

Rhodium-Catalyzed [3 + 2]-Annulation of *ortho*-Diazoquinones with Enol Ethers: Diversity-Oriented Total Synthesis of Aflatoxin B₂

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A simple and efficient approach for synthesizing substituted and fused polycyclic 2,3-dihydrobenzofurans has been developed through a Rh-catalyzed [3 + 2]-annulation of *ortho*-diazo-

quinones with enol ethers. This methodology has a broad substrate scope and has been employed for the concise total synthesis of natural product aflatoxin B₂.

Introduction

Polycyclic acetals are prevalent in bioactive compounds, and mainly, tetrahydrofuro/pyrano-[2,3-*b*]benzofuran scaffold is frequently found in naturally occurring molecules with specific biological function. The representative examples having 2,3-dihydrobenzofuran core include erysenegalsein J, versicolorin B, microminutinin, rocaglamide, and members of the aflatoxin family (Figure 1).^[1]

The Aflatoxins are a group of structurally similar compounds belonging to the mycotoxins^[2] family produced by certain strains of *Aspergillus flavus*.^[3] These molecules are recognized as highly toxic and carcinogenic. Besides, they showed platelet-aggregation inhibition, antimicrobial, and antimitotic activities, which attracted synthetic community attention.^[4] Among the family members, Aflatoxin B₂ (1) gained significant attention in the scientific community, and several reports for its total synthesis are present in the literature.^[5] Most of the aflatoxins syntheses begin with the construction of tetrahydrofuro[2,3-*b*]benzofuran fragment, which is the ABC ring core structure of aflatoxins, followed by the late-stage installation of the cyclopentano-coumarin ring (D and E) using oxocyclopentene carboxylate fragment.^[5,6] In 2005, a one-step protocol for the installation of the cyclopentano-coumarin ring was developed by Corey^[5c] via Buchi's Pechmann type annulation.^[7] However, this transformation proceeded with a low (36 %) yield. Recently, the Zu group has also developed an efficient approach to aflatoxin B₂.^[5d]

Furthermore, several methods are available to synthesize ABC fragment tetrahydrofuro[2,3-*b*]benzofuran skeleton, as depicted in Scheme 1. For example, the Canesi group in 2008 demonstrated [3 + 2]-cycloaddition of phenols with furan,

allylsilanes, enol ethers, and electron-rich olefins using hyper-valent iodine reagent (Scheme 1a).^[8] However, this method exerts an insufficient degree of regiocontrol. Later, the Mazet group developed a method for synthesizing tetrahydrofurobenzofurans *via* a Pd-catalyzed enantioselective carboetherification of dihydrofurans (Scheme 1b).^[9] In 2013, the Lee group demonstrated the use of ceric ammonium nitrate (CAN) reagent for [3 + 2]-cycloaddition of 1,4-naphthoquinones with olefins for the synthesis of dihydronaphtho[1,2-*b*]furans, and showed applications of these compounds in medicinal chemistry (Scheme 1c).^[10] Further, this reaction was performed under

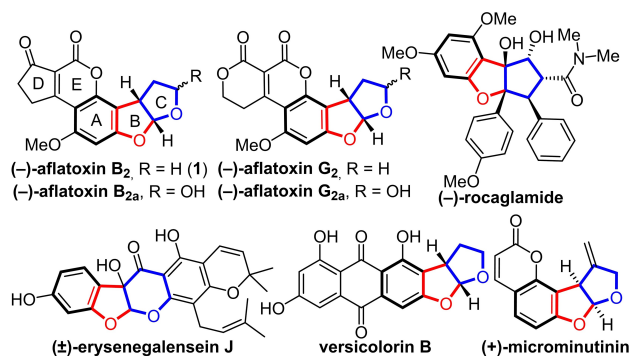
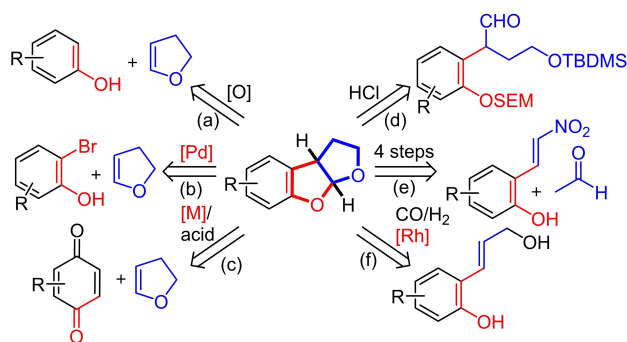


Figure 1. Representative natural products containing furo/pyrano-fused tetrahydrobenzofuran skeleton.



Scheme 1. Selected disconnections for tetrahydrofuro[2,3-*b*]benzofurans.

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Supporting information for this article is available on the WWW under
https://doi.org/10.1002/ejoc.202100186

asymmetric organocatalytic conditions to get high enantioselectivity and regioselectivity.^[11] Recently, the Lee group established a method for enantioselective synthesis of this tricyclic moiety *via* a sequence of organocatalytic Michael – acetalization – reduction – Nef reactions and demonstrated its application for formal synthesis of aflatoxin B₂ (Scheme 1e).^[6i] Additionally, the Eilbracht group employed rhodium – catalyzed tandem hydroformylation/acetalization of *o*-hydroxy cinnamyl alcohols and alkenediols to provide furobenzofurans and perhydrofurofurans/pyrans, respectively (Scheme 1f).^[12]

Although several methods are available, there is still a lack of a general approach, which could provide a diversity-oriented synthesis to this core structure. Building upon our work in the field of rhodium carbene chemistry,^[13] we sought to demonstrate additional applications of rhodium carbene chemistry for the synthesis of furo-/pyrano-benzofurans. We envisioned a retrosynthesis involving diazoquinones as a carbene precursor. Although rhodium-catalyzed decomposition of diazoquinones/naphthoquinones is known in the literature, their utility is not explored.^[14] Considering these facts, we began our efforts towards the synthesis of furo-/pyrano-benzofurans from *ortho*-diazoquinones.

