C, 72.26; H, 8.49. Found: C, 72.08; H, 8.52.

(3aα,8aα)-3β-Methyloctahydro-2*H*-cyclohepta[*b*]furan-2-one (17b). $NaBH_4$ (33 mg, 0.87 mmol) was added to a solution of **14b** (118 mg, 0.71 mmol) in methanol (3 mL) and the mixture was stirred for 2 h at room temperature and worked up as usual to give an oily crude product (135 mg), which was chromatographed over silica gel (6 g, 2 cm i.d. column) and eluted with chloroform to give **17b** (116 mg, 97%) as a colorless oil: IR (neat) 1770 cm^{-1}; ^1H NMR (200 MHz) δ 1.18 (3 H, d, J = 7.0 Hz, C_3-Me), 2.25 (1 H, ddd, J = 13.0, 9.0, 5.8 Hz, C_8-H_α), 2.53 (1 H, dddd, J = 10.5, 9.0, 5.8, 2.0 Hz, C_{3a}-H), 2.86 (1 H, dq, J = 9.0, 7.0 Hz, C_3-H), 4.65 (1 H, ddd, J = 9.8, 5.8, 5.8 Hz, C_{8a}-H); MS, m/e (relative intensity) 168 (M^+, 2), 124 (25), 109 (20), 96 (70), 95 (100), 82 (44), 81 (24), 78 (22), 77 (28). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.17; H, 9.66.

(3aα,8aα)-3α-Methyloctahydro-2*H*-cyclohepta[*b*]furan-2-one (18b). A mixture of **17b** (23 mg, 0.14 mmol) and 1 M NaOMe in methanol (3 mL) was allowed to stand at room temperature for 2 h and poured into a saturated NaCl aqueous solution (50 mL). The mixture was worked up as usual to give an oily crude product, which was separated by HPLC [10-μm silica gel (Kyowa gel MIC-SI-10, 25 cm × 8 mm i.d. column, EtOAc–hexane (2:8), flow rate 3.1 mL/min] to give **18** b (t_R 7.6 min, 13 mg, 57%) as a colorless oil: IR (neat) 1767 cm^{-1}; ^1H NMR (200 MHz) δ 1.25 (3 H, d, J = 6.5 Hz, C_3-Me), 4.58 (1 H, ddd, J = 11.0, 8.2, 2.8 Hz, C_{8a}-H), 2.32 (1 H, dq, J = 10.4, 6.5 Hz, C_3-H), 2.34 (1 H, m, C_{3a}-H). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.68; H, 9.73.

Attempted Epimerization of 17b in Acetic Acid in the Presence of 48% HBr. A mixture of **17b** (24 mg, 0.14 mmol) and a 48% HBr aqueous solution (40 μL) in acetic acid (4 mL) was allowed to stand at room temperature for 20 h and poured into a saturated NaCl aqueous solution (60 mL). The mixture was worked up as usual to give an oily product (24 mg), which was recovered **17b** by the analyses of the ^1H NMR spectrum and HPLC.

(3aα,8aα)-3-Methyleneoctahydro-2*H*-cyclohepta[*b*]-furan-2,8-dione (16). Chromic anhydride (1.54 g, 18.3 mmol) was added to a mixture of anhydrous methylene chloride (19.3 mL) and anhydrous pyridine (3.1 mL, 38.4 mmol) at 0 °C, and the mixture was stirred for 15 min. Then **14a** (130 mg, 0.72 mmol) dissolved in methylene chloride (10 mL) was added over 15 min. The mixture was stirred at 0 °C for 4 h and then worked up as usual to give oily crude product, which was chromatographed over silica gel (5 g, 2 cm i.d. column) and eluted with a mixture of chloroform and ethyl acetate (9:1) to give **16** (96 mg, 74%) as a colorless oil: IR (neat) 1775, 1730, 1665 cm^{-1}; ^1H NMR (200 MHz) δ 3.40 (1 H, dddd, J = 10.0, 9.3, 3.0, 2.5 Hz, C_{3a}-H), 5.26 (1 H, d, J = 9.3 Hz, C_{8a}-H), 5.70 (1 H, d, J = 2.5 Hz, C_9-H_a), 6.42 (1 H, d, J = 3.0 Hz, C_9-H_b). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.85; H, 6.65.

(3aα,8aα)-3β-Methyloctahydro-2*H*-cyclohepta[*b*]furan-2,8-dione (4c). Chromic anhydride (2.0 g, 20 mmol) was added a mixture of anhydrous methylene chloride (20 mL) and pyridine (4.0 mL, 49.6 mmol) at 0 °C, and the mixture was stirred for 15 min. Then **17a** (159 mg, 0.86 mmol) dissolved in methylene chloride (15 mL) was added over 10 min. The mixture was stirred at 0 °C for 6 h and worked up as usual to give an oily crude product (155 mg), which was passed through a short column of silica gel and recrystallized from ether to give **4c** (145 mg, 92%) as colorless needles: mp 105–105.5 °C; IR (KBr) 1780, 1720 cm^{-1}; ^1H NMR (90 MHz) δ 1.20 (3 H, d, J = 6.8 Hz, C_9-H), 1.00–2.10 (6 H, m), 2.33–2.73 (2 H, m, C_7-H), 2.73–3.10 (2 H, m, C_{3a}-H, C_3-H), 5.03 (1 H, d, J = 6.3 Hz, C_{8a}-H); MS, m/e (relative intensity) 182 (M^+, 21), 154 (82), 125 (36), 112 (97), 111 (59), 97 (58), 82 (48), 81 (100), 70 (23), 69 (31), 68 (40), 67 (33), 56 (27), 55 (80). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.74; H, 7.78.

