EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Carbazomycin G: Method development and total synthesis

Authors: Vijayaragavan Elumalai, Cristian Gambarotti, and Hans-René Bjørsvik

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201800359

Link to VoR: http://dx.doi.org/10.1002/ejoc.201800359

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

Accepted Article
European Journal of Organic Chemistry - ejoc.201800359

Carbazomycin G: Method Development and Total Synthesis

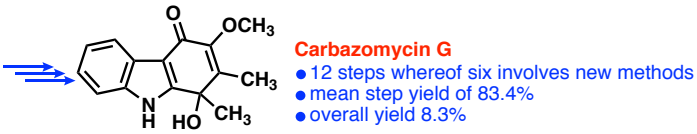
Vijayaragavan Elumalai,[a] Cristian Gambarotti,[b] and Hans-René Bjørsvik[a,*]

[a]*Department of Chemistry, University of Bergen, Allégaten 41, N-5007 Bergen, Norway*

[b]*Department of Chemistry, Materials, and Chemical Engineering, Politecnico di Milano, Piazza Leonardo da Vinci 32, I-20133 Milan, Italy*

eMail: hans.bjorsvik@kj.uib.no, telephone: +47 55 58 34 52, web: http://folk.uib.no/nkjhn/

Graphical abstract



Text for the table of content

The carbazole alkaloid carbazomycin G was synthesised via a novel synthetic route composed of twelve synthetic steps whereof six new synthetic methods that including two various oxidation methods, a reduction method, Suzuki cross-coupling, and a Pd catalysed tandem C–H activation and C–N bond formation for making the carbazole scaffold.

Key Topic

Total synthesis

Abstract

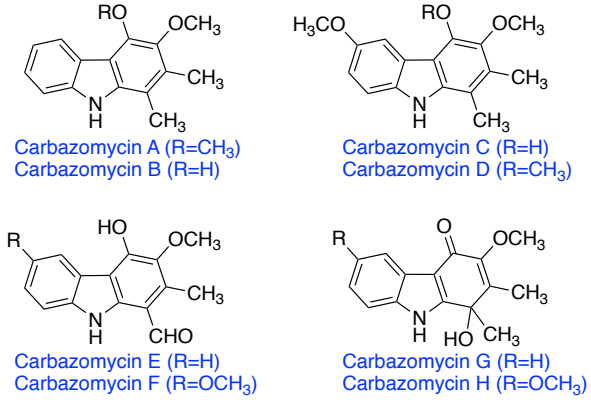
A novel total synthesis leading to the carbazole alkaloid carbazomycin G was designed and developed. The outlined synthetic route is composed of twelve synthetic steps including the transformations of the very first simple substrate and intermediates. In order to realize the designed synthesis, in total six new synthetic methods were developed and implemented in the new total synthesis, which afforded target molecule in an overall yield of 8.3%.

Introduction

For almost four decades ago, a distinct class of carbazole alkaloids named carbazomycin A–H were discovered, isolated, and structure elucidated,[1] Scheme 1. These carbazole alkaloids are characterized by an unusual unsymmetrical substitution pattern, which consists in the fact that one of the two carbocycles moieties that make up integral parts of the carbazole scaffold is completely naked and the other one is highly crowded as it carries substituents in all the positions that are not occupied by the bonds that make up the carbazole framework.

Investigations of the biological activity of the carbazomycins A-H, revealed anticancer,[2] antibacterial,[3] and antifungal[4] activities. Their biological activities and challenging molecular structure made the carbazomycins to be an interesting target scaffold for the synthetic organic chemist, which has resulted in a series of distinct synthetic routes.[5]

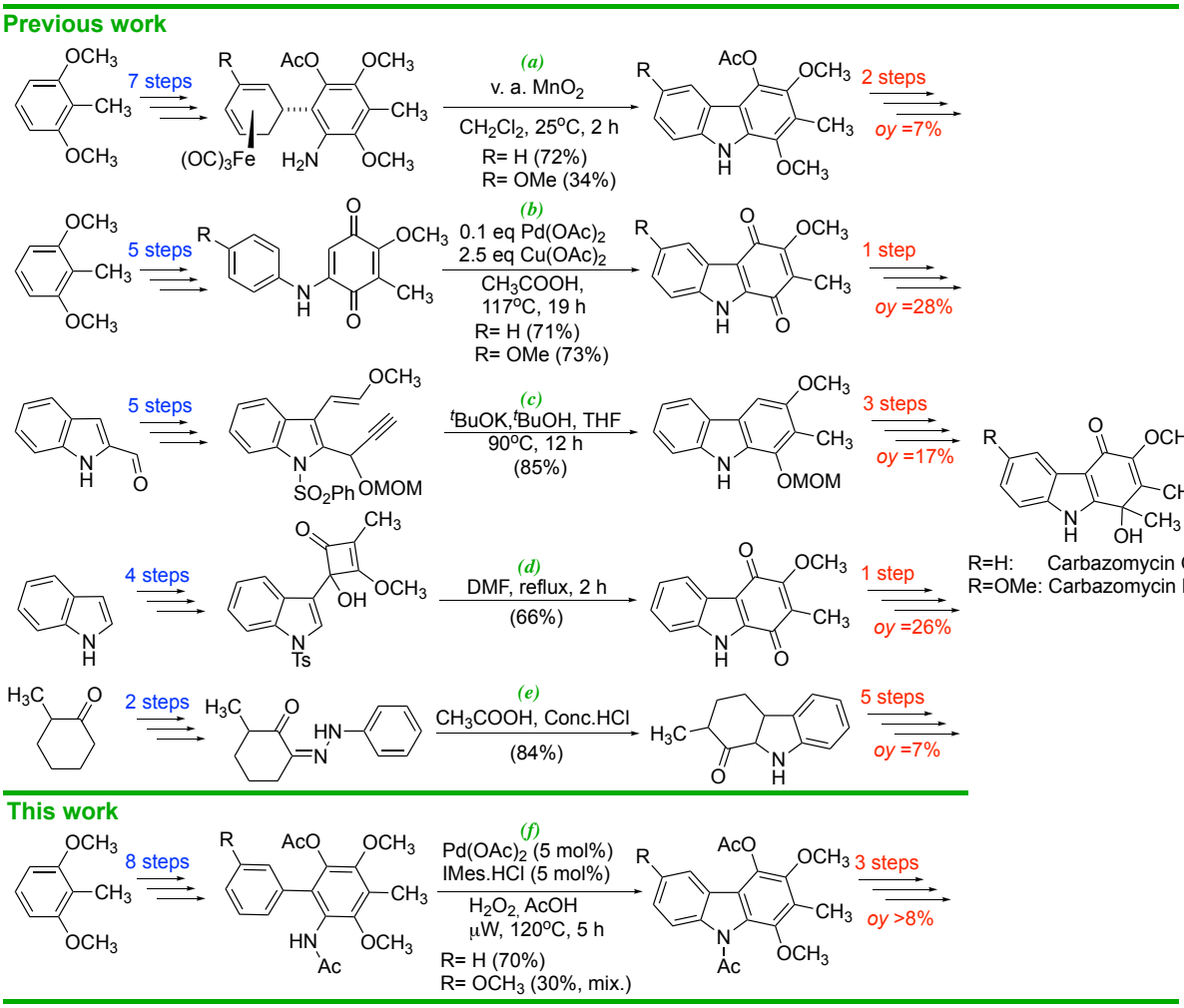
Scheme 1. Structure of the carbazomycins A-H



The carbazomycins as synthetic targets attracted us as we recognized several synthetic challenges, especially for the synthesis of the carbazomycin G and H. Synthetic routes leading to carbazomycin G have previously been reported.[5] In particular, approaches involving consecutive transition metal-mediated C–C bond and C–N bond formations are crucial in the total syntheses of the carbazomycins A,[6] B,[6] C,[7] D,[7] and E,[8] but also for a few other important carbazole alkaloids.[9] Knölker and collaborators[10] developed initially an iron-mediated total synthesis of carbazomycin G and H (pathway *a* of Scheme 2), but in addition a pathway *(b)* involving Pd-catalyzed oxidative cyclization of arylamino-1,4-benzoquinone for the synthesis of both of the carbazomycin G and H scaffolds. [11] Hibino and collaborators[12] disclosed a carbazomycin G synthesis that involved an allene mediated electrocyclic reaction (pathway *(c)* of Scheme 2). Recently, Hu and collaborators[13] disclosed a carbazomycin G synthesis that involved a method comprising a thermal ring expansion and self-redox cascade reaction, see pathway *(d)* of Scheme 2. Chakraborty and Saha[14] disclosed a carbazomycin G total synthesis based on a method utilizing the Fischer indole cyclization, outlined in pathway *(e)* of Scheme 2.