Results and Discussion

In the initial study, various metal salts known for the decomposition of diazo compounds were investigated for the proposed reaction (Table 1). At first, the feasibility of the annulation of diazoquinone **2a** with 2,3-dihydrofuran (**3a**) was studied in the presence of Rh₂(OAc)₄ in dichloromethane at room temperature in a screw-capped vial. Although the

reaction was incomplete, it afforded the cyclized product **4aa** with 29% yield with high regio- and diastereoselectivity (Table 1, entry 1). The syn-stereochemistry was further confirmed by X-ray crystallography (CCDC number 2038490). To our delight, the yield of **4aa** was increased to 69% on heating the reaction at 60 °C (Table 1, entry 2). Furthermore, the various complexes of metals like rhodium, silver, gold, and copper were explored to improve the reaction yield (Table 1, entry 1 to 10). Surprisingly, the Rh₂(TPA)₄ provided the highest 86% yield of **4aa** among all screened catalysts. In the presence of Cu(OTf)₂ and [Cu(CH₃CN)₄]PF₆, the reaction became sluggish, and no product formation was noticed. With these results in hand, we next examined the compatibility of other solvents such as THF, toluene, and 1,2-dichloroethane (DCE) on the reaction. However, these efforts were unsuccessful in improving the yield of **4aa** (Table 1, entry 11 to 13). Additional experiments were also carried out to determine the optimal catalyst loadings and temperature for the annulation reaction. Fruitfully, 1 mol% catalyst loading provided an excellent yield of **4aa**.

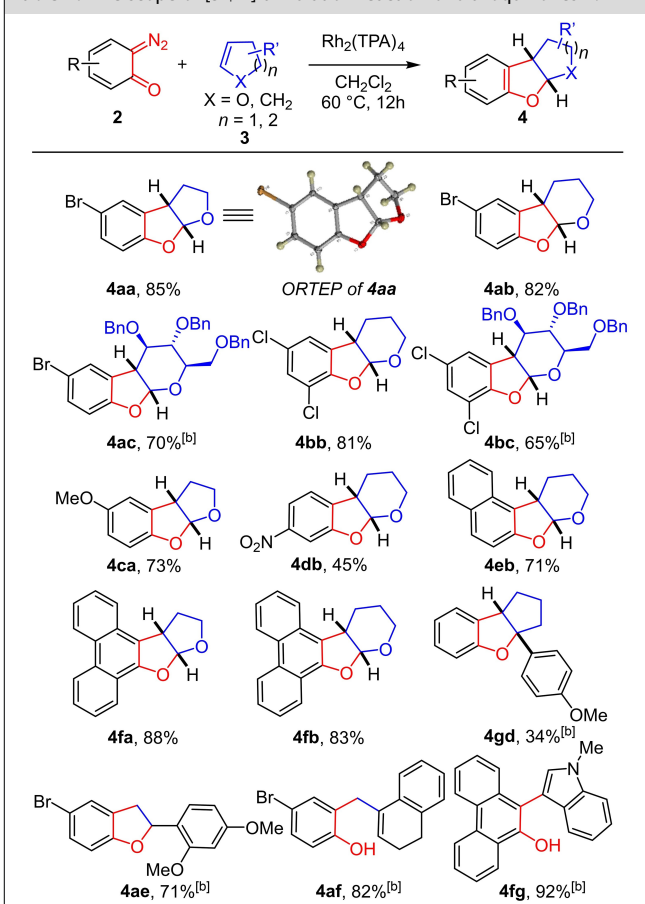
Having optimal reaction conditions in hand, the scope and limitations of the rhodium – catalyzed [3 + 2]-annulation were examined by employing substituted diazoquinones (Table 2).

Table 1. Optimization table for [3 + 2]-annulation.

Entry ^[a]	Catalyst	Solvent	Temp [°C]	Yield ^[b] [%]
1	Rh ₂ (OAc) ₄	CH ₂ Cl ₂	rt	29
2	Rh ₂ (OAc) ₄	CH ₂ Cl ₂	60	69
3	Rh ₂ (esp) ₂	CH ₂ Cl ₂	60	62
4	Rh ₂ (TFA) ₄	CH ₂ Cl ₂	60	43
5	Rh ₂ (HFB) ₄	CH ₂ Cl ₂	60	51
6	Rh ₂ (TPA) ₄	CH ₂ Cl ₂	60	86
7	AgPF ₆	CH ₂ Cl ₂	60	trace
8	AgPF ₆ , (PPh ₃)AuCl ^[c]	CH ₂ Cl ₂	60	trace
9	Cu(OTf) ₂	CH ₂ Cl ₂	60	–
10	[Cu(CH ₃ CN) ₄]PF ₆	CH ₂ Cl ₂	60	–
11	Rh ₂ (TPA) ₄	THF	60	35
12	Rh ₂ (TPA) ₄	toluene	60	79
13	Rh ₂ (TPA) ₄	DCE	60	81
14 ^[c]	Rh ₂ (TPA) ₄	CH ₂ Cl ₂	60	86 (85) ^[e]
15 ^[d]	Rh ₂ (TPA) ₄	CH ₂ Cl ₂	60	65
16	Rh ₂ (TPA) ₄	CH ₂ Cl ₂	40	76
17	Rh ₂ (TPA) ₄	CH ₂ Cl ₂	rt	53

[a] Reaction conditions: **2a** (0.2 mmol), **3a** (0.6 mmol), catalyst (5 mol%), and additives; solvent (1.5 mL). [b] Yields were calculated by crude ¹H NMR. [c] 1 mol% catalyst loading was used. [d] 0.5 mol% catalyst loading was used. [e] Isolated yield after column chromatography.

Table 2. The scope of [3 + 2]-annulation reaction of diazoquinones **2**.^[a]



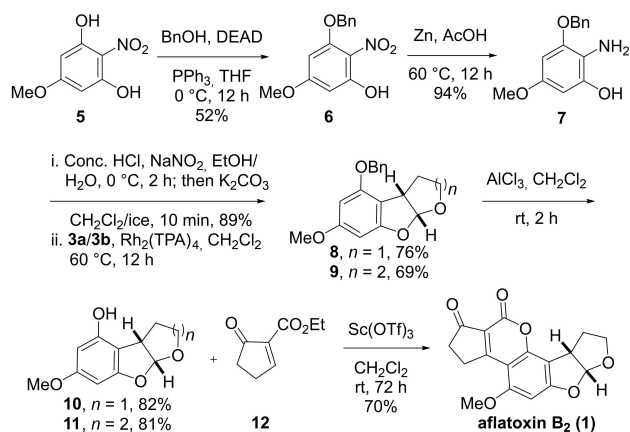
[a] Reaction conditions: **2** (0.2 mmol), **3** (0.6 mmol), Rh₂(TPA)₄ (1 mol%), dichloromethane (1.5 mL), 60 °C, 12 h; isolated yields after column chromatography. [b] 0.24 mmol of **3** was used.

