Naturally Occurring 5-Lipoxygenase Inhibitors. VII.[1] Practical Synthesis of Ardisiaquinones D, E and F

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The convergent synthesis of ardisiaquinones D (1), E (3) and F (4), isolated as 5-lipoxygenase inhibitors from *Ardisia sieboldii*, has been achieved efficiently by a cross-coupling reaction *via* an acetylene between two benzene units bearing appropriate functional groups readily derived from 2,5-dimethoxy-1,4-benzoquinone.

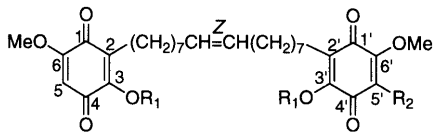
Key words *Ardisia sieboldii*; ardisiaquinones D, E, F; 1,4-benzoquinone; 1,4-benzoquinone synthesis; 5-lipoxygenase inhibitor

In the arachidonic acid cascade of prostaglandin biosynthesis, 5-lipoxygenase is a key enzyme which plays an important role in catalyzing the oxygenation of arachidonic acid specifically at C-5, the initial step in the biosynthesis of the slow-reacting substances of anaphylaxis such as leukotrienes C4, D4, and E4. A group of leukotrienes is regarded as one of the chemical mediators of bronchial asthma. Hence, from a medicinal point of view, it is significant to seek a specific inhibitor of 5-lipoxygenase in natural products.[1]

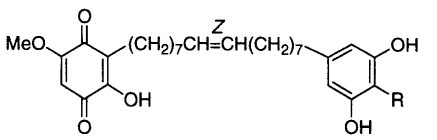
As a part of our project on naturally occurring 1,4-benzoquinones with the ability to inhibit 5-lipoxygenase,[2,3] we have been involved not only in the synthesis of maesanin,[3,4] ardisiaquinone A (**2**),[5] belamcandaquinones A and B,[6] and laurequinone,[7] but also in the evaluation of their 5-lipoxygenase inhibitory activities. Ardisiaquinones D (**1**), E (**3**) and F (**4**), isolated from *Ardisia sieboldii*, are naturally occurring 1,4-benzoquinone derivatives which exhibit respectively 44%, 28% and 29% inhibition of 5-lipoxygenase activity at 0.3 μM.[1] These simple dimeric structures with unique biological activity have prompted us to synthesize them in order to have enough material to perform *in vivo* experiments. In this paper, we report the practical synthesis of ardisiaquinones D (**1**), E (**3**) and F (**4**) which are structurally related to ardisiaquinone A (**2**),[8] a potent 5-lipoxygenase inhibitor. Their synthesis conforms to convergent procedures successfully applied to the preparation of ardisiaquinone A[5] and maesaquinone.[9]

Synthesis of Ardisiaquinone D (1) During the structural studies of ardisiaquinone D,[1] and attempts to synthesize ardisiaquinone A[5] and maesaquinone,[9] we have observed that the sterically hindered inside methoxy group on the 1,4-benzoquinone ring of ardisiaquinone A methyl ether (**2a**) can be cleanly hydrolyzed with acid, while acid treatment of ardisiaquinone D methyl ether (**1a**) gives a complex mixture. Thus, both units A-2 and B-2, which were used for the preparation of **2**, were unsuitable for the synthesis of **1**. Instead, we considered units A-1 and B-1 in order to accomplish the selective deprotection of all methoxymethyl groups on the fully substituted 1,4-benzoquinone nucleus without touching the methoxy groups at the later stage after both units are linked together *via* an acetylene. Fortunately, units A-1 and B-1 have been already prepared from 2,5-dimethoxy-1,4-benzoquinone as key intermediates for the synthesis of maesaquinone.[9]

Compound **9** corresponding to unit A-1 was prepared by displacement of the bromine in **8**[9] with sodium iodide in 98% yield. Cross-coupling of **9** with lithium acetylide *in situ* prepared at −78 °C from compound **5**[9] with lithium diisoproylamide (LDA) smoothly proceeded to give the coupling production **6** in 72% yield. Catalytic hydrogenation of the triple bond in **6** under a hydrogen atmosphere in the presence of Pd–$BaSO_4$ catalyst yielded only the *Z* olefin **7** in 92% yield. All six methoxymelthyl (MOM) groups on both the benzene rings of **7** were simultaneously removed with 48% HBr in MeOH to produce an unstable phenol, which on exposure to an oxygen atmosphere gave rise to ardisiaquinone



1: R_1 = H, R_2 = Me
1a: R_1 = R_2 = Me
2: R_1 = R_2 = H
2a: R_1 = Me, R_2 = H



3: R = H
4: R = Me

Fig. 1

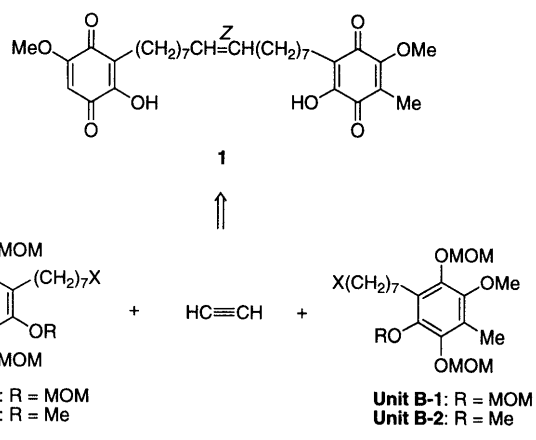


Chart 1. Synthetic Plan of Ardisiaquinone D (**1**)

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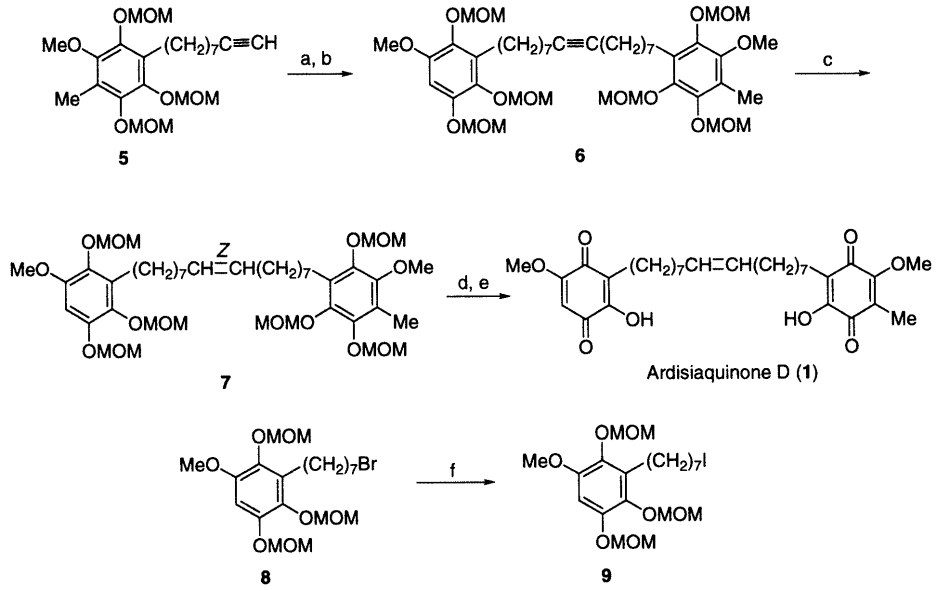
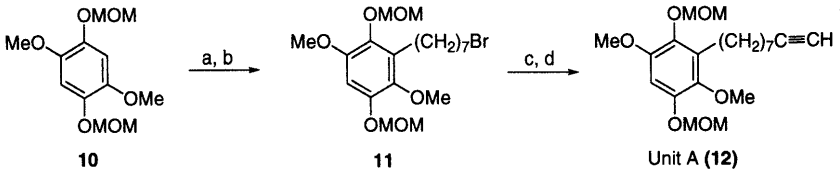


