Synthesis of *dl*-Shikonin by Vanadium(II)-Assisted Cross-Coupling and Electrooxidation of Aromatic Nuclei

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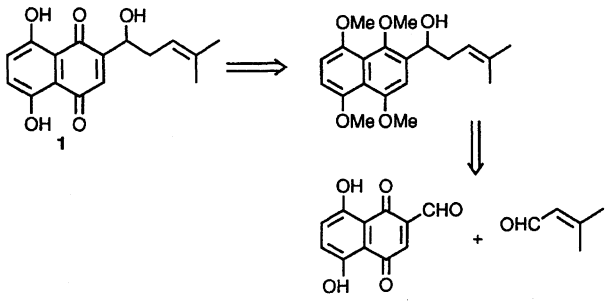
Vanadium(II)-assisted cross-coupling of 1,4,5,8-tetramethoxynaphthalene-2-carbaldehyde and 3-methyl-2-butenal was employed for introduction of the side chain of *dl*-shikonin. 2-(1-Hydroxy-4-methyl-3-pentenyl)-1,4,5,8-tetramethoxynaphthalene was prepared by the pinacol coupling and the subsequent palladium-catalyzed hydrogenolysis of the carbon–oxygen bond at the allylic position of the diol carbonate. Electrochemical oxidation of the 2-substituted 1,4,5,8-tetramethoxynaphthalene, followed by reductive acetylation with zinc and the subsequent electrooxidation of the resulting 5,8-diacetoxy-1,4-dimethoxynaphthalene, afforded the corresponding 5,8-diacetoxy-1,4-naphthoquinone, whose alkaline hydrolysis furnished *dl*-shikonin.

Shikonin derived from the root of *Lithospermum erythorhizon Sieb. et Zucc* has been used as a purple pigment.[1] The naturally occurring shikonin and its homologues bear considerable promise as drugs because of their antiinflammatory,[2] antibacterial,[3] and antitumor activities.[4] Such practical importance renders this naphthoquinone derivatives an attractive target for synthetic chemists. The total synthesis of *dl*-shikonin has been attained by the coupling reaction of 2-naphthalenecarbaldehyde derivatives with Grignard reagents.[5]

Our synthetic strategy of *dl*-shikonin (shikalkin) **1** involves two principal steps which concern the construction of the side-chain, 1-hydroxy-4-methyl-3-pentenyl moiety, attached to the 1,4-naphthoquinone ring and with the building of the 5,8-dihydroxy-1,4-naphthoquinone skeleton, as shown in Scheme 1. Accordingly, the synthetic approaches for introducing the homoallyl alcohol group onto an aromatic nuclei while avoiding undesired electrophilic cyclization of the side chain[6] and for constructing the 5,8-dihydroxy-1,4-naphthoquinone moiety become key operations in our synthetic efforts.

We now report the synthesis of *dl*-shikonin by reductive coupling of aromatic aldehyde with alkenal for the introduction of the side chain; then follows demethylation of 5,8-dimethoxy groups on naphthalene ring through (1) regioselective electrooxidation, (2) reductive acetylation, and again (3) electrooxidation completed by hydrolysis. We could perform an intermolecular pinacol cross-coupling reaction by the aid of vanadium(II) reagent, $[V_2Cl_3(THF)_6]_2$.[7] Efficiency of the V(II) reagent has been demonstrated by high diastereoselectivity of the chelation-controlled pinacol cross-coupling.[8]

