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A Versatile Synthesis of Fumaquinone

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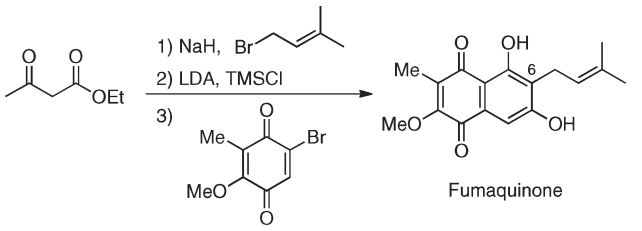


Fumaquinone, a novel prenylated naphthoquinone antibiotic, was synthetized from ethyl acetoacetate in three steps (58% overall yield). The key step of the synthesis is the construction of the naphthoquinone skeleton by a regioselective Diels−Alder reaction between a 2-alkyl 1,3-bis(trimethylsilyloxy)-1,3-diene derivative and a bromoquinone. This short and versatile approach confirms the structure of fumaquinone and allows the synthesis of derivatives at the C-6 position.

Fumaquinone is a novel prenylated naphthoquinone antibiotic isolated from cultures of *Streptomyces fumanus* (LL-F42248) in 2005.[1] It belongs to a relatively small group of meroterpenoids, hybrid compounds with polyketide-terpenic origin, with antitumor, antibiotic, and antioxidative activity.[2] Members of this family are furaquinocins[3] and neomarinone,[4] although the fumaquinone skeleton is present in other related compounds such as fibrostatin D[5] (Figure 1). Fumaquinone exhibits antimicrobial activity against selected Gram-positive bacteria with MIC of about 64 μg/mL. Structurally, fumaquinone presents a 1,4-naphthoquinone unit functionalized with an isoprenic side chain that differences the members of the family. Thus, fibrostatin D possesses a *N*-acetylcysteine group attached, while neomarinone and furaquinocin C present the naphthoquinone unit combined with a dihydrofurane ring. The relationship between the structure of the side chain and biological activity is unknown. Herein, we present the first synthesis of fumaquinone and derivatives modified at the side chain.

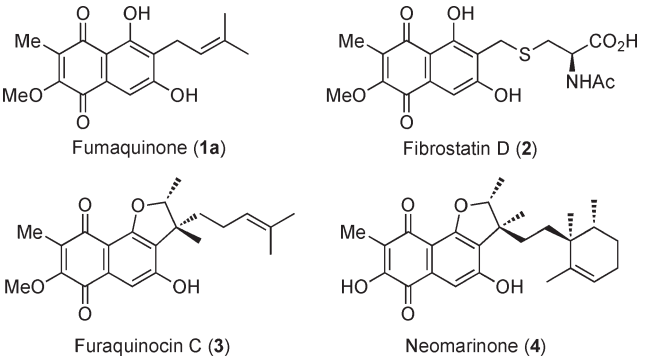
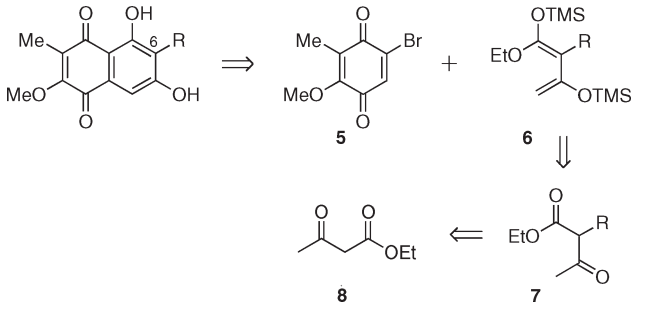


FIGURE 1. Structure of fumaquinone, fibrostatin D, furaquinocin C, and neomarinone.

The synthesis of fumaquinone was envisaged based in the construction of the 5,7-dihydroxy-2-methoxy-3-methyl-1,4-naphthoquinone skeleton by a regioselective Diels−Alder reaction between a 2-alkyl-1,3-bis(trimethylsilyloxy)-1,3-diene (**6**) and the bromoquinone **5**[6] (Scheme 1). The preparation of the 1,3-bis(silyloxy)diene **6** was proposed from a 2-alkylated β-ketoester **7**. This short and versatile synthetic approach should also provide access to potentially active fumaquinone derivatives at the C-6 position.

