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Palladium catalyzed intramolecular cascade type cyclizations: interesting Approach towards naphthoquinone derivatives having an O-containing heterocyclic skeleton

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ABSTRACT

Important naphthoquinones fused with an O-containing six-, seven- and eight-membered ring along with one tetracyclic compound, which are normally difficult to construct, have been synthesized using intramolecular Heck reaction where 6-*exo trig*, 7-*endo trig* and 8-*endo trig* cyclizations take place, respectively.

1. Introduction

The diversity of chemical structures of the naphthoquinone family and their useful biological activities made these compounds attractive targets in synthetic organic chemistry.[1] Pyranonaphthoquinone based compounds comprise a large class of natural products that show varied bioactivity such as anticancer, antibiotics, fungicides and anticoccidial agents.[2] They have also been proposed to act as bioreductive alkylating agents.[3] The biosynthetic origins of some of the higher molecular weight dimeric products[4] have been of interest to biochemists, and the biological activity of some of the compounds has inspired interest in their synthesis.

There are several procedures reported regarding the synthesis of various kinds of pyranonaphthoquinones.[5] Recently, the synthesis of a particular group of naturally occurring pyranonaphthoquinones, such as pentalongin, *C*(1)-and *C*(3)[5f]-substituted pentalongin (Fig. 1) were synthesized by us as an effort towards the discovery of new biologically active pyranonaphthoquinone derivatives using intramolecular Heck reaction with 2-allyloxy compounds.[6] Pentalongin is a natural product from the Central-East African medicinal plant *Pentas longiflora*, which is reported to be used for the treatment of malaria and skin diseases in Rwanda and Kenya.[7]

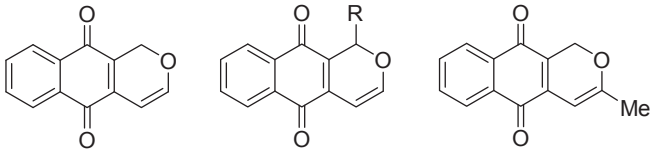

Fig. 1. Pyranonaphthoquinone based natural products.

6*H*-Naphtho[2,3-*c*]chromene-7,12-diones, i.e., 3,4-dehydro-pyranonaphthoquinones in which the double bond at C3–C4 is part of an aromatic system have been reported by De Kimpe et al. from 2-bromo-3-aryloxymethyl-1,4-naphthoquinones.[8] Inspired by their work and in continuation of our synthetic efforts towards physiologically active pentalongin derivatives, we are now reporting here a convenient synthesis of one tetracyclic reduced pyranonaphthoquinone along with some naphthoquinones having an O-containing six-, seven- and eight-membered ring via palladium catalyzed intramolecular cyclization.

2. Results and discussion

In our previous report[6] we had discussed about the formation of the pyran ring system containing one exocyclic double bond (**2**) via palladium catalyzed intramolecular cyclization of 2-allyloxymethyl-3-bromo-1,4-dimethoxynaphthalene (Scheme 1).

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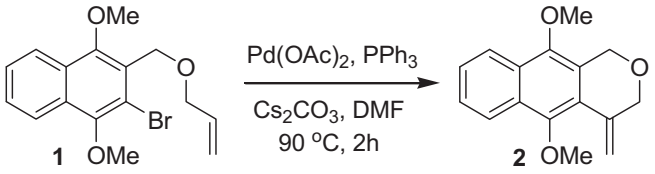
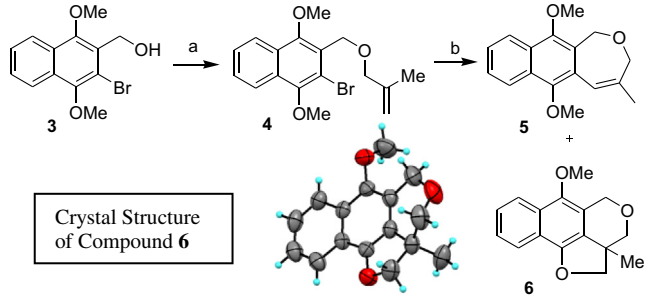


Scheme 1.

The easy synthesis of the fused pyran ring from *O*-allylated compound (**1**) prompted us to treat the *O*-methylallylated compound (**4**) under the same reaction condition and here it was expected an sp^3 C–H activated product.[9] For this reason *O*-methylallylated compound (**4**) was synthesized from alcohol **3**[6] using 3-bromo-2-methylpropene. Now this *O*-methylallylated product (**4**) when treated under Heck reaction conditions using $Pd(OAc)_2$, PPh_3, Cs_2CO_3, in DMF at 120 °C, interestingly gives compound **5** having an O-containing seven-membered ring and the tetracyclic compound **6** having a novel heterocyclic skeleton (Scheme 2) in 9:1 ratio. Next we optimized the reaction condition to get compound **6** in better yield and we found that using $PdCl_2(PPh_3)_2$, NaOAc, in DMA at 120 °C we got compound **6** as yellow crystalline solid[10] in good yield (Table 1, entry 4).



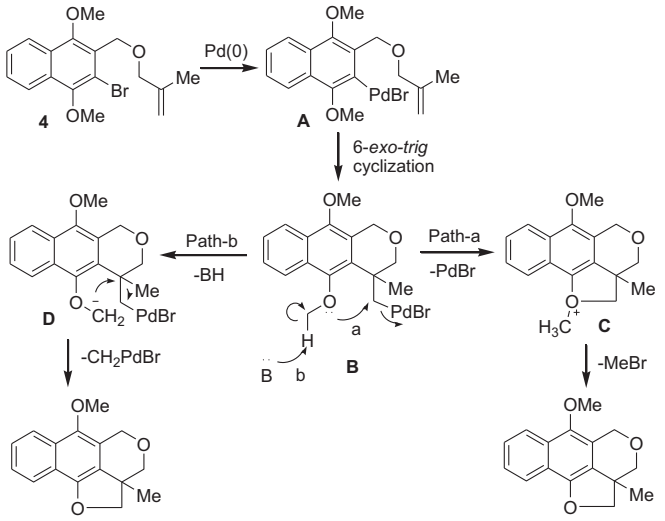
Scheme 2. Reagents and conditions: (a) 3-bromo-2-methylpropene (2 equiv), NaH (0.66 mmol), THF, 0 °C, 5 h, 85%; (b) NaOAc (1.2 equiv), $PdCl_2(PPh_3)_2$ (10 mol %), TBAC (1 equiv), DMA, 120 °C, 1 h, 73%.

Table 1
Optimization studies for the Heck reaction towards compound **6**

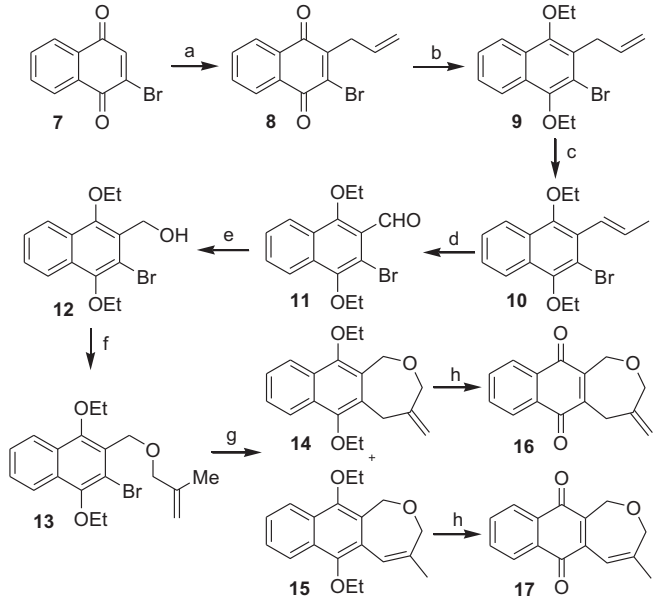
Entry	Solvent	Catalyst	Base	Yield (%)	Product ratio (**5**/**6**)
1	DMF	$Pd(OAc)_2$	Cs_2CO_3	64	9:1
2	DMA	$Pd(OAc)_2$	Cs_2CO_3	60	8:2
3	DMA	$PdCl_2(PPh_3)_2$	Cs_2CO_3	69	5:5
4	DMA	$PdCl_2(PPh_3)_2$	NaOAc	73	3:7