The reactions of bromo- and chloro-substituted diazoquinones (**2a** and **2b**) with enol ethers like 2,3-dihydrofuran (**3a**), 3,4-dihydro-2H-pyran (**3b**), and D-glucal derivative **3c** were smooth, giving the corresponding annulation products in good to excellent yields (Table 2, **4aa** to **4bc**). The annulation of the electron-donating group like methoxy substituted diazoquinone provided good yield (Table 2, **4ca**; 73%); however, the reaction of electron-withdrawing nitro group substituted diazoquinone was quite sluggish and gave moderate yield (Table 2, **4db**; 45%). Subsequently, it has been observed that when the additional aromatic rings are present in diazoquinones, the yields are good (Table 2, **4eb** to **4fb**). These results indicated that the reaction is sensitive to the electronic properties of the substituents present on the diazoquinones.

After having substrate scope with enol ethers, we looked up to verify olefins and enamines' reactivity towards [3 + 2]-annulations with diazoquinones. At first instance, the annulation of diazoquinone **2g** was attempted with cyclopentene derivative **3d** to achieve the core structure of rolaglamide (Figure 1). The reaction was incomplete, and a considerable amount of starting material **3d** was found intact in the reaction mixture even after 36 h. However, the desired product **4gd** was obtained in 34% yield, and cyclopentene derivative **3d** (62%) was recovered (Table 2). On the other hand, when the reaction was carried out with 2,4-dimethoxy styrene (**3e**), the reaction was facile and provided **4ae** in 71% yield. Surprisingly, unsubstituted styrene could not offer a related product. These experiments suggested that the electron-rich olefins are obligatory to undergo [3 + 2]-annulation reactions with diazoquinones.

Next, the feasibility of the annulation reaction of terminal olefins and heteroaromatic compounds with diazoquinones was investigated. To our delight, the annulation reaction with terminal olefin proceeded in good yield (Table 2, **4ae**). However, undesired addition products were observed with 1-methylenetetrahydronaphthalene and *N*-methylindole instead of annulation (Table 2, **4af**, and **4fg**). The found outcomes were rational since the subsequent addition of the electron-rich center of olefin to the carbene center of diazoquinone provides stable carbocation, which undergoes spontaneous elimination to gain aromaticity (**4fg**). Furthermore, the reactions were attempted with enamine as well. Unfortunately, the annulation reaction provided the complex reaction mixture.

After successfully exploring and investigating [3 + 2]-annulation reactions of *ortho*-diazoquinones with enol ethers and olefins, we focused on applying the developed methodology to the diversity – oriented total synthesis of aflatoxin B₂ (**1**). In this vein, we planned to employ the developed methodology to synthesize tetrahydrofuro[2,3-*b*]benzofuran skeleton, followed by a step known protocol for installation of cyclopentano-coumarin ring to complete total synthesis of aflatoxin B₂. Accordingly, the synthesis was commenced with the mono-alkylation reaction of commercially available resorcinol derivative **5** (Scheme 2). Initially, several reactions were attempted for mono-benylation of **5** by using benzyl bromide with various base and solvent systems like K₂CO₃/acetone, K₂CO₃/DMF, NaH/THF, NaH/DMF at different reaction temperatures. However,



Scheme 2. Total synthesis of aflatoxin B₂.

these reactions were found unsuccessful as the desired nitrophenol **6** was obtained in trace amount along with major dibenylation product and recovered starting **5**. Afterward, the successful mono-alkylation was achieved by using the Mitsunobu reaction. The reaction of **5** proceeded smoothly with benzyl alcohol in the presence of DEAD and PPh₃ to afford nitrophenol **6** in moderate yield. Following this, the reduction of the nitro group of **6** was carried out by the treatment of zinc metal in AcOH to acquire aniline **7** with 94% yield. The obtained aniline **7** was further subjected to diazotization by using conc. HCl and NaNO₂, followed by the treatment of K₂CO₃ to get requisite diazoquinone.

At this point, we had the key diazoquinone precursor, the building block for the intended annulation reaction. Inevitably, we carried out [3 + 2]-annulation of synthesized diazoquinone with enol ethers **3a** and **3b** under established reaction conditions. The requisite annulation products **8** and **9** were obtained with 76% and 69% yields, respectively. Next, the benzyl group deprotection using AlCl₃ in CH₂Cl₂ gave the phenols **10** and **11** with good yields. After synthesizing tetrahydrofuro[2,3-*b*]benzofuran skeleton of aflatoxin B₂, we moved for the installation of the cyclopentano-coumarin ring to complete total synthesis. The reaction of tetrahydrobenzofuran **10** with carboxylate **12** proceeded through one-pot Pechmann type annulation followed by aerobic oxidation in the presence of Lewis acid Sc(OTf)₃ in CH₂Cl₂ to afford 70% yield.^[5d] Thus, the total synthesis of aflatoxin B₂ (**1**) was accomplished with an overall 19% yield from commercially available resorcinol derivative **5** in a linear six steps sequence.

Conclusion

In summary, we have developed an efficient approach for the synthesis of tetrahydrofuro/pyrano[2,3-*b*]benzofuran core, which is present in a variety of natural products. This [3 + 2]-annulation reaction accommodates a variety of substituted *ortho*-diazoquinones, enol ethers, and electron-rich olefins. The utility of these annulation reactions has been demon-

strated by accomplishing a diversity-oriented total synthesis of aflatoxin B₂.

