Synthesis of Siloxy-α-Lapachone Derivatives by Chemo- and Regioselective Diels–Alder Reactions of 3-Methylene-1,2,4-naphthotrones with Silyl Enol Ethers

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Abstract: α-Quinone methides, generated in situ from the Knoevenagel condensation of 2-hydroxy-1,4-naphthoquinone with aliphatic and aromatic aldehydes, take part in chemoselective hetero-Diels–Alder reactions with silyl enol ethers to give a series of siloxy-containing naphtho[2,3-b]pyran-5,10-dione (α-lapachone) derivatives in moderate to high yield. These reactions regioselectively gave α-lapachone derivatives with an acetal structure. This regioselectivity can be rationalized by considering the frontier molecular orbital interactions of the α-quinone methide with the silyl enol ether, and by taking into account the energetically more favorable pathway leading to a zwitterion-like transition state of lower energy in a Michael addition between the two reactants.

Key words: α-lapachone, α-quinone methide, silyl enol ether, Diels–Alder reaction, regioselectivity

Naturally occurring naphthoquinones comprise an important class of natural products with a wide range of biological activity, arising from their ability to cause DNA damage and generation of reactive oxygen species. In the structurally diverse naphthoquinone natural products, dihydro-pyranonaphthoquinones (α- and β-lapachones) have attracted special attention because of their promising antitumor activity, among various other bioactivities. Heterocyclic naphthoquinones of the lapachone family are found as minor components in the stem bark of many trees of the Tabebuia genus in Central and South America. α-Lapachones have a wider distribution than β-lapachones, and are additionally found in Ekmanianthe longiflora in America and in Capalta ovata trees in many east Asian countries. Of these pyranonaphthoquinones, β-lapachone derivatives have so far received the most extensive investigations, mainly owing to their stronger antitumor activity. However, more recent investigations have shown that α-lapachone is an effective DNA topoisomerase II inhibitor and is a potential lead compound for the development of drugs for the treatment of multidrug resistant cell lines with low expressions of topoisomerase II. In addition, α-lapachone derivatives possess their own special biological activities ranging across antibacterial, antipsoriatic, antifungal and trypanosidal activity. Furthermore, in the recently rapidly developing research area of cancer chemoprevention as a promising tool in cancer control, quinone compounds have proven to be one of the most important classes of potential cancer chemopreventing agents (antitumor promoters). Extensive studies of a large variety of quinone compounds points to the 1,4- and 1,2-naphthoquinones, including α- and β-lapachones, as privileged structures, with 1,4-naphthoquinones having great cancer-preventing potential. Structure–activity relationship studies in lapachones have shown that structural modification to the redox center (the quinone functionality) and the C-ring leads to significant changes in bioactivities and are important in the search for possible lead compounds with more potent pharmaceutical activity and less toxicity. Lapachones are minor components in plants and are not easily available in large quantities from natural sources. This fact, and the need for unnatural analogues, demands the development of convenient and versatile synthetic methods for lapachones.

There are several synthetic approaches to α- and β-lapachones (Scheme 1).

1. Acid-catalyzed cyclization of lapachol or its derivatives (equation 1). The lapachol derivative itself needs to be synthesized by alkylation of the lithium salt of 2-hydroxy-1,4-naphthoquinone (1) with an alkyl bromide. Although this reaction has been the subject of intensive investigation, the yield of the lapachol products has never exceeded 50% due to the complication of O-alkylation. In a very recent report, lapachol was prepared by palladium-catalyzed [Pd(PPh3)4] alkylation of quinone 1 with 3-methylbut-2-en-1-ol in 43% yields.

2. Michael addition of quinone 1 to α,β-unsaturated compounds, followed by acid-catalyzed cycloketolization of the Michael adduct (equation 2). In these cyclization reactions, only α-lapachone derivatives were formed in moderate overall yields.

