EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201300467

Total Synthesis of Carbazomycin G

Suchandra Chakraborty[a] and Chandan Saha*[a]

Keywords: Medicinal chemistry / Antibiotics / Total synthesis / Alkaloids / Cerium / Oxidation / Quinones

A concise total synthesis of carbazomycin G has been completed in five steps. Cerium(IV) ammonium nitrate (CAN)–SiO_2-mediated oxidation of 2-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one afforded a carbazole-1,4-quinone derivative, 2-methyl-1*H*-carbazole-1,4(9*H*)-dione, the synthetic precusor, which on, which, on Thiele acetylation under newly developed HBF_4 catalysis conditions, yielded 4-hydroxy-2-methyl-9*H*-carbazole-1,3-diyl diacetate. Finally, CAN-SiO_2-mediated oxidative hydrolysis of the acetylation product and *O*-methylation using a stoichiometric amount of diazomethane and subsequent regioselective nucleophilic addition of methyllithium led to carbazomycin G.

Introduction

The carbazomycins A–F, a new group of antibiotics, were first isolated from *Streptoverticillium ehimense* H 1051-MY 10 by Nakamura and his group (Figure 1).[1] Nakamura et al. also isolated carbazomycins G and H (Figure 1) possessing a unique quinol moiety from the same microorganism.[1f] This group described the structure elucidation and biogenesis of carbazomycins, and pointed out that the biogenesis of carbazomycins, which are derived from tryptophan, was unlike that of carbazole alkaloids isolated from terrestrial plants.[1d] These carbazomycin alkaloids have promising biological activities including the antifungal activity[2] against *Trichophyton* species by carbazomycin G. Although carbazomycin G has a stereogenic centre at C-1, the compound elicits no optical rotation, which leads to the conclusion that carbazomycin G is a racemate in nature.[2]

The complex substitution pattern of all these carbazomycins means that these naturally occurring compounds are a challenging synthetic target. Nevertheless, the promising biological activities of carbazomycins led to the development of the total syntheses of this class of compounds by several groups.[3] Knölker et al.[4,5] communicated the first iron-mediated total synthesis of carbazomycin G and H. They constructed the carbazole framework by means of consecutive C–C and C–N bond formation using tricarbonyliron complexed cyclohexadienylium cations and suitably substituted aromatic amine. The same group also synthesised carbazomycin G and H in the following year by using an alternative, convergent route to carbazoles utilising palladium-catalysed[6] cyclisation of *N*,*N*-diarylamines. A third total synthesis of carbazomycin G, through an allene-mediated electrocyclic reaction starting from 3-vinylindole, was reported more recently by Hibino and co-workers.[7] Recently, a synthetic methodology for the synthesis of carbazoloquinones through single-step oxidation with cerium(IV) ammonium nitrate (CAN) from keto-tetrahydrocarbazoles was developed in our laboratory.[8] Here, we communicate the total synthesis of carbazomycin G, employing this methodology of quinone preparation as a key step.

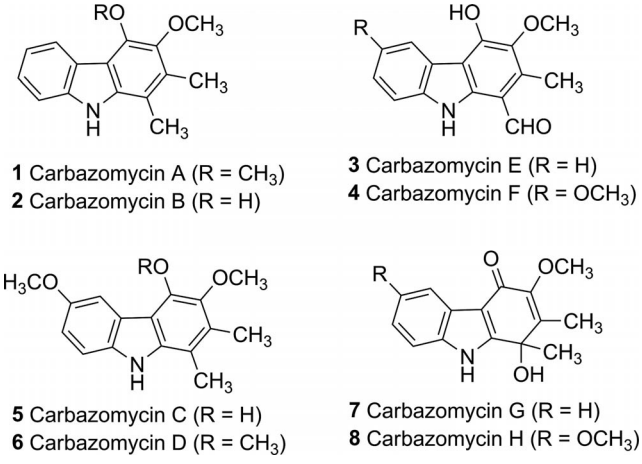


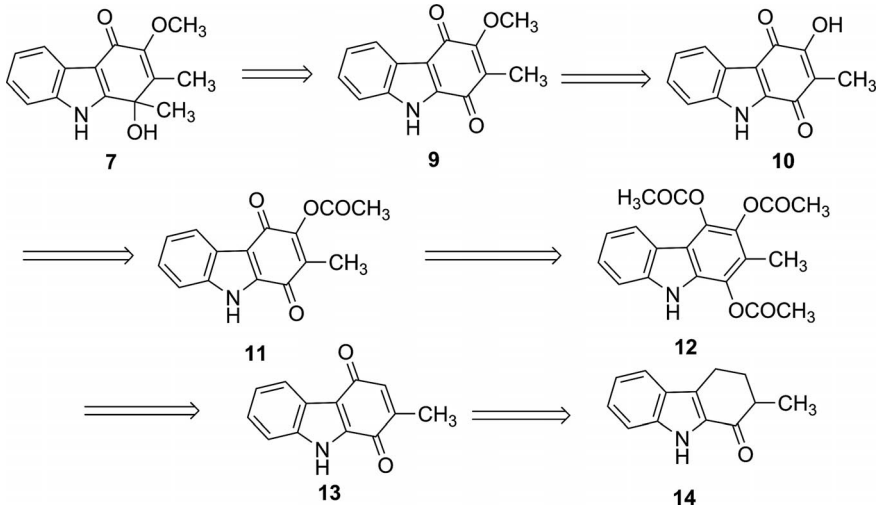
Figure 1. Naturally occurring carbazomycins.

