Synthesis of Hydroxylated Naphthoquinone Derivatives

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The use of the Stobbe condensation for the synthesis of juglone derivatives is presented, together with studies towards their further functionalization. The regiospecific oxidation of the above products to $o$- or $p$-naphthoquinones was also investigated. Finally, the preparation of useful intermediates for the synthesis of related natural products such as alkannin and shikonin is proposed.

Introduction

Hydroxylated naphthoquinone derivatives constitute a very important class of biologically active compounds including juglones and naphthazarines. Even the simplest homologues of this class are challenging synthetic targets, due to their high chemical reactivity and polyoxygenated nature. Consequently, several diversified synthetic approaches such as Diels–Alder reaction,[1] Fischer carbene complexes,[5–8] Hauser annulation,[9–11] $o$-substituted tertiary benzamide chemistry,[12,13] cyclobutenedione chemistry,[14,15] Stobbe condensation,[16] naphthol oxidation,[17,18] etc. have been reported. The most common synthetic problems associated with these compounds involve low yields in the final deprotection steps and constraints on the functionalization of the aromatic skeleton. Stobbe condensation of various benzaldehydes (1, Scheme 1) with diethyl succinate (2), employing simple and often commercially available starting materials, may address both problems. By this approach, the formation of a highly functionalized aromatic skeleton (3) may be achieved in two steps. These useful synthetic intermediates may, after regioselective oxidation, be successfully converted into $p$- and $o$-naphthoquinones 4 and 5, respectively, of which the former could be further transformed to the naturally occurring compounds alkannin and shikonin. This strategy allows orthogonal protection of hydroxyl groups, a crucial prerequisite for efficient deprotection in the final steps. Additionally, by taking advantage of the carboxyl moiety of key intermediate 3, several side chains, including $\beta$-keto alyl derivatives (6, Scheme 1), may be constructed. The results of our related studies are presented here.

Results and Discussion

The protected juglone derivatives 3a, 3b, and 3d were prepared by application of standard Stobbe conditions[19] to benzaldehydes 1a, 1b, and 1d (Scheme 2). This method was found to be unsuitable for the preparation of silylated juglones, since benzaldehyde 1c afforded only the peracetylated compound 3c.

Side chain modifications followed preparation of the aromatic core. Attachment of the prenyl group was considered to be of high priority, since this group appears in the structure of many natural products, including the title compounds. However, most reported syntheses concerning $\alpha$-prenylation[20–27] of aldehydes or acid derivatives were expected to result in multistep and "tricky" synthetic procedures. On the other hand, it has been demonstrated[28] that

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the allyl moiety in compounds such as 11 (Scheme 3) is efficiently transformed into the respective prenyl component. Thus, compound 3a, after saponification and subsequent selective silylation, was converted through carboxylic acid 7 into the S-pyridin-2-yl ester 8.[29,30] the imidazolide 9,[31,32] or the Weinreb amide 10,[33,34] functionalities suitable for monoalkylation (Scheme 3). Controlled allylation of substrates 9 and 10 at low temperature afforded the desired compound 11 in good to excellent chemical yields. In contrast, S-pyridin-2-yl ester 8 remained completely unreactive at low temperature, while at higher temperature it exclusively furnished the disubstituted derivative 12. Although it has been reported[35] that such derivatives can be transformed into the corresponding propenyl ketones (similar to 11) upon treatment with a strong base (e.g., tBuOK, DMF, 60 °C), that was not the case with compound 12. Under the same reaction conditions, benzylated analogue 13 (prepared in three steps from naphthol 3a) was also unreactive.

The use of benzyl ether as a protective group was thought to be a highly promising alternative to methyl ether protection, due to its mild deprotection conditions. Thus, the model compound 16 was synthesized in high yield (77%) from 3b (Scheme 4). Treatment of 16 with CAN at 25 °C afforded a mixture of products, among which structures 17 and 18 were identified (yields 20–40%). The 17/18 ratio varied according to reaction time and molar equivalents of CAN. It should be noted that substrates 20b and 21 (Scheme 5) under the same conditions afforded the corresponding p-quinones 22b and 22c, respectively, in less than 10% yield, among many other unidentified products. On the other hand, under radical conditions generated by use of 4,4′-di-tert-butylbiphenyl or naphthalene and lithium metal,[36–38] complete cleavage of the benzyl ether groups and the aromatic silyl ether occurred, affording juglone derivative 19 in 25–30% yield after aerial oxidation. Several other trials were even more disappointing, and so the use of benzyl ethers was not studied further.

The preparation of o- and/or p-naphthoquinone derivatives by the regiospecific oxidation of the corresponding juglones was also investigated. Treatment of acetates 3a and 3b with alkaline ethanol furnished naphthols 20a and 20b in almost quantitative yields, whereas exhaustive DIBAL reduction of acetate 3a and subsequent selective silylation provided naphthol 21 (Scheme 5). According to the literature, all these juglone derivatives should be transformable into the respective naphthazarines upon salcomine-catalyzed oxidation.[39] In this respect, the presented synthetic approach should give rise to either juglone or naphthazarine derivatives. However, as has been recently reported by