SCHEME 1. Retrosynthetic Analysis



During the last years, 1,3-bis(silyloxy)dienes have been shown as useful reagents in organic synthesis.[7] As 1,3-dianion synthons they participate in fundamental organic transformations, such as alkylation, acylation reactions, and oxidative cyclizations.[8] As dienes, they react efficiently with different dienophiles in Diels−Alder reactions giving rise to a wide variety of polycyclic structures.[9] This methodology has been

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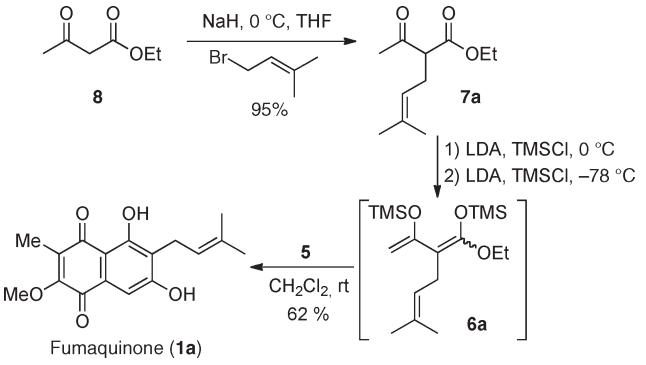
SCHEME 2. Synthesis of Fumaquinone

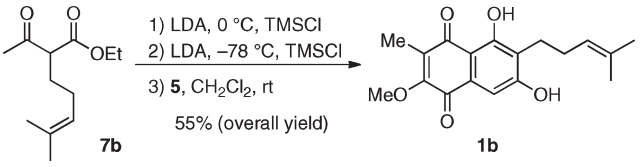


successfully applied to the synthesis of natural products,[10] such as furaquinocin C,[11] and more recently in our group to the synthesis of neomarinone.[12]

1,3-Bis(silyloxy)dienes can be efficiently prepared from 1,3-dicarbonyl compounds in a one- or two-step procedure.[13] They are sensitive to the hydrolysis although in some cases they can be isolated and stored at low temperature. 2-Alkyl-1-alkoxy-1,3-bis(trimethylsilyloxy)-1,3-dienes (**6**) are particularly labile due to the facile 1,5 O→C trimethylsilyl rearrangement and their synthetic utility is more limited.[14]

Our synthesis started with the introduction of the terpenic side chain of fumaquinone in ethyl acetoacetate. Selective *C*-alkylation of 1,3-dicarbonyl compounds has encountered some problems associated with the low reactivity of the generated enolates, low regioselectivity, and dialkylation.[15] In our case, the treatment of ethyl acetoacetate with NaH in THF at 0 °C followed by addition of 3,3-dimethylallyl bromide afforded the desired *C*-monoalkylated product **7a** in 95% yield (Scheme 2). With **7a** in hand, we attempted the synthesis of the corresponding 1,3-bis(silyloxy)diene accordingly to our previously developed procedure.[9] In this way, the sequential treatment of **7a** with LDA (1.1 equiv) and TMSCl (1.5 equiv) twice at 0 °C and −78 °C, respectively, produced the desired 1,3-bis(trimethylsilyloxy)-1,3-diene **6a**. As was anticipated, the resulting silyloxydiene was unstable to purification by destillation or column chromatography over silica gel and was used directly in the Diels−Alder reaction immediately after its preparation. According to this procedure, the reaction of a solution of the crude diene **6a** with bromoquinone **5** (1.5 equiv) in CH_2Cl_2 afforded, after 12 h at room temperature, a single isolated reaction product as a nice orange solid, which was identified as fumaquinone (**1a**) in 62% overall yield. It is worth noting that the overall process requires, besides the Diels−Alder reaction, elimination of HBr and EtOH, and trimethylsilyl enol ether hydrolysis, a process that is initiated in the reaction mixture and completed during the workup and chromatography.[16] The spectral data of synthetic fumaquinone (NMR, MS, UV) are coincident with those reported in the literature.[1] Overall, fumaquinone was synthesized in only 3 steps and 58% yield from commercial ethyl acetoacetate (Scheme 2).

SCHEME 3. Synthesis of Fumaquinone Analogue 1b



With fumaquinone in hand, we also explored the utility of this synthetic approach for the synthesis of derivatives with different side chains at the C-6 position. For this purpose we decided the synthesis of a hybrid derivative of fumaquinone furnished with the side chain of furaquinocin C. The synthesis of hybrid antibiotics is a useful approach for establishing structure−activity relationships.[17]

As previously, the first step in the synthesis was the alkylation of ethyl acetoacetate (**8**). The treatment of **8** with NaH at room temperature and addition of 5-iodo-4-methylpent-2-ene[18] led to the desired alkylated product **7b** in low yield. Fortunately, when the reaction was heated at reflux, the ethyl 2-acetyl-6-methylhept-5-enoate (**7b**)[19] was formed in 49% yield (67% based on recovered **8**). Accordingly with the experimental procedure described before, the bis(trimethylsilyl)oxy-1,3-diene was prepared in a one-pot procedure by sequential treatment of **7b** with LDA and TMSCl and the Diels−Alder reaction with bromoquinone **5** provided the fumaquinone derivative **1b** in 55% overall yield as a brilliant red solid (Scheme 3). In this case, the addition of catalytic amounts of TsOH to the Diels−Alder cycloadduct was required to favor the aromatization.