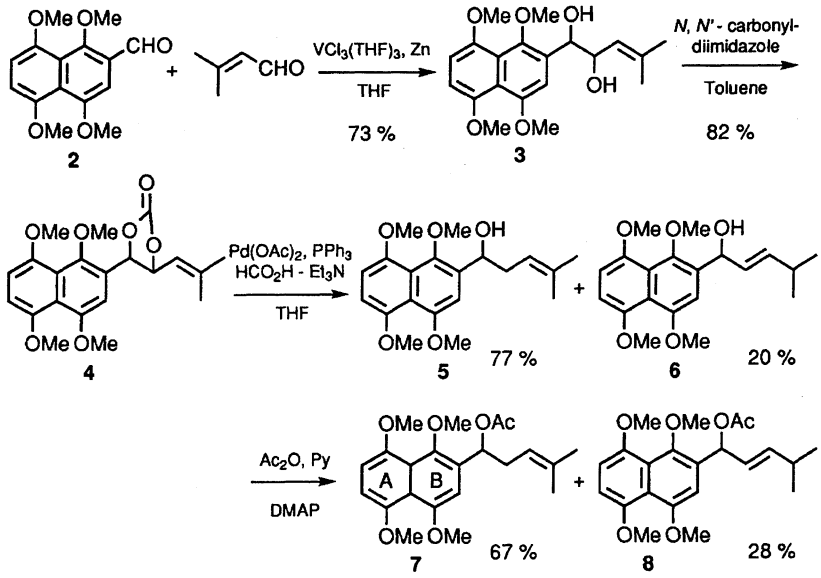


Scheme 1.

Results and Discussion

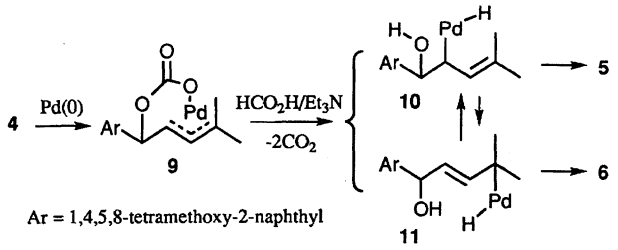
The side chain elongation of the 1,4,5,8-tetramethoxynaphthalene-2-carbaldehyde **2**, derived by bromination of 1,5-dimethoxynaphthalene,[9] subsequent methoxylation[10] and formylation,[11] was achieved by the V(II)-promoted cross-coupling with 3-methyl-2-butenal (Scheme 2). Thus, the reaction of the aldehyde **2** with 3-methyl-2-butenal in THF in the presence of $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ generated in situ from $VCl_3(THF)_3$ and zinc dust gave the cross-coupled product **3** in 73% yield, together with homo-coupling pinacol-type diols of **2** (*syn*/*anti*=5.5/1, 8% combined yield based on **2**). Use of an excess of the alkenal (**2**: Alkenal=1 : 5) tends preferentially to afford the desired cross-coupling product **3**.[12] The separation of the cross-coupling product from the homo-coupling product was achieved by column chromatography. The hetero/homo ratio was greatly affected by the choice of solvent; 73% yield of the cross-coupling product was obtained by using THF as a solvent, in contrast to the result in dichloromethane.[13]

Selective allylic deoxygenation must be the choice



Scheme 2.

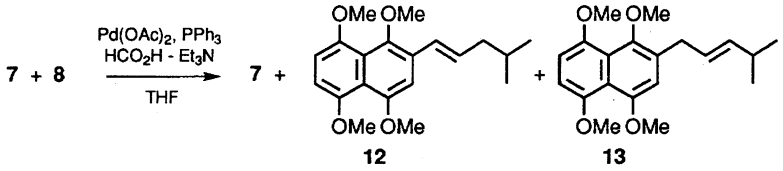
for the formation of a homoallyl alcohol moiety of the side-chain. First, we converted the diol into the corresponding carbonate **4** in order to cleave one of the carbon–oxygen bonds to hydroxy groups.[14] The treatment of **3** with *N*,*N*′-carbonyldiimidazole gave 2-(1,2-carbonyldioxy-4-methyl-3-pentenyl)-1,4,5,8-tetramethoxynaphthalene **4** in 82% yield. The construction of the homoallylic side chain was performed by the palladium-catalyzed carbon–oxygen bond cleavage reaction at the allylic position of **4**.[15] Preliminary experiments on reductive removal of an acetoxy group of the diacetate derived from the diol **3** with $Pd(OAc)_2$–HCO_2H/Et_3N failed, so only the unchanged diacetate was recovered. To our delight, the cleavage of the carbon–oxygen bond of the carbonate **4** with $Pd(OAc)_2$–HCO_2H/Et_3N proceeded[16] smoothly at the allylic position to give the desired homoallyl alcohol **5**, together with the double bond migration product **6**. Thus, the carbonate **4** was treated with an excess of triethylamine and formic acid in the presence of $Pd(OAc)_2$ and triphenylphosphine in THF, affording a mixture of **5** and **6** (97%, **5**:**6**=79:21 ratio). The reductive cleavage of the carbon–oxygen bond at the allylic position of **4** proceeded in a regiospecific manner. Predominant formation of the homoallyl alcohol **5** rather than the allylic alcohol **6** may be explained by assuming an intramolecular palladium–oxygen interaction[17] at the benzylic hydroxy group. This would preferentially form a π-allylpalladium complex **10** as an intermediate via an initial complex **9** (Scheme 3). The other intermediate **11** would produce the isomer **6**.



