Indoloquinones, Part 7. Total Synthesis of the Potent Lipid Peroxidation Inhibitor Carbazoquinocin C by an Intramolecular Palladium-Catalyzed Oxidative Coupling of an Anilino-1,4-benzoquinone

Hans-Joachim Knölker,* Wolfgang Fröhner, Kethiri R. Reddy
Institut für Organische Chemie, Technische Universität Dresden, Bergstraße 66, 01069 Dresden, Germany
Fax +49(351)46337030; E-mail: hans-joachim.knoelker@chemie.tu-dresden.de
Received 17 December 2001
Dedicated to Professor Ekkehard Winterfeldt on the occasion of his 70th birthday

Abstract: A highly efficient total synthesis of the potent lipid peroxidation inhibitor carbazoquinocin C is presented. The key-step is a palladium(II)-catalyzed oxidative cyclization of an anilino-1,4-benzoquinone to a carbazole-1,4-quinone which proceeds in up to 91% yield. Using this approach the natural product is obtained in four steps and 39% overall yield starting from aniline.

Key words: quinones, palladium catalysis, oxidative cyclization, total synthesis, carbazole alkaloids

Introduction

Oxygen-derived free radicals play a key role in the initiation of a variety of diseases, like myocardial and cerebral ischemia, arteriosclerosis, inflammation, rheumatism, senility, autoimmune diseases, and cancer. Therefore, free radical scavengers are believed to provide lead compounds for the development of potential novel drugs against these diseases. During their screening program for antioxidative substances Seto and co-workers isolated structurally unprecedented carbazole-3,4-quinone alkaloids from different Streptomyces species (Figure 1).

Carquinostatin A (1), isolated from Streptomyces exfoliatus 2419-SVT2 and lavanduquinocin (2), isolated from Streptomyces viridochromogenes 2942-SVS3, represent potent neuronal cell protecting compounds due to their antioxidative activity. The carbazoquinocins A–F (3a–f) were isolated from Streptomyces violaceus 2448-SVT2 and exhibit a strong inhibitory activity against lipid peroxidation induced by free radicals. In view of the large number of biologically active carbazole alkaloids which were isolated from natural sources, several groups became interested in their synthesis. We have an ongoing research project directed towards the development of novel transition metal-mediated and -catalyzed methodologies for the total synthesis of carbazole alkaloids. Using the iron-mediated construction of the carbazole framework by oxidative coupling of a fully functionalized arylamine and cyclohexa-1,3-diene we described the first total syntheses of carquinostatin A (1) and lavanduquinocin (2). A more direct synthesis of carquinostatin A (1) was achieved by oxidative coupling of 4-prenylaniline with an appropriately substituted 1,2-benzoquinone. In 1996 Ogasawara et al. reported the total synthesis of the first members of the carbazoquinocin family, carbazoquinocin A (3a) and carbazoquinocin D (3d). We anticipated that the application of our transition metal-mediated and/or -catalyzed processes furnishing the car-
bazole nucleus should provide convergent and therefore more simple routes to the carbazoquinocin family.

**Retrosynthetic Considerations**

The iron-mediated oxidative coupling of cyclohexa-1,3-diene (4) and 2-heptyl-4,5-dimethoxy-3-methylaniline (5) via a consecutive C–C and C–N bond formation led to the first total synthesis of carbazoquinocin C (3c) (Scheme 1).17

Our second approach utilized the palladium-catalyzed oxidative coupling of aniline (6) and 2-methoxy-3-methyl-1,4-benzoquinone (7) followed by regioselective alkylation for the total synthesis of carbazoquinocin C (3c).18

In a third total synthesis of carbazoquinocin C (3c) we applied the palladium-mediated oxidative coupling of aniline (6) and 4-heptyl-3-methyl-1,2-benzoquinone (8).15

Further total syntheses of carbazoquinocin C were subsequently reported by the groups of Hibino and Pindur.19,20

