Iron-Mediated Synthesis of Carbazomycin G and Carbazomycin H, the First Carbazole-1,4-quinol Alkaloids from *Streptoverticillium ehimense*[‡]

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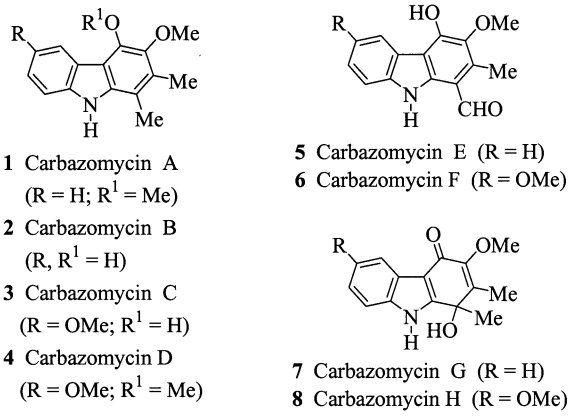
The total synthesis of the carbazole-1,4-quinol alkaloids carbazomycin G (**7**) and carbazomycin H (**8**) was achieved by a highly convergent iron-mediated construction of the carbazole framework. Electrophilic substitution of the arylamine **15** using the iron complex salts **13** and **14,** followed by oxidative iron-mediated arylamine cyclization, afforded the carbazole derivatives **11** and **12**, respectively. These carbazoles were transformed to the corresponding carbazole-1,4-quinones **9** and **10** by oxidation with cerium(IV) ammonium nitrate. Finally, regioselective addition of methyllithium at C–1 provided carbazomycin G (**7**) and carbazomycin H (**8**).

Introduction

The carbazomycin alkaloids **1**–**8** were first isolated by Nakamura and his group from *Streptoverticillium ehimense* H 1051-MY 10 (Scheme 1).[2] They described the structural elucidation and biogenesis of these alkaloids, which represent an unprecedented class of antibiotics with a carbazole framework.[2] The biogenesis of the carbazomycins, which are derived from tryptophan, was found to be quite different from that of previous carbazole alkaloids, mainly isolated from terrestrial plants.[2d] Marumo reported the isolation of carbazomycin E (carbazomycinal; **5**) and carbazomycin F (6-methoxycarbazomycinal; **6**) from the *Streptoverticillium* species KCC U-0166.[2e] The same alkaloids were obtained by Nakamura from *Streptoverticillium ehimense*, along with carbazomycin C (**3**) and carbazomycin D (**4**).[2f] Carbazomycin A (**1**) and carbazomycin B (**2**) inhibit the growth of phytopathogenic fungi and show antibacterial and antiyeast activities.[2a] Compounds **2** and **3** have been found to inhibit 5-lipoxygenase.[3] Carbazomycin G (**7**) exhibits antifungal activity against *Trichophyton* species.[2g] The unique structural feature of **7** and **8** is the quinol of ring A. Although **7** has a stereogenic center at C-1, it shows no optical rotation and crystallizes in the space group $P2_1/a$. Both observations led to the conclusion that **7** exists as a racemate in nature.[2g] The same can be assumed for natural **8**.



1 Carbazomycin A (R = H; R^1 = Me)
2 Carbazomycin B (R, R^1 = H)
3 Carbazomycin C (R = OMe; R^1 = H)
4 Carbazomycin D (R = OMe; R^1 = Me)
5 Carbazomycin E (R = H)
6 Carbazomycin F (R = OMe)
7 Carbazomycin G (R = H)
8 Carbazomycin H (R = OMe)

Scheme 1

The carbazomycins exhibit an unusually congested substitution pattern, which initiated the development of novel synthetic routes to carbazoles.[4] The challenging structures of the carbazomycins and their promising biological activities, have prompted several groups to investigate strategies for the total synthesis of these compounds.[5–10] Our approach is based on an iron-mediated construction of the carbazole ring system via consecutive C–C and C–N bond formation. This methodology has been applied to the total synthesis of the carbazomycins A, B,[5a–5d] C, D,[6] E,[7] G, H[8] and a broad variety of further carbazole alkaloids.[11] In addition to the iron-mediated synthesis,[8] we have developed a palladium-catalyzed approach for the total synthesis of the carbazomycins G and H.[9] A third total synthesis of carbazomycin G was reported more recently by Hibino.[10] In the present paper we describe full details of the iron-mediated synthesis of carbazomycins G and H.

Synthetic Plan

Retrosynthetic analysis of **7** and **8**, based on the iron-mediated construction of the carbazole nucleus, led us to

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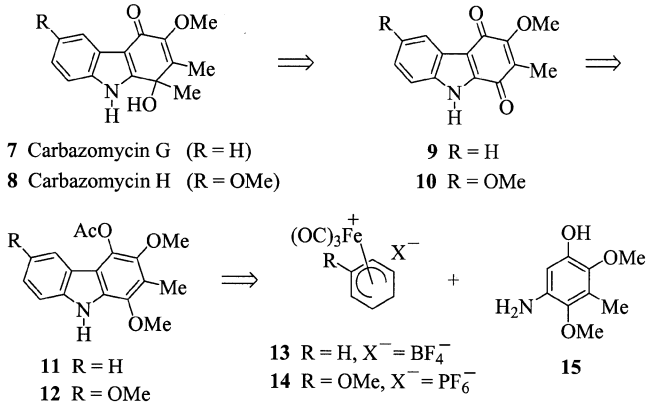


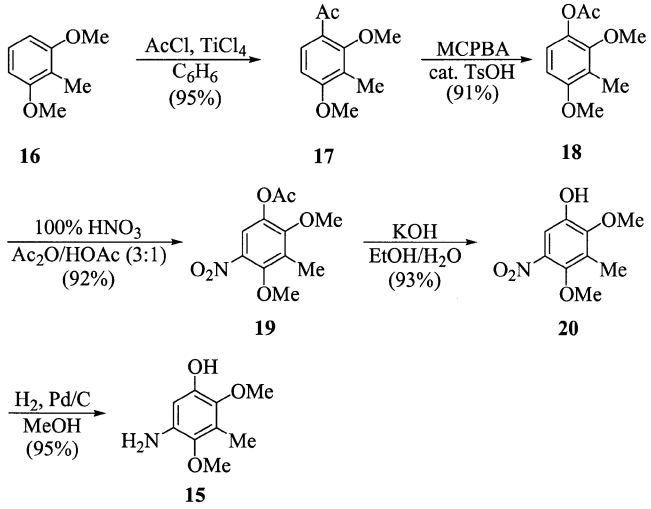
Scheme 2

the carbazole-1,4-quinones **9** and **10** as key intermediates (Scheme 2). Compounds **9** and **10** are accessible by oxidation of the carbazoles **11** and **12**, which can be prepared by coupling of the arylamine **15** with the iron complexes **13** and **14**, respectively.[8] Alternatively, **9** and **10** can be provided by a palladium-catalyzed oxidative cyclization of the corresponding arylaminobenzo-1,4-quinones.[9]