Retrosynthetic Plan

Retrosynthetic analysis of carbazomycin G (**7**), with the unique quinol moiety, led us to carbazole-1,4-quinone **9**, which was originally introduced as a precursor for carbazomycin G in 1997 by Knölker et al.[4] (Scheme 1). Franzblau and Knölker described the significant anti-TB activity of **9**[9] and, in 2011, Lumyong et al. isolated this compound from natural sources.[10,3c] Because CAN-SiO_2-mediated

[a] Department of Clinical and Experimental Pharmacology, School of Tropical Medicine,
C. R. Avenue, Kolkata 700073, India
E-mail: katichandan@yahoo.co.in
Homepage: www.stmkolkata.org

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300467.



Scheme 1. Retrosynthetic pathway for carbazomycin G.

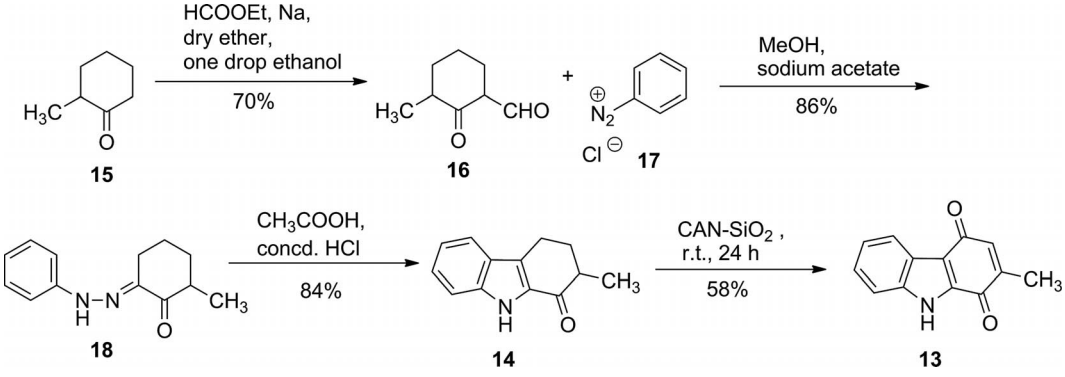
oxidation[8] of 2-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**14**) leads to **13**, our attention was drawn towards the accessibility of **9** through hydrolysis of the acetoxy group of quinone **11** and subsequent *O*-methylation. The required 2-methyl-1,4-dioxo-4,9-dihydro-1*H*-carbazol-3-yl acetate (**11**) can be synthesised from carbazoloquinone **13** through Thiele acetylation followed by oxidation of intermediate **12**. To obtain quinone **13**, the key intermediate, required access to 2-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**14**), which can be synthesised through Fischer indole cyclization of substituted cyclohexane-1,2-dione-1-phenylhydrazone formed by the Japp–Klingemann procedure from phenyldiazonium chloride and suitably substituted 1,3-dicarbonyl compound.

Synthesis of Key Intermediate 2-Methyl-1*H*-carbazole-1,4(9*H*)-dione (13)

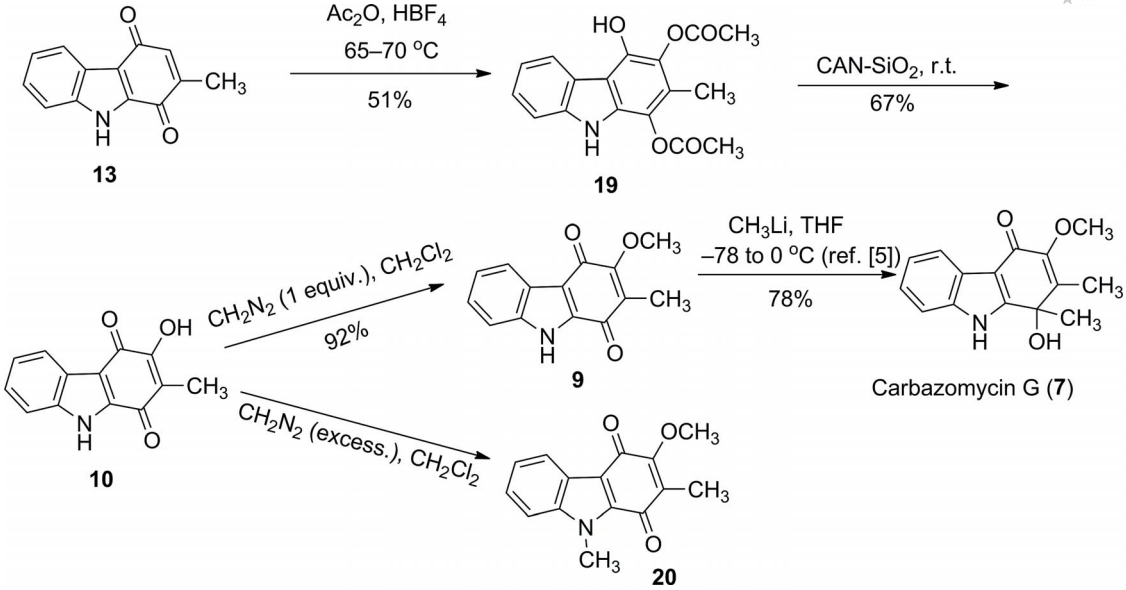
The synthesis of **14** was initiated from commercially available 2-methylcyclohexanone (**15**; Scheme 2). Claisen condensation[11] on **15** with ethyl formate using metallic sodium in anhydrous ether in the presence of one drop of ethanol afforded 3-methyl-2-oxocyclohexanecarbaldehyde (**16**, which exists in two tautomeric forms as evident from NMR studies), which, on condensation with phenyldiazonium chloride (**17**) under Japp–Klingemann conditions,[12] furnished 2-methyl-6-(2-phenylhydrazono)cyclohexanone (**18**). The required compound **14** was obtained through Fischer indole cyclisation[12] of **18** by heating to reflux in glacial acetic acid in the presence of concentrated hydrochloric acid for 3 min. CAN-SiO_2-mediated oxidation[8] of **14** at room temperature afforded the expected quinone **13** in 58% yield (Scheme 2). The first synthesis of carbazolequinone **13** was described by Knölker et al. using an approach involving palladium-catalysis .[13]