**Scheme 1** Retrosynthetic analyses of carbazoquinocin C (3c)

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**Biographical Sketches**

**Hans-Joachim Knölker** was born in 1958 in Rehren, Germany. He studied chemistry at the universities of Göttingen and Hannover, where he received his diploma degree in 1983 and his Ph.D. in 1985 with Professor E. Winterfeldt. He became interested in organometallic chemistry during his postdoctoral studies in the research group of Professor K. P. C. Vollhardt at the University of California in Berkeley. In 1987 he returned to the University of Hannover and finished his habilitation in 1990. He became Full Professor of Organic Chemistry in 1991 at the University of Karlsruhe. In 1998 he received a fellowship of the Japan Society for the Promotion of Science. In 2001 he moved to the Institute of Organic Chemistry at the Technical University of Dresden.

**Wolfgang Fröhner** was born in 1963 in Heidelberg, Germany. His professional training started at Teroson GmbH in Heidelberg where he graduated as a technician in chemistry. He studied chemistry at the University of Heidelberg and received his diploma degree in the group of Professor G. Ege in 1994. Subsequently, he joined the research group of Professor H.-J. Knölker at the University of Karlsruhe and received his Ph.D. in 1998. After six months at Rüters VFT in Castrop Rauxel he returned to the group of Professor H.-J. Knölker in Karlsruhe as a postdoctoral fellow (1999–2000). Since November 2000 he is a research scientist at the Nucleotide Analogue Design (NAD) AG in München.

**Kethiri Raghava Reddy** was born in 1963 in Garamilla Pally, Andhra Pradesh, India. He studied chemistry at Kakatiya University in Warangal, where he received his BSc in 1984 and MSc in 1987. After qualifying for the National Educational Test, he joined the group of Professor H. Ila at the North-Eastern Hill University in Shillong for a PhD, which he completed in 1995. He continued in the same group as research associate (CSIR) until 1996, when he moved as an Alexander von Humboldt fellow (1997–1999) to the research group of Professor H.-J. Knölker at the University of Karlsruhe, Germany. He continued as a post-doctoral fellow in the same group until 2001, when he followed the Knölker research group to the Technical University of Dresden as a staff scientist.
In the present article we describe full details of an optimized total synthesis of carbazoquinocin C (3c) based on the palladium-catalyzed oxidative coupling of aniline (6) and 2-methoxy-3-methyl-1,4-benzoquinone (7). Although being not as convergent as the two alternative syntheses depicted in Scheme 1, this approach to the natural product is currently the only one which is catalytic with respect to the transition metal. Moreover, the optimization of the second route is of more general importance for the total synthesis of biologically active carbazole alkaloids, since the same strategy has been applied previously to the palladium-catalyzed total synthesis of carbazomycin G, an antifungal carbazolequinol alkaloid isolated by Nakamura and co-workers from Streptovorticillium ehimense.

**Total Synthesis**

Our procedure for the preparation of 2-methoxy-3-methyl-1,4-benzoquinone (7) starts from commercial 2,6-dimethoxytoluene (9) (Scheme 2). It follows the first two steps for the preparation of the precursor for the iron-mediated synthesis of carbazomycin G, in which a 2,3,6-tri-oxygenated toluene has already been described. The titanium tetrachloride promoted Friedel-Crafts acylation of 2,6-dimethoxytoluene (9) provided the acetophenone (10). Compound 10 was transformed to the aryl acetate (11) by a proton-catalyzed Baeyer–Villiger oxidation. Cleavage of the ester led to the phenol (12). Oxidation of the phenol (12) with ceric ammonium nitrate (CAN) in a mixture of acetonitrile and water at 0 °C afforded 2-methoxy-3-methyl-1,4-benzoquinone (7).