The iron complex **13** can be prepared quantitatively on a large scale by 1-azabutadiene-catalyzed complexation of cyclohexa-1,3-diene with pentacarbonyliron[12] and subsequent hydride abstraction using triphenylcarbenium tetrafluoroborate.[13] Complex **14** was prepared in three steps from 1,3-dimethoxybenzene, following the procedure described by Birch.[14]

Synthesis of the Arylamine Precursor

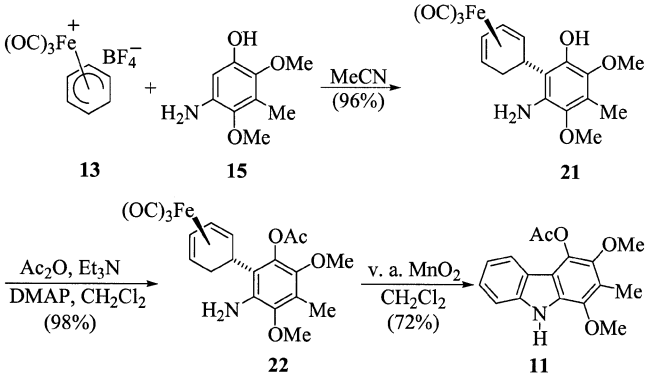
The synthesis of the arylamine **15** starts from commercially available 2,6-dimethoxytoluene **16** (Scheme 3). Friedel–Crafts acylation of **16**, promoted by titanium tetrachloride, provided the acetophenone **17**. This compound was transformed into the aryl acetate **18** by a proton-catalyzed Baeyer–Villiger oxidation. Regioselective nitration of **18** with fuming nitric acid in a 3:1 mixture of acetic anhydride and glacial acetic acid afforded the desired nitro derivative **19** in 92% yield. Our earlier studies demonstrated that 5-hydroxyanilines provide high yields in electrophilic aromatic substitutions with tricarbonyliron-complexed cyclohexadienyl cations.[5a–5c,6] Therefore, we first cleaved the acetate of compound **19** with potassium hydroxide in aqueous ethanol to give the nitrophenol **20**. Subsequent hydrogenation with palladium on activated carbon led to the arylamine **15**.[15] The present sequence provides **15** on a multigram scale in five steps. The overall yield is 70%, based on **16**.



Scheme 3

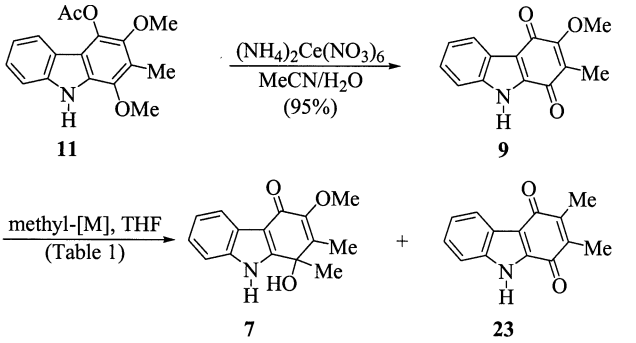
Synthesis of Carbazomycin G (7)

Reaction of the iron complex **13** with two equivalents of **15** in acetonitrile at room temperature provided the iron complex **21** in 96% yield (Scheme 4). From previous results we knew that the free hydroxy group of compound **21** had to be protected prior to the iron-mediated arylamine cyclization.[5b,5c] This was achieved by chemoselective *O*-acetylation to the corresponding acetate **22**. The iron-mediated arylamine cyclization of **22** with very active manganese dioxide[16] in dichloromethane at room temperature afforded the carbazole **11** in 72% yield.



Scheme 4

Oxidation of **11** with ceric(IV) ammonium nitrate gave the carbazole-1,4-quinone **9** in 95% yield (Scheme 5). The important final step for the synthesis of **7** was the regioselective introduction of the methyl group at C-1. In the total synthesis of carbazoquinocin C the introduction of a heptyl side chain to **9** led, depending on the reaction conditions,



Scheme 5

Table 1. Addition of methylmetal reagents to the carbazole-1,4-quinone **9**

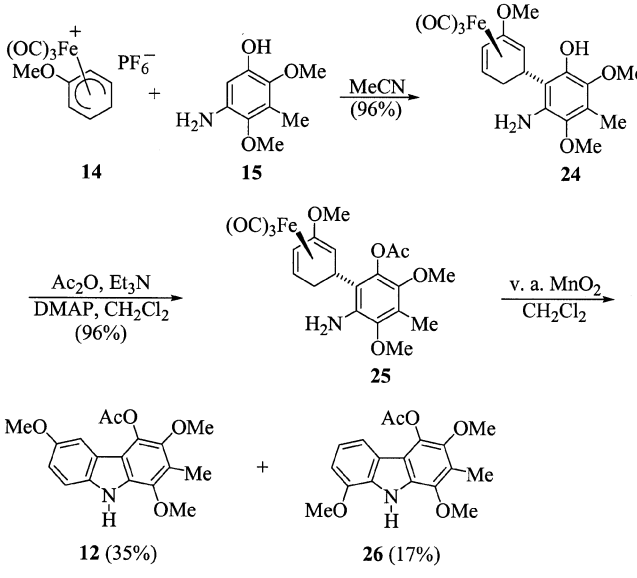
Methyl-[M] (equiv.)	Reaction conditions	**7**, yield (%)	**23**, yield (%)
MeMgCl (7.5)	−78 °C, 4.5 h	18	5
MeMgCl (12.5)	−78 °C, 2.5 h	30	25
MeMgCl (10.0)	−78 °C, 4.5 h	36	17
MeLi (5.0)	−78 °C, 6 h	50	27
MeLi (7.5)	−78 °C, 3 h	54	19
MeLi (10.0)	−78 °C, 2.5 h	59	27
MeLi (10.0)	−78 °C, 5 h; room temp., 12 h	69	17
MeLi (4.6)	−78 °C, 15 min; room temp., 30 min	71	12

to all three possible regioisomeric products, by 1,2-addition at C-1, 1,4-addition at C-3 followed by elimination of the methoxy group, or 1,2-addition at C-4.[17] Addition of 7.5 equivalents of methylmagnesium chloride to **9** in tetrahydrofuran at −78 °C provided **7** (the product of 1,2-addition at C-1) along with 2,3-dimethylcarbazole-1,4-quinone (**23**; the product of 1,4-addition at C-3 followed by elimination of the methoxy group) as a by-product. The regioisomeric carbazolequinol resulting from 1,2-addition at C-4 was not detected. Increasing the equivalents of the Grignard reagent led to an increase in the yields of both products, with a maximum yield of 36% of **7** (Table 1). However, use of methyllithium afforded significantly higher yields of **7**. Using optimized reaction conditions, **7** was obtained in 71% yield along with 12% of **23** (Table 1). This route leads to **7** in five steps with an overall yield of 46%, based on the iron complex **13**.

