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Synthesis of 5-Carbapterocarpens by α-Arylation of Tetralones Followed by One-Pot Demethylation/Cyclization with BBr_3

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5-Carbapterocarpens, one of them displaying estrogenic activity, were prepared from α-aryltetralones in high yields through a one-pot, BBr_3-promoted *O*-demethylation and cyclization sequence. The key α-aryltetralone intermediates were obtained by direct α-arylation of tetralones with *o*-alkoxybromoarenes in the presence of $Pd_2(dba)_3$ (2.5 mol-%) and tBu_3PHBF_4 (10 mol-%) as catalysts, together with 2.5 equiv. of KOH in dioxane/H_2O (4:1), under microwave irradiation conditions (80 W, 100 °C, 40 min), leading to α-monoaryltetralones in good yields.

Introduction

Estrogen receptors (ERs) are a group of intracellular proteins activated by the hormone estrogen [17β-estradiol (**1**), Figure 1].[1] These receptors, divided into ERα and ERβ subtypes, play a central role in toxicology and human disease, exerting pleiotropic effects on tissues such as ovary, testis, prostate, breast, uterus, bone, and liver, as well as the immune system and cardiovascular and central nervous systems.[1] Estrogen receptor antagonists are potentially useful in the chemotherapy of hormone-dependent cancers: tamoxifen (**2**, Figure 1), for example, has being used in breast cancer treatment.[2] In 2006, Miller et al. reported[3] the synthesis of pterocarpens and analogues such as **3** and **4**, respectively, and the affinities of these compounds for estrogen receptors were studied. The natural ligand **1** binds to ERα (IC_{50} 3 nM) and to ERβ (IC_{50} 4 nM) with similar affinities, whereas **3** had the same affinity for ERβ but showed a lower affinity for ERα, thus being more selective (ERα, IC_{50} 129 nM; ERβ, IC_{50} 4 nM). Compound **4** also showed essentially the same affinity as **1** and **3** for ERβ but was less selective (ERα, IC_{50} 18 nM; ERβ, IC_{50} 3 nM). These compounds were claimed to be useful for the treatment of hormone-sensitive cancers.[3] The bioselectivity observed in the case of the 5-carbapterocarpen showed its potential as a scaffold for prospecting new estrogen receptors.

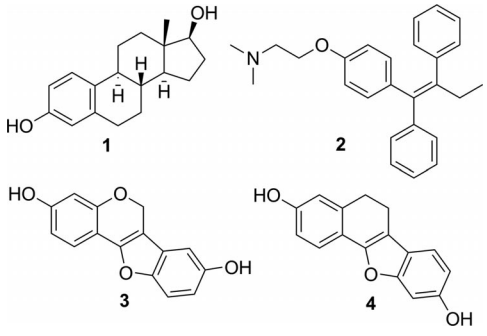

Figure 1. Estrogen (**1**), tamoxifen (**2**), pterocarpen (**3**), and 5-carbapterocarpen (**4**).

5-Carbapterocarpens such as **4** and analogues **5** can be prepared through multistep synthesis from α-aryl-α-tetralones **6** or substituted dihydronaphthalenes **7** as precursors. Miller et al.[3] (Scheme 1) reported a five-step synthesis of 5-carbapterocarpens such as **4** and analogues **5**, the last step being the phenol deprotection followed by the cyclization, but these reactions were accomplished only under drastic conditions, leading to low yields of products. α-Aryl-α-tetralones **6** were obtained through Suzuki or Stille coupling between compounds **8** (prepared from the corresponding halides) and α-bromoenol acetate derivatives of **9**.

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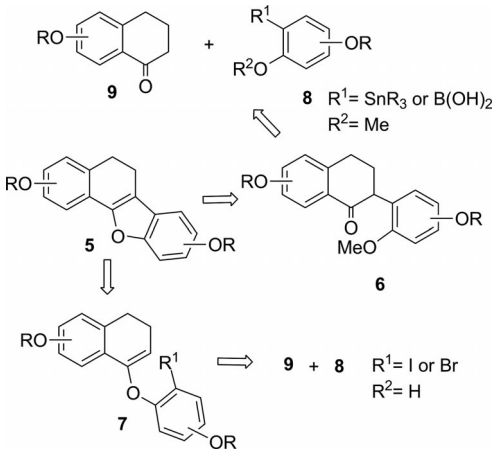
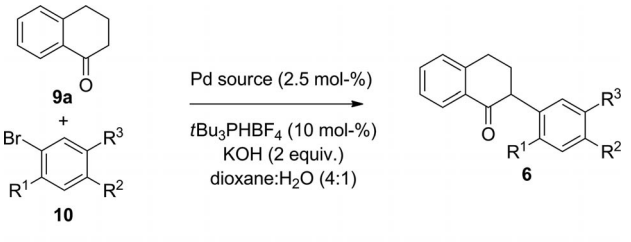
It is worth mentioning that was necessary to use anhydrous conditions to prepare compounds **8** and that stoichiometric amounts of tin or boron had to be used in the C–C bond-formation step.

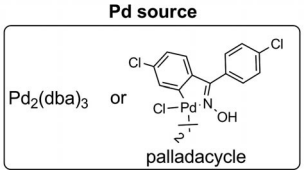


Scheme 1. Strategies for the synthesis of pterocarpens and 5-carbapterocarpens.

In our lab, 5-carbapterocarpens **5** were prepared through a seven-step synthesis, with intramolecular Heck coupling of compounds **7** as the last (Scheme 1).[4a] In these cases, higher yields were observed when iodo derivatives (**7**, R^1 = I) were employed. More direct methods for the synthesis of 5-carbapterocarpens have also been described, but in these cases only products not oxygenated in the A- or the D-ring were prepared. In one case the synthesis proceeded through α-arylation of α-tetralones with *ortho*-bromophenol, followed by acid-catalyzed cyclization to give benzo[*b*]furans in good yields.[4b] In the other, dihalogenated arenes were used for α-arylation of α-tetralones, followed by intramolecular *O*-arylation of the resulting aryltetralones.[4c]



a: R^1 = OMe; R^2 = R^3 = H
b: R^1 = OBn; R^2 = R^3 = H
c: R^1 = OMOM; R^2 = R^3 = H
d: R^1 = R^2 = OMe; R^3 = H
e: R^1 = OMOM; R^2 = R^3 = OCH_2O
f: R^1 = OMOM; R^2 = H; R^3 = NO_2



Scheme 2. α-Arylation of α-tetralone (**9a**) with *O*-alkylated *o*-bromophenols **10a**–**g**.

