A Concise and Convergent Total Synthesis of Two Novel Cytotoxic Hydroquinones, Lanneaquinol and (*R*)-2′-Hydroxylanneaquinol

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A short and efficient approach for the total synthesis of two novel cytotoxic hydroquinones, lanneaquinol (**1**) and (*R*)-2′-hydroxylanneaquinol (**2**) isolated from the organic extract of the plant *Lannea welwitschii*, has been developed. Enantioselective organocatalytic *McMillan* hydroxylation has been successfully utilized for the creation of the stereogenic center bearing the OH group of (*R*)-2′-hydroxylanneaquinol (**2**). The hydroquinone core was constructed through the alkylation of cyclohexane-1,4-dione with a corresponding aldehyde. Both hydroquinone natural products can be synthesized by a mere change in the synthetic strategy.

Introduction. – The hydroquinone motif is widely distributed in Nature [1] and was found to exhibit a broad spectrum of biological activities such as inhibition of HIV 1 reverse transcriptase [2], and antimicrobial [3] and antitumor [4] properties. Hydroquinones are known to reduce pigmentation of birth marks and other bodily marks, and are active in cellular respiration [5], photosynthesis [6], and blood coagulation [7]. *Boyd* and co-workers [8] reported the isolation of two novel, cytotoxic alkylated hydroquinones, lanneaquinol (**1**) and (*R*)-2′-hydroxylanneaquinol (**2**; *Fig.*), from the organic extract of *Lannea welwitschii* (HIERN) ENGL. (family *Anacardiaceae*). These two alkylated hydroquinones exhibited modest cytotoxicities against the *NCI* panel of 60 human tumor cell lines [9]. To date, there have been no reports on the synthesis of **1**, but the synthesis of **2** has been reported recently [10].

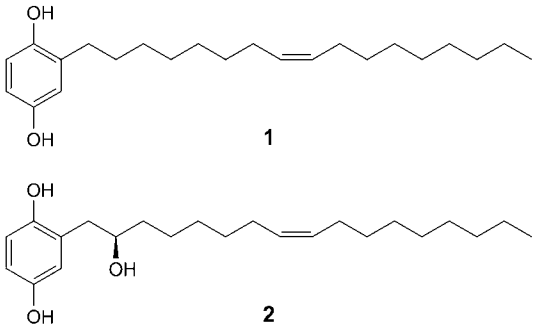

Figure. *Cytotoxic hydroquinones, lanneaquinol* (**1**) *and (*R*)-2′-hydroxylanneaquinol* (**2**)

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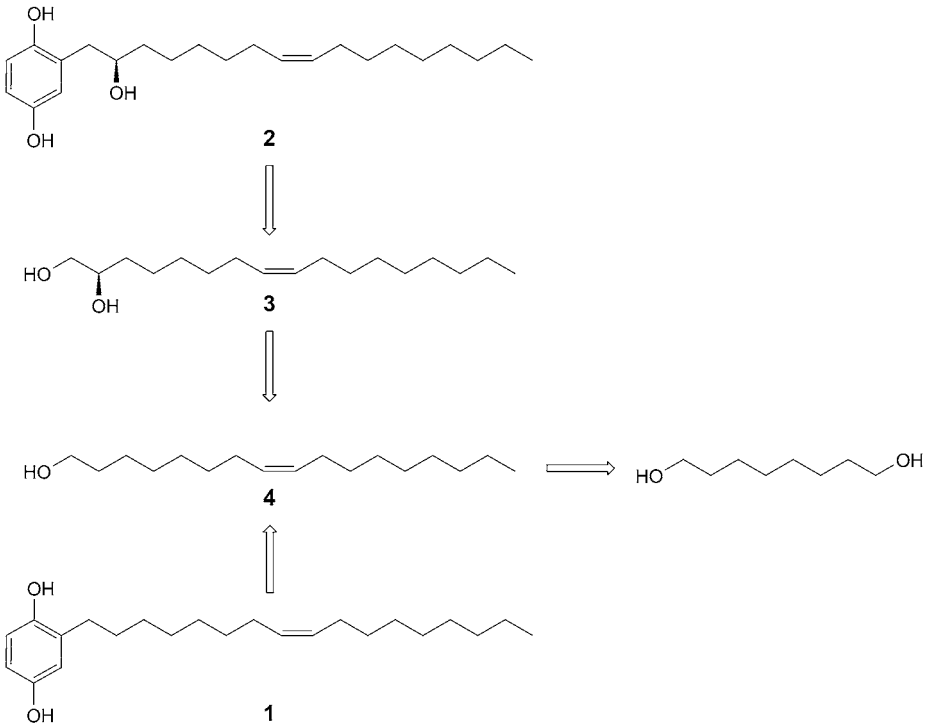
Results and Discussion. – Following our interest in the total synthesis of biologically active molecules [11], we herein report a concise and efficient total synthesis of lanneaquinol (**1**) and (*R*)-2′-hydroxylanneaquinol (**2**) starting from a readily available octane-1,8-diol. The retrosynthetic analysis of hydroquinones **1** and **2** is outlined in *Scheme 1*. The target molecule, **1** could be synthesized by a coupling of cyclohexane-1,4-dione with an aldehyde obtained from a common intermediate alcohol **4**, which could in turn be obtained from octane-1,8-diol *via Wittig* olefination. The other natural product, **2**, could be synthesized by the coupling of cyclohexane-1,4-dione with a corresponding aldehyde derived from diol **3**. The diol **3** could in turn be obtained by oxidation and a subsequent *MacMillan* α-hydroxylation of the corresponding alcohol **4** (*Scheme 1*).

