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Synthetic and Isolation Studies Related to the Marine Natural Products (+)-Elisabethadione and (+)-Elisabethamine

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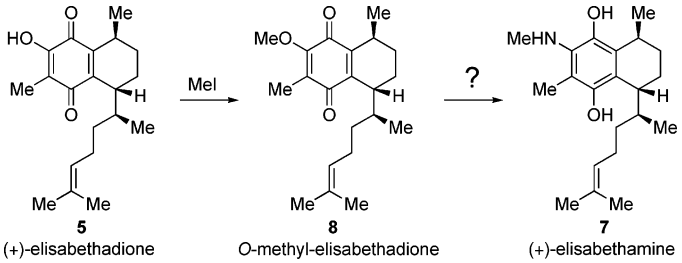

These studies were conducted to determine the discrepancies between the spectroscopic data of the isolated and synthetic samples of the marine natural product (+)-elisabethadione. Attempts at the re-isolation of (+)-elisabethadione from *Pseudopterogorgia elisabethae* were unsuccessful, but during these efforts, two related natural products of *O*-methylelisabethadione (**8**) and *O*-methyl-*nor*-elisabethadione (**9**) were discovered. The total syntheses of these new natural products were accomplished by using the combined C−H activation/Cope rearrangement as the key step and the previously synthesized elisabethadione was converted to *O*-methylelisabethadione. These studies confirmed that the synthetic sample of (+)-elisabthadione was assigned the correct structure. The considerable differences in the data between the synthetic and natural samples of (+)-elisabethadione lead to the conclusion that the structure of the natural material was either miss-assigned or the published spectral data were incorrect. During the course of these studies, questions arose about the assigned structure of another natural product, elisabethamine, which was proposed to be an aminohydroquinone. Attempts at the synthesis of this compound revealed that the aminohydroquinone structure was unstable in air as it was readily oxidized to the quinone.

Introduction

The marine soft coral *Pseudopterogorgia elisabethae* has been a very rich source of a large family of diterpenes.[1] Well over 100 natural products have been isolated, including some notable members such as (−)-colombiasin A (**1**),[2,3] (−)-elisapterosin B (**2**),[4] (+)-erogorgiaene (**3**),[5] and the pseudopterosins (**4**).[6] All members of this class of diterpenes have three distinctive stereogenic centers because all are presumably derived from the same biosynthetic precursor. In 2003, the Kerr group described the isolation of (+)-elisabethadione (**5**), a compound of considerable interest because it was a more potent anti-inflammatory agent than the pseudopteosins, which are commercially used in skin creams.[6,7] The gross structure of **5** was determined from a combination of extensive NMR (^{1}H NMR. ^{13}C NMR, COSY, TOCSY, HMQC, HMBC) and mass spec-

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(1) For a general review on the isolation, synthesis, and biosynthesis of these natural products, see: Heckrodt, T. J.; Mulzer, J. *Top. Curr. Chem.* **2005**, *244*, 1−42.

(2) Colombiasin A: (a) Isolation: Rodriguez, A. D.; Ramirez, C. *Org. Lett.* **2000**, *2*, 507−510. Total synthesis: (b) Nicolaou, K. C.; Vassilikogiannakis, G.; Magerlein, W.; Kranich, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2482−2486. (c) Nicolaou, K. C.; Vassilikogiannakis, G.; Magerlein, W.; Kranich, R. *Chem. Eur. J.* **2001**, *7*, 5359−5371. (d) Kim, A. I.; Rychnovsky, S. D. *Angew. Chem., Int. Ed.* **2003**, *42*, 1267−1270. (e) Harrowven, D. C.; Pascoe, D. D.; Demurtas, D.; Bourne, H. O. *Angew. Chem., Int. Ed.* **2005**, *44*, 1221−1222. (f) Boezio, A. A.; Jarvo, E. R.; Lawrence, B. M.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 6046−6050.