3. Base-catalyzed addition reaction of quinone 1 with an α,β-unsaturated aldehyde, followed by electrolycrlization of the adduct (equation 3). Ten lapachone derivatives have been prepared using this reaction sequence in moderate to high yield (40–90%). The resulting dehydro-α-lapachones can then be converted to the α-lapachones by palladium-catalyzed hydrogenation.
4. Knoevenagel condensation of quinone 1 with formaldehyde, followed by Diels–Alder reaction of the o-quinone methide intermediate with a 1,3-diene or an enol ether. Mixtures of α- and β-lapachone derivatives were formed in moderate to high total yields (30–95%). The last protocol represents a new example of the increasing synthetic applications of the novel tandem reaction sequence of Knoevenagel condensation of an o-hydroxyquinone with an aldehyde, followed by hetero-Diels–Alder reaction of the o-quinone methide with an electron-rich alkene, in the synthesis of heterocyclic natural products and their analogues.

Taking into account the ready availability of the starting materials, the synthetic efficiency in respect of product yields, the versatility in allowing structural modification of the product, and the simple one-pot procedures, we envisioned that this last synthetic strategy would be more advantageous for the synthesis of lapachone derivatives. In particular, since the aldehyde in the Knoevenagel condensation and the alkene in the Diels–Alder reaction can be changed, the introduction of different substituents at the C-ring can be easily achieved. However, only formaldehyde as the aldehyde and 1,3-dienes and a few enol ethers as the alkene, have been applied so far. We report here the synthesis of a series of silicon-containing α-lapachone derivatives by the Diels–Alder reaction of the o-quinone methides derived from 1 with silyl enol ethers.

Silyl enol ethers are highly electron-rich alkenes and are excellent dienophiles in inverse-electron-demand Diels–Alder reactions. Use of the special biological activity of organosilicon compounds in the design of new drugs has aroused considerable recent attention. Furthermore, since silyl serves as a protecting group for hydroxy groups, hydrolysis of the silyloxy-containing α-lapachone derivatives would provide easy access to an additional series of 1,4-naphthoquinone derivatives. To our knowledge, this is the first report on the use of silyl enol ethers as dienophiles in the inverse-electron-demand Diels–Alder reactions of any o-quinone methide.

Benzaldehyde, formaldehyde and butyraldehyde have been used as the aldehydes in the Knoevenagel condensation with 2-hydroxy-1,4-naphthoquinone (1) to give the corresponding o-quinone methides I (Scheme 2), II (Scheme 3) and III (Scheme 4), respectively. The o-quinone methides were allowed to participate in cycloadditions with the silyl enol ethers in refluxing dioxane solution. The silyl enol ethers employed were α-(trimethylsiloxy)styrene (2a), 2-(trimethylsiloxy)propene (2b), 1-(trimethylsiloxy)cyclohexene (2c) and (Z)-1-(trimethylsiloxy)-1-butene (2d). The results of these reactions are summarized in Scheme 2, Scheme 3 and Scheme 4.

Reaction of o-quinone methide I, derived from quinone 1 and benzaldehyde, with silyl enol ether 2a afforded two products: 3a (27% yield) and 4a (18% yield). The structures of both were determined by X-ray crystallographic analysis; it turns out that 3a and 4a constitute a pair of diastereomeric α-lapachone derivatives (Figure 1 and Figure 2). Since β-Lapachone derivatives were not found as products in this reaction, the [4+2] cycloaddition of I with the silyl enol ether must occur exclusively at one of the 1-oxadiene units [the O(4)=C(3)–C(2)=C(1) moiety, see Scheme 2]. Compounds 3a and 4a have distinguishable differences in their physical and spectroscopic properties. The trans-isomer 3a has a lower polarity than the...
cis-isomer 4a, thus, 3a is eluted before 4a in the chromatographic separation. In the $^1$H NMR spectra, the two methylene protons in 3a not only absorb at higher field strength ($\delta = 1.92$ and 2.62 ppm) than those in 4a ($\delta = 2.37$ and 2.71 ppm), but also have a larger $\Delta\delta$ value ($\Delta\delta$ for the two methylene protons is 0.70 ppm) than that in 4a ($\Delta\delta = 0.34$ ppm). In the IR spectra, 3a has a strong C–O stretching band at 1260 cm$^{-1}$, while 4a has the strong C–O band at 1201 cm$^{-1}$.