The formation of product **5** can easily be explained by 7-*endo trig* cyclization[11] but the formation of compound **6** is quite uncertain. A plausible mechanism for the tetracyclic product formation is shown in Scheme 3. Initially an alkenylpalladium(II) intermediate **A** was formed by oxidative addition of Pd(0) to the sp^2 C–Br bond, which undergoes addition to the unactivated double bond to produce an alkylpalladium complex **B**. Since no elimination is possible due to the absence of a β-H in the alkylpalladium complex, oxygen lone pair takes part in the reaction and yielded the intermediate **C** from which we got our desired product **6** (*path-a*, Scheme 3). Alternatively base can abstract the methoxy proton (complex **D**, Scheme 3) and the anion then attack on the carbon centre bearing $-CH_2PdBr$ as a leaving group, which is very uncertain (*path-b*, Scheme 3). Considering the leaving group *path-a* should be more preferable.

As we got the interesting tetracyclic compound (**6**) from methoxy derivative (**4**), next we performed the reaction with the ethoxy compound, which was prepared from bromoquinone **7** (Scheme 4). But here we did not get any tetrasubstituted product,



Scheme 3. Plausible reaction pathway towards tetracyclic compound formation.

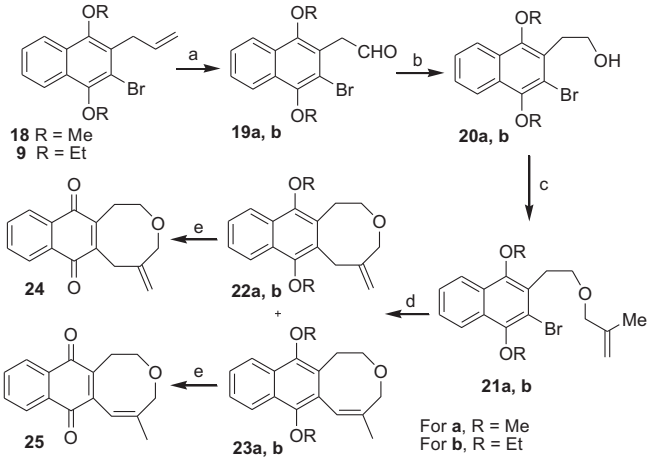


Scheme 4. Reagents and conditions: (a) vinylacetic acid (1.3 equiv), $AgNO_3$ (0.3 equiv), $(NH_4)_2S_2O_8$ (2.0 equiv), $MeCN/H_2O$, 2:1, 65 °C, 3 h, 75%; (b) $Na_2S_2O_4$ (5.0 equiv), Et_2O/EtOAc/H_2O, 10:1:10, 25 °C, 30 min; NaH (1.01 mmol), EtI (2.2 equiv), DMF, −15 °C, 1 h, 79%; (c) *t*-BuOK (2.0 equiv), THF, 0 °C, 2 h, 96%; (d) OsO_4 (0.01 equiv), $NaIO_4$ (2.4 equiv), THF/H_2O, 2:1, 70 °C, 18 h, 86%; (e) $NaBH_4$ (2 equiv), CH_3CN, 25 °C, 3 h, 93%; (f) 3-bromo-2-methylpropene (2 equiv), NaH (0.82 mmol), THF, 0 °C, 85%; (g) PPh_3 (0.25 equiv), Cs_2CO_3 (1.2 equiv), $Pd(OAc)_2$ (10 mol %), TBAC (1 equiv), DMF, 85–90 °C, 2 h, 83%, (**14**/**15**=3:6); (h) CAN (3 equiv), CH_3CN/H_2O (1:2), 0 °C, 15 min, 25 °C, 15 min, 93–94%.

which may be due to the presence of bulky ethyl group (causes steric interaction) preventing the attack of bromide ion for the elimination of ethyl bromide (for *path-a*) or may be due to the electron donating effect of the methyl group of ethoxy derivative, which decreases the electrophilicity of the hydrogen of CH_2 group and prevent the abstraction of hydrogen by the base in complex **B** (Scheme 3, *path-b*). Instead of the tetracyclic compound here we found two other isomeric products having O-containing seven-membered ring (Scheme 4, compounds **14** and **15**) from which we can easily prepared their quinone derivatives by treating the compounds with cerium(IV)ammonium nitrate (Scheme 4, compounds **16** and **17**). Here if we use $PdCl_2(PPh_3)_2$ as a catalyst in the cyclization step, i.e., the condition reported in Table 1, entry 4, we

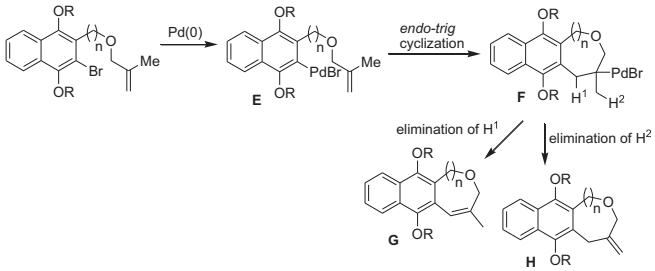
got mainly one isomer, which is compound **14** (yield: 85%, product ratio **14**/**15**=9:1).

Naphthoquinones fused with an O-containing eight-membered ring (compounds **24** and **25**, Scheme 5) are new scaffolds for combinatorial chemistry. For this reason after getting the seven-membered ring system next we performed the reaction to get the higher homologue, i.e., the compound having the O-containing eight-membered ring system, which is difficult to construct. For this purpose we treated compound **18** (for R=Me)[6] and compound **9** (for R=Et) with osmium tetroxide in presence of sodium periodate and here we got the higher homologue of β-bromo vinyl aldehydes (compounds **19a** and **19b** in Scheme 5). Then in a similar way reduction of **19a**,**b** using sodium borohydride followed by methallylation using sodium hydride and 3-bromo-2-methylpropene afforded compounds **21a**,**b**. After that Heck reaction was performed on these compounds, which yielded eight-membered ring fused reduced naphthoquinones (compounds **22a**, **b** and **23a**, **b** in Scheme 5). Cerium ammonium nitrate treatment of these reduced naphthoquinones finally afforded the corresponding naphthoquinones (compound **24** and **25** in Scheme 5).



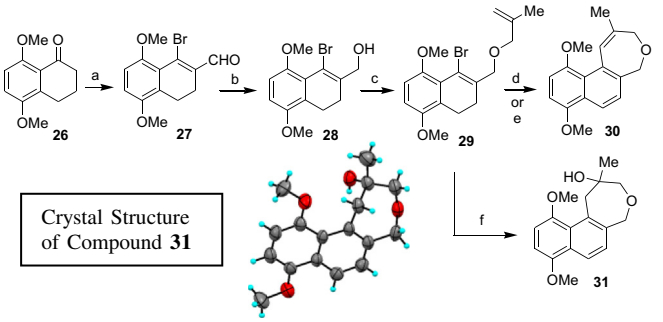
Scheme 5. Reagents and conditions: (a) OsO_4 (0.01 equiv), $NaIO_4$ (2.4 equiv), THF/H_2O, 2:1, 70 °C, 18 h, 82–84%; (b) $NaBH_4$ (2 equiv), CH_3CN, 25 °C, 3 h, 88–92%; (c) 3-bromo-2-methylpropene (2 equiv), NaH (1.12 mmol), THF, 0 °C, 87–90%; (d) PPh_3 (0.25 equiv), Cs_2CO_3 (1.2 equiv), $Pd(OAc)_2$ (10 mol %), TBAC (1 equiv), DMF, 85–90 °C, 2 h, 79–84%, (**22**/**23**≈6:4); (e) CAN (3 equiv), CH_3CN/H_2O (1:2), 0 °C, 15 min, 25 °C, 15 min, 91–94%.