Synthesis of Carbazomycin G

Because we required quinone **9** as a precursor for the synthesis of carbazomycin G, Thiele acetylation was carried out on **13** under milder conditions using HBF_4 as catalyst at 65–70 °C. Such treatment afforded 4-hydroxy-2-methyl-9*H*-carbazole-1,3-diyl diacetate (**19**) instead of **12** (Scheme 3). The spectroscopic data (^1H and ^{13}C NMR) of **19** suggested the presence of two acetyl groups instead of three. In addition, the structure of **19** was supported by the mechanistic rationale[14] of Thiele acetylation.



Scheme 2. Synthesis of 2-methyl-1*H*-carbazole-1,4(9*H*)-dione (**13**).



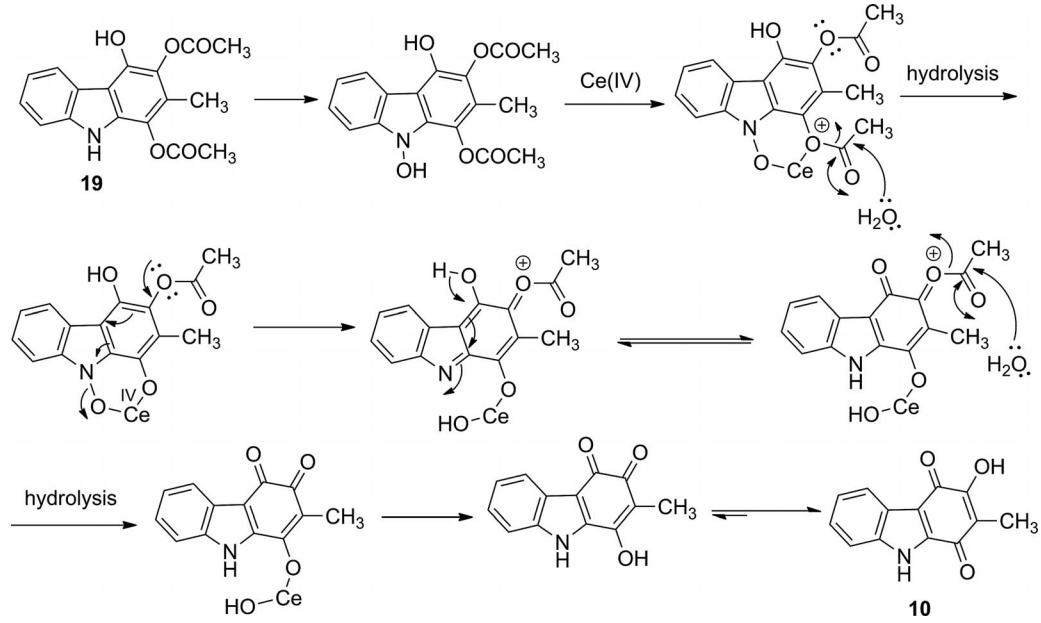
Scheme 3. Synthesis of carbazomycin G.

In practice, Thiele acetylation on **13** under usual conc. H_2SO_4 conditions[15] proved to be unsuccessful in our hands, resulting in the formation of a tarry mass together with a small amount of **19** (26%). This important Thiele acetylation was then studied under several acid catalysis conditions (Table 1). It was found that the use of HBF_4 as catalyst afforded significantly higher yields of **19**. Under the optimised conditions, **19** was obtained in 51% yield, which is, to the best of our knowledge, the first report of Thiele acetylation performed under HBF_4 catalysis conditions.

Table 1. Screening of acid catalysts for the Thiele acetylation of **13**.