Reactions of o-quinone methide I with silyl enol ethers 2a–d

Reactions of o-quinone methide I with silyl enol ether 2b, similarly gave two diastereomeric cycloaddition products 3b (22% yield) and 4b (5% yield), and a hydrolysis product 5b (32% yield). The steric structure of trans-3b was also established by an X-ray crystallographic analysis.$^{29}$ Again, trans-3b had lower polarity than the cis-isomer 4b. Their spectroscopic data display similar regular differences as for compounds 3a and 4a. In the $^1$H NMR spectra, the methylene protons in 3b lie at higher field strength ($\delta = 1.87$ and 2.40 ppm) with a larger $\Delta\delta$ value (0.53 ppm) than in 4b, where the methylene protons absorb at lower field ($\delta = 2.25$ and 2.41 ppm) with a smaller $\Delta\delta$ value (0.16 ppm). In the IR spectra, 3b has a strong C–O stretching band at 1265 cm$^{-1}$, while the corresponding C–O band in 4b is at 1179 cm$^{-1}$. $^1$H NMR data reveal that 5b occurs cleanly in the open-chain keto-form in chloroform-$d$ solution, and the phenol proton absorbs at $\delta = 7.60$ ppm.

In the reactions of o-quinone methide I with silyl enol ether 2c, only a hydrolysis product 3c (22% yield) was obtained. This exists in chloroform-$d$ solution as a pair of diastereomeric cyclic hemiacetals in a ratio of 1:0.31. The reaction of o-quinone methide I with silyl enol ether 2d, afforded 3d and 4d as diastereomers (total yield 33%).
Compound 3d was not fully separated from 4d during the column chromatographic separation, however, a pure sample of 4d was obtained and its steric structure was shown by an X-ray crystallographic analysis (Figure 3).

Reaction of quinone 1, paraformaldehyde and silyl enol ether 2a in refluxing dioxane, gave products 6a (31% yield) and 7a (40% yield). While 6a is the Diels–Alder cycloadduct, 7a is a hydrolysis product of 6a. NMR data for 7a showed that it was in the open-chain keto-form in chloroform-d solution, with the hydroxy proton absorption occurring at δ = 7.75 ppm in 1H NMR spectrum and the three carbonyl carbon absorptions at δ = 199.9, 185.1 and 181.6 ppm in the 13C NMR spectrum. Reactions of o-quinone methide II with silyl enol ether 2b, gave the expected cycloadduct 6b (43% yield) and a hydrolysis product 7b (36% yield). Again, 1H NMR data show that 7b exists in chloroform-d solution cleanly in the open-chain keto-form, with the phenol proton absorption at δ = 7.59 ppm. In the reaction of o-quinone methide II with silyl enol ether 2c, products 6c (21% yield) and 7c (45% yield)
were formed. 1H NMR data show that 7c in chloroform-d solution exists as a mixture of the cyclic hemiacetal and its open-chain keto-form in a ratio of ~1:0.7. In the keto-form, the phenol proton absorption occurs at δ = 7.94 ppm. A similar reaction of o-quinone methide II with silyl enol ether 2d, gave cycloadduct 6d (45% yield) and hydrolysis product 7d (28% yield). 1H NMR data showed that 7d in chloroform-d solution exists as a mixture of two diastereomeric cyclic hemiacetals in a ratio of 1:0.7, together with a trace amount of the open-chain aldehyde form.