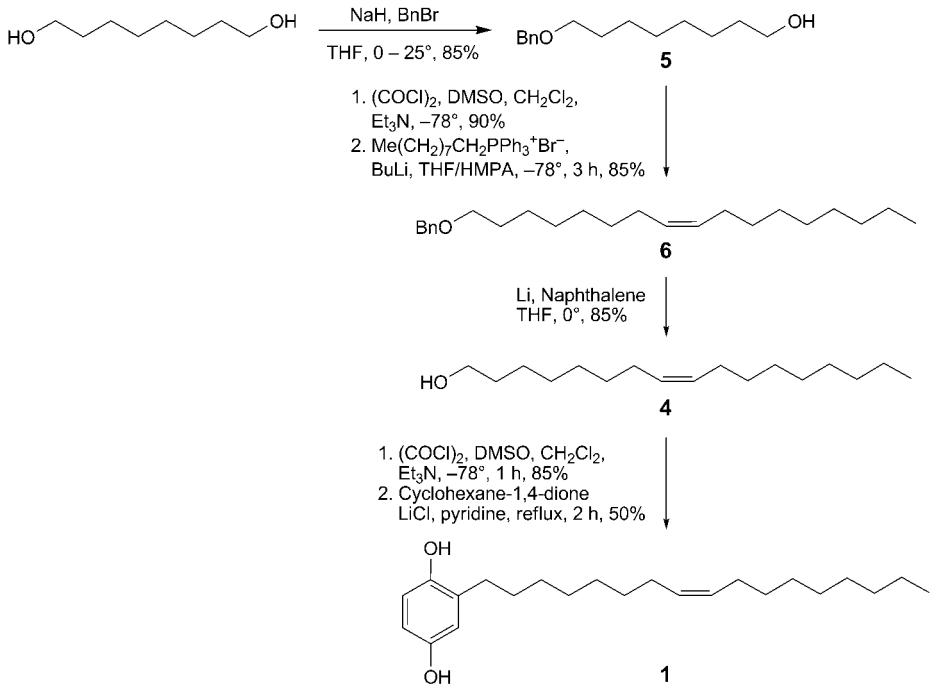
Scheme 1. *Retrosynthetic Analysis of Lanneaquinol* (**1**) *and (*R*)-2′-Hydroxylanneaquinol* (**2**). HMPA = Hexamethylphosphoric triamide.