Scheme 3.

Next, we devised a separation method for the mixture of **5** and **6** because of difficulties in obtaining **5** by a routine column chromatography. The tactics involve a set of operations which deal with 1) acetoxylation of the mixed alcohols and 2) removal of the acetoxy group at the allylic position of **6** by Pd-catalyzed reduction. Acetylation of the mixture of **5** and **6** with acetic anhydride, DMAP, and pyridine in dichloromethane gave a mixture of 2-(1-acetoxy-4-methyl-3-pentenyl)-1,4,5,8-tetramethoxynaphthalene **7** and its isomer **8** (95%, **7**:**8**=71:29 ratio). The mixed acetates **7** and **8** were treated with a $Pd(OAc)_2$–HCO_2H/Et_3N system in THF. Under the above conditions, only the acetate **8** could undergo the reduction to give the deacetoxylated **12** and a trace amount of the isomer **13** (Scheme 4). As a result, the desired acetate **7** was obtained in 67% yield.

The electrooxidation of di- and trimethoxylated naphthalenes at 1,2-, 1,4-, 1,5-, and 1,4,5-positions[18] has been well documented. The half-oxidation potential of 1,4,5,8-tetramethoxynaphthalene (TMNA) has been shown to be $E_{1/2}$ (MeCN) 1.33 V vs. SCE.[19] Cyclic voltammograms of the alcohol **5** and the acetate **7** displayed oxidation peaks at 0.84, 0.96, and 1.52 V and at 0.84, 1.00, and 1.63 V vs. Ag/Ag^+ in MeCN. Two sets of very close peaks at 0.84 and 0.96 and at 0.84 and 1.00 V are assigned to the oxidation potentials of either the A or the B ring of substituted naphthalenes. In particular, the regioselective electrooxidation of 2-substituted TMNA needed to be clarified. First, we investigated the electrooxidation of **7** in acetonitrile while varying the water content in $LiClO_4$–(Pt/Pt) or $LiClO_4$–/(C/C) system. The electrooxidation of the acetate **7** in an $MeCN/H_2O(9:1)$–$LiClO_4$–(Pt/Pt) system



Scheme 4.

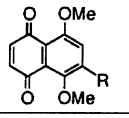
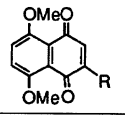
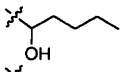
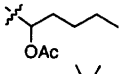
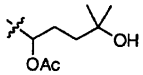
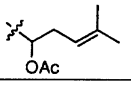
in an undivided cell afforded the corresponding naphthoquinones **14** and **15** in 74 and 23% yields as shown in Scheme 5 (see Table 1). The results reveal a regioselective electrooxidation occurring at the A ring of the acetate **7**. A variety of 2-substituted 1,4,5,8-tetramethoxynaphthalenes was subjected to electrooxidation, the results are listed in Table 2. In every case, competitive electrooxidation proceeded in both A and B rings, and the corresponding quinones preferentially formed in the less substituted ring of naphthalene. In contrast to the above results, chemical oxidation of the acetate **7** with CAN in $MeCN/H_2O$ (5/1) afforded a mixture of **14** (31%) and **15** (41%), indicating that the B ring of the acetate **7** can be more easily oxidized under the employed conditions. These results reveal that the regioselectivity of oxidation of either the A or the B ring could not be improved by electrochemical and chemical oxidation owing to their small difference of oxidation potentials.

Table 1. Electrooxidation of 2-(1-Acetoxy-5-methyl-3-pentenyl)-1,4,5,8-tetramethoxynaphthalene **7**[a)]

Run	Electrolyte	Electrode	Solvent	Applied voltage/V	Yield/% **14**	**15**
1	$LiClO_4$	(Pt)–(Pt)	$MeCN–H_2O$ (1 : 1)	2	45	13
2	$LiClO_4$	(Pt)–(Pt)	$MeCN–H_2O$ (9 : 1)	2	74	23
3	$LiClO_4$	(C)–(C)	$MeCN–H_2O$ (9 : 1)	2	36	8
4	$LiClO_4$	(Pt)–(Pt)	$MeCN–H_2O$ (15 : 1)	2	65	25
5	$LiClO_4$	(Pt)–(Pt)	MeCN	3	55	5

