Synthesis of (−)-Hyatellaquinone and Revision of Absolute Configuration of Naturally Occurring (+)-Hyatellaquinone

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More than a hundred sesquiterpene quinones or quinols from marine sources have been reported, the majority of which have been isolated from sponges. Many of them exhibit a variety of promising biological activities such as antimicrobial, antiviral, cytotoxic, and immunomodulatory effects.[1] However, their absolute configuration has been difficult to establish and still remains the subject of controversy. Among them is the marine natural product (+)-hyatellaquinone **1**, which was isolated from the active anti-HIV RTs extracts of the sponge *Hyatella intestinalis* (Spongidae) by Kashman et a1.[2] Although the authors correctly assigned the relative configuration of (+)-hyatellaquinone as **1a** on the basis of comparison of spectral data with that of naturally occurring (+)-zonarol **2a**,[3] the absolute configuration of zonarol, a seaweed metabolite, was later revised after chemical degradation[4] and two enantiomerically controlled syntheses[5,6] and assigned as **2b** with (1*R*,4a*R*,8a*R*) stereochemistry at the chiral centers of the drimane skeleton. The same sesquiterpene quinone **1a** was reported by Capon et al[7] from *Spongia* sp. as an isomer of spongiaquinone, but the absolute configuration was not firmly established because of the paucity of available material (Figure 1).

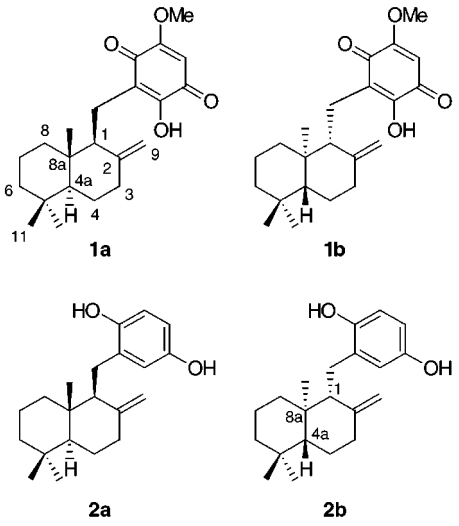
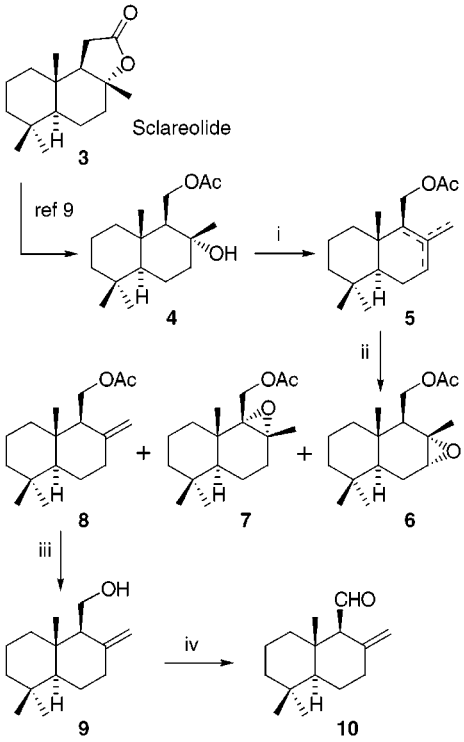


Figure 1.

As a part of our program directed toward the synthesis of bioactive marine natural products, we undertook the synthesis of **1a**, starting from the optically active (+)-sclareolide (**3**) bearing the right stereochemistry of the chiral centers at C-1, C-4a, and C-8a required for the drimane skeleton. The strategy that we adopted for the synthesis of **1a** (vide infra) is based on coupling the aldehyde **10** derived from sclareolide with the lithium anion of 1,2,4,5-tetramethoxybenzene as precursor of the quinone moiety. Previously, we have reported [8] that a quinone system such as **1** could be prepared by oxidation of substituted 1,2,4,5-tetramethoxybenzene with ceric ammonium nitrate (CAN), which provokes formation of the quinone and deprotection of the more hindered methyl ether in one step to provide the desired 2-hydroxy-5-methoxy-1,4-benzoquinone. As outlined below, herein we report the total synthesis of (1*S*,4a*S*,8a*S*)-hyatellaquinone **1a**, which enabled us to assign the (1*R*,4a*R*,-8a*R*) stereochemistry to the naturally occurring (+)-hyatellaquinone **1b** by comparison of optical rotations.