The addition of aniline (6) to two equivalents of 2-methoxy-3-methyl-1,4-benzoquinone (7) in methanol at room temperature provided 5-anilino-2-methoxy-3-methyl-1,4-benzoquinone (13) (Scheme 3). The observed regioselectivity resulted from vinylogous addition of the amine to the more reactive carbonyl group. In this reaction the second equivalent of 2-methoxy-3-methyl-1,4-benzoquinone (7) was used for the oxidation of the initially formed anilinohydroquinone to the anilinobenzoquinone. Therefore, one equivalent of 2-methoxy-3-methylhydroquinone was generated during this process along with the desired product (78% yield). After separation of the anilinobenzoquinone by crystallization, the 2-methoxy-3-methylhydroquinone remaining in the mother-liquor was reoxidized to 2-methoxy-3-methyl-1,4-benzoquinone (7) with commercial 1,4-benzoquinone. The recycled 2-methoxy-3-methyl-1,4-benzoquinone (7) was reacted once again with aniline (6) to afford additional anilinobenzoquinone. Thus, the anilinobenzoquinone, which represents the precursor for the intramolecular palladium(II)-catalyzed oxidative coupling, could be obtained in a total yield of 84%.

The palladium-mediated oxidative cyclization of N,N-diarylamines described by Åkermark represents a highly efficient procedure for the synthesis of substituted carbazoles. The application of this method to the oxidative cyclization of 2-anilino-1,4-benzoquinones provided carbazole-1,4-quinones and was reported first by Furukawa and co-workers. However, the drawback of these intramolecular palladium(II)-mediated oxidative couplings is that stoichiometric amounts of palladium(II) were required because the final step is a reductive elimination which generates one equivalent of palladium(0). For the development of an oxidative cyclization which is catalytic with respect to the transition metal an in situ reoxidation of palladium(0) to palladium(II) was required because the final step is a reductive elimination which generates one equivalent of palladium(0). For the development of an oxidative cyclization which is catalytic with respect to the transition metal an in situ reoxidation of palladium(0) to palladium(II) was required. In the well-known Wacker process the reoxidation of palladium(0) is achieved with copper(II). The feasibility to achieve a palladium(II)-catalyzed oxidative cyclization by reoxidation of palladium(0) with copper(II) was demonstrated first in our earlier study describing the synthesis of benzocarbazole-6,11-diones. Åkermark and co-work-
ers subsequently reported the use of tert-butyl hydroperoxide for the reoxidation of palladium(0).32

The oxidative cyclization of the anilinobenzoquinone 13 using stoichiometric amounts of palladium(II) acetate in glacial acetic acid at reflux for 5 h under argon atmosphere provided the carbazole-1,4-quinone 14 in 83% yield (Scheme 3, Table 1). When the reaction was performed with 10 mol% of palladium(II) acetate in the presence of an excess of copper(II) acetate (2.5 equiv) in the air, the carbazole-1,4-quinone 14 was obtained in 71% yield after a reaction time of 17 h. However, the reaction did not become catalytic in copper(II). Decreasing the amount of copper(II) acetate led at the same time to a decrease of the yield of 14 down to a yield of only 24% with 25 mol% of copper(II). These results show that in contrast to the Wacker process mentioned above our oxidative cyclization under the reaction conditions applied in this study did not become catalytic in copper(II). We then investigated the variation of the amount of the palladium catalyst. Using 5 mol% of palladium(II) acetate provided the carbazole-1,4-quinone 14 in 56% yield. An increase of the amount of palladium catalyst to 20 mol% led only to an insignificant increase of the yield of 14 (73%), when the reaction time was about the same as in the 10 mol% experiment. However, we found that with 10 mol% of palladium(II) acetate the yield of the carbazole-1,4-quinone 14 could be increased to 78% by an extension of the reaction time to 4 days. Finally, using 30 mol% of palladium(II) acetate the oxidative cyclization of the anilinobenzoquinone 13 provided the carbazole-1,4-quinone 14 in 91% yield after a reaction time of 3 days.