Formation of compounds **14**, **15**, **22** and **23** can be explained by *endo trig* cyclization of the corresponding alkenylpalladium (II) intermediate **E**, which form complex **F** (Scheme 6). Then elimination of proton afforded **G** type compound where endocyclic double bond is present and on the other hand elimination of H^2 proton afforded **H** type compound where exocyclic double bond is present.



Scheme 6. Plausible reaction pathway towards seven- and eight-membered ring formation.

As we got the unexpected results from *O*-methylallylated derivatives of 1,4-dimethoxy/diethoxynaphthalenes (**4**, **13** and **20**) under Heck reaction condition, we were very much interested to know the results with *O*-methylallylated derivative of 5,8-dimethoxynaphthalene system. For this reason we took 5,8-dimethoxy-1-tetralone (**26**) as a starting material, which on reaction with Arnold–Vilsmeier reagent (PBr_3/DMF) yielded the bromovinylaldehyde (**27**). Sodium borohydride reduction followed by methallylation afforded the Heck reaction precursor **29**. Now the Heck reaction was performed on this *O*-methylallylated product (**29**) under the two different conditions (Table 1, entries 1 and 4) and here we got compound **30** having O-containing seven-membered ring (Scheme 7) as a major product in both cases and it was formed via 7-*endo trig* cyclization followed by ring aromatization. Here we did not found any tetracyclic product, i.e., the methoxy group does not take part in the reaction. Here also we observe an interesting result, i.e., when we use $Pd(OAc)_2$, PPh_3, Cs_2CO_3 and dry DMF, after 3 h we got compound **30** but if we use normal DMF (containing moisture) after 12 h we got compound **31** as white crystalline solid.[12] Probably compound **31** was formed from compound **30** by the addition of water, which took place due to the prolonged reaction time, which form an interesting class of compound.



Scheme 7. Reagents and conditions: (a) PBr_3 (2.7 equiv), DMF (3 equiv), $CHCl_3$, 0 °C to rt, $NaHCO_3$ work up, 82%; (b) $NaBH_4$ (2 equiv), CH_3CN, 25 °C, 3 h, 94%; (c) 3-bromo-2-methylpropene (2 equiv), NaH (0.76 mmol), THF, 0 °C, 83%; (d) PPh_3 (0.25 equiv), Cs_2CO_3 (1.2 equiv), $Pd(OAc)_2$ (10 mol %), TBAC (1 equiv), DMF, 120 °C, 1 h, 60%; (e) $PdCl_2(PPh_3)_2$ (10 mol %), NaOAc (1 equiv), TBAC (1 equiv), DMA, 120 °C, 1 h, 56%; (f) PPh_3 (0.25 equiv), Cs_2CO_3 (1.2 equiv), $Pd(OAc)_2$ (10 mol %), TBAC (1 equiv), DMF, 120 °C, 12 h, 70%.

3. Conclusions

In short, we have introduced some new class of naphthoquinones fused with a six-, seven- and eight-membered O-containing ring along with one interesting tetracyclic compound, which could show bioactivity. We are gratified to prove that the method of preparation of these compounds has the potential to be of great benefit in the convergent synthesis of a number of naphthoquinone based natural products.

4. Experimental section

4.1. General methods

Melting points were determined in open-end capillary tubes and are uncorrected. Solvents were dried and distilled following the standard procedure. TLC was carried out on precoated plates (Merck silica gel 60 f_{254}), and the spots were visualized with UV light. Column chromatography was performed on silica gel (60–120 mesh). ^1H NMR and ^{13}C NMR spectra for most of the compounds were recorded at 200 or 400 MHz and 50 or 100 MHz, respectively, in $CDCl_3$. Chemical shifts are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: 7.26 ppm). Data are reported as follows: chemical shifts, multiplicity (s=singlet,

d=doublet, t=triplet, br s=broad singlet, m=multiplet, dd=double doublet, q=quartet), coupling constant (Hz). HRMS (ESI) spectra were taken using micromass, Q-Tofmicro (IACS, Kolkata) and Waters Xevo G2 QTof mass spectrometer (IIT Kharagpur). Elemental analysis was carried out by using an Elemental Analyzer VARIO EL instrument (IIT Kharagpur). The IR spectra were recorded on a Parkin–Elmer model 883 spectrometer (IIT Kharagpur).

4.2. Typical experimental procedures

*4.2.1. 2-((2-Methylallyloxy)methyl)-3-bromo-1,4-dimethoxynaphthalene (**4**).* NaH (0.66 mmol) taken in a two-neck round bottom flask, was thoroughly washed with benzene (two times). It was then dried under vacuum and dry THF (4 mL) was added in it. The alcohol **3** (0.22 mmol) was dissolved in THF (4 mL) and slowly added into the NaH solution in ice-cold condition. After half an hour 3-bromo-2-methylpropene (2 equiv) was added and stirring was continued at room temperature for 5 h. The reaction mixture was quenched in saturated ammonium chloride solution and extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Then the product was purified by column chromatography on silica gel 60–120 mesh with 5% ethyl acetate in petroleum ether, which gave compound **4** as colourless oil.

*Compound **4***: colourless oil; yield 85%; R_f (2% EtOAc in hexane) 0.42; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.85 (s, 3H, Me), 3.99 (s, 3H, OMe), 4.01 (s, 3H, OMe), 4.10 (s, 2H, OCH_2), 4.81 (s, 2H, OCH_2), 4.96 (s, 1H, $CH_aH_bC(Me)CH_2$), 5.09 (s, 1H, $CH_aH_bC(Me)CH_2$), 7.53–7.57 (m, 2H, ArH), 8.09–8.14 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 19.8, 61.3, 64.0, 66.6, 75.2, 112.9, 116.5, 122.5, 123.0, 126.7, 126.8, 127.3, 127.9, 129.2, 142.3, 150.2, 152.8. Anal. Calcd for $C_{17}H_{19}BrO_3$: C, 58.13; H, 5.45. Found: C, 58.31; H, 5.63.

4.2.2. General procedure for the palladium catalyzed cyclization. The O-methylallylated compound **4** (0.20 mmol), $Pd(OAc)_2$ (10 mol %), PPh_3 (0.25 equiv), TBAC (1 equiv), Cs_2CO_3 (1.2 equiv) was flashed with argon and dimethylformamide (5 mL) was added to it. After degasifying with argon it was heated to 120 °C for 1 h. The reaction mixture was cooled to room temperature, diluted with ice water and extracted with diethyl ether. The solvent was evaporated after drying (Na_2SO_4) and the product was purified by silica gel (60–120 mesh) column chromatography.

*4.2.2.1. (Z)-1,3-Dihydro-6,11-dimethoxy-4-methylnaphtho[2,3-c]oxepine (**5**).* Yellow solid; yield 54%; mp 95–96 °C; R_f (5% EtOAc in hexane) 0.25; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.92 (s, 3H, Me), 3.89 (s, 3H, OMe), 3.91 (s, 3H, OMe), 4.49 (s, 2H, OCH_2), 4.92 (s, 2H, OCH_2), 6.85 (s, 1H, $CHC(Me)CH_2$), 7.46–7.50 (m, 2H, ArH), 8.02–8.11 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 21.7, 62.3, 63.2, 66.1, 76.7, 100.0, 119.4, 122.5, 125.8, 126.0, 126.3, 127.5, 128.5, 129.0, 140.0, 148.6, 150.1; IR (liquid film): ν_{max} 1615, 1540, 793, 751 cm^{-1}. Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.32; H, 6.99; HRMS (ESI) m/z $[M+H]^+$ for $C_{17}H_{19}O_3$: 271.1329, found: 271.1322.