Reaction of the o-quinone methide III, derived from quinone I and butyraldehyde, with silyl enol ether 2a, furnished two diastereomeric cycloaddition products 8a (46% yield) and 8b (19% yield) without formation of any hydrolysis product. The steric configurations of 8a and 8b were assigned by comparison of their spectral data with those of compounds 3a and 4a mentioned above. A similar reaction of o-quinone methide III with silyl enol ether 2d gave the hydrolysis product 9a (81% yield) as the sole product. The 1H NMR spectrum reveals that 9a exists in chloroform-d solution as a pair of diastereomeric cyclic hemiacetals in a roughly 1:1 ratio. In accordance with this, the 13C NMR spectrum reveals four carbonyl carbon absorptions at δ = 184.8, 184.7, 181.3 and 180.7 ppm.

As seen in Scheme 2, Scheme 3 and Scheme 4, all the cycloadditions between the o-quinone methides (QMs) I–III and the silyl enol ethers 2a–d, are regioselective and give products with an acetal structure only. We have not observed the formation of other regioisomers throughout this series of reactions. To gain insight into this regioselectivity, HF and DFT (B3LYP) calculations of the QMs I–III and the silyl enol ethers 2a–d have been carried out using a 6-31G (d) basis set. The frontier molecular orbital (FMO) properties are outlined in Figure 4 and Figure 5. In the inverse-electron-demand Diels–Alder reactions of the electron-deficient QMs with the highly electron-rich silyl enol ethers, the preferential FMO interaction should be the LUMO(QM)–HOMO(2) interaction. Calculated FMO energies of both methods show that this FMO interaction pair indeed has a much smaller energy gap than the HOMO(QM)–LUMO(2) interaction for all the QM–silyl ether combinations. The requirement of maximum positive orbital overlap in the predominant LUMO(QM)–HOMO(2) interaction predicts the regioselectivity, which is rationalized by HF calculation. However, in the DFT calculation, the relative magnitudes of the atomic coefficients at C(1) and O(4) are rather close in magnitude, the FMO interaction consideration could not give a definite prediction of the regioselectivity for the reactions of QM II and III with silyl enol ethers 2a–d.

Considering the [4+2] cycloaddition of the QM with the enol ether as proceeding in a highly asynchronous fashion by a Michael addition pathway via a zwitterion-like transition state, would provide an alternative mechanistic rationalization of the observed regioselectivity (Scheme 5). Nucleophilic attack of the silyl enol ether at the exocyclic methylene carbon atom would proceed via the energetically more favorable pathway, leading to the more stable A with the positive charge delocalized to the oxygen atom, rather than the regioisomeric B with a localized positive charge at C(6). This rationale of the observed regioselectivity is supported by recent computational studies on the inverse-electron-demand Diels–Alder reactions of o-quinone methides and electron-deficient heter dienes with highly electron-rich alkenes such as enol ethers. These computational results suggest that the [4+2] cycloadditions take place with a large charge-transfer from the alkene to the QM via a zwitterionic transition state, and the ortho-approach of the enol ether to QMs...
Synthesis of Siloxy-\(\alpha\)-Lapachone Derivatives

Figure 4  FMO energies and atomic orbital coefficients calculated by HF (in parentheses are the LUMO orbital coefficients)

Figure 5  FMO energies and atomic orbital coefficients calculated by DFT (in parentheses are the LUMO orbital coefficients)

Scheme 5  Alternative mechanistic rationalization

(leading to the product in which the \(\alpha\)-carbon atom of the enol ether is bonded to the oxygen atom in QM) is energetically more feasible than the meta-approach pathway (leading to the regiosomeric product with the \(\alpha\)-carbon atom of the enol ether linked to the exocyclic methylene carbon atom in QM).

In summary, we have shown that the \(o\)-quinone methides I–III, generated in situ from the Knoevenagel condensation of 2-hydroxy-1,4-naphthoquinone (1) with aliphatic and aromatic aldehydes, take part in [4+2] reactions with silyl enol ethers 2a–d selectively at one of the 1-oxadiene units [the O(4)=C(3)–C(2)=C(1) unit, Scheme 2] to give a series of previously unknown siloxy-containing \(\alpha\)-lapachone derivatives in moderate to high yields. These reactions are also regioselective and give only the products with an acetal structure. Therefore, these highly chemo-
and regioselective hetero-Diels–Alder cycloadditions provide a convenient and efficient one-pot synthesis of siloxy-containing α-lapachone derivatives, with different C-ring-substitution patterns, from readily available starting materials.

