 189.9, 157.8, 156.0, 139.6, 137.7, 136.5, 125.6, 122.4, 121.3, 120.6, 112.4, 111.1, 109.1, 63.1, 61.7, 61.0; HRMS (DART/TOF) *m/z*: $[M + H]^+$ calcd. for $C_{16}H_{16}NO_4$, 286.1079; found, 286.1087.

*2,3,4-Trimethoxy-9-tosyl-9H-carbazole-1-carbaldehyde (**11**).*

A flame-dried 200-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with formylated carbazole **3** (2.961 g, 10.4 mmol, 1.0 equiv) and DMF (20.0 mL). After the pale yellow solution was cooled to 0 °C, NaH (60% in oil, 0.468 g, 12 mmol, 1.1 equiv) was added to the flask. After stirring for 20 min, the reaction mixture was treated with *p*-toluenesulfonyl chloride (2.183 g, 11.4 mmol, 1.1 equiv) at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was treated with saturated aqueous ammonium chloride (20 mL) followed by diethyl ether (80 mL). After being partitioned, the organic layer was washed with water (40 mL) five times, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/EtOAc = 19:1 to 4:1, gradient) to provide the title compound as a pale yellow solid (3.867 g, 8.80 mmol, 85%). R_f = 0.38 (hexane/diethyl ether = 1:2); mp 110–111 °C; IR (ATR, cm^{-1}): 2942, 2862, 1701, 1577, 1490, 1449, 1417, 1369, 1347, 1314, 1296, 1213, 1188, 1173, 1125, 1089, 1071, 1040, 984, 814, 761, 665; ^1H NMR (400 MHz, $CDCl_3$): δ 10.54 (s, 1H), 8.12 (d, 1H, *J* = 8.0 Hz), 7.90 (d, 1H, *J* = 8.0 Hz), 7.38 (ddd, 1H, *J* = 8.0, 8.0, 1.2 Hz), 7.29 (ddd, 1H, *J* = 8.0, 8.0, 1.2 Hz), 7.03 (d, 2H, *J* = 8.4 Hz), 6.87 (d, 2H, *J* = 8.4 Hz), 4.10 (s, 3H), 4.06 (s, 3H), 3.94 (s, 3H), 2.18 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 186.4, 154.7, 151.7, 145.0, 143.8, 140.6, 136.6, 132.1, 129.1, 127.6, 127.1, 126.9, 125.9, 122.5, 119.3, 118.9, 118.6, 63.5, 61.9, 61.0, 21.6; HRMS (DART/TOF) *m/z*: $[M + H]^+$ calcd. for $C_{23}H_{22}NO_6S$, 440.1168; found, 440.1187.

*2-Hydroxy-3,4-trimethoxy-9-tosyl-9H-carbazole-1-carbaldehyde (**12**).*

A flame-dried 200-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with *N*-tosylcarbazole **11** (3.222 g, 7.33 mmol, 1.0 equiv) and CH_2Cl_2 (37.0 mL). The solution was cooled to −78 °C. To the solution was added BCl_3 (1.0 M in CH_2Cl_2, 11.0 mL, 11 mmol, 1.5 equiv). After stirring at 0 °C for 30 min, the reaction mixture was treated with water (40 mL). After being partitioned, the aqueous layer was extracted with CH_2Cl_2 (10 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was triturated with a mixed solvent (hexane/diethyl ether = 1:1) to provide the title compound as a pale yellow solid (2.712 g, 6.39 mmol, 87%). R_f = 0.52 (hexane/diethyl ether = 1:2); mp 187–188 °C; IR (ATR, cm^{-1}): 2927, 2850, 1636, 1448, 1431, 1415, 1389, 1366, 1293, 1265, 1215, 1187, 1174, 1135, 1063, 1046, 812; ^1H NMR (400 MHz, $CDCl_3$): δ 12.40 (s, 1H), 10.37 (s, 1H), 8.12 (d, 1H, *J* = 8.0 Hz), 7.81 (dd, 1H, *J* = 8.0, 1.2 Hz), 7.34 (ddd, 1H, *J* = 8.0, 8.0, 1.2 Hz), 7.27 (ddd, 1H, *J* = 8.0, 8.0, 1.2 Hz), 6.95 (d, 2H, *J* = 8.8 Hz), 6.84 (d, 2H, *J* = 8.8 Hz), 4.18 (s, 3H), 3.96 (s, 3H), 2.18 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 193.3, 158.2, 153.6, 145.1, 140.1, 137.4, 137.2, 131.3, 129.0, 128.3, 127.2, 126.2, 126.1, 121.9, 118.7, 115.3, 109.2, 61.5, 61.0, 21.6; HRMS (DART/TOF) *m/z*: $[M + H]^+$ calcd. for $C_{22}H_{20}NO_6S$, 426.1011; found, 426.1026.