We envisaged that a most straightforward and green approach to the preparation of these compounds would be the direct α-arylation of α-tetralones **9** with *O*-protected *o*-halophenols **10** (Scheme 2),[5] followed by in situ deprotection and cyclization of the resulting α-tetralones **6**. Here we report the synthesis of **4** and of seven new analogues, with different patterns of oxygenated substituents in the A- and the D-rings, from commercially available starting materials by this approach.

Results and Discussion

Palladium-catalyzed direct coupling between enolizable ketones and aryl halides, described by Buchwald,[6a] Hartwig,[6b] and Miura,[6c] is a well-established methodology.[6] In spite of intensive study of α-arylations of ketones,[6] however, only scattered examples of reactions between substituted tetralones and aryl halides bearing alkoxy groups at their *ortho*-positions have been described.[5,7]

We starting by studying the α-arylation of **9a** (Scheme 2) with *o*-chloroanisole, but high reaction times and low conversion were observed, so we then moved to bromoarenes **10a**–**f**. Initially we used 2 equiv. of tetralone (**9a**) and 1 equiv. of *o*-bromoanisoles **10a**–**f** in the presence of $Pd_2(dba)_3$ and tBu_3PHBF_4 as catalysts and KOH as base, in dioxane/H_2O as solvent (Scheme 2 and Table 1). These conditions, except for the use of KOH instead of $KHCO_3$, were described by Bellina et al., for the α-arylation of chromanones.[8] In this work we also tested the robust oxime-derived palladacycle **4**[9] as a palladium source.

Table 1. Major conditions and yields for reactions shown in Scheme 2.

Entry	ArBr	**9a/10**	Pd [a]	Conditions[b]	**6**	Yield [%][c]
1	**10a**	2:1	$Pd_2(dba)_3$	CH	**6a**	80
2	**10a**	2:1	$Pd_2(dba)_3$	MW	**6a**	78
3[d]	**10a**	2:1	palladacycle	MW	**6a**	70
4	**10b**	2:1	$Pd_2(dba)_3$	MW	**6b**	58
5	**10c**	2:1	$Pd_2(dba)_3$	MW	**6c**	81
6	**10d**	2:1	$Pd_2(dba)_3$	MW	**6d**	71
7	**10e**	2:1	$Pd_2(dba)_3$	MW	**6e**	81
8	**10f**	2:1	$Pd_2(dba)_3$	MW	**6f**	64
9	**10a**	1:1.2	$Pd_2(dba)_3$	MW	**6a**	77
10	**10d**	1:1.2	$Pd_2(dba)_3$	MW	**6d**	62

[a] 2.5 mol-%. [b] CH: conventional heating (reflux, 16 h). MW: microwave heating (80 W, 120 °C, 1 h). Entries 9 and 10: 80 W, 100 °C, 40 min. [c] After purification by chromatography on silica gel. [d] 20 mol-% of TBAB was added.

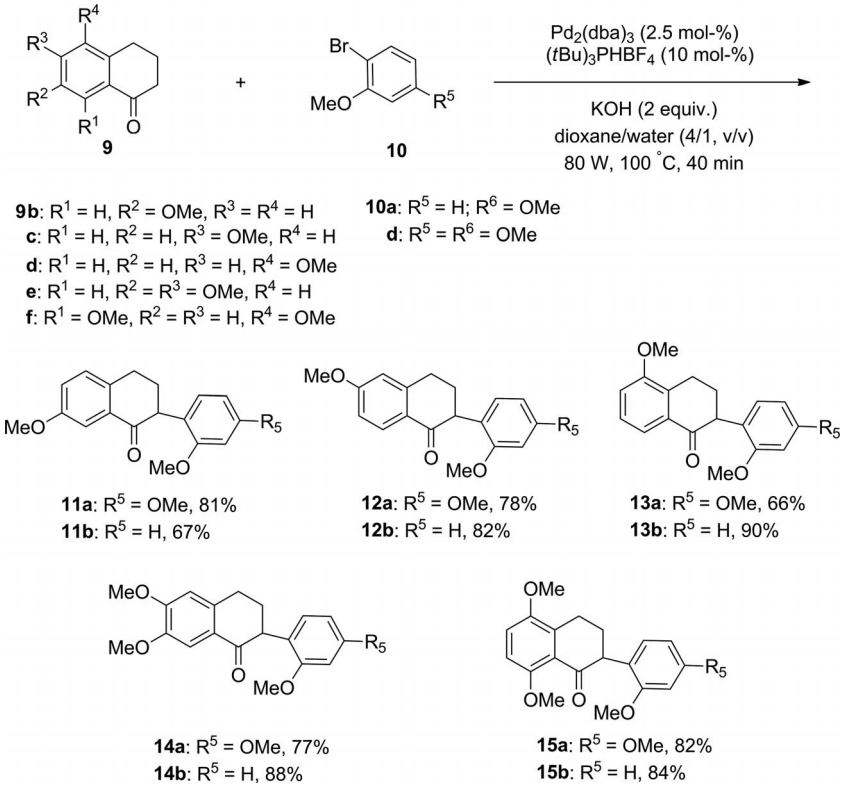
When the arylation of **9a** in the presence of $Pd_2(dba)_3$ was performed under reflux for 16 h, total conversion of *o*-bromoanisole (**10a**) was observed, leading to **6a** in 80% isolated yield (Entry 1). The reaction was faster under microwave heating conditions (1 h), furnishing **6a** in 78% yield (Entry 2). The oxime-derived palladacycle was also tested under these latter conditions, but in this case it was necessary to use tetra-*n*-butylammonium bromide (TBAB, 20 mol-%) as additive. Total conversion of **10a** was observed, but **6a** was obtained in lower yield (70%, Entry 3). In the next experiments we decided to use $Pd_2(dba)_3$ and

microwave heating, which had been selected as the best conditions. The use of benzyl as a protecting group for *o*-bromophenol (compound **10b**) in the reaction with **9a** led to **6b** in a moderate 58% yield (Entry 4), whereas the use of MOM as protecting group (compound **10c**) furnished adduct **6c** in 81% yield (Entry 5). The use of less activated bromoarenes **10d** and **10e** gave rise to adducts **6d** and **6e**, respectively, in good yields (Entries 6 and 7). Surprisingly, activated bromoarene **10f** led to **6f** in only moderate yield (Entry 8).