Reagents and Conditions; a) LDA, DMPU, THF, -78°C. b) **9**, THF, 72%. c) H_2, $Pd/BaSO_4$, py., 92%. d) 48%HBr, MeOH, 50°C. e) O_2, MeOH, 78%. f) NaI, acetone, reflux, 98%.

Chart 2. Synthesis of Ardisiaquinone D (**1**)



Reagents and Conditions; a) *n*-BuLi, TMEDA, toluene, -78°C. b) $Br(CH_2)_7Br$, HMPA, toluene, 73%. c) LiC≡CTMS, HMPA, THF. d) TBAF, THF, 92%.

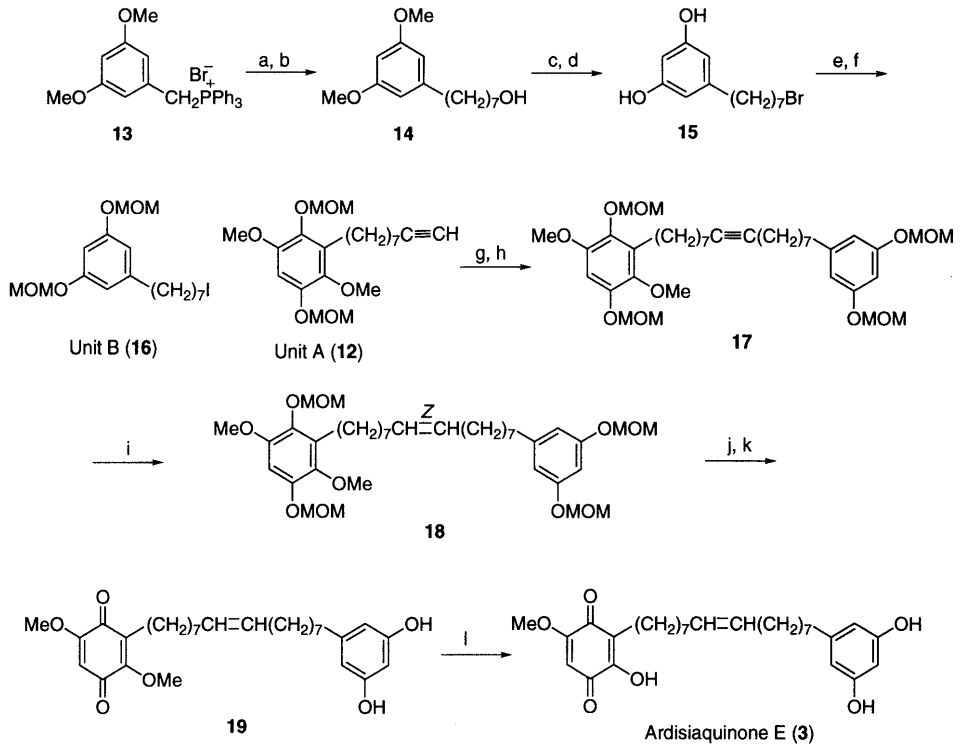
Chart 3. Synthesis of Unit A (**12**) for Ardisiaquinones E (**3**) and F (**4**)

D (**1**) in 78% yield.

Thus, we accomplished the first synthesis of ardisiaquinone D (**1**). The above practical procedure should be applicable to the preparation of the remaining ardisiaquinones E (**3**) and F (**4**)

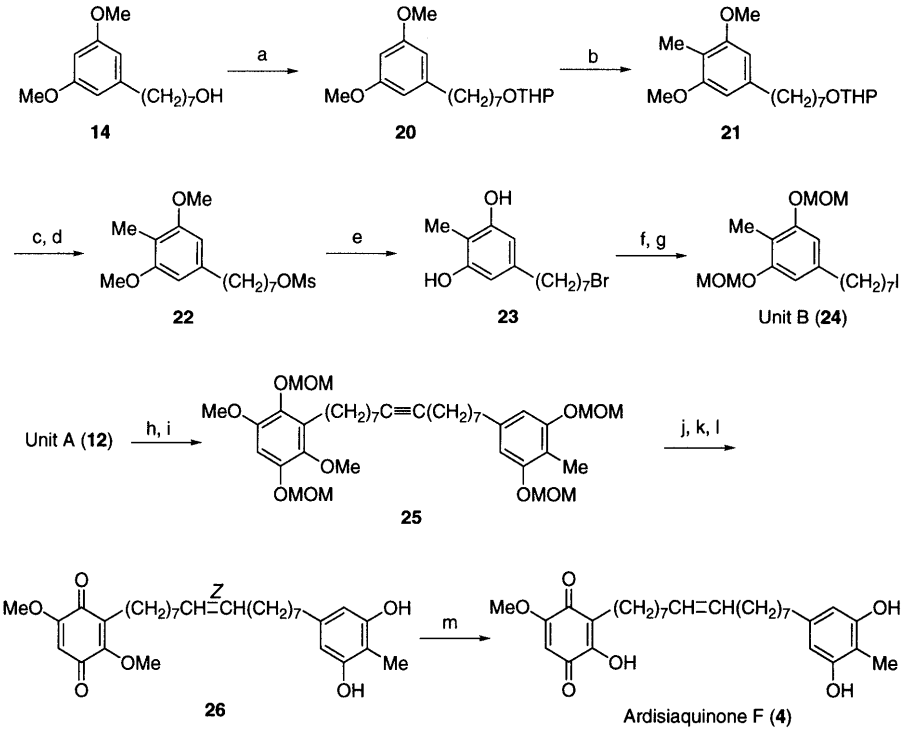
Synthesis of Ardisiaquinone E (3) 1,4-Dimethoxy-2,5-dimethoxymethyloxybenzene (**10**) was lithiated at −78 °C with *n*-BuLi in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) followed by alkylation with 1,7-dibromoheptane to give **11** in 73% yield, according to the same procedure used for the synthesis of ardisiaquinone A.[5] Unit A (**12**) was prepared in 90% yield by displacement of the bromine in **11** with lithium trimethylsilylacetylide[10] followed by desilylation with tetrabutylammonium fluoride (TBAF). In addition, unit B (**16**) was prepared according to the same method used for the syntheses of belamcandols A and B, and maesanin.[3] The phosphonium salt **13**[3,11] was converted into its ylide and then allowed to react with 6-benzyloxyhexanal followed by catalytic hydrogenation to give compound **14** in 67% yield. Mesylation and then treatment of **14** with boron tribromide afforded **15**, which was quantitatively converted to unit B (**16**) by methyloxymethylation and then displacement with NaI. Next, the cross-coupling reaction of unit B (**16**) with lithium acetylide *in situ* prepared at −78 °C from unit A **12** with LDA proceeded smoothly to give the requisite coupled product **17** in 55% yield. Catalytic hydrogenation of the triple bond in **17** under a hydrogen atmosphere in the presence of $Pd–BaSO_4$ catalyst furnished only the *Z* olefin **18** in 85% yield. Removal of all the MOM groups in **18** with 48% HBr in MeOH gave a phenol, which on exposure to an oxygen atmosphere in presence of $NaHCO_3$, gave rise to the *p*-benzoquinone **19** in 91% yield. Finally, treatment of **19** with a few drops of 70% $HClO_4$ excluded selectively the more hindered methoxy group to yield ardisiaquinone E (**3**) in 63% yield, identical in all respects to the natural one.