*1-Formyl-3,4-dimethoxy-9-tosyl-9H-carbazol-2-yl trifluoromethanesulfonate (**13**).*

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with hydroxycarbazole **12** (1.856 g, 4.36 mmol, 1.0 equiv) and CH_2Cl_2 (22.0 mL). The solution was cooled to 0 °C. To the solution were added 4-(*N*,*N*-dimethylamino)pyridine (1.598 g, 13.1 mmol, 3.0 equiv) and 2-[*N*,*N*-bis(trifluoromethanesulfonyl)amino]-5-chloropyridine (Comins' reagent; 2.566 g, 6.54 mmol, 1.5 equiv). After stirring at 0 °C for 15 min, the reaction mixture was treated with water (20 mL) and CH_2Cl_2 (60 mL). After being partitioned, the aqueous layer was extracted with CH_2Cl_2 (10 mL) three times. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether/CH_2Cl_2 = 80:10:10 to 70:15:15, gradient) to provide the title compound as a colorless solid (2.421 g, 4.35 mmol, quantitative). R_f = 0.49 (hexane/diethyl ether = 1:2); mp 132–134 °C; IR (ATR, cm^{-1}): 2926, 2855, 1707, 1577, 1564, 1466, 1429, 1374, 1240, 1205, 1175, 1160, 1137, 1041, 860, 802, 762, 751, 730, 664, 625; ^1H NMR (400 MHz, $CDCl_3$): δ 10.32 (s, 1H), 8.23 (d, 1H, *J* = 8.0 Hz), 7.96 (d, 1H, *J* = 8.0 Hz), 7.52 (ddd, 1H, *J* = 8.0, 8.0, 1.2 Hz), 7.39 (ddd, 1H, *J* = 8.0, 8.0, 1.2 Hz), 7.00 (d, 2H, *J* = 8.0 Hz), 6.86 (d, 2H, *J* = 8.0 Hz), 4.10 (s, 3H), 3.97 (s, 3H), 2.19 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 183.3, 151.6, 145.5, 142.7, 141.1, 140.9, 136.7, 131.0, 129.1, 128.4, 127.2, 126.8, 126.6, 123.5, 123.2, 119.0, 118.9 (q, $^1J_{C-F}$ = 319 Hz), 117.8, 62.3, 61.1, 21.6; HRMS (DART/TOF) *m/z*: $[M + H]^+$ calcd. for $C_{23}H_{19}F_3NO_8S_2$, 558.0504; found, 558.0506.

*1,2,10,11-Tetramethoxy-7,16-ditosyl-7,8,16,17-tetrahydro-8,17-epoxy[1,5]dioxocino[3,2-a:7,6-a']dicarbazole (**14**).*

A flame-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and rubber septum was charged with hydroxycarbazole **12** (63.8 mg, 0.150 mmol, 1.0 equiv) and CH_2Cl_2 (0.75 mL). The solution was cooled to 0 °C. To the solution was added triethylamine (0.062 mL, 0.45 mmol, 3.0 equiv) and trifluoromethanesulfonic anhydride (0.038 mL, 0.23 mmol, 1.5 equiv). After stirring at 0 °C for 2 h, the reaction mixture was treated with saturated aqueous sodium hydrogen carbonate (1 mL). After being partitioned, the aqueous layer was extracted with CH_2Cl_2 (1 mL) three times. The combined organic extracts were washed with brine (4 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 9:1 to 7:3, gradient) to provide the title compound as a pale yellow solid (37.3 mg, 0.0447 mmol, 60%). R_f = 0.43 (hexane/diethyl ether = 1:2); mp 134–135 °C; IR (ATR, cm^{-1}): 2925, 2853, 1498, 1449, 1418, 1371, 1326, 1211, 1189, 1175, 1155, 1132, 1081, 1034, 986, 930; ^1H NMR (400 MHz, $CDCl_3$): δ 8.18–8.12 (m, 4H), 7.77 (d, 2H, *J* = 7.6 Hz), 7.32 (ddd, 2H, *J* = 7.6, 7.6, 1.6 Hz), 7.25–7.17 (m, 6H), 6.92 (d, 4H, *J* = 8.4 Hz), 3.89 (s, 6H), 3.68 (s, 6H), 2.22 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 148.6, 146.3, 144.7, 140.7, 139.5, 133.3, 131.8, 128.9, 128.5, 127.3, 126.1, 125.9, 121.9, 119.1, 118.2, 108.6, 87.4, 61.4, 60.9, 21.6; HRMS (ESI/TOF) *m/z*: $[M + Na]^+$ calcd. for $C_{44}H_{36}N_2O_{11}S_2Na$, 855.1658; found, 855.1643.