Table 1  Optimization of the Oxidative Cyclization to the Carbazole-1,4-quinone 14

<table>
<thead>
<tr>
<th>Pd(OAc) 2 (equiv)</th>
<th>Cu(OAc) 2 (equiv)</th>
<th>Time (h)</th>
<th>Reaction Conditions</th>
<th>14 Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>–</td>
<td>5</td>
<td>HOAc, 117 °C, Ar</td>
<td>83</td>
</tr>
<tr>
<td>0.1</td>
<td>2.5</td>
<td>17</td>
<td>HOAc, 117 °C, air</td>
<td>71</td>
</tr>
<tr>
<td>0.1</td>
<td>2.2</td>
<td>17</td>
<td>HOAc, 117 °C, air</td>
<td>69</td>
</tr>
<tr>
<td>0.1</td>
<td>1.0</td>
<td>17</td>
<td>HOAc, 117 °C, air</td>
<td>54</td>
</tr>
<tr>
<td>0.1</td>
<td>0.25</td>
<td>18</td>
<td>HOAc, 117 °C, air</td>
<td>24</td>
</tr>
<tr>
<td>0.05</td>
<td>2.5</td>
<td>19</td>
<td>HOAc, 117 °C, air</td>
<td>56</td>
</tr>
<tr>
<td>0.05</td>
<td>2.5</td>
<td>40</td>
<td>HOAc, 117 °C, air</td>
<td>56</td>
</tr>
<tr>
<td>0.2</td>
<td>2.5</td>
<td>22</td>
<td>HOAc, 117 °C, air</td>
<td>73</td>
</tr>
<tr>
<td>0.1</td>
<td>2.5</td>
<td>96</td>
<td>HOAc, 117 °C, air</td>
<td>78</td>
</tr>
<tr>
<td>0.3</td>
<td>2.5</td>
<td>72</td>
<td>HOAc, 117 °C, air</td>
<td>91</td>
</tr>
</tbody>
</table>

The next important step for the total synthesis of carbazoquinocin C (3c) was the regioselective introduction of the heptyl side chain at C-1. We expected the 1,2-addition at C-4 to be disfavored due to the more deactivating effect of the vinylogous amide resonance contribution as compared to the vinylogous ester resonance of the C-1 carbonyl group. However, the addition of heptyllithium in tetrahydrofuran at –78 °C provided almost quantitatively a mixture of the desired carbazoquinol 15 and 3-heptyl-2-methylcarbazole-1,4-quinone 16 in a ratio of 1:2 along with a trace of the regioisomeric carbazoquinol 17 (Scheme 4, Table 2). Surprisingly, the major product was compound 16, resulting from a vinylogous addition of the metal reagent followed by elimination of methoxide. By changing to the corresponding Grignard reagent the carbazoquinol 15 became the major product with the best result (55% yield) being obtained at –78 °C. The structural assignment for the carbazoquinol 15 was based on comparison of its characteristic UV, 1H NMR, and 13C NMR spectral data with those of synthetic21,24 as well as natural22 carbazomycin G.

Table 2  Results of the Nucleophilic Addition of the Heptylmetal Reagents to the Carbazole-1,4-quinone 14

<table>
<thead>
<tr>
<th>C 7 H 15 –met (equiv)</th>
<th>Reaction Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C 7 H 15 Li (7.5)</td>
<td>THF, –78 °C, 2 h</td>
<td>33</td>
</tr>
<tr>
<td>C 7 H 15 MgCl (10.5)</td>
<td>THF, –78 °C, 0.5 h; then 25 °C, 17 h</td>
<td>43 23 31</td>
</tr>
<tr>
<td>C 7 H 15 MgCl (15)</td>
<td>THF, –78 °C, 3 h</td>
<td>55 8 0 trace</td>
</tr>
</tbody>
</table>

Cleavage of the methyl ether along with elimination of water was achieved by treatment of the carbazoquinol 15 with concentrated hydrogen bromide in methanol (1:2.5) and provided carbazoquinocin C (3c) in 92% yield (Scheme 5).
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Total Synthesis of the Potent Lipid Peroxidation Inhibitor Carbazoquinocin C