*4.2.2.2. 6-Methoxy-2a-methyl-2a,5-dihydro-2H,3H-1,4-dioxaaceanthrylene (**6**).* Yellow solid; yield 58% (using condition 4, Table 1); mp 110–111 °C; R_f (5% EtOAc in hexane) 0.23; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.50 (s, 3H, Me), 3.54 (d, 1H, J=10.0 Hz, OCH_aH_b), 3.90 (s, 3H, OMe), 4.12 (d, 1H, J=10.2 Hz, OCH_aH_b), 4.29 (d, 1H, J=8.4 Hz, OCH_aH_b), 4.64 (d, 1H, J=8.4 Hz, OCH_aH_b), 4.81 (d, 1H, J=16.0 Hz, OCH_aH_b), 5.18 (d, 1H, J=15.8 Hz, OCH_aH_b), 7.41–7.46 (m, 2H, ArH), 7.87–7.92 (m, 1H, ArH), 8.01–8.06 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 23.2, 41.2, 61.5, 62.6, 72.7, 84.2, 120.5, 120.6, 121.4, 122.5, 124.8, 125.2, 125.5, 128.3, 144.9, 149.9. Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.21; H, 6.43; HRMS (ESI) m/z $[M+H]^+$ for $C_{16}H_{17}O_3$: 257.1172, found: 257.1167.

*4.2.3. 2-Allyl-3-Bromo-1,4-diethoxynaphthalene (**9**).* To a solution of bromonapthoquinone **8** (0.52 mmol) in EtOAc (1 mL), Et_2O (10 mL), and H_2O (10 mL) at 25 °C was added $Na_2S_2O_4$ (5.0 equiv) and the reaction mixture was stirred vigorously for 30 min. Upon consumption of starting material (TLC), the biphasic reaction mixture was extracted with EtOAc (3×10 mL), the combined organic layers washed with brine (15 mL), dried (Na_2SO_4), and concentrated. The resulting oil was then dissolved in DMF (5 mL) and cooled to −15 °C. NaH (44 mg, 1.10 mmol, 2.1 equiv) was added portionwise to the reaction mixture, and then EtI (2.2 equiv) was added drop-wise over 5 min, and the reaction mixture was stirred at −15 °C for 30 min. The reaction mixture was then quenched with satd aq NH_4Cl (10 mL) and the biphasic reaction mixture was extracted with EtOAc (3×10 mL), and the combined organic layers washed with brine (25 mL), dried (Na_2SO_4), and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc 8:1) gave ethyl protected hydroquinone **9**.

Yellow oil; yield 79%; R_f (5% EtOAc in hexane) 0.45; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.53 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.57 (t, 3H, J=7.2 Hz, OCH_2CH_3), 3.76–3.79 (m, 2H, CH_2), 4.03 (q, 2H, J=7.0 Hz, OCH_2), 4.12 (q, 2H, J=7.0 Hz, OCH_2), 4.97–5.10 (m, 2H, CH_2), 5.97–6.16 (m, 1H, $CHCH_2$), 7.45–7.55 (m, 2H, ArH), 8.01–8.11 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 15.9 (2C), 34.8, 70.1, 71.1, 100.2, 115.9, 117.2, 122.8, 122.9, 126.5, 126.6, 128.6, 129.1, 136.1, 149.5, 150.2; IR (liquid film): ν_{max} 1635, 1561, 1497, 1160, 812, 791 cm^{-1}. Anal. Calcd for $C_{17}H_{19}BrO_2$: C, 60.91; H, 5.71. found: C, 60.77; H, 5.97; HRMS (ESI) m/z $[M+H]^+$ for $C_{17}H_{20}BrO_2$: 335.0641, found: 335.0636.

*4.2.4. 2-Bromo-1,4-diethoxy-3-((E)-prop-1-enyl)naphthalene (**10**).* To a cold (0 °C) solution of ethyl protected hydroquinone **9** (0.34 mmol) in THF (4 mL) was added *t*-BuOK (2 equiv) and the reaction mixture was stirred for 2 h at 0 °C. The reaction mixture was then quenched with H_2O (5 mL) and the biphasic reaction mixture was extracted with EtOAc (3×5 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and double bond migrated naphthoquinone **10** (96% yield) was used without further purification.

Pale yellow oil; yield 96%; R_f (5% EtOAc in hexane) 0.45; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.47 (t, 3H, J=7.0 Hz, OCH_2CH_3), 1.59 (t, 3H, J=7.0 Hz, OCH_2CH_3), 2.03 (d, 3H, J=5.0 Hz, Me), 3.97 (q, 2H, J=7.0 Hz, OCH_2), 4.15 (q, 2H, J=7.0 Hz, OCH_2), 6.44–6.56 (m, 1H, CHCH), 6.59 (d, 1H, J=5.0 Hz, CHCH), 7.46–7.56 (m, 2H, ArH), 8.07–8.17 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 15.9, 16.0, 19.5, 69.1, 69.9, 116.1, 123.1, 123.2, 125.8, 126.3, 126.6, 127.7, 128.1, 128.8, 133.1, 149.1, 149.7; IR (liquid film) ν_{max} 1611, 1535, 1480, 797, 715 cm^{-1}. Anal. Calcd for $C_{17}H_{19}BrO_2$: C, 60.91; H, 5.71. Found: C, 61.09; H, 5.99; HRMS (ESI) m/z $[M+H]^+$ for $C_{17}H_{20}BrO_2$: 335.0641, found: 335.0645.

*4.2.5. General procedure for the formation of compounds **11** and **19**.* To a solution of compound **9** or **10** or **18** (0.50 mmol) in THF (4 mL) and H_2O (2 mL) at 25 °C were added OsO_4 (0.01 equiv) and $NaIO_4$ (2.4 equiv). The reaction mixture was then heated to 70 °C and stirred for 18 h. The reaction mixture was then quenched with satd aq $Na_2S_2O_3$ (5 mL) and stirred vigorously for 30 min. The biphasic reaction mixture was then extracted with EtOAc and the combined organic layers were washed with brine (15 mL), dried (Na_2SO_4), and concentrated. Column chromatography (silica gel 60–120 mesh) provided the aldehyde compounds.

*4.2.5.1. 3-Bromo-1,4-diethoxynaphthalene-2-carbaldehyde (**11**).* White solid; yield 86%; mp 104–105 °C; R_f (5% EtOAc in hexane) 0.54; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.49 (t, 6H, J=7.0 Hz, OCH_2CH_3), 4.08 (q, 4H, J=7.0 Hz, OCH_2), 7.47–7.62 (m, 2H, ArH), 8.02 (d, 1H, J=7.6 Hz, ArH), 8.12 (d, 1H, J=7.6 Hz, ArH), 10.45 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 15.5, 15.6, 70.1, 73.9, 111.7, 122.7,

123.6, 124.1, 127.3, 128.5, 129.8, 131.7, 149.6, 156.3, 190.5. Anal. Calcd for $C_{15}H_{15}BrO_3$: C, 55.75; H, 4.68 Found: C, 55.58; H, 4.83.

*4.2.6. (2-Bromo-1,4-diethoxynaphthalen-3-yl)methanol (**12**).* To a solution of 3-bromo-1,4-diethoxynaphthalene-2-carbaldehyde **11** (0.54 mmol) in acetonitrile (6 mL), sodium borohydride (2 equiv) was added portionwise. Stirring was continued for 3 h at room temperature and then the reaction mixture was poured into a diluted hydrochloric acid solution, and extracted with ethyl acetate. The extract was washed with brine, dried (Na_2SO_4), and evaporated at reduced pressure. Column chromatography on silica gel with 20% ethyl acetate in petroleum ether gave (2-bromo-1,4-diethoxynaphthalen-3-yl)methanol **12**.