*3,4-Dimethoxy-2-methyl-9-tosyl-9H-carbazole-1-carbaldehyde (**15**).*

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and rubber septum was charged with triflate **13** (2.585 g, 4.63 mmol, 1.0 equiv), DABAL-Me_3 (596.4 mg, 2.33 mmol, 0.5 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (96.2 mg, 0.0929 mmol, 2 mol%), and 2-(dicyclohexylphosphino)biphenyl (CyJohnPhos; 64.9 mg, 0.180 mmol, 4 mol%), and THF (23.0 mL). The Schlenk tube was placed in a preheated oil bath and heated at 80 °C for 1 h. After cooling to room temperature, the reaction mixture was treated with water (10 mL) and CH_2Cl_2 (60 mL). After being partitioned, the aqueous layer was extracted with CH_2Cl_2 (10 mL) three times. The combined organic extracts were washed with brine (50 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (CH_2Cl_2) to provide the title compound as a gray solid (1.707 g, 4.03 mmol, 87%). R_f = 0.50 (hexane/diethyl ether = 1:2); mp 101–103 °C; IR (ATR, cm^{-1}): 2944, 2838, 1697, 1656, 1596, 1580, 1488, 1447, 1413, 1369, 1345, 1290, 1186, 1173, 1122, 1072, 1009, 969, 813; ^1H NMR (400 MHz, $CDCl_3$): δ 10.46 (s, 1H), 8.15 (d, 1H, *J* = 7.6 Hz), 7.89 (dd, 1H, *J* = 7.6, 1.2 Hz), 7.41 (ddd, 1H, *J* = 7.6, 7.6, 1.2 Hz), 7.31 (ddd, 1H, *J* = 7.6, 7.6, 1.2 Hz), 6.91 (d, 2H, *J* = 8.4 Hz), 6.82 (d, 2H, *J* = 8.4 Hz), 4.01 (s, 3H), 3.85 (s, 3H), 2.71 (s, 3H), 2.17 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 188.8, 151.0, 149.3, 144.9, 140.8, 139.1, 134.6, 131.4, 128.8, 128.0, 127.2, 126.2, 123.3, 122.5, 122.3, 119.0, 61.0, 60.6, 21.6,

13.3; HRMS (DART/TOF) *m/z*: [M + H]$^+$ calcd. for $C_{23}H_{22}NO_5S$, 424.1219; found, 424.1216.

*Carbazomycin E (**1**).*

An oven-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar was charged with 2-methylcarbazole **15** (213.5 mg, 0.504 mmol, 1.0 equiv), sodium hydroxide (210.0 mg, 5.25 mmol, 10 equiv), and DMF (5 mL). After stirring at 60 °C for 1 h, the mixture was cooled to room temperature. To the Schlenk tube was added 1-dodecanethiol (0.178 mL, 0.750 mmol, 1.5 equiv), and the reaction mixture was stirred at 130 °C for 24 h. After cooling to room temperature, the reaction mixture was treated with 1 M HCl aq. (6 mL) and ethyl acetate (15 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (5 mL) three times. The combined organic extracts were washed with water (15 mL) five times, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/EtOAc/CH_2Cl_2 = 80:10:10 to 60:20:20, gradient) to provide carbazomycin E (**1**) as a dark yellow solid (71.1 mg, 0.278 mmol, 55%), whose ^{1}H and ^{13}C NMR data were almost identical to those reported in the literature.[3a,4] R_f = 0.38 (hexane/diethyl ether = 1:2); mp 202–203 °C; IR (ATR, cm^{-1}): 3355, 2925, 2854, 1651, 1610, 1583, 1568, 1481, 1465, 1453, 1433, 1408, 1342, 1287, 1264, 1215, 1157, 1142, 1105, 1050, 1007, 872; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.62 (br s, 1H), 10.41 (s, 1H), 8.23 (dd, 1H, *J* = 7.6, 1.2 Hz), 7.49 (dd, 1H, *J* = 7.6, 1.2 Hz), 7.43 (ddd, 1H, *J* = 7.6, 7.6, 1.2 Hz), 7.29 (ddd, 1H, *J* = 7.6, 7.6, 1.2 Hz), 6.88 (s, 1H), 3.87 (s, 3H), 2.78 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, pyridine-d_5): δ 189.4, 154.4, 140.6, 139.4, 139.3, 134.7, 125.5, 123.0, 122.7, 120.4, 111.8, 111.6, 110.9, 60.9, 11.0; HRMS (DART/TOF) *m/z*: [M + H]$^+$ calcd. for $C_{15}H_{14}NO_3$, 256.0974; found, 256.0981.