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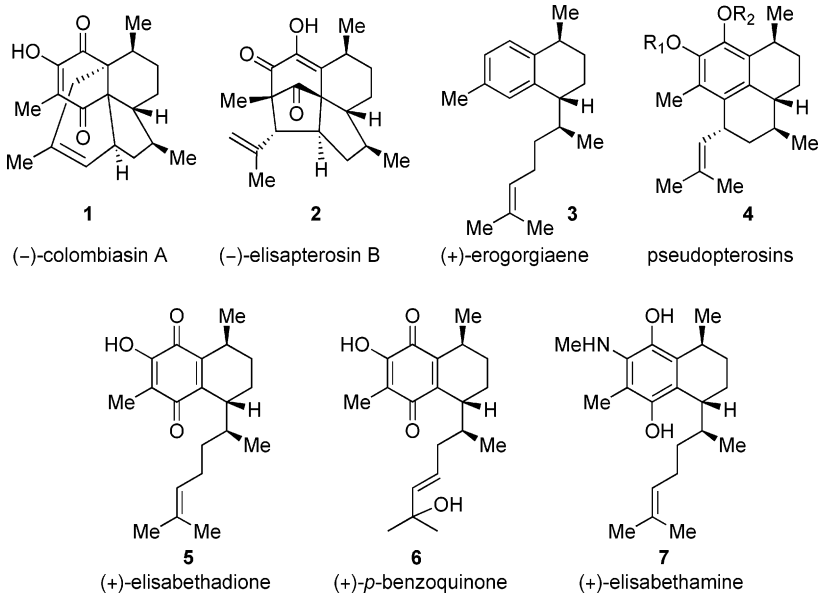


FIGURE 1. Natural products **1**−**7**.

troscopic techniques while the relative and absolute configuration were assumed by analogy to the other members of this class.

In 2005, the Davies group developed a universal strategy for the one-step synthesis of the three key stereogenic centers in these natural products and successfully applied it to the synthesis of (−)-colombiasin A(**1**), (−)-elisapterosin B (**2**),[8] and (+)-erogorgiaene (**3**).[5c] The new methodology was then applied to the synthesis of (+)-elisabethadione (**5**) but the spectral data for the synthetic material[9] and the published data for the natural material[7] were clearly different. Evidence to support that the synthetic process had produced the assigned structure of (+)-elisabethadione (**5**) was indirectly obtained by using related reactions to prepare the benzoquinone natural product **6**.[9] In this case the spectral data for the natural and synthetic material were identical. To fully resolve the differences between the synthetic and natural material, the Kerr and Davies groups have collaborated to re-examine the structural assignment of elisabethadione, and the details of these studies are described herein. During the course of these studies, the assigned structure of another natural product, (+)-elisabethamine (**7**),[10] came to question, especially as it was proposed to contain a methylaminohydroquinone functionality, which is generally considered to be very unstable.[11] The synthetic efforts toward verification of the structure of elisabethamine will be described.

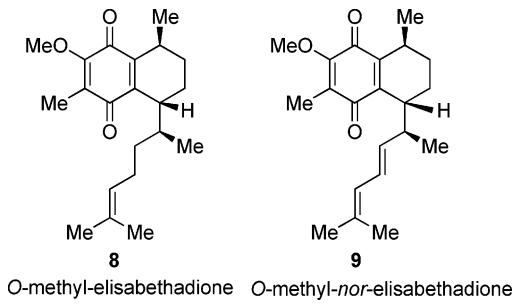


FIGURE 2. *O*-Methylelisabethadione (**8**) and *O*-methyl-*nor*-elisabethadione (**9**).

Results and Discussions

Due to the lack of any remaining supplies of elisabethadione, a new effort was made to re-isolate (+)-elisabethadione from a new harvest of *Pseudopterogorgia elisabethae*. Unfortunately, no (+)-elisabethadione could be isolated, but two new closely related natural products, *O*-methylelisabethadione (**8**) and *O*-methyl-*nor*-elisabethadione (**9**), were identified.

O-Methylelisabethadione (**8**) is a very useful probe to test which set of the spectroscopic data for elisabethadione (**5**) are most likely to be correct. As the only difference between the two compounds is a hydroxy versus a methoxy group, the spectroscopic data for the two natural products would be expected to be very similar. A comparison of the ^{1}H NMR

(3) For approaches toward colombiasin A: (a) Harrowven, D. C.; Tyte, M. J. *Tetrahedron Lett.* **2001**, *42*, 8709−8711. (b) Chaplin, J. H.; Edwards, A. J.; Flynn, B. L. *Org. Biomol. Chem.* **2003**, *1*, 1842−1844.

(4) Elisapterosin B: (a) Isolation: Rodriguez, A. D.; Ramirez, C.; Rodriguez, I. I.; Barnes, C. L. *J. Org. Chem.* **2000**, *65*, 1390−1398. Total synthesis: (b) Waizumi, N.; Stankovic, A. R.; Rawal, V. H. *J. Am. Chem. Soc*. **2003**, *125*, 13022−13023. References 2d, 2e, and 2f.

(5) Erogorgiaene: (a) Isolation: Rodriguez, A. D.; Ramirez, C. *J. Nat. Prod.* **2001**, *64*, 100−102. Total synthesis: (b) Cesati, R. R.; Armas, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 96−101. (c) Davies, H. M. L.; Walji, A. M. *Angew. Chem., Int. Ed. Engl.* **2005**, *44* (11), 1733−1735. Formal synthesis: (d) Harmata, M.; Hong, X. *Tetrahedron Lett.* **2005**, *46*, 3847−3849.