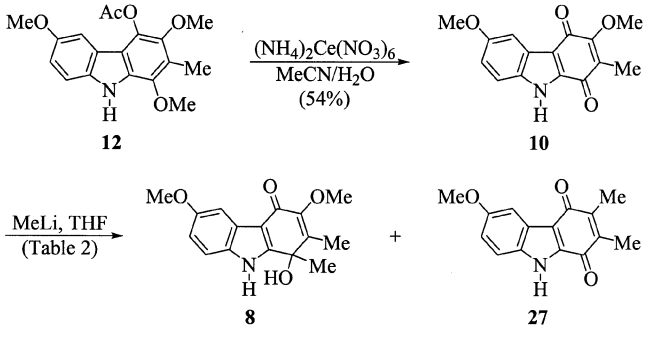
Synthesis of Carbazomycin H (8)

Electrophilic substitution of the arylamine **15**, by reaction with the iron complex **14** in acetonitrile at room temperature, afforded the iron complex **24** (Scheme 6). Subsequent *O*-acetylation provided the corresponding acetate **25**. For the total synthesis of **8**, the iron complex **25**, which has a 3-methoxycyclohexadiene ligand, had to be cyclized regioselectively. Previous studies with deuterium-labelled cyclohexadiene ligands have shown that cyclizations by two-electron oxidants (such as manganese dioxide) initially lead to the product resulting exclusively from attack at C-4 of the cyclohexadiene ligand.[18] In the present example, this regioselectivity would provide the undesired 8-methoxycarbazole **26**. However, a proton-catalyzed rearrangement to a 6-methoxycarbazole can occur at the stage of the tricarbonyl(η^4-4a,9a-dihydrocarbazole)iron complex.[6,18] The driving force behind this isomerization is the well-established regiodirecting effect of the 2-methoxy substituent of the intermediate tricarbonyl(η^5-2-methoxycyclohexadienyl)-iron cation.[19] The regiodirecting effect causes a preferential attack of the incoming amino group at the 5-position of the ligand (*para* to the methoxy group). Dehydrogenation of the thermodynamic product by manganese dioxide provides the desired 6-methoxycarbazole **12**.[20] This regiocontrol has been efficiently utilized for our syntheses of 4-deoxycarbazomycin C, carbazomycin C (**3**), and carbazomycin D (**4**).[6] In the present case, however, the dehydrogenation to the 8-methoxycarbazole **26** at the kinetic product stage can obviously compete with the proton-catalyzed rearrangement, thus leading to a 2:1 ratio of the 6-methoxycarbazole **12** and 8-methoxycarbazole **26**.

Oxidation of **12** with ceric(IV) ammonium nitrate afforded the carbazole-1,4-quinone **10**, which is the direct synthetic precursor of **8** (Scheme 7). The final step for transformation of **10** to **8** was, again, the regioselective introduction of the methyl group at C-1. Addition of an excess of methyllithium to **10** in tetrahydrofuran at −78 °C provided, after some optimization, a best yield of 42% for



Scheme 6



Scheme 7

Table 2. Addition of methyllithium to the carbazole-1,4-quinone **10**

MeLi (equiv.)	Reaction conditions	**8**, yield (%)	**27**, yield (%)
10.0	−78 °C, 2.5 h	20	22
10.0	−78 °C, 5 h; room temp., 16 h	42	5
7.5	−78 °C, 2 h	35	32
5.0	−78 °C, 6 h	42	14

8 (the product of 1,2-addition at C-1), along with 14% of 6-methoxy-2,3-dimethylcarbazole-1,4-quinone (**27**; the product of 1,4-addition at C-3 followed by elimination; Table 2). The regioisomeric carbazolequinol formed by 1,2-addition at C-4 could not be isolated. The present synthesis provides **8** in five steps with an overall yield of 7%, based on the iron complex **14**.

Experimental Section

General: All reactions were carried out using dry solvents and under an argon atmosphere, unless otherwise stated. Flash chromatography: Merck silica gel (0.03−0.06 mm). M.p.: Büchi 535. UV spectra: Perkin−Elmer Lambda 2 (UV/Vis spectrometer). IR spectra: Bruker IFS 88 (FT-IR). ^{1}H NMR and ^{13}C NMR spectra: Bruker AM-400 and Bruker DRX-500; internal standard: TMS or the signal of the deuterated solvent; δ in ppm; coupling constants (*J*) in Hz. MS: Finnigan MAT-90; ionization potential: 70 eV. Elemental analyses: Heraeus CHN-Rapid.

1-(2,4-Dimethoxy-3-methylphenyl)ethanone (17): For synthesis and spectroscopic data, see ref.[17b]

2,4-Dimethoxy-3-methylphenyl Acetate (18): For synthesis and spectroscopic data, see ref.[17b]