Scheme 3. Functionalization of carboxylates; reagents and conditions: i) LiOH aq. 3 n/THF/MeOH, 1:1:1, 60 °C, 2 h; ii) TBSCI, imidazole, cat. DMAP, DMF, 70% (based on 3a); iii) Aldrithiol-2TM, PPh3, C2H5CN, 1 h, 90%; iv) Im2CO, THF, 10 min, 94%; v) MeONHMe·HCl, CBr4, pyridine, PPh3, C2H5Cl2, 30 min, 87%; vi) Organometallic reagent, Et2O or THF, −100 or −20 °C, for yields see table; vii) EtONa, EtOH, reflux 1 h, 89%; viii) PhCH2Br, Cs2CO3, DMF, cat. Bu4NI, 5 h, 87%; ix) Excess allylmagnesium bromide, Et2O, 0 °C, 94%, 100 or 20 °C; x) Excess allylmagnesium bromide, Et2O, 0 °C, 94%, TBSCI = tert-butyldichloromethylsilane, DMAP = 4-dimethylaminopyridine, Aldrithiol-2TM = 2,2′-dipyridyl disulfide, Im2CO = carbonyldimidazole
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Scheme 4. Deprotection attempts on substrate 16; reagents and conditions: i) EtONa, EtOH, reflux 1 h, 93%; ii) TBSCl, imidazole, cat. DMAP, DMF, 2 h, 97%; iii) DIBAL, CH₂Cl₂, −78 °C, 20 min, 98%; iv) NMO, cat. TPAP, CH₂Cl₂, 2 h, 98%; v) allylmagnesium bromide, Et₂O, 0 °C, 15 min; vi) TBSCl, imidazole, cat. DMAP, DMF, 1.5 h, 89% (based on 15); vii) CANaq., CH₃CN; viii) Li, DTBBP, THF, −78 to −20 °C or Li, naphthalene, THF, −20 to −0 °C; DIBAL = diisobutylaluminium hydride, NMO = 4-methylmorpholine N-oxide, TPAP = tetrapropylammonium perruthenate, CAN = ammonium cerium(IV) nitrate, DTBBP = 4,4'-di-tert-butylbiphenyl.

Our group,[40] this is not the case, and the corresponding o-naphthoquinones are exclusively formed in high yields (Scheme 5; entries 1, 4, 8). After a number of attempts with various oxidants on both electron-rich and electron-poor substrates, it was evident that only hypervalent iodide reagents[41] could oxidize the p-position regiospecifically. According to the most widely accepted mechanism,[41,42] hypervalent iodide oxidations take place through intermediate 24 (Scheme 6), which is attacked by a molecule of water, preferably at the para position. Thus, the alkyl derivative 21, upon oxidation with PIFA, furnished the expected quinone 22c (Scheme 5, entry 7). Surprisingly, oxidation of the carboxylated analogues 20a and 20b proceeded only up to the intermediate hydroxy-enones 25a and 25b (Scheme 6; entries 9, 11–13).[43] Several attempts to force this oxidation to quinones 22a and 22b respectively, by changing the reaction conditions, were unsuccessful, and the use of a second oxidant as well as the addition of a strong mineral acid was necessary. After experimentation with CAN, CrO₃, HgO, and DDQ, the combination of ferric chloride and HCl provided the best results (Scheme 6; entries 10, 14).

These compounds were efficiently transformed into useful and versatile synthetic intermediates. From quinones 22a and 22b, for example, esters 26 and 27, respectively (Scheme 7), were produced after reduction with Na₂S₂O₄ and protection of the phenolic groups as silyl ethers. Reduction of 26 and 27 with DIBAL and subsequent oxidation of the resulting benzyl alcohols with NMO/TPAP afforded aldehydes 28 and 29, respectively, in high yields (based on

Scheme 5. Oxidation of juglone derivatives to p- or o-quinones; reagents and conditions: i) EtONa, EtOH, reflux 1 h, 89–93%; ii) DIBAL, CH₂Cl₂, −78 °C, 2 h, 95%; iii) 1.1 equiv. TBSCl, imidazole, cat. DMAP, DMF, 12 h, 85%
22a and 22b). These aldehydes resemble the common intermediate of most synthetic schemes so far reported for alkannin and shikonin,[44] with the additional advantage of orthogonal protection of the aromatic hydroxyl groups. As has recently been demonstrated,[28] intermediate 29 has been converted into the above natural products in good yields.

![Scheme 7. Preparation of aldehyde 29](image)

Conclusion

In conclusion, the utility of the Stobbe condensation for the preparation of naphthoquinone derivatives has been demonstrated. Functionalization of the side chain and regiospecific oxidation of various naphthols was also thoroughly investigated. These functionalized and orthogonally protected naphthoquinones are useful synthetic intermediates for biologically important classes of compounds. Furthermore, several juglone derivatives, as well as o- and p-naphthoquinones and the naturally occurring alkannin and shikonin, have been successfully synthesized by this route.

Experimental Section

General Remarks: All reactions were carried out under anhydrous conditions and argon atmosphere, using dry, freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were distilled from sodium/benzophenone, dichloromethane (CH₂Cl₂) from P₂O₅, and toluene from sodium. Yields refer to chromatographically and spectroscopically (1H NMR) determined yields. Chromatography (TLC) carried out on 0.25 mm Merck silica gel according to ref. [19] All reactions were monitored by thin-layer chromatography (TLC). Melting points (m.p.) are uncorrected and were recorded on a Perkin-Elmer DSC7 instrument. Melting points (m.p.) are uncorrected and were recorded on a Gallenkamp melting point apparatus. General Procedure for the Preparation of Compounds 3b–3d: tBuOK (2.1 g, 18.8 mmol) was added portionwise to a stirred solution of benzaldehyde 1b (3.0 g, 9.4 mmol) and diethyl succinate (4.1 g, 23.6 mmol) in tBuOH (35 mL). Upon completion of the addition, the mixture was stirred at 25 °C for 1 h, and then poured into HCl solution (1 N, 60 mL) and extracted with EtOAc (2 × 40 mL). The organic layer was separated and treated with saturated aqueous Na₂CO₃ solution. The aqueous layer was then extracted with EtOAc (30 mL) and then acidified under reduced pressure to afford crude 4-(2,5-bis(benzoyloxy)-phenyl)-3-(ethoxy carbonyl)-3-butoenoic acid. The crude carboxylic acid was cyclized in boiling acetic anhydride (2.9 g, 28.4 mmol) and anhydrous sodium acetate (927.0 mg, 11.3 mmol) for 5 h. The mixture was allowed to cool overnight and then poured into ice/water (150 mL). The yellow-orange amorphous solid was filtered and washed with water (4 × 50mL). The air-dried crude product was finally recrystallized from EtOAc and CH₂O to afford 3b as a pale orange, crystalline solid (2.4 g, 53% yield based on 1b). 3b: Rf = 0.55 (hexanes/EtOAc: 8:2); m.p. 178–180 °C IR (KBr): v = 2930, 1751, 1720, 1608, 1454, 1363, 1264, 1225, 1023, 752 cm⁻¹. 1H NMR (250 MHz, CDCl₃, 25 °C): δ = 1.39 (t, J = 7.1 Hz, 3 H, CH₃CH₂), 1.66 (s, 3 H, OAc), 4.39 (q, J = 7.1 Hz, 2 H, CH₂CH₂), 5.01 (s, 2 H, OCH₂Ph), 5.22 (s, 2 H, OCH₂Ph), 6.83 (ABq, J = 8.8 Hz, Δv = 23.3 Hz, 2 H, CH₃Ph), 7.26–7.56 (m, 10 H, CH₂), 7.64 (s, 1 H, CH₃Ph), 9.00 (s, 1 H, CH₃Ph) ppm. 13C NMR (62.9 MHz, CDCl₃, 25 °C): δ = 14.3, 20.2, 61.2, 70.7, 71.6, 106.7, 109.5, 119.7, 127.2, 127.9, 128.4, 128.6, 128.7, 128.8, 136.4, 136.9, 146.6, 148.9, 149.5, 165.9, 170.2 ppm. HRMS (MALDI) calcd. for C₂₉H₂₆O₆ ([M + Na⁺]; R = 156.66, 156.67): m/z = 493.1621, found 493.1631.