Our approach disclosed herein, pathway *(f)* Scheme 2, is based on two distinct Pd-catalysed reactions, first a Suzuki cross-coupling to obtain a 2-nitro-1,1'-biphenyl intermediate that is reduced and protected and then submitted for a concomitant intramolecular C–H activation that is followed by a C–N bond formation to obtain the congested carbazole intermediate.[15]

Scheme 2. Previously described synthetic methods leading to carbazomycin G

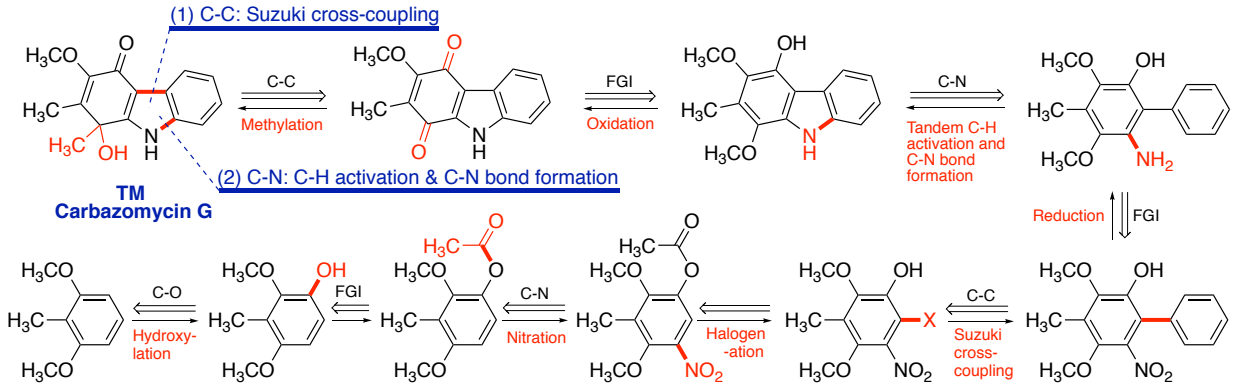


Methods and results

Retrosynthetic analysis. Our retrosynthetic analysis of carbazomycin G is shown in Scheme 3. We envisioned two Pd-catalysed key steps that together might provide the carbazole framework; (1) a Suzuki cross-coupling that produce the 2-*N*-substituted-1,1'-biphenylic moiety, and (2) a simultaneous C–H activation and C–N formation that ultimately afford the carbazole scaffold embedded with requested functionality.

The outlined retrosynthetic analysis looked alluring to us, but after we had started to implement our synthetic plan, twelve steps in total, it turned out to be requirement for several new synthetic methods that we developed during the course of the elaboration of the total synthesis presented herein.

Scheme 3. Retrosynthetic analysis of carbazomycin G. The natural product **TM** was envisioned to arise through two key disconnections that would enable the generation of the most of the molecular complexity. Two key steps: a Suzuki cross-coupling that afford a biphenyl core moiety and a concomitant C–H activation and C–N bond formation, which ultimately afford the carbazole framework that subsequently, by means of a handful of transformations, afford the natural product carbazomycin G **TM**.



Realization of the total synthesis. With the basis in our retrosynthetic analysis, Scheme 3, we commenced the design of a total synthesis (Scheme 4) using the commercially available 2,6-dimethoxytoluene **1** as the very first starting material. Originally, we planned to utilize a three steps sequence previously described by Knölker and collaborators [16] for the production of the phenol **2**. This pathway is composed by a Friedel-Crafts acylation, step *(a')*, that produce the acetophenone **1a**. In the following step *(a'')*, the compound **1a** is submitted for a Baeyer-Villiger oxidation that gives the phenyl acetate **3**, which in the ultimate step *(a''')* is hydrolysed to obtain the anticipated phenol **2**. For this sequence, we undertook a modification of the Baeyer-Villiger oxidation step *(a'')* by replacing *meta*-chloroperbenzoic acid (*m*CPBA) as the oxidation reagent with a more environmental benign procedure composed of hydrogen peroxide in acetic acid with trifluoroacetic acid as reaction medium. During this oxidation, a by-product **3b** was formed in small quantities (≈7%) along with the target oxidation product 5-hydroxy-2,4-dimethoxy-3-methylphenyl acetate **3**. The by-product hydroxyphenyl acetate **3b**, materialized to be produced as a result of direct hydroxylation of the aromatic kernel. This observation prompted us to undertake a thoroughly investigation of the by-product formation,[17] from which a high yielding direct hydroxylation method for methyl and methoxy substituted benzenes, step *(a)* Scheme 4, was established using H_2O_2 in acetic acid with the presence of trifluoroacetic acid as oxidizing system. The organic peracid oxidation mechanisms that clearly can follow either the Baeyer-Villiger oxidation mechanism or the direct aromatic ring hydroxylation was later explored in-depth by means of multivariate modelling of designed multi-response experiments.[18]

In order to be able to perform nitration of the phenol **2**, it was necessary to protect the free hydroxy group. Treatment with acetyl chloride, step *(b),* afforded the *O*-acetyl intermediate **3**, which allowed nitration of the aromatic kernel using standard conditions using nitric acid (65%) in a mixture of acetic acid and acetic anhydride.

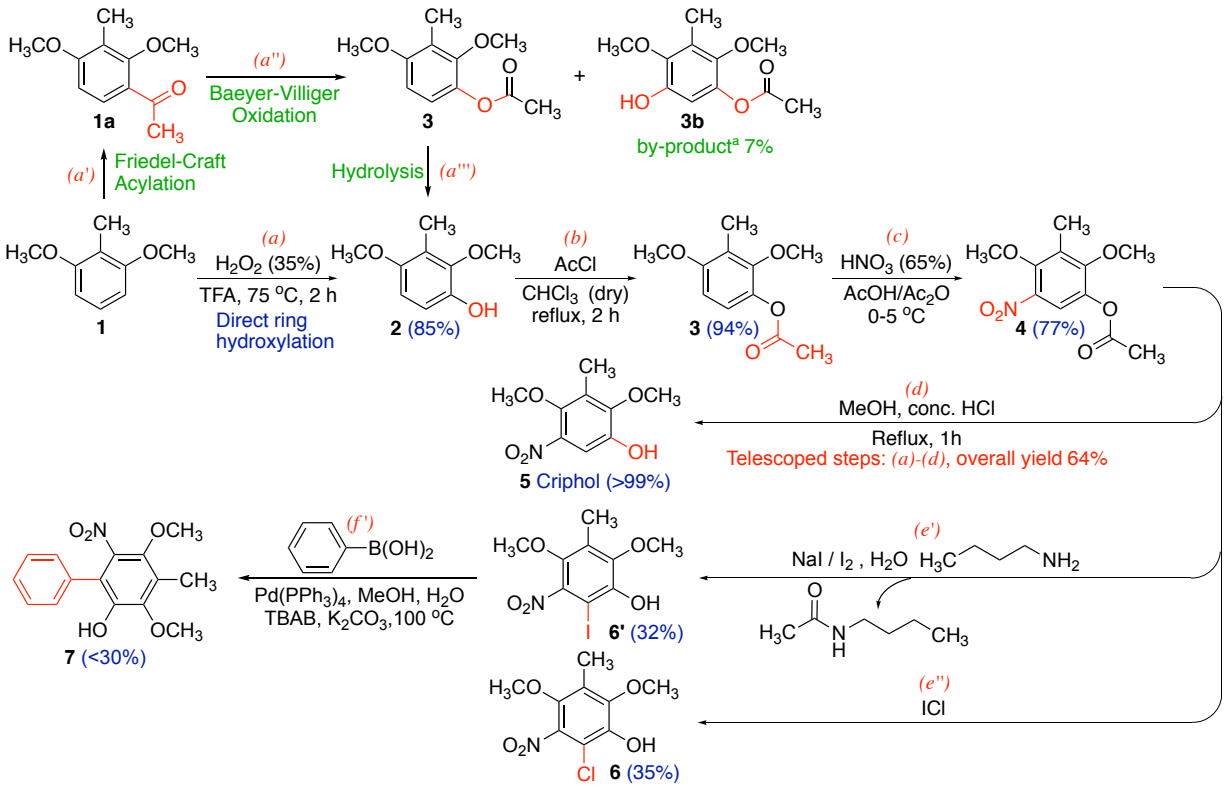
Iodination of intermediate **4**, step (*e'*) was initially performed according to a protocol using I_2 in the presence of *n*-butylamine,[19] a reaction that afforded target iodinated intermediate **6'**, although in low yield (32%) only. Along with the challenging iodination, we designed and developed a well operating Suzuki cross-coupling reaction allowing producing 2-nitro-1,1'-biphenyl. This method as well with our the congested iodoarene **6'** to produce **7**.