2,4-Dimethoxy-3-methyl-5-nitrophenyl Acetate (19): A solution of HNO_3 (100%, 0.87 mL, 21 mmol) in HOAc/Ac_2O (1:3, 4 mL) was added to a solution of **18** (2.20 g, 10.5 mmol) in HOAc/Ac_2O (1:3, 12 mL) at 0 °C, with vigorous stirring, over a period of 45 min. After the addition was complete, the reaction mixture was quenched with ice-water (20 mL). On cooling, a concentrated aqueous solution of NH_3 (20 mL) was added portionwise. The aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (2 × 20 mL), then washed with H_2O (20 mL) and dried over sodium sulfate. Evaporation of the solvent and flash chromatography (hexane/EtOAc, 4:1) of the residue on silica gel gave an orange oil, which crystallized on addition of pentane. Recrystallization from MeOH provided **19** as light yellow crystals. Yield: 2.44 g (92%), m.p. 44 °C (MeOH). UV (MeOH): λ = 194, 212 (sh), 275 nm. IR (drift): ṽ = 3109, 2950, 1762, 1583, 1530, 1476, 1418, 1349, 1306, 1245, 1207, 1113, 1046, 991, 893, 787 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 (s, 3 H), 2.36 (s, 3 H), 3.85 (s, 3 H), 3.90 (s, 3 H), 7.56 (s, 1 H) ppm. ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 9.93 (CH_3), 20.58 (CH_3), 60.87 (CH_3), 61.99 (CH_3), 117.97 (CH), 128.91 (C), 138.76 (C), 138.98 (C), 151.18 (C), 155.13 (C), 168.61 (C=O) ppm. MS (36 °C): *m*/*z* (%) = 255 (10) [M$^+$], 213 (100), 166 (7), 43 (18). HRMS ($C_{11}H_{13}NO_6$): calcd. 255.0743; found 255.0752. $C_{11}H_{13}NO_6$ (255.23): calcd. C 51.76, H 5.13, N 5.49; found C 51.65, H 5.07, N 5.69.

2,4-Dimethoxy-3-methyl-5-nitrophenol (20): A solution of KOH (4.10 g, 89 mmol) in H_2O (5 mL) was added at room temperature to a stirred solution of **19** (5.65 g, 22.1 mmol) in EtOH (50 mL). On moderate warming, a dark red solution was formed. This solution was stirred at room temperature for 2 h. The EtOH was evaporated in vacuo and H_2O (100 mL) was added. The aqueous layer was washed with Et_2O (2 × 20 mL). The solution of the phenolate was acidified with conc. HCl (5 mL) and extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with H_2O (100 mL) and dried over sodium sulfate. Removal of the solvent gave an orange oil, which crystallized on addition of pentane. Recrystallization from CCl_4 gave **20** as yellow crystals. Yield: 4.40 g (93%), m.p. 64 °C (CCl_4). UV (MeOH): λ = 195, 213 (sh), 245, 285, 342 nm. IR (drift): ṽ = 3419 (br), 2937, 1586, 1507, 1347, 1333, 1265, 1237, 1116, 1045, 991, 772 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 3.859 (s, 3 H), 3.863 (s, 3 H), 6.09 (br. s, 1 H), 7.35 (s, 1 H) ppm. ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 10.00 (CH_3), 61.03 (CH_3), 62.15 (CH_3), 109.47 (CH), 127.53 (C), 139.94 (C), 145.10 (C), 146.34 (C), 150.25 (C) ppm. MS (55 °C): *m*/*z* (%) = 213 (100) [M$^+$], 166 (12), 152 (12), 137 (14), 125 (11), 122 (9), 109 (7). HRMS ($C_9H_{11}NO_5$): calcd. 213.0637; found 213.0627. $C_9H_{11}NO_5$ (213.20): calcd. C 50.70, H 5.20, N 6.57; found C 50.70, H 5.11, N 6.62.

5-Amino-2,4-dimethoxy-3-methylphenol (15): Palladium on carbon (10%, 250 mg) was added to a solution of **20** (2.51 g, 11.8 mmol) in MeOH (25 mL). This mixture was vigorously stirred under a hydrogen atmosphere (800−900 Torr) at room temperature until no further hydrogen uptake was detected (2.5 h). Evaporation of the solvent in vacuo and flash chromatography (hexane/EtOAc, 2:1) of the residue on silica gel afforded a light red solid, which was recrystallized from hexane/EtOAc (5:1) to give **15** as light red crystals. Yield: 2.04 g (95%), m.p. 102−103 °C (hexane/EtOAc, dec.). UV (MeOH): λ = 203, 232 (sh), 292 nm. IR (drift): ṽ = 3388, 3304, 2934 (br), 1593, 1517, 1464, 1430, 1364, 1271, 1240, 1219, 1123, 1059, 990, 834 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.04 (s, 3 H), 3.52 (s, 3 H), 3.55 (s, 3 H), 4.45 (br. s, 2 H), 6.08 (s, 1 H), 8.51 (s, 1 H) ppm. ^{13}C NMR and DEPT (100 MHz, [D$_6$]DMSO): δ = 9.18 (CH_3), 58.67 (CH_3), 59.56 (CH_3), 100.31 (CH), 123.38 (C), 136.20 (C), 136.92 (C), 136.96 (C), 146.10 (C) ppm. MS (30 °C): *m*/*z* (%) = 183 (54) [M$^+$], 168 (100), 153 (21), 140 (9), 125 (14). HRMS ($C_9H_{13}NO_3$): calcd. 183.0895; found 183.0880. $C_9H_{13}NO_3$ (183.21): calcd. C 59.00, H 7.15, N 7.65; found C 59.00, H 7.16, N 7.73.

[(1-4-η)-5-(2-Amino-6-hydroxy-3,5-dimethoxy-4-methylphenyl)-cyclohexa-1,3-diene]tricarbonyliron (21): A solution of **15** (445 mg, 2.43 mmol) and tricarbonyl(η^5-cyclohexadienylium)iron tetrafluoroborate (**13**; 370 mg, 1.21 mmol) in degassed acetonitrile (20 mL) was stirred for 2 days at room temperature in the absence of light. Removal of the solvent and flash chromatography (hexane/EtOAc, 2:1) of the residue on silica gel gave **21** as a light yellow solid. Yield: 468 mg (96%), m.p. 168−170 °C (dec.). UV (MeOH): λ = 205, 225 (sh), 292 nm. IR (drift): ṽ = 3443, 3345, 2040, 1967,

1459, 1420, 1060, 981, 857, 622 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 1.92 (m, 2 H), 2.05 (s, 3 H), 3.05 (dd, *J* = 5.4, 2.5 Hz, 1 H), 3.33 (m, 1 H), 3.51 (s, 3 H), 3.52 (s, 3 H), 3.87 (m, 1 H), 4.07 (br. s, 2 H), 5.61 (m, 1 H), 5.75 (m, 1 H), 8.15 (s, 1 H) ppm. ^{13}C NMR and DEPT (100 MHz, [D_6]DMSO): δ = 9.14 (CH_3), 25.65 (CH_2), 34.01 (CH), 58.96 (CH_3), 60.12 (CH_3), 61.82 (CH), 66.43 (CH), 84.84 (CH), 85.81 (CH), 112.83 (C), 120.99 (C), 134.66 (C), 137.05 (C), 137.80 (C), 143.99 (C), 212.74 (3 CO) ppm. MS (100 °C): *m*/*z* (%) = 401 (22) [M^+], 373 (12), 345 (26), 317 (88), 315 (100), 302 (17), 285 (19), 284 (19), 261 (12), 259 (11), 246 (10), 244 (21), 224 (29), 223 (37), 208 (45), 168 (10). HRMS ($C_{18}H_{19}FeNO_6$): calcd. 401.0562; found 401.0544. $C_{18}H_{19}FeNO_6$ (401.21): calcd. C 53.89, H 4.77, N 3.49; found C 54.04, H 4.73, N 3.53.