When the above conditions were applied to benzaldehyde 1c (acetic acid was used instead of hydrochloric acid during the acidification step), the only isolated product was triacetate 3c (55% yield based on 1c). 3c: Rf = 0.40 (hexanes/EtOAc, 8:2); m.p. 154–156 °C IR (KBr): v = 2992, 1772, 1724, 1466, 1368, 1238, 1188, 1032, 897 cm⁻¹. 1H NMR (250 MHz, CDCl₃, 25 °C): δ = 1.38 (t, J = 7.1 Hz, 3 H, CH₃CH₂), 2.34 (s, 3 H, OAc), 2.36 (s, 3 H, OAc), 2.44 (s, 3 H, OAc), 4.39 (q, J = 7.1 Hz, 2 H, CH₂CH₂), 7.26 (ABq, J = 8.4 Hz, Δv = 31.1 Hz, 2 H, CH₂), 7.73 (d, J = 1.5 Hz, 1 H, CH₃), 8.55 (d, J = 1.5 Hz, 1 H, CH₃) ppm. 13C NMR (62.9 MHz, CDCl₃, 25 °C): δ = 14.2, 20.1, 61.2, 70.7, 71.6, 106.7, 109.5, 119.7, 127.2, 127.9, 128.4, 128.6, 128.7, 128.8, 136.4, 136.9, 146.6, 148.4, 149.5, 165.9, 170.2 ppm. HRMS (MALDI) calcd. for C₂₉H₂₆O₆ ([M + Na⁺]; R = 156.66, 156.67): m/z = 493.1621, found 493.1631.

For the preparation of compound 3d, sodium hydride was used instead of tBuOK. A catalytic amount of ethanol (0.1 mL) was added to a stirred solution of sodium hydride (345.6 mg, 14.4 mmol) in toluene (10 mL), followed by dropwise addition of a solution of benzaldehyde 1d (1 g, 6.0 mmol) in diethyl 2-methylsuccinate (2.8 g, 15.0 mmol). The reaction mixture was further
treated as above to afford 3d as pale orange crystalline solid (737.8 mg, 37% yield based on 1d). 3d: Rf = 0.40 (hexanes/EtOAc, 8:2); m.p. 128–130 °C. IR (KBr): v = 2933, 2858, 1681, 1595, 1507, 1456, 1384, 1282, 918, 834 cm⁻¹. 1H NMR (250 MHz, CDCl₃, 25 °C): δ = 0.23 (s, 6 H, Me₂Si), 3.00 (s, 3 H, CH₂), 4.35 (q, J = 6.7 Hz, 2 H, CH₂), 6.80 (d, J = 8.5 Hz, 2 H, CH₃), 10.52 (s, 1 H, CH₃) ppm. 13C NMR (62.9 MHz, CDCl₃, 25 °C): δ = 27.2, 28.3, 55.9, 104.0, 107.7, 113.7, 116.9, 122.9, 123.4, 128.1, 129.1, 130.8, 133.5, 137.1, 150.8, 150.4, 150.7, 151.7, 153.0, 189.1 ppm. HRMS (MALDI) calcd. for C₂₄H₂₁NO₇Si [M + H⁺]*: 456.1659; found 456.1680.

Preparation of Imidazole 9: Carboxyldimidazolide (84.3 mg, 0.52 mmol) was added in one portion to a stirred solution of 7 (100.0 mg, 0.26 mmol) in anhydrous THF (4 mL). The mixture was stirred at 25 °C for 10 min (monitored by TLC) and the solvent was then evaporated under reduced pressure. The easily hydrolyzed crude product was purified by small column filtration (silica gel, hexanes/EtOAc, 6:4) to afford 9 as a yellow solid (101.9 mg, 94% yield). Rf = 0.50 (hexanes/EtOAc, 7:3); m.p. 99–101 °C. IR (KBr): v = 3117, 2932, 2858, 1718, 1599, 1326, 1236, 1058, 921, 805 cm⁻¹. 1H NMR (250 MHz, CDCl₃, 25 °C): δ = 0.21 (s, 6 H, Me₂Si), 1.01 (s, 9 H, tBuSi), 3.83 (3 s, 3 H, OMe), 3.88 (3 s, 3 H, OMe), 6.78 (ABQ, J = 8.6 Hz, Aν = 19.0 Hz, 2 H, CH2), 7.14 (s, 1 H, CH₃), 7.18 (s, 1 H, CH₃), 7.58 (s, 1 H, CH₃), 8.14 (s, 1 H, CH₃), 8.28 (s, 1 H, CH₃) ppm. 13C NMR (62.9 MHz, CDCl₃, 25 °C): δ = 2.6, 18.4, 25.7, 55.7, 105.2, 107.9, 115.1, 118.1, 118.5, 122.5, 127.8, 128.5, 130.7, 138.3, 149.8, 150.6, 153.3, 165.9 ppm.