Total Synthesis of Carbazomycin F.

*3,4-Trimethoxy-2-methyl-9H-carbazole-1-carbaldehyde (**8**).*

A flame-dried 100-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with carbazole **15** (846.4 mg, 2.00 mmol, 1.0 equiv) and THF (20.0 mL). To the solution was added tetrabutylammonium fluoride (1.0 M in THF, 10.0 mL, 10 mmol, 5.0 equiv). After the solution was stirred at 80 °C for 1 h, the reaction mixture was cooled to room temperature and treated with water (15 mL) followed by ethyl acetate (15 mL). After being partitioned, the organic layer was washed with water (15 mL) three times, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/EtOAc = 95:5 to 85:15, gradient) to provide the title compound as a pale yellow solid (497.4 mg, 1.85 mmol, 93%). R_f = 0.53 (hexane/diethyl ether = 1:2); mp 155–157 °C; IR (ATR, cm^{-1}): 3383, 2938, 2861, 1655, 1598, 1582, 1573, 1486, 1453, 1346, 1318, 1290, 1233, 1172, 1062, 1008, 971, 923, 880; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.54 (br s, 1H), 10.49 (s, 1H), 8.23 (d, 1H, *J* = 7.6 Hz), 7.48 (d, 1H, *J* = 7.6 Hz), 7.43 (ddd, 1H, *J* = 7.6, 7.6, 1.2 Hz), 7.27 (ddd, 1H, *J* = 7.6, 7.6, 1.2 Hz) 4.24 (s, 3H), 3.87 (s, 3H), 2.75 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 191.0, 155.0, 143.3, 139.7, 138.4, 135.5, 126.1, 122.7, 121.2, 120.6, 115.6, 113.3, 111.2, 61.3, 60.8, 11.0; HRMS (DART/TOF) *m/z*: [M + H]$^+$ calcd. for $C_{16}H_{16}NO_3$, 270.1130; found, 270.1144.

*6-Bromo-3,4-trimethoxy-2-methyl-9H-carbazole-1-carbaldehyde (**16**).*

A 50-mL vial equipped with a Teflon-coated magnetic stirring bar was charged with 2-methylcarbazole **8** (471.5 mg, 1.75 mmol, 1.0 equiv) and DMF (8.8 mL). To the solution was added *N*-bromosuccinimide (342.6 mg, 1.92 mmol, 1.1 equiv), the mixture was stirred at room temperature for 40 min. The reaction mixture was treated with saturated aqueous sodium thiosulfate (6 mL) and CH_2Cl_2 (15 mL). After being partitioned, the aqueous layer was extracted with CH_2Cl_2 (10 mL) three times. The combined organic extracts were washed with water (15 mL) five times, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was triturated with a mixed solvent (hexane/diethyl ether = 1:1) to provide the title compound as a pale yellow solid (505.5 mg, 1.45 mmol, 83%). R_f = 0.48 (hexane/diethyl ether = 1:2); mp 194–195 °C; IR (ATR, cm^{-1}): 3372, 2926, 2851, 1651, 1583, 1487, 1459, 1447, 1339, 1322, 1290, 1279, 1233, 1066, 1048, 1021, 1010, 979, 922, 805; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.52 (br s, 1H), 10.49 (s, 1H), 8.34 (d, 1H, *J* = 2.0 Hz), 7.51 (dd, 1H, *J* = 8.4, 2.0 Hz), 7.35 (d, 1H, *J* = 8.4 Hz), 4.26 (s, 3H), 3.85 (s, 3H), 2.76 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 190.9, 155.0, 143.3, 138.5, 138.2, 136.6, 128.7, 125.2, 123.0, 114.6, 113.3, 113.2, 112.5, 61.2, 60.8, 11.1; HRMS (DART/TOF) *m/z*: [M + H]$^+$ calcd. for $C_{16}H_{15}{}^{79}BrNO_4$, 348.0235; found, 348.0223.