Experimental Section

General Experimental Remarks: Reagents: Reagents and solvents were obtained from Sigma-Aldrich, Chem-Impex, or Acros Organics and used without further purification unless otherwise indicated. Dry solvents dichloromethane, dichloroethane were distilled over CaH under N₂ unless otherwise indicated. THF purchased from Sigma-Aldrich was distilled over Na metal with benzophenone indicator. Toluene was obtained from Sigma-Aldrich. **Reactions:** All reactions were performed in flame-dried glassware under positive N₂ pressure with magnetic stirring unless otherwise noted. Liquid reagents and solutions were transferred through rubber septa via syringes flushed with N₂ prior to use. Cold baths were generated as follows: 0 °C with wet ice/water. **Chromatography:** TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with potassium permanganate (KMnO₄), cerium ammonium molybdate (CAM), phosphomolybdic acid (PMA), and ninhydrin. Silica flash chromatography was performed on Sorbtech 230–400 mesh silica gel 60. **Analytical Instrumentation:** IR spectra were recorded on a Thermo Scientific Nicolet 6700 FTIR spectrometer with peaks reported in cm^{−1}. NMR spectra were recorded on a Varian V NMRS 400, 500, and 600 MHz NMR spectrometer in CDCl₃ unless otherwise indicated. Chemical shifts are expressed in ppm relative to solvent signals: CDCl₃ (¹H, 7.26 ppm, ¹³C, 77.0 ppm); coupling constants are expressed in Hz. NMR spectra were processed using Mnova. Mass spectra were obtained on an Advion Expression LCMS Mass Spectrometer or at the OU Analytical Core Facility on an Agilent 6538 High Mass-Resolution QTOF Mass Spectrometer and an Agilent 1290 UPLC. X-ray crystallography analysis was carried out at the University of Oklahoma using a Bruker APEX ccd area detector (1) and graphite monochromated Mo Kα radiation (λ = 0.71073 Å) source. Crystal structures were visualized using CCDC Mercury software. The diazo compounds **2a–2d** and **2g** were synthesized by following the literature protocol from the corresponding anilines.^[15] The diazo compounds **2e**,^[16] **2f**^[17] and the olefins **3c**,^[18] **3d**,^[19] **3e**,^[20] **3f**^[21] were synthesized by following literature protocol.

6-Diazo-4-methoxycyclohexa-2,4-dien-1-one (2c). ¹H NMR (400 MHz, CDCl₃) δ 7.11 (d, *J* = 3.1 Hz, 1H), 6.79 (d, *J* = 9.8 Hz, 1H), 6.38 (d, *J* = 3.1 Hz, 2H), 3.75 (s, 3H) ppm.

General Procedure for [3+2]-Annulation: To the solution of diazoquinone, **2** (0.20 mmol) in CH₂Cl₂ (1.5 mL) in a flame-dried thick glass vial, enol ether **3** (0.60 mmol or 0.24 mmol) was added and stirred at 0 °C for 5 minutes under argon atmosphere. Then, Rh₂(TPA)₄ (1 mol%) was added to the reaction mixture, and the vial was closed with a cap. The reaction mixture was heated at 60 °C for 12 h. The crude reaction mixture was concentrated using rotary evaporation, and the crude was purified using flash column chromatography (0–15 % EtOAc in hexanes).

5-Bromo-2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran (4aa).^[8] White solid; mp = 58 °C (41 mg, 85 %). TLC: R_f 0.4 (9:1 hexanes/EtOAc). IR (neat): 2979, 2949, 2873, 1471, 1324, 1276, 1153, 992, 919, 819 cm^{−1}. ¹H NMR (400 MHz, CDCl₃) δ 7.30–7.29 (m, 1H), 7.24 (ddd, *J* = 6.7, 2.1, 0.7 Hz, 1H), 6.69 (d, *J* = 8.5 Hz, 1H), 6.31 (d, *J* = 5.7 Hz, 1H), 4.09 (t, *J* = 8.1 Hz, 1H), 3.99 (dd, *J* = 8.4, 5.9 Hz, 1H), 3.62 (ddd, *J* = 12.1, 8.8, 4.9 Hz, 1H), 2.30 (tdd, *J* = 12.2, 8.6, 7.7 Hz, 1H), 2.05 (ddd, *J* = 12.4, 4.8, 0.4 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 158.6, 131.5, 130.1, 127.7, 112.8, 111.4, 110.8, 67.3, 46.5, 33.4 ppm. The characterization data matches with the reported literature value.

6-Bromo-3,4,4a,9a-tetrahydro-2H-pyrano[2,3-*b*]benzofuran (4ab).^[8] Orange oil (42 mg, 82 %). TLC: R_f 0.3 (9:1 hexanes/EtOAc). IR (neat): 2940, 1485, 1467, 1321, 1226, 1111, 947, 810 cm^{−1}. ¹H NMR (400 MHz, CDCl₃) δ 7.26–7.25 (m, 2H), 6.5 (d, *J* = 8.4 Hz, 1H), 5.89 (d, *J* = 6.3 Hz, 1H), 3.81–3.69 (m, 2H), 3.32 (q, *J* = 5.9 Hz, 1H), 2.11–2.02 (m, 1H), 1.90–1.83 (m, 1H), 1.68–1.62 (m, 1H), 1.57–1.50 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 157.5, 131.9, 131.1, 126.9, 112.9, 111.4, 104.5, 61.1, 38.8, 22.6, 19.9 ppm. The characterization data matches with the reported literature value.

(2R,3S,4R)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-6-bromo-3,4,4a,9a-tetrahydro-2H-pyrano[2,3-*b*]benzofuran (4ac). Pale yellow oil (83 mg, 70 %). TLC: R_f 0.5 (8:2 hexanes/EtOAc). IR (neat): 2989, 2850, 1615, 1507, 1441, 1274, 1261, 1135, 1052, 954, 897 cm^{−1}. ¹H NMR (500 MHz, CDCl₃) δ 7.38–7.32 (m, 9H), 7.30–7.27 (m, 3H), 7.26–7.24 (m, 2H), 7.12 (d, *J* = 7.5 Hz, 2H), 6.72 (d, *J* = 8.5 Hz, 2H), 6.10 (d, *J* = 6.9 Hz, 1H), 4.76 (d, *J* = 11.6 Hz, 1H), 4.64–4.56 (m, 3H), 4.53 (d, *J* = 12.1 Hz, 1H), 4.45 (d, *J* = 11.4 Hz, 1H), 3.82–3.72 (m, 3H), 3.71–3.66 (m, 2H), 3.52 (t, *J* = 6.2 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 157.3, 137.9, 137.7, 132.5, 131.6, 128.6 (2C), 128.5 (2C), 128.4 (2C), 128.1, 128.0 (2C), 127.9 (2C), 127.8, 127.8, 127.7, 127.6 (2C), 117.2, 111.2, 110.0, 104.8, 79.9, 76.1, 73.5, 73.5, 73.0, 72.5, 69.1, 44.6 ppm. HRMS (ESI) *m/z* calcd for C₃₃H₃₁BrO₅Na ([M + Na]⁺) 609.1253; found 609.1260.