Preparation of Weinreb Amide 10: N,O-Dimethylhydroxylamine hydrochloride (30.4 mg, 0.31 mmol), carbon tetrabromide (103.5 mg, 0.31 mmol), pyridine (25.2 µL, 0.31 mmol), and PPh₃ (81.3 mg, 0.31 mmol) in small portions, were added successively, to a stirred solution of 7 (100.0 mg, 0.26 mmol) in anhydrous CH₂Cl₂ (5 mL). The mixture was stirred at 25 °C until no starting material was observed (monitored by TLC; about 30 min) and the solvent was then evaporated under reduced pressure. The gummy residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 8:2) to afford 10 as a white solid (91.7 mg, 87% yield). Rf = 0.64 (hexanes/EtOAc, 7:3); m.p. 104–105 °C. IR (KBr): v = 2933, 2858, 1651, 1599, 1506, 1463, 1386, 1257, 1101, 1057, 860, 842 cm⁻¹. 1H NMR (250 MHz, CDCl₃, 25 °C): δ = 0.20 (s, 6 H, Me₂Si), 1.02 (s, 9 H, tBuSi), 3.35 (3 s, 3 H, MeO), 3.52 (3 s, 3 H, OMe), 3.83 (3 s, 3 H, ArOMe), 3.90 (3 s, 3 H, ArOMe), 6.70 (2 s, 2 H, CH₂), 7.14 (s, 1 H, CH₃), 8.21 (s, 1 H, CH₃) ppm. 13C NMR (62.9 MHz, CDCl₃, 25 °C): δ = 2.7, 18.6, 25.9, 33.9, 55.7, 55.8, 61.0, 104.3, 106.1, 115.7, 116.0, 121.2, 131.2, 149.8, 150.6, 151.0, 169.6 ppm. HRMS (MALDI) calcd. for C₄₂H₃₉NO₁₅Si ([M + H⁺]*): 406.2044; found 406.2051.

General Procedure for Alkylation: The organometallic reagent (0.11 to 0.22 mmol) was added dropwise to a stirred solution of 8, 9, or 10 (0.1 mmol) in the appropriate solvent (concentration was between 0.2–0.3 m) and at the desired temperature. The reaction mixture was stirred at the same temperature until no starting material could be observed by TLC analysis and then quenched with a saturated aqueous solution of NH₄Cl (3–4 mL). The organic layer was separated and washed with brine (7 mL) whereas the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried with Na₂SO₄ and the solvent was evaporated under reduced pressure. The crude mixture was purified by flash column chromatography (silica gel, hexanes/EtOAc, 95:5 to 9:1) to afford 11 and/or 12 as pale yellow solids (for yields see table in Scheme 3).

Compound 11: Rf = 0.85 (hexanes/EtOAc, 95:5); m.p. 82–84 °C. IR (KBr): v = 2932, 2858, 1684, 1597, 1463, 1362, 1257, 1076, 919, 839, 780 cm⁻¹. 1H NMR (250 MHz, CDCl₃, 25 °C): δ = 0.22 (s, 6 H, Me₂Si), 1.03 (s, 9 H, tBuSi), 3.77–3.90 (m, 5 H, H, OMe and COCH₂), 3.94 (3 s, 3 H, OMe), 5.17–5.28 (m, 2 H, CH₂), 6.02–6.21 (m, 1 H, CH=CH₂), 6.75 (ABQ, J = 8.6 Hz, Aν = 17.1 Hz, 2 H, CH₃), 7.40 (d, J = 1.5 Hz, 1 H, CH₃), 8.49 (d, J = 1.5 Hz, 1 H, CH₃) ppm. 13C NMR (62.9 MHz, CDCl₃, 25 °C): δ = 2.7, 18.6, 25.9, 43.3, 55.8, 104.6, 107.6, 113.8, 117.2, 118.5, 122.6, 128.2, 131.4, 133.8, 135.2, 150.2, 150.8, 152.9, 197.8 ppm. HRMS (MALDI) calcd. for C₂₂H₁₈O₇Si ([M + H⁺]*): 387.1974.

Compound 12: Rf = 0.80 (hexanes/EtOAc, 95:5); m.p. 97–99 °C. IR (KBr): v = 3522, 2928, 2860, 1602, 1597, 1507, 1463, 1374,
1262, 1058, 842 cm⁻¹. 1H NMR (250 MHz, CDCl₃, 25 °C): δ = 0.19 (s, 6 H, Me₂Si), 1.04 (s, 9 H, tBuSi), 2.28 (s, 1 H, OH), 2.46–2.80 (m, 4 H, CH₂CH=), 3.83 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 4.99–5.15 (m, 4 H, =CH₂), 5.49–5.70 (m, 2 H, CH=CH₂), 6.64 (ABq, J = 8.6 Hz, Δν = 11.5 Hz, 2 H, CH₆), 6.91 (d, J = 1.9 Hz, 1 H, CH₆), 7.88 (d, J = 1.9 Hz, 1 H, CH₆) ppm. 13C NMR (62.9 MHz, CDCl₃, 25 °C): δ = 2.7–2.8, 16.6, 46.8, 55.6, 75.1, 103.8, 104.2, 111.0, 119.0, 128.3, 128.6, 133.4, 143.6, 149.3, 150.7, 152.0 ppm. HRMS (MALDI) calcd. for C₂₉H₃₇O₉Si [(M + H)⁺]: m/z 429.2455; found 429.2440.