(6) (a) Look, S. A.; Fenical, W.; Jacobs, R. S.; Clardy, J. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 6238−6240. (b) Lazerwith, S. E.; Johnson, T. W.; Corey, E. J. *Org. Lett.* **2000**, *2* (15), 2389−92. (c) Corey, E. J.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 12777−12782.

(7) Ata, A.; Kerr, R. G.; Moya, C. E.; Jacobs, R. S. *Tetrahedron* **2003**, *59*, 4215−4222.

(8) Davies, H. M. L.; Dai, X.; Long, M. L. *J. Am. Chem. Soc.* **2006**, *128*, 2485−2490.

(9) Davies, H. M. L.; Dai, X. *Tetrahedron* **2006**, *62*, 10477−10484.

(10) Ata, A.; Kerr, R. G. *Tetrahedron Lett.* **2000**, *41*, 5821−5825.

(11) (a) Carpino, L. A.; Triolo, S. A.; Berglund, R. A. *J. Org. Chem.* **1989**, *54*, 3303−3310. (b) Watanabe, T.; Takeuchi, T.; Otsuka, M.; Umezawa, K. *Chem. Commun.* **1994**, *4*, 437. (c) Harger, R. N. *J. Am. Chem. Soc.* **1924**, *46*, 2540.

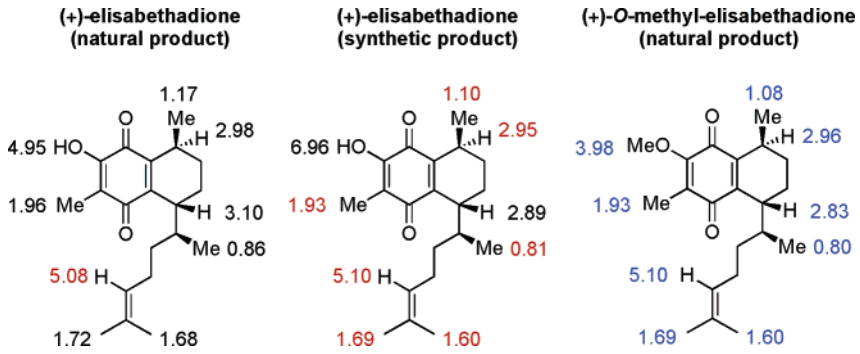
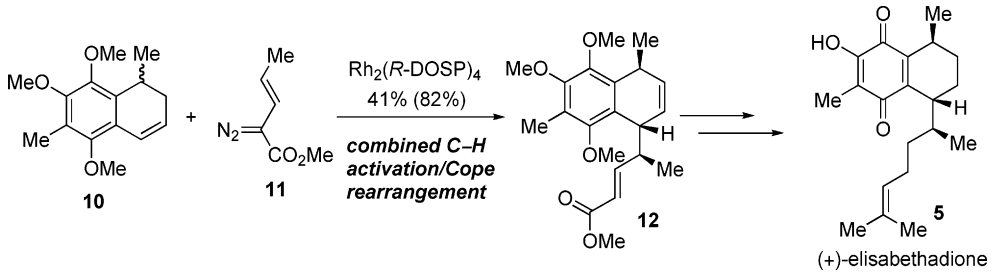
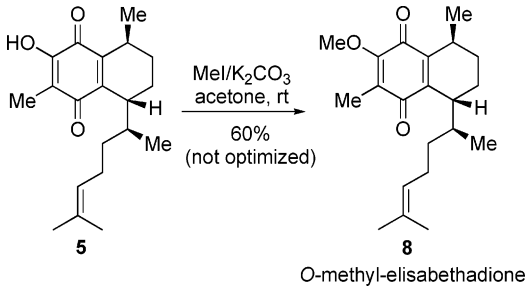


FIGURE 3. ^{1}H NMR data of elisabethadione (natural and synthetic) and *O*-methylelisabethadione (The red data indicate the NMR signals of natural and synthetic samples of elisabethadione, which are within 0.02 ppm of the data of natural *O*-methylelisabethadione (in blue).)

SCHEME 1



SCHEME 2



reveals that the data for synthetic elisabethadione are very close to the data for the newly isolated *O*-methylelisabethadione (**8**), while the published data for the natural elisabethadione have many differences from the data for **8** (Figure 3). The majority of the proton signals of synthetic (+)-elisabethadione are within 0.02 ppm of those of natural *O*-methylelisabethadione (**8**) compared to only one signal of the published spectrum of natural elisabethadione. This would suggest that either the published spectroscopic data or the assigned structure of natural elisabethadione is incorrect.