All spectral data described by Seto and co-workers for the natural product (UV, IR, \( ^1H \) NMR, and \( ^13C \) NMR) are in full agreement with those of our synthetic carbazoquinocin C (3c). The melting point for the carbazoquinocin C (3c) from the present synthesis (mp: 227–228 °C) from MeOH/H\(_2\)O is in good agreement with the value obtained by Hibino for his synthetic 3c (mp: 227–229 °C) from EtOAc).\(^{19}\) Whereas Seto reported a lower value for the natural product (mp: 210–212 °C from MeOH/H\(_2\)O),\(^5\) which was confirmed by the synthetic 3c from our iron-mediated synthesis (mp: 211–212 °C from pyridine)\(^{17}\) and by the synthetic 3c described by Pindur (mp: 212–213 °C from MeOH).\(^{20}\) This difference may be explained by polymorphism.

Conclusion

The synthesis reported above provides carbazoquinocin C (3c) in four steps and 39% overall yield based on aniline (6). The crucial step of our approach is the intramolecular palladium(II)-catalyzed oxidative coupling of the anilinobenzoquinine 13 to the carbazole-1,4-quinone 14 which was achieved in up to 91% yield. However, the best result could be obtained only when using 30 mol% of the palladium(II) catalyst and, in contrast to the Wacker oxidation copper(I) could not be used in catalytic amounts. These two facts emphasize that optimization is still required. The impact of the present work for the total synthesis of biologically active carbazole alkaloids is even broader than described, since the carbazole-1,4-quinone 14 could be applied to the synthesis of the other members of the carbazoquinocin family and, it represents also a precursor for carbazocycin B and G.\(^{21}\)

All reactions were carried out using dry solvents and under argon atmosphere unless otherwise stated. Flash chromatography: Merck silica gel (0.03–0.06 mm). Mps: Büchi 535. UV spectra: Perkin–Elmer Lambda 2 (UV/VIS spectrometer). IR spectra: Bruker IFS 88 (FT-IR). \(^1H\) NMR and \(^13C\) NMR spectra: Bruker AC-250, Bruker AM-400, and Bruker DRX-500; internal standard: TMS or the signal of the deuterated solvent; \(\delta\) in ppm; coupling constants (J) in Hz. MS: Finngan MAT-90: ionization potential: 70 eV. Elemental analyses: Heraeus CHN-Rapid.

1-(2,4-Dimethoxy-3-methylphenyl)ethanone (10)
Acetyl chloride (14.5 mL, 16.0 g, 204 mmol) was added to TiCl\(_4\) (22.6 mL, 39.1 g, 206 mmol) at −10 °C (on moderate warming a yellow solution was formed). After the temperature had dropped again, a solution of 2,6-dimethoxytoluene (9) (15.6 g, 102.5 mmol) in benzene (50 mL) was added within 10 min under vigorous stirring. During this addition the temperature was kept below 8 °C. After the addition was completed, the orange solution was stirred for 30 min at 0 °C. The reaction mixture was subsequently poured into cold HCl (5%, 450 mL) and extracted with Et\(_2\)O (3 × 100 mL). The combined organic layers were washed with HCl (5%, 2 × 100 mL), a sat. aq solution of NaHCO\(_3\) (2 × 100 mL), H\(_2\)O (100 mL) and dried (Na\(_2\)SO\(_4\)). After removal of the solvent the residue was distilled in vacuo to provide the acetophenone 10 as a pale yellow oil (bp: 87 °C/0.02 Torr), which crystallized in the refrigerator overnight, colorless crystals, yield: 18.9 g (95%), mp 35–36 °C (hexane) (Lit.\(^{21}\) 31–32 °C).

IR (DRIFT): 2965, 1660, 1588, 1358, 1273, 1110, 1002, 822 cm\(^{-1}\).