It is worth mentioning that no diarylated products could be detected in the crude reaction mixtures in any of these reactions. As **9a** and the α-arylated adduct **6** have similar R_f values on silica gel, however, the use of an excess of **9a** makes purification troublesome, requiring carefully chromatographic separation in silica gel. In addition, some oxygenated derivatives of **9a** are expensive, making these conditions less attractive. Because bromoarenes **10** are sterically hindered, we suspected that in this case the diarylation step might be disfavored relative to reactions between other ketones and bromoarenes not substituted at their *o*-positions, in which the ketones were used in excess to minimize diarylation.[8] We therefore reinvestigated the α-arylation of **9a** with **10a** and **10d**, and after some experimentation we changed the ketone/bromoarene ratio to 1.0:1.2 and also lowered the reaction temperature and time (Entries 9 and 10). Under these new MW conditions, α-aryltetralones **6a** and **6d** were obtained in similar yields (compare with Entries 2 and 6). In addition, although bromoarenes **10a**–**d** are highly apolar, arylated products **6a** and **6d** could easily be purified by flash chromatography on silica gel.

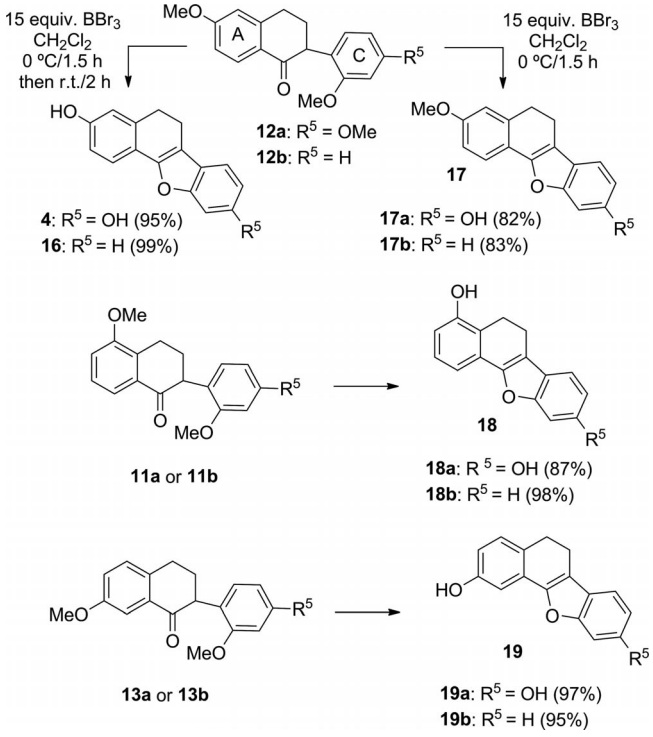
Our next goal was to study palladium-catalyzed α-arylation of commercially available tetralones **9b**–**f** (Scheme 3, 1 equiv.) with **10a** and also with the less activated bromoarene **10d** (1.2 equiv.), both substituted with MeO groups, under MW conditions. The resulting 5-carbapterocarpens bearing methoxy or hydroxy groups have oxygenation patterns in the A- and D-rings similar to those observed in the naturally occurring pterocarpens and in natural isoflavonoids in general. Although the introduction of methoxy groups onto the tetralone aromatic ring reduces the acidity of the α-hydrogen and consequently makes the enolate formation required for α-arylation reaction more difficult,[10] the α-monoarylation products **11a** and **11b** to **15a** and **15b** could be obtained in reasonable to excellent yields under the conditions used, in spite of the oxygenation patterns on **9** and **10**. In these experiments we observed only traces of diarylation side products by GC, and the desired α-aryl-α-tetralones could easily be purified just by filtration through a pad of silica gel.

As mentioned above, 5-carbapterocarpens **4** and some analogues have been synthesized by a laborious route by Miller et al.[3] In our hands, **4** could be obtained in only two steps, by direct α-arylation of tetralone **9c** with bromoarene **10d** (78% yield) followed by one-pot demethylation/cyclization of the resulting **12a** (95% yield), in the presence of an excess of BBr_3[11] in CH_2Cl_2 at 0 °C, followed by allowing the reaction mixture to warm to room tempera-



Scheme 3. α-Arylation reactions of substituted tetralones **9**.

ture, as shown in Scheme 4. Under these reaction conditions compound **16** was obtained from **12b** in excellent yields. The demethylation reaction was site-selective, and 3-methoxy-5-carbapterocarpens **17a** and **17b** could be obtained from **12a** and **12b** respectively, just by keeping the reaction temperature at 0 °C.



Scheme 4. Synthesis of 5-carbapterocarpens from α-arylated-α-tetralones.

The structures of these compounds were assigned by 2D NMR experiments (COSY, HMBC and HSQC). In cases in which the oxygen atoms of the methoxy groups in the A-ring in **12a** and **12b**, as well in **17a** and **17b**, are less basic (conjugation with the carbonyl group and the double bond, respectively), they should have weaker affinities for coordinating with BBr_3, explaining the site selectivity observed.[11] In contrast, in cases in which the methoxy group in the A-ring was not conjugated with the carbonyl group, as in **11a**, **11b**, **13a**, and **13b**, completely deprotected products **18a**, **18b**, **19a**, and **19b**, respectively, were obtained even at 0 °C. Because it was impossible to observe non-cyclized products, even with use of short reaction times, the high reactivity of an *o*-methoxy group in the α-aryl moiety can be explained in terms of a favorable coordination of BBr_3 with the carbonyl group in the tetralone moiety, through a complex-induced proximity effect (CIPE).[12]

Conclusions

In conclusion, an efficient two-step route for the synthesis of 5-carbapterocarpens has been achieved. Use of palladium-catalyzed α-arylation of α-tetralones with alkoxylated bromoarenes under microwave heating conditions in dioxane/water allowed the corresponding α-aryl-α-tetralones to be obtained in good yields. By controlling the temperature, demethylation of α-aryltetralones **11a**, **11b**, **12a**, **12b**, **13a**, and **13b** in the presence of BBr_3, followed by one-pot cyclization, could be smoothly and selectively accomplished, affording 5-carbapterocarpens in high yields. These compounds are strong candidates for evaluation as ligands for estrogenic receptors.

Experimental Section

General: ^1H NMR and ^{13}C NMR spectra were obtained with a Bruker AC-300, a Varian 400-MR, or a Varian 500-NMR with $CDCl_3$ or MeOD as solvent and TMS as internal standard. Low-resolution electron impact (GC-EI) mass spectra were obtained at 70 eV with a Shimadzu QP-5000, and HRMS (GC-EI) were recorded with a Finnigan MAT 95S instrument. Analytical TLC was performed with Schleicher & Schuell F1400/LS silica gel plates, and the spots were visualized under UV light (λ = 254 nm). Melting points were determined with a Fisatom 430 apparatus and are uncorrected. For flash chromatography we employed Merck silica gel 60 (0.040–0.063 mm). CEM Discover and Explorer-Coolmate accessory were employed in the microwave-assisted reactions for the generation of α-aryltetralones.