White semi-solid; yield 93%; R_f (50% EtOAc in hexane) 0.55; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.47 (t, 6H, J=7.0 Hz, OCH_2CH_3), 2.93 (br s, 1H, OH), 4.05 (q, 2H, J=7.0 Hz, OCH_2), 4.07 (q, 2H, J=7.0 Hz, OCH_2), 4.95 (s, 2H, CH_2OH), 7.42–7.51 (m, 2H, ArH), 7.97–8.05 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 15.6, 15.7, 60.0, 69.9, 72.4, 115.6, 122.5, 123.0, 126.6, 127.1, 128.2, 128.9, 129.2, 149.2, 150.8; IR (liquid film): ν_{max} 3216, 1564, 815 cm^{-1}. Anal. Calcd for $C_{15}H_{17}BrO_3$: C, 55.40; H, 5.27. Found: C, 55.28; H, 5.09; HRMS (ESI) m/z $[M+H]^+$ for $C_{15}H_{18}BrO_3$: 325.0433, found: 325.0429.

*4.2.6.1. 2-((2-Methylallyloxy)methyl)-3-bromo-1,4-diethoxynaphthalene (**13**).* Yellow liquid; yield 85%; R_f (2% EtOAc in hexane) 0.47; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.49 (t, 6H, J=7.0 Hz, OCH_2CH_3), 1.85 (s, 3H, Me), 4.10 (s, 2H, OCH_2), 4.13–4.21 (m, 4H, OCH_2), 4.81 (s, 2H, OCH_2), 4.97 (s, 1H, $CH_aH_bC(Me)CH_2$), 5.10 (s, 1H, $CH_aH_bC(Me)CH_2$), 7.51–7.57 (m, 2H, ArH), 8.07–8.14 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 15.8 (2C), 19.9, 66.9, 69.9, 72.6, 75.2, 112.9, 116.9, 122.6, 123.2, 126.6, 126.9, 127.2, 128.3, 129.6, 142.4, 149.4, 151.8. Anal. Calcd for $C_{19}H_{23}BrO_3$: C, 60.17; H, 6.11. Found: C, 59.96; H, 6.29.

*4.2.6.2. 6,11-Diethoxy-1,3,4,5-tetrahydro-4-methylenenaphtho[2,3-c]oxepine (**14**).* Yellow liquid; yield 80% (using condition 4, Table 1); R_f (10% EtOAc/PET ether) 0.49; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.49–1.57 (m, 6H, OCH_2CH_3), 3.76 (s, 2H, CH_2), 4.01 (q, 4H, J=6.8 Hz, OCH_2), 4.30 (s, 2H, OCH_2), 4.78 (s, 2H, OCH_2), 5.0 (s, 1H, $CH_aH_bC(CH_2)CH_2$), 5.06 (s, 1H, $CH_aH_bC(CH_2)CH_2$), 7.64–7.71 (m, 2H, ArH), 7.97–8.10 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 15.8, 15.9, 32.7, 70.4,70.6, 74.2, 74.9, 112.7, 122.5 (2C), 125.6 (2C), 128.0, 128.1, 129.0, 129.8, 147.7, 149.0, 149.5; IR (liquid film): ν_{max} 1645, 1563, 1323, 1132, 854, 813 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.70; H, 7.25; HRMS (ESI) m/z $[M+H]^+$ for $C_{19}H_{23}O_3$: 299.1642, found: 299.1639.

*4.2.6.3. (Z)-6,11-Diethoxy-1,3-dihydro-4-methylnaphtho[2,3-c]oxepine (**15**).* Yellow semi-solid; yield 55% (using condition 1, Table 1); R_f (5% EtOAc in hexane) 0.42; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.49 (t, 3H, J=6.6 Hz, OCH_2CH_3), 1.52 (t, 3H, J=6.6 Hz, OCH_2CH_3), 1.91 (s, 3H, Me), 4.01 (q, 4H, J=6.8 Hz, OCH_2), 4.48 (s, 2H, OCH_2), 4.91 (s, 2H, OCH_2), 6.85 (s, 1H, $CHC(Me)CH_2$), 7.44–7.48 (m, 2H, ArH), 7.95–8.11 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 15.9, 16.0, 21.9, 66.5, 70.8, 71.7, 76.8, 120.0, 122.7, 122.8, 126.0 (2C), 126.3, 127.9, 129.0, 129.3, 139.7, 147.5, 149.3; IR (liquid film): ν_{max} 1622, 1495, 1256, 918, 765, cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.64; H, 7.60; HRMS (ESI) m/z $[M+H]^+$ for $C_{19}H_{23}O_3$: 299.1642, found: 299.1644.

*4.2.7. 4,5-Dihydro-4-methylenenaphtho[2,3-c]oxepine-6,11(1H,3H)-dione (**16**).* A solution of compound **14** (0.26 mmol) in acetonitrile (2 mL) was added drop-wise to a solution of cerium(IV) ammonium nitrate (3 equiv) in water (5 mL) at 0 °C for 15 min. The stirred mixture was allowed to warm to room temperature over a period of 30 min, poured into water, and extracted with ethyl acetate. The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated at reduced pressure. Column chromatography on silica gel 60–120 mesh was done to get the final products.

Yellow solid; yield 93%; mp 94–95 °C; R_f (40% EtOAc in hexane) 0.56; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.65 (s, 2H, CH_2), 4.36 (s, 2H, OCH_2), 4.79 (s, 2H, OCH_2), 5.01 (s, 1H, $CH_aH_bC(CH_2)CH_2$), 5.06 (s, 1H, $CH_aH_bC(CH_2)CH_2$), 7.67–7.73 (m, 2H, ArH), 7.99–8.12 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 31.3, 66.1, 75.9, 114.4, 126.2, 126.7, 131.9, 132.1, 133.8, 133.9, 144.1, 144.3, 145.3, 184.5, 184.8; IR (liquid film): ν_{max} 1687, 1636, 1392, 804, 781 cm^{-1}. Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.10; H, 5.15; HRMS (ESI) m/z $[M+H]^+$ for $C_{15}H_{13}O_3$: 241.0859, found: 241.0861.

*4.2.7.1. (4Z)-4-Methylnaphtho[2,3-c]oxepine-6,11(1H,3H)-dione (**17**).* Yellow solid; yield 94%; mp 101–102 °C; R_f (40% EtOAc in hexane) 0.48; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.96 (s, 3H, Me), 4.48 (s, 2H, OCH_2), 4.77 (s, 2H, OCH_2), 6.80 (s, 1H, $CHC(Me)CH_2$), 7.66–7.75 (m, 2H, ArH), 8.03–8.12 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 22.6, 65.7, 77.1, 117.9, 126.3, 126.8, 131.9, 132.3, 133.7, 134.0, 139.9, 142.2, 155.5, 183.8, 184.7; IR (liquid film): ν_{max} 1679, 1623, 1311, 781, 737, 691 cm^{-1}. Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.13; H, 4.89; HRMS (ESI) m/z $[M+H]^+$ for $C_{15}H_{13}O_3$: 241.0859, found: 241.0857.

*4.2.7.2. 2-(2-Bromo-1,4-dimethoxynaphthalen-3-yl)acetaldehyde (**19a**).* White solid; yield 84%; mp 92–93 °C; R_f (10% EtOAc in hexane) 0.39; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.83 (s, 3H, OMe), 3.96 (s, 3H, OMe), 4.11 (s, 2H, CH_2), 7.51–7.56 (m, 2H, ArH), 8.02–8.12 (m, 2H, ArH), 9.85 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 45.2, 61.4, 62.5, 115.9, 122.7, 123.1, 127.0, 127.2, 127.7 (2C), 128.8, 150.4, 151.9, 198.6. Anal. Calcd for $C_{14}H_{13}BrO_3$: C, 54.39; H, 4.24. Found: C, 54.56; H, 4.39.

*4.2.7.3. 2-(2-Bromo-1,4-diethoxynaphthalen-3-yl)acetaldehyde (**19b**).* White solid; yield 82%; mp 102–103 °C; R_f (10% EtOAc in hexane) 0.44; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.47 (t, 3H, J=7.0 Hz, OCH_2CH_3), 1.55 (t, 3H, J=7.0 Hz, OCH_2CH_3), 3.95 (q, 2H, J=7.0 Hz, OCH_2), 4.10 (s, 2H, CH_2), 4.13 (q, 2H, J=7.0 Hz, OCH_2), 7.47–7.56 (m, 2H, ArH), 7.98–8.12 (m, 2H, ArH), 9.83 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 15.7, 15.8, 45.5, 70.1, 71.0, 116.2, 122.7 (2C), 123.1, 126.8, 127.0, 128.0, 129.1, 149.6, 150.9, 198.9. Anal. Calcd for $C_{16}H_{17}BrO_3$: C, 56.99; H, 5.08. Found: C, 56.86; H, 5.21.