Entry	Catalyst	Temp. [°C]	Time [h]	Yield (%)
1	Conc. H_2SO_4	90–100	5	26
2	Conc. H_2SO_4	60–70	5	14
3	BF_3·AcOH (ca. 40% soln.)[16]	r.t.	4	0
4	60% $HClO_4$	r.t.	4	10
5	48% HBF_4 soln.	65–70	2.5	36
6	48% HBF_4 soln.	65–70	5	51
7	48% HBF_4 soln.	65–70	7	45

Compound **19**, on further solid-phase CAN-SiO_2-mediated oxidation,[8] afforded 3-hydroxy-2-methyl-1*H*-carbazole-1,4(9*H*)-dione (**10**) in 67% yield through oxidation with concomitant hydrolysis of the C-3 acetoxy group. The chemistry of Ce^{IV}-mediated oxidations of organic molecules is dominated by radical and radical cation chemistry,[17,18] and the fate of these reactive intermediates determines the nature of the organic oxidation products. Thus, the key step for oxidation of **19** was anticipated to be N-hydroxylation,



Scheme 4. Plausible mechanistic rationale for the conversion of **19** into **10** under CAN-SiO_2 conditions.

which has been documented.[8] Ce^{IV} may participate in the process by forming a complex[8,19] as shown in Scheme 4, which ultimately leads to the hydrolysis of the C-1 acetoxy group. Subsequently, cleavage of the N–O bond is aided by the acetoxy group at C-3, followed by concomitant hydrolysis[20] of the acetoxy group, which ultimately leads to the formation of **10**. The latter is the 3-hydroxy-derivative of **13** and is obtained without recourse to hydrolysis of **11**, which was the proposed synthetic intermediate in the retrosynthetic analysis presented in Scheme 1.

Compound **10**, on methylation using excess diazomethane, yielded the N-methylated derivative of carbazomycin G, i.e., 3-methoxy-2,9-dimethyl-1*H*-carbazole-1,4(9*H*)-dione (**20**). Thus, methylation[21] of **10** was carried out using a stoichiometric amount of diazomethane to furnish the precursor of carbazomycin G, quinone **9**, in 95% yield. It sould be mentioned that the well-established regioselective methylation at C-1 was used in the final step to generate carbazomycin G.[5]

Conclusions

A five-step total synthesis of carbazomycin G has been established, whereby the initial carbazoloquinone was synthesised through CAN-SiO_2-mediated oxidation of easily available **14** followed by Thiele acetylation on **13** under HBF_4 catalysed conditions and then subsequent oxidative hydrolysis using CAN-SiO_2 in the solid phase to give **10** as the synthetic precursor. Standard functional group interconversion of the latter generated carbazomycin G. The present study thus expands the application of two renowned reagents, CAN-SiO_2 and HBF_4.

Experimental Section

General: All reactions were carried out with anhydrous solvents. Melting points were determined in open capillaries and are uncorrected. Reagent grade chemicals were purchased from commercial sources and used without further purification. All reaction mixtures and column eluents were monitored by TLC using commercial aluminium TLC plates (Merck Kieselgel 60 F254). The plates were observed under UV light at 254 and 365 nm. IR spectra were recorded in KBr discs with a Shimadzu FTIR-8300 spectrophotometer, and ^1H and ^{13}C NMR spectra were recorded with a Bruker AV 500 instrument. High-resolution mass spectra (HRMS) were performed with a Q-TOF Micro YA263 instrument.

3-Methyl-2-oxocyclohexanecarbaldehyde (16): A solution of 2-methylcyclohexanone (**15**; 11.2 g, 0.1 mol) containing ethyl formate (18.0 mL, 0.15 mol) and metallic sodium (2.3 g, 0.1 mol) in sodium-dried diethyl ether (200 mL) was placed in a conical flask with a magnetic stirrer and guard tube. To initiate the reaction, five drops of ethanol were added to the stirred mixture, while placing it in a cold water bath. Stirring was continued for 4 h, whereupon the sodium salt of 3-methyl-2-oxocyclohexanecarbaldehyde was obtained as a cake-like mass. Further ethanol (5 mL) was added, and the mixture was stirred for an additional 30 min to quench any unreacted metallic sodium. Water (150 mL) was then added and the mixture was shaken in a separating funnel. The aqueous layer was collected and the organic layer was further extracted with water (50 mL) and the combined aqueous extracts were washed with diethyl ether (50 mL). The aqueous layer was acidified with 6 N hydrochloric acid (8.0 mL) and extracted with diethyl ether (2× 80 mL). The organic layer was extracted and washed with brine and then dried with anhydrous sodium sulfate. The organic layer, on evaporation followed by vacuum distillation (70 °C/0.5 Torr), gave product **16** (10 g, 70% yield) as a colourless oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.21 (d, J = 7.0 Hz, 3 H, CH_3), 1.37–1.42 (m, 1 H), 1.57–1.60 (m, 1 H), 1.76–1.80 (m, 1 H), 1.85–1.89 (m, 1 H), 2.32–2.35 (m, 2 H), 2.45–2.49 (m, 1 H), 8.60 (s, 1 H, CHO), 14.55 (br. s, 1 H, enol-OH) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 17.47 (CH_3), 20.99 (CH_2), 23.77 (CH_2), 30.03 (CH_2), 35.86 (CH), 108.31 (CH), 187.00 (C), 188.62 (C) ppm. HRMS (Q-TOF): *m*/*z* calcd. for $C_8H_{13}O_2$ $[M + H]^+$ 141.0912; found 141.0917.