*Attempt to synthesize 3,4,6-trimethoxy-2-methyl-9H-carbazole-1-carbaldehyde (**9**).*

An oven-dried 10-mL screw-top test tube equipped with a Teflon-coated magnetic stirring bar was charged with 6-bromocarbazole **16** (62.3 mg, 0.180 mmol, 1.0 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (5.9 mg, 5.7 μmol, 3.2 mol%), *t*-BuBrettPhos (11.0 mg, 22.7 μmol, 13 mol%), and sodium *tert*-butoxide (34.0 mg, 0.353 mmol, 2.0 equiv). The tube was then evacuated and backfilled with argon three times. Methanol (73 μL, 1.8 mmol, 10 equiv) and 1,4-dioxane (0.6 mL) were added to the tube via syringe. The test tube was placed in a preheated oil bath and heated at 100 °C for 19 h. The reaction mixture was treated with saturated aqueous ammonium chloride (1 mL) and CH_2Cl_2 (2 mL). After being partitioned, the aqueous layer was extracted twice with CH_2Cl_2 (2 mL). The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated under the reduced pressure to give a complex mixture. The desired product **9** was not detected.

*3,4,6-Trimethoxy-1-(methoxymethyl)-2-methyl-9H-carbazole (**17**).*

A flame-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with 6-bromocarbazole **16** (580.6 mg, 1.67 mmol, 1.0 equiv), copper iodide (637.1 mg, 3.35 mmol, 2.0 equiv), DMF (17.0 mL) and a methanol solution of sodium methoxide (28%, 17.0 mL). After stirring at 80 °C for 20 h, the reaction mixture was treated with saturated aqueous ammonium chloride (17 mL) followed by ethyl acetate (17 mL).

After being partitioned, the aqueous layer was extracted with ethyl acetate (17 mL) three times. The combined organic extracts were washed with water (40 mL) three times, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/diethyl ether = 90:10 to 70:30, gradient) to provide methoxymethylcarbazole **17** as a pale brown oil (197.2 mg, 0.625 mmol, 37%) and formylated carbazole **9** as a pale yellow solid (144.5 mg, 0.483 mmol, 29%).

Methoxymethylcarbazole **17**: R_f = 0.45 (hexane/diethyl ether = 1:2); IR (ATR, cm^{-1}): 3330, 2931, 2829, 1483, 1400, 1340, 1290, 1216, 1144, 1073, 1031; ^1H NMR (400 MHz, $CDCl_3$): δ 8.64 (br s, 1H), 7.76 (d, 1H, *J* = 2.4 Hz), 7.31 (d, 1H, *J* = 8.8 Hz), 7.04 (dd, 1H, *J* = 8.8, 2.4 Hz), 4.85 (s, 2H), 4.13 (s, 3H), 3.94 (s, 3H), 3.89 (s, 3H), 3.47 (s, 3H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.7, 147.5, 143.7, 137.5, 134.6, 128.3, 122.6, 115.3, 114.4, 114.0, 111.1, 105.5, 70.4, 61.2, 60.7, 58.3, 56.2, 12.2; HRMS (DART/TOF) *m/z*: $[M + H]^+$ calcd. for $C_{18}H_{22}NO_4$, 316.1549; found, 316.1535.