Scheme 1



i: 2.5 equiv of $SOCl_2$, 1 equiv of 4-DMAP, pyridine, -30 to 0 °C, 1 h; ii: 0.375 equiv of mCPBA, CH_2Cl_2-5% aq $NaHCO_3$ (1:1), 0 °C, 1 h (60% for 2 steps); iii: 3 equiv of KOH, MeOH, rt, 1 h (100%); iv: 2 equiv of PDC, CH_2Cl_2, 0 °C to rt, 4 h (84%).

The commercially available sclareolide **3** was transformed to the known acetate **4** over two steps according

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(1) Capon, R. J. Marine Sesquiterpene/Quinones. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science: New York, 1995; Vol. 15, pp 289−326.

(2) Talpir, R.; Rudi, A.; Kashman, Y.; Loya, Y.; Hizi, A. *Tetrahedron* **1994**, *50*, 4179.

(3) Fenical, W.; Sims, J. J.; Squatrito, D.; Wing, R. M.; Radlick, P. *J. Org. Chem*. **1973**, *38*, 2383.

(4) Cimino, G.; de Stephano, S.; Fenical, W.; Minale, L.; Sims, J. J. *Experientia* **1975**, *31*, 1250.

(5) Mori, K.; Komatsu, M. *Bull. Soc. Chim. Belg*. **1986**, *95*, 771.

(6) Akita, H.; Nozawa, M.; Shimizu, H. *Tetrahedron: Asymmetry* **1998**, *9*, 1789.

(7) Capon, R. J.; Groves, D. R.; Urban, S.; Watson, R. *Aust. J. Chem*. **1993**, *46*, 1245.

(8) (a) Poigny, S.; Guyot, M.; Samadi, M. *J. Org. Chem*. **1998**, *63*, 5890. (b) Poigny, S.; Guyot, M.; Samadi, M. *Tetrahedron* **1998**, *54*, 14791.

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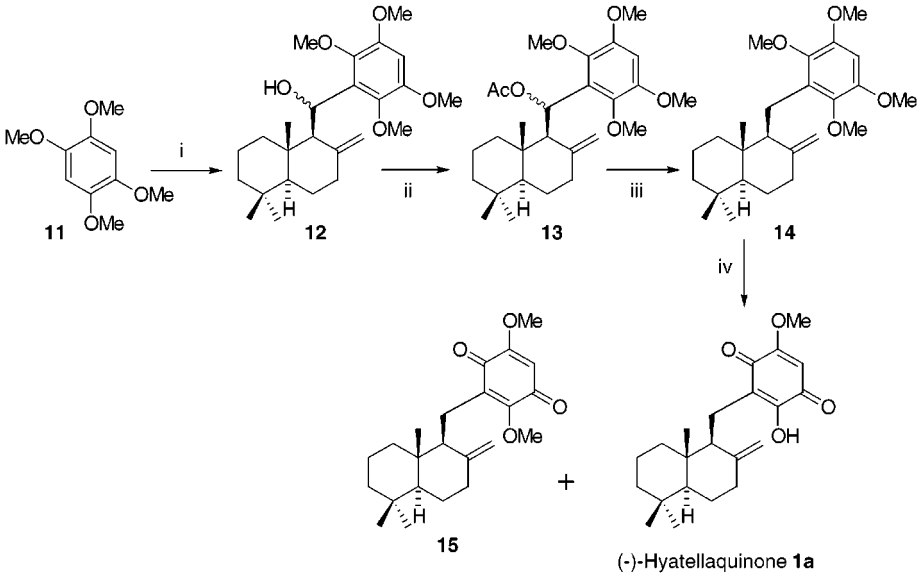
Scheme 2



(i) 3 equiv of **11**, 2.5 equiv BuLi, THF, 0 °C, 30 min, then 1 equiv of **10**, THF, rt, 30 min (74%); (ii) Ac_2O, cat 4-DMAP, pyridine, rt, 24 h; (iii) 10 equiv of Li, liquid NH_3, THF, -78 °C, 15 min (93% for 2 steps); (iv) 2.5 equiv of CAN, CH_3CN-H_2O, 0 °C to rt, 4 h (58% for **1a**, 26% for **15**).