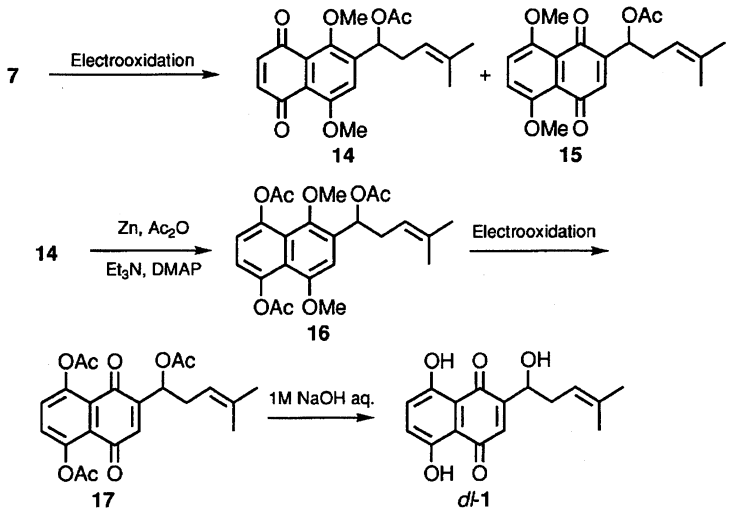
a) Carried out in an undivided cell.

Table 2. Electrooxidation of 2-Substituted 1,4,5,8-Tetramethoxynaphthalenes

Run[a)]	R	Yield/% 	
1	H		86
2		42	23
3		62	Trace
4[b)]		84	12
5		74	23

a) Conditions: $CH_3CN/H_2O–LiClO_4–(Pt)/(Pt)$, 3 V constant voltage electrolysis undivided cell, room temperature. b) CH_3CN/H_2O (buffered at pH 7.0) was used.

The structure of isomers **14** and **15** were determined based on the ^1H NMR spectra after separation by column chromatography.[20)] The signals of quinonoid ring protons are usually observed at higher field than those of benzenoid ring protons. The final task before reach-



Scheme 5.

ing our synthetic goal is to build up the quinone moiety of shikonin. The strategy involves the following steps: 1) initial electrooxidation of the A ring of **7**, 2) protection of 1,4-dihydroquinone intermediate by reductive acetoxylation, and 3) electrooxidation of the B ring, leading to the desired quinone skeleton.

First, we attempted the conversion of **14** to the corresponding acetate **16** and the subsequent electrooxidation of **16** in order to transfer the quinone moiety into the B ring in the naphthalene nuclei of **14**. Thus, the reductive acetylation of **14** with Zn in Ac_2O and Et_3N gave 2-(1-acetoxy-4-methyl-3-pentenyl)-5,8-diacetoxy-1,4-dimethoxynaphthalene **16** in 81% yield. The electrooxidation of the 5,8-diacetoxy-1,4-dimethoxynaphthalene skeleton was favored at the dimethoxylated aromatic ring rather than at the diacetoxylated one, and gave the corresponding 5,8-diacetoxy-1,4-naphthoquinone **17** in 43% yield. The compound **17** was hydrolyzed in aqueous 1 M sodium hydroxide (1 M=1 mol dm^{-3}) and neutralization with acetic acid gave *dl*-shikonin **1** in 72% yield.

Experimental

^{1}H NMR spectra were taken in $CDCl_3$ ($CHCl_3$ as an internal standard) on Varian VXR-200 (200 MHz) spectrometer. Chemical shifts were reported in δ values. ^{13}C NMR spectra were taken by Varian VXR-200 (50 MHz) spectrometer, in which chemical shifts were reported in δ values. IR spectra were recorded on a JASCO FT-5000 spectrometer. Column chromatography was carried out by using a Merck Kieselgel 60 (silica gel) with hexane–AcOEt as an eluent. The melting point was determined with a Yanaco micromelting point apparatus.