The synthesis of **1** and **2** started from octane-1,8-diol. Accordingly, monoprotection of octane1,8-diol with BnBr using NaH gave the benzyloxy derivative **5** in 85% yield. *Swern* oxidation of **5** afforded the corresponding aldehyde [12], which was then subjected to *Wittig* olefination, with (nonyl)(triphenyl)phosphonium bromide in the presence of Buli at $-78°$ in THF/HMPA to give the (*Z*)-olefin **6** in 85% yield [13]. The reductive cleavage of **6** with Li/naphthalene gave the primary alcohol **4**, which was further oxidized under *Swern* conditions to give the corresponding aldehyde in 85% yield. The resulting aldehyde was then treated with cyclohexane-1,4-dione in the

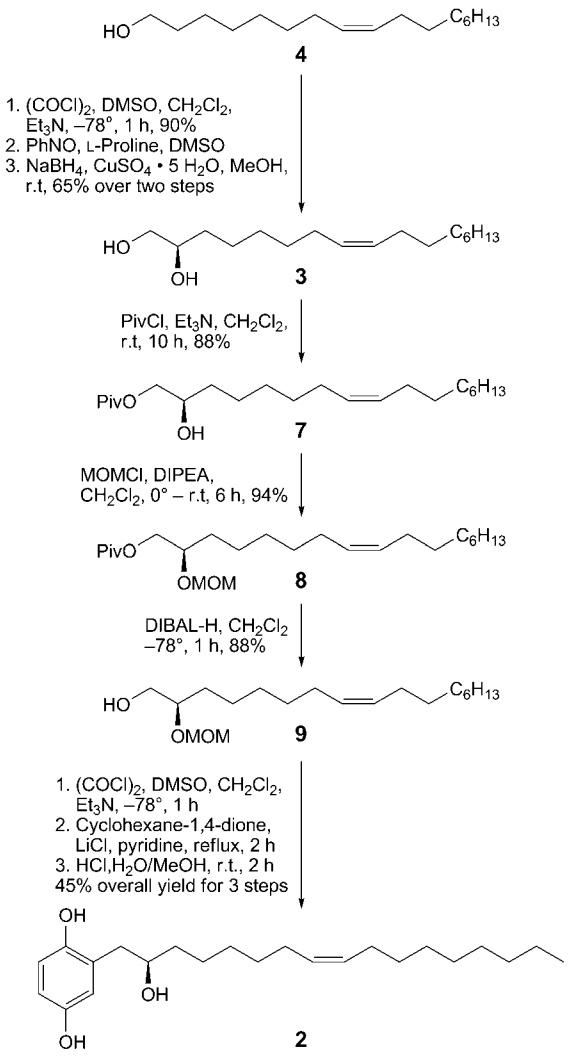
presence of LiCl in dry pyridine to give the target molecule lanneaquinol (**1**) in 50% yield (*Scheme 2*) [14].

Scheme 2. *Synthesis of Lanneaquinol* (**1**)



Next, we initiated the synthesis of **2** from an aldehyde, which was obtained *via Swern* oxidation of alcohol **4** (*Scheme 3*). We employed the well-established *MacMillan* α-hydroxylation [15] of the aldehyde using PhNO and L-proline in DMSO, followed by reduction with $NaBH_4$, leading to the unstable anilinoxy compound, which was further treated with 10 mol-% of $CuSO_4 \cdot 5\ H_2O$ in MeOH at room temperature to cleave the N–O bond to furnish the diol **3** in 65% yield and with high enantioselectivity (97% ee (HPLC)). The primary alcohol of **3** was protected as its pivaloyl derivative **7** using pivaloyl chloride and Et_3N in dry CH_2Cl_2. The secondary alcohol **7** was then protected as its methoxymethyl (MOM) ether using methoxymethyl chloride (MOMCl) in the presence of the *Hünig*'s base (EtN^iPr_2 (DIPEA)) in dry CH_2Cl_2 to give compound **8**. Reductive removal of the pivaloate moiety with diisobutylaluminium hydride (DIBAL-H) gave the primary alcohol **9** in 88% yield, which was further oxidized to the corresponding aldehyde under *Swern* oxidation conditions. Treatment of the aldehyde with cyclohexane-1,4-dione in the presence of LiCl in dry pyridine [14] gave the corresponding 2-alkylated hydroquinone, which, on further treatment with 5M HCl, resulted in the formation of the target molecule **2** in 45% overall yield (*Scheme 3*). The analytical and spectroscopic data of compounds **1** and **2** were in good agreement with those reported in the literature [8][10].