2-Methyl-6-(2-phenylhydrazono)cyclohexanone (18): An aqueous solution of sodium acetate trihydrate (20 g) in water (80 mL) was added to a solution of **16** (14 g, 0.1 mol) in methanol (160 mL) cooled to 0 °C, then a solution of phenyldiazonium chloride (prepared from 0.1 mol aniline) was added dropwise with stirring. The yellow solid compound **18**, thus obtained, was collected by filtration and washed with water. Upon crystallization from aqueous methanol, **18** (18.5 g, yield 86%) was obtained as yellow crystals; m.p. 98 °C (ref.[22] 97 °C); R_f = 0.8 (benzene/chloroform/diethylamine, 14:5:1). UV (MeOH): λ = 236, 300, 358 nm. IR (drift): $\tilde{\nu}$ = 3495 (br), 3292, 2965, 1678, 1620, 1536, 1498, 1442 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.21 (d, J = 7.0 Hz, 3 H, CH_3), 1.51–2.78 (m, 7 H, 2× 3-H, 2× 4-H, 2× 5-H, 2-H), 6.98 (d, J = 7.5 Hz, 2 H, Ar-H), 7.21–7.30 (m, 3 H, Ar-H), 13.71 (s, 1 H, NH; exch.) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 14.83 (CH_3), 16.32 (CH_2), 22.06 (CH_2), 31.69 (CH_2), 43.71 (CH), 114.36 (CH), 122.84 (CH), 125.91 (CH), 128.99 (CH), 129.40 (CH), 132.29 (C), 143.31 (C), 200.13 (C=O) ppm. HRMS (Q-TOF): *m*/*z* calcd. for $C_{13}H_{16}N_2ONa$ $[M + Na]^+$ 239.1154; found 239.1156.

2-Methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (14): A solution of **18** (10.8 g, 50.0 mmol) in glacial acetic acid (80 mL) containing conc. hydrochloric acid (20 mL) was heated to reflux for 4 min. The reaction mixture was poured into ice-water (300 mL) and the solid thus obtained was collected by filtration, washed with water, and dried. The residue was subjected to flash chromatography (hexane/CH_2Cl_2, 7:3) on silica gel to give a white solid. Recrystallization of the solid from dichloromethane/hexane provided **14** (8.4 g, 84%) as white crystals; m.p. 172–173 °C (ref.[22] 173 °C); R_f = 0.7 (benzene/chloroform/diethylamine, 14:5:1). UV (MeOH): λ = 238, 312 nm. IR (drift): $\tilde{\nu}$ = 3284, 2932, 1688, 1516, 1492 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.38 (d, J = 8.0 Hz, 3 H, CH_3), 2.02 (m, 1 H, 3-H), 2.32 (m, 1 H, 3-H), 2.72 (m, 1 H, 2-H), 2.97 (m, 1 H, 4-H), 3.09 (m, 1 H, 4-H), 7.13 (t, 1 H, Ar-H), 7.35 (t, 1 H, Ar-H), 7.46 (d, J = 8.5 Hz, 1 H, Ar-H), 7.64 (d, J = 8.5 Hz, 1 H, Ar-H), 9.68 (s, 1 H, NH; exch) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 15.28 (CH_3), 20.60 (CH_2), 33.23 (CH_2), 41.99 (CH), 112.75 (CH), 120.26 (CH), 121.25 (CH), 125.84 (CH), 126.84 (C), 129.05 (C), 130.98 (C), 138.35 (C), 194.57 (C=O) ppm. HRMS (Q-TOF): *m*/*z* calcd. for $C_{13}H_{13}NONa$ $[M + Na]^+$ 222.0890; found 222.0893.

2-Methyl-1*H*-carbazole-1,4(9*H*)-dione (13): A solution of ceric ammonium nitrate (8.3 g, 15.0 mmol) in anhydrous acetonitrile (30 mL) was mixed with silica gel (35 g), then the solvent was evaporated at room temperature and the reagent thus obtained was soaked with a solution of **14** (0.495g, 2.5 mmol) in dichloromethane (20 mL) followed by evaporation of the solvent in air. The mixture was kept overnight at room temperature, then the reaction mixture was extracted with dichloromethane (3× 50 mL) and the solvent was evaporated to dryness. The residue was purified by chromatog-

raphy (hexane/CH_2Cl_2, 2:3) over silica gel to furnish a red-coloured solid, which was crystallized from dichloromethane/hexane to yield **13** (305 mg, 58%) as a red solid; m.p. 225–232 °C (dec.) [ref.[23] 237–239 °C (dec)]. R_f = 0.5 (benzene/chloroform/diethylamine, 14:5:1). UV (MeOH): λ = 316 (sh), 257, 217 nm. IR (drift): $\tilde{\nu}$ = 3220 (br), 2915, 2883, 1618, 1508, 1490, 1366 cm^{-1}. ^1H NMR (500 MHz, [D_6]DMSO): δ = 3.32 (s, 3 H, CH_3), 6.54 (d, J = 5.5 Hz, 1 H, 3-H, doublet due to long range coupling with allylic proton of CH_3 gr), 7.26 (t, 1 H, Ar-H), 7.35 (t, 1 H, Ar-H), 7.50 (d, J = 8.5 Hz, 1 H, Ar-H), 7.97 (t, 1 H, Ar-H), 12.79 (s, 1 H, NH, exch) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 15.42 (CH_3), 114.21 (CH), 116.06 (CH), 122.15 (CH), 123.69 (CH), 124.19 (CH), 126.77 (C), 135.26 (C), 136.16 (C), 138.12 (C), 144.49 (C), 180.64 (C=O), 183.81 (C=O) ppm. HRMS (Q-TOF): m/z calcd. for $C_{13}H_{10}NO_2$ $[M + H]^+$ 212.0708; found 212.0710.