\(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) = 2.16 (s, 3 H), 2.62 (s, 3 H), 3.75 (s, 3 H), 3.87 (s, 3 H), 6.68 (d, 1 H, J = 8.8 Hz), 7.62 (d, 1 H, J = 8.8 Hz).

\(^13C\) NMR and DEPT (100 MHz, CDCl\(_3\)) \(\delta\) = 8.90 (CH\(_3\)), 30.28 (CH\(_3\)), 55.76 (CH\(_3\)), 61.85 (CH\(_3\)), 105.89 (CH\(_3\)), 120.20 (C), 125.53 (C), 128.98 (CH), 159.34 (C), 162.15 (C), 198.89 (C=O).

2,4-Dimethoxy-3-methylphenyl Acetate (11)
A solution of anhyd 3-chloropero benzoic acid (70–75%, 49.2 g, 200 mmol) in CH\(_2\)\(_2\)Cl\(_2\) (240 mL) was added over a period of 30 min to a vigorously stirred solution of the acetophenone 10 (25.9 g, 133.3 mmol) and TsoH (200 mg) in CH\(_2\)Cl\(_2\) (30 mL) at 0 °C. The resulting suspension was stirred for 30 min at 0 °C and for 4 h at r.t. Subsequently, an aq solution of Na\(_2\)SO\(_4\) (1 M, 100 mL) was added at 0 °C and the suspension stirred for 15 min at r.t. to destroy excess peracid. After the addition of an aq solution of Na\(_2\)CO\(_3\) (2 M, 100 mL) the suspension stirred for additional 15 min at r.t. The organic layer was separated and the aq layer was extracted with CH\(_2\)Cl\(_2\) (50 mL). The combined organic layers were washed with an aq solution of Na\(_2\)CO\(_3\) (10%, 100 mL), H\(_2\)O (100 mL), and dried (Na\(_2\)SO\(_4\)). Evaporation of the solvent and distillation of the residue in vacuo afforded a yellow oil (bp: 84 °C/0.02 Torr), which became a yellow solid (mp: 37–38 °C) in the refrigerator. A crystallization from hexane–Et\(_2\)O (5:1) at low temperature (−30 °C) provided the aryl acetate 11 as colorless crystals, yield: 25.6 g (91%), mp 40–41 °C (hexane–Et\(_2\)O, 5:1).

IR (DRIFT): 2965, 1758, 1486, 1228, 1210, 1108 cm\(^{-1}\).

\(^1H\) NMR (250 MHz, CDCl\(_3\)) \(\delta\) = 2.15 (s, 3 H), 2.32 (s, 3 H), 3.74 (s, 3 H), 3.81 (s, 3 H), 6.60 (d, 1 H, J = 8.9 Hz), 6.86 (d, 1 H, J = 8.9 Hz).

\(^13C\) NMR and DEPT (100 MHz, CDCl\(_3\)) \(\delta\) = 9.18 (CH\(_3\)), 20.77 (CH\(_3\)), 55.73 (CH\(_3\)), 60.78 (CH\(_3\)), 105.53 (CH), 119.68 (CH), 121.16 (C), 137.52 (C), 150.40 (C), 156.34 (C), 169.76 (C=O).

2,4-Dimethoxy-3-methylphenyl (12)
A solution of KOH (16.6 g, 296 mmol) in H\(_2\)O (20 mL) was added at r.t. over a period of 10 min to a stirred solution of the aryl acetate 11 (15.6 g, 74.2 mmol) in EtOH (200 mL). With moderate warming a brown solution was formed, which was stirred at r.t. for 1 h. Then, H\(_2\)O (80 mL) was added and the EOH was evaporated in vacuo. The aq layer was washed with Et\(_2\)O (100 mL). The solution of the phenolate was acidified with HCl (conc, about 21 mL) to pH < 1 and extracted with Et\(_2\)O (2 × 75 mL). The combined organic layers were washed with H\(_2\)O (100 mL) and dried (Na\(_2\)SO\(_4\)). Removal of the solvent and distillation of the residue in vacuo provided a red oil (bp: 83–84 °C/0.35 Torr), which became a light orange solid in the refrigerator, yield: 11.25 g (90%), mp 33–34 °C (Lit.\(^{26}\) 32.5–34 °C from pentane).