Preparation of Compound 13: Cs₂CO₃ (94.2 mg, 0.29 mmol), benzyl bromide (37.9 µL, 0.32 mmol), and a catalytic amount of Bu₄NI were added successively at 0 °C to a stirred solution of 20a (41.0 mg, 0.15 mmol, detailed procedure for the preparation of 20a is given later in this section) in anhydrous DMF (0.5 mL) at 25 °C. The reaction mixture was stirred at the same temperature for 10 min (monitored by TLC) and then quenched with a saturated solution of NH₄Cl was added (7 mL), followed by addition of EtOAc (8 mL). The organic layer was separated, whereas the aqueous layer was extracted with EtOAc (10 mL). The combined organic extracts were washed with brine (10 mL) and dried with Na₂SO₄, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexanes/ EtOAc, 95:5) to afford ethyl 5,8-bis(benzyloxy)-4-(tert-butyldimethylsilyloxy)-2-naphthoate as a colorless oil (194.8 mg, 97% yield). Rₚ = 0.75 (hexanes/EtOAc, 9:1). IR (film): ν = 2929, 1719, 1597, 1456, 1367, 1231, 1052, 836 cm⁻¹. 1H NMR (250 MHz, CDCl₃, 25 °C): δ = 0.20 (s, 6 H, Me₂Si), 0.99 (s, 9 H, tBuSi), 1.42 (t, J = 7.1 Hz, 3 H, CH₃CH₂), 4.41 (q, J = 7.1 Hz, 2 H, CH₂CH₃), 5.41 (s, 2 H, CH=CH₂), 6.79 (ABq, J = 8.6 Hz, Δν = 12.7 Hz, 2 H, CH₃CH₂CH=CH₂), 7.26–7.55 (m, 11 H, CH₆), 8.37 (d, J = 1.9 Hz, 1 H, CH₃CH₆) ppm. 13C NMR (62.9 MHz, CDCl₃, 25 °C): δ = 2.4, 14.3, 18.7, 26.0, 60.9, 70.5, 71.5, 106.3, 109.6, 110.5, 115.4, 118.0, 123.0, 127.1, 127.3, 127.5, 128.3, 128.4, 137.2, 137.6, 149.5, 149.8, 152.7, 166.6 ppm.

A stirred solution of the above ester (180.1 mg, 0.33 mmol) in anhydrous CH₂Cl₂ (10 mL) was cooled to ~78 °C and a solution of Dibal-CH₂Cl₂ (1 m, 0.76 mL, 0.76 mmol) was added dropwise. The mixture was stirred at the same temperature for 20 min (monitored by TLC) and then quenched with methanol (0.5 mL). The dry ice-acetone bath was removed, allowing the mixture to reach 25 °C, and a saturated aqueous solution of sodium potassium tartrate (10 mL) was then added. Stirring was continued until the cloudy solution became clear (about 2 h), and the mixture was extracted with EtOAc (3 × 10 mL). The organic extracts were washed with brine (15 mL) and dried with Na₂SO₄, the solvents were evaporated under reduced pressure, and the crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc, 7:3) to afford 5,8-bis(benzyloxy)-4-(tert-butyldimethylsilyloxy)napth-2-ylmethyl as a white solid (161.9 mg, 98%). Rₚ = 0.35 (hexanes/EtOAc, 9:1); m.p. 137–139 °C. IR (KBr): ν = 3414, 2934, 1606, 1461, 1372, 1283, 1081, 836 cm⁻¹. 1H NMR (250 MHz, CDCl₃, 25 °C): δ = 0.17 (s, 6 H, Me₂Si), 0.97 (s, 9 H, tBuSi), 1.73 (s, 1 H, OH), 4.74 (s, 2 H, CH₂OH), 5.11 (s, 1 H, OCH₃Ph), 5.18 (s, 2 H, OCH₂Ph), 6.62 (ABq, J = 8.6 Hz, Δν = 14.1 Hz, 2 H, CH₃CH₂CH=CH₂), 7.33 (d, J = 1.9 Hz, 1 H, CH₃CH₆) ppm. 13C NMR (62.9 MHz, CDCl₃, 25 °C): δ = 23.3, 18.7, 26.1, 65.5, 70.4, 71.3, 105.7, 107.9, 112.8, 115.6, 120.3, 127.3, 127.4, 127.5, 128.4, 128.5, 129.2, 137.3, 137.9, 138.6, 148.6, 149.9, 152.8 ppm.

A solution of the above alcohol (150.0 mg, 0.34 mmol) in anhydrous CH₂Cl₂ (10 mL) was treated with 4-methylmorpholine N-oxide (86.4 mg, 0.74 mmol) and TPAP (20.7 mg, 0.06 mmol) at 25 °C for 2 h (monitored by TLC). The reaction mixture was then filtered through a pad of silica gel (CH₂Cl₂) and the organic solvent was concentrated under reduced pressure to afford 15 as a yellow oil (146.6 mg, 98% yield). Rₚ = 0.60 (hexanes/EtOAc, 9:1). IR (film): ν = 3068, 2928, 1694, 1601, 1512, 1453, 1376, 1252, 1050, 836 cm⁻¹. 1H NMR (250 MHz, CDCl₃, 25 °C): δ = 0.22 (s, 6 H, Me₆Si), 0.99 (s, 9 H, tBuSi), 1.56 (s, 2 H, OCH₃Ph), 5.20 (s, 2 H, OCH₂Ph), 6.77 (ABq, J = 8.6 Hz, Δν = 17.9 Hz, 2 H, CH₃CH₂CH=CH₂), 7.26–7.53 (m, 11 H, CH₆), 7.88 (d, J = 1.9 Hz, 1 H, CH₃CH₆) ppm. 13C NMR (62.9 MHz, CDCl₃, 25 °C): δ = 23.3, 18.6, 26.0, 70.6, 71.5, 106.6, 111.1, 111.9, 122.7, 123.8, 127.3, 127.4, 127.6, 128.1, 128.3, 130.4, 136.8, 137.5, 149.5, 153.6, 192.2 ppm.