Scheme 3. *Synthesis of (*R*)-2′-Hydroxylanneaquinol* (**2**)



Conclusions. – In summary, we have developed a convergent approach for the total synthesis of the two cytotoxic hydroquinones, lanneaquinol (**1**) and (*R*)-2′-hydroxylanneaquinol (**2**), isolated from the organic extract of the plant *Lannea welwitschii*. *McMillan* α-hydroxylation has been successfully utilized for the creation of the stereogenic center in **2**. The hydroquinone core was constructed through the alkylation of cyclohexane-1,4-dione with a corresponding aldehyde. Both hydroquinone natural products have been synthesized by applying a similar strategy.

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Experimental Part

General. All solvents were purified by standard techniques. Column chromatography (CC): *Merck* 60–120 mesh silica gel (SiO_2). Optical rotations: *JASCO DIP-370* Polarimeter at 25°. IR Spectra: *Perkin-Elmer FT-IR 240-c* spectrophotometer using KBr optics; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker-300* (300 MHz) and *Varian Unity 75* spectrometers (75 MHz) in $CDCl_3$ with Me_4Si as internal standard; δ in ppm, J in Hz. Mass spectra: *Finnigan MAT 1020* mass spectrometer; at 70 eV; in *m/z*.

8-(Benzyloxy)octan-1-ol (**5**). To a stirred suspension of NaH (3.2 g, 60% with mineral oil, 133 mmol) in dry THF (150 ml) was added a soln. of octane-1,8-diol (10 g, 68 mmol) in dry THF (100 ml) at 0°, and stirring was continued for 20 min. Then, BnBr (11.12 g, 65 mmol) in dry THF was added slowly. The mixture was warmed to r.t., and the stirring was continued for 3 h. Then, the reaction was quenched with NH_4Cl, and the mixture was extracted with AcOEt (3 × 150 ml). The org. extracts were combined and washed with H_2O and brine, and dried (anh. Na_2SO_4), and the solvent was evaporated under reduced pressure, followed by purification of the crude product by CC, to afford **5** (13.7 g, 85% yield). Pale-yellow liquid. R_f (AcOEt/hexane 3:7) 0.4. IR (neat): 3352, 2931, 2858, 1464, 1373, 1253, 1058, 834, 774. ^1H-NMR ($CDCl_3$, 300 MHz): 7.30–7.22 (*m*, 5 H); 4.45 (*s*, 2 H); 3.54 (*t*, J = 6.4, 2 H); 3.42 (*t*, J = 6.4, 2 H); 2.24 (br. *s*, 1 H); 1.64–1.47 (*m*, 4 H); 1.42–1.33 (*m*, 8 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 138.4; 128.3; 127.6; 127.4; 72.8; 70.2; 63.2; 32.4; 30.2; 29.8; 29.5; 26.0; 25.4. ESI-MS: 259 ($[M+Na]^+$).

Benzyl (8Z)-Heptadec-8-en-1-yl Ether (**6**). To a stirred soln. of $(COCl)_2$ (10.6 g, 84 mmol) in CH_2Cl_2 (50 ml) was added a pre-mixed soln. of DMSO (13.2 g, 169 mmol) and CH_2Cl_2 (75 ml) at −78°. After 20 min, a soln. of **5** (10.0 g, 42 mmol) in CH_2Cl_2 (50 ml) was added at the same temp. The resulting mixture was stirred for 20 min at −78°, and then Et_3N (34.2 g, 338 mmol) was added. The mixture was warmed to r.t., and the stirring was continued for 1 h at the same temp. A sat. soln. of NH_4Cl (15 ml) was added slowly to quench the reaction, and then the mixture was extracted with CH_2Cl_2. The combined org. extracts were washed with brine, dried (Na_2SO_4), concentrated *in vacuo*, and the resulting aldehyde purified by flash chromatography (FC). To a stirred soln. of (nonyl)(triphenyl)phosphonium bromide (32 g, 68 mmol) in THF/HMPA 4:1 (150 ml) was added BuLi (52.5 ml of 1.6M in hexane, 84 mmol) dropwise at −78°, and then the mixture was stirred for 30 min at the same temp. To this mixture was added the above aldehyde (8.0 g, 34 mmol) in dry THF (50 ml), and the stirring was continued for another 3 h at −78°. The reaction was quenched with sat. NH_4Cl soln., and the mixture was extracted with Et_2O (3 × 150 ml). The combined org. extracts were washed with brine and dried (anh. Na_2SO_4). Removal of the solvent gave the crude product, which was purified by CC to give **6** (10.0 g, 85% yield from aldehyde). Colorless oil. R_f (AcOEt/hexane 1:9) 0.6. IR (neat): 3420, 2922, 2854, 1645, 1453, 1096, 970, 699. ^1H-NMR ($CDCl_3$, 300 MHz): 7.33–7.18 (*m*, 5 H); 5.36–5.24 (*m*, 2 H); 4.46 (*s*, 2 H); 3.42 (*t*, J = 6.6, 2 H); 2.05–1.92 (*m*, 4 H); 1.65–1.53 (*m*, 2 H); 1.45–1.19 (*m*, 22 H); 0.88 (*t*, J = 6.7, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 138.6; 129.9; 129.7; 128.2; 127.5; 127.4; 72.8; 70.4; 31.8; 2 × 29.7; 29.6; 29.4; 29.3; 2 × 29.29; 29.2; 2 × 27.1; 26.1; 22.6; 14.0. ESI-MS: 344 (M^+).