6,8-Dichloro-3,4,4a,9a-tetrahydro-2H-pyrano[2,3-*b*]benzofuran (4bb). Pale yellow oil (40 mg, 81 %). TLC: R_f 0.4 (9:1 hexanes/EtOAc). IR (neat): 2997, 2852, 1451, 1346, 1257, 1159, 1086, 1042, 969, 852, 786 cm^{−1}. ¹H NMR (500 MHz, CDCl₃) δ 7.18 (d, *J* = 1.8 Hz, 1H), 7.01 (d, *J* = 1.6 Hz, 1H), 5.99 (d, *J* = 6.4 Hz, 1H), 3.84–3.75 (m, 2H), 3.35 (q, *J* = 6.2 Hz, 1H), 2.11–2.04 (m, 1H), 1.84–1.78 (m, 1H), 1.70–1.65 (m, 1H), 1.58–1.52 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 153.1, 132.8, 128.5, 128.3, 122.6, 112.0, 105.3, 61.1, 39.3, 23.0, 19.8 ppm. The compound was not found to be active in the ESI-MS.

(2R,3S,4R)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-6,8-dichloro-3,4,4a,9a-tetrahydro-2H-pyrano[2,3-*b*]benzofuran (4bc). Orange oil (76 mg, 65 %). TLC: R_f 0.4 (8:2 hexanes/EtOAc). IR (neat): 2989, 2850, 1615, 1507, 1441, 1274, 1261, 1135, 1052, 954, 897 cm^{−1}. ¹H NMR (500 MHz, CDCl₃) δ 7.38–7.28 (m, 13H), 7.17–7.12 (m, 3H), 6.98 (d, *J* = 1.9 Hz, 1H), 6.17 (d, *J* = 6.9 Hz, 1H), 4.77 (d, *J* = 11.4 Hz, 1H), 4.63 (dd, *J* = 11.7, 6.0 Hz, 2H), 4.56–4.49 (m, 3H), 3.85–3.70 (m, 5H), 3.51 (t, *J* = 6.5 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 152.8, 137.9, 137.7, 137.6, 130.5, 128.8, 128.6 (2C), 128.4 (2C), 128.4 (2C), 128.1, 128.0 (2C), 127.9 (2C), 127.8, 127.7, 127.6 (2C), 126.0, 123.4, 115.6, 105.7, 80.1, 75.9, 73.8, 73.5, 73.3, 72.9, 68.7, 45.5 ppm. HRMS (ESI) *m/z* calcd for C₃₃H₃₀Cl₂O₅Na ([M + Na]⁺) 599.1368; found 599.1374.

5-Methoxy-2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran (4ca).^[22] Pale yellow oil (28 mg, 73 %). TLC: R_f 0.5 (8:2 hexanes/EtOAc). ¹H NMR (500 MHz, CDCl₃) δ 6.76 (d, *J* = 2.5 Hz, 1H), 6.73–6.67 (m, 2H), 6.29 (d, *J* = 5.6 Hz, 1H), 4.06 (t, *J* = 8.1 Hz, 1H), 3.98 (dd, *J* = 8.5, 6.1 Hz, 1H), 3.76 (s, 3H), 3.63 (ddd, *J* = 12.2, 8.8, 5.0 Hz, 1H), 2.28 (tt, *J* = 12.1, 8.1 Hz, 1H), 2.07 (dd, *J* = 11.8, 4.9 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 154.6, 153.5, 128.5, 113.6, 111.1, 110.8, 109.2, 67.2, 56.0, 47.0, 33.5 ppm. The characterization data matches with the reported literature value.

7-Nitro-3,4,4a,9a-tetrahydro-2H-pyrano[2,3-*b*]benzofuran (4db). Pale yellow solid; mp = 101 °C (20 mg, 45 %). TLC: R_f 0.3 (8:2 hexanes/EtOAc). IR (neat): 3004, 2989, 2854, 1518, 1475, 1344, 1333, 1259, 1205, 1156, 1072, 922, 839 cm^{−1}. ¹H NMR (500 MHz, CDCl₃) δ 7.85 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.68 (d, *J* = 2.0 Hz, 1H), 7.26 (dd, *J* = 8.1, 0.5 Hz, 1H), 6.01 (d, *J* = 6.3 Hz, 1H), 3.83–3.74 (m, 2H), 3.39 (q, *J* = 6.0 Hz, 1H), 2.17–2.10 (m, 1H), 1.89 (dq, *J* = 14.0, 5.5 Hz, 1H), 1.73–1.66 (m, 1H), 1.56–1.48 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 158.8,

137.6, 123.9, 117.0, 110.5, 105.3, 105.2, 61.1, 38.6, 22.6, 19.8 ppm. The compound was not found to be active in the ESI-MS.

7a,10,11,11a-Tetrahydro-9H-naphtho[1',2':4,5]furo[2,3-b]pyran (4eb).^[8] Brown oil (32 mg, 71 %). TLC: R_f 0.3 (9:1 hexanes/EtOAc). IR (neat): 3053, 2939, 1627, 1593, 1483, 1392, 1235, 1154, 925, 808, 745 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ 7.81 (d, J = 8.3 Hz, 1H), 7.70 (d, J = 8.7 Hz, 1H), 7.66 (d, J = 8.3 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.15 (d, J = 8.7 Hz, 1H), 6.12 (d, J = 6.9 Hz, 1H), 3.96–3.92 (m, 2H), 3.62 (q, J = 6.9 Hz, 1H), 2.32–2.27 (m, 1H), 1.78–1.72 (m, 2H), 1.58–1.56 (m, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ 154.8, 130.4, 129.5, 129.2, 129.1, 126.7, 122.9, 122.4, 122.2, 112.2, 105.7, 61.2, 37.4, 24.0, 20.7 ppm. The characterization data matches with the reported literature value.