General Procedure for the Microwave-Assisted Synthesis of α-Aryl-α-tetralones: A suspension of $Pd_2(dba)_3$ (6.9 mg, 0.0075 mmol), tBu$_3$PHBF$_4$ (8.7 mg, 0.03 mmol), KOH (42 mg, 0.75 mmol), aryl bromide **9** (0.36 mmol), and tetralone **10** (0.3 mmol) in a mixture of dioxane/water (4:1, v/v, 3 mL) was degassed and heated under Ar by microwave irradiation (80 W initial power, 100 °C, 40 min, infrared probe). The mixture was then allowed to cool to room temp., diluted in AcOEt, washed with saturated NH_4Cl solution, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography.

2-(2-Methoxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (6a): The crude product was purified by preparative TLC with a mixture of hexane/AcOEt (95:5) as eluent, to give **6a** as a brown solid; m.p. 78–80 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.10 (dd, J = 7.8, 1.2 Hz, 1 H), 7.49 (td, J = 7.5, 1.4 Hz, 1 H), 7.33 (t, J = 7.6 Hz, 1 H), 7.30–7.23 (m, 2 H), 7.11 (dd, J = 7.5, 1.7 Hz, 1 H), 6.96–6.89 (m, 2 H), 4.05 (dd, J = 12.2, 4.7 Hz, 1 H), 3.75 (s, 3 H), 3.13 (ddd, J = 16.2, 11.7, 4.4 Hz, 1 H), 3.00 (dt, J = 16.5, 4.1 Hz, 1 H), 2.50 (dtd, J = 16.4, 12.0, 4.4 Hz, 1 H), 2.27 (ddd, J = 13.1, 8.7, 4.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.1, 157.1, 144.1, 133.2, 133.1, 129.4, 129.3, 128.7, 128.2, 127.6, 126.6, 120.8, 111.1, 55.5, 50.0, 30.0, 29.5 ppm. MS (EI): *m*/*z* (%) = 252 (33) $[M]^+$, 234 (11), 90 (100), 63 (18). HRMS: calcd. for $C_{17}H_{16}O_2$ 252.1150; found 252.1142.

2-[2-(Benzyloxy)phenyl]-1-tetralone (6b): The crude product was purified by preparative TLC with a mixture of hexane/AcOEt (95:5) as eluent, to give **6b** as a pale brown oil. ^1H NMR: δ = 8.10–6.90 (m, 13 H), 5.02 (s, 2 H), 4.04 (dd, J = 12.3, 4.7 Hz, 1 H), 3.20–2.90 (m, 2 H), 2.60–2.45 (m, 1 H), 2.30–2.20 (m, 1 H) ppm. ^{13}C NMR: δ = 198.1, 156.3, 144.2, 137.1, 133.2, 133.1, 130.0, 129.8, 128.7, 128.5, 128.3, 127.8, 127.7, 127.2, 126.7, 121.2, 112.4, 70.3, 50.8, 30.1, 29.6 ppm. MS (EI): *m*/*z* (%) = 328 (7) $[M]^+$, 237 (59), 91 (100). HRMS: calcd. for $C_{23}H_{20}O_2$ 328.1463; found 328.1483.

2-[2-(Methoxymethoxy)phenyl]-1-tetralone (6c): The crude product was purified by preparative TLC with a mixture of hexane/AcOEt

(95:5) as eluent, to give **6c** as a brown oil. ^{1}H NMR: δ = 8.14–6.89 (m, 8 H), 5.11 (d, J = 6.6 Hz, 1 H), 5.07 (d, J = 6.7 Hz, 1 H), 4.03 (dd, J = 12.3, 4.7 Hz, 1 H), 3.38 (s, 3 H), 3.20–2.95 (m, 2 H), 2.60–2.45 (m, 1 H), 2.35–2.25 (m, 1 H) ppm. ^{13}C NMR: δ = 197.89, 154.92, 144.18, 133.22, 129.90, 129.72, 128.79, 128.31, 127.67, 126.75, 121.99, 114.40, 94.55, 56.14, 50.55, 30.11, 29.60 ppm. MS (EI): *m*/*z* (%) = 282 (19) $[M]^+$, 250 (41), 237 (73), 218 (100), 189 (57), 165 (28), 118 (25), 90 (36). HRMS: calcd. for $C_{18}H_{18}O_3$ 282.1256; found 282.1260.

2-(2,4-Dimethoxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (6d): The crude product was purified by column chromatography with a mixture of hexane/AcOEt (95:5) as eluent, to give **6d** as a pale yellow solid; m.p. 114–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J = 7.8 Hz, 1 H), 7.49 (t, J = 7.4 Hz, 1 H), 7.33 (t, J = 7.6 Hz, 1 H), 7.26 (s, 1 H), 7.01 (d, J = 8.2 Hz, 1 H), 6.49 (s, 1 H), 6.47 (d, J = 8.3 Hz, 1 H), 3.98 (dd, J = 12.3, 4.5 Hz, 1 H), 3.80 (s, 3 H), 3.73 (s, 3 H), 3.13 (ddd, J = 16.0, 12.0, 4.0 Hz, 1 H), 3.01 (dt, J = 16.5, 3.5 Hz, 1 H), 2.47 (qd, J = 12.3, 4.0 Hz, 1 H), 2.25 (ddd, J = 12.6, 8.3, 4.1 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 198.4, 159.8, 158.1, 144.1, 133.2 133.1, 129.6, 128.6, 127.6, 126.5, 121.7, 104.4, 99.1, 55.4, 55.3, 49.4, 30.1, 29.5 ppm. MS (EI): *m*/*z* (%) = 282 (100) $[M]^+$, 264 (10), 151 (38), 131 (27), 118 (33). HRMS: calcd. for $C_{18}H_{18}O_3$ 282.1256; found 282.1244.