Petroleum ether (PE), where used, had a boiling range of 60–90 °C. Melting points were recorded using a Keyi XT3A microscopic melting point apparatus and are uncorrected.

1H NMR spectra were measured on a Bruker DPX 300 spectrometer at 300 MHz with CDCl₃ as solvent unless otherwise stated. The chemical shifts (δ) are reported in ppm relative to the residual deuterated solvent signal (δ_HOD = 4.79 ppm) and coupling constants (J) are given in Hz.

13C NMR spectra were measured on a Bruker Avance 400 spectrometer as a KBr pellet. Mass spectra were taken on a VG ZAB-HS spectrometer in the EI ionization mode (70 eV). Elemental analyses were performed with a Perkin–Elmer 240C analyzer. For X-ray diffraction analysis, a Siemens P4 diffractometer, employing graphite-monochromated (MoKα) radiation (λ = 0.71073 Å) and operating in the θ/2θ scan mode. Data collection and cell refinement were performed with CAD-4 software.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 641918, CCDC 641919 and CCDC 641920. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk].

**anti-2,4-Diphenyl-2-(trimethylsiloxy)-3,4-dihydro-2H-naphtho[2,3-b]pyran-5,10-dione (3a)**

A mixture of 2-hydroxy-1,4-naphthoquinone (1; 348 mg, 2 mmol), silyl enol ether 2a (1.15 g, 6 mmol) and benzaldehyde (849 mg, 8 mmol) in anhydrous dioxide (20mL) was refluxed under an argon atmosphere for 18 h until complete conversion of 1 was observed (TLC). The solvent was removed under reduced pressure, and the residual solid was separated by flash chromatography on silica gel column (PE–EtOAc, gradient elution) to give the products 3a and 4a.

**3a**

Yield: 241 mg (27%); yellow solid; mp 163–165 °C.

**4a**

Yield: 165 mg (18%); yellow solid; mp 180–181 °C.

**trans-2-Methyl-4-phenyl-2-(trimethylsiloxy)-3,4-dihydro-2H-naphtho[2,3-b]pyran-5,10-dione (4a)**

A mixture of 2-hydroxy-1,4-naphthoquinone (1; 348 mg, 2 mmol), silyl enol ether 2b (782 mg, 6 mmol) and benzaldehyde (849 mg, 8 mmol) in anhydrous dioxide (20 mL) was refluxed under an argon atmosphere for 18 h until complete conversion of 1 was observed (TLC). Workup as described above gave the products 3b, 4b and 5b.

**3b**

Yield: 175 mg (22%); yellow solid; mp 136–138 °C.

**4b**

Yield: 38 mg (5%); yellow solid; mp 114–116 °C.

**5b**

Yield: 203 mg (32%); yellow solid; mp 143–145 °C.

**Experimental Section**

Melting points were recorded using a Keyi XT3A microscopic melting point apparatus and are uncorrected. 1H NMR spectra were recorded with a Shimadzu IR 440 spectrometer as a KBr pellet. Mass spectra were taken on a VG ZAB-HS spectrometer in the EI ionization mode (70 eV). Elemental analyses were performed with a Perkin–Elmer 240C analyzer. For X-ray crystallography analysis, the X-ray diffraction intensities and the unit-cell parameters were determined on an Enraf–Nonius CAD-4 diffractometer, employing graphite-monochromated (MoKα) radiation (λ = 0.71073 Å) and operating in the θ/2θ scan mode. Data collection and cell refinement were performed with CAD-4 software.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 641918, CCDC 641919 and CCDC 641920. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk].
A mixture of 2-hydroxy-1,4-naphthoquinone (1; 348 mg, 2 mmol), silyl enol ether 2c (1.02 g, 6 mmol) and benzaldehyde (849 mg, 8 mmol) in anhydrous dioxane (20 mL) was refluxed under an argon atmosphere for 18 h until the reaction was complete (TLC). Workup as described above gave the product 3c.