[(1-4-η)-5-(2-Acetoxy-6-amino-3,5-dimethoxy-4-methylphenyl)-cyclohexa-1,3-diene]tricarbonyliron (22): A solution of acetic anhydride (180 mg, 1.73 mmol) and triethylamine (180 mg, 1.79 mmol) in degassed dichloromethane (15 mL) was added to a mixture of **21** (650 mg, 1.62 mmol) and DMAP (20 mg). The orange solution was stirred at room temperature for 4 h, then heated at reflux for a short period. Evaporation of the solvent in vacuo and flash chromatography (hexane/EtOAc, 2:1) of the residue on silica gel afforded a light yellow oil. This oil became solid in Et_2O to give **22** as a light yellow solid. Yield: 707 mg (98%), m.p. 50−60 °C. UV (MeOH): λ = 204, 224 (sh), 297 nm. IR (drift): $\tilde{\nu}$ = 3464, 3378, 2940, 2044, 1968, 1760, 1462, 1417, 1370, 1343, 1264, 1203, 1118, 1058, 1011, 622 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.87−1.91 (m, 1 H), 1.98−2.05 (m, 1 H), 2.18 (s, 3 H), 2.38 (s, 3 H), 2.99 (m, 1 H), 3.24 (m, 1 H), 3.60−3.63 (m, 1 H), 3.64 (s, 3 H), 3.70 (s, 3 H), 3.87 (br. s, 2 H), 5.46 (m, 1 H), 5.54 (m, 1 H) ppm. ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 9.49 (CH_3), 20.66 (CH_3), 25.07 (CH_2), 35.99 (CH), 59.34 (CH_3), 60.47 (CH), 60.80 (CH_3), 64.14 (CH), 83.96 (CH), 85.81 (CH), 118.31 (C), 123.58 (C), 134.45 (C), 139.04 (C), 141.96 (C), 143.75 (C), 169.63 (C=O), 211.67 (3 CO) ppm. MS (90 °C): *m*/*z* (%) = 443 (23) [M^+], 415 (14), 387 (33), 359 (100), 357 (19), 344 (87), 331 (11), 329 (12), 316 (16), 314 (13), 284 (36), 281 (41), 266 (30), 251 (13), 244 (10), 238 (22), 208 (23), 150 (23). HRMS ($C_{20}H_{21}FeNO_7$): calcd. 443.0667; found 443.0687. $C_{20}H_{21}FeNO_7$ (443.25): calcd. C 54.20, H 4.78, N 3.16; found C 54.36, H 4.86, N 3.24.

4-Acetoxy-1,3-dimethoxy-2-methyl-9*H*-carbazole (11): Alox B "Super 1" (ICN, 1.75 g) and very active manganese dioxide (3.50 g) were added to a solution of **22** (387 mg, 873 μmol) in degassed dichloromethane (25 mL). The heterogeneous reaction mixture was vigorously stirred for 2 h at room temperature. The mixture was filtered through a short length of Celite. The Celite was subsequently washed, first with CH_2Cl_2 (150 mL) and then with CH_2Cl_2/Et_2O (10:1, 150 mL). The solvent was removed from the combined filtrates and the residue was subjected to flash chromatography (hexane/EtOAc, 2:1) on silica gel to provide **11** as a colorless oil. Crystallization from hexane/EtOAc (4:1) at −30 °C provided **11** as colorless crystals. Yield: 188 mg (72%), m.p. 133−135 °C (hexane/EtOAc). UV (MeOH): λ = 223 (sh), 239, 247 (sh), 258 (sh), 282 (sh), 290, 325, 338 nm. IR (drift): $\tilde{\nu}$ = 3399, 2991, 2961, 2936, 1753, 1612, 1504, 1455, 1412, 1385, 1370, 1320, 1291, 1216, 1167, 1125, 1110, 1073, 1022, 1010, 922, 888, 754, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3 H), 2.53 (s, 3 H), 3.815 (s, 3 H), 3.822 (s, 3 H), 7.16 (dt, *J* = 1.3, 7.3 Hz, 1 H), 7.29−7.36 (m, 2 H), 7.86 (d, *J* = 7.8 Hz, 1 H), 8.29 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 9.86 (CH_3), 20.85 (CH_3), 60.58 (CH_3), 61.21 (CH_3), 110.90 (CH), 115.44 (C), 119.55 (CH), 121.43 (CH), 121.90 (C), 122.47 (C), 125.82 (CH), 130.49 (C), 134.47 (C), 139.59 (C), 140.83 (C), 143.52 (C), 169.18 (C=O) ppm. MS (100 °C): *m*/*z* (%) = 299 (29) [M^+], 257 (52), 256 (14), 242 (100), 226 (10), 213 (13), 198 (11), 170 (13). HRMS ($C_{17}H_{17}NO_4$): calcd. 299.1158; found 299.1167. $C_{17}H_{17}NO_4$ (299.33): calcd. C 68.22, H 5.72, N 4.68; found C 68.03, H 5.85, N 4.55.

3-Methoxy-2-methyl-9*H*-carbazole-1,4-quinone (9): A solution of ceric(IV) ammonium nitrate (650 mg, 1.19 mmol) in H_2O (5 mL) was added dropwise over a period of 1 h to a vigorously stirred solution of **11** (118 mg, 394 μmol) in acetonitrile (5 mL) at 0 °C. A dark green precipitate was formed. Ice-water (10 mL) was added and stirring was continued for 1 h at 0 °C. The precipitate was isolated by filtration, washed with a large volume of H_2O, and dried in vacuo to give the product **9** as a dark green solid. Recrystallization from EtOAc gave **9** as dark green crystals. Yield: 90 mg (95%), m.p. 248−256 °C (EtOAc, dec.). For spectral data, see ref.[17b]

Carbazomycin G (1,4-Dihydro-1-hydroxy-3-methoxy-1,2-dimethyl-9*H*-carbazol-4-one; 7) and 2,3-Dimethyl-9*H*-carbazole-1,4-quinone (23): A solution of methyllithium in Et_2O (1.6 M, 0.25 mL, 0.4 mmol) was added dropwise to a solution of **9** (21 mg, 87 μmol) in degassed THF (10 mL) at −78 °C. The reaction mixture was warmed to room temperature over a period of 30 min, then quenched with a 10% aqueous solution of ammonium chloride (10 mL). The aqueous layer was extracted with ethyl acetate (10 mL) and the combined organic layers were dried over sodium sulfate. The solvent was removed in vacuo. Flash chromatography (hexane/EtOAc, 1:2) of the residue on silica gel provided **23** as the less polar fraction and **7** as the more polar fraction. Compound **7** was recrystallized from ethanol.