Further confirmation of the assigned structures was obtained from synthetic studies. The Davies strategy for the synthesis of these compounds relies on an enantiodivergent C−H activation/Cope rearrangement as the key step, which sets up the three common stereogenic centers present in these natural products (Scheme 1). One enantiomer of the dihydronapthalene undergoes the combined C−H activation/Cope rearrangement to form **12** while the other enantiomer undergoes cyclopropanation. A detailed analysis of the stereochemistry of this reaction has been published.[5c] After the key step the completion of the synthesis of (+)-elisabethadione (**5**) is very direct.[9]

With synthetic elisabethadione (**5**) in hand, further confirmation of its structure could be obtained by its conversion to *O*-methylelisabethadione by treatment of synthetic compound **5** with methyl iodide at room temperature to give the desired (+)-*O*-methylelisabethadione (**8**) in 60% yield (not optimized) (Scheme 2). The spectroscopic data of synthetic and natural *O*-methylelisabethadione (**8**) were in full agreement.

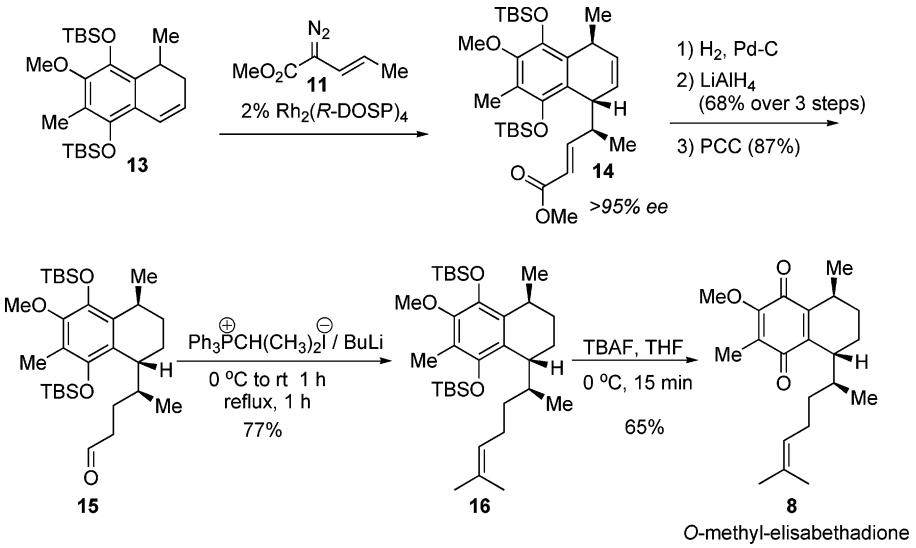
An alternative and more efficient synthetic route to (+)-*O*-methylelisabethadione (**8**) by using intermediates that were previously used in the synthesis of colombiasin A and elisapterosin B[8] is outlined in Scheme 3. Starting from aldehyde **15**, which was obtained from the C−H/Cope product **14** with three traditional steps, a Wittig reaction furnished the desired alkene **16** in 77% yield. Treating the alkene **17** with 2 equiv of TBAF in an open bottle at 0 °C for 15 min afforded (+)-*O*-methylelisabethadione (**8**) in 65% yield.

A major advantage of the combined C−H activation/Cope rearrangement strategy is that it can be easily altered to produce a range of natural products because not only are the three stereogenic centers formed but the side chain functionality is ideally suited for further manipulation. This can be readily seen in the direct synthesis of *O*-methyl-*nor*-elisabethadione (**9**), which was achieved in four steps from the same intermediate aldehyde **15** used in the synthesis of elisabethadione[9] (Scheme 4). A Grignard addition to **15** generated the allylic alcohol **17**, which was ready to convert to the triflate followed by elimination affording the diene **18**. Treatment of **18** with 1 equiv of HCl in ether at room temperature for 30 min gave complete isomerization of **18** to the more stable internal diene **19**. Synthesis of the natural product **9** was completed in 80% yield over two steps by desilylation/air oxidation of **19** (Scheme 4). Once again, the spectroscopic data for synthetic and natural **9** were identical.