2-(1,2-Dihydroxy-4-methyl-3-pentenyl)-1,4,5,8-tetramethoxynaphthalene (3): To a solution of $VCl_3(THF)_3$ (3.74 g, 10 mmol) in THF (5 ml) was added zinc powder (0.65 g, 10 mmol) under argon atmosphere, and the mixture was stirred for 5 min. Upon cooling in an ice water bath, to this solution was added a mixture of 1,4,5,8-tetramethoxynaphthalene-2-carbaldehyde **2** (0.50 g, 1.8 mmol) and 3-methyl-2-butenal (0.76 g, 9.0 mmol) in THF (10 ml), and then the mixture was stirred for 3 h. The reaction was quenched with aqueous 5% tartaric acid and the mixture was extracted with AcOEt. The organic layers were washed with aqueous saturated $NaHCO_3$ and then with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography to give 480 mg (73%) of **3** as an unisolable mixture of *erythro*- and *threo*-isomers (5.5:1). **3** (major isomer). ^{1}H NMR δ=1.45 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.60 (broad, 2H, OH), 3.75 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.91 (s, 6H, OCH_3), 4.60 (dd, J=8.2, 8.0 Hz, 1H, C<u>H</u>(OH)), 5.03 (d, J=7.2 Hz, 1H, Ar-C<u>H</u>(OH)), 5.26 (d, J=8.9 Hz, 1H, HC=C), 6.82 (s, 2H, Ar-H), 6.91 (s, 1H, Ar-H). ^{13}C NMR δ=18.2, 25.6, 56.9, 57.0, 57.5, 62.7, 71.7, 72.4, 106.8, 108.0 (2C), 120.1, 122.3, 123.4, 130.3, 137.1, 147.2, 150.0, 151.2, 152.9. IR (neat) 3376 (OH), 2840 and 1077 cm^{-1} (OCH_3). Found: C, 65.93; H 6.90%. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23%.

2-(1,2-Carbonyldioxy-4-methyl-3-pentenyl)-1,4,5,8-tetramethoxynaphthalene (4): A mixture of 2-(1,2-dihydroxy-4-methyl-3-pentenyl)-1,4,5,8-tetramethoxynaphthalene **3** (130 mg, 0.36 mmol) and *N,N'*-carbonyldiimidazole (175 mg, 1.08 mmol) was dissolved in toluene (7 ml). The mixture was heated to reflux for 1 h. Upon cooling to room temperature, the reaction was quenched with aqueous 5% HCl and the mixture was extracted with AcOEt. The organic layers were washed with aqueous $NaHCO_3$ and then with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography to give 114 mg (82%) of **4**: ^{1}H NMR (major isomer) δ=1.52 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.35 (dd, J=8.8, 8.8 Hz, 1H, CH–O), 5.43 (d, J=9.9 Hz, 1H, HC=C), 5.77 (d, J=7.1 Hz, 1H, Ar-C<u>H</u>–O), 6.81 (s, 1H, Ar-H), 6.87 (s, 2H, Ar-H). ^{13}C NMR δ=18.5, 25.8, 56.9, 57.1, 57.7, 63.3, 79.2, 80.5, 104.1, 108.6, 109.6, 119.1, 121.3, 122.4, 124.5, 143.7, 148.8, 150.2, 151.4, 154.0, 154.8. IR (neat) 2842 and 1071 (OCH_3), 1802 cm^{-1} (Carbonate). Found: C, 65.08; H 6.21%. Calcd for $C_{21}H_{24}O_7$: C, 64.94; H, 6.23%.

2-(1-Hydroxy-4-methyl-3-pentenyl)-1,4,5,8-tetramethoxynaphthalene (5) and 2-(1-Hydroxy-4-methyl-2-pentenyl)-1,4,5,8-tetramethoxynaphthalene (6): To a mixture of $Pd(OAc)_2$ (11 mg, 0.05 mmol), PPh_3 (51 mg, 0.19 mmol), and THF (3 ml) was added consecutively HCOOH (0.20 ml, 5.30 mmol), Et_3N (0.75 ml, 5.40 mmol), and a solution of 2-(1,2-carbonyldioxy-4-methyl-3-pentenyl)-1,4,5,8-tetramethoxynaphthalene **4** (212 mg, 0.55 mmol) in THF (7 ml) under argon. The resulting mixture was stirred for 3 h. The solution was poured into aqueous 5% HCl, and then extracted with AcOEt. The organic layers were washed with aqueous $NaHCO_3$ and then with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography to give 184 mg (97%) of **5** and **6**. The ratio of **5** to **6** was determined by ^{1}H NMR to be 79:21. Found: C, 69.07; H, 7.84%. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56%. Isolation of **5** was carried out by an acetoxylation, followed by deacetoxylation operation, as described below.