Nevertheless, it turned out that the iodination step *(e')* became impossible to reproduce. We believe this relied on the inferior iodine quality we gradually needed to use (new supplies) compared to the superior iodine quality we used at the outset when the method was developed.

Additional iodination trials were conducted by using the well-established ICl as iodination reagent, step *(e'')* of Scheme 4. Surprisingly, the chlorinated product **6** was produced in the place of the expected iodinated product **6'**, although in low yield only (35%). Unfortunately, we were not able to acquire further supplies of the initial iodine quality, which forced us to abandon this methodology, that is the iodination step *(e')*, which thus appeared to be a "dead-end" for our overall strategy.

In spite of this, the steps *(a–d)* were further developed to approach a telescoped synthesis, that is, without purification of the intermediates to obtain the Criphol **5** in a good overall yield of ≈64%.

Scheme 4. Synthesis of the key intermediates Criphol **5** and 2-nitro-1,1'-biphenyl **7** for the total synthesis of Carbazomycin G.



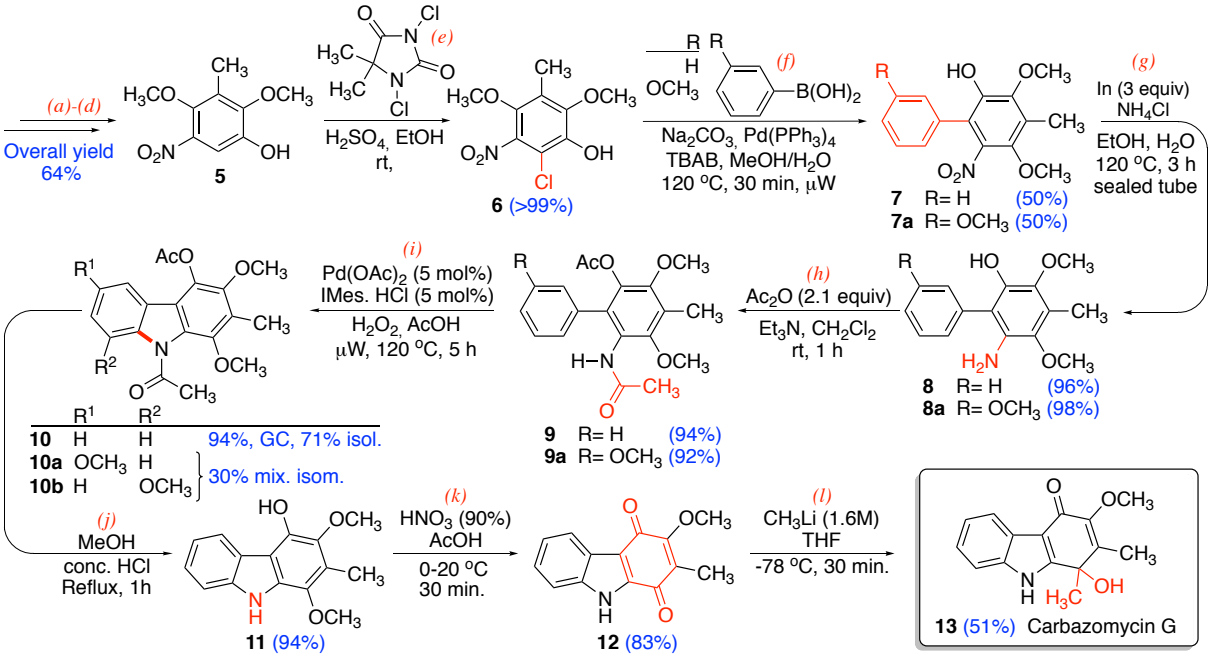
Long time after the effort developing the pathways outlined in Scheme 4, a new method for fast halogenation of heterocycles using *N*,*N*′-dihalo-5,5-dimethylhydantoin was developed by our group.[20] The excellent result we achieved with this method propelled us to attempt the method for the purpose to iodinate the intermediates **4** and **5**, trials that unfortunately failed. Subsequently, we attempted to perform bromination of the Criphol **5** using *N*,*N*′-dibromo-5,5-dimethylhydantoin (DBH) as brominating agent and *N*,*N*′-dichloro-5,5-dimethylhydantoin (DCH) as chlorination agent, respectively. The bromination failed, but the chlorination was highly successfully resulting in a quantitative yield of **6**, Scheme 5.

With compound **6** in hand, we needed a new Suzuki cross-coupling protocol for coupling with phenylboronic acid as the coupling partner. We set-out to utilize our previous disclosed Suzuki cross-coupling method (involving iodoarene **6'**),[21] but we achieved only low yield (29%) of the bi-phenyl **7**, which called for a further development of the method. Thus, our previously disclosed method (involving iodoarene) was tailored to operate with chloroarenes for the synthesis of our congested 2-nitrobiphenyl **7**,[22] to achieve a yield of 50%.

With access to the nitro-biphenyl **7**, we could proceed further with our synthesis to Carbazomycin G. For the next step *(g)*, we needed access to a nitro-reduction method to obtain 2-amino-1,1'-biphenyl **8**. For this purpose, we developed a new improved indium in ammonium chloride based reduction

protocol [23] that furthermore showed up a high functional group tolerance and allowed for a very simple work-up.

Scheme 5. Synthesis of the carbazole alkaloid Carbazomycin G



The 2-nitro-1,1'-biphenyl intermediate **7** and **7a** (Scheme 5) was achieved in yields of 50% (R=H) and 50% (R=OCH_3). Reduction of nitro group yielded **8** and **8a**. Several synthetic methods were available for nitro group reduction. [24] However, we screened the reaction with various experimental conditions using indium powder based on a method reported by Moody et al.[25] We initially tested the method with two different indium powders (Purchased from Aldrich and Alfa Aesar). Both methods afforded only 3% yield at 100 °C. An increased reaction time (3 h) and temperature (120 °C) afforded a quantitative yield of target amine **8**.

Both nitro compounds **7** and **7a** were successfully converted into their corresponding amines using indium mediated reduction method. Amine **8** underwent direct cyclization using our new method involves intramolecular C-H activation and C-N bond formation.[15] However, this method was not successful to compounds bearing oxidizible functional groups such as methoxy and hydroxyl groups. The hydroxyl groups of compounds (**8**) was protected with tert-butyl dimethylsilylchloride (TBS-Cl) operated well (98% yield), however, the subsequent ring closure failed resulting in only decomposition of products.

Since the direct ring closing failed, we attempted to perform the ring closing step when the 2-amino group was acetylated.[15] The acetylation procedure, step *(h)* was conducted by using acetic anhydride that afforded **9** (both hydroxyl and amine was acetylated) in a yield of 94%. The ring closing step *(i)*

proceeded successfully to obtain **10** in a medium yield (37 %). Prolonged reaction time up to 5 h afforded a yield of 71% isolated yield. In the case of the intermediate **9a** (intermediate for Carbazomycin H), the ring closing took place, although in a poor selectivity producing the two isomers **10a**,**b**, which were difficult to separate. Therefore, we abandoned the further pathway designed for the synthesis of Carbazomycin H.

Thus, we focused to complete the synthesis of Carbazomycin G, which implied removal of the acetyl groups step *(j)* that involved an acidic hydrolysis in methanol to achieve compound **11** in a yield of 94%. The last two steps involve oxidation of **11** and a regio selective methylation, respectively. The oxidation step *(k)* was performed by using nitric acid. This method was developed by our group on an early stage of this project.[17] The oxidation product 1,4-quinone **12** was successfully obtained in a yield of 83%. The final step *(l)*[5c] comprising a regio-selective methylation of **12** that afforded the ultimate target molecule Carbazomycin G (**13**) in a yield of 51% and a not structure elucidated side product (15-20%, MW 225).