2-[3,4-Methylenedioxy-6-(methoxymethoxy)phenyl]-1-tetralone (6e): The crude product was purified by preparative TLC with a mixture of hexane/AcOEt (95:5) as eluent, to give **6e** as a brown solid; m.p. 78–81 °C. ^{1}H NMR: δ = 8.11–7.23 (m, 4 H), 6.79 (s, 1 H), 6.60 (s, 1 H), 5.91 (d, J = 1.4 Hz, 1 H), 5.90 (d, J = 1.4 Hz, 1 H), 5.01 (d, J = 6.7 Hz, 1 H), 4.98 (d, J = 6.7 Hz, 1 H), 3.99 (dd, J = 12.6, 4.7 Hz, 1 H), 3.40 (s, 3 H), 3.22–2.97 (m, 2 H), 2.52–2.36 (m, 1 H), 2.31–2.21 (m, 1 H) ppm. ^{13}C NMR: δ = 198.12, 149.86, 147.04, 144.14, 142.39, 133.31, 133.11, 128.81, 127.72, 126.77, 122.29, 108.82, 101.33, 98.69, 95.84, 56.08, 49.98, 30.42, 29.71 ppm. MS (EI): *m*/*z* (%) = 326 (13) $[M]^+$, 308 (4), 281 (43), 262 (100), 233 (24), 176 (36). HRMS: calcd. for $C_{19}H_{18}O_5$ 326.1154; found 326.1172.

2-[2-(Methoxymethoxy)-5-nitrophenyl]-1-tetralone (6f): The crude product was purified by preparative TLC with a mixture of hexane/AcOEt (95:5) as eluent, to give **6f** as a pale brown solid; m.p. 85–89 °C. ^{1}H NMR: δ = 8.20–7.19 (m, 7 H), 5.22 (d, J = 6.8 Hz, 1 H), 5.17 (d, J = 6.8 Hz, 1 H), 4.09 (dd, J = 13.2, 4.6 Hz, 1 H), 3.41 (s, 3 H), 3.30–3.03 (m, 2 H), 2.67–2.52 (m, 1 H), 2.38–2.27 (m, 1 H) ppm. ^{13}C NMR: δ = 196.31, 160.04, 143.90, 142.15, 133.68, 132.62, 130.72, 128.94, 127.73, 126.98, 125.53, 124.66, 113.70, 94.45, 56.64, 50.58, 29.74, 29.51 ppm. MS (EI): *m*/*z* (%) = 281 (18), 265 (100), 252 (15), 235 (15), 217 (47), 207 (32), 189 (69), 176 (11), 163 (16), 152 (11), 139 (9), 115 (15), 90 (31), 76 (10), 63 (13). HRMS: calcd. for $C_{18}H_{17}NO_5$ 327.1107; found 327.1139.

2-(2,4-Dimethoxyphenyl)-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (11a): The crude product was purified by column chromatography with a mixture of hexane/AcOEt (95:5) as eluent, to give **11a** as a pale yellow solid; m.p. 109–111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, J = 2.8 Hz, 1 H), 7.19 (d, J = 8.4 Hz, 1 H), 7.07 (dd, J = 8.4, 2.8 Hz, 1 H), 6.99 (d, J = 8.2 Hz, 1 H), 6.50 (d, J = 2.3 Hz, 1 H), 6.47 (dd, J = 8.2, 2.3 Hz, 1 H), 3.96 (dd, J = 12.2, 4.6 Hz, 1 H), 3.85 (s, 3 H), 3.81 (s, 3 H), 3.74 (s, 3 H), 3.05 (ddd, J = 16.0, 11.6, 4.3 Hz, 1 H), 2.94 (dt, J = 16.3, 4.1 Hz, 1 H), 2.43 (qd, J = 12.3, 4.3 Hz, 1 H), 2.23 (dq, J = 12.9, 4.3 Hz, 1 H) ppm. ^{13}C NMR (by HSQC and HMBC): δ = 198.4, 159.8, 158.2, 158.0, 136.8, 133.9, 129.9, 129.6, 121.8, 121.4, 109.7, 104.3, 99.1, 55.5, 55.4, 55.3, 49.2, 30.3, 28.6 ppm. MS (EI): *m*/*z* (%) = 312 (100) $[M]^+$, 294 (16), 174 (50), 161 (45), 151 (36), 120 (34). HRMS: calcd. for $C_{19}H_{20}O_4$ 312.1362; found 312.1403.

7-Methoxy-2-(2-methoxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (11b): The crude product was purified by column chromatography with a mixture of hexane/AcOEt (97:3) as eluent, to give **11b** as a pale brown solid; m.p. 84–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, J = 2.8 Hz, 1 H), 7.29–7.23 (m, 1 H), 7.20 (d, J = 8.4 Hz, 1 H), 7.12–7.05 (m, 2 H), 6.96–6.89 (m, 2 H), 4.03 (dd, J = 12.1, 4.7 Hz, 1 H), 3.85 (s, 3 H), 3.76 (s, 3 H), 3.06 (ddd, J = 16.1, 11.6, 4.3 Hz, 1 H), 2.95 (dt, J = 16.3, 4.2 Hz, 1 H), 2.47 (qd, J = 12.4, 4.3 Hz, 1 H), 2.25 (dq, J = 13.0, 4.3 Hz, 1 H) ppm. ^{13}C NMR (by HSQC and HMBC): δ = 197.9, 158.3, 156.9, 136.6, 133.6, 129.7, 129.2, 128.1, 121.3, 120.5, 111.0, 109.5, 55.4, 55.3, 49.7, 30.0, 28.5 ppm. MS (EI): *m*/*z* (%) = 282 (100) $[M]^+$, 264 (31), 161 (46), 148 (29), 120 (53). HRMS: calcd. for $C_{18}H_{18}O_3$ 282.1256; found 282.1227.

2-(2,4-Dimethoxyphenyl)-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (12a): The crude product was purified by column chromatography with a mixture of hexane/AcOEt (90:10) as eluent, to give **12a** as a pale brown solid; m.p. 110–111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, J = 8.7 Hz, 1 H), 6.98 (d, J = 8.3 Hz, 1 H), 6.85 (dd, J = 8.7, 2.5 Hz, 1 H), 6.73 (d, J = 2.3 Hz, 1 H), 6.49 (d, J = 2.4 Hz, 1 H), 6.45 (dd, J = 8.3, 2.4 Hz, 1 H), 3.95 (dd, J = 11.9, 4.6 Hz, 1 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 3.74 (s, 3 H), 3.08 (ddd, J = 16.0, 11.6, 4.3 Hz, 1 H), 2.95 (dt, J = 16.3, 4.1 Hz, 1 H), 2.43 (dtd, J = 12.9, 11.9, 4.2 Hz, 1 H), 2.27–2.17 (m, 1 H) ppm. ^{13}C NMR (by HSQC and HMBC): δ = 197.5, 164.0, 160.4, 159.2, 148.1, 131.0, 130.3, 127.3, 122.8, 114.3, 114.1, 105.8, 99.9, 56.7, 56.6, 56.4, 49.9, 30.9, 30.2 ppm. MS (EI): *m*/*z* (%) = 312 (100) $[M]^+$, 161 (45), 148 (94). HRMS: calcd. for $C_{19}H_{20}O_4$ 312.1362; found 312.1310.