Preparation of Compound 16: A solution of freshly prepared allyl-magnesium bromide (1 m in Et₂O, 0.35 mL, 0.35 mmol) was added

EtOAc (10 mL). The organic layer was separated and washed with brine (8 mL) whereas the aqueous layer was extracted with EtOAc (2 × 8 mL). The combined organic extracts were dried with Na2SO4 and the solvents were evaporated under reduced pressure. The crude product was dissolved in anhydrous DMF (1 mL) and cooled at 0 °C, followed by addition of imidazole (35.9 mg, 0.53 mmol), TBSCI (66.6 mg, 0.44 mmol), and a catalytic amount of DMAP. The ice bath was removed and the reaction mixture was stirred at 25 °C for 2 h, and then quenched with a saturated aqueous solution of NH4Cl (6 mL) and diluted with EtOAc (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL). The combined organic extracts were washed with brine (15 mL) and dried with Na2SO4, the solvents were evaporated under reduced pressure, and the crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc, 95:5 to 9:1) to afford 19 as a colorless oil (32.3 mg, 30% yield). Rf = 0.75 (hexanes/EtOAc, 9:1). IR (film): v = 2925, 1648, 1591, 1257, 1088, 829 cm−1. 1H NMR (250 MHz, CDCl3, 25 °C): δ = −0.01 (s, 3 H, MeSi), 0.03 (s, 3 H, MeSi), 0.87 (s, 9 H, tBuSi), 2.39 (t, J = 6.3 Hz, 2 H, CH2CH2), 4.72 (t, J = 5.6 Hz, 1 H, CHOSi), 4.89−5.07 (m, 2 H, =CH2), 5.60−5.82 (m, 1 H, CH=CH2), 6.90 (s, 2 H, H110102), 7.23 (1 H, CHar), 7.52 (d, J = 1.5 Hz, 1 H, CHar), 11.87 (s, 1 H, OH).

**General Procedure for the Preparation of Naphthols 20a and 20b:** A catalytic amount of sodium ethoxide was added to a stirred solution of either 3a or 3b (4.25 mmol) in absolute ethanol (40 mL). The mixture was heated under reflux for 1 h (monitored by TLC). Upon completion of the reaction, half of the solvent was evaporated under reduced pressure, and saturated aqueous NH4Cl solution (20 mL) and EtOAc (35 mL) were added. The organic layer was separated, washed with brine (30 mL), and dried with Na2SO4. Evaporation of the organic solvents under reduced pressure afforded crude naphthols, which were recrystallized from EtOAc and EtO to afford 20a and 20b, respectively, as pale yellow, crystalline solids. General Procedure for the Preparation of Naphthols 20a and 20b: A solution of CAN (0.30−0.90 mmol) in water (4 mL) was added dropwise at 25 °C to a stirred solution of 16 (100 mg, 0.15 mmol) in CH3CN (10 mL). The mixture was stirred at the same temperature for 10−40 min (monitored by TLC) and then diluted with water (8 mL) and EtOAc (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 8 mL). The combined organic extracts were washed with brine (10 mL) and dried with Na2SO4, the solvents were evaporated under reduced pressure, and the residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 9:1 to 73) to afford 17 as a colorless oil and 18 as an orange oil (yields of 17 and 18 vary from 20 to 40%). 1H NMR (250 MHz, CDCl3, 25 °C): δ = 0.80 (hexanes/EtOAc, 9:1); 18: Rf = 0.50 (hexanes/EtOAc, 8:2). IR (film): v = 2925, 1659, 1577, 1279, 1093, 836 cm−1. 1H NMR (250 MHz, CDCl3, 25 °C): δ = −0.02 (s, 3 H, MeSi), 0.07 (s, 3 H, MeSi), 0.89 (s, 9 H, tBuSi), 2.24−2.61 (m, 2 H, CH2CH2), 4.89−5.09 (m, 3 H, =CH2 and CHOSi), 5.17 (s, 2 H, OCH2Ph), 5.19 (s, 2 H, OCH2Ph), 5.68−5.89 (m, 1 H, CH=CH2), 6.85 (d, J = 1.5 Hz, 1 H, CH11052), 7.22 (s, 2 H, H11051), 7.27−7.59 (m, 10 H, CHar). **Preparation of Juglone Derivative 19:** A solution of lithium naphthalenide or lithium 4,4′-di-tert-butylphenylide (4.5 mmol) in THF was added dropwise at −20 °C to a stirred solution of 16 (200 mg, 0.30 mmol) in anhydrous THF (15 mL). Lithium naphthalenide and lithium 4,4′-di-tert-butylphenylide were prepared according to literature procedures (see refs[368−38]). Upon completion of the addition, the temperature was allowed to rise to 0 °C and the mixture was stirred for about 2 h (monitored by TLC). The reaction was quenched with a saturated aqueous solution of NH4Cl (6 mL) and diluted with EtOAc (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (10 mL). The combined organic extracts were washed with brine (15 mL) and dried with Na2SO4, the solvents were evaporated under reduced pressure, and the crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc, 95:5 to 9:1) to afford 19 as a colorless oil (32.3 mg, 30% yield). Rf = 0.75 (hexanes/EtOAc, 9:1). IR (film): v = 2925, 1648, 1591, 1257, 1088, 829 cm−1. 1H NMR (250 MHz, CDCl3, 25 °C): δ = 1.87 (s, 1 H, CH=OH), 3.90 (s, 3 H, OMe), 3.97 (s, 3 H, OMe), 4.73 (s, 2 H, CH2), 6.62 (s, 2 H, CH1106), 6.89 (s, 1 H, CHar), 7.65 (s, 1 H, CH11052), 9.42 (s, 1 H, ArOH) ppm. 13C NMR (62.9 MHz, CDCl3, 25 °C): δ = 55.7, 56.2, 65.5, 103.3, 103.4, 110.0, 110.6, 115.0, 128.3, 140.3, 150.0, 150.2, 154.7. HRMS (MALDI) calc. for C19H13O4 [M]+: 324.0887; found 324.0883.