Conclusion

We have developed a total synthesis leading to the carbazole alkaloid carbazomycin G. The synthesis is composed of in total twelve steps, whereof each step afford medium to excellent yields, which resulting in an overall yield of 8.3%. This total synthesis is associated with a couple of fascinating organic reactions including Suzuki cross-coupling of congested chloroarenes and intramolecular C–H activation followed by C–N bond formation for the synthesis of novel congested intermediates.

Experimental section

Experimental Details. All reagents and solvents were purchased from commercial sources and used as received. Melting points were determined in open capillaries. Reagent grade chemicals were purchased from commercial sources and used without further purification. All reaction mixtures and column eluents were monitored by means of TLC (TLC plates Merck Kieselgel 60 F254). The TLC plates were observed under UV light at λ = 254 nm and λ = 365 nm. IR spectra were recorded as KBr discs with a Shimadzu FTIR-8300 spectrophotometer, and ^{1}H and ^{13}C NMR spectra were recorded with the Brüker instruments AC-200F (compounds **6** and **6'**), DMX 400WB, DPX 400, AV 500, and Biospin 850SB. High-resolution mass spectra (HRMS) were performed with a Q-TOF Micro YA263 instrument.

General Methods. GC analyses were performed with a capillary gas chromatograph equipped with a fused silica column (l25 m, 0.20 mm i.d., 0.33 mm film thickness) at a helium pressure of 200 kPa,

split less/split injector and flame ionization detector. Mass spectra were obtained with a GC–MS instrument, with a gas chromatograph equipped with a fused silica column (l30 m, 0.25 mm i.d., 0.25 mm film thickness) and helium as the carrier gas. DART mass spectra were obtained by using PEG as an internal standard in positive ionization mode with a TOF mass analyzer. ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature at a frequency of 400, 500, and 850 MHz and 100, 125, 212.5 MHz respectively. The chemical shifts are reported in ppm relative to residual $CDCl_3$ for proton (δ = 7.26 ppm), $CDCl_3$ for carbon (δ = 77.0 ppm), DMSO-d_6 for proton (δ = 2.50 ppm), and DMSO-d_6 for carbon (δ = 39.51 ppm) with tetramethylsilane as an external reference. Flash chromatography was performed by using the indicated solvent system and silica gel (230–400 mesh). All reagents used were commercially available from Aldrich Chemical Co. For intermediates and new compounds, HRMS data were also recorded.

The microwave-assisted experiments were performed by means of a Biotage Initiator Sixty EXP Microwave System, that operates at 0–400 W at 2.45 GHz, in the temperature range of 40–250 °C, a pressure range of 0–20 bar (2 MPa, 290 psi), and with reactor vial volumes of 0.2–20 mL.

2,4-Dimethoxy-3-methyl phenol (2) [19676-67-6]. To a solution of 2, 6-dimethoxy toluene **1** (3 g, 19.7 mmol) in acetonitrile (25 mL), was added trifluoroacetic acid (1.3 mL, 19.7 mmol) and hydrogen peroxide (35%, 3.5 mL, 39.4 mmol). The reaction mixture was stirred for 2 h at 75 ºC. The reaction mixture was cooled to room temperature and the solvent acetonitrile was removed under reduced pressure. The crude mixture was diluted with water (30 mL) and extracted with EtOAc (2 × 40 mL). The organic layers were combined and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The title compound was isolated by silica gel column chromatography [(EtOAc:Hx, 20:80)] as orange liquid (2.85 g, 85%); R_f = 0.49 [(EtOAc:Hx, 20:80)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.67 (d, *J*= 9 Hz, 1H), 6.46 (d, *J*= 9 Hz, 1H), 5.10 (s, br, 1H), 3.69 (s, 6H), 2.09 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$,): δ =151.9, 145.9, 142.8, 120.1, 111.8, 106.9, 60.9, 56.1, 9.3; MS (EI): m/z (%); 168 (100, M^+), 153 (61), 125 (49), 107 (23), 93 (9), 79 (11), 65 (21), 53 (12); IR (cm^{-1}): 3406, 2996, 2940, 2834, 1486, 1259, 1098, 730.

2,4-Dimethoxy-3-methylphenyl acetate (3) [96502-90-8]. To a solution of 2, 4-Dimethoxy-3-methyl phenol **2** (1.5 g, 8.9 mmol) in $CHCl_3$ (15 mL), was added acetyl chloride (1.3 mL, 17.8 mmol). The reaction mixture was heated for 2 h under reflux. The reaction mixture was cooled to ambient temperature and the solvent was removed under reduced pressure to afford the title compound as a dark orange liquid (1.75 g, 94%); R_f = 0.78 [(EtOAc:Hx, 40:60)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ =

6.86 (d, *J*= 8.5 Hz, 1H), 6.60 (d, *J*= 8.5 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 2.32 (s, 3H), 2.17 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.7, 156.4, 150.5, 137.6, 121.2, 119.7, 105.6, 60.8, 55.7, 20.7, 9.2; MS (EI): m/z (%): 210 (9, M^+), 168 (100), 153 (53), 139 (4), 125 (19), 107 (12), 79 (6), 65 (8), 53 (7); IR (cm^{-1}): 2940, 2838, 1759, 1484, 1199, 1106, 728.

2,4-Dimethoxy-3-methyl-5-nitrophenyl acetate (4) [192188-84-4]. 2,4-Dimethoxy-3-methylphenyl acetate **3** (1.6 g, 7.6 mmol) was dissolved in a solution of AcOH/Ac_2O (1:3 ratio, 12 mL) at 0-5 °C. A solution of HNO_3 (65 %, 1.0 mL, 14.5 mmol) in AcOH/Ac_2O (1:3 ratio, 12 mL) was added dropwise to the reaction mixture under vigorous stirring at 0-5 °C. When the addition was completed, the reaction mixture was stirred for 30 minutes at ambient temperature. The reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined and washed with $NaHCO_3$ (2 × 50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the title compound as a yellow liquid (1.49 g, 77 %); R_f = 0.70 [(EtOAc:Hx, 40:60)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.54 (s, 1H), 3.87 (s, 3H,), 3.83 (s, 3H), 2.33 (s, 3H), 2.26 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 168.7, 155.2, 151.3, 139.1, 138.8, 129, 118, 62.1, 60.9, 20.6, 10; MS (EI): m/z (%): 255 (4, M^+), 213 (100), 166 (26), 152 (8), 137 (8), 123 (11), 107 (10), 77 (14), 53 (14); IR (cm^{-1}): 2946,1770, 1522, 1343, 1187, 988, 729.

2,4-Dimethoxy-3-methyl-5-nitrophenol (5) [136763-93-3]. A solution of conc. HCl (12 mL) in MeOH (25 mL) was added dropwise to 2,4-dimethoxy-3-methyl-5-nitrophenyl acetate **4** (1.5 g, 5.9 mmol) at 0 °C . The reaction mixture was stirred for 1 h at 70 °C under reflux. The reaction mixture was cooled to ambient temperature and the solvent was removed under reduced pressure. The crude product was diluted with water (40 mL) and extracted with EtOAc (2 × 40 mL). The organic layers were combined and dried over Na_2SO_4 to afford the Criphol **5** as an orange colored solid (1.25 g, 99 %); R_f = 0.34 [(EtOAc:Hx, 20:80)]; mp 53-55 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (s, 1H), 3.78 (s, 6H), 2.21 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$): δ = 150.2, 146.3, 145.1, 140.0, 127.5, 109.4, 62.1, 61.0, 10; MS (EI): m/z (%): 213 (100, M^+), 166 (59), 152 (21), 137 (36), 125 (43), 122 (28), 91(23), 83(40), 77 (32), 53 (49); IR (cm^{-1}): 3418, 2944, 1519, 1338, 1245, 1102, 988, 733.