to the procedure described in the literature.[9] Dehydration of tertiary alcohol **4** (2.5 equiv of $SOCl_2$, 1 equiv of 4-DMAP, pyridine) afforded, in quantitative yield, an inseparable mixture of exo and endo olefins **5** ($\Delta^{2,9}$:$\Delta^{2,3}$:$\Delta^{1,2}$ in a ratio of 6.25:2.5:1.25). To circumvent this difficulty, partial epoxidation of the crude mixture of olefins **5** by careful treatment with 0.375 equiv of *m*-CPBA at 0 °C for 1 h gave the more polar epoxides **6** and **7** and left the unreacted pure $\Delta^{2,9}$-*exo*-olefin **8** in 60% yield over two steps. Deprotection of acetate **8** (3 equiv of KOH, MeOH) provided alcohol **9**, which was identical in all respects (IR, NMR, MS, $[\alpha]_D$) with the known naturally occurring (+)-albicanol, a potent fish antifeedant, isolated both from the liverwort *Diplophyllum albicans*[10] and the marine dorid nudibranch *Cadlina luteomarginata*.[11] Oxidation of alcohol **9** with PDC in CH_2Cl_2 furnished the desired aldehyde **10**[12] in 84% yield (Scheme 1).

Coupling the above aldehyde **10** with the lithium anion of 1,2,4,5-tetramethoxybenzene **11**[8b,13] (3 equiv of **11**, 2.5 equiv of BuLi, THF, 0 °C) afforded the addition compound **12** as a mixture of diastereomers in 74% yield. Benzylic deoxygenation was accomplished by first acetylating **12** (Ac_2O, catalytic 4-DMAP, pyridine, room temperature) to give **13** and then deacetoxylating this (10 equiv of Li, liquid NH_3, THF, −78 °C) to provide **14** in 93% yield over two steps. Finally, compound **14** was treated with ceric ammonium nitrate to accomplish deprotection of the methyl ether and formation of the quinone system. Thus, slow addition of a solution of ceric ammonium nitrate (2.5 equiv, CH_3CN-H_2O) to compound **14** at 0 °C and stirring for 4 h at room temperature afforded the desired hyatellaquinone **1a** (58%) along with compound **15** (26%) (Scheme 2).

The synthetic hyatellaquinone **1a** obtained here was identical by IR, NMR, and MS with natural hyatellaquinone. However, the optical rotation for the synthetic product **1a** ($[\alpha]_D$ −16.1) was of opposite sign to that of the natural product ($[\alpha]_D$ +15.6).[1] Moreover, the optical rotation of the synthetic dimethoxy *p*-quinone **15** ($[\alpha]_D$ −37) has the opposite sign to the methylated natural hyatellaquinone[7] ($[\alpha]_D$ +37) prepared by Capon et al. These results confirm that the absolute configuration at the stereogenic centers of the natural (+)-hyatellaquinone **1b** is (1*R*,4a*R*,8a*R*), as depicted in Figure 1.

In summary, we have described the first total synthesis of the enantiomer **1a** of the naturally occurring (+)-hyatellaquinone **1b**, which allowed us to establish its absolute stereochemistry and a short synthesis of (+)-albicanol[14] from the readily available sclareolide. Preliminary biological study showed that the synthetic (−)-hyatellaquinone **1a** is cytotoxic, with an IC_{50} of 14 μM against KB cells. Further biological evaluation of **1a** is currently underway.

Experimental Section

All of the reactions were carried out under an argon atmosphere. All reagents were obtained from commercial suppliers and used without further purification. THF was freshly distilled from sodium/benzophenone. Methylene chloride was distilled from CaH_2. Flash chromatography was carried out using silica

(9) Kuchkova, K. I.; Chumakov, Y. M.; Simonov, Y. A.; Bocelli, G.; Panasenko, A. A.; Vlad, P. F. *Synthesis* **1997**, 1045.

(10) Ohta, Y.; Andersen, N. H.; Liu, C. B. *Tetrahedron* **1977**, *33*, 617.

(11) Hellou, J.; Andersen, R. J.; Thompson, J. E. *Tetrahedron* **1982**, *38*, 1875.

(12) Toyota, H.; Ooisa, Y.; Kusuyama, T.; Asakawa, Y. *Phytochemistry* **1994**, *35*, 1263. Weyerstahl, P.; Schwieger, R.; Schwope, I.; Hashem, M. A. *Liebigs Ann.* **1995**, 1389.

(13) Benington, F.; Morin, R. D. *J. Org. Chem.* **1955**, *20*, 102. Keegstra, E. M. D.; Huisman, B.-H.; Paardekooper, E. M.; Hoogesteger, F. J.; Zwikker, J. W.; Jenneskens, L. W.; Kooijman, H.; Schouten, A.; Veldman, N.; Spek, A. L. *J. Chem. Soc., Perkin Trans. 2* **1995**, 229.