Synthesis of Ardisiaquinone F (4) Ardisiaquinone F (**4**) differs from **3** only in the presence of a methyl group on the right hand resorcinol part. Introduction of the extra methyl group on the resorcinol ring of compound **20**, which was derived from **14**, was readily accomplished by direct lithiation with *n*-BuLi followed by the addition of MeI in 94% yield. Removal of the tetrahydropyranyl (THP) ether of **21** produced an alcohol, which was converted to the mesylate **22** in 74% yield. Treatment of **22** with boron tribromide caused not only demethylation but also displacement of the mesyl group with bromine atom giving rise to **23** in high yield, the hydroxy groups of which were again protected as MOM ethers followed by conversion of the bromide into the iodide to afford unit B (**24**) in 80% yield. The cross-coupling reaction between unit A (**12**) and unit B (**24**) was carried out under the same conditions used for the synthesis of ardisiaquinone E (**3**) to give the coupled product **25** in 56% yield. Catalytic



Reagents and Conditions; a) *n*-BuLi, THF, rt, then $BnO(CH_2)_5CHO$, THF, 79%. b) H_2, 10%Pd/C, EtOH, 85%. c) MsCl, Et_3N, CH_2Cl_2. d) BBr_3, CH_2Cl_2, -78°C → rt, 100%. e) MOMCl, *i*-Pr_2NEt, CH_2Cl_2. f) NaI, acetone, 86%. g) LDA, DMPU, THF, -78°C. h) **16**, THF, -78°C → rt, 55%. i) H_2, $Pd/BaSO_4$, py., 85%. j) 48%HBr, MeOH, 50°C. k) O_2, $NaHCO_3$, MeOH, 91%. l) 70%$HClO_4$, CH_2Cl_2/THF, 63%.

Chart 4. Synthesis of Ardisiaquinone E (**3**)



Reagents and Conditions; a) DHP, Amberlist-15, CH_2Cl_2, rt, 96%. b) *n*-BuLi, TMEDA/THF, -20°C, and then MeI, THF, 94%. c) TsOH, MeOH. d) MsCl, Et_3N, CH_2Cl_2, 67%. e) BBr_3, CH_2Cl_2, -78°C → rt, 94%. f) MOMCl, *i*-Pr_2NEt, CH_2Cl_2. g) NaI, acetone, reflux, 80%. h) LDA, DMPU/THF, -78°C. i) **24**, THF, -78°C → rt, 56%. j) H_2, $Pd/BaSO_4$, py. k) 48%HBr, MeOH, 50°C. l) O_2, $NaHCO_3$, MeOH, 56%. m) 70%$HClO_4$, CH_2Cl_2/THF, 80%.

Chart 5. Synthesis of Ardisiaquinone F (**4**)

hydrogenation of the triple bond in **25** under a Pd–$BaSO_4$ catalyst and then deprotection of all the MOM groups in **25** with 48% HBr in MeOH yielded a phenol, which on exposure to air-oxidative conditions in presence of weak base, gave rise to the *p*-benzoquinone **26** in 56% yield. Finally, selective hydrolysis of the inside methyl ether on the 1,4-benzoquinone ring in **26** with acid cleanly took place to afford ardisiaquinone F (**4**) in 80% yield, identical in all respects to the natural one.

Thus, we have accomplished the first syntheses of ardisiaquinones D, E and F by using essentially the same convergent procedures developed for the synthesis of ardisiaquinone A[5] and maesaquinone.[9] Our practical synthesis described herein could also provide enough ardisiaquinones and their derivatives to perform *in vivo* pharmacological evaluations.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO 5300 FTIR spectrometer. ^{1}H-NMR spectra were taken on a Varian unity-200 or a JEOL GX-400 spectrometer. Chemical shifts are expressed in δ units (part per million downfield from Me_4Si). Mass spectra (MS) were recorded on a JEOL AX-500. Air- and moisture-sensitive reagents were transferred *via* syringe or cannula, and reactions involving these materials were carried out in oven-dried flasks under a positive pressure of argon. Silica-gel (Wako, C-300) was used for column chromatography. Analytical thin-layer chromatography (TLC) was performed with Merck precoated TLC plates (Kieselgel 60 F_{254}, 0.25 mm), and spots were visualized with ultraviolet light and 40% $CeSO_4$–H_2SO_4.