This alcohol (300.0 mg, 1.28 mmol) was dissolved in anhydrous DMF (0.5 mL) and cooled to 0 °C, followed by addition of imida-
zole (113.0 mg, 1.66 mmol) and TBSCI (212.5 mg, 1.41 mmol). The ice bath was removed and the reaction mixture was stirred overnight at 25 °C. Upon consumption of the starting material (monitored by TLC), the reaction mixture was quenched with methanol (0.15 mL) and a saturated aqueous solution of NH₄Cl was added (10 mL), followed by EtOAc (15 mL). The organic layer was separated and washed with brine (15 mL), and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc, 9:1) to afford 21 as a white solid of low melting point (379.2 mg, 85% yield). Rf = 0.70 (hexanes/EtOAc, 8:2). IR (KBr): v = 3380, 2929, 2854, 1645, 1620, 1516, 1463, 1386, 1251, 1093, 842, 780 cm⁻¹. ¹H NMR (250 MHz, CDCl₃, 25 °C): δ = 0.09 (s, 6 H, Me₃Si), 0.95 (s, 9 H, BuSi), 3.90 (s, 3 H, OMe), 3.97 (s, 3 H, OMe), 4.82 (s, 2 H, CH₂), 6.61 (s, 2 H, CH₉), 6.89 (s, 1 H, CH₉), 7.64 (s, 1 H, CH₉), 9.40 (s, 1 H, OH) ppm. ¹³C NMR (62.9 MHz, CDCl₃, 25 °C): δ = 38.8, 18.8, 26.0, 55.8, 65.2, 65.2, 102.7, 102.9, 109.9, 110.0, 114.5, 128.4, 140.9, 150.0, 150.2, 154.2 ppm. HRMS (MALDI) calcld. for C₁₅H₁₆O₆ [M + Na⁺]: 371.1649; found 371.1651.

**General Procedure for Saloinencal-Catalyzed Oxidation**:
Saloinencal (32.0 mg, 0.09 mmol) was added to a stirred solution of 20a, 20b, or 21 (0.47 mmol) in CHCl₃ (35 mL), and the mixture was stirred under air at 25 °C for 20–24 h (until no starting material was observed by TLC analysis). The dark red solution was then filtered through a pad of Celite and the solvent was evaporated under reduced pressure to afford 23a, 23b, or 23c, respectively, as shiny dark red crystals.

**Compound 23a**: Yield 90%; Rf = 0.60 (CHCl₃/MeOH, 95:5); m.p. 172–174 °C. ¹H NMR (250 MHz, CDCl₃, 25 °C): δ = 1.37 (t, J = 7.1 Hz, 3 H, CH₂CH₃), 3.92 (s, 3 H, OMe), 3.94 (s, 3 H, OMe), 4.36 (q, J = 7.1 Hz, 2 H, CH₂CH₃), 7.19 (ABq, J = 9.5 Hz, Δν = 9.7 Hz, 2 H, CH₂), 8.66 (s, 1 H, CH₉qpp). ¹³C NMR (62.9 MHz, CDCl₃, 25 °C): δ = 14.8, 56.6, 62.1, 119.5, 121.4, 122.2, 126.1, 143.9, 152.5, 157.3, 163.2, 177.1, 177.2 ppm. HRMS (MALDI) calcld. for C₁₅H₁₆O₆ [M + Na⁺]: 313.0683; found 313.0682.

**Compound 23b**: Yield 90%; Rf = 0.60 (CHCl₃/MeOH, 95:5); m.p. 179–181 °C. IR (KBr): v = 2926, 1730, 1635, 1604, 1452, 1383, 1194, 1006, 726 cm⁻¹; ¹H NMR (250 MHz, CDCl₃, 25 °C): δ = 1.30 (t, J = 7.1 Hz, 3 H, CH₂CH₃), 4.26 (q, J = 7.1 Hz, 2 H, CH₂CH₃), 5.08 (s, 2 H, OCH₂Ph), 5.10 (s, 2 H, OCH₂Ph), 7.11 (ABq, J = 9.5 Hz, Δν = 18.8 Hz, 2 H, CH₂), 7.20–7.57 (m, 10 H, CH), 8.66 (s, 1 H, CH₉qpp). ¹³C NMR (62.9 MHz, CDCl₃, 25 °C): δ = 14.0, 61.4, 70.6, 71.5, 120.6, 122.2, 124.6, 127.2, 127.7, 128.4, 128.5, 128.7, 135.4, 135.7, 143.8, 151.6, 155.9, 163.2, 177.1, 177.2 ppm. HRMS (MALDI) calcld. for C₁₅H₁₆O₆ ([M + Na⁺]⁺): 465.1309; found 465.1322.

**Compound 23c**: Yield 93%; Rf = 0.30 (hexanes/EtOAc, 7:3); m.p. 137–139 °C. IR (KBr): v = 2938, 2858, 1653, 1362, 1485, 1276, 1196, 1079, 845, 782 cm⁻¹. ¹H NMR (250 MHz, CDCl₃, 25 °C): δ = 0.06 (s, 6 H, Me₃Si), 0.91 (s, 9 H, BuSi), 3.81 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 4.48 (s, 2 H, CH₂), 7.01 (ABq, J = 9.3 Hz, Δν = 4.2 Hz, 2 H, CH₂), 7.96 (s, 1 H, CH₉qpp) ppm. ¹³C NMR (62.9 MHz, CDCl₃, 25 °C): δ = 3.7, 18.3, 28.8, 56.4, 56.7, 59.4, 115.8, 118.6, 120.8, 124.2, 133.8, 137.5, 150.7, 157.0, 178.8, 180.1 ppm. HRMS (MALDI) calcld. for C₁₅H₁₆O₆ ([M + Na⁺]⁺): 363.1622; found 363.1624.

**General Procedure for the Oxidation with PIFA/FeCl₃**: A stirred solution of either 20a or 20b (0.35 mmol) in a 2:1 mixture of CH₃CN/H₂O (17 mL) was cooled to 0 °C, and PIFA (227.9 mg, 0.53 mmol) was added. The ice bath was then removed, the mixture was stirred for 1 h at 25 °C, and a solution of FeCl₃/6H₂O (270.3 mg, 1.00 mmol) in HCl (1 N, 2.5 mL) was then added. The reaction mixture was stirred for 6 h at 25 °C and then diluted with water (10 mL) and EtOAc (18 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (12 mL). The combined organic extracts were washed with brine (20 mL) and dried with Na₂SO₄, the solvents were evaporated under reduced pressure, and the crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc, 7:3) to afford 22a or 22b, respectively, as orange solids.