9a,11,12,12a-Tetrahydrofuro[2,3-b]phenanthro[9,10-d]furan (4fa). Pale yellow oil (46 mg, 88 %). TLC: R_f 0.5 (9:1 hexanes/EtOAc). IR (neat): 2922, 2852, 1654, 1593, 1450, 1276, 1061, 925, 752, 725 cm^{-1} . ^1H NMR (500 MHz, CDCl_3) δ 8.69–8.66 (m, 2H), 8.15 (dd, J = 7.8, 1.3 Hz, 1H), 7.77 (dd, J = 9.0, 1.0 Hz, 1H), 7.70–7.60 (m, 3H), 7.53 (ddd, J = 8.3, 7.0, 1.4 Hz, 1H), 6.67 (d, J = 5.9 Hz, 1H), 4.43 (dd, J = 8.3, 6.1 Hz, 1H), 4.17 (t, J = 8.5 Hz, 1H), 3.70 (ddd, J = 11.9, 8.8, 5.2 Hz, 1H), 2.43 (tdd, J = 11.9, 8.6, 7.6 Hz, 1H), 2.35 (dd, J = 12.0, 5.0 Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 152.7, 131.5, 129.4, 127.4, 127.2, 127.0, 126.7, 123.7, 123.6, 122.9, 122.6, 122.6, 121.3, 113.7, 112.0, 67.5, 46.9, 31.6 ppm. The compound was not found to be active in the ESI-MS.

9a,12,13,13a-Tetrahydro-11H-phenanthro[9',10':4,5]furo[2,3-b]pyran (4fb). Pale yellow oil (46 mg, 83 %). TLC: R_f 0.5 (9:1 hexanes/EtOAc). ^1H NMR (600 MHz, CDCl_3) δ 8.68 (t, J = 9.0 Hz, 2H), 8.16 (d, J = 7.5 Hz, 1H), 7.72 (d, J = 7.7 Hz, 1H), 7.66 (dt, J = 16.1, 7.5 Hz, 2H), 7.59 (t, J = 7.8 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 6.28 (d, J = 7.0 Hz, 1H), 4.03–3.95 (m, 2H), 3.71 (q, J = 7.0 Hz, 1H), 2.38–2.35 (m, 1H), 1.82–1.75 (m, 2H), 1.60–1.57 (m, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ 150.9, 131.1, 129.5, 127.1 (2C), 126.8, 126.6, 123.7, 123.5, 123.0, 122.8, 122.4, 121.8, 118.0, 105.8, 61.3, 38.0, 23.9, 20.5 ppm. The compound was not found to be active in the ESI-MS.

3a-(4-Methoxyphenyl)-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran (4gd). White solid; mp = 108 °C (18 mg, 34 %). TLC: R_f 0.6 (9:1 hexanes/EtOAc). IR (neat): 3005, 2981, 1849, 1609, 1513, 1435, 1294, 1275, 1108, 1024, 910, 830, 794 cm^{-1} . ^1H NMR (500 MHz, CDCl_3) δ 7.39 (d, J = 7.1 Hz, 1H), 7.35 (d, J = 8.8 Hz, 2H), 7.30–7.27 (m, 1H), 7.19 (d, J = 7.3 Hz, 1H), 7.06–7.02 (m, 1H), 6.86 (d, J = 8.7 Hz, 2H), 4.00 (d, J = 8.7 Hz, 1H), 3.78 (s, 3H), 2.53 (dd, J = 13.8, 5.7 Hz, 1H), 2.25–2.13 (m, 2H), 2.04–1.99 (m, 1H), 1.93–1.88 (m, 1H), 1.78–1.71 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 159.1, 153.9, 135.6, 131.7, 130.1, 126.1 (2C), 124.1, 121.1, 118.4, 113.9 (2C), 101.5, 55.3, 54.2, 41.8, 36.4, 25.0 ppm. The compound was not found to be active in the ESI-MS.

5-Bromo-2-(2,4-dimethoxyphenyl)-2,3-dihydrobenzofuran (4ae). White solid; mp = 72 °C (48 mg, 71 %). TLC: R_f 0.5 (9:1 hexanes/EtOAc). IR (neat): 2991, 2968, 2936, 1616, 1586, 1503, 1474, 1320, 1234, 1170, 981, 802 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.29–7.22 (m, 3H), 6.74 (d, J = 8.3 Hz, 1H), 6.49–6.45 (m, 2H), 5.98 (t, J = 8.7 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.59 (dd, J = 16.0, 9.5 Hz, 1H), 3.09 (dd, J = 16.0, 7.7 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 160.7, 158.9, 157.3, 130.6, 129.7, 127.8, 126.8, 122.3, 112.0, 110.7, 104.1, 98.6, 80.2, 55.4 (2C), 37.1 ppm. The compound was not found to be active in the ESI-MS.

4-Bromo-2-((3,4-dihydronaphthalen-1-yl)methyl)phenol (4af). Brown oil (52 mg, 82 %). TLC: R_f 0.4 (9:1 hexanes/EtOAc). IR (neat): 2924, 1486, 1416, 1321, 1275, 1164, 1103, 866 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 7.28–7.16 (m, 6H), 6.71 (d, J = 8.5 Hz, 1H), 5.83 (s, 1H), 5.13 (s, 1H), 3.75 (s, 2H), 2.79 (t, J = 8.0 Hz, 2H), 2.32–2.30 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 153.4, 136.6,

134.1, 133.6, 133.3, 130.6, 127.7, 127.5, 127.5, 127.3, 126.5, 122.9, 117.6, 112.9, 33.6, 28.1, 23.2 ppm. The compound was not found to be active in the ESI-MS.