Formylated carbazole **9**: R_f = 0.55 (hexane/diethyl ether = 1:2); mp 160–162 °C; IR (ATR, cm^{-1}): 3395, 2948, 2833, 1650, 1588, 1574, 1487, 1460, 1435, 1340, 1320, 1307, 1289, 1247, 1212, 1154, 1134, 1110, 1060, 987, 933; ^1H NMR (400 MHz, $CDCl_3$): δ 10.49 (s, 1H), 10.41 (br s, 1H), 7.74 (d, 1H, *J* = 2.4 Hz), 7.38 (d, 1H, *J* = 8.8 Hz), 7.08 (dd, 1H, *J* = 8.8, 2.4 Hz), 4.24 (s, 3H), 3.93 (s, 3H), 3.86 (s, 3H), 2.76 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 190.9, 155.0, 154.5, 142.9, 139.0, 135.7, 134.5, 121.7, 115.6, 114.9, 113.3, 111.8, 105.8, 61.3, 60.8, 56.2, 11.0; HRMS (DART/TOF) *m/z*: $[M + H]^+$ calcd. for $C_{17}H_{18}NO_4$, 300.1236; found, 300.1234.

*3,4,6-Trimethoxy-2-methyl-9H-carbazole-1-carbaldehyde (**9**).*

A 30-mL test tube equipped with a Teflon-coated magnetic stirring bar was charged with formylated carbazole **17** (199.0 mg, 0.631 mmol, 1.0 equiv), CH_2Cl_2 (12.5 mL), and H_2O (1.3 mL). To the resulting mixture was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 144.4 mg, 0.636 mmol, 1.0 equiv), and the reaction mixture was stirred at room temperature for 15 min. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate (10 mL). After being partitioned, the organic layer was dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/EtOAc = 90:10 to 80:20, gradient) to provide the title compound as a pale yellow solid (142.4 mg, 0.476 mmol, 75%).

*Carbazomycin F (**2**).*

An oven-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar was charged with 6-methoxycarbazole **9** (260.1 mg, 0.869 mmol, 1.0 equiv), sodium hydroxide (181.0 mg, 4.53 mmol, 5.2 equiv), 1-dodecanethiol (0.310 mL, 1.3 mmol, 1.5 equiv), and DMF (9 mL). The Schlenk tube was evacuated and backfilled with argon. The reaction mixture was heated at 130 °C for 14 h. After cooling to room temperature, the reaction mixture was treated with 1 M HCl aq. (10 mL) and ethyl acetate (10 mL). After being partitioned, the aqueous layer was extracted with ethyl acetate (10 mL) three times. The combined organic extracts were washed with water (40 mL) five times, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (hexane/EtOAc/CH_2Cl_2 = 80:10:10 to 60:20:20, gradient) to provide carbazomycin F (**2**) as a yellow solid (195.6 mg, 0.686 mmol, 79%), whose ^1H and ^{13}C NMR data were almost identical to those reported in the literature.[3a] R_f = 0.33 (hexane/diethyl ether = 1:2); mp 202–204 °C; IR (ATR, cm^{-1}): 3402, 3260, 2933, 2858, 1649, 1588, 1568, 1484, 1465, 1439, 1344, 1307, 1288, 1263, 1247, 1207, 1131, 1106, 1048, 1013, 969, 870; ^1H NMR (400 MHz, $CDCl_3$): δ 10.50 (br s, 1H), 10.39 (s, 1H), 7.73 (d, 1H, *J* = 2.4 Hz), 7.38 (d, 1H, *J* = 8.8 Hz), 7.06 (dd, 1H, *J* = 8.8, 2.4 Hz), 6.87 (s, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 2.77 (s, 3H); ^1H NMR (400 MHz, pyridine-d_5): δ 12.06 (br s, 1H), 10.59 (s, 1H), 8.41 (d, 1H, *J* = 2.4 Hz), 7.72 (d, 1H, *J* = 8.8 Hz), 7.26 (dd, 1H, *J* = 8.8, 2.4 Hz), 3.81 (s, 3H), 3.65 (s, 3H), 2.69 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 189.9, 154.7, 151.1, 139.9, 137.7, 134.3, 133.4, 121.8, 115.0, 111.8, 110.8, 110.0, 105.5, 62.1, 56.2, 11.3; $^{13}C\{^1H\}$ NMR (100 MHz, pyridine-d_5): δ 189.3, 154.9, 154.5, 140.1, 139.0, 135.4, 134.9, 123.4, 114.4, 112.4, 111.8, 111.0, 106.4, 61.0, 55.8, 11.0; HRMS (DART/TOF) *m/z*: $[M + H]^+$ calcd. for $C_{16}H_{16}NO_4$, 286.1079; found, 286.1087.

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Notes

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(19) CCDC 2344507 contains the supplementary crystallographic data for carbazomycin F (**2**). The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.