(8Z)-Heptadec-8-en-1-ol (**4**). To a stirred soln. of naphthalene powder (26.0 g, 203 mmol) in dry THF (150 ml) was added Li metal (1.01 g, 144 mmol). The mixture was stirred for 3 h at r.t., then cooled to −10°, and compound **6** (10.0 g, 29 mmol) in dry THF (100 ml) was added. After stirring for 30 min at −10°, the reaction was quenched with sat. aq. NH_4Cl soln., and the mixture was extracted with Et_2O (3 × 200 ml). The org. layer was washed with H_2O and brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by CC (SiO_2) to afford **4** (6.2 g, 85% yield). Light-yellow liquid. R_f (AcOEt/hexane 1:9) 0.2. IR (neat): 3405, 3030, 2931, 2857, 1655, 1456, 1363, 1097, 737. ^1H-NMR ($CDCl_3$, 300 MHz): 5.32–5.28 (*m*, 2 H); 3.60 (*t*, J = 6.8, 2 H); 2.03–1.95 (*m*, 4 H); 1.71–1.65 (*m*, 1 H); 1.57–1.50 (*m*, 2 H); 1.37–1.23 (*m*, 20 H); 0.88 (*t*, J = 6.8, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 129.9; 129.7; 63.0; 32.7; 31.8; 29.7; 29.6; 29.5; 29.35; 29.3; 29.25; 29.2; 27.2; 27.1; 25.6; 22.6; 14.0. ESI-MS: 255 ($[M+H]^+$); 277 ($[M+Na]^+$).

(2R,8Z)-Heptadec-8-ene-1,2-diol (**3**). To a soln. of DMSO (6.6 ml, 93 mmol) in CH_2Cl_2 (50 ml) was added $(COCl)_2$ (4.4 ml, 46 mmol) in CH_2Cl_2 (25 ml) at −78°. After stirring 20 min, a soln. of **4** (6.0 g, 23 mmol) in CH_2Cl_2 (50 ml) was added at the same temp. The resulting mixture was stirred for 20 min at −78° and then Et_3N (26 ml, 188 mmol) was added. The reaction was warmed to r.t., and stirring was continued for another 30 min at the same temp. A sat. aq. NH_4Cl soln. (15 ml) was added to quench the