*4.2.7.4. 2-(2-Bromo-1,4-dimethoxynaphthalen-3-yl)ethanol (**20a**).* White semi-solid; yield 92%; R_f (50% EtOAc in hexane) 0.46; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.04 (s, 1H, OH), 3.30 (t, 2H, J=6.8 Hz, CH_2CH_2), 3.87 (s, 2H, CH_2CH_2), 3.93 (s, 3H, OMe), 3.96 (s, 3H, OMe), 7.50–7.54 (m, 2H, ArH), 8.01–8.10 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 33.8, 61.4, 62.1, 62.5, 116.5, 122.6 (2C), 126.7 (2C), 127.4, 127.7, 128.2, 150.3, 151.4. Anal. Calcd for $C_{14}H_{15}BrO_3$: C, 54.04; H, 4.86. Found: C, 53.82; H, 4.99; HRMS (ESI) m/z $[M+H]^+$ for $C_{14}H_{16}BrO_3$: 311.0277, found: 311.0273.

*4.2.7.5. 2-(2-Bromo-1,4-diethoxynaphthalen-3-yl)ethanol (**20b**).* White semi-solid; yield 88%; R_f (50% EtOAc in hexane) 0.55; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.54 (t, 3H, J=6.8 Hz, OCH_2CH_3), 1.56 (t, 3H, J=6.8 Hz, OCH_2CH_3), 2.73 (br s, 1H, OH), 3.30 (t, 2H, J=7.0 Hz, CH_2CH_2), 3.89 (t, 2H, J=7.0 Hz, CH_2CH_2), 4.03 (q, 2H, J=7.0 Hz, OCH_2), 4.11 (q, 2H, J=7.0 Hz, OCH_2), 7.43–7.54 (m, 2H, ArH), 7.97–8.09 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 15.8, 15.9, 34.1, 62.2, 69.9, 70.9, 116.8, 122.6, 122.7, 126.5, 126.6, 127.6, 127.9, 128.5, 149.5, 150.3. Anal. Calcd for $C_{16}H_{19}BrO_3$: C, 56.65; H, 5.65. Found: C, 56.81; H, 5.43; HRMS (ESI) m/z $[M+H]^+$ for $C_{16}H_{20}BrO_3$: 339.0590, found: 339.0594.

*4.2.7.6. 2-(2-(2-Methylallyloxy)ethyl)-3-bromo-1,4-dimethoxynaphthalene (**21a**).* Yellow liquid; yield 90%; R_f (2% EtOAc

in hexane) 0.39; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.74 (s, 3H, Me), 3.35 (t, 2H, J=7.8 Hz, CH_2), 3.69 (t, 2H, J=7.8 Hz, OCH_2), 3.96 (s, 5H, OMe & OCH_2), 3.97 (s, 3H, OMe), 4.89 (s, 1H, $CH_aH_bC(Me)CH_2$), 4.99 (s, 1H, $CH_aH_bC(Me)CH_2$), 7.47–7.58 (m, 2H, ArH), 8.03–8.12 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 19.5, 31.0, 61.3, 62.7, 68.8, 74.8, 112.1, 116.7, 122.6, 122.7, 126.6, 126.7, 127.5, 127.9, 128.2, 142.4, 150.1, 151.5. Anal. Calcd for $C_{18}H_{21}BrO_3$: C, 59.19; H, 5.79. Found: C, 59.40; H, 5.56.

*4.2.7.7. 2-(2-(2-Methylallyloxy)ethyl)-3-bromo-1,4-diethoxynaphthalene (**21b**).* Yellow liquid; yield 87%; R_f (2% EtOAc in hexane) 0.44; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.56 (t, 3H, J=7.0 Hz, OCH_2CH_3), 1.57 (t, 3H, J=7.0 Hz, OCH_2CH_3), 1.75 (s, 3H, Me), 3.33 (t, 2H, J=7.2 Hz, CH_2), 3.66 (t, 2H, J=7.2 Hz, OCH_2), 3.96 (s, 2H, OCH_2), 4.03 (q, 2H, J=7.0 Hz, OCH_2), 4.11 (q, 2H, J=7.0 Hz, OCH_2), 4.89 (s, 1H, $CH_aH_bC(Me)CH_2$), 4.98 (s, 1H, $CH_aH_bC(Me)CH_2$), 7.47–7.53 (m, 2H, ArH), 7.99–8.10 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 15.9, 16.0, 19.6, 31.3, 68.9, 70.0, 71.1, 74.9, 112.2, 117.1, 122.7 (2C), 126.5, 126.6, 127.6, 128.2, 128.6, 142.5, 149.4, 150.5. Anal. Calcd for $C_{20}H_{25}BrO_3$: C, 61.07; H, 6.41. Found: C, 61.29; H, 6.24.

*4.2.7.8. 2,4,5,6-Tetrahydro-7,12-dimethoxy-5-methylene-1H-naphtho[2,3-d]oxocine (**22a**).* Yellow liquid; yield 84%; R_f (10% EtOAc in hexane) 0.59; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.24 (t, 2H, J=4.8 Hz, CH_2), 3.87 (s, 2H, CH_2), 3.91 (s, 3H, OMe), 3.94 (s, 3H, OMe), 3.94–3.99 (m, 4H, OCH_2), 4.96 (s, 1H, $CH_aH_bC(CH_2)CH_2$), 5.20 (s, 1H, $CH_aH_bC(CH_2)CH_2$), 7.47–7.54 (m, 2H, ArH), 8.03–8.11 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 29.9, 32.7, 62.5, 62.7, 74.2, 75.2, 113.4, 122.7 (2C), 125.9 (2C), 127.9, 128.1, 129.2, 129.8, 147.6, 150.0, 150.6; IR (liquid film): ν_{max} 1641, 1515, 1496, 1364, 1130, 984, 813 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.25; H, 7.26; HRMS (ESI) m/z $[M+H]^+$ for $C_{18}H_{21}O_3$: 285.1485, found: 285.1482.

*4.2.7.9. 7,12-Diethoxy-2,4,5,6-tetrahydro-5-methylene-1H-naphtho[2,3-d]oxocine (**22b**).* Yellow liquid; yield 82%; R_f (10% EtOAc in hexane) 0.65; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.55 (t, 3H, J=7.0 Hz, OCH_2CH_3), 1.57 (t, 3H, J=7.0 Hz, OCH_2CH_3), 3.24 (t, 2H, J=5.2 Hz, CH_2), 3.86 (s, 2H, CH_2), 3.92–4.09 (m, 8H, OCH_2), 4.94 (s, 1H, $CH_aH_bC(CH_2)CH_2$), 5.18 (s, 1H, $CH_aH_bC(CH_2)CH_2$), 7.44–7.51 (m, 2H, ArH), 8.0–8.07 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 15.7, 15.8, 29.9, 32.6, 70.3, 70.5, 74.1, 74.9, 112.6, 122.4 (2C), 125.5 (2C), 127.9, 128.1, 128.9, 129.7, 147.6, 148.8, 149.5; IR (liquid film): ν_{max} 1638, 1498, 1384, 1235, 963, 828, 777 cm^{-1}. Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.66; H, 7.95; HRMS (ESI) m/z $[M+H]^+$ for $C_{20}H_{25}O_3$: 313.1798, found: 313.1797.