In summary, following a short and versatile synthetic approach, fumaquinone was prepared in three steps from commercial ethyl acetoacetate. The key step of the synthesis is a straightforward regioselective Diels−Alder reaction between a functionalized 1,3-bis(trimethylsilyloxy)-1,3-diene and a bromoquinone. The synthesis confirms the structure of fumaquinone and allows the synthesis of derivatives functionalized at the C-6 position. In this case, an analogue of fumaquinone with the side chain of furaquinocin C was prepared. The synthesis and biological evaluation of new derivatives of fumaquinone and congeners of this family of meroterpenoids are now in progress.

Experimental Section[20]

Ethyl 2-Acetyl-5-methylhex-4-enoate (7a). To a suspension of sodium hydride (0.378 g, 15.69 mmol) in THF (15 mL) at 0 °C

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(16) The overall process can be accelerated by using acid catalysis.

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(20) For General Methods, see the Supporting Information.

was added ethyl acetoacetate (2.0 mL, 15.69 mmol) dropwise via syringe. After 20 min, a solution of 3,3-dimethylallyl bromide (2.0 mL, 17.26 mmol) in THF (5 mL) was added, and the mixture was left at room temperature overnight. The solvent was removed under reduced pressure, and the residue was dissolved in Et_2O (10 mL) and washed with brine (25 mL). The organic layer was dried and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (10% EtOAc/hexanes) to afford **7a** (2.97 g, 14.9 mmol, 95%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, J = 7.13 Hz, 3H), 1.63 (s, 3H), 1.68 (s, 3H), 2.22 (s, 3H), 2.54 (t, J = 7.41 Hz, 2H), 3.42 (t, J = 7.41 Hz, 1H), 4.19 (q, J = 7.13 Hz, 2H), 5.03 (dt, J = 7.41 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (CH_3), 17.7 (CH_3), 25.7 (CH_3), 26.9 (CH_2), 29.0 (CH_3), 59.8 (CH), 61.2 (CH_2), 119.7 (CH), 134.7 (C), 169.6 (C), 203.1 (C); IR (ATR) 2978, 2916, 1737, 1715 cm^{-1}; MS (EI) m/z (%) 198 (M^+, 3), 155 ($M^+ - C_2H_3O$, 33), 109 (100); HRMS (EI) m/z calcd for $C_{11}H_{18}O_3$ (M^+) 198.1250, found 198.1242.

5,7-Dihydroxy-2-methoxy-3-methyl-6-(3-methylbut-2-enyl)-naphthalene-1,4-dione (1a). To a cooled solution of 2-acetyl-5-methylhex-4-enoate (**7a**, 0.421 g, 2.12 mmol) in THF (5 mL) at 0 °C was added a solution of LDA in THF (3.45 mL, 0.68 M, 2.34 mmol) dropwise via syringe. After 30 min, freshly distilled TMSCl (0.41 mL, 3.18 mmol) was added and the reaction was warmed at room temperature and cooled at −78 °C. Then, a solution of LDA (3.75 mL, 0.68 M in THF, 2.55 mmol) was added via syringe over 5 min period. After 40 min, freshly distilled TMSCl (0.41 mL, 3.18 mmol) was added via syringe, and the reaction mixture was allowed to reach room temperature for 1 h. The solvent was evaporated at reduced pressure and the residue was dissolved in Et_2O (25 mL) then filtered and the filtrate was concentrated to afford the corresponding 1,3-(trimethylsilyloxy)-1,3-diene **6a** as a yellow oil. **6a**: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 0.21 (s, 9H), 0.23 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H), 1.63−1.71 (m, 6H), 2.81 (d, J = 6.8 Hz, 2H), 3.83 (q, J = 7.1 Hz, 2H), 4.29 (s, 1H), 4.36 (s, 1H), 5.02−5.11 (m, 1H).