reaction, and the mixture was extracted with CH_2Cl_2. The combined org. extracts were washed with brine, dried (Na_2SO_4), concentrated *in vacuo*, and the resulting aldehyde was purified by FC for immediate use in the next reaction. To a soln. of the above aldehyde (5.0 g, 19 mmol) in anh. DMSO (75 ml), were added PhNO (2.3 g, 21 mmol, 1.1 equiv) and L-proline (1.02 g, 8.9 mmol, 0.45 equiv.) consecutively at 20° under N_2. The mixture was stirred vigorously for 25 min (the color of the mixture changed from green to yellow during this time), then cooled to 0°, and diluted with MeOH (380 ml). To this soln., $NaBH_4$ (2.2 g, 59 mmol) was added portionwise, and stirring was continued for another 1 h at r.t., and then the mixture was cooled to 0°. At this temp., NH_4Cl (0.29 g, 6 mmol) and $Cu(OAc)_2$ (0.36 g, 2 mmol) were added sequentially. The resulting mixture was stirred for 24 h at r.t., and then MeOH was evaporated under vacuum. The mixture was diluted with H_2O (100 ml) and extracted with Et_2O (3 × 200 ml). The combined org. layers were washed with H_2O and sat. NaCl soln., dried (Na_2SO_4) and concentrated in vacuum. The residue was purified by FC to give **3** (3.48 g, 65%). Yellowish liquid. R_f (AcOEt/hexane 1:1) 0.2. $[\alpha]_D^{27} = +0.65$ ($c = 0.46$, $CHCl_3$). IR (neat): 3438, 2924, 2855, 1644, 1456, 1202, 1092. ^{1}H-NMR ($CDCl_3$, 300 MHz): 5.32–5.28 (*m*, 2 H); 3.71–3.57 (*m*, 2 H); 3.42–3.36 (*m*, 1 H); 2.04–1.95 (*m*, 4 H); 1.45–1.20 (*m*, 20 H); 0.89 (*t*, $J = 6.8$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 130.1; 129.5; 72.3; 66.8; 33.1; 31.8; 29.7; 29.6; 29.5; 29.4; 29.3; 29.2; 27.2; 27.1; 25.4; 22.6; 14.0. ESI-MS: 270 (M^+).

*(2*R*,8*Z*)-2-Hydroxyheptadec-8-en-1-yl 2,2-Dimethylpropanoate* (**7**). A mixture of **3** (2.0 g 7.4 mmol), dry pyridine (5 ml) and 4-(dimethylamino)pyridine (DMAP; 150 mg, 1.4 mmol) in dry CH_2Cl_2 (15 ml) was stirred under N_2. The mixture was cooled to 0°, and pivaloyl chloride (0.97 g, 1 ml, 8.1 mmol) was added dropwise over 15 min. The resulting mixture was further stirred for 1 h at r.t., then the reaction was quenched with sat. $NaHCO_3$ (10 ml), and the mixture was extracted with CH_2Cl_2 (3 × 25 ml). The combined org. layers were washed with sat. $CuSO_4$ soln. and brine. The org. layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by CC (SiO_2) to give the **7** (2.3 g, 88% yield). Colorless oil. R_f (AcOEt/hexane 2:8) 0.5. $[\alpha]_D^{25} = -1.05$ ($c = 0.66$, $CHCl_3$). IR (neat): 3451, 2924, 2854, 1728, 1660, 1158, 1032, 757. ^{1}H-NMR ($CDCl_3$, 300 MHz): 5.34–5.22 (*m*, 2 H); 4.06 (*dd*, $J = 11.3$, 3.0, 1 H); 3.90 (*dd*, $J = 11.3$, 6.7, 1 H); 3.81–3.66 (*m*, 1 H); 2.02–1.83 (*m*, 4 H); 1.46–1.17 (*m*, 21 H); 1.16 (*s*, 9 H); 0.81 (*t*, $J = 6.7$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 178.7; 130.0; 129.5; 70.1; 68.5; 34.0; 33.3; 31.8; 29.7; 29.6; 29.5; 29.29; 29.20; 27.1; 27.0; 25.2; 24.8; 22.6; 14.1. ESI-MS: 355 ($[M + H]^+$); 377 ($[M + Na]^+$).

*(2*R*,8*Z*)-2-(Methoxymethoxy)heptadec-8-en-1-yl 2,2-Dimethylpropanoate* (**8**). To a stirred soln. of **7** (500 mg, 1.4 mmol) in anh. CH_2Cl_2 (10 ml) was added EtN^iPr_2 (728 mg, 0.97 ml, 5.6 mmol) dropwise at 0°, and stirring was continued for 15 min. Then, methoxymethyl chloride (MOMCl) (0.35 ml, 4.2 mmol) was added slowly at 0° under N_2, and the mixture was stirred at r.t. for 6 h. The reaction was quenched with ice flakes, and the mixture was extracted with CH_2Cl_2. The org. extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by CC (SiO_2) to give **8** (528 mg, 94%). Colorless oil. R_f (AcOEt/hexane, 1:9) 0.6. $[\alpha]_D^{25} = +5.74$ ($c = 0.36$, $CHCl_3$). IR (neat): 2927, 1733, 1453, 1377, 1161, 1036, 760, 537. ^{1}H-NMR ($CDCl_3$, 300 MHz): 5.34–5.22 (*m*, 2 H); 4.63 (*dd*, $J = 27.1$, 6.7, 2 H); 4.11–4.04 (*m*, 1 H); 4.00–3.93 (*m*, 1 H); 3.72–3.64 (*m*, 1 H); 3.32 (*s*, 3 H); 2.01–1.85 (*m*, 4 H); 1.58–1.15 (*m*, 20 H); 1.14 (*s*, 9 H); 0.81 (*t*, $J = 6.7$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 178.0; 130.0; 129.5; 95.9; 75.2; 66.3; 55.5; 38.7; 31.9; 31.8; 29.7; 29.6; 29.5; 2 × 29.3; 29.0; 2 × 27.1; 25.1; 22.6; 14.0. ESI-MS: 421 ($[M + Na]^+$).