Telescoped procedure 1→5 [2,4-Dimethoxy-3-methyl-5-nitrophenol (5)]. 2,6-dimethoxy-toluene **1** (6.02 g, 40 mmol) was dissolved in glacial acetic acid (40 mL) that were added CF_3COOH (1.33 mL) and H_2O_2 (35%, 80 mmol) under vigorous stirring. The reaction mixture was continuously stirred for 2 h at 75 °C. After that, the post-reaction mixture was concentrated under reduced pressure. The

isolated product was added to water (100 mL), whereupon the resulting suspension was extracted with dichloromethane (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure, whereupon the residue was dissolved in $CHCl_3$ (70 mL) and AcCl (8 mL) was slowly added under vigorous stirring. The resulting mixture was stirred at reflux for 2 hours. Thereafter, the mixture was cooled at ambient temperature and the solvent removed under vacuum. The new crude product, containing **3** and unreacted **1,** was then dissolved in a solution of glacial acetic acid (12 mL) in acetic anhydride (36 mL) and the resulting mixture was cooled at ≈5°C in a ice-water bath. The mixture of HNO_3 (65 %, 2.27 mL) in AcOH (3 mL) and Ac_2O (12 mL) was then added drop-wise to the previous cooled mixture over a period of 2 h "in the dark"; at the end of this period all the solvents were removed under reduced pressure. The residue was dissolved in EtOH (80 mL) and a aqueous solution of NaOH (30%, 12 mL) was slowly added under vigorous stirring. The resulting mixture was stirred at ambient temperature for 2 h. The solvent was removed under reduced pressure, whereupon water (100 mL) was added and the resulting aqueous mixture was washed with CH_2Cl_2 (2 × 50 mL). The aqueous layer was acidified (pH ≈ 2) by adding conc. HCl under vigorous stirring and then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure, to obtain 3.8 g of Criphol **5** (45% yield) as dark solid product.

2-Iodo-4, 6-dimethoxy-5-methyl-3-nitrophenol (6') [1872386-67-8].[26] A solution of KI (0.332 g, 2 mmol) and iodine (0.295 g, 1.16 mmol) in H_2O (1 mL) was drop-wise added to a aqueous solution of $BuNH_2$ (20 %, 1.5 mL) and acetic acid 2,4-dimethoxy-3-methyl-5-nitrophenyl **4** (0.170 g, 0.67 mmol), for 1-2 min. at room temperature. The resulting dark mixture was stirred for 30 min. at room temperature, and then poured into CH_2Cl_2 (50 mL). The organic layer was washed with aqueous sodium thiosulfate (10 % , 30 mL), dried over anhydrous Na_2SO_4 and filtrated. After removal of the solvent under reduced pressure, the final crude (0.100 g) contained Criphol **5** as major product in a yield of 32 % (with a purity of 81 %), and 2,4-dimethoxy-3-methyl-5-nitrophenol as a major impurity. $C_9H_{10}NO_5I$ MW 339.09. ^1H NMR (200 MHz, $CDCl_3$, ppm): δ = 3.85 (s, 3H, -Ome), 3.79 (s, 3H, -Ome), 2.26 (s, 3H, -Me). ^{13}C NMR (200 MHz, $CDCl_3$, ppm): δ =146.7, 146.0, 144.3, 127.0, 71.1, 62.9, 61.1, 10.1. MS *m/z* (%): 339 (100), 324 (3), 278 (14), 263 (19), 248 (6), 235 (6), 207 (8), 179 (14), 167 (19), 151 (13), 136 (22), 123 (15), 108 (39), 93 (13), 79 (38), 67 (47), 53 (40), 43 (16).

2-Chloro-4, 6-dimethoxy-5-methyl-3-nitrophenol (6) [1872386-65-6]. To a solution of 2,4-dimethoxy-3-methyl-5-nitrophenol **5** (0.311 g, 0.145 mmol) in EtOH (15 mL), DCH (146 mg, 0.074

mmol) was added followed by drop-wise addition of conc. H_2SO_4 (≈ 24 drops) under good stirring. After the addition was completed, the reaction mixture was quenched with NaOH (4.1 M, 5 mL). A heavy red precipitation was observed during the addition of NaOH, which was neutralized with acetic acid (pH ≈ 4), and the resulting mixture was diluted with water (25 mL) and extracted with diethyl ether (3 × 40 mL). The organic layers were combined and dried with Na_2SO_4. The crude product was isolated by silica gel column chromatography (CH_2Cl_2/hexane, 40:60) to afford the title compound as pale yellow crystals (0.34 g, 95 %), m.p. 118.5 °C. R_f = 0.29 (CH_2Cl_2/hexane, 60:40). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.91 (s, 1 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 2.26 (s, 3 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 147.5, 144.0, 142.7, 125.6, 109.3, 62.9, 61.0, 9.9 ppm. MS (EI): *m*/*z* (%) = 247 (100, M^+), 217 (5), 213 (16), 186 (25), 171 (27), 138 (26), 108 (20), 83 (22), 77 (48), 67 (32). HRMS (EI): Calcd. for $C_9H_{10}ClNO_5$ 247.0248; Found 247.0248. IR (cm^{-1}) = 3406, 3083, 2970, 2929, 2846, 1500, 1108.

3,5-Dimethoxy-4-methyl-6-nitrobiphenyl-2-ol (7) [1872386-66-7]. In a microwave tube, 2-chloro4,6-dimethoxy-5-methyl-3-nitrophenol **6** (0.21 g, 0.85 mmol), phenylboronic acid (0.155 g, 1.27 mmol), Na_2CO_3 (0.10 g, 0.97 mmol), TBAB (0.021 g, 0.065 mmol) and $Pd(PPh_3)_4$ (0.025 g, 0.022 mmol) were added. The reaction mixture was carefully flushed with argon before adding a mixture of MeOH (4 mL) and water (1 mL), The tube was sealed and placed in the microwave cavity for 30 min. at 120 °C. The reaction mixture was diluted with water (40 mL) and extracted with diethyl ether (2 × 30 mL). The organic layers were combined and dried over Na_2SO_4. The crude product was isolated by silica gel column chromatography [(DCM:Hx, 40:60)] eluent to afford the title compound as yellow solid (0.122 g, 50 %); R_f =0.1 (CH_2Cl_2/hexane, 40:60); mp: 102.7°C; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.46-7.40 (m, 3H), 7.37-7.35 (m, 2H), 5.55 (s, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 2.33 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 147.2, 143.2, 142.9, 142.6, 130.8, 129.4, 128.9, 128.8, 125.6, 119.4, 62.8, 61.0, 10; MS (EI): m/z (%): 289 (100, M^+), 272 (7), 246 (20), 207 (24), 199 (13), 169 (13), 141 (20), 129 (40), 115 (33), 102 (12), 83 (23), 77 (20); HR-MS (EI): $(M+Na)^+$: Calcd for $C_{15}H_{15}NNaO_5$ 312.0848; Found 312.0846);: IR (cm^{-1}) = 3413, 2937, 2929, 2849, 1528, 1101, 991, 748.

3,3',5-trimethoxy-4-methyl-6-nitro-[1,1'-biphenyl]-2-ol (7a) [NEW]. In a microwave reactor tube, 2-chloro-4,6-dimethoxy-5-methyl-3-nitrophenol **6** (0.168 g, 0.68 mmol), 3-methoxy phenylboronic acid (0.155 g, 1.02 mmol), Na_2CO_3 (0.079 g, 0.75 mmol), TBAB (0.019 g, 0.05 mmol) and $Pd(PPh_3)_4$ (0.020 g, 0.018 mmol) were added. The reaction mixture was carefully flushed with argon before

adding a mixture of MeOH (4 mL) and water (1 mL), The tube was sealed and submerged in the microwave cavity for 30 min at 120 °C. The reaction mixture was diluted with water (40 mL) and extracted with diethyl ether (2 × 30 mL). The organic layers were combined and dried over Na_2SO_4. The crude product was isolated by silica gel column chromatography [(DCM:Hx, 40:60)] eluent to afford the title compound as yellow oil (0.109 g, 50 %); R_f =0.1 (CH_2Cl_2/hexane, 40:60); ^{1}H- NMR (500 MHz, $CDCl_3$): δ = 7.28 (t, *J*= 8Hz, 1H), 6.88-6.85 (m, 2H), 6.82 (s, 1H), 5.48 (s, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H), 2.25 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): *δ* = 159.8, 147.2, 143.2, 142.8, 142.4, 131.9, 130, 125.7, 121.6, 119.2, 114.9, 114.8, 62.8, 60.9, 10; MS (EI): m/z (%): 320 (17), 319 (100, M^+), 276 (33), 257 (15), 244 (22), 159 (32), 128 (35), 115 (45), 83 (38), 55 (22); HR-MS (DART): $(M+H)^+$: Calcd for $C_{16}H_{18}NO_6$ 320.1134; Found 320.1136); IR (cm^{-1}) = 3450, 2942, 2837, 1530, 1238, 1103, 997, 765.