2-(1-Acetoxy-4-methyl-3-pentenyl)-1,4,5,8-tetramethoxynaphthalene (7) and 2-(1-Acetoxy-4-methyl-2-pentenyl)-1,4,5,8-tetramethoxynaphthalene (8): To a mixture of **5** and **6** (119 mg, 0.34 mmol) in CH_2Cl_2 (5 ml) were added pyridine (0.14 ml, 1.72 mmol), Ac_2O (0.16 ml, 1.72 mmol), and 4-dimethylaminopyridine (DMAP) (3.7 mg, 0.03 mmol). The mixture was stirred at room temperature for 2 h. The reaction was quenched with aqueous 5% HCl; then the products were extracted with CH_2Cl_2. The organic layers were washed with aqueous saturated $NaHCO_3$ and then with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography to give 124 mg (95%) of **7** and **8** (71:29 ratio). Found: C, 68.34; H 7.18%. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.26%

2-(1-Acetoxy-4-methyl-3-pentenyl)-1,4,5,8-tetramethoxynaphthalene (7), 2-(4-Methyl-1-pentenyl)-1,4,5,8-tetramethoxynaphthalene (12), and 2-(4-Methyl-2-pentenyl)-1,4,5,8-tetramethoxynaphthalene (13): To a mixture of $Pd(OAc)_2$ (9 mg, 0.04 mmol), PPh_3 (42 mg, 0.16 mmol) and THF (3 ml) were added HCOOH (0.09 ml, 2.39 mmol), Et_3N (0.34 ml, 2.45 mmol). To this mixture was added a mixture of **7** and **8** (171 mg, 0.45 mmol, **7**:**8**=71:29) in THF (7 ml). The mixture was stirred at room temperature for 3 h, then poured into aque-

ous 5% HCl, and extracted with AcOEt. The organic layers were washed with aqueous $NaHCO_3$ and then with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography. The first eluting fraction was a mixture of **12** and **13**, (R_f=0.40, hexane : AcOEt=1 : 1, 41 mg, 94% based on **8**). The next fraction was found to be **7** (116 mg, 96% recovery: ^{1}H NMR δ=1.55 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 2.09 (s, 3H, OAc), 2.59 (dd, J=7.0, 7.0 Hz, 2H, CH_2), 3.83 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.93 (s, 6H, OCH_3), 5.14 (t, J=7.2 Hz, 1H, CH=C), 6.35 (dd, J=7.1, 6.1 Hz, 1H, Ar-CH(OAc)), 6.82 (s, 2H, Ar-H), 6.87 (s, 1H, Ar-H). ^{13}C NMR δ=17.9, 21.3, 25.7, 34.5, 56.9, 57.3, 57.8, 62.5, 70.8, 106.2, 107.8, 108.6, 119.2, 120.8, 122.6, 130.6, 134.6, 146.8, 150.4, 151.3, 153.2, 170.2. IR (neat) 2840 and 1073 (OCH_3), 1740 cm^{-1} (OAc). Found: C, 67.78; H 7.46%. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.26%.

12. ^{1}H NMR δ=0.96 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.68—1.92 (m, 1H, CH), 2.19 (dt, J=6.6, 1.4 Hz, 2H, CH_2), 3.73 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.19—6.36 (m, 1H, C=CH), 6.81 (ABq, J=10.8 Hz, 2H, Ar-H), 6.91 (dt, J=16, 1.4 Hz, 1H, Ar-CH=C), 7.02 (s, 1H, Ar-H). IR (KBr) 2994, 2951, 2924, 2868, 2838, 1603, 1515, 1458, 1429, 1389, 1369, 1337, 1260, 1223, 1199, 1087, 1070, 1020, 988, 966, 830, 806, 800 cm^{-1}. Found: C, 72.93; H 7.95%. Calcd for $C_{20}H_{25}O_4$: C, 72.92; H, 7.65%.

6-(1-Acetoxy-4-methyl-3-pentenyl)-5,8-dimethoxy-1,4-naphthoquinone (14) and 2-(1-Acetoxy-4-methyl-3-pentenyl)-5,8-dimethoxy-1,4-naphthoquinone (15). Into an undivided cell fitted with two platinum foils (1×1.5 cm^2) was placed $LiClO_4$ (180 mg, 1.70 mmol) dissolved in H_2O (0.5 ml). To this solution was added a solution of 2-(1-acetoxy-4-methyl-3-pentenyl)-1,4,5,8-tetramethoxynaphthalene **7** (65 mg, 0.17 mmol) in MeCN (4.5 ml). The entire mixture was electrolyzed under a constant applied voltage of 2 V at room temperature. Most of the starting compound was consumed by passage of 4 F mol^{-1} of electricity. The products were extracted with AcOEt. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography to give 44 mg (74%) of **14** and 14 mg (23%) of **15**.