7: Light yellow crystals. Yield: 16 mg (71%), m.p. 266−268 °C (EtOH, dec.) (ref.[2g] 241−243 °C; ref.[10] 266−268 °C from EtOAc). UV (MeOH): λ (ε) = 212 (39600), 251 (20200), 270 (sh, 8500), 277 (7300), 340 (5800) nm. IR (drift): $\tilde{\nu}$ = 3209 br, 1643, 1620, 1611, 1482, 1453, 1401, 1377, 1317, 1292, 1189, 1150, 1093, 1012, 962, 925, 879, 807, 750 cm^{-1}. ^1H NMR (500 MHz, [D_6]DMSO): δ = 1.57 (s, 3 H), 1.98 (s, 3 H), 3.68 (s, 3 H), 5.93 (s, 1 H), 7.15−7.23 (m, 2 H), 7.44 (dd, *J* = 7.8, 0.8 Hz, 1 H), 8.01 (d, *J* = 7.8 Hz, 1 H), 12.21 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, [D_6]DMSO): δ = 10.19 (CH_3), 27.89 (CH_3), 59.26 (CH_3), 67.30 (C), 108.42 (C), 112.05 (CH), 120.47 (CH), 121.51 (CH), 122.98 (CH), 123.79 (C), 136.46 (C), 140.82 (C), 147.61 (C), 154.32 (C), 177.51 (C=O) ppm. MS (160 °C): *m*/*z* (%) = 257 (100) [M^+], 242 (77), 241 (17), 240 (46), 239 (28), 238 (12), 226 (25), 225 (21), 224 (13), 214 (28), 210 (14), 199 (36), 198 (20), 197 (24), 196 (16). HRMS ($C_{15}H_{15}NO_3$): calcd. 257.1052; found 257.1062. $C_{15}H_{15}NO_3$ (257.30): calcd. C 70.02, H 5.88, N 5.45; found C 70.27, H 6.06, N 5.27.

23: Red crystals. Yield: 2.4 mg (12%), m.p. 276−278 °C (hexane/EtOAc). UV (MeOH): λ = 224, 256, 264 (sh), 293, 382 nm. IR (drift): $\tilde{\nu}$ = 3212, 1658, 1632, 1603, 1541, 1471, 1405, 1385, 1328, 1237, 1053, 756, 747, 687 cm^{-1}. ^1H NMR (500 MHz, [D_6]DMSO) = 1.99 (s, 3 H), 2.01 (s, 3 H), 7.28 (br. t, *J* = 7.5 Hz, 1 H), 7.35 (br. t, *J* = 7.5 Hz, 1 H), 7.50 (d, *J* = 8.2 Hz, 1 H), 8.0 (d, *J* = 8.0 Hz, 1 H), 12.75 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, [D_6]DMSO): 11.78 (CH_3), 12.24 (CH_3), 113.74 (CH), 115.10 (C), 121.71 (CH), 123.58 (C), 123.63 (CH), 126.09 (CH), 135.63 (C), 137.54 (C), 138.52 (C), 142.00 (C), 179.90 (C=O), 182.76 (C=O) ppm. MS (130 °C): *m*/*z* (%) = 225 (100) [M^+], 197 (28), 196 (18), 168 (12), 143 (12), 115 (20). HRMS ($C_{14}H_{11}NO_2$): calcd. 225.0790; found 225.0773.

[(1-4-η)-6-(2-Amino-6-hydroxy-3,5-dimethoxy-4-methylphenyl)-2-methoxycyclohexa-1,3-diene]tricarbonyliron (24): A solution of **15**

(1.143 g, 6.24 mmol) and tricarbonyl(η^5-3-methoxycyclohexadienylium)iron hexafluorophosphate **14** (1.23 g, 3.12 mmol) in degassed acetonitrile (40 mL) was stirred at room temperature for 3.5 h, then heated at reflux for a short time. The acetonitrile was evaporated and the residue was subjected to flash chromatography (hexane/EtOAc, 2:1) on silica gel. After removal of the solvent, the solid was washed twice with boiling Et_2O (5 mL) to afford **24** as a light yellow solid. Yield: 1.29 g (96%), m.p. 194−195 °C (dec.). UV (MeOH): λ = 204, 225 (sh), 293 nm. IR (drift): ṽ = 3475, 3388, 2933, 2046, 1955, 1628, 1605, 1490, 1463, 1426, 1415, 1347, 1316, 1259, 1224, 1065, 1000, 629 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 1.78−1.82 (m, 2 H), 2.04 (s, 3 H), 2.88 (m, 1 H), 3.21 (m, 1 H), 3.50 (s, 3 H), 3.52 (s, 3 H), 3.56 (s, 3 H), 3.67 (m, 1 H), 4.09 (br. s, 2 H), 5.63 (m, 1 H), 8.13 (s, 1 H) ppm. ^{13}C NMR and DEPT (100 MHz, [D$_6$]DMSO): δ = 9.19 (CH_3), 26.61 (CH_2), 35.90 (CH), 50.50 (CH), 54.56 (CH_3), 58.17 (CH), 59.06 (CH_3), 60.17 (CH_3), 67.98 (CH), 113.50 (C), 121.02 (C), 134.84 (C), 137.18 (C), 137.98 (C), 140.35 (C), 144.27 (C), 212.29 (3 CO) ppm. MS (115 °C): *m*/*z* (%) = 431 (4) [M^+], 403 (3), 375 (64), 347 (100), 345 (74), 332 (26), 315 (10), 300 (15), 224 (21), 223 (28), 208 (31). HRMS ($C_{19}H_{21}FeNO_7$): calcd. 431.0667; found 431.0654. $C_{19}H_{21}FeNO_7$ (431.23): calcd. C 52.92, H 4.91, N 3.25; found C 52.93, H 4.96, N 3.41.