4-Hydroxy-2-methyl-9*H*-carbazole-1,3-diyl diacetate (19): The volume of 48% HBF_4 solution (1.0 mL) was reduced to 0.2 mL under vacuum at 70 °C and then cooled to 0 °C. To this HBF_4 solution at 0 °C, cold acetic anhydride (5.0 mL) was added. The temperature of the reaction mixture immediately raised due to an exothermic reaction. The reaction flask was placed over an oil-bath keeping the temperature 65–70 °C and solid compound **14** (100.0 mg, 0.5 mmol) was added portionwise to the reaction mixture with continuous stirring over 1 h. After complete addition, the reaction was continued for a further 5 h. The reaction mixture was then cooled to 0 °C and poured into ice-water (ca. 100 mL) to obtain a green solid. The precipitate was isolated by filtration, washed with a large volume of H_2O, and dried in vacuo. Column chromatography (hexane/CH_2Cl_2, 1:9) of the residue on silica gel furnished **19** (80 mg, 51%) as a yellow solid; m.p. 138 °C (dec); R_f = 0.2 (benzene/chloroform/diethylamine, 14:5:1). UV (MeOH): λ = 233, 293, 384 nm. IR (drift): $\tilde{\nu}$ = 3410, 2920, 2856, 1742, 1648, 1610, 1474 cm^{-1}. ^1H NMR (500 MHz, [D_6]DMSO): δ = 2.36 (s, 3 H, Ar-CH_3), 2.43 (s. 6 H, $COCH_3$), 7.02 (s, 1 H, Ar-H), 7.32 (m, 1 H, Ar-H), 8.22 (d, J = 7.5 Hz, 1 H, Ar-H), 8.33 (d, J = 8.5 Hz, 1 H, Ar-H), 9.83 (s, 1 H, NH, exch), 11.60 (br. s, 1 H, Ar-OH) ppm. ^{13}C NMR and DEPT (125 MHz, [D_6]DMSO): δ = 16.55 (CH_3), 21.40 (CH_3), 21.83 (CH_3), 114.88 (CH), 116.90 (CH), 120.22 (CH), 121.92 (C), 122.68 (CH), 125.31 (C), 129.94 (C), 130.22 (C), 132.71 (C), 133.33 (C), 135.09 (C), 142.58 (C), 169.46 (C=O), 169.57 (C=O) ppm. HRMS (Q-TOF): m/z calcd. for $C_{17}H_{16}NO_5$ $[M + H]^+$ 314.1023; found 314.1026.

3-Hydroxy-2-methyl-1*H*-carbazole-1,4(9*H*)-dione (10): Ceric ammonium nitrate (548 mg, 1.0 mmol) dissolved in anhydrous acetonitrile (10 mL), was added to silica gel (2.0 g) and the solvent was then evaporated at room temperature. The reagent was impregnated with a solution of **19** (156 mg, 0.5 mmol) in dichloromethane (30 mL) followed by evaporation of solvent. The reaction mixture was kept overnight at room temperature, then extracted with dichloromethane (3 × 50 mL) and the solvent was evaporated. The residue was purified by chromatography (hexane/CH_2Cl_2, 1:4) over silica gel to provide a red-coloured solid, which was purified by crystallization from dichloromethane/hexane to yield **10** (78 mg, 67%) as an orange-red solid; m.p. 221 °C; R_f = 0.4 (benzene/chloroform/diethylamine, 14:5:1). UV (MeOH): λ = 374 (sh), 298, 252 nm. IR (drift): $\tilde{\nu}$ = 3482 (br), 3376, 2945, 2895, 1628, 1614, 1510 cm^{-1}. ^1H NMR (500 MHz, [D_6]DMSO): δ = 2.15 (s, 3 H, CH_3), 7.54–7.63 (m, 1 H, Ar-H), 7.77 (dd, J = 7.5, 8.0 Hz, 1 H, Ar-H), 8.02–8.07 (m, 1 H, Ar-H), 8.24 (s, 1 H, Ar-H), 13.58 (s, 1 H, NH, exch), 13.71 (s, 1 H, OH) ppm. ^{13}C NMR and DEPT (125 MHz, [D_6]DMSO): δ = 13.97 (CH_3), 112.87 (CH), 114.79 (CH), 118.93 (CH), 122.60 (CH), 126.55(C), 138.46 (C), 139.38 (C), 140.56 (C), 142.56 (C), 144.85 (C), 172.92 (C=O), 177.24 (C=O) ppm. HRMS (Q-TOF): m/z calcd. for $C_{13}H_{10}NO_3$ $[M + H]^+$ 228.0657; found 228.0660.