*4.2.7.10. (Z)-2,4-Dihydro-7,12-dimethoxy-5-methyl-1H-naphtho[2,3-d]oxocine (**23a**).* Yellow liquid; yield 80%; R_f (10% EtOAc in hexane) 0.47; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.55 (s, 3H, Me), 3.33 (t, 2H, J=8.0 Hz, CH_2), 3.58 (q, 2H, J=7.2 Hz, OCH_2), 3.90 (t, 2H, J=8.0 Hz, OCH_2), 3.95 (s, 3H, OMe), 3.96 (s, 3H, OMe), 5.89 (s, 1H, $CHC(Me)CH_2$), 7.51–7.58 (m, 2H, ArH), 8.02–8.10 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 19.6, 31.1, 56.4, 61.4, 62.6, 70.3, 110.7, 116.6, 122.6, 122.7, 126.7 (2C), 126.9, 127.9, 128.2, 140.0, 150.2, 151.5; IR (liquid film): ν_{max} 1624, 1498, 1386, 978, 812, 782 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.88; H, 7.30; HRMS (ESI) m/z $[M+H]^+$ for $C_{18}H_{21}O_3$: 285.1485, found: 285.1487.

*4.2.7.11. (Z)-7,12-Diethoxy-2,4-dihydro-5-methyl-1H-naphtho[2,3-d]oxocine (**23b**).* Yellow liquid; yield 79%; R_f (5% EtOAc in hexane) 0.53; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.47–1.57 (m, 6H, OCH_2CH_3), 1.91 (s, 3H, Me), 3.32 (t, 2H, J=5.0 Hz, CH_2), 4.02 (t, 4H, J=7.0 Hz, OCH_2), 4.48 (s, 2H, OCH_2), 4.91 (s, 2H, OCH_2), 6.87 (s, 1H, $CHC(Me)CH_2$), 7.42–7.52 (m, 2H, ArH), 7.99–8.12 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 15.9, 16.0, 22.0, 31.1, 66.7, 70.9, 71.8, 76.9, 120.1, 122.7, 122.8, 126.0 (2C), 126.2, 128.0, 129.1, 129.3, 139.8, 147.6, 149.6; IR (liquid film): ν_{max} 1619, 1516, 1477, 882, 765, 719 cm^{-1}. Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 77.06; H, 7.93; HRMS (ESI) m/z $[M+H]^+$ for $C_{20}H_{25}O_3$: 313.1798, found: 313.1796.

*4.2.7.12. 1,2,5,6-Tetrahydro-5-methylene-4H-naphtho[2,3-d]oxocine-7,12-dione (**24**).* Yellow solid; yield 94%; mp 88–89 °C; R_f (40% EtOAc in hexane) 0.49; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.09 (t, 2H, J=5.2 Hz, CH_2), 3.63 (s, 2H, CH_2), 3.85 (t, 2H, J=5.4 Hz, OCH_2), 4.08 (s, 2H, OCH_2), 5.02 (s, 1H, $CH_aH_bC(CH_2)CH_2$), 5.17 (s, 1H, $CH_aH_bC(CH_2)CH_2$), 7.67–7.72 (m, 2H, ArH), 8.05–8.09 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 28.2, 33.2, 71.3, 75.5, 116.1, 126.5, 126.6, 132.2, 132.4, 133.6, 133.7, 144.4, 145.8 (2C), 184.0, 184.5; IR (liquid film): ν_{max} 1682, 1640, 1428, 834, 767 cm^{-1}. Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.66; H, 5.67; HRMS (ESI) m/z $[M+H]^+$ for $C_{16}H_{15}O_3$: 255.1016, found: 255.1016.

*4.2.7.13. (5Z)-1,2-Dihydro-5-methyl-4H-naphtho[2,3-d]oxocine-7,12-dione (**25**).* Yellow solid; yield 91%; mp 84–85 °C; R_f (40% EtOAc in hexane) 0.54; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.97 (s, 3H, Me), 3.66 (t, 2H, J=5.6 Hz, CH_2), 4.48 (s, 2H, OCH_2), 4.78 (s, 2H, OCH_2), 6.81 (s, 1H, $CHC(Me)CH_2$), 7.69–7.75 (m, 2H, ArH), 8.06–8.11 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 22.6, 31.3, 65.7, 75.9, 117.9, 126.3, 126.8, 132.0, 132.3, 133.7, 134.0, 139.9, 142.2, 155.5, 183.8, 184.7; IR (liquid film): ν_{max} 1673, 1617, 1462, 1392, 839, 745, 711 cm^{-1}. Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.45; H, 5.69; HRMS (ESI) m/z $[M+H]^+$ for $C_{16}H_{15}O_3$: 255.1016, found: 255.1017.

*4.2.8. General procedure for the formation of compound **27**.* A mechanically stirred solution of dimethylformamide (3 equiv) in anhydrous chloroform was cooled in ice bath while phosphorus tribromide (2.7 equiv) was added drop-wise over a period of 15 min. The resulting white suspension was warmed to room temperature and stirred for additional 20 min. A solution of starting ketomethyl compound **26** (4.85 mmol) in chloroform was added drop-wise over 10 min. Stirring was continued for 8 h at room temperature. The reaction mixture was then poured in ice water. Solid sodium bicarbonate was carefully added to neutralize the acids and the mixture was extracted several times with dichloromethane. The organic part was then washed with cold water thoroughly, dried with sodium sulfate and evaporated. Purification of the residue was done by silica gel (60–120 mesh) column chromatography yielded the bromoaldehyde **27**.

*4.2.8.1. 1-Bromo-5,8-dimethoxy-3,4-dihydronaphthalene-2-carbaldehyde (**27**).* Yellow solid; yield 82%; mp 105–106 °C; R_f (10% EtOAc in hexane) 0.47; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.31 (t, 2H, J=8.2 Hz, CH_2), 2.59 (t, 2H, J=7.8 Hz, CH_2), 3.71 (s, 3H, OMe), 3.77 (s, 3H, OMe), 6.74 (d, 1H, J=9.0 Hz, ArH), 6.84 (d, 1H, J=9.0 Hz, ArH), 10.16 (d, 1H, J=1.4 Hz, CHO); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 21.1, 21.9, 56.1, 56.2, 111.5, 114.5, 123.7, 130.7, 133.5, 136.9, 149.5, 152.4, 192.8. Anal. Calcd for $C_{13}H_{13}BrO_3$: C, 52.55; H, 4.41. Found: C, 52.71; H, 4.55; HRMS (ESI) m/z $[M+H]^+$ for $C_{13}H_{14}BrO_3$: 297.0121, found: 297.0117.

*4.2.8.2. (4-Bromo-1,2-dihydro-5,8-dimethoxynaphthalen-3-yl)-methanol (**28**).* Colourless oil; yield 94%; R_f (40% EtOAc in hexane) 0.35; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.38 (t, 2H, J=7.8 Hz, CH_2), 2.73 (t, 2H, J=7.8 Hz, CH_2), 3.82 (s, 3H, OMe), 3.86 (s, 3H, OMe), 4.55 (s, 2H, CH_2OH), 4.83 (s, 1H, OH), 6.83 (s, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 21.9, 27.1, 56.4, 56.9, 65.8, 111.9, 112.1 (2C), 124.6, 128.9, 141.5, 149.8, 151.1. Anal. Calcd for $C_{13}H_{15}BrO_3$: C, 52.19; H, 5.05. Found: C, 52.35; H, 4.89; HRMS (ESI) m/z $[M+H]^+$ for $C_{13}H_{16}BrO_3$: 299.0277, found: 299.00273.

*4.2.8.3. 2-((2-Methylallyloxy)methyl)-1-bromo-3,4-dihydro-5,8-dimethoxynaphthalene (**29**).* Yellow oil; yield 83%; R_f (4% EtOAc in

hexane) 0.45; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.78 (s, 3H, Me), 2.34 (t, 2H, J=8.0 Hz, CH_2), 2.71 (t, 2H, J=7.8 Hz, CH_2), 3.79 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.93 (s, 2H, OCH_2), 4.41 (s, 2H, OCH_2), 4.93 (s, 1H, $CH_aH_bC(Me)CH_2$), 5.02 (s, 1H, $CH_aH_bC(Me)CH_2$), 6.80 (s, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 19.8, 21.7, 26.4, 56.3, 56.9, 72.1, 74.3, 111.8, 112.2, 112.4, 113.6, 124.7, 129.1, 139.8, 142.4, 149.9, 151.1. Anal. Calcd for $C_{17}H_{21}BrO_3$: C, 57.80; H, 5.99. Found: C, 57.61; H, 6.13; HRMS (ESI) m/z $[M+H]^+$ for $C_{17}H_{22}BrO_3$: 353.0747, found: 353.0750.