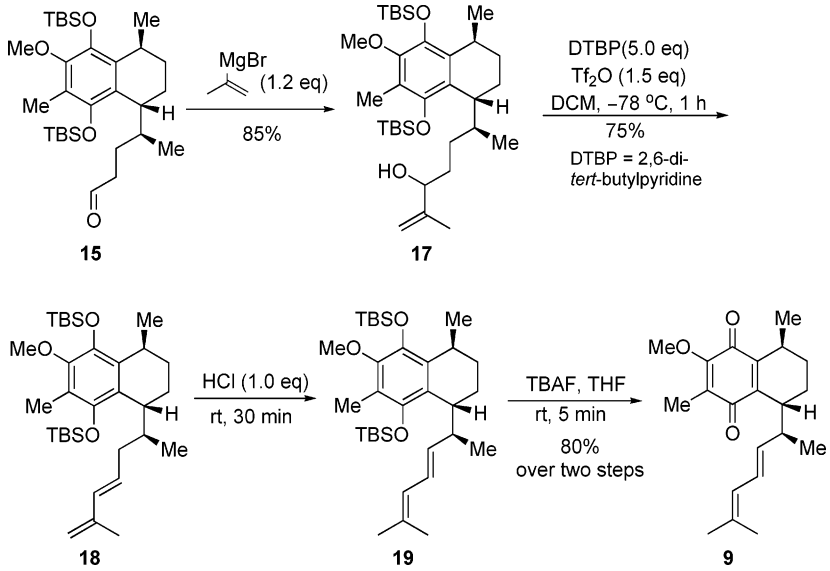
During the course of these studies, we became concerned about the assigned structure of elisabethamine (**7**),[10] because *N*-alkylaminohydroquinones are known to be extremely unstable

(12) (a) Fieser, L. F. *J. Am. Chem. Soc.* **1926**, *48*, 2922−2937. (b) Fieser, L. F. *J. Am. Chem. Soc.* **1928**, *50*, 439−465. (c) Cheng, H.; Cao, X.; Xian, M.; Fang, L.; Cai, T. B.; Ji, J. J.; Tunac, J. B.; Sun, D.; Wang, P. G. *J. Med. Chem.* **2005**, *48*, 645−652.

SCHEME 3



SCHEME 4



in air.[11] With (+)-*O*-methylelisabethadione (**8**) in hand, it is straightforward to complete the synthesis of (+)-elisabethamine (**7**). Because of its ester-like reactivity, the methoxy group in **8** could be replaced by amino groups upon direct interaction with the desired amines.[12] Thus, upon treating **9** with an excess of methylamine in ethanol at room temperature, (+)-*O*-methylelisabethadione (yellow solution in ethanol) completely converted to the desired amino benzoquinone **20** (red solution in ethanol) in 20 h (Scheme 5).

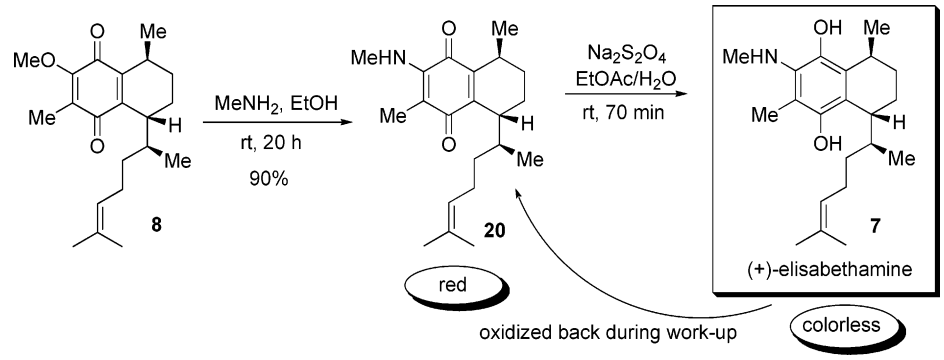
It is well-known that the benzoquinone could be easily reduced to the hydroquinone in the presence of sodium hydrosulfite.[13] When the amino benzoquinone **20** was subjected to these reduction conditions, and maintained for 70 min at room temperature under argon, the red reaction solution turned colorless, which indicated that the hydroquinone was formed (Scheme 5). During workup, however, the distinctive red color of the quinone returned and the ^{1}H NMR data proved it was the starting material amino benzoquinone **20**. These studies indicate that the assigned structure of (+)-elisabethamine is unstable in air, and indeed this is not surprising because it is known that electron-rich hydroquinones, especially aminohydroquinones, are very sensitive to air oxidation.[11] As no special precautions were reported to exclude oxygen during the isolation of (+)-elisabethamine, it is highly unlikely that the hydroquinone structure would have remained unoxidized. We speculate that elisabethamine was initially isolated as a salt that would be considerably more stable than the free amine. Unfortunately, the originally isolated material is not available.