*(2*R*,8*Z*)-2-(Methoxymethoxy)heptadec-8-en-1-ol* (**9**). To a stirred soln. of **8** (400 mg, 1.0 mmol) in dry CH_2Cl_2 (15 ml) in a 50-ml round-bottom two-neck flask, under N_2 at −78°, was added DIBAL-H; (2.1 ml, 25% soln. in hexane, 4.0 mmol) dropwise. After 30 min, the reaction (monitored by TLC) was quenched with MeOH (1.0 ml), and the mixture was transferred to a 250-ml separating funnel containing a sat. soln. of sodium potassium tartrate (25 ml) and CH_2Cl_2 (30 ml). The org. layer was separated and dried (Na_2SO_4). Evaporation of the solvent, followed by purification by CC (SiO_2) afforded pure **9** (277 mg, 88%). Colorless liquid. R_f (AcOEt/hexane 2:8) 0.3. $[\alpha]_D^{25} = -13.25$ ($c = 0.16$, $CHCl_3$). IR (neat): 3382, 2924, 2854, 1647, 1274, 1173, 1119. ^{1}H-NMR ($CDCl_3$, 300 MHz): 5.40–5.31 (*m*, 2 H); 4.71 (*dd*, $J = 24.9$, 6.9, 2 H); 3.64–3.47 (*m*, 3 H); 3.43 (*s*, 3 H); 2.99 (br. *s*, 1 H); 2.06–1.95 (*m*, 4 H); 1.61–1.50 (*m*, 2 H); 1.48–1.23 (*m*, 18 H); 0.88 (*t*, $J = 6.9$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 130.0; 129.5; 96.9; 82.4; 65.7; 55.6; 31.8; 31.6; 29.7; 29.69; 29.61; 29.5; 29.3; 29.2; 27.2; 27.0; 25.4; 22.6; 14.1. ESI-MS: 337 ($[M + Na]^+$).

Lanneaquinol (=*2-[(8Z)-Heptadec-8-en-1-yl]benzene-1,4-diol*; **1**). To a soln. of DMSO (1.1 ml, 15.5 mmol) in CH_2Cl_2 (15 ml) was added $(COCl)_2$ (0.73 ml, 7.6 mmol) in CH_2Cl_2 (15 ml) at $-78°$. After stirring for 20 min , a soln. of **4** (1.0 g, 3.83 mmol) in CH_2Cl_2 (10 ml) was added at the same temp. Then, the mixture was stirred for 20 min at $-78°$, and then Et_3N (4.3 ml, 31.3 mmol) was added. The mixture was warmed to r.t., and stirring was continued for 30 min. A sat. aq. NH_4Cl (5 ml) soln. was added to quench the reaction, and the mixture was extracted with CH_2Cl_2. The combined org. extracts were washed with brine, dried (Na_2SO_4), concentrated *in vacuo*, and the resulting aldehyde was purified by FC for immediate use in next reaction. The aldehyde (150 mg, 0.5 mmol) was dissolved in dry pyridine (8 ml). To this mixture, cyclohexane-1,4-dione (80 mg, 0.71 mmol) and LiCl (50 mg, 1.19 mmol) were added concurrently under N_2. The resulting mixture was refluxed for 2 h under N_2, the reaction was quenched with 2% HCl, and the mixture was extracted with AcOEt (3×10 ml). The combined org. extracts were washed with brine, dried (Na_2SO_4), concentrated *in vacuo*, and purified by CC to give **1** (100 mg, 50%). White amorphous solid. R_f (AcOEt/hexane 3:7) 0.3. IR (KBr): 3435, 2924, 2852, 1460, 1202, 1090, 722. ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.66 (*d*, *J* = 8.3, 1 H); 6.55 (*d*, *J* = 3.0, 1 H); 6.47 (*dd*, *J* = 8.3, 3.0 , 1 H); 5.33–5.26 (*m*, 2 H); 2.46 (*t*, *J* = 7.5, 2 H); 1.98–1.91 (*m*, 4 H); 1.56–1.38 (*m*, 2 H); 1.30–1.16 (*m*, 20 H); 0.80 (*t*, *J* = 6.8, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 149.3; 147.3; 130.0; 129.9; 129.7; 116.7; 115.9; 113.2; 31.8; 30.0; 29.7; 29.6; 29.5; 29.45; 29.4; 29.3; 29.2; 29.1; 29.0; 27.2; 27.1; 22.6; 14.0. ESI-MS: 346 (M^+).