1-(3-Methoxy-2,5,6-trimethoxymethyloxy-4-methylphenyl)-16-(3-methoxy-2,5,6-trimethoxymethyloxyphenyl)hexadecan-8-yne (6) A solution of *n*-BuLi (0.25 ml, 1.6 M hexane sol., 0.35 mmol) was added to a solution of *N,N*-diisopropylamine (0.07 ml, 0.53 mmol) in THF (1 ml) at −78 °C under an argon atmosphere, and the mixture was stirred for 30 min at −78 °C. A solution of **5**[9] (150 mg, 0.35 mmol) in THF (1 ml) containing 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone [(DMPU) (0.2 ml, 1.77 mmol)] was added to the LDA solution and the mixture was stirred for 1.5 h at −78 °C. To this solution was added dropwise a solution of **9** (217 mg, 0.43 mmol) in tetrahydrofuran (THF) (1 ml). The reaction mixture was stirred for 30 min at −78 °C and then at room temperature overnight. The reaction was quenched with saturated NH_4Cl solution, and then extracted with ether. The organic layer was washed with water, saturated NaCl solution, and dried over $MgSO_4$. Evaporation of the solvent left a residue, which was chromatographed on silica-gel [hexane/EtOAc (6 : 1)] to give **6** (203 mg, 72%) as an oil. IR (film): 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.36 (20H, m), 2.12 (4H, m), 2.19 (3H, s), 2.67 (4H, m), 3.51 (3H, s), 3.59 (15H, s), 3.74 (3H, s), 3.79 (3H, s), 5.02 (4H, s), 5.03 (4H, s), 5.06 (2H, s), 5.14 (2H, s), 6.65 (1H, s). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 9.8, 14.1, 18.7, 25.2, 25.4, 28.8, 28.9, 29.1, 29.2, 29.3, 30.0, 30.1, 30.3, 55.9, 56.1, 57.28, 57.3, 57.4, 57.5, 60.0, 77.2, 80.0, 80.1, 95.8, 99.0, 99.1, 99.3, 99.8, 123.7, 128.7, 131.6. 138.8, 139.1, 144.6, 144.9, 145.1, 146.2, 147.5, 148.6. EI-MS *m/z* (rel. int.): 808 (M^+, 10), 732 (20), 656 (18), 387 (48), 580 (74), 305 (19), 283 (32), 181 (35). HR–MS Calcd for $C_{43}H_{68}O_{14}$: 808.1609. Found: 808.1618.

1-(3-Methoxy-2,5,6-trimethoxymethyloxy-4-methylphenyl)-16-(3-methoxy-2,5,6-trimethoxymetyloxyphenyl)-8-*Z*-hexadecaene (7) A suspension of **6** (110 mg, 0.13 mmol) and palladium on barium sulfate (11 mg) in pyridine (2 ml) was stirred under a hydrogen atmosphere for 36 h. After filtering the catalyst, the filtrate was concentrated *in vacuo* to leave a residue, which was chromatographed on silica-gel [hexane/EtOAc (2 : 1)] to afford **7** (101 mg, 92%) as an oil. IR (film): 1595 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.32 (20H, m), 2.00 (3H, s), 2.02 (4H, m), 2.67 (4H, m), 3.51 (3H, s), 3.59 (15H, s), 3.74 (3H, s), 3.79 (3H, s), 5.03 (4H, s), 5.06 (4H, s), 5.14 (2H, s), 5.34 (2H, t, J=4.6 Hz), 6.65 (1H, s). ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 9.9, 25.2, 25.4, 27.2, 29.29, 29.3, 29.4, 29.7, 29.8, 29.9, 30.1, 30.2, 30.3, 30.4, 56.0, 56.1, 56.2, 57.3, 57.4, 57.5, 57.6, 60.1, 95.7, 95.8, 99.07, 99.1, 99.3, 99.8, 123.7, 128.8, 129.77, 129.8, 131.7, 138.8, 139.2, 144.6, 144.8, 145.1, 146.2, 147.5, 148.6. EI-MS *m/z* (rel. int.): 810 (M^+, 7), 734 (13), 658 (28), 582 (100), 284 (14),. 181 (17). HR-MS Calcd for $C_{43}H_{70}O_{14}$: 810.4748. Found: 810.4748.

9-Iodo-1-(5-methoxy-2,3,6-trimethoxymethyloxyphenyl)heptane (9) A mixture of **8**[9] (350 mg, 0.75 mmol) and NaI (147 mg, 0.98 mmol) in acetone (5 ml) was refluxed for 3 h. Water was added and the mixture was extracted with ether (3 times). The combined organic layer was washed with water and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to afford **9** (376 mg, 98%) as an oil. IR (film): 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.37 (8H, m), 1.82 (2H, m), 2.72 (2H, t, J=7.9 Hz), 3.18 (2H, J=7.0 Hz), 3.51 (3H, s), 3.59 (6H, s), 3.80 (3H, s), 5.02 (2H, s), 5.03 (2H, s), 5.16 (2H, s), 6.65 (1H, s). EI-MS *m/z* (rel.int): 512 (M^+, 45), 391 (47). HR-MS Calcd for $C_{20}H_{33}IO_7$: 512.1271. Found: 512.1248.

Ardisiaquinone D (1) To a solution of **7** (40 mg, 0.05 mmol) in MeOH (2 ml) was added one drop of 48% hydrobromic acid and the mixture was stirred at 50 °C for 10 min. After removal of the solvent, the crude mixture was dissolved in MeOH (4 ml) and stirred under an oxygen atmosphere overnight. Evaporation of the solvent gave a crude mixture, which was chromatographed on silica-gel [hexane/EtOAc (9 : 1)] to yield **1** (21 mg, 78%) as an orange powder, mp 89—90 °C. IR (KBr): 3370, 1660, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.30 (16H, m), 1.44 (4H, m), 1.93 (3H, s), 2.01 (4H, m), 2.40 (2H, t, J=7.8 Hz), 2.44 (2H, t, J=7.7 Hz), 3.86 (3H, s), 4.09 (3H, s), 5.33 (2H, J=4.8 Hz), 5.84 (1H, s). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 8.0, 22.5, 27.2, 28.0, 28.2, 28.6, 28.7, 28.9, 29.1, 29.2, 29.5, 29.6, 29.7, 56.7, 61.5, 102.1, 118.7, 119.2, 122.7, 129.8, 150.7, 151.5, 157.1, 161.0, 181.7, 182.8, 183.6, 184.1. EI-MS *m/z* (rel. int.): 542 (M^+, 100), 514 (18), 183 (43), 169 (36), 168 (33). HR-MS Calcd for $C_{31}H_{42}O_8$: 542.2879. Found: 542.2879.

7-Bromo-1-(2,5-dimethoxy-3,6-dimethoxymethyloxyphenyl)heptane (11) To a solution of **10** (200 mg, 0.77 mmol) and TMEDA (0.08 ml, 0.9 mmol) in toluene (1 ml) was added dropwise *n*-BuLi (0.58 ml, 1.6 M hexane sol., 0.93 mmol) at −78 °C under an argon atmosphere. After being stirred for 1 h at −78 °C, a solution of 1,7-dibromoheptane (0.16 ml, 0.93 mmol) and hexamethylphosphoramide (HMPA) (0.16 ml, 0.93 mmol) in toluene (1 ml) was added. The mixture was stirred for 30 min and then at room temperature for 2 h. The reaction was terminated by the addition of saturated NH_4Cl solution and the mixture was extracted with ether (3 times). The combined organic layer was washed with water and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica-gel [hexane/EtOAc (15 : 1)] to afford **11** (237 mg, 73%) as an oil. IR (film): 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.38 (10H, m), 2.66 (2H, dd, J=6.4, 6.4 Hz), 3.40 (2H, t, J=6.9 Hz), 3.53 (3H, s), 3.58 (3H, s), 3.78 (6H, s), 5.02 (2H, s), 5.18 (2H, s), 6.65 (1H, s). EI-MS *m/z* (rel.int): 436 (M^+, 25), 434 (M^+, 25), 389 (12), 361 (9). HR-MS Calcd for $C_{19}H_{31}{}^{79}BrO_6$: 434.1304. Found: 434.1319.