\(^1H\) NMR (250 MHz, CDCl\(_3\)) \(\delta\) = 2.17 (s, 3 H), 3.77 (s, 6 H), 5.40 (br s, 1 H), 6.53 (d, 1 H, J = 8.8 Hz), 6.75 (d, 1 H, J = 8.8 Hz).

Synthesis 2002, No. 4, 557–564 ISSN 0039-7881 © Thieme Stuttgart · New York
2-Methoxy-3-methyl-1,4-benzoquinone (7)

A solution of CAN (8.22 g, 15.0 mmol) in H₂O (10 mL) was added via a syringe pump over a period of 20 min to a stirred solution of the phenol 12 (1.01 g, 6.01 mmol) in MeCN (10 mL) at 0 °C. After stirring for additional 10 min at 0 °C, H₂O (50 mL) was added and the aq layer was extracted with Et₂O (3 × 20 mL). The combined organic layers were washed with H₂O (2 × 20 mL) and dried (Na₂SO₄). Evaporation of the solvent afforded a yellow oil which by a cycle of freeze in liquid nitrogen and thaw in vacuum (30 min) provided 2-methoxy-3-methyl-1,4-benzoquinone (7) as a yellow solid, yield: 820 mg (90%), mp 31–33 °C (Lit.²⁵ 29–30 °C).

1H NMR (250 MHz, CDCl₃): δ = 1.96 (s, 3 H), 4.03 (s, 3 H), 6.61 (d, 1 H, J = 10.0 Hz), 6.70 (d, 1 H, J = 10.0 Hz).

UV (MeOH): max = 212, 253, 277, 342 nm.

IR (DRIFT): 1640, 1619, 1534, 1300, 1104, 746, 740 cm⁻¹.

1H NMR (400 MHz, DMSO-d₆): δ = 1.90 (s, 3 H), 4.03 (s, 3 H), 7.28–7.38 (m, 2 H), 7.52 (d, 1 H, J = 7.8 Hz), 8.00 (d, 1 H, J = 7.5 Hz), 12.84 (br s, 1 H).

13C NMR and DEPT (100 MHz, DMSO-d₆): δ = 84.0 (CH₃), 60.97 (CH), 113.56 (C), 113.78 (CH), 121.36 (CH), 123.39 (CH), 123.73 (CH), 125.83 (CH), 126.24 (C), 135.98 (C), 137.47 (C), 157.59 (C), 178.32 (C=O), 180.45 (C=O).

MS (85 °C): m/z (%) = 241 (M⁺, 100), 240 (9), 226 (9), 212 (12), 198 (10), 170 (12).


1,4-Dihydro-1-heptyl-1-hydroxy-3-methoxy-2-methyl-9H-carbazol-4-one (15)

A solution of heptylmagnesium chloride in Et₂O (1.6 M, 1.35 mL, 2.16 mmol) was added dropwise to a stirred solution of the carbazolequinone 14 (50 mg, 0.205 mmol) in THF (10 mL) at –78 °C. After stirring for 30 min at –78 °C the resulting black colored reaction mixture was allowed to warm up to r.t. and the stirring was continued for 17 h. The mixture was poured into a sat. aq solution of NH₄Cl (25 mL) and extracted with Et₂O (3 × 25 mL). The combined organic layers were washed with H₂O (25 mL) and dried (Na₂SO₄). Removal of the solvent in vacuo and flash chromatography of the residue on silica gel (hexane–EtOAc, 1:5) afforded in the sequence of increasing polarity the compounds 16 as red crystals, yield: 15 mg (23%), 17 as a light yellow powder, yield: 22.3 mg (31%), and 15 as light yellow crystals, yield: 30.4 mg (43%).