*(*R*)-2′-Hydroxylanneaquinol* (=*2-[(2*R*,8*Z*)-2-Hydroxyheptadec-8-en-1-yl]benzene-1,4-diol*; **2**). A soln. of $(COCl)_2$ (80 mg, 0.06 ml, 0.6 mmol) in CH_2Cl_2 (3 ml) was added to a pre-mixed soln. of DMSO (100 mg, 0.09 ml, 1.2 mmol) and CH_2Cl_2 (3 ml) at $-78°$. After 20 min, a soln. of **9** (100 mg, 0.3 mmol) in CH_2Cl_2 (3 ml) was added at the same temp. Then, the mixture was stirred for 20 min at $-78°$, and then Et_3N (257 mg, 0.35 ml, 2.5 mmol) was added. The mixture was warmed to r.t., and stirring was continued for another 30 min at the same temp. A sat. aq. NH_4Cl (2 ml) soln. was added to quench the reaction, and the mixture was extracted with CH_2Cl_2. The combined org. extracts were washed with brine, dried (Na_2SO_4), concentrated *in vacuo*, and the resulting aldehyde was purified by FC for immediate use in the next reaction. The aldehyde (50 mg, 0.16 mmol) was dissolved in dry pyridine (6 ml). To this mixture, cyclohexane-1,4-dione (21.5 mg, 0.2 mmol) and LiCl (13.4 mg, 0.3 mmol) were added under N_2. The resulting mixture was refluxed for 2 h under N_2. After complete conversion (TLC), the mixture was transferred to a soln. of 5M HCl (3 ml) in MeOH (5 ml) and stirred for 2 h at r.t. Then, MeOH was removed *in vacuo*, and the org. compound was extracted with AcOEt (3×10 ml). The combined org. extracts were washed with brine, dried (Na_2SO_4), concentrated *in vacuo*, and purified by CC to give **2** (26 mg, 45% yield). White amorphous solid. R_f (AcOEt/hexane 4:6) 0.3. $[\alpha]_D^{27} = +0.75$ ($c = 0.8$ $CHCl_3$). IR (KBr): 3435, 2924, 2852, 1460, 1202, 1090, 722. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.72 (br. *s*, 1 H); 6.73 (*d*, *J* = 8.3 , 1 H); 6.56 (*dd*, *J* = 8.3, 2.8, 1 H); 6.50 (*d*, *J* = 2.8, 1 H); 5.33–5.26 (*m*, 2 H); 4.96 (br. *s*, 1 H); 3.93 (*m*, 1 H); 2.75 (*dd*, *J* = 14.2, 2.8, 1 H); 2.70 (*dd*, *J* = 14.2, 7.5, 1 H); 2.06–1.94 (*m*, 4 H); 1.71 (br. *s*, 1 H); 1.50–1.48 (*m*, 2 H); 1.27 (br. *s*, 17 H); 0.88 (*t*, *J* = 6.8, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 149.2; 148.9; 130.2; 129.4; 126.5; 118.0; 117.8; 114.5; 74.4; 38.6; 36.9; 31.9; 29.7; 29.5; 29.4; 29.3; 29.2; 29.0; 27.2; 27.0; 25.5; 22.6; 14.0. ESI- MS: 362 (M^+).

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