9-(2,5-Dimethoxy-3,6-dimethoxymethyloxyphenyl)nonana-1-yne (12) To a solution of trimethylsilylacetylene (0.2 ml, 1.4 mmol) and HMPA (0.24 ml, 1.4 mmol) in THF (1 ml) was added dropwise *n*-BuLi (0.65 ml, 1.6 M hexane sol., 1.38 mmol) at −78 °C under an argon atmosphere. After being stirred for 1h at −78 °C, a solution of **11** (300 mg, 0.69 mmol) in THF (1 ml) was added and the mixture was stirred for 30 min and then at room temperature for 4 h. Saturated NH_4Cl solution was added and the mixture was extracted with ether (4 times). The combined organic layer was washed with water and saturated NaCl solution, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica-gel [hexane/EtOAc (5 : 1)] to afford the trimethylsilylacetylene (287 mg, 92%) as an oil. IR (film): 2713, 1643, 1597 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.14 (9H, s), 1.39 (10H, m), 2.20 (2H, t, J=7.2 Hz), 2.67 (2H, t, J=7.7 Hz), 3.53 (3H, s), 3.58 (3H, s), 3.79 (3H, s), 5.02 (2H, s), 5.17 (2H, s), 6.64 (1H, s). EI-MS *m/z* (rel. int.): 452 (M^+, 75), 420 (17), 376 (46), 73 (46). HR-MS Calcd for $C_{24}H_{40}O_6Si$: 452.2632. Found: 452.2613. To a stirred solution of this trimethylsilylacetylene (77 mg, 0.17 mmol) in THF (2 ml) was added 1.0 M THF solution of TBAF (0.34 ml, 0.34 mmol) at room temperature, and stirring was continued for 1h under an argon atmosphere. The reaction mixture was extracted with ether, washed with water, saturated NaCl solution, and dried over $MgSO_4$. Evaporation of the solvent afforded unit A (**12**) (64 mg, 98%) as an oil. IR (film): 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.37 (10H, m), 1.93 (1H, t, J=2.6 Hz), 2.17 (2H, td, J=6.8, 2.6 Hz), 2.67 (2H, dd, J=7.4, 7.4 Hz), 3.53 (3H, s), 3.58 (3H, s), 3.79 (6H, s), 5.02 (2H, s), 5.17 (2H, s), 6.64 (1H, s). EI-MS *m/z* (rel. int.): 380 (M^+, 38), 354 (9), 181 (14). HR-MS Calcd for $C_{21}H_{32}O_6$: 380.2237. Found: 380.2218.

7-(3,5-Dimethoxyphenyl)-1-heptanol (14) To a solution of 3,5-dimethoxybenzyltriphenylphosphonium bromide (**13**)[11] (1 g, 1.81 mmol) in THF (50 ml) was added dropwise *n*-BuLi (1.13 ml, 1.6 M hexane sol., 1.81 mmol) at room temperature under argon. After being stirred for 15 min, a solution of 6-benzyloxyhexanal (307 mg, 1.5 mmol) in THF (5 ml) was

added dropwise and the reaction mixture was stirred for another 3 h. Ice water was added and the mixture was extracted with ether. The organic layer was washed with water and with sat. NaCl sol., dried over $MgSO_4$, and concentrated *in vacuo* to give a crude product, which was purified by chromatography on silica-gel [hexane/EtOAc (4 : 1)] to afford the coupled product (488 mg, 79%) as an oil. This coupled product (480 mg) was dissolved in EtOH (20 ml) and hydrogenated over 10% Pd–C (50 mg) under normal hydrogen pressure for 24 h. After filtering off the catalyst, the filtrate was concentrated *in vacuo* to give **14** (367 mg, 85%) as an oil. IR (film): 3358, 1597 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.35 (6H, m), 1.57 (4H, m), 2.55 (2H, dd, J=7.7, 7.6 Hz), 3.64 (2H, t, J=6.5 Hz), 3.80 (6H, s), 6.30 (1H, t, J=2.0 Hz), 6.35 (2H, d, J=2.3 Hz). EI-MS *m/z* (rel. int.): 252 (M^+, 15), 165 (24), 152 (100). HR-MS Calcd for $C_{15}H_{24}O_3$: 252.1725. Found: 252.1720.

1-Bromo-7-(3,5-dihydroxyphenyl)heptane (15) A mixture of **14** (1 g, 3.97 mmol), triethylamine (0.66 ml, 4.76 mmol) and methanesulfonyl chloride (0.38 ml, 4.76 mmol) in methylene chloride (5 ml) was stirred at 0 °C for 15 min. Ice water was added and the mixture was extracted with ether. The organic layer was washed with water and with sat. NaCl sol., dried over $MgSO_4$, and concentrated *in vacuo* to give a crude mesylate (1.41 g), which was dissolved in methylene chloride (5 ml) and then cooled to −78 °C. To this solution was added a 1.0 M CH_2Cl_2 solution of boron tribromide (9.5 ml, 9.5 mmol). After being stirred at −78 °C and then at room temperature for 2 h, ice water was added and the mixture was extracted with EtOAc. The organic layer was washed with water and with sat. NaCl sol., dried over $MgSO_4$, and concentrated *in vacuo* to give a crude product (1.41 g), which was chromatographed on silica-gel [hexane–EtOAc (2 : 1)] to afford **15** (1.29 g, 100%) as an oil. IR (film): 1601 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.34 (8H, m), 1.85 (2H, m), 2.49 (2H, dd, J=7.6, 7.6 Hz), 3.41 (2H, t, J=6.8 Hz), 5.05 (2H, s, OH), 6.18 (1H, t, J=2.2 Hz), 6.24 (2H, d, J=2.2 Hz). EI-MS *m/z* (rel. int.): 288 (M^+, 12), 286 (M^+, 12), 207 (18), 137 (14), 124 (100). HR-MS Calcd for $C_{13}H_{19}BrO_2$: 286.0596. Found: 286.0582.