14. ^{1}H NMR δ=1.51 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 2.12 (s, 3H, OAc), 2.37—2.63 (m, 2H, CH_2), 3.90 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 5.11 (t, J=7.3 Hz, 1H, CH=C), 6.13 (dd, J=7.2, 5.1 Hz, 1H, Ar-CH(OAc)), 6.77 (s, 2H, Quinone-Ring CH=C), 7.26 (s, 1H, Ar-H). ^{13}C NMR δ=17.7, 21.0, 25.6, 33.9, 56.6, 61.9, 70.4, 116.7, 118.0, 120.0, 125.1, 135.6, 137.7, 138.8, 144.3, 150.5, 155.9, 169.8, 184.1, 184.6. IR (neat) 2840 and 1073 (OCH_3), 1740 (OAc), 1653 cm^{-1} (Quinone C=O). Found: C, 67.11; H 6.26%. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19%.

15. ^{1}H NMR δ=1.50 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 2.05 (s, 3H, $OCOCH_3$), 2.30—2.62 (m, 2H, CH_2), 3.90 (s, 6H, OCH_3), 5.05 (t, J=7.4 Hz, 1H, CH=C), 5.85 (ddd, J=7.0, 4.5, 1.2 Hz, 1H, Ar-CH(OAc)), 6.61 (d, 1H, J=1.2 Hz, Quinone-Ring CH=C), 7.26 (s, 2H, Ar-H). ^{13}C NMR δ=17.9, 20.9, 25.7, 32.7, 56.8, 69.7, 108.0, 118.0, 120.3, 120.8, 121.0, 133.2, 135.6, 148.1, 153.5, 153.9, 169.7, 183.4, 184.6. IR (neat) 2840 (OCH_3), 1734 (OAc), 1634 cm^{-1} (Quinone C=O). Found: C, 66.97; H 6.28%. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19%.

2-(1-Acetoxy-4-methyl-3-pentenyl)-5,8-diacetoxy-1,4-dimethoxynaphthalene (16). To a mixture of 6-(1-acetoxy-4-methyl-3-pentenyl)-5,8-dimethoxy-1,4-naphthoquinone **14** (70 mg, 0.10 mmol), Ac_2O (5 ml), and Et_3N (1 ml) was added DMAP (2.4 mg, 0.02 mmol); the new mixture was stirred for 1 h at room temperature. To it was added Zn powder (130 mg, 1.0 mmol) in portions at room temperature. After being stirred for an additional 30 min, the mixture was poured into water and then extracted with AcOEt. The organic layer was washed with aqueous $NaHCO_3$ and then with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (SiO_2, hexane–AcOEt) to give 70 mg (81%) of **16**. ^{1}H NMR δ=1.53 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 2.09 (s, 3H, OAc), 2.34 (s, 3H, OAc), 2.35 (s, 3H, OAc), 2.39—2.67 (m, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 5.09 (t, J=7.2 Hz, 1H, CH=C), 6.25 (dd, J=9.0, 6.0 Hz, 1H, Ar-CH(OAc)), 6.82 (s, 1H, Ar-H), 7.03 (d, J=6.5 Hz, 1H, Ar-

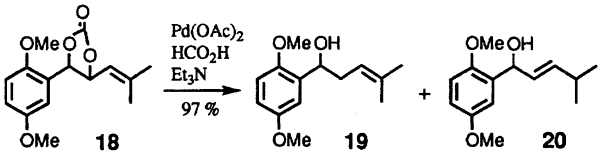


Table 3. Reductive Cleavage of the Carbon–Oxygen Bond of **18**[a)]