Yield: 161 mg (22%); yellow solid; mp 220–222 °C.

IR (KBr): 3442, 2925, 2928, 2853, 1670, 1658, 1610, 1595, 1578, 1494, 1452, 1364, 1338, 1260, 1200, 1177, 1095, 956, 892, 724, 700 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.5 Hz, 1 H), 7.57 (t, J = 1.5 Hz, 2 H), 7.38–7.47 (d, J = 6.3 Hz, 3 H), 7.33 (d, J = 6.6 Hz, 2 H), 7.63–7.70 (m, 2 H), 7.94–7.97 (m, 1 H), 8.07–8.11 (m, 2 H).

MS (EI): m/z (%) = 360 (44) [M⁺], 343 (18), 342 (13), 289 (5), 231 (100), 202 (15), 177 (11), 149 (11), 115 (21), 105 (19), 91 (12), 77 (19), 44 (40).


Yield: 267mg (33%); yellow solid; mp 135–136 °C.

IR (KBr): 2962, 2924, 1676, 1650, 1619, 1602, 1583, 1454, 1423, 1328, 1294, 1261, 1101, 1026, 972, 936, 887, 849, 803, 707, 667 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 0.12 (s, 9 H), 1.00 (t, J = 7.5 Hz, 3 H), 1.13–1.26 (m, 1 H), 1.51–1.60 (m, 1 H), 2.05–2.07 (m, 1 H), 4.20 (d, J = 6.9 Hz, 1 H), 5.74 (s, 1 H), 7.18–7.75 (d, J = 6.3 Hz, 3 H), 7.33 (d, J = 6.6 Hz, 2 H), 7.63–7.70 (m, 2 H), 7.94–7.97 (m, 1 H), 8.11–8.16 (m, 1 H).

MS (EI): m/z (%) = 406 (80) [M⁺], 377 (26), 316 (39), 262 (24), 233 (27), 178 (9), 129 (71), 105 (34), 73 (100), 45 (23).


2-Phenyl-2-(trimethylsilyloxy)-3,4-dihydro-2H-naphtho[2,3-b]pyran-5,10-dione (6a) and 2-Hydroxy-3-(3-oxo-3-phenylpropyl)-1,4-naphthalenedione (7a)

A mixture of 2-hydroxy-1,4-naphthoquinone (1; 348 mg, 2 mmol), silyl enol ether 2a (1.15 g, 6 mmol) and paraformaldehyde (240 mg, 8 mmol) in anhydrous dioxane (20 mL) was refluxed under an argon atmosphere for 18 h until complete conversion of 1 was observed (TLC). Workup as described above gave the products 6a and 7a.

Yield: 233 mg (31%); yellow solid; mp 78–80 °C.

IR (KBr): 2961, 2938, 1679, 1649, 1611, 1592, 1578, 1448, 1383, 1339, 1261, 1224, 1199, 1138, 1056, 997, 950, 870, 844, 721, 699 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 0.04 (s, 9 H), 1.70–1.80 (m, 1 H), 2.32–2.36 (m, 2 H), 2.72–2.77 (m, 2 H), 7.39–7.44 (m, 3 H), 7.62 (d, J = 7.2 Hz, 2 H), 7.72–7.76 (m, 2 H), 8.12–8.16 (m, 2 H).

MS (EI): m/z (%) = 378 (53) [M⁺], 350 (7), 288 (11), 231 (12), 191 (34), 177 (30), 105 (100), 75 (54), 44 (26).

Anal. Calcd for C₂₃H₂₀O₄Si: C, 69.84; H, 5.82. Found: C, 69.80; H, 5.88.