**Compound 22a**: Yield = 48%; Rf = 0.65 (CHCl₃/MeOH, 95:5); m.p. 110–112 °C. IR (KBr): v = 2923, 2858, 1729, 1659, 1482, 1288, 1115, 1016, 831 cm⁻¹; ¹H NMR (250 MHz, CDCl₃, 25 °C): δ = 1.34 (t, J = 7.1 Hz, 3 H, CH₂CH₃), 3.92 (s, 3 H, OMe), 3.93 (s, 3 H, OMe), 4.34 (q, J = 7.1 Hz, 2 H, CH₂CH₃), 7.02 (s, 1 H, CH₉qpp), 7.12 (m, 3 H, CH₉qpp).
7.30 (ABq, J = 9.7 Hz, CH$_2$-CH$_2$O) ppm. $^{13}$C NMR (62.9 MHz, CDCl$_3$, 25 °C): $\delta$ = 14.1, 56.8, 56.9, 62.2, 120.2, 121.1, 137.4, 139.8, 153.5, 153.8, 163.6, 181.0, 184.2 ppm. HRMS (MALDI) calcld. for C$_{15}$H$_{24}$O$_4$ ([M + Na$^+$]): 313.0683; found 313.0681.

**Compound 22b:** Yield = 67%; $R_t$ = 0.65 (CHCl$_3$/MeOH, 95:5); m.p. 117–119 °C. IR (KBr): $\nu$ = 2924, 1740, 1664, 1567, 1448, 1284, 1118, 1021, 742 cm$^{-1}$. $^{1}$H NMR (250 MHz, CDCl$_3$, 25 °C): $\delta$ = 1.35 (t, J = 7.1 Hz, 3 H, CH$_2$CH$_3$), 4.36 (q, J = 7.1 Hz, 2 H, CH$_2$CH$_2$O), 5.17 (s, 4 H, OCH$_2$Ph), 7.02 (s, 1 H, CH$_{quin}$), 7.20–7.57 (m, 12 H, CH$_r$) ppm. $^{13}$C NMR (62.9 MHz, CDCl$_3$, 25 °C): $\delta$ = 14.1, 62.2, 71.6, 71.7, 122.3, 123.1, 126.8, 127.0, 127.9, 128.0, 128.6, 136.1, 136.2, 137.3, 139.8, 152.6, 152.9, 163.6, 180.6, 183.9 ppm. HRMS (MALDI) calcld. for C$_{22}$H$_{24}$O$_5$ ([M + Na$^+$]): 465.1309; found 465.1310.

**Preparation of Aldehyde 29:** A saturated aqueous solution of Na$_2$SO$_4$ (1 mL) was added at 25 °C to a stirred solution of 22a (72.6 mg, 0.25 mmol) in CHCl$_3$ (5 mL) and the mixture was vigorous stirred for 15 min (disappearance of the orange color of the quinone moiety). It was then diluted with water (5 mL) and the organic layer was separated. The aqueous layer was extracted with CHCl$_3$ (2 × 5 mL), and the combined organic extracts were washed with brine (10 mL), dried with Na$_2$SO$_4$ and concentrated under reduced pressure to afford the crude hydroquinone, which was used in the next step without further purification.

A solution of the crude product in anhydrous DMF (0.5 mL) was treated at 0 °C with imidazole (51.1 mg, 0.75 mmol) and TBSCI (95.0 mg, 0.63 mmol), and a catalytic amount of DMAP. The ice bath was removed and the reaction mixture was stirred overnight. The reaction mixture was then quenched with MeOH (0.3 mL) and a saturated aqueous solution of NH$_4$Cl (5 mL) was added, followed by extraction with EtOAc (2 × 7 mL). The organic layer was washed with brine (10 mL), dried with Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc, 9:1) to afford 27 as a white solid of low melting point (115.9 mg, 89% yield based on 22a). $R_t$ = 0.75 (hexanes/EtOAc, 8:2). IR (thin film): $\nu$ = 2951, 2857, 1739, 1608, 1576, 1384, 1346, 1264, 1134, 1061, 930 cm$^{-1}$. $^{1}$H NMR (500 MHz, CDCl$_3$, 25 °C): $\delta$ = 0.00 (s, 6 H, Me$_2$Si), 0.20 (s, 6 H, Me$_2$Si), 1.03 (s, 9 H, BuSi), 1.07 (s, 9 H, BuSi), 1.39 (t, J = 7.1 Hz, 3 H, CH$_2$CH$_3$), 3.82 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 4.39 (q, J = 7.1 Hz, 2 H, CH$_2$CH$_2$O), 6.73 (ABq, $\Delta$ = 8.5 Hz, $\Delta v$ = 39.0 Hz, 2 H, CH$_2$O), 7.18 (s, 1 H, CH$_3$O) ppm. $^{13}$C NMR (125.7 MHz, CDCl$_3$, 25 °C): $\delta$ = -5.1, -4.5, 14.3, 18.0, 18.2, 20.2, 25.9, 26.0, 55.3, 55.7, 62.1, 105.7, 107.5, 116.8, 119.9, 123.2, 123.9, 146.0, 146.8, 150.2, 152.0, 167.7 ppm.

A solution of DIBAL in CHCl$_3$ (1.0 mL, 0.44 mL, 0.44 mmol) was added dropwise at -78 °C to a stirred solution of 27 (104.2 mg, 0.20 mmol) in CHCl$_3$ (7 mL). The reaction mixture was stirred at the same temperature for 1 h (monitored by TLC) and then quenched with MeOH (0.4 mL), followed by addition of a saturated aqueous solution of sodium potassium tartrate (8 mL) and EtOAc (5 mL). The resulting mixture was vigorously stirred for 2 h, whereupon the organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 8 mL). The combined organic extracts were washed with brine (10 mL), dried with Na$_2$SO$_4$ and concentrated under reduced pressure, and the crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc, 8:2) to afford 1,4-bis(tet-3341–3350

It should be mentioned that the structures of compounds 25a and 25b were wrongly assigned as 22a and 22b, respectively, in a previous communication by our group (see ref. [40]). That confusing report is clarified here.

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