[(1-4-η)-6-(2-Acetoxy-6-amino-3,5-dimethoxy-4-methylphenyl)-2-methoxycyclohexa-1,3-diene]tricarbonyliron (25): A solution of acetic anhydride (122 mg, 1.2 mmol) and triethylamine (121 mg, 1.2 mmol) in degassed dichloromethane (30 mL) was added to a mixture of the iron complex **24** (435 mg, 1.01 mmol) and DMAP (30 mg). The orange solution was stirred at room temperature for 24 h, then the solvent was removed in vacuo. Flash chromatography (hexane/EtOAc, 2:1) of the residue on silica gel gave a light yellow oil. This oil became solid in Et_2O to give **25** as a light yellow solid. Yield: 460 mg (96%), m.p. 53−63 °C (dec.). UV (MeOH): λ = 202, 225 (sh), 297 nm. IR (drift): ṽ = 3480, 3381, 2939, 2042, 1962, 1760, 1619, 1484, 1462, 1424, 1206, 1014, 623 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.70 (br. d, *J* = 15.1 Hz, 1 H), 1.88 (ddd, *J* = 15.1, 11.0, 4.1 Hz, 1 H), 2.17 (s, 3 H), 2.37 (s, 3 H), 2.80 (ddd, *J* = 6.3, 4.1, 2.0 Hz, 1 H), 3.31 (t, *J* = 2.5 Hz, 1 H), 3.54−3.58 (m, 1 H), 3.59 (s, 3 H), 3.64 (s, 3 H), 3.69 (s, 3 H), 3.81 (br. s, 2 H), 5.35 (dd, *J* = 6.6, 2.0 Hz, 1 H) ppm. ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 9.50 (CH_3), 20.61 (CH_3), 25.81 (CH_2), 37.49 (CH), 48.72 (CH), 54.67 (CH_3), 56.63 (CH), 59.36 (CH_3), 60.77 (CH_3), 67.33 (CH), 118.85 (C), 123.56 (C), 134.44 (C), 139.04 (C), 140.48 (C), 141.99 (C), 143.90 (C), 169.54 (C=O), 211.11 (3 CO) ppm. MS (105 °C): *m*/*z* (%) = 473 (6) [M^+], 445 (4), 417 (73), 389 (88), 387 (10), 374 (100), 359 (15), 346 (18), 314 (23), 281 (44), 266 (22), 228 (19). HRMS ($C_{21}H_{23}FeNO_8$): calcd. 473.0773; found 473.0762. $C_{21}H_{23}FeNO_8$ (473.27): calcd. C 53.30, H 4.90, N 2.96; found C 53.30, H 4.90, N 2.95.

4-Acetoxy-1,3,6-trimethoxy-2-methyl-9*H*-carbazole (12) and 4-Acetoxy-1,3,8-trimethoxy-2-methyl-9*H*-carbazole (26): Alox B "Super 1" (ICN, 470 mg) and very active manganese dioxide (3.53 g) were added to a solution of **25** (235 mg, 0.497 mmol) in degassed dichloromethane (30 mL). The heterogeneous reaction mixture was stirred vigorously for 45 min at room temperature. The mixture was filtered through a short length of Celite, which was subsequently washed with CH_2Cl_2 (300 mL). The solvent was evaporated from the combined organic filtrates. Flash chromatography (CH_2Cl_2/Et_2O, 10:1) of the residue on silica gel gave **26** as the less polar fraction and **12** as the more polar fraction. Both carbazoles were recrystallized at −30 °C from hexane/EtOAc (4:1).

12: Light yellow crystals. Yield: 57 mg (35%), m.p. 113−114 °C (hexane/EtOAc). UV (MeOH): λ = 230, 243, 253 (sh), 263 (sh), 288 (sh), 298, 339, 353 nm. IR (drift): ṽ = 3378, 3004, 2939, 2835, 1750, 1576, 1507, 1488, 1467, 1435, 1409, 1376, 1308, 1269, 1217, 1178, 1127, 1112, 1014, 908, 801, 775, 603 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 2.51 (s, 3 H), 3.77 (s, 3 H), 3.81 (s, 3 H), 3.86 (s, 3 H), 6.96 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.14 (d, *J* = 8.8 Hz, 1 H), 7.36 (d, *J* = 2.5 Hz, 1 H), 8.31 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 9.82 (CH_3), 20.78 (CH_3), 55.93 (CH_3), 60.42 (CH_3), 61.20 (CH_3), 104.76 (CH), 111.54 (CH), 114.46 (CH), 115.32 (C), 122.30 (C), 122.38 (C), 131.38 (C), 134.32 (C), 134.69 (C), 140.90 (C), 143.12 (C), 153.54 (C), 169.22 (C=O) ppm. MS (95 °C): *m*/*z* (%) = 329 (52) [M^+], 287 (66), 272 (100), 257 (6). HRMS ($C_{18}H_{19}NO_5$): calcd. 329.1263; found 329.1273. $C_{18}H_{19}NO_5$ (329.36): C 65.64, H 5.81, N 4.25; found C 65.59, H 5.84, N 4.46.

26: Light brown crystals. Yield: 28 mg (17%), m.p. 172−173 °C (hexane/EtOAc). UV (MeOH): λ = 228 (sh), 243, 251 (sh), 276, 286, 323, 337 nm. IR (drift): ṽ = 3376, 2947, 2842, 1757, 1578, 1499, 1434, 1410, 1303, 1268, 1250, 1214, 1127, 1073, 1016, 788, 736 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3 H), 2.52 (s, 3 H), 3.81 (s, 3 H), 3.90 (s, 3 H), 3.98 (s, 3 H), 6.87 (d, *J* = 7.9 Hz, 1 H), 7.11 (t, *J* = 7.9 Hz, 1 H), 7.47 (d, *J* = 7.9 Hz, 1 H), 8.44 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 9.86 (CH_3), 20.83 (CH_3), 55.49 (CH_3), 60.69 (CH_3), 61.19 (CH_3), 105.99 (CH), 113.99 (CH), 115.92 (C), 120.08 (CH), 122.42 (C), 122.91 (C), 129.89 (C), 130.30 (C), 134.42 (C), 141.17 (C), 143.62 (C), 145.68 (C), 169.02 (C=O) ppm. MS (95 °C): *m*/*z* (%) = 329 (54) [M^+], 287 (63), 286 (10), 272 (100). HRMS ($C_{18}H_{19}NO_5$): calcd. 329.1263; found 329.1257. $C_{18}H_{19}NO_5$ (329.36): calcd. C 65.64, H 5.81, N 4.25; found C 65.46, H 5.79, N 3.93.