Conclusions

In summary, these studies have led to the conclusion that the published NMR spectral data for natural (+)-elisabethadione (**5**) do not fit the assigned structure. It is still not clear at this stage whether this is because the isolated natural material does not have the assigned structure or because the published spectra were not the correct data for this compound. These studies also

(13) (a) Caldwell, W. T.; Thompson, T. R. *J. Am. Chem. Soc.* **1939**, *61*, 765−7. (b) Sato, K.; Fujima, Yo.; Yamada, A. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 442−4. (c) Hegedus, L. S.; Mulhern, T. A.; Mori, A. *J. Org. Chem.* **1985**, *50*, 4282−4288.

SCHEME 5



raise doubts about the assigned structure of (+)-elisabethamine (**7**) because the aminohydroquinone structure is known to be highly sensitive to air. This was confirmed for this specific case because the assigned structure of elisabethamine obtained through synthesis readily converts to the corresponding quinone.

Experimental Section

Isolation of Natural Products 8 and 9: Collection of *Pseudopterogorgia elisabethae*. *Pseudopterogorgia elisabethae* was collected by SCUBA from the Florida Keys at a depth of about 80 ft in August 2001 and was immediately flash frozen with liquid nitrogen. The flash frozen coral material was stored at −80 °C and then lyophilized prior to its extraction for chemical analysis.

Extraction and Isolation. Dried *Pseudopterogorgia elisabethae* (400.0 g) was blended and extracted with ethyl acetate and methylene chloride (v/v 1:1; 3 × 1000 mL), and after filtration and combination, the crude extracts were evaporated to dryness under reduced pressure to yield a deep green gummy residue (110.6 g). After the crude extract was partitioned between hexanes and H_2O, the resulting organic fraction was concentrated under reduced pressure to afford 68.3 g of oil. The oil was fractionated by silica gel flash chromatography with hexanes as eluent to yield a nonpolar fraction of 2.42 g of yellow oil. Further elution with a stepwise increasing gradient of EtOAc (10−100%, v/v) in hexanes afforded an additional 10 fractions. Fraction 1 (4.40 g) was subjected to semipreparative RP-C18 HPLC by using a gradient of CH_3CN/water (80−100%) as the mobile phase, followed by normal phase HPLC with EtOAc/hexanes as eluent to afford elisabethadone-*O*-Me (**8**, 1.21 mg) and *nor*-elisabethadione-*O*-Me (**9**, 1.12 mg). Detailed structure elucidation and bioactivity data will be reported in a subsequent paper.

Elisabethadione *O*-Me (8, natural): yellow oil; R_f 0.56 (80% methylene chlorid/hexane); UV (hexane) λ_{max} 276, 382 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.107 (br t, J = 7.0 Hz, 1H), 3.980 (s, 3H), 2.962 (m, 1H), 2.828 (br t, J = 5.0 Hz, 1H), 2.02 (m, 2H), 1.934 (s, 3H), 1.85 (m, 1H), 1.82 (m, 1H), 1.76 (m, 1H), 1.686 (s, 3H), 1.61 (m, 1H), 1.602 (s, 3H), 1.47 (m, 1H), 1.30 (m, 2H), 1.075 (d, J = 7.0 Hz, 3H), 0.795 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.8, 183.5, 155.0, 145.2, 146.1, 131.5, 129.1, 124.8, 61.0, 36.7, 36.2, 35.5, 26.5, 26.4, 26.4, 25.9, 21.2, 18.1, 17.9, 17.7, 9.1; IR (film) 2970, 2865, 1650, 1612, 1368, 1333, 1220, 1141 cm-1; HRMS (ESI) calcd for $C_{21}H_{31}O_3$ [M + H]$^+$, required *m*/*z* 331.2268, found 331.2268.

***nor*-Elisabethadione *O*-Me (9, natural):** yellow oil; R_f 0.48 (80% methylene chloride/hexane); UV (hexane) λ_{max} 275, 369 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (dd, J = 15.0, 10.8 Hz, 1H), 5.67 (d, J = 10.8 Hz, 1H), 5.30 (dd, J = 15.0, 8.0 Hz, 1H), 3.92 (s, 3H), 2.96 (m, 1H), 2.88 (br t, J = 6.0 Hz, 1H), 2.35 (m, 1H), 1.89 (m, 1H), 1.86 (s, 3H), 1.77 (m, 1H), 1.71 (s, 3H), 1.67−1.61 (m, 1H), 1.65 (s, 3H), 1.48 (m, 1H), 1.08 (d, J = 7.2 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.4, 183.4, 155.2, 146.2, 144.5, 137.3, 133.7, 129.7, 125.4, 124.9, 60.7, 41.2, 36.7, 26.2, 25.8, 25.0, 21.0, 18.9, 18.4, 18.2, 8.7; IR (film) 2974, 2865, 1649, 1606, 1551, 1364, 1303, 1220, 1140 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{29}O_3$ [M + H]$^+$, required *m*/*z* 329.2111, found 329.2117.