(14) For previous synthesis of racemic and (+)-albicanol, see: Armstrong, R. J.; Harris, F. L.; Weiler, L. *Can. J. Chem.* **1986**, *64*, 10002. Ragoussis, V.; Liapis, M.; Ragoussis, N. *J. Chem. Soc., Perkin Trans. 1* **1987**, 987. Shishido, K.; Tokunaga, Y.; Omachi, N.; Hiroya, K.; Fukumoto, K.; Kamentani, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2481. Nakano, T.; Villamizar, J.; Maillo, M. A. *J. Chem. Res., Synop.* **1995**, 330. Banerjee, A. K.; Correa, J. A.; Laya-Mimmo, M. *J. Chem. Res., Synop.* **1998**, 710.

gel 60 F254 (Merck) with mixtures of ethyl acetate and hexane as eluent unless specified otherwise. TLC analyses were performed on thin-layer analytical plates 60 F254 (Merck).

1-Naphthalenemethanol, Decahydro-5,5,8a-trimethyl-2-methylene Acetate (1*S*,4a*S*,8a*S*)- [(+)-Albicanyl acetate (8)]. To a solution of acetate **4** (1 mmol, 294 mg) and 4-DMAP (1 mmol, 122 mg) in dry pyridine (5 mL) at −30 °C was added $SOCl_2$ (2.5 mmol, 0.182 mL) dropwise. The mixture was stirred for 1 h at this temperature and then warmed to 0 °C. The reaction was quenched with ice, and the pyridine was removed in vacuo. The residue was dissolved in ether, washed successively with water, saturated $NaHCO_3$, and brine, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give compound **5**, which was dissolved in a 1:1 mixture of CH_2Cl_2 and 5% aqueous $NaHCO_3$ (10 mL) followed by addition of *m*-CPBA (0.375 mmol, 65 mg) at 0 °C. The mixture was stirred at this temperature for 1 h, extracted with CH_2Cl_2, and washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified over silica gel using hexanes−EtOAc (98:2) as eluent to afford the *exo*-olefin **8** (161 mg, 61%) as a colorless oil: R_f 0.48 (hexanes−EtOAc, 95:5); $[\alpha]_D$ +23.1 (*c* 1.1, $CHCl_3$); lit. $[\alpha]_D$ +22 (*c* 0.37, $CHCl_3$); MS *m*/*z* (CI) 265 (MH^+); IR (neat) 1735, 1640, 895 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.85 (d, J = 1.2 Hz, 1H), 4.51 (d, J = 1.2 Hz, 1H), 4.33 (dd, J = 11.4 Hz, 3.9 Hz, 1H), 4.18 (dd, J = 11.2 Hz, 9.0 Hz, 1H), 2.40 (m, 1H), 2.02 (s, 3H), 0.88 (s, 3H), 0.86 (s, 3H), 0.78 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.4, 146.8, 107.1, 61.5, 60.5, 55.0, 54.7, 41.9, 39.0, 37.6, 33.6, 33.4, 23.9, 21.7, 21.1, 19.1, 15.1; HRMS (CI) calcd for $C_{17}H_{29}O_2$ (MH^+) 265.2168, found 265.2163.

1-Naphthalenemethanol, Decahydro-5,5,8a-trimethyl-2-methylene-(1*S*,4a*S*,8a*S*)- [(+)-Albicanol (9)]. To a solution of olefin **8** (0.6 mmol, 160 mg) in MeOH (4 mL) was added KOH (3 mmol, 168 mg), and the mixture was stirred at room temperature for 1 h. The solvent was removed in vacuo, and the residue was dissolved with ether. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated. Purification over silica gel using hexanes−EtOAc (8:2) gave compound **9** (134 mg, 100%) as a white solid: mp 67−68 °C; lit.[11] mp 68−69 °C; R_f: 0.42 (hexanes−EtOAc, 8:2); $[\alpha]_D$ +13.4 (*c* 0.84, $CHCl_3$); lit. $[\alpha]_D$ +13.0 (*c* 0.6, $CHCl_3$); MS *m*/*z* (CI) 223 (MH^+); IR (KBr) 3350, 2920, 1635, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.95 (s, 1H), 4.64 (d, J = 1.1 Hz, 1H), 3.84 (dd, J = 10.9 Hz, 1H), 3.75 (t, J = 10.9 Hz, 1H), 2.42 (m, 1H), 2.05 (m, 1H), 0.86 (s, 3H), 0.82 (s, 3H), 0.76 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.7, 106.3, 59.0, 58.6, 55.1, 41.9, 38.9 (2C), 37.8, 33.6, 33.4, 24.1, 21.7; 19.1, 15.2; HRMS (CI) calcd for $C_{15}H_{27}O$ (MH^+) 223.2062, found 223.2059.