1-Iodo-7-(3,5-dimethoxymethyloxyphenyl)heptane (16) A mixture of **15** (1.23 g, 4.3 mmol), *N,N*-diisopropylamine (3 ml, 17 mmol), chloromethyl methyl ether (1.3 ml, 17 mmol) in methylene chloride (5 ml) was stirred at room temperature for 48 h. Water was added and the mixture was extracted with ether. The combined organic layers were washed with water and with sat. NaCl sol., dried over $MgSO_4$, and concentrated *in vacuo* to give a crude product (1.41 g), which was chromatographed on silica-gel [hexane/EtOAc (2 : 1)] to afford the bis(methoxymethyl)ether product (1.23 g, 87%) as an oil. IR (film): 1595 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.34 (8H, m), 1.60 (2H, m), 2.54 (2H, dd, J=7.7, 7.7 Hz), 3.48 (6H, s), 3.53 (2H, t, J=6.8 Hz), 5.15 (4H, s), 6.53 (2H, d, J=2.0 Hz), 6.57 (1H, J=2.0 Hz). EI-MS *m/z* (rel. int.): 332 (M^+, 26), 330 (M^+, 26), 212 (30), 182 (8). HR-MS Calcd for $C_{17}H_{27}BrO_4$: 330.1597. Found:330.1575. This bisMOM product (1.23 g, 3.7 mmol) was dissolved in acetone (10 ml) and NaI (640 mg, 4.4 mmol) was added. The mixture was refluxed for 48 h. After removal of the solvent, water was added and the mixture was extracted with ether, washed with water, saturated NaCl solution, and dried over $MgSO_4$. Evaporation of the solvent afforded unit B (**16**) (1.5 g, 98%) as an oil. IR (film): 1595 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.34 (8H, m), 1.85 (2H, m), 2.54 (2H, dd, J=7.6, 7.6 Hz), 3.19 (2H, t, J=7.0 Hz), 3.58 (6H, s), 5.15 (4H, s), 6.53 (2H, d, J=2.2 Hz), 6.57 (1H, t, J=2.2 Hz). EI-MS *m/z* (rel. int.): 422 (M^+, 55), 295 (12), 231 (16). HR-MS Calcd for $C_{17}H_{27}IO_4$: 422.0954. Found: 422.0955.

1-(2,5-Dimethoxy-3,6-dimethoxymethyloxyphenyl)-16-(3,5-dimethoxymethyloxy- phenyl)hexadeca-8-yne (17) A solution of *n*-BuLi (0.2 ml, 1.6 M hexane sol., 0.32 mmol) was added to a solution of *N,N*-diisopropylamine (0.06 ml, 0.4 mmol) in THF (1 ml) at −78 °C under an argon atmosphere, and the mixture was stirred for 30 min at −78 °C. A solution of unit A (**12**) (100 mg, 0.26 mmol) in THF (1 ml) containing DMPU (0.16 ml) was added to the LDA solution and the mixture was stirred for 2 h at −78 °C. To this solution was added dropwise a solution of unit B (**16**) (133 mg, 0.32 mmol) in THF (1 ml). The reaction mixture was stirred for 30 min at −78 °C and then at room temperature overnight. The reaction was quenched with saturated NH_4Cl solution, and then extracted with ether. The organic layer was washed with water, saturated NaCl solution, and dried over $MgSO_4$. Evaporation of the solvent left the residue, which was chromatographed on silica-gel [hexane/EtOAc (4 : 1)] to give **17** (96 mg, 55%) as an oil. IR (film): 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.33 (20H, m), 2.13 (4H, t, J=6.7 Hz), 2.53 (2H, dd, J=7.4, 7.4 Hz), 2.66 (2H, dd, J=7.3, 7.3 Hz), 3.47 (3H, s), 3.53 (3H, s), 3.58 (3H, s), 3.79 (6H, s), 5.02 (2H, s), 5.14 (4H, s), 5.17 (2H, s), 6.53 (2H, d, J=2.0 Hz), 6.56 (1H, t, J=2.0 Hz), 6.64 (1H, s). EI-MS *m/z* (rel. int.): 674 (M^+, 5), 642 (14), 533 (29), 183 (22). HR-MS Calcd for $C_{38}H_{58}O_{10}$: 674.4030. Found: 674.4057.

1-(2,5-Dimethoxy-3,6-dimethoxymethyloxyphenyl)-16-(3,5-dimethoxymethyloxy- phenyl)-8-Z-hexadecene (18) A suspension of **17** (130 mg) and palladium on barium sulfate (13 mg) in pyridine (2 ml) was stirred under a hydrogen atmosphere for 36 h. After filtering off the catalyst, the filtrate was concentrated *in vacuo* to leave the residue, which was chromatographed on silica-gel [hexane/EtOAc (2 : 1)] to afford **18** (110 mg, 85%) as an oil. IR (film) 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.31 (20H, m), 2.54 (4H, m), 2.67 (2H, m), 3.48 (6H, s), 3.53 (3H, s), 3.59 (3H, s), 3.79 (6H, s), 5.02 (2H, s), 5.15 (4H, s), 5.18 (2H, s), 5.34 (2H, t, J=4.6 Hz), 6.55 (2H, d, J=2.4 Hz), 6.56 (1H, t, J=2.4 Hz), 6.64 (1H, s). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 25.1, 27.27, 27.3, 29.1, 29.3, 29.35, 29.39, 29.4, 29.5, 29.6, 29.8, 29.9, 30.2, 30.5, 31.3, 56.0, 56.3, 57.4, 61.0, 94.5, 95.9, 99.2, 100.2, 102.1, 109.8, 110.0, 129.8, 123.0, 131.5, 139.3, 141.9, 154.6, 146.7, 148.5, 158.2. EI-MS *m/z* (rel. int.): 676 (M^+, 20), 644 (25), 600 (17), 536 (26), 491 (13), 183 (13). HR-MS Calcd for $C_{38}H_{60}O_{10}$: 676.4187. Found: 676.4171.

1-(3,6-Dimethoxy-1,4-benzoquinon-2-yl)-16-(3,5-dihydroxyphenyl)-8-Z-hexadecene (19) To a solution of **18** (100 mg) in MeOH (3 ml) was added one drop of 48% hydrobromic acid and the mixture was stirred at 50 °C for 30 min. After removal of the solvent, the crude mixture was dissolved in MeOH (4 ml) and $NaHCO_3$ (5 mg) was added. The mixture was stirred under an oxygen atmosphere for 10 min. Evaporation of the solvent gave a crude mixture, which was chromatographed on silica-gel [hexane/EtOAc (1 : 1)] to yield **19** (80 mg, 91%) as an orange oil. IR (film) 3379, 1649, 1599 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.30 (16H, m), 1.59 (4H, m), 1.99 (4H, m), 2.44 (4H, m), 3.80 (3H, s), 4.06 (3H, s), 5.34 (2H, t, J=4.7 Hz), 5.74 (1H, s), 6.23 (1H, t, J=1.9 Hz), 6.25 (2H, d, J=1.9 Hz). EI-MS *m/z* (rel. int.): 498 (M^+, 82), 163 (23), 123 (35). HR EI-MS Calcd for $C_{30}H_{42}O_6$: 498.2982. Found: 498.2971.