6-amino-3,5-dimethoxy-4-methyl-[1,1'-biphenyl]-2-ol (8) [NEW]. 3,5-Dimethoxy-4-methyl-6-nitro-[1,1'-biphenyl]-2-ol **7** (0.20 g, 0.69 mmol) was dissolved in EtOH (4 mL) and transferred to a tube reactor. Then, a mixture of NH_4Cl (0.073 g, 1.38 mmol) in H_2O (1.2 mL) and indium powder (0. 238 g, 2.01 mmol) were added whereupon a magnetic stirrer bar was transferred to the tube. The tube was then sealed and the reaction mixture was stirred and heated at 120 °C for 3 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (30 mL) and filtered through a pad of celite. Another portion (20 mL) of ethyl acetate was used to wash through the filter pad. The resulting organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to obtain compound **8** as a purple oil (0.175 g, 98%).; R_f = 0.44 [(EtOAc:Hx, 30:70)]; ^{1}H-NMR (500 MHz, $CDCl_3$): *δ*= 7.50-7.47 (m, 3H), 7.43-7.40 (m, 2H), 5.30 (s, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 2.27 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): *δ*= 142.8, 138.5, 137.2, 134.4, 134.0, 130.5, 129.1, 127.7, 123.3, 113.0, 61.1, 59.5, 9.5; MS (EI): m/z (%): 260 (9), 259 (58, M^+), 244 (100), 229 (9), 216 (22), 201 (36), 184 (11), 144 (14), 128(11), 89 (8), 77(9); HR-MS (DART): $(M+H)^+$: Calcd for $C_{15}H_{18}NO_3$ 260.1287; Found 260.1287); IR (cm^{-1}): 3458, 3334, 3057, 2933, 2849, 1580, 1460, 994, 727.

6-amino-3,3',5-trimethoxy-4-methyl-[1,1'-biphenyl]-2-ol (8a) [NEW]. 3,3',5-trimethoxy-4-methyl-6-nitro-(1,1'-biphenyl)-2-ol **(7a)** (0.08 g, 0.25 mmol) was dissolved in EtOH (4 mL) and transferred to a tube reactor. Then, a slurry of NH_4Cl (0.027 g, 0.50 mmol) in H_2O (1.2 mL) and indium powder (0. 086 g, 0.75 mmol, 99.99% 100 mesh), use preferably a freshly opened bottle or stored under Ar) were added whereupon a magnetic stirrer bar was transferred to the tube. The tube

was then sealed and the reaction mixture was stirred and heated at 120 °C for 3 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (20 mL) and filtered through a pad of celite. Another portion (20 mL) of ethyl acetate was used to wash through the filter pad. The resulting organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure using a rotary evaporator to obtain the compound **8a** in purple oil (0.071 g, 98%).; R_f = 0.36 [(EtOAc:Hx, 30:70)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ= 7.40 (t, J = 8 Hz, 1H), 6.99-6.97 (m, 1H), 6.95-6.94 (m, 1H), 6.93-6.91 (m, 1H), 5.29 (s, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 2.27 (s, 3H),; ^{13}C-NMR (125 MHz, $CDCl_3$): δ= 160.1, 142.8, 138.5, 137.1, 135.3, 134.4, 130.2, 123.4, 122.7, 115.8, 113.6, 112.8, 61.0, 59.5, 55.3, 9.5; MS (EI): m/z (%): 290 (12), 289 (74, M^+), 274 (100), 259 (12), 246 (26), 231 (25), 137 (14), 130 (32), 115 (15), 83 (14), 77(10);HR-MS (DART): $(M+H)^+$: Calcd for $C_{16}H_{20}NO_4$ 290.1392; Found 290.1395); IR (cm^{-1}): 3458, 3341, 3057, 2933, 2849, 1580, 1360, 994, 727.

6-acetamido-3,5-dimethoxy-4-methyl-(1,1'-biphenyl)-2-yl acetate (9) [2041574-03-0]. In a round bottom flask (50 mL), 6-amino-3,5-dimethoxy-4-methyl-(1,1'-biphenyl)-2-ol **8** (0.12 g, 0.46 mmol) was dissolved in dry CH_2Cl_2 (10 mL) under inert atmosphere. To the stirred solution added triethylamine (0.14 mL, 0.97 mmol). The solution was cooled under ice bath and added acetic anhydride (0.09 mL, 1.01 mmol) dropwise to the reaction mixture. The reaction mixture was stirred at room temperature for 1 hour. The residue was diluted in EtOAc (50 mL) and washed with water (40 mL). The organic layer was washed with $NaHCO_3$ (30 mL) and finally dried over Na_2SO_4. The solvent was evaporated under reduced pressure to obtain the acetylated product **9** (0.148 g, purple liquid) in 94 % crude yield. R_f = 0.74 [(EtOAc:Hx, 50:50)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.34 (m, 3H), 7.20 (m, 2H), 6.50 (s, br, 1H), 3.76 (d, J=8.5Hz, 6H), 2.29 (s, 3H), 2.17 (s, 3H), 1.99 (s, 3H); MS (EI): m/z (%): 343 (11, M^+), 301 (46), 270 (24), 244 (100), 201 (24), 144 (51), 128 (39), 115 (60), 89 (72), 83(94), 77(47), 55(43); HR-MS (DART): $(M+H)^+$: Calcd for $C_{19}H_{22}NO_5$ 344.14980; Found 344.14999; IR (cm^{-1}): 2928, 2552, 1669, 1603, 1451, 1422, 1290, 1205, 707.

6-acetamido-3,3',5-trimethoxy-4-methyl-(1,1'-biphenyl)-2-yl acetate (9a) [NEW]. In a round bottom flask (50 mL), 6-amino-3,3',5-trimethoxy-4-methyl-(1,1'-biphenyl)-2-ol **8a** (0.13 g, 0.45 mmol) was dissolved in dry CH_2Cl_2 (10 mL) under inert atmosphere. Triethylamine (0.13 mL, 0.97 mmol) was then added to the stirred mixture. The solution was cooled under ice bath and added acetic anhydride (0.09 mL, 1.01 mmol) drop-wise to the reaction mixture. The reaction mixture was stirred at room temperature for 1 hour. The residue was diluted in EtOAc (50 mL) and washed with water

(40 mL). The organic layer was washed with $NaHCO_3$ (30 mL) and finally dried over Na_2SO_4. The solvent was evaporated under reduced pressure to obtain the acetylated product **9a** (0.131 g, purple liquid) in 92% crude yield. R_f = 0.67 [(EtOAc:Hx, 50:50)]; MS (EI): m/z (%): 373 (16, M^+), 332 (12), 331 (68), 316(7), 300 (26), 274 (100), 256 (11), 242 (13), 231 (11), 174 (12), 115 (9), 83 (15). The acetylated product **9a** was used in the next step without further purification.

9-acetyl-1,3-dimethoxy-2-methyl-9*H*-carbazol-4-yl acetate (10) [2041574-04-1]. 6-Acetamido-3,5-dimethoxy-4-methyl-(1,1'-biphenyl)-2-yl acetate **9** (0.063 g, 0.183 mmol) was dissolved in glacial acetic acid (5 mL), $Pd(OAc)_2$ (2.1 mg, 0.009 mmol), IMes · HCl (3.2 mg, 0.009 mmol), and H_2O_2 (35%, 0.05 mL, 0.53 mmol) were added. The vial was sealed whereupon a magnetic stirrer bar was transferred to the tube. The tube was submerged in the microwave cavity at 120 °C for 5 h. The reaction mixture was monitored by means of GC (94% yield). The crude product was dissolved in EtOAc (20 mL) and washed with water (25 mL). The water phase was extracted with EtOAc (2 × 15 mL). The combined layer was washed with aq. $NaHCO_3$ (20 mL). The organic layer was dried over Na_2SO_4 and filtered off. The solvent was evaporated under reduced pressure. The crude product was purified by using silica gel column chromatography (20:80, EtOAc:Hx) to obtain the *N*-acetyl Carbazole compound **10** (0.043 g, brown liquid) in 71% yield. R_f = 0.33 [(EtOAc:Hx, 20:80)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.26 (d, *J*= 8.5 Hz, 1H), 7.83 (d, *J*= 7.5 Hz, 1H), 7.45 (t, *J*= 7.5 Hz, 1H), 7.33 (t, *J*= 7.5 Hz, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 2.62 (s, 3H), 2.54 (s, 3H), 2.39 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 172.8, 168.6, 147.4, 144.0, 140.4, 134.8, 128.5, 127.7, 124.9, 123.7, 123.6, 121.1, 119.7, 115.1, 61.1, 60.0, 26.8, 20.8, 10.2; MS (EI): m/z (%): 341 (11, M^+), 299 (19), 257 (46), 242 (100), 226 (11), 196 (12), 168 (22), 154 (23), 127 (22), 115 (27), 89(12), 77(12), 55(12);HR-MS (DART): $(M+H)^+$: Calcd for $C_{19}H_{20}NO_5$ 342.1341; Found 342.1343); IR (cm^{-1}): 2935, 1766, 1702, 1445, 1398, 1367, 1269, 1254, 1183, 1082, 1002, 749.