1-Naphthalenecarboxaldehyde, Decahydro-5,5,8a-trimethyl-2-methylene-(1*S*,4a*S*,8a*S*)- [(−)-Albicanal (10)]. To a solution of alcohol **9** (0.92 mmol, 204 mg) in dry CH_2Cl_2 (5 mL) was added PDC (1.83 mmol, 690 mg) at 0 °C, and the reaction was stirred for 4 h at room temperature. The CH_2Cl_2 was evaporated in vacuo, the residue was triturated with ether and filtered, and the solvent was evaporated under reduced pressure. The residue was subjected to flash chromatography using hexanes−EtOAc (95:5) as eluent to give aldehyde **10** (170 mg, 84%) as a colorless oil; R_f: 0.72 (hexanes−EtOAc, 95:5); $[\alpha]_D$ −67.3 (*c* 1.83, $CHCl_3$); lit.[12] $[\alpha]_D$ −69.8 (*c* 0.5, $CHCl_3$); MS *m*/*z* (CI) 237 ($MH^+ + CH_4$); IR (neat) 2929, 2726, 1720; 1643, 1472, 892 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.79 (d, J = 4.5 Hz, 1H), 4.84 (s, 1H), 4.43 (s, 1H), 2.36 (m, 2H), 2.03 (m, 1H), 1.63 (m, 1H), 1.52 (m, 1H), 1.15 (m, 2H), 1.07 (s, 3H), 0.81 (s, 3H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 205.0, 144.8, 109.0; 67.6, 53.7; 41.7, 39.6, 38.8, 36.5, 33.3, 33.2, 22.9, 21.7, 18.5, 15.8; HRMS (CI) calcd for $C_{15}H_{25}O$ (MH^+) 221.1905, found 221.1903.

3-[[(1*S*,4a*S*,8a*S*)-Decahydro-5,5,8a-trimethyl-2-methylene-1-naphthalenyl]methyl]-2,3,5,6-tetramethoxybenzene (14). To a solution of 1,2,4,5-tetramethoxybenzene **11** (1.02 mmol, 202 mg) in dry THF (2 mL) was added dropwise *n*-BuLi (1.6 M in hexane, 0.53 mL, 0.85 mmol) at 0 °C. After 30 min of stirring at this temperature, a solution of aldehyde **10** (0.34 mmol, 75 mg) in dry THF (2 mL) was added. The reaction was stirred for an additional 30 min at 25 °C, quenched with saturated NH_4Cl, and extracted with ether. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was purified over silica gel (hexanes−EtOAc, 7:3) to give compound **12** (106 mg, 74%), which was dissolved in pyridine (2 mL), followed by addition of 4-DMAP (0.05 mmol, 6 mg) and acetic anhydride (2.5 mmol, 0.24 mL). The mixture was stirred overnight at 25 °C and concentrated in vacuo. The residue was dissolved in ether, washed successively with water, saturated $NaHCO_3$, 0.5 N HCl, and brine, dried over $MgSO_4$, and concentrated. Flash chromatography gave acetylated compound **13** (116 mg, 100%), which was dissolved in dry THF and added dropwise to a stirred solution of Li (2.54 mmol, 18 mg, 10 equiv) in liquid ammonia at −78 °C. The reaction was stirred for an additional 15 min at −78 °C. Solid ammonium chloride was added, and NH_3 was allowed to evaporate. Water was added, and the mixture was extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified over silica gel using hexanes−EtOAc (9:1) as eluent to give **14** (94 mg, 93%) as a white solid: mp 181 °C; R_f 0.29 (hexanes−EtOAc, 9:1); $[\alpha]_D$ −34.2 (*c* 1.03, $CHCl_3$); MS *m*/*z* (EI) 402 (M^+); IR (KBr) 2926, 1629, 1596, 1490, 1089, 895 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.39 (s, 1H), 5.01 (s, 1H), 4.67 (d, J = 0.9 Hz; 1H), 3.82 (s, 6H), 3.75 (s, 6H), 2.76 (m, 2H), 2.58 (m, 1H), 2.24 (m, 1H), 1.90 (m, 2H), 0.86 (s, 3H), 0.82 (s, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.8, 148.7, 141.2, 130.6, 106.9, 96.3, 60.7, 56.0, 55.7, 55.5, 42.2, 40.1, 38.6, 38.5, 33.7, 33.6, 24.5, 21.8; 20.1, 19.6, 14.1; HRMS (EI) calcd for $C_{25}H_{38}O_4$ (M^+) 402.2770, found 402.2758.