Ardisiaquinone E (3) To a solution of **19** (75 mg, 0.15 mmol) in THF and methylene chloride (5 : 1, 3.0 ml) was added three drops of 70% perchloric acid, and the mixture was stirred at room temperature for 15 h. The reaction mixture was diluted with EtOAc and washed with water, saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by column chromatography on silica-gel, eluting with hexane–EtOAc (3 : 2) to afford ardisiaquinone E (**1**) (25.3 mg, 63%) as a yellow oil. IR (film): 3390, 1643, 1609 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.29 (16H, m), 2.19 (4H, m), 2.44 (2H, dd, J=7.6, 7.6 Hz), 2.47 (2H, dd, J=7.8, 7.8 Hz), 3.84 (3H, s), 5.34 (2H, t, J=5.4 Hz), 5.83 (1H, s), 6.20 (1H, t, J=2.2 Hz), 6.25 (2H, d, J=2.2 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 22.6, 27.06, 27.14, 28.0, 29.06, 29.14, 29.3, 29.47, 29.6, 29.7, 31.0, 35.8, 56.8, 100.2, 102.2, 108.0, 119.3, 129.9, 130.0, 146.0, 1151.7, 156.7, 161.1, 182.0, 182.9. EI-MS *m/z* (rel. int.): 484 (M^+, 100), 168 (38). HR–MS Calcd for $C_{29}H_{40}O_6$: 484.2882. Found: 484.2853.

1,3-Dimethoxy-5-[7-(2-tetrahydroxypyranyloxy)heptyl]benzene (20) A mixture of **14** (1.5 g, 5.9 mmol), 3,4-dihydropyrane (516 mg, 7.1 mmol) and Amberlist-15 (10 mg) in methylene chloride (5 ml) was stirred at room temperature for 3 h. After filtering off Amberlist-15, removal of the solvent gave the residue, which was chromatographed on silica-gel [hexane/EtOAc (4 : 1)] to yield **20** (1.92 g, 96%) as an oil. IR (film): 1597 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.34 (4H, m), 1.60 (8H, m), 2.54 (2H, dd, J=7.6, 7.6 Hz), 3.53—3.32 (2H, m), 3.78 (6H, s), 3.87—3.67 (6H, m), 4.57 (1H, m), 6.30 (1H, t, J=2.3 Hz), 6.34 (2H, d, J=2.3 Hz). EI-MS *m/z* (rel. int.): 336 (M^+, 7), 252 (16), 165 (26), 152 (100). HR-MS Calcd for $C_{20}H_{32}O_4$: 336.2301. Found: 336.2322.

1,3-Dimethoxy-2-methyl-5-[7-(2-tetrahydroxypyranyloxy)heptyl]benzene (21) To a solution of **20** (1.9 g, 6.2 mmol) and TMEDA (2 ml) in THF (3 ml) was added dropwise *n*-BuLi (11.6 ml, 1.6 M hexane sol., 18.6 mmol) at −20 °C under an argon atmosphere . After stirring for 1 h at −20 °C, a solution of methyl iodide (4.5 g, 31 mmol) in THF (1 ml) was added. The mixture was stirred at room temperature for 4 h, then the reaction was terminated by the addition of saturated NH_4Cl solution and the mixture was extracted with ether (3 times). The combined organic layer was washed with water and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica-gel [hexane/EtOAc (4 : 1)] to afford **21** (2.04 g, 94%) as an oil. IR (film) 1589 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.36 (10H, m), 2.06 (3H, s), 2.57 (2H, dd, J=7.7, 7.7 Hz), 3.35—3.53 (2H, m), 3.71—3.81 (6H, m), 3.81 (6H, s), 4.57 (1H. m), 6.37 (2H, s). EI-MS *m/z* (rel. int.): 350 (M^+, 23), 266 (60), 166 (100). HR-MS Calcd for $C_{21}H_{34}O_4$: 350.2533. Found: 350.2495.

1,3-Dimethoxy-2-methyl-5-(7-methansulfonylheptyl)benzene (22) A mixture of **21** (2 g, 5.7 mmol) and *p*-toluenesulfonic acid (100 mg) in MeOH was stirred for 24 h. Water was added and the solution extracted with EtOAc. The combined organic layers were washed with water, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated

in vacuo. The residue was chromatographed on silica-gel [hexane/EtOAc (4 : 1)] to afford the alcohol (1.02 g, 67%) as an oil. This alcohol was dissolved in methylene chloride (5 ml) and cooled to 0 °C. To this solution were added triethylamine (0.63 ml, 4.5 mmol) and methanesulfonyl chloride (0.36 ml, 4.5 mmol). The mixture was stirred for 15 min, ether was added and the mixture was washed with water and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica-gel [hexane/EtOAc (4 : 1)] to afford **22** (1.3 g) as an oil. IR (film) 1608, 1587 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.37 (4H, m), 1.60 (2H, m), 1.75 (2H, m), 2.06 (3H, s), 2.57 (2H, dd, J=7.7, 7.7 Hz), 3.00 (3H, s), 3.82 (6H, s), 4.22 (2H, t, J=6.5 Hz), 6.36 (2H, s). EI-MS *m/z* (rel. int.): 344 (M^+, 35), 179 (17), 166 (100). HR-MS Calcd for $C_{17}H_{28}O_5S$: 344.1658. Found: 344.1654.

1,3-Dihydroxy-2-methyl-5-(7-bromoheptyl)benzene (23) To a solution of **22** (1.3 g) in methylene chloride (3 ml) was added a 1.0 M CH_2Cl_2 solution of boron tribromide (9 ml, 9 mmol) at −78 °C. After being stirred at −78 °C and then at room temperature for 2 h, ice water was added and the mixture was extracted with EtOAc. The organic layer was washed with water and with sat. NaCl sol., dried over $MgSO_4$, and concentrated *in vacuo* to give a crude product, which was chromatographed on silica-gel [hexane/EtOAc (2 : 1)] to afford **23** (1.1 g, 94%) as an oil. IR (film): 3408, 1628, 1591 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.30 (8H, m), 1.83 (2H, m), 2.10 (3H, s), 2.45 (2H, dd, J=7.6, 7.6 Hz), 3.40 (2H, t, J=6.8 Hz), 4.94 (2H, s, OH), 6.23 (2H, s). EI-MS *m/z* (rel. int.): 302 (M^+, 15), 300 (M^+, 15), 221(34), 151 (13), 138 (100). HR-MS Calcd for $C_{14}H_{21}BrO_2$: 300.0725. Found: 300.0725.