6-Methoxy-2-(2-methoxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (12b): The crude product was purified by column chromatography with a mixture of hexane/AcOEt (95:5) as eluent, to give **12b** as a pale yellow solid; m.p. 78–80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, J = 8.7 Hz, 1 H), 7.27–7.22 (m, 1 H), 7.09 (d, J = 7.3 Hz, 1 H), 6.95–6.89 (m, 2 H), 6.85 (dd, J = 8.7, 2.2 Hz, 1 H), 6.73 (d, J = 2.3 Hz, 1 H), 4.03 (dd, J = 11.8, 4.6 Hz, 1 H), 3.87 (s, 3 H), 3.76 (s, 3 H), 3.09 (ddd, J = 16.0, 11.7, 4.2 Hz, 1 H), 2.96 (dt, J = 16.5, 4.0 Hz, 1 H), 2.47 (qd, J = 12.2, 4.1 Hz, 1 H), 2.30–2.20 (m, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 197.1, 163.4, 157.2, 146.6, 130.1, 129.4, 129.4, 128.1, 126.8, 120.7, 113.0, 112.5, 111.1, 55.5, 55.4, 49.6, 30.0, 29.7 ppm. MS (EI): *m*/*z* (%) = 282 (94) $[M]^+$, 264 (8), 161 (42), 148 (100). HRMS: calcd. for $C_{18}H_{18}O_3$ 282.1256; found 282.1259.

2-(2,4-Dimethoxyphenyl)-5-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (13a): The crude product was purified by column chromatography with a mixture of hexane/AcOEt (90:10) as eluent, to give **13a** as a pale brown solid; m.p. 98–100 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70 (d, J = 7.8 Hz, 1 H), 7.29 (t, J = 8.0 Hz, 1 H), 7.03 (d, J = 8.0 Hz, 1 H), 7.00 (d, J = 8.3 Hz, 1 H), 6.50 (d, J = 1.9 Hz, 1 H), 6.47 (dd, J = 8.3, 2.1 Hz, 1 H), 3.99 (dd, J = 12.6, 4.5 Hz, 1 H), 3.88 (s, 3 H), 3.80 (s, 3 H), 3.74 (s, 3 H), 3.18 (dt, J = 17.4, 3.8 Hz, 1 H), 2.85–2.77 (m, 1 H), 2.41 (qd, J = 12.6, 4.3 Hz, 1 H), 2.25 (dq, J = 12.9, 4.3 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.5, 159.8, 158.1, 156.7, 134.2, 133.1, 129.4, 126.7, 121.5, 119.3, 113.9, 104.3, 98.9, 55.7, 55.4, 55.3, 48.7, 29.3, 22.8 ppm. MS (EI): *m*/*z* (%) = 312 (100) $[M]^+$, 294 (14), 161 (48), 151 (43), 148 (29). HRMS: calcd. for $C_{19}H_{20}O_4$ 312.1362; found 312.1364.

5-Methoxy-2-(2-methoxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (13b): The crude product was purified by column chromatography with a mixture of hexane/AcOEt (95:5) as eluent, to give **13b** as a brown solid; m.p. 109–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ =

7.71 (d, J = 7.8 Hz, 1 H), 7.33–7.22 (m, 2 H), 7.10 (dd, J = 7.5, 1.6 Hz, 1 H), 7.04 (d, J = 8.1 Hz, 1 H), 6.96–6.89 (m, 2 H), 4.06 (dd, J = 12.5, 4.6 Hz, 1 H), 3.88 (s, 3 H), 3.76 (s, 3 H), 3.19 (dt, J = 17.5, 4.1 Hz, 1 H), 2.88–2.76 (m, 1 H), 2.45 (qd, J = 12.6, 4.4 Hz, 1 H), 2.28 (dq, J = 13.1, 4.6 Hz, 1 H) ppm. ^{13}C NMR (by HSQC and HMBC): δ = 198.1, 157.1, 156.7, 134.0, 133.0, 129.3, 128.9, 128.1, 126.7, 120.7, 119.2, 113.9, 110.9, 55.6, 55.4, 49.1, 28.9, 22.6 ppm. MS (EI): m/z (%) = 282 (100) $[M]^+$, 264 (29), 161 (55), 148 (38). HRMS: calcd. for $C_{18}H_{18}O_3$ 282.1256; found 282.1244.

2-(2,4-Dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydronaphthalen-1(2*H*)-one (14a): The crude product was purified by column chromatography with a mixture of hexane/AcOEt (85:15) as eluent, to give **14a** as a pale brown solid; m.p. 134–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (s, 1 H), 6.98 (d, J = 8.3 Hz, 1 H), 6.70 (s, 1 H), 6.50 (d, J = 2.4 Hz, 1 H), 6.45 (dd, J = 8.3, 2.4 Hz, 1 H), 3.99–3.91 (m, 1 H), 3.95 (s, 3 H), 3.92 (s, 3 H), 3.80 (s, 3 H), 3.76 (s, 3 H), 3.05 (ddd, J = 15.9, 11.3, 4.4 Hz, 1 H), 2.91 (dt, J = 16.3, 4.3 Hz, 1 H), 2.43 (dtd, J = 12.8, 11.7, 4.3 Hz, 1 H), 2.23 (dq, J = 13.2, 4.4 Hz, 1 H) ppm. ^{13}C NMR (by HSQC and HMBC): δ = 197.5, 159.7, 158.0, 153.0, 147.7, 138.8, 129.5, 126.3, 121.6, 110.1, 109.0, 104.2, 98.9, 56.4, 55.8, 55.3, 55.1, 48.5, 30.3, 28.9 ppm. MS (EI): m/z (%) = 342 (100) $[M]^+$, 324 (9), 204 (26), 191 (67), 178 (51), 151 (35), 150 (47). HRMS: calcd. for $C_{20}H_{22}O_5$ 342.1467; found 342.1455.