2,5-Cyclohexadiene-1,4-dione, 3-[[(1*S*,4a*S*,8a*S*)-Decahydro-5,5,8a-trimethyl-2-methylene-1-naphthalenyl]methyl]-2-hydroxy-5-methoxy- [(−)-Hyatellaquinone (1a)] and 2,5-Dimethoxy-2,5-cyclohexadiene-1,4-dione, 3-[[(1*S*,4a*S*,-8a*S*)-Decahydro-5,5,8a-trimethyl-2-methylene-1-naphthalenyl]methyl]- (15). To a solution of olefin **13** (40.2 mg, 0.1 mmol) in CH_3CN (5 mL) was added a solution of ammonium cerium(IV) nitrate (137 mg, 0.25 mmol) in CH_3CN-H_2O (2 mL, 1:1) dropwise at 0 °C over 1 h. The reaction was allowed to stir at room temperature for 4 h, and the mixture diluted with ether. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified over silica gel using hexanes−EtOAc (7:3) as eluent to give compounds **15** (9.6 mg, 26%), and hyatellaquinone **1a** (20.7 mg, 58%).

(−)-Hyatellaquinone 1a: yellow oil; R_f 0.28 (hexanes−EtOAc, 7:3); $[\alpha]_D$ −16.1 (*c* 0.4, $CHCl_3$); lit.[2] $[\alpha]_D$ +15.6 (*c* 0.5, $CHCl_3$); MS *m*/*z* (CI) 359 (MH^+); IR: 3400, 2930, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (s, 1H), 5.80 (s, 1H), 4.70 (s, 1H), 4.67 (s, 1H), 3.84 (s, 3H), 2.58 (dd, J = 13.6 Hz, 10.6 Hz, 2H), 2.47 (dd, J = 14.0 Hz, 3.0 Hz, 1H), 2.37 (d, J = 10.0 Hz, 1H), 2.30 (ddd, J = 12.5 Hz, 3.8 Hz, 2.3 Hz, 1H), 1.92 (td, J = 12.6 Hz, 4.8 Hz, 1H), 1.72 (d, J = 12.3 Hz, 1H), 1.09 (dd, J = 12.5 Hz, 2.2 Hz, 1H), 0.87 (s, 3H), 0.81 (s, 3H), 0.77 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 182,5, 182.0, 161.2, 151.5, 148.8, 119.3, 106.6, 102.0, 56.7, 55.4, 54.2, 42.1, 40.1, 38.7, 38.3, 33.6, 29.7, 24.4, 21.7, 19.5, 18.8, 14.1; HRMS (CI) calcd for $C_{22}H_{31}O_4$ (MH^+) 359.2222, found 359.2228.

Compound 15: yellow oil; R_f 0.48 (hexanes−EtOAc, 7:3); $[\alpha]_D$ −37.1 (*c* 0.15, $CHCl_3$); lit.[7] $[\alpha]_D$ +37 (*c* 0.4, $CHCl_3$); MS *m*/*z* (CI) 373 (MH^+); ^1H NMR ($CDCl_3$) δ 5.67 (s, 1H), 4.68 (s, 1H), 4.67 (s, 1H), 4.06 (s, 3H), 3.78 (s, 3H), 2.68 (dd, J = 13.7 Hz, 10.8 Hz, 1H), 2.50 (dd, J = 13.7 Hz, 3.1 Hz, 1H), 2.29 (m, 2H), 1.91 (td, J = 12.1 Hz, 4.5 Hz, 1H), 0.87 (s, 3H), 0.81 (s, 3H), 0.76 (s, 3H); HRMS (CI) calcd for $C_{23}H_{33}O_4$ ($M + H^+$) 373.2379, found 373.2372.

Supporting Information Available: ^1H and ^{13}C NMR of (−)-hyatellaquinone **1a** and compounds **8**−**10** and **12**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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