2-Methyl-2-(trimethylsilyloxy)-3,4-dihydro-2H-naphtho[2,3-b]pyran-5,10-dione (6b) and 2-Hydroxy-3-(3-oxo-3-phenylbutyl)-1,4-naphthalenedione (7b)

A mixture of 2-hydroxy-1,4-naphthoquinone (1; 348 mg, 2 mmol), silyl enol ether 2b (782 mg, 6 mmol) and paraformaldehyde (240 mg, 8 mmol) in anhydrous dioxane (20 mL) was refluxed under an argon atmosphere for 18 h until complete conversion of 1 was observed (TLC). Workup as described above gave the products 6b and 7b.

Yield: 273 mg (43%); yellow solid; mp 117–118 °C.

IR (KBr): 2990, 2943, 1679, 1645, 1617, 1594, 1578, 1418, 1380, 1305, 1267, 1254, 1198, 1082, 1005, 946, 896, 841, 727 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 0.15 (s, 9 H), 1.67–1.69 (m, 1 H), 1.72 (s, 3 H), 2.07–2.13 (m, 1 H), 2.59–2.70 (m, 2 H), 7.66–7.74 (m, 2 H), 8.11 (td, J = 6.6, 1.3 Hz, 2 H).

MS (EI): m/z (%) = 316 (33) [M⁺], 301 (29), 274 (15), 258 (46), 130 (17), 115 (40), 102 (13), 75 (65), 73 (100).

Anal. Calcd for C₂₃H₂₀O₄Si: C, 64.56; H, 6.33. Found: C, 64.55; H, 6.52.

Yield: 177 mg (36%); yellow-green solid; mp 140–142 °C.

IR (KBr): 3326, 3066, 2917, 1699, 1671, 1640, 1591, 1578, 1560, 1371, 1347, 1269, 1212, 1184, 1070, 971, 941, 849, 729, 691 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 2.24 (s, 3 H), 2.77 (t, J = 7.0 Hz, 2 H), 2.88 (t, J = 7.0 Hz, 2 H), 7.59 (s, 1 H), 7.68–7.80 (m, 2 H), 8.11 (td, J = 1.5, 8.7 Hz, 2 H).
A mixture of 2-hydroxy-1,4-naphthoquinone (1; 348 mg, 2 mmol), silyl enol ether 2e (1.02 g, 6 mmol) and paraformaldehyde (240 mg, 8 mmol) in anhydrous dioxane (20 mL) was refluxed under an argon atmosphere for 18 h until complete conversion of 1 was observed (TLC). Workup as described above gave the products 6c and 7e.

**6c**

Yield: 153 mg (21%); yellow oil.

**7c**

Yield: 255 mg (45%); yellow solid; mp 180–182 °C.

**8a**

Yield: 383 mg (46%); yellow oil.

**8b**

Yield: 158 mg (19%); yellow solid; mp 95–96 °C.
3-Ethyl-2-hydroxy-4-propyl-3,4-dihydro-2H-naphtho[2,3-b]pyran-5,10-dione (9a)

A mixture of 2-hydroxy-1,4-naphthoquinone (1; 348 mg, 2 mmol), silyl enol ether 2d (866 mg, 6 mmol) and butyraldehyde (577 mg, 8 mmol) in anhydrous dioxane (20 mL) was refluxed under an argon atmosphere for 18 h until complete conversion of 1 was observed (TLC). Workup as described above gave the product 9a.

Yield: 485 mg (81%); yellow solid; mp 158–160 °C.

IR (KBr): 3373, 2955, 1684, 1611, 1575, 1458, 1268, 1200, 1168, 96.0, 40.6, 38.7, 37.3, 34.7, 34.3, 32.8, 25.2, 21.2, 20.8, 18.2, 14.4, 13.3, 11.1, 7.6, 7.2, 4.5 (cm⁻¹).

13C NMR (75 MHz, CDCl3): δ = 9.0 Hz, 1 H), 3.01 (d, J = 6.6 Hz, 1 H), 5.67 (s, 1 H), 5.75 (s, 1 H), 7.65–7.76 (m, 4 H), 7.92–8.11 (m, 4 H).

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