6,7-Dimethoxy-2-(2-methoxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (14b): The crude product was purified by column chromatography with a mixture of hexane/AcOEt (90:10) as eluent, to give **14b** as a pale brown solid; m.p. 141–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (s, 1 H), 7.25 (td, J = 8.0, 1.7 Hz, 2 H), 7.08 (dd, J = 7.8, 1.6 Hz, 1 H), 6.95–6.89 (m, 2 H), 6.70 (s, 1 H), 4.03 (dd, J = 11.6, 4.7 Hz, 1 H), 3.96 (s, 3 H), 3.92 (s, 3 H), 3.78 (s, 3 H), 3.05 (ddd, J = 15.9, 11.2, 4.3 Hz, 1 H), 2.92 (dt, J = 16.4, 4.3 Hz, 1 H), 2.47 (dtd, J = 13.0, 11.5, 4.3 Hz, 1 H), 2.26 (dq, J = 13.2, 4.5 Hz, 1 H) ppm. ^{13}C NMR (by HSQC and HMBC): δ = 197.2, 157.1, 153.2, 147.8, 138.8, 129.3, 127.9, 126.2, 120.9, 120.5, 110.2, 110.0, 109.0, 56.1, 55.8, 55.1, 51.1, 30.0, 28.4 ppm. MS (EI): m/z (%) = 312 (100) $[M]^+$, 294 (16), 191 (43), 178 (37), 150 (52). HRMS: calcd. for $C_{19}H_{20}O_4$ 312.1362; found 312.1341.

2-(2,4-Dimethoxyphenyl)-5,8-dimethoxy-3,4-dihydronaphthalen-1(2*H*)-one (15a): The crude product was purified by column chromatography with a mixture of hexane/AcOEt (70:30) as eluent, to give **15a** as a pale brown solid; m.p. 134–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.04–6.96 (m, 2 H), 6.82 (d, J = 8.9 Hz, 1 H), 6.48–6.43 (m, 2 H), 3.98 (dd, J = 12.3, 4.8 Hz, 1 H), 3.83 (s, 6 H), 3.79 (s, 3 H), 3.72 (s, 3 H), 3.17 (dt, J = 17.5, 3.6 Hz, 1 H), 2.83–2.71 (m, 1 H), 2.38–2.17 (m, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 198.0, 159.6, 158.0, 154.1, 150.2, 134.7, 129.6, 124.2, 121.9, 115.0, 110.6, 104.2, 98.8, 56.6, 56.0, 55.4, 55.3, 49.9, 29.0, 23.4 ppm. MS (EI): m/z (%) = 342 (100) $[M]^+$, 324 (13), 191 (69), 178 (81), 151 (41). HRMS: calcd. for $C_{20}H_{22}O_5$ 342.1467; found 342.1498.

5,8-Dimethoxy-2-(2-methoxyphenyl)-3,4-dihydronaphthalen-1(2*H*)-one (15b): The crude product was purified by column chromatography with a mixture of hexane/AcOEt (85:15) as eluent, to give **15b** as a brown solid; m.p. 100–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.19 (m, 1 H), 7.12 (d, J = 7.4 Hz, 1 H), 6.99 (d, J = 9.0 Hz, 1 H), 6.91 (t, J = 7.4 Hz, 1 H), 6.87 (d, J = 8.2 Hz, 1 H), 6.82 (d, J = 9.0 Hz, 1 H), 4.05 (dd, J = 12.2, 4.9 Hz, 1 H), 3.84 (s, 6 H), 3.74 (s, 3 H), 3.18 (dt, J = 17.4, 3.9 Hz, 1 H), 2.83–2.71 (m, 1 H), 2.41–2.2 (m, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 197.7, 157.0, 154.1, 150.2, 134.7, 129.5, 129.4, 127.8, 124.1, 120.5, 115.1, 110.8, 110.5, 56.6, 56.1, 55.4, 50.5, 28.9, 23.3 ppm. MS (EI): m/z (%) = 312 (100) $[M]^+$, 294 (20), 191 (63), 178 (84), 163 (29). HRMS: calcd. for $C_{19}H_{20}O_4$ 312.1362; found 312.1373.

General Procedure for the Synthesis of 5-Carbapterocarpens: The aryltetralone **12a** (50 mg, 0.16 mmol) was dissolved in anhydrous CH_2Cl_2 (3 mL) and stirred in the dark under Ar at 0 °C for 15 min. BBr_3 (226 μL, 2.4 mmol) was then added dropwise with vigorous stirring. The mixture was stirred at 0 °C for 90 min to prepare compound **17**. The reaction mixture was allowed to warm to room temperature and stirred for more 2 h to prepare dihydroxylated product **4**. After that, the reaction mixture was carefully added to water (20 mL) at 0 °C with continuous stirring over 20 min. The resulting suspension was extracted with EtOAc (4 × 15 mL). The combined organic extracts were washed with brine and then dried with anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure to afford a pure product as a solid.

5,6-Dihydronaphtho[1,2-*b*]benzofuran-3,9-diol (4): The reaction yielded a pure product as a pale purple solid; m.p. 207–208 °C. ^{1}H NMR (500 MHz, CD_3OD): δ = 7.35 (d, J = 8.2 Hz, 1 H), 7.24 (d, J = 8.3 Hz, 1 H), 6.88 (d, J = 2.1 Hz, 1 H), 6.72 (dd, J = 8.3, 2.0 Hz, 2 H), 6.67 (dd, J = 8.2, 2.3 Hz, 1 H), 2.98 (t, J = 7.9 Hz, 2 H), 2.83 (t, J = 7.9 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, CD_3OD): δ = 156.6, 156.0, 154.7, 150.7, 137.2, 121.1, 120.6, 119.9, 118.3, 115.1, 112.7, 111.2, 110.9, 97.5, 28.6, 18.8 ppm. MS (EI): m/z (%) = 252 (100) $[M]^+$, 251 (64), 234 (5), 223 (14). HRMS: calcd. for $C_{16}H_{12}O_3$: 252.0786; found 252.0765.

5,6-Dihydrobenzo[*d*]naphtho[1,2-*b*]furan-3-ol (16): The reaction yielded a pure product as a pale brown solid; m.p. 129–130 °C. ^{1}H NMR (500 MHz, CD_3OD): δ = 7.48–7.40 (m, 3 H), 7.23–7.16 (m, 2 H), 6.74 (s, 1 H), 6.70 (dd, J = 8.2, 2.0 Hz, 1 H), 3.01 (t, J = 7.8 Hz, 2 H), 2.88 (t, J = 7.8 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, CD_3OD): δ = 157.2, 154.9, 152.0, 138.1, 128.3, 122.9, 122.3, 121.3, 119.4, 118.2, 115.1, 112.8, 110.8, 110.4, 28.6, 18.7 ppm. HRMS: calcd. for $C_{16}H_{11}O_2$ 235.0765 [M – H]; found 235.0770.