10-(1-Methyl-1H-indol-3-yl)phenanthren-9-ol (4fg).^[23] Gray solid; mp = 129 °C (60 mg, 92 %). TLC: R_f 0.4 (8:2 hexanes/EtOAc). IR (neat): 3454, 3061, 2921, 1673, 1595, 1448, 1309, 1270, 1203, 1003, 835 cm^{-1} . ^1H NMR (600 MHz, CDCl_3) δ 8.75 (d, J = 8.3 Hz, 1H), 8.70 (d, J = 8.4 Hz, 1H), 8.41 (d, J = 7.9 Hz, 1H), 7.73 (t, J = 7.1 Hz, 1H), 7.67 (t, J = 7.5 Hz, 1H), 7.60 (d, J = 8.3 Hz, 1H), 7.51–7.48 (m, 2H), 7.39 (t, J = 7.5 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.3–7.29 (m, 2H), 7.12 (t, J = 7.5 Hz, 1H), 5.95 (s, 1H), 3.97 (s, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 147.8, 137.6, 133.3, 131.0, 129.6, 128.2, 127.1, 126.7, 126.5, 126.4, 125.8, 124.9, 123.8, 123.1, 122.6, 122.5 (2C), 120.4, 120.1, 109.6, 109.2, 106.8, 33.2 ppm. The characterization data matches with the reported literature value.

3-(Benzyloxy)-5-methoxy-2-nitrophenol (6). A mixture of nitro resorcinol (5) (1.00 g, 5.40 mmol), PPh_3 (1.42 g, 5.40 mmol), and BnOH (0.56 mL, 5.40 mmol) was dissolved in THF (30 mL) and cooled to 0 °C. At the same temperature, DEAD (40 % solution in toluene; 2.46 mL, 5.40 mmol) was added in slowly. The reaction was stirred for 12 hours from 0 °C to room temperature. The reaction mixture was partitioned between water and EtOAc, and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under vacuum. The resulting crude residue purified by silica gel column chromatography (10 → 30 % EtOAc in hexanes) afforded **6** (776 mg, 52 %) as a yellow solid; mp = 119 °C. TLC: R_f 0.4 (7:3 hexanes/EtOAc). IR (neat): 3115, 2941, 1625, 1580, 1548, 1398, 1306, 1229, 1128, 1023, 950, 911, 831 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 11.49 (s, 1H), 7.49 (d, J = 7.4 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.34 (t, J = 7.3 Hz, 1H), 6.18 (d, J = 2.6 Hz, 1H), 6.11 (d, J = 2.6 Hz, 1H), 5.17 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 165.7, 159.5, 156.7, 135.3, 128.7 (2C), 128.2, 126.8 (3C), 94.1, 93.9, 71.3, 55.9 ppm. The compound was not found to be active in the ESI-MS.

2-Amino-3-(benzyloxy)-5-methoxyphenol (7). To a solution of the nitro compound **6** (500 mg, 1.82 mmol) in AcOH (20 mL), zinc powder (475 mg, 7.27 mmol) was added, and the reaction was heated at 60 °C. The reaction was stirred at the same temperature for 12 h. Completion of the reaction was confirmed by thin-layer chromatography (TLC); thereafter, the reaction mixture was passed through a Celite pad, and crude was extracted by using EtOAc (2 × 100 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (20 → 50 % EtOAc in hexanes) gave **7** (420 mg, 94 %) as a brown oil. TLC: R_f 0.2 (7:3 hexanes/EtOAc). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.47 (d, J = 7.0 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 7.3 Hz, 1H), 6.14 (d, J = 2.6 Hz, 1H), 6.04 (d, J = 2.6 Hz, 1H), 5.05 (s, 2H), 3.59 (s, 3H), 3.33 (br s, 2H), 2.49 (br s, 1H); ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ 151.0, 146.6, 145.0, 137.6, 128.4 (2C), 127.6, 127.4 (2C), 118.6, 94.7, 92.0, 69.6, 55.1 ppm. The compound was not found to be active in the ESI-MS.

4-(Benzyloxy)-6-methoxy-2,3,3a,8a-tetrahydrofuro[2,3-b]benzofuran (8).^[6b] At 0 °C, conc. HCl (1.39 mL, 16.31 mmol) was added to solution of aniline **7** (400 mg, 1.63 mmol) in EtOH (10 mL). After 5 minutes, a solution of NaNO_2 (337 mg, 4.89 mmol) in water (5 mL) was added to the reaction mixture over 10 minutes, and then the reaction was vigorously stirred at 0 °C for 2 hours. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and ice cubes (approx. 30 g). Then, K_2CO_3 (1.51 g, 10.93 mmol) was added to the reaction mixture by slow addition, and the reaction was stirred again for 10 minutes. The crude was extracted by using CH_2Cl_2 (2 × 50 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under vacuum. The resulting crude residue was recrystallized using CH_2Cl_2 /hexanes mixture to afford diazoquinone as a Brown solid (372 mg, 89 %).

The reaction of above diazoquinone (50 mg, 0.20 mmol) with dihydrofuran (41 mg, 0.59 mmol) was carried out by following the **general procedure for [3+2]-annulation**. The desired product **8** (44 mg, 76%) was obtained as a white solid; mp = 91 °C. **TLC**: R_f 0.2 (9:1 hexanes/EtOAc). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.44–7.33 (m, 5H), 6.30 (d, J = 5.7 Hz, 1H), 6.09 (d, J = 1.9 Hz, 2H), 5.09 (d, J = 12.0 Hz, 1H), 5.06 (d, J = 12.0 Hz, 1H), 4.07 (t, J = 8.0 Hz, 1H), 4.01 (dd, J = 8.0, 5.8 Hz, 1H), 3.75 (s, 3H), 3.66 (ddd, J = 12.1, 8.7, 5.0 Hz, 1H), 2.22 (dd, J = 12.3, 5.0 Hz, 1H), 2.19–2.07 (m, 1H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 161.9, 161.3, 155.7, 136.9, 128.6 (2C), 128.0, 127.2 (2C), 111.9, 106.7, 92.7, 88.1, 69.8, 67.5, 55.6, 44.6, 31.6 ppm. The characterization data matches with the reported literature value.