3-Methoxy-2-methyl-1*H*-carbazole-1,4(9*H*)-dione (9): A solution of **10** (100.0 mg, 0.4 mmol) in dichloromethane (20 mL) was added slowly to a solution of diazomethane[24] in CH_2Cl_2 (6.5 mL, 0.26% diazomethane solution, 16.8 mg, 0.4 mmol) at room temperature. After 30 min, vigorous evolution of nitrogen was observed and the reaction mixture was kept overnight at room temperature. Evaporation of the solvent and column chromatography (hexane/CH_2Cl_2, 1:4) of the residue on silica gel afforded **9** (89 mg, 92.5%) as an orange-yellow solid; m.p. 242–245 °C (dec.) [ref.[5] 248–256 °C (dec)]. R_f = 0.5 (benzene/chloroform/diethylamine, 14:5:1). UV (MeOH): λ = 362 (sh), 287, 258 nm. IR (drift): $\tilde{\nu}$ = 3464 (br), 3286, 2960, 2895, 1625, 1612, 1525 cm^{-1}. ^1H NMR (500 MHz, [D_6]-DMSO): δ = 2.50 (s, 3 H, CH_3), 3.82 (s, 3 H, OCH_3), 7.84 (d, J = 8.0 Hz, 1 H, Ar-H), 8.10 (dd, J = 7.5, 8.0 Hz, 2 H, Ar-H), 8.24 (t, 1 H, Ar-H), 9.67 (s, 1 H, NH, exch) ppm. ^{13}C NMR and DEPT (125 MHz, [D_6]DMSO): δ = 13.87 (CH_3), 58.15 (CH_3), 113.15 (CH), 114.82 (CH), 118.95 (CH), 123.65 (CH), 126.55(C), 138.49 (C), 139.38 (C), 140.56 (C), 143.65 (C), 145.82 (C), 175.92 (C=O), 180.04 (C=O) ppm. HRMS (Q-TOF): m/z calcd. for $C_{14}H_{11}NO_3Na$ $[M + Na]^+$ 264.0632; found 264.0636.

Carbazomycin G (1,4-Dihydro-1-hydroxy-3-methoxy-1,2-dimethyl-9*H*-carbazol-4-one; 7): A solution of methyllithium (1.09 M in Et_2O, 2 mL, 2.2 mmol) was added dropwise to a solution of **9** (50 mg, 0.2 mmol) in THF (10 mL) at –78 °C. The reaction mixture was warmed to room temperature for a period of 30 min, then the reaction was quenched by the addition of 10% aqueous NH_4Cl (10 mL). The aqueous layer was extracted with dichloromethane (3 × 20 mL) and the combined organic layers were dried with sodium sulfate. The solvent was evaporated and column chromatography (hexane/CH_2Cl_2, 3:7) of the residue on silica gel provided compound **7** (40 mg, 78%) as a yellow solid; m.p. 260–262 °C (dec.) [ref.[5] 266–268 °C (dec)]. R_f = 0.5 (benzene/chloroform/diethylamine, 14:5:1). IR (drift): $\tilde{\nu}$ = 3209 (br), 1643, 1620, 1611, 1482, 1453 cm^{-1}. ^1H NMR (500 MHz, [D_6]DMSO): δ = 1.93 (s, 3 H, CH_3), 2.39 (s, 3 H, CH_3), 3.84 (s, 3 H, OCH_3), 5.45 (s, 1 H, OH), 7.26–7.44 (m, 2 H, Ar-H), 7.54–7.58 (m, 1 H, Ar-H), 7.66 (d, J = 8.0 Hz, 1 H, Ar-H), 12.17 (s, 1 H, NH, exch) ppm. ^{13}C NMR and DEPT (125 MHz, [D_6]DMSO): δ = 11.26 (CH_3), 13.45 (CH_3), 59.17 (CH_3), 65.33 (C), 112.35 (CH), 114.22 (CH), 120.95 (CH), 122.85 (CH), 127.54 (C), 137.49 (C), 139.78 (C), 141.51 (C), 143.25 (C), 149.66 (C), 177.82 (C=O) ppm. HRMS (Q-TOF): m/z calcd. for $C_{15}H_{16}NO_3$ $[M + H]^+$ 258.1125; found 258.1128.

3-Methoxy-2,9-dimethyl-1*H*-carbazole-1,4(9*H*)-dione (20): A solution of **10** (50.0 mg, 0.2 mmol) in dicholoromethane was added slowly to a solution of diazomethane[24] in dichloromethane (10 mL, 0.26% diazomethane solution, 25.8 mg, 0.6 mmol) at room temperature. Vigorous evolution of nitrogen was observed after 20 min and the reaction mixture was kept overnight. Evaporation of the solvent and column chromatography (hexane/CH_2Cl_2, 1:4) of the residue on silica gel afforded **20** (33 mg, 65%) as a red solid; m.p. 189 °C (dec.); R_f = 0.4 (benzene/chloroform/diethylamine, 14:5:1). IR (drift): $\tilde{\nu}$ = 3360 (br), 2893, 1634, 1625, 1570 cm^{-1}. ^1H NMR (500 MHz, [D_6]DMSO): δ = 2.51 (s, 3 H, CH_3), 3.36 (s, 3 H, OCH_3), 3.38 (s, 3 H, N-CH_3), 7.55- 7.59 (m, 2 H, Ar-H), 7.67–7.71 (m, 2 H, Ar-H) ppm. ^{13}C NMR and DEPT (125 MHz, [D_6]-DMSO): δ = 13.61 (CH_3), 33.23 (CH_3), 59.51 (CH_3), 112.45 (CH), 114.82 (CH), 119.95 (CH), 123.65 (CH), 125.51 (C), 138.19 (C), 139.58 (C), 141.56 (C), 143.15 (C), 145.52 (C), 177.62 (C=O), 178.85 (C=O) ppm. HRMS (Q-TOF): m/z calcd. for $C_{15}H_{14}NO_3$ $[M + H]^+$ 256.0969; found 256.0971.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra for all key intermediates and final products.