1,3-Dihydroxy-2-methyl-5-(7-iodoheptyl)benzene (24) A mixture of **23** (540 mg, 1.8 mmol), *N,N*-diisopropylethylamine (0.7 ml, 1.8 mmol) and chloromethyl methyl ether (0.3 ml, 3.9 mmol) in methylene chloride (6 ml) was stirred at room temperature for 48 h. Water was added and the mixture was extracted with ether. The combined organic layers were washed with water and with sat. NaCl sol., dried over $MgSO_4$, and concentrated *in vacuo* to give a crude product (1.41 g), which was chromatographed on silica-gel [hexane/EtOAc (4 : 1)] to afford the bis(methoxymethyl)ether product (529 mg, 86%) as an oil. This product (200 mg, 0.58 mmol) was dissolved in acetone (5 ml) and NaI (133 mg, 0.76 mmol) was added. The mixture was refluxed for 48 h. After removal of the solvent, water was added and the mixture was extracted with ether, washed with water, saturated NaCl solution, and dried over $MgSO_4$. Evaporation of the solvent affored unit B (**24**) (240 mg, 95%) as an oil. IR (film): 1610, 1587 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.34 (8H, m), 1.82 (2H, m), 2.12 (3H, s), 2.53 (2H, dd, J=7.3, 7.3 Hz), 3.18 (2H, t, J=7.0 Hz), 3.49 (6H, s), 5.18 (4H, s), 6.59 (2H, s). EI-MS *m/z* (rel. int.): 436 (M^+, 32), 391 (2), 344 (10). HR-MS Calcd for $C_{18}H_{29}IO_4$: 436.1110. Found: 436.1097.

1-(2,5-Dimethoxy-3,6-dimethoxymethyloxyphenyl)-16-(3,5-dimethoxymethyloxy-4-methylphenyl)hexadeca-8-yne (25) A solution of *n*-BuLi (0.2 ml, 1.6 M hexane sol., 0.32 mmol) was added to a solution of *N,N*-diisopropylamine (0.06 ml, 0.4 mmol) in THF (1 ml) at −78 °C under an argon atmosphere, and the mixture was stirred for 30 min at −78 °C. A solution of unit A (**12**) (100 mg, 0.26 mmol) in THF (1 ml) containing DMPU (0.16 ml) was added to the LDA solution and the mixture was stirred for 2 h at −78 °C. To this solution was added dropwise a solution of unit B (**24**) (133 mg, 0.32 mmol) in THF (1 ml). The reaction mixture was stirred for 30 min at −78 °C and then at room temperature overnight. The reaction was quenched with saturated NH_4Cl solution, and then extracted with ether. The organic layer was washed with water, saturated NaCl solution, and dried over $MgSO_4$. Evaporation of the solvent left the residue, which was chromatographed on silica-gel [hexane/EtOAc (4 : 1)] to give **25** (65 mg, 56%) as an oil. IR (film) 1589 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.34 (16H, m), 2.12 (3H, s), 2.13 (4H, m), 2.53 (2H, dd, J=7.5, 7.5 Hz), 2.66 (2H, dd, J=7.4, 7.4 Hz), 3.49 (6H, s), 3.53 (3H, s), 3.58 (3H, s), 3.79 (6H, s), 5.02 (2H, s), 5.17 (6H, s), 6.59 (2H, s), 6.64 (1H, s). EI-MS *m/z* (rel. int.): 688 (M^+, 10), 656 (31), 612 (24), 580 (30), 535 (37), 183 (24). HR-MS Calcd for $C_{39}H_{60}O_{10}$: 688.4186. Found: 688.4202.

1-(3,6-Dimethoxy-1,4-benzoquinon-2-yl)-16-(3,5-dihydroxy-4-methylphenyl)-8-Z-hexadecene (26) A suspension of **25** (60 mg) and palladium on barium sulfate (6 mg) in pyridine (1.5 ml) was stirred under a hydrogen atmosphere for 36 h. After filtering off the catalyst, the filtrate was concentrated *in vacuo* to leave a residue, which was chromatographed on silica-gel [hexane–EtOAc (2 : 1)] to afford a *Z*-olefin (34.6 mg), which was dissolved in MeOH (1 ml) and one drop of 48% hydrobromic acid was added. The mixture was stirred at 50 °C for 15 min. After removal of the solvent, the obtained crude mixture was dissolved in MeOH (4 ml) and $NaHCO_3$ (5 mg) was added. The mixture was stirred under an oxygen atmosphere for 20 min. Evaporation of the solvent gave a crude mixture, which was chromatographed on silica-gel [hexane/EtOAc (1 : 1)] to yield **26** (13 mg, 56%) as an orange oil. IR (film): 3420, 1647, 1595 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.29 (16H, m), 1.55 (4H, m), 1.98 (4H, m), 2.10 (3H, s), 2.44 (2H, t, J=7.3 Hz), 3.80 (3H, s), 4.05 (3H, s), 5.34 (2H, t, J=4.6 Hz), 5.73 (1H, s), 6.25 (2H, s). EI-MS *m/z* (rel. int.): 512 (M^+, 100), 177 (23), 137 (34). HR-MS Calcd for $C_{31}H_{44}O_6$: 512.3138. Found: 512.3110.

Ardisiaquinone F (4) To a solution of **26** (10 mg) in THF and methylene chloride (5 : 1, 0.5 ml) was added one drop of 70% perchloric acid, and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with EtOAc and washed with water, saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by column chromatography on silica-gel, eluting with hexane–EtOAc (3 : 2) to afford ardisiaquinone F (**4**) (6.4 mg, 80%) as a yellow powder, mp 85—87 °C. IR (film): 3373, 1645, 1606 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.29 (16H, m), 1.60 (2H, m), 1.90 (2H, m), 2.00 (4H, m), 2.10 (3H, s), 2.44 (2H, t, J=7.6 Hz), 3.85 (3H, s), 5.34 (2H, t, J=6.5 Hz), 5.83 (1H, s), 6.25 (2H, s). ^{13}C-NMR ($CDCl_3$, 100 MHz,): δ 7.7, 22.6, 27.1, 29.0, 29.1, 29.2, 29.3, 29.5, 29.6, 31.1, 35.5, 56.7, 102.1, 107.3, 119.2, 130.0, 141.9, 154.5, 161.1, 181.8, 182.7. EI-MS *m/z* (rel. int.): 498 (M^+, 70), 169 (50), 168 (78), 138 (100), 137 (97). HR-MS Calcd for $C_{30}H_{42}O_6$: 498.2981. Found: 498.2972.

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References and Notes

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