Run	Pd Cat.	Ligand	Reducing Reagent	Temp	Yield/% **19**+**20**[c)]	Selectivity[b)] **19** : **20**
1	$Pd(OAc)_2$	PPh_3	$NaBH_4$	Reflux	54	81 : 19
2	$Pd(OAc)_2$	PPh_3	$NaBH_4$	R.T.	58	67 : 33
3	$Pd_2(dba)_3$[d)]	—	$NaBH_4$	R.T.	48	77 : 23
4	$Pd(OAc)_2$	PPh_3	HCO_2H–Et_3N	R.T.	97	79 : 21
5	$Pd_2(dba)_3$	PPh_3	HCO_2H–Et_3N	Reflux	98	73 : 27

a) The compound **18**: ^{1}H NMR ($CDCl_3$) δ=5.30—5.50 (m, 2H, CH=C, Ph-CH-O), 5.20 (dd, J=9.3, 6.4 Hz, 1H, C=C-CH-O); IR 1800 cm^{-1} (Carbonate). Found: C, 64.47; H, 6.71%. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52%. b) Determined by ^{1}H NMR spectrum. c) Products **19** and **20**: IR 3368 cm^{-1} (OH). Found: C, 70.91; H, 8.34%. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53%. d) dba: dibenzylideneacetone.

H), 7.09 (d, J=6.5 Hz, 1H, Ar-H). ^{13}C NMR δ=17.8, 20.7, 20.9, 21.2, 25.7, 34.6, 56.5, 62.6, 70.4, 105.0, 118.7, 119.4, 120.4, 121.2, 123.6, 131.5, 135.0, 143.8, 144.3, 152.0, 169.3, 170.2. IR (neat) 2850 (OCH_3), 1734 cm^{-1} (OAc). Found: C, 64.81; H 6.53%. Calcd for $C_{24}H_{28}O_8$: C, 64.90; H, 6.35%.

2-(1-Acetoxy-4-methyl-3-pentenyl)-5,8-diacetoxy-1,4-naphthoquinone (17).[5] Into an undivided cell fitted with two platinum foils (1×1.5 cm^2) was placed $LiClO_4$ (149 mg, 1.40 mmol) dissolved in H_2O (0.5 ml). To this solution was added a solution of 2-(1-acetoxy-4-methyl-3-pentenyl)-5,8-diacetoxy-1,4-dimethoxynaphthalene **16** (55 mg, 0.12 mmol) in MeCN (4.5 ml). The entire mixture was electrolyzed under a constant applied voltage of 2 V at room temperature. The starting compound was consumed by passage of 4 F mol^{-1} of electricity. The products were extracted with AcOEt. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography to give 22 mg (43%) of **17**. ^{1}H NMR δ=1.56 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 2.09 (s, 3H, OAc), 2.43 (s, 6H, OAc), 2.30—2.60 (m, 2H, CH_2), 5.07 (t, J=7.4 Hz, 1H, CH=C), 5.87 (ddd, J=7.2, 4.4, 1.5 Hz, 1H, Ar-CH(OAc)), 6.66 (s, 1H, Quinone-Ring CH=C), 7.38 (s, 2H, Ar-H). IR (neat) 1734 (OAc), 1661 cm^{-1} (Quinone C=O).

2-(1-Hydroxy-4-methyl-3-pentenyl)-5,8-dihydroxy-1,4-naphthoquinone (*dl*-Shikonin,1): 2-(1-Acetoxy-4-methyl-3-pentenyl)-5,8-diacetoxy-1,4-naphthoquinone **17** was dissolved in aqueous 1 M NaOH (10 ml); then the mixture was stirred for 2.5 h. The solution was filtered and the filtrate was acidified with acetic acid until the solution turned red. The product extracted with AcOEt was washed with aqueous $NaHCO_3$, brine and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by column chromatography (SiO_2, hexane–AcOEt) to give 13 mg (72%) of *dl*-**1**: Mp 146.5 °C (lit, 148 °C); ^{1}H NMR ($CDCl_3$) δ=1.65 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.27—2.43 (m, 1H, CH_2), 2.36 (d, J=4.5 Hz, 1H, OH), 2.57—2.71 (m, 1H, CH_2), 4.86—4.96 (m, 1H, Ar-C<u>H</u>(OH)), 5.21 (t, J=7.5 Hz, 1H, CH=C), 7.17 (s, 1H, Ar-H), 7.19 (s, 2H, Ar-H), 12.49 (s, 1H, Ar-OH), 12.60 (s, 1H, Ar-OH). IR (KBr) 3410 (OH), 1618 (Quinone C=O), 1576, 1077 cm^{-1}. Found: C, 66.33; H 5.78%. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59%.

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