3,6-Dimethoxy-2-methyl-9*H*-carbazole-1,4-quinone (10): A solution of ceric(IV) ammonium nitrate (449 mg, 0.82 mmol) in H_2O (5 mL) was added dropwise over 20 min to a vigorously stirred solution of **12** (90 mg, 0.273 mmol) in acetonitrile (5 mL) at 0 °C. A black precipitate formed during the addition. The reaction mixture was stirred for 40 min at 0 °C. Ice-water (15 mL) was added and stirring was continued for 30 min at 0 °C. The precipitate was isolated by filtration, washed with a large volume of H_2O, and dried in vacuo. The residual solid was dissolved in acetone (50 mL). Silica gel (3 g) was added and the solvent was removed in vacuo. The residue was subjected to flash chromatography (EtOAc/MeOH, 10:1) on silica gel. Evaporation of the solvent and recrystallization from THF at −30 °C provided **10** as black-green crystals. Yield: 40 mg (54%), m.p. 270−275 °C (THF, dec.). UV (MeOH): λ = 224, 260, 297, 309, 441 nm. IR (drift): ṽ = 3244, 2955, 1637, 1601, 1529, 1489, 1296, 1263, 1219, 1106, 1029, 835, 810, 753, 643 cm^{-1}. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 1.88 (s, 3 H), 3.80 (s, 3 H), 4.01 (s, 3 H), 6.97 (dd, *J* = 8.9, 2.6 Hz, 1 H), 7.38−7.41 (m, 2 H), 12.76 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, [D$_6$]DMSO): δ = 8.50 (CH_3), 55.33 (CH_3), 61.03 (CH_3), 101.47 (CH), 113.41 (C), 114.99 (CH), 117.18 (CH), 124.46 (C), 126.46 (C), 132.71 (C), 135.96 (C), 156.92 (C), 157.75 (C), 178.32 (C=O), 180.22 (C=O) ppm. MS (125 °C): *m*/*z* (%) = 271 (100) [M^+], 257 (56), 256 (40), 242 (14), 228 (16), 200 (12). HRMS ($C_{15}H_{13}NO_4$): calcd. 271.0845; found 271.0828. $C_{15}H_{13}NO_4$ (271.28): calcd. C 66.41, H 4.83, N 5.16; found C 65.97, H 5.00, N 4.77.

Carbazomycin H (1,4-Dihydro-1-hydroxy-3,6-dimethoxy-1,2-dimethyl-9*H*-carbazol-4-one; 8) and 6-Methoxy-2,3-dimethyl-9*H*-carbazole-1,4-quinone (27): A solution of methyllithium in cumene/THF (9:1; 1 M, 1.85 mL, 1.85 mmol) was added dropwise to a solution of **10** (100 mg, 0.37 mmol) in degassed THF (100 mL) at −78 °C. Stirring was continued for a further 6 h at −78 °C. The reaction mixture was quenched at −78 °C by addition of an aque-

ous solution of ammonium chloride (50 mL). The aqueous layer was extracted with EtOAc (4 × 50 mL). The combined organic layers were washed with H_2O (3 × 50 mL) and dried over sodium sulfate. Evaporation of the solvent and flash chromatography (hexane/EtOAc, 1:2) of the residue on silica gel provided **27** as the less polar fraction and **8** as the more polar fraction.

8: Light yellow crystals. Yield: 44.2 mg (42%), m.p. 208−209 °C (EtOAc, dec.) (ref.[2g] 228−230 °C). UV (MeOH): λ (ε) = 210 (33600), 253 (19400), 259 (sh, 17700), 293 (6600), 342 (6400) nm. IR (drift): $\tilde{\nu}$ = 3360 (sh), 3170, 2987, 2938, 1637, 1630, 1615, 1604 (sh), 1482, 1463, 1288, 1261, 1218, 1166, 1129, 1103, 1069, 1003, 980, 926, 909, 887, 848, 806, 769, 676 cm^{-1}. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 1.54 (s, 3 H), 1.96 (s, 3 H), 3.67 (s, 3 H), 3.78 (s, 3 H), 5.91 (s, 1 H), 6.83 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.32 (d, *J* = 8.8 Hz, 1 H), 7.50 (d, *J* = 2.5 Hz, 1 H), 12.08 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, [D$_6$]DMSO): δ = 10.18 (CH_3), 28.00 (CH_3), 55.28 (CH_3), 59.25 (CH_3), 67.32 (C), 102.39 (CH), 108.40 (C), 112.58 (CH), 112.80 (CH), 124.49 (C), 131.22 (C), 140.65 (C), 147.59 (C), 154 41 (C), 155.16 (C), 177.47 (C=O) ppm. MS (155 °C): *m*/*z* (%) = 287 (100) [M^+], 272 (74), 271 (18), 270 (21), 256 (28), 255 (14), 254 (11), 244 (20), 229 (27), 228 (19), 227 (17), 226 (13). HRMS ($C_{16}H_{17}NO_4$): calcd. 287.1158; found 287.1172. $C_{16}H_{17}NO_4$ (287.32): calcd. C 66.89, H 5.96, N 4.87; found C 66.40, H 6.15, N 4.22.

27: Red crystals. Yield: 13.5 mg (14%), m.p. 259−261 °C (hexane/EtOAc). UV (MeOH): λ = 224, 259, 282 (sh), 444 nm. IR (drift): $\tilde{\nu}$ = 3225, 2956, 2836, 1651, 1631, 1606, 1532, 1482, 1382, 1261, 1235, 1218, 1094, 828, 715, 684 cm^{-1}. ^1H NMR (500 MHz, [D$_6$]DMSO) = 1.99 (s, 3 H), 2.01 (s, 3 H), 3.80 (s, 3 H), 6.99 (dd, *J* = 9.0, 2.5 Hz, 1 H), 7.40 (d, *J* = 9.0 Hz, 1 H), 7.42 (d, *J* = 2.5 Hz, 1 H), 12.67 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, [D$_6$]DMSO): 11.77 (CH_3), 12.19 (CH_3), 55.30 (CH_3), 101.65 (CH), 114.80 (C), 114.86 (CH), 117.32 (CH), 124.51 (C), 132.80 (C), 135.63 (C), 138.59 (C), 141.98 (C), 156.72 (C), 179.56 (C=O), 182.58 (C=O) ppm. MS (135 °C): *m*/*z* (%) = 255 (100) [M^+], 240 (14), 227 (15), 212 (12), 184 (7). HRMS ($C_{15}H_{13}NO_3$): calcd. 255.0895; found 255.0891.

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