b) A solution of heptylmagnesium chloride in Et₂O (1.6 M, 1.92 mL, 3.07 mmol) was added at once to a stirred solution of the carbazolequinone 14 (50 mg, 0.205 mmol) in THF (10 mL) at –78 °C. After stirring at –78 °C for 3 h, the mixture was poured into a sat. aq solution of NH₄Cl (25 mL) and extracted with Et₂O (3 × 25 mL). The combined organic layers were washed with H₂O (25 mL) and dried (Na₂SO₄). Removal of the solvent and flash chromatography of the residue on silica gel (hexane–EtOAc, 1:5) afforded in the sequence of increasing polarity the compounds 16 as red crystals, yield: 4.9 mg (8%), 17 as a trace, and 15 as light yellow crystals, yield: 38.4 mg (55%).

1,4-Dihydro-1-heptyl-1-hydroxy-3-methoxy-2-methyl-9H-carbazol-4-one (15)

A solution of heptylmagnesium chloride in Et₂O (1.6 M, 1.35 mL, 2.16 mmol) was added dropwise to a stirred solution of the carbazolequinone 14 (50 mg, 0.205 mmol) in THF (10 mL) at –78 °C. After stirring for 30 min at –78 °C the resulting black colored reaction mixture was allowed to warm up to r.t. and the stirring was continued for 17 h. The mixture was poured into a sat. aq solution of NH₄Cl (25 mL) and extracted with Et₂O (3 × 25 mL). The combined organic layers were washed with H₂O (25 mL) and dried (Na₂SO₄). Removal of the solvent in vacuo and flash chromatography of the residue on silica gel (hexane–EtOAc, 1:5) afforded in the sequence of increasing polarity the compounds 16 as red crystals, yield: 15 mg (23%), 17 as a light yellow powder, yield: 22.3 mg (31%), and 15 as light yellow crystals, yield: 30.4 mg (43%).

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FEATURE ARTICLE

Total Synthesis of the Potent Lipid Peroxidation Inhibitor Carbazoquinocin C

(92%), mp 227–228 °C (MeOH–H₂O) (Lit.⁶ 210–212 °C from MeOH–H₂O; Lit.⁷ 211–212 °C from pyridine; Lit.⁸ 227–229 °C from EtOAc; Lit.⁹ 212–213 °C from MeOH).

UV (MeOH): λₓₒ = 228, 265, 401 nm.

IR (DRIFT): 3216, 2927, 2856, 1640, 1627, 1467, 1249, 752 cm⁻¹.

1H NMR (500 MHz, DMSO-d₆); δ = 0.85 (t, 3 H, J = 6.8 Hz), 1.24–1.34 (m, 6H), 1.44 (m, 2 H), 1.54 (m, 2 H), 1.89 (s, 3 H), 2.64 (t, 2 H, J = 7.8 Hz), 7.23 (m, 2 H), 7.49–7.51 (m, 1 H), 7.84–7.86 (m, 1 H), 12.32 (br s, 1 H).

11C NMR and DEPT (125 MHz, DMSO-d₆); δ = 11.45 (CH₃), 13.94 (CH₂), 22.06 (CH₂), 28.06 (CH₂), 28.52 (CH₂), 29.00 (CH₃), 31.25 (CH), 111.04 (C), 113.37 (CH), 120.26 (CH), 123.95 (CH), 124.17 (CH₂), 125.66 (C), 131.10 (C), 137.06 (C), 142.12 (C), 145.62 (C), 172.71 (C=O), 183.46 (C=O).

MS (105 °C); m/z (%) = 311 (M⁺ + 2, 85), 310 (M⁺ + 1, 18), 309 (M⁺, 31), 281 (67), 238 (9), 226 (100), 225 (23), 197 (23), 196 (21), 168 (9), 167 (11).


Acknowledgement

We are grateful to the Fonds der Chemischen Industrie and the Alexander von Humboldt Stiftung for the financial support of our project.

References