9-acetyl-1,3,6-trimethoxy-2-methyl-9*H*-carbazol-4-yl acetate (10a) & 9-acetyl-1,3,8-trimethoxy-2-methyl-9*H*-carbazol-4-yl acetate (10b) (mixture of isomers). 6-Acetamido-3,3',5-trimethoxy-4-methyl-[1,1'-biphenyl]-2-yl acetate **9a** (0.130 g, 0.348 mmol) was dissolved in glacial acetic acid (5 mL), $Pd(OAc)_2$ (8 mg, 0.024 mmol), IMes · HCl (12 mg, 0.024 mmol) and H_2O_2 (35%, 0.09 mL, 1.0 mmol) were added. The vial was sealed whereupon a magnetic stirrer bar was transferred to the tube. The tube was submerged in the microwave cavity at 120 °C for 5 hours. The reaction mixture was monitored by means of GC (50% yield). Acetic acid was removed under reduced pressure. The crude product was dissolved in EtOAc (40 mL) and washed with water (25 mL). The

water phase was extracted with EtOAc (2 × 40mL). The combined organic layer was washed with aq. $NaHCO_3$ (30 mL). The organic layer was dried over Na_2SO_4 and filtered off. The solvent was evaporated under reduced pressure. The crude product was purified by using silica gel column chromatography (20:80, EtOAc:Hx) afforded a mixture of the isomers **10a** and **10b** in a yield of 30%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.13 (d, *J*= 9 Hz, 1H), 7.64 (d, *J*= 7.5 Hz, 1H), 7.54-7.55 (m, 1H), 7.32 (t, *J*= 8 Hz, 1H), 7.25 (m, 1H), 6.96-6.98 (dd, *J*= 2.5, 9 Hz, 1H), 3.82 (s, 1H), 3.79 (s, 3H), 3.77 (s, 1H), 3.65 (s, 3H), 2.54 (s, 3H), 2.47 (s, 3H), 2.31 (s, 3H),; ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 172.5, 168.6, 159.6, 156.3, 147.4, 144.2, 135.1, 134.7, 130.5, 129.5, 129.1, 125.1, 124.6, 122.6, 120.4, 119.7, 116.2, 114.4, 114.3, 105.5, 61.1, 59.9, 55.8, 55.5, 26.6, 20.8, 10.2; MS (EI): m/z (%): 371 (7, M^+), 331 (11), 287 (28), 272 (62), 207 (69), 115 (34), 96 (38), 83 (42), 77(76).

1,3-dimethoxy-2-methyl-9*H*-carbazol-4-ol (11) [NEW]. To a stirred solution of 9-acetyl-1,3-dimethoxy-2-methyl-9*H*-carbazol-4-yl acetate **10** (0.023 g, 0.07 mmol) in methanol (10 mL) at 0 °C , was added a solution of Conc.HCl (2 mL) in MeOH (5 mL) dropwise. The reaction mixture was stirred for 1 h at 70 °C. The reaction mixture was cooled to room temperature. The reaction mixture was diluted with water (40 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layer was dried over Na_2SO_4. The solvent was filtered off to obtain the compound **11** as a brown solid (0.017 g, 94%). R_f = 0.42[(EtOAc:Hx, 20:80)]; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.24 (d, *J*= 8 Hz, 1H), 8.10 (s, br, 1H), 7.41 (m, 1H), 7.39-7.35 (td, *J*= 1.0 Hz, 6.5 Hz, 1H), 7.24-7.20 (m, 1H), 6.03 (s, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 2.42 (s, 3H),; ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 140.7, 139.1, 137.6, 135.8, 130.7, 125.0, 123.2, 122.6, 121.0, 119.5, 110.6, 110.2, 61.3, 60.8, 9.8; HR-MS (DART): $(M+H)^+$: Calcd for $C_{15}H_{16}NO_3$ 258.1130; Found 258.1133); IR (cm^{-1}): 3309, 3244, 2973, 2924, 2896, 1624, 1321, 1087, 1046, 879.

3-methoxy-2-methyl-1-carbazole-1,4 (9*H*)-dione (12) [192188-88-8]. To a solution of 1,3-dimethoxy-2-methyl-9*H*-carbazol-4-ol **(11)** (40 mg, 0.155 mmol) in glacial acetic acid (3 mL), HNO_3 (90%, 0.01 mL, 0.186 mmol) was added slowly at 0-5 °C. Then, the reaction mixture was stirred at ambient temperature for 15 min. After the reaction time, H_2O (20 mL) was added to the solution and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with H_2O (2 × 40 mL) and dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. The crude product was purified by using silica gel column chromatography (50:50, DCM:Hx) to obtain the compound **12** as a pale-green solid (36 mg, 0.124 mmol) R_f = 0.86[(EtOAc:Hx, 50:50)]; ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 12.85 (s, br, 1H), 8.01 (d, *J*= 8 Hz, 1H), 7.53 (m, , 1H), 7.35-7.38 (td, *J*=

1.0, 8.0 Hz, 1H), 7.29-7.32 (td, *J*= 1.0 Hz, 8.0 Hz, 1H), 4.03 (s, 3H), 1.92 (s, 3H); ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 180.5, 178.7, 157.8, 137.6, 136.4, 129.3, 128.4, 126.6, 126.0, 123.8, 121.4, 113.7, 61.2, 8.4; HR-MS (ESI-): $(M-H)^+$: Calcd for $C_{14}H_{10}NO_3$ 240.06606; Found 240.06632); IR (cm^{-1}): 3257, 2958, 2923, 2853, 1639, 1258, 1094, 1022, 794.

Carbazomycin G (1-hydroxy-3-methoxy-1,2-dimethyl-1,9-dihydro-4*H*-carbazol-4-one) (13) [115920-44-0]. To a vacuum dried Schlenk tube, the solution of compound **12** (0.022 g, 0.091 mmol) dissolved in THF (10 mL) was added under Ar atmosphere. The solution was cooled at –78 °C (using a dry ice and acetone mixture). A solution of methyllithium (1.6 M in Et_2O, 0.26 mL, 0.42 mmol) was added dropwise at –78 °C. The reaction mixture was left (≈30 min.) to approach room temperature. Then NH_4Cl (10%, 10 mL) was added to quenched the reaction, whereupon the post-reaction mixture was extracted with EtOAc (2 × 50 mL). The organic extracts were combined and dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by using silica gel column chromatography (50:50, EtOAc:Hx) to obtain the compound **13** as a pale-yellow solid (51%, 12 mg, 0.047 mmol) R_f = 0.41[(EtOAc:Hx, 50:50)]; ^{1}H-NMR (850 MHz, DMSO-d_6): δ = 12.19 (s, br, 1H), 8.01 (d, *J*= 7.7 Hz, 1H), 7.44 (d, *J*= 7.7 Hz, 1H), 7.22 (t, *J*= 7.7 Hz, 1H), 7.17 (t, *J*= 7.7 Hz, 1H), 5.92 (s, 1H), 3.69 (s, 3H), 1.98 (s, 3H), 1.57 (s, 3H); ^{13}C-NMR and DEPT (212.5 MHz, DMSO-d_6): δ = 177.6 (C=O), 154.4 (C), 147.7 (C), 140.8 (C), 136.5 (C), 123.9 (C), 122.9 (CH), 121.4 (CH), 120.5 (CH), 112.0 (CH), 108.4 (C), 67.4 (C), 59.2 (CH_3), 27.9 (CH_3), 10.1 (CH_3); HR-MS (ESI-): $(M-H)^+$: Calcd for $C_{15}H_{14}NO_3$ 256.09737; Found 256.09799); IR (cm^{-1}): 3255 br, 2924, 2853, 1719, 1643, 1618, 1468, 1375, 1289, 1138, 1092, 1011, 961, 804, 748.