The diene **6a** was dissolved in CH_2Cl_2 (3 mL) at room temperature and the bromoquinone **5** (0.730 g, 3.18 mmol) was added in portions during 5 min. After 12 h, the reaction mixture was concentrated at reduced pressure and purified by column chromatography over silica gel (10% EtOAc/hexanes) to afford fumaquinone (**1a**, 0.400 g, 1.31 mmol, 62%) as a orange solid (mp 159−161 °C). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 1.65 (s, 3H), 1.78 (s, 3H), 1.99 (s, 3H), 3.39 (d, J = 7.13 Hz, 2H), 4.07 (s, 3H), 5.24 (t, J = 7.13 Hz, 1H), 7.11 (s, 1H), 9.71 (br s, 1H), 12.79 (br s, 1H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 8.8 (CH_3), 18.0 (CH_3), 22.7 (CH_2), 25.9 (CH_3), 61.3 (CH_3), 108.2 (CH), 109.1 (C), 122.1 (CH), 122.4 (C), 131.6 (C), 131.7 (C), 132.7 (C), 158.9 (C), 161.9 (C), 162.3 (C), 181.0 (C), 191.1 (C); IR (ATR) 3392, 2924, 2853, 1657, 1628, 1583 cm^{-1}; HRMS (ESITOF) m/z calcd for $C_{17}H_{17}O_5$ ($[M - H]^-$) 301.1081, found 301.1076; UV (λ) 220, 269, 304, 427 nm. Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.12; H, 5.66.

Ethyl 2-Acetyl-6-methylhept-5-enoate (7b). To a suspension of sodium hydride (0.195 g, 8.04 mmol) in THF (15 mL) at 0 °C was added ethyl acetoacetate (1.05 mL, 8.04 mmol) dropwise via syringe. After 20 min, a solution of 5-iodo-2-methylpent-2-ene[18] (1.408 g, 6.70 mmol) in THF (7 mL) was added and the mixture was refluxed during 4 h. The solvent was removed at reduced pressure, and the residue was dissolved in Et_2O (20 mL) and washed with a solution of brine (20 mL). The organic layer was dried and filtered, and the filtrate was concentrated. The residue was purified by column chromatography (10% EtOAc/hexanes) affording 0.700 g of **7b** (3.94 mmol, 49%) as a yellow oil (67% based on 0.280 g of ethyl acetoacetate recovered). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, J = 7.13 Hz, 3H), 1.59 (s, 3H), 1.69 (s, 3H), 1.86−2.01 (m, 4H), 2.23 (s, 3H), 3.42 (t, J = 7.41 Hz, 1H), 4.20 (q, J = 7.13 Hz, 2H), 5.07 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (CH_3), 17.6 (CH_3), 25.6 (CH_3), 25.7 (CH_2), 28.2 (CH_2), 28.8 (CH_3), 59.2 (CH), 61.2 (CH_2), 122.8 (CH), 133.2 (C), 169.9 (C), 203.3 (C); IR (ATR) 2969, 2927, 1739, 1714 cm^{-1}; MS (EI) m/z (%) 212 (M^+, 12), 169 ($M^+ - C_2H_3O$, 29), 109 (100); HRMS (EI) m/z calcd for $C_{12}H_{20}O_3$ (M^+) 212.1407, found 212.1410.

5,7-Dihydroxy-2-methoxy-3-methyl-6-(4-methylpent-3-enyl)-naphthalene-1,4-dione (1b). Following the experimental procedure developed for **1a**, the reaction of 1,3-(trimethylsilyloxy)-1,3-diene **6b** with bromoquinone **5** afforded, after purification by column chromatography over silica gel (30% EtOAc/hexanes), naphthoquinone **1b** in 55% yield (0.168 g, 0.53 mmol) as a brilliant red solid (mp 169−171 °C). **6b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.21 (s, 9H), 0.22 (s, 9H), 1.24 (t, J = 7.0 Hz, 3H), 1.61 (s, 3H), 1.68 (s, 3H), 1.99−2.11 (m, 4H), 3.82 (q, J = 7.1 Hz, 2H), 4.30 (s, 1H), 4.36 (s, 1H), 5.05−5.21 (m, 1H). **1b**: ^{1}H NMR (300 MHz, CD_3COCD_3) δ 1.57 (s, 3H), 1.65 (s, 3H), 1.99 (s, 3H), 2.23 (q, J = 7.5 Hz, 2H), 2.70 (t, J = 7.9 Hz, 2H), 4.07 (s, 3H), 5.22−5.26 (m, 1H), 7.18 (s, 1H), 9.93 (br s, 1H), 12.82 (br s, 1H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 7.8 (CH_3), 16.7 (CH_3), 22.7 (CH_2), 24.9 (CH_3), 26.7 (CH_2), 60.2 (CH_3), 107.4 (CH), 107.9 (C), 121.9 (C), 123.9 (CH), 130.5 (C), 130.7 (C), 131.5 (C), 157.9 (C), 161.4 (C), 161.5 (C), 180.1 (C), 190.1 (C); IR (ATR) 3409, 2928, 2853, 1656, 1624, 1580 cm^{-1}; HRMS (ESITOF) m/z calcd for $C_{18}H_{19}O_5$ ($[M - H]^-$) 315.1232, found 315.1216.

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Supporting Information Available: Copies of the ^{1}H NMR and ^{13}C NMR spectra for all compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.