Synthetic Procedures: Alkene 16. *n*-BuLi (*n*-hexane solution, 0.17 mL, 0.27 mmol, 2.90 equiv) was added dropwise to a solution of isopropyltriphenylphosphonium iodide (121 mg, 0.28 mmol, 3.0 equiv) in dry THF (8 mL) at 0 °C under argon. The mixture was stirred for 1 h at the same temperature. A solution of **15** (50 mg, 0.093 mmol) in dry THF (4 mL) was charged into the solution at 0 °C, and the resulting solution was stirred for an additional 30 min. The reaction was allowed warm to room temperature for 30 min, and then was refluxed under argon for another 2 h. After cooling, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The organic layer was washed with brine and dried over Na_2SO_4, then concentrated in vacuo. Purification by column chromatography on silica gel (eluting with 1% ether/pentane) gave **16** (40 mg, 77% yield): R_f 0.43 (1% ether/pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04 (br t, J = 7.0 Hz, 1H), 3.63 (s, 3H), 3.14 (m, 1H), 2.87 (br t, J = 5.0 Hz, 1H), 2.09 (s, 3H), 2.00−1.92 (m, 2H), 1.81 (m, 2H), 1.72 (m, 1H), 1.65 (s, 3H), 1.55 (s, 3H), 1.38 (m, 1H), 1.31−1.20 (m, 3H), 1.06 (d, J = 7.0 Hz, 3H), 1.00 (s, 9H), 0.97 (s, 9H), 0.65 (d, J = 7.0 Hz, 3H), 0.25 (s, 3H), 0.15 (s, 3H), 0.14 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 145.9, 140.4, 132.8, 130.7, 126.6, 125.2, 119.3, 59.5, 37.2, 36.5, 35.6, 27.3, 26.8, 26.2 (6C), 25.6, 22.6, 18.8, 18.7, 17.6, 17.3, 11.4, −2.9, −3.0, −3.4, −4.9; IR (neat) 2929, 1412, 1252, 1069, 825 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{61}O_3Si_2$ [M + H]$^+$, required *m*/*z* 561.4154, found 561.4135.

(+)-Elisabethadione *O*-Me (8). To a solution of the alkene **16** (30 mg, 0.053 mmol) in THF (5 mL) at 0 °C under argon was added TBAF (130 μL, 0.13 mmol, 1.0 M solution in THF, 2.4 equiv). The yellow solution turned red immediately and then turned orange yellow. After 15 min, the reaction was quenched with H_2O (5 mL) and extracted with Et_2O (2 × 20 mL). The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated. Purification by column chromatography on silica gel (eluting with 1% ether/pentane) gave **8** (11.4 mg, 65% yield) as a yellow oil: R_f 0.38 (1% ether/pentane); $[\alpha]_D^{25}$ 133 (*c* 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11 (br t, J = 7.0 Hz, 1H), 3.98 (s, 3H), 2.97 (m, 1H), 2.83 (br t, J = 5.0 Hz, 1H), 2.06−1.95 (m, 2H), 1.94 (s, 3H), 1.85−1.73 (m, 3H), 1.69 (s, 3H), 1.62 (m, 1H), 1.61 (s, 3H), 1.45 (m, 1H), 1.36−1.22 (m, 2H), 1.08 (d, J = 7.0 Hz, 3H), 0.80 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.6, 183.2, 155.4, 145.9, 145.0, 131.3, 128.9, 124.6, 60.8, 36.5, 36.0, 35.3, 26.3, 26.25, 26.23, 25.7, 21.0, 18.0, 17.7, 17.5, 8.9; IR (neat) 2929, 1649, 1450, 1304 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{30}O_3$ [M]$^+$, required *m*/*z* 330.2189, found 330.2189.

(5*S*,8*R*)-5,6,7,8-Tetrahydro-2,5-dimethyl-3-(methylamino)-8-((*S*)-6-methylhept-5-en-2-yl)naphthalene-1,4-dione (20). To a solution of dione **8** (40 mg, 0.121 mmol) in EtOH (5 mL) at 23 °C under argon was added $MeNH_2$ (1.21 mL, 2.42 mmol, 2.0 M solution in THF, 20.0 equiv). The yellow solution was stirred at rt