*4.2.8.4. (Z)-3,5-Dihydro-8,11-dimethoxy-2-methylnaphtho[2,1-c] oxepine (**30**).* Colourless oil; yield 60%; R_f (10% EtOAc in hexane) 0.49; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.06 (d, 3H, J=1.4 Hz, Me), 3.82 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.91 (s, 2H, OCH_2), 4.43 (s, 2H, OCH_2), 6.70 (q, 2H, J=15.6, 7.0 Hz, ArH), 7.34 (d, 1H, J=8.6 Hz, ArH), 7.60 (s, 1H, $CHC(Me)CH_2$), 8.10 (d, 1H, J=8.4 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 23.1, 55.9, 56.5, 69.0, 69.6, 100.0, 103.7, 106.8, 114.1, 121.2, 127.5, 131.3, 134.9, 136.2, 139.3, 149.9, 151.8; IR (liquid film): ν_{max} 1624, 1475, 1394, 863, 761 cm^{-1}. Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.32; H, 6.99; HRMS (ESI) m/z $[M+H]^+$ for $C_{17}H_{19}O_3$: 271.1329, found: 271.1324.

*4.2.8.5. 1,2,3,5-Tetrahydro-8,11-dimethoxy-2-methylnaphtho[2,1-c]oxepin-2-ol (**31**).* Brown solid; yield 70%; mp 139–140 °C; R_f (10% EtOAc in hexane) 0.28; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.33 (s, 3H, Me), 1.86 (br s, 1H, OH), 3.58 (d, 1H, J=14.2 Hz, OCH_2), 3.87 (q, 2H, J=27.2, 12.0 Hz, OCH_2), 3.99 (s, 3H, OMe), 4.01 (s, 3H, OMe), 4.48 (d, 1H, J=14.4 Hz, OCH_2), 4.95 (s, 2H, OCH_2), 6.79 (q, 2H, J=22.4, 14.0 Hz, ArH), 7.36 (d, 1H, J=8.4 Hz, ArH), 8.19 (d, 1H, J=8.4 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 26.4, 42.2, 56.0, 56.1, 69.5, 74.8, 82.7, 103.2, 106.4, 121.1, 126.6, 126.9, 127.9, 133.7, 139.3, 150.2, 151.2; IR (liquid film): ν_{max} 3310, 1524, 1429, 1261, 867 cm^{-1}. Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.67; H, 7.14; HRMS (ESI) m/z $[M+H]^+$ for $C_{17}H_{21}O_4$: 289.1434, found: 289.1435.

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra of all compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.12.016.

References and notes

1. (a) Schmid, H.; Ebnother, A. *Helv. Chim. Acta* **1951**, *64*, 1041; (b) Bergy, M. E. *J. Antibiot.* **1968**, *21*, 454; (c) Zeeck, A.; Zahrer, H.; Mardin, M. *Justus Liebigs Ann. Chem.* **1974**, 1101; (d) Omura, S.; Tanaka, H.; Koyama, Y.; Oiwa, R.; Awaya, J.; Nagai, T.; Tata, H. *J. Antibiot.* **1974**, *27*, 263; (e) Tanaka, H.; Koyama, Y.; Awaya, J.; Marumo, H.; Oiwa, R.; Katagiri, M.; Nagai, T.; Omura, S. *J. Antibiot.* **1975**, *28*, 860; (f) Tanaka, H.; Koyama, Y.; Nagai, T.; Maruma, H.; Omura, S. *J. Antibiot.* **1975**, *28*, 868; (g) Omura, S.; Tanaka, H.; Okada, Y.; Maruyama, H. *J. Chem. Soc., Chem. Commun.* **1976**, 320; (h) Brimble, M. A.; Duncalf, L. J.; Nairn, M. R. *Nat. Prod. Rep.* **1999**, *16*, 267.
2. (a) Thomson, R. H. *Naturally Occurring Quinones*, 2nd ed.; Academic: London, UK, 1971; p 282 see also p 597; (b) Wang, W.; Li, T.; Milburn, R.; Yates, J.; Hinnant, E.; Luzzio, M. J.; Noble, S. A.; Attardo, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1579; (c) Lee, H.; Hong, S. S.; Kim, Y. H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 933.
3. Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249.
4. Krone, B.; Zeeck, A.; Floss, H. G. *J. Org. Chem.* **1982**, *47*, 4721.
5. (a) Hayashi, T.; Smith, F. T.; Lee, K. H. *J. Med. Chem.* **1987**, *30*, 2005; (b) Naito, T.; Makita, Y.; Yazaki, S.; Kaneko, C. *Chem. Pharm. Bull.* **1986**, *34*, 1505; (c) Kesteleyn, B.; De Kimpe, N.; Van Puyvelde, L. *J. Org. Chem.* **1999**, *64*, 1173; (d) Nguyen Van, T.; De Kimpe, N. *Tetrahedron Lett.* **2004**, *45*, 3443; (e) Claessens, S.; Verniest, G.; Jacobs, J.; Van Hende, E.; Habonimana, P.; Nguyen Van, T.; Van Puyvelde, L.; De Kimpe, N. *Synlett* **2007**, 829; (f) Kesteleyn, B.; De Kimpe, N. *J. Org. Chem.* **2000**, *65*, 640.
6. Nandi, S.; Singha, R.; Samanta, S.; Ray, J. K. *Tetrahedron Lett.* **2012**, *53*, 2659.
7. (a) Hari, L.; De Buyck, L. F.; De Pooter, H. L. *Phytochemistry* **1991**, *30*, 1726; (b) De Kimpe, N.; Van Puyvelde, L.; Schripsema, J.; Erkelens, C.; Verpoorte, R. *Magn. Reson. Chem.* **1993**, *31*, 329; (c) Van Puyvelde, L.; Hakizayezu, D.; Brioen, P.; De Kimpe, N.; De Vroey, C.; Bogaerts, J.; Hakizamungu, E. *Presented at International Congress on Natural Products Research, July 31 to August 4, **1994**, Halifax, Canada*, **1994**.
8. Nguyen Van, T.; De Kimpe, N. *Tetrahedron* **2003**, *59*, 5941.
9. (a) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759; (b) Lee, J. M.; Chang, S. *Tetrahedron Lett.* **2006**, *47*, 1375.
10. Crystal data for compound **6**: CCDC reference no. 844938; $C_{16}H_{16}O_3$, M=256.29, orthorhombic, $P2(1)2(1)2(1)$, a=8.6959(10) Å, b=10.2220(11) Å, c=14.5826(16) Å, α=90.0, β=90.0, γ=90.0, V=1296.2(2) Å^3, Z=4, D_{calcd} (Mg/m^3)=1.313, 1489 reflections out of 3089 unique reflections with $I>2/s(I)$, $2.43<\theta<28.0$, final R-factors R_1=0.0500, wR_2=0.1323.
11. Samanta, S.; Mohapatra, H.; Jana, R.; Ray, J. K. *Tetrahedron Lett.* **2008**, *49*, 7153.
12. Crystal data for compound **31**: CCDC reference no. 852506; $C_{17}H_{20}O_4$, M=288.34, monoclinic, $C2/c$, a=14.902(3) Å, b=13.024(3) Å, c=16.208(3) Å, α=90.0, β=110.813, γ=90.0, V=2940.5(11) Å^3, Z=8, D_{calcd} (Mg/m^3)=1.303, 1176 reflections out of 3496 unique reflections with $I>2/s(I)$, $2.14<\theta<28.0$, final R-factors R_1=0.0841, wR_2=0.2303.