Acknowledgments

V. E. gratefully acknowledges Department of Chemistry at the University of Bergen for his research fellowship. C. G. acknowledges financial support from Department of Chemistry at University of Bergen in connection with several research stays. Dr. Bjarte Holmelid is acknowledged for excellent technical support with the HRMS analyses.

References

[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. g) M. Kaneda,T. Naid, T.

Kitahara, S. Nakamura, T. Hirata, T. Suga, *J. Antibiot.***1988**, *41*, 602-608. h) D. J. Hook, J. J. Yacobucci, S. O'Connor, M. Lee, E. Kerns, B. Krishnan, J. Matson, G. Hesler, *J. Antibiot.* **1990***, 43,* 1347-1348.

[2] T. Nishiyama , N. Hatae , T. Yoshimura , S. Takaki, T. Abe, M. Ishikura , S. Hibino, T. Choshi, *Eur. J. Med. Chem*. **2016**, *121*, 561-577.

[3] K. Sakano, K. Ishimaru, S. Nakamura, *J. Antibiot.* **1980**, *33*, 683-689.

[4] M. Kaneda, T. Naid, T. Kitahara, S. Nakamura, T. Hirata, T. Suga, *J. Antibiot.* **1988**, *41*, 602–608.

[5] a) H.-J. Knölker, K. R. Reddy. *Chem. Rev*. **2002**, *102*, 4303-4427. b) H. Hagiwara, T. Choshi, H. Fujimoto, H. Hibino. *Tetrahedron*, **2000**, *56*, 5807-5811. c) H.-J. Knölker, W. Frihner, K. R. Reddy. *Eur. J. Org. Chem*. **2003**, 740-746. d) H.-J. Knölker, W. Frihner. *Tetrahedron Lett.* **1997**, *38*, 4051-4054. e) S. Chakraborty, C. Saha. *Eur. J. Org. Chem*. **2013**, 5731-5736. f) Y. An, Y. Wang, X. Hu. *Eur. J. Org. Chem*. **2014**, 3715-3718; g) C. J. Moody, *Synlett* **1994**, 681-688.

[6] a) H.-J. Knölker, M. Bauermeister, D. Blaser, R. Boese, J.-B. Pannek, *Angew. Chem.* **1989***, 101*, 225-227. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 223-225. b) H.-J. Knolker, M. Bauermeister, *J. Chem. Soc. Chem. Commun.* **1989**, 1468-1470**;** H.-J. Knolker, M. Bauermeister, *Helv. Chim. Acta.* **1993***, 76*, 2500-2514.

[7] H.-J. Knölker, G. Schlechtingen, *J. Chem. Sot. Perkin Trans. 1* **1997**, 349-350

[8] H.-J. Knölker, M. Bauermeister, *Heterocycles.* **1991**, *32*, 2443-2450.

[9] a) H.-J. Knölker, in *Transition Metals for Organic Synthesis*, vol. 1 (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**, chap. 3.13. b) H.-J. Knölker, *Chem. Soc. Rev.* **1999**, *28*, 151-157. c) H.-J. Knölker, A. Braier, D. J. Bröcher, S. Cämmerer, W. Fröhner, P. Gonser, H. Hermann, D. Herzberg, K. R. Reddy, G. Rohde, *Pure Appl. Chem.* **2001**, *73*, 1075-1086.

[10] a) H.-J. Knölker, W. Frohner, *Tetrahedron Lett.* **1997**, *38*, 4051–4054. b) H.-J. Knölker, W. Frohner, K. R. Reddy, *Eur. J. Org. Chem.* **2003**, 740–746.

[11] 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.

[12] H. Hagiwara, T. Choshi, H. Fujimoto, E. Sugino, S. Hibino, *Tetrahedron.* **2000**, *56*, 5807–5811.

[13] Y. An, Y. Wang, X. Hu. *Eur. J. Org. Chem*. **2014**, 3715-3718.

[14] S. Chakraborty, C. Saha. *Eur. J. Org. Chem*. **2013**, 5731-5736.

[15] H.-R Bjørsvik , V. Elumalai. *Eur. J. Org. Chem*, **2016**, 5474-5479.

[16] a) D. L. J. Clive, N. Etkin, T. Joseph, J. W. Lown. *J. Org. Chem*. **1993**, *58*, 2442-2445. b) H.-J. Knölker, R. W. Fröhner, K. R. Reddy. *Eur. J. Org. Chem.* **2003**, 740-746.

[17] R. R. González, C. Gambarotti, L. Liguori, H.-R. Bjørsvik, *J. Org. Chem.* **2006**, *71*, 1703-1706.

[18] C. Gambarotti, H.-R. Bjørsvik. *J. Phys. Org. Chem.* **2015**, *28*, 619–628.

[19] D. Crich, S. Rumthao, *Tetrahedron.* **2004**, *60*, 1513–1516.

[20] A. H. Sandtorv, H.-R. Bjørsvik, *Adv. Synth. Catal.* **2013**, *355*, 499–507.

[21] R. R. González, L. Liguori, A. M. Carrillo, H.-R. Bjørsvik, *J. Org. Chem.* **2005**, *70*, 9591–9594.

[22] V. Elumalai, A. H. Sandtorv, H.-R. Bjørsvik. *Eur. J. Org. Chem*, **2016**, 1344-1354.

[23] V. Elumalai, H.-R. Bjørsvik. *Tetrahedron Lett.* **2016**, *57*, 1224–1226.

[24] a) R. J. Rahaim, R. E. Maleczka, *Org. Lett.* **2005**, *7*, 5087–5090. b) M. Suchy, P. Winternitz and M. Zeller, **1991**, Patent WO1991000278. c) C. Macleod, G. McKiernan, E. Guthrie, L. Ferrugia, D. Hamprecht and R. Harteley, *J. Org. Chem*. **2003**, *68*, 387–401. d) Y. Liu, Y. Lu, M. Prashad, O. Repic and T. Blacklock, *Adv. Synth. Catal*. **2005**, *347*, 217-219. e) B. A. Fox, T. L. Threlfall, *Org. Synth*. **1973**, *Coll. Vol. 5*, 346-351. e) A. Albert, W. H. Linnel, *J. Chem. Soc*. **1936**, 1614-1619. f) F. D. Bellamy, K. Ou, *Tetrahedron. Lett*. **1984**, *25*, 839–842. g) M. K. Basu, *Tetrahedron Lett*. **2000**, *41*, 5603–5606. h) J. Matthews, M. Greco, L. Hecker, W. Hoekstra, P. Andrade-Gordon, L. De Garavilla, K. Demarest, E. Ericson, J. Gunnet, W. Hageman, R. Look, J. Moore and B. Marynoff, *Bioorg. Med. Chem. Lett*. **2003,** *13*, 753-756. i) J. Edwards, L. Zhi, C. L. F. Pooley, C. Tegley, S. West, M.-W. Wang, M. Gottardis, C. Patharanna, W. Scharader, T. Jones, *J. Med. Chem.*, **1998**, *41*, 2779-2875. j) A. Burawoy and J. Critchley, *Tetrahedron*, **1959**, *5*, 340-351. k) B. Raju, R. Ragul, B. N. Sivasankar, *Indian J. Chem*. **2009**,

48, 1315–1318. l) M. Somei, K. Kato, S. Inoue, *Chem. Pharm. Bull.* **1980**, *28*, 2515–2518. m) C. T. Redemann, C. E. Redemann, *Org. Synth*. **1955**, Coll. Vol. 3, 69.

[25] a) C. J. Moody, M. R. Pitts, *Synlett*. **1988**, 1028. b) M. R. Pitts, J. R. Harrison, C. J. Moody, *J. Chem. Soc., Perkin Trans. 1*. **2001**, 955–977.

[26] D. Crich, S. Rumthao, *Tetrahedron.* **2004**, *60*, 1513 – 1516