Acknowledgments

The authors are thankful to Dr. Nandita Basu (Director) and Prof. Santanu Tripathi (Head of the Department) of Clinical & Experimental Pharmacology of the School of Tropical Medicine, Kolkata. The authors are also thankful to the Council of Scientific and Industrial Research (CSIR), New Delhi for providing a Senior Research Fellowship [grant number 09/951(0001)/2008-EMR-I] to one of the authors (S. C.).

[1] a) K. Sakano, K. Ishimaru, S. Nakamura, *J. Antibiot.* **1980**, *33*, 683–689; b) K. Sakano, S. Nakamura, *J. Antibiot.* **1980**, *33*, 961–966; c) M. Kaneda, K. Sakano, S. Nakamura, Y. Kushi, Y. Iitaka, *Heterocycles* **1981**, *15*, 993–998; d) K. Yamasaki, K. Kaneda, K. Watanabe, Y. Ueki, K. Ishimaru, S. Nakamura, R. Nomi, N. Yoshida, T. Nakajima, *J. Antibiot.* **1983**, *36*, 552–558; e) S. Kondo, M. Katayama, S. Marumo, *J. Antibiot.* **1986**, *39*, 727–730; f) T. Naid, T. Kitahara, M. Kaneda, S. Nakamura, *J. Antibiot.* **1987**, *40*, 157–164.
[2] M. Kaneda, T. Naid, T. Kitahara, S. Nakamura, T. Hirata, T. Suga, *J. Antibiot.* **1988**, *41*, 602–608.
[3] a) H.-J. Knölker, K. R. Reddy, *Chem. Rev.* **2002**, *102*, 4303–4427; b) H.-J. Knölker, *Top. Curr. Chem.* **2005**, *244*, 115–148; c) A. W. Schmidt, K. R. Reddy, H.-J. Knölker, *Chem. Rev.* **2012**, *112*, 3193–3328.
[4] H.-J. Knölker, W. Frohner, *Tetrahedron Lett.* **1997**, *38*, 4051–4054.
[5] H.-J. Knölker, W. Frohner, K. R. Reddy, *Eur. J. Org. Chem.* **2003**, 740–746.
[6] a) H.-J. Knölker, W. Frohner, *J. Chem. Soc. Perkin Trans. 1* **1998**, 173–175; b) H.-J. Knölker, W. Frohner, K. R. Reddy, *Synthesis* **2002**, 557–564; c) H.-J. Knölker, *Curr. Org. Synth.* **2004**, *1*, 309–331.
[7] H. Hagiwara, T. Choshi, H. Fujimoto, E. Sugino, S. Hibino, *Tetrahedron* **2000**, *56*, 5807–5811.
[8] S. Chakraborty, G. Chattopadhyay, C. Saha, *J. Heterocycl. Chem.* **2011**, *48*, 331–338.
[9] a) T. A. Choi, R. Czerwonka, W. Fröhner, M. P. Krahl, K. R. Reddy, S. G. Franzblau, H.-J. Knölker, *ChemMedChem* **2006**, *1*, 812–815; b) T. A. Choi, R. Czerwonka, R. Forke, A. Jäger, J. Knöll, M. P. Krahl, T. Krause, K. R. Reddy, S. G. Franzblau, H.-J. Knölker, *Med. Chem. Res.* **2008**, *17*, 374–385.
[10] P. Ruanpanun, Z. T. Dame, H. Laatsch, S. Lumyong, *FEMS Microbiol. Lett.* **2011**, *322*, 77–81.
[11] C. Ainsworth, *Org. Synth., Coll. Vol. IV* **1963**, 536–539.
[12] C. Saha, A. Chakraborty, B. K. Chowdhury, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1996**, *35*, 677–680.
[13] H.-J. Knölker, K. R. Reddy, *Heterocycles* **2003**, *60*, 1049–1052.
[14] B. S. Furniss, A. J. Hannaford, P. W. G. Smith, A. R. Tatchell, in: *Vogel's Textbook of Practical Organic Chemistry*, 4th ed., ELBS, Longman, London, **1986**, p. 786.
[15] E. B. Vliet, *Org. Synth., Coll. Vol. I* **1941**, 317–318.
[16] J. M. Blatchly, J. F. W. McOmie, *J. Chem. Soc.* **1963**, 5311–5313.
[17] J. R. Hwu, K. Y. King, *Curr. Sci.* **2001**, *81*, 1043–1053.
[18] G. A. Molander, *Chem. Rev.* **1992**, *92*, 29–68.
[19] R. Sathunuru, U. Narasimha Rao, E. Biehl, *ARKIVOC* **2003**, *15*, 124–133.
[20] A. Ates, A. Gautier, B. Leroy, J. M. Plancher, Y. Quesnel, I. E. Marko, *Tetrahedron Lett.* **1999**, *40*, 1799–1802.
[21] B. S. Furniss, A. J. Hannaford, P. W. G. Smith, A. R. Tatchell, in: *Vogel's Textbook of Practical Organic Chemistry*, 4th Ed., ELBS, Longman, London, **1986**, p. 292.
[22] H. K. Sen, S. K. Ghosh, *J. Indian Chem. Soc.* **1927**, *4*, 477–480.
[23] M. Yogo, C. Ito, H. Furukawa, *Chem. Pharm. Bull.* **1991**, *39*, 328–344.
[24] F. Arndt, *Org. Synth., Coll. Vol. II* **1943**, 165–167.

Received: April 1, 2013
Published Online: July 18, 2013