3-Methoxy-5,6-dihydronaphtho[1,2-*b*]benzofuran-9-ol (17a): The reaction yielded a pure product as a pale brown solid; m.p. 82–83 °C. ^{1}H NMR (500 MHz, CD_3OD): δ = 7.41 (d, J = 8.3 Hz, 1 H), 7.24 (d, J = 8.3 Hz, 1 H), 6.89 (s, 1 H), 6.82 (s, 1 H), 6.79 (d, J = 8.3 Hz, 1 H), 6.73 (d, J = 8.2 Hz, 1 H), 3.79 (s, 3 H), 3.00 (t, J = 7.8 Hz, 2 H), 2.82 (t, J = 7.7 Hz, 2 H) ppm. ^{13}C NMR (by HSQC and HMBC): δ = 158.9, 156.2, 154.9, 150.4, 137.1, 121.0, 120.9, 120.4, 118.3, 114.0, 111.6, 111.3, 111.0, 97.4, 54.1, 28.6, 18.8 ppm. MS (EI): m/z (%) = 266 (100) $[M]^+$, 265 (23), 251 (58), 221 (11). HRMS: calcd. for $C_{17}H_{14}O_3$ 266.0943; found 266.0959.

3-Methoxy-5,6-dihydrobenzo[*d*]naphtho[1,2-*b*]furan (17b): The reaction yielded a pure product as a pale brown solid; m.p. 74–75 °C. ^{1}H NMR (500 MHz, CD_3OD): δ = 7.51 (d, J = 8.4 Hz, 1 H), 7.46 (t, J = 8.3 Hz, 2 H), 7.24–7.17 (m, 2 H), 6.87 (s, 1 H), 6.83 (d, J = 8.4 Hz, 1 H), 3.81 (s, 3 H), 3.06 (t, J = 7.8 Hz, 2 H), 2.90 (t, J = 7.9 Hz, 2 H) ppm. ^{13}C NMR (by HSQC and HMBC): δ = 159.6, 155.0, 151.7, 137.9, 128.3, 123.2, 122.3, 121.1, 120.5, 118.4, 114.1, 111.4, 111.1, 110.5, 54.3, 28.4, 18.5 ppm. HRMS: calcd. for $C_{17}H_{15}O_2$ [M + H] 251.1072; found 251.1070.

5,6-Dihydrobenzo[*d*]naphtho[1,2-*b*]furan-4,9-diol (18a): The reaction yielded a pure product as a brown solid; m.p. 186–187 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.29 (d, J = 8.4 Hz, 1 H), 7.07 (s, 1 H), 7.05 (d, J = 2.0 Hz, 1 H), 6.91 (d, J = 1.9 Hz, 1 H), 6.75 (dd, J = 8.4, 2.0 Hz, 1 H), 6.72–6.67 (m, 1 H), 3.02 (t, J = 8.1 Hz, 2 H), 2.85 (t, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR (by HSQC and HMBC): δ = 155.7, 154.0, 150.3, 128.8, 126.6, 121.5, 120.7, 120.4, 118.7, 114.1, 113.5, 111.3, 111.2, 97.4, 20.4, 18.2 ppm. HRMS: calcd. for $C_{16}H_{11}O_3$ [M – H] 251.0714; found 251.0717.

5,6-Dihydrobenzo[*d*]naphtho[1,2-*b*]furan-4-ol (18b): The reaction yielded a pure product as a beige solid; m.p. 140–141 °C. ^{1}H NMR (500 MHz, CD_3OD): δ = 7.51–7.44 (m, 1 H), 7.26–7.22 (m, 1 H), 7.20 (t, J = 7.2 Hz, 1 H), 7.14 (d, J = 7.4 Hz, 1 H), 7.09 (t, J = 7.8 Hz, 1 H), 6.75 (d, J = 8.0 Hz, 1 H), 3.06 (t, J = 8.1 Hz, 1 H), 2.89 (t, J = 8.2 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, CD_3OD): δ = 155.2, 154.2, 151.7, 128.4, 128.2, 126.7, 123.7, 122.4, 121.4, 118.7, 114.8, 113.4, 111.8, 110.6, 20.5, 18.2 ppm. HRMS: calcd. for $C_{16}H_{11}O_2$ [M – H] 235.0765; found 235.0762.

5,6-Dihydrobenzo[*d*]naphtho[1,2-*b*]furan-2,9-diol (19a): The crude product was diluted in CH_2Cl_2 and filtered through diatomaceous earth to yield a pure product as a brown solid; m.p. 160–161 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.24 (d, J = 8.4 Hz, 1 H), 7.00 (d, J = 8.1 Hz, 1 H), 6.97 (d, J = 2.5 Hz, 1 H), 6.90 (d, J = 2.1 Hz, 1 H), 6.73 (dd, J = 8.4, 2.1 Hz, 1 H), 6.57 (dd, J = 8.1, 2.5 Hz, 1 H), 2.89 (t, J = 7.8 Hz, 2 H), 2.80–2.74 (t, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, CD_3OD): δ = 156.3, 155.8, 155.3, 150.3, 128.6, 128.5, 126.0, 120.8, 118.9, 114.3, 113.2, 111.5, 106.5, 97.6, 27.4, 19.2 ppm. HRMS: calcd. for $C_{16}H_{11}O_3$ [M – H] 251.0714; found 251.0709.

5,6-Dihydrobenzo[*d*]naphtho[1,2-*b*]furan-2-ol (19b): The crude product was diluted in CH_2Cl_2 and filtered through diatomaceous earth to yield a pure product as a beige solid; m.p. 115–117 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.49–7.44 (m, 2 H), 7.27–7.16 (m, 2 H), 7.09–7.04 (m, 2 H), 6.65 (dd, J = 8.2, 2.5 Hz, 1 H), 2.98–2.90 (m, 1 H), 2.88–2.81 (m, 1 H) ppm. ^{13}C NMR (101 MHz, CD_3OD): δ = 156.0, 155.1, 151.6, 128.6, 28.2, 128.1, 126.7, 123.8, 122.5, 118.8, 114.1, 114.0, 110.7, 107.0, 27.3, 19.0 ppm. HRMS: calcd. for $C_{16}H_{11}O_2$ [M – H] 235.0765; found 235.0760.

Supporting Information (see footnote on the first page of this article): NMR spectra of all compunds.

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