for 20 h and then concentrated. Purification by pipet column on silica gel (eluting with 1/7 to 1/3 ether/pentane) gave **20** (36 mg, 90% yield) as a red oil: R_f 0.32 (1/5 ether/pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49 (br s, NH, 1H), 5.12 (br t, J = 7.0 Hz, 1H), 3.14 (s, 3H), 2.93−2.85 (m, 2H), 2.11 (s, 3H), 2.08−1.94 (m, 2H), 1.88 (m, 1H), 1.78 (m, 1H), 1.72 (m, 1H), 1.69 (s, 3H), 1.61 (m, 1H), 1.60 (s, 3H), 1.41 (m, 1H), 1.34 (m, 1H), 1.26 (m, 1H), 1.05 (d, J = 7.0 Hz, 3H), 0.80 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.5, 184.1, 148.3, 144.7, 142.8, 131.1, 124.8, 108.6, 36.9, 36.0, 35.7, 32.7, 26.4, 26.3, 26.2, 25.7, 20.8, 18.3, 17.7, 17.5, 10.3; IR (neat) 2929, 1641, 1592, 1512, 1253 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{31}NO_2Na$ [M + Na]$^+$, required *m/z* 352.2247, found 352.2249.

(5*S*,8*R*)-5,6,7,8-Tetrahydro-3-methoxy-2,5-dimethyl-8-((*S*,*E*)-6-methylhepta-3,5-dien-2-yl)naphthalene-1,4-dione (**9**). To a solution of diene **18** (13 mg, 0.023 mmol) in 4 mL of dry DCM at 23 °C was added 1.0 equiv of HCl (23 μL, 1.0 M in ether). The resulting colorless solution was then stirred at 23 °C for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with ether. The organic layer was washed with brine and dried over Na_2SO_4, then concentrated in vacuo. The crude product **19** was redissolved in 4 mL of dry THF in an open bottle, shielded from light with aluminum foil. Then TBAF (46 μL, 1.0 M in THF, 2.0 equiv) was added at room temperature. The color of the solution changed from colorless to yellow, then to red, then to light orange. After 5 min, the reaction was quenched with H_2O (2 mL). The mixture was extracted with ether (30 mL), washed with brine, dried over Na_2SO_4, and concentrated. Purification by pipet column on silica gel (eluent: pentane to 1% ether/hexane) gave **9** (6.0 mg, 80% for two steps) as a yellow gum.

Data for 19: R_f 0.37 (1% ether/pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (dd, J = 15.0, 10.5 Hz, 1H), 5.70 (d, J = 10.5 Hz, 1H), 5.55 (dd, J = 15.0, 7.5 Hz, 1H), 3.62 (s, 3H), 3.15 (m, 1H), 2.91 (m, 1H), 2.45 (m, 1H), 2.02 (s, 3H), 1.97 (m, 1H), 1.83−1.73 (m, 2H), 1.71 (s, 3H), 1.60 (s, 3H), 1.41 (m, 1H), 1.06 (d, J = 6.5 Hz, 3H), 1.00 (s, 9H), 0.99 (s, 9H), 0.85 (d, J = 6.5 Hz, 3H), 0.25 (s, 3H), 0.14 (s, 3H), 0.13 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 145.9, 137.1, 132.2, 131.8, 126.0, 125.4, 124.8, 123.0, 119.5, 59.6, 41.3, 37.4, 29.7, 27.3, 26.2 (6C), 25.8, 25.6, 22.7, 19.1, 18.7, 18.0, 17.5, 11.0, −3.0, −3.2, −3.5, −4.9; IR (neat) 2925, 1463, 1257, 1068, 920 cm^{-1}; HRMS (EI) calcd for $C_{33}H_{58}O_3Si_2$ [M]$^+$, required *m/z* 558.3919, found 558.3919.

Data for 9: R_f 0.28 (1% ether/pentane); $[\alpha]_D^{25}$ 34 (*c* 0.45, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97 (dd, J = 15.0, 11.0 Hz, 1H), 5.67 (d, J = 11.0 Hz, 1H), 5.30 (dd, J = 15.0, 8.0 Hz, 1H), 3.92 (s, 3H), 2.96 (m, 1H), 2.87 (br t, J = 6.0 Hz, 1H), 2.36 (m, 1H), 1.89 (m, 1H), 1.86 (s, 3H), 1.77 (m, 1H), 1.71 (s, 3H), 1.67−1.61 (m, 1H), 1.65 (s, 3H), 1.48 (m, 1H), 1.08 (d, J = 7.0 Hz, 3H), 1.03 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.2, 183.2, 155.0, 145.9, 144.3, 137.1, 133.5, 129.4, 125.2, 124.7, 60.7, 41.2, 36.7, 26.2, 25.8, 25.0, 21.0, 18.9, 18.4, 18.2, 8.7; IR (neat) 2962, 2933, 1652, 1609, 1304, 1226, 1149 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{28}O_3Na$ [M + Na]$^+$, required *m/z* 351.1931, found 351.1922.

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Supporting Information Available: Spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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