5-(Benzyloxy)-7-methoxy-3,4,4a,9a-tetrahydro-2H-pyrano[2,3-b]benzofuran (9). The reaction of above diazoquinone (50 mg, 0.20 mmol) with 3,4-dihydro-2H-pyran (49 mg, 0.59 mmol) was carried out by following the **general procedure for [3+2]-annulation**. The desired product **9** (42 mg, 69%) was obtained as a white solid; mp = 86 °C. **TLC**: R_f 0.3 (7:3 hexanes/EtOAc). **IR** (neat): 3005, 2988, 1610, 1501, 1469, 1435, 1379, 1264, 1192, 1144, 1040, 950, 823 cm^{-1} . $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.39–7.32 (m, 5H), 6.11 (dd, J = 13.3, 2.0 Hz, 2H), 5.91 (d, J = 6.9 Hz, 1H), 5.06 (d, J = 11.7 Hz, 1H), 5.02 (d, J = 11.8 Hz, 1H), 3.83–3.77 (m, 2H), 3.75 (s, 3H), 3.38 (q, J = 5.9 Hz, 1H), 2.05–1.89 (m, 2H), 1.69–1.62 (m, 1H), 1.56–1.51 (m, 1H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 161.8, 156.3, 136.9, 128.6 (2C), 127.3, 127.2 (2C), 119.2, 109.16, 105.2, 92.7, 88.8, 69.8, 60.7, 55.6, 36.7, 21.8, 20.0 ppm. The compound was not found to be active in the ESI-MS.

6-Methoxy-2,3,3a,8a-tetrahydrofuro[2,3-b]benzofuran-4-ol (10).^[5d] To a solution of the compound **8** (40 mg, 0.13 mmol) in CHCl_3 (2 mL), AlCl_3 (36 mg, 0.27 mmol) was added and the reaction was stirred at room temperature for 2 h. Completion of the reaction was confirmed by thin-layer chromatography (TLC); thereafter, the reaction was quenched by sat. NH_4Cl solution and crude was extracted by using CH_2Cl_2 , and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (10→25% EtOAc in hexanes) gave **10** (23 mg, 82%) as a white solid; mp = 150 °C. **TLC**: R_f 0.3 (7:3 hexanes/EtOAc). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 6.31 (d, J = 5.7 Hz, 1H), 6.03 (d, J = 2.0 Hz, 1H), 5.90 (d, J = 2.0 Hz, 1H), 5.02 (br s, 1H), 4.08 (t, J = 7.6 Hz, 1H), 3.98 (t, J = 7.1 Hz, 1H), 3.72 (s, 3H), 3.68–3.64 (m, 1H), 2.19–2.13 (m, 2H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 161.8, 161.7, 152.5, 112.0, 105.4, 94.9, 88.6, 67.4, 55.5, 44.1, 31.5 ppm. The characterization data matches with the reported literature value.

7-Methoxy-3,4,4a,9a-tetrahydro-2H-pyrano[2,3-b]benzofuran-5-ol (11). The reaction compound **9** (40 mg, 0.13 mmol) with AlCl_3 (36 mg, 0.27 mmol) was carried out by following the above procedure for debenzoylation. The phenol **11** (23 mg, 81%) was obtained as brown oil. **TLC**: R_f 0.3 (7:3 hexanes/EtOAc). **IR** (neat): 3115, 2941, 1625, 1580, 1548, 1398, 1306, 1229, 1128, 1023, 950, 911, 831 cm^{-1} . $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 6.09 (d, J = 2.0 Hz, 1H), 5.91 (d, J = 6.8 Hz, 1H), 5.90 (d, J = 2.0 Hz, 1H), 4.73 (br s, 1H), 3.85–3.76 (m, 2H), 3.74 (s, 3H), 3.36 (q, J = 6.3 Hz, 1H), 2.05–2.00 (m, 1H), 1.91–1.86 (m, 1H), 1.70–1.65 (m, 1H), 1.59–1.54 (m, 1H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 161.3, 160.3, 152.9, 107.4, 105.1, 94.9, 89.4, 60.7, 55.5, 36.3, 21.9, 19.9 ppm. The compound was not found to be active in the ESI-MS.

Aflatoxin B₂ (1).^[5d] To a solution of the compound **10** (10 mg, 48 μmol) in CH_2Cl_2 (1 mL), methyl carboxylate **12** (7 mg, 48 μmol) and $\text{Sc}(\text{OTf})_3$ (23 mg, 48 μmol) were added and the reaction was stirred at room temperature for 72 h. Completion of the reaction was confirmed by thin-layer chromatography (TLC); the solvent was removed under reduced pressure. Purification of the residue by silica gel column chromatography (60→90% EtOAc in hexanes) gave **1** (10.5 mg, 70%) as a white solid; mp = 298 °C (decomposed).

TLC: R_f 0.3 (2:8 hexanes/EtOAc). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 6.47 (d, J = 5.7 Hz, 1H), 6.33 (s, 1H), 4.18–4.13 (m, 2H), 3.94 (s, 3H), 3.63 (q, J = 8.4 Hz, 1H), 3.39 (ddd, J = 6.8, 3.6, 1.3 Hz, 2H), 2.63–2.61 (m, 2H), 2.32–2.25 (m, 2H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 201.4, 177.1, 167.2, 161.7, 155.3, 153.4, 117.0, 113.9, 106.9, 103.8, 90.0, 67.9, 56.41, 44.0, 35.0, 31.6, 29.0 ppm. The characterization data matches with the reported literature value.

Deposition Number 2038490 (for **4 aa**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Acknowledgements

We thank Dr. Susan Nimmo, Dr. Steven Foster, and Dr. Douglas R. Powell from the Research Support Services, University of Oklahoma, for expert NMR, mass spectral, and X-ray crystallographic (NSF CHE-1726630) analyses, respectively. We also thank Dr. Kiran Chinthapally and Dr. Arianne C. Hunter for helpful discussions. The NSF CHE-1753187 grant supported this work.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Aflatoxin B₂ • [3+2]-Annulation • Diazoquinones • 2,3-Dihydrobenzofurans • Rhodium carbenoid

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Manuscript received: February 16, 2021
Revised manuscript received: March 2, 2021
Accepted manuscript online: March 7, 2021