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Cycloshikonin and Its Derivatives.[1] A Synthetic Route of Shikonin

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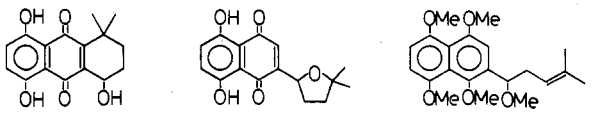
Intramolecular cyclizations of 5,8-dihydroxy-2-(1,4-dihydroxy-4-methylpentyl)-1,4-naphthoquinone (**4**) and 2-(1-hydroxy-4-methyl-4-pentenyl)-1,4,5,8-tetramethoxynaphthalene (**9**) with *p*-toluenesulfonic acid gave 5,8-dihydroxy-2-(5,5-dimethyl-2-tetrahydrofuranyl)-1,4-naphthoquinone (**2**), and 2-(5,5-dimethyl-2-tetrahydrofuranyl)-1,4,5,8-tetramethoxynaphthalene (**6**), respectively. Demethylation of **6** with CAN and AgO–40% HNO_3 gave **2**. Ring-opening of **2** in acetic anhydride with *p*-toluenesulfonic acid was successful to afford 5,8-diacetoxy-2-(1,4-diacetoxy-4-methylpentyl)-1,4-naphthoquinone (**12**), and the following hydrolysis by alkali produced **4**, which could be derived to (±)-shikonin.

The cyclizations of the side chain of shikonin and alkannin, an enantiomer of shikonin, to form cycloshikonin and cycloalkannin have been well-known by many previous investigators.[3] The structures of cycloshikonin and cycloalkannin had been considered to be a hydroanthraquinone (**1**) up to recently. However, Sankawa et al.[4] have corrected the structure and shown that cycloalkannin was a tetrahydrofuran compound, 5,8-dihydroxy-2-(5,5-dimethyl-2-tetrahydrofuranyl)-1,4-naphthoquinone (**2**).



1 2 3

During our synthetic studies on shikonin and its derivatives, we have found that the 1,4,5,8-tetramethoxynaphthalene compound **3** having a side chain similar to that of shikonin could also cyclize to **2** by Lewis acid.[2b] As cycloshikonin is supposed to be chemically more stable than shikonin itself toward Lewis acid, we expected that

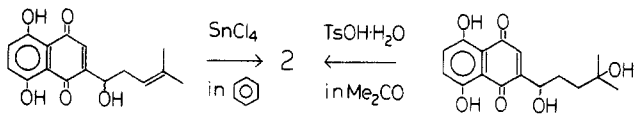
(1) Synthesis on Naphthoquinone Derivatives. 3. For 2, see 2b.
(2) (a) Terada, A.; Tanoue, Y.; Hatada, A.; Sakamoto, H. *J. Chem. Soc. Chem. Commun.* **1983**, 987; (b) *Bull. Chem. Soc. Jpn.* **1987**, *60*, 205.
(3) (a) Coffey, S. *Rodd's Chemistry of Carbon Compounds*; Elsevier Sci. Publ.: Amsterdam, 1978; III G, p 238. (b) Brockmann, H. *Ann.* **1935**, *521*, 1. (c) Thomson, R. H. *Naturally Occurring Quinones*, 2nd ed.; Academic Press: London, 1971; p 250. (d) Sankawa, U.; Ebizuka, Y.; Miyazaki, T.; Isomura, Y.; Otsuka, H.; Shibata, S.; Inomata, M.; Fukuoka, F. *Chem. Pharm. Bull.* **1977**, *25*, 2392.
(4) Sankawa, U.; Otuka, H.; Kataoka, Y.; Iitaka, Y.; Hoshi, A.; Kuretani, K. *Chem. Pharm. Bull.* **1981**, *29*, 116.

0022-3263/87/1952-1437$01.50/0

the 5,5-dimethyl-2-tetrahydrofuranyl side chain in **6** would survive such drastic conditions as cleavages of the four methoxyl groups of **6** to **2**. This cyclized compound **6** is easily obtainable from a Grignard reaction of 4-chloro-2-methyl-1-butene and 2-formyl-1,4,5,8-tetramethoxynaphthalene (**8**) and cyclization. Therefore, this process through cycloshikonin will be a more favorable route to (±)-shikonin. This paper describes the chemistry of cycloshikonin and derivatives and a new synthetic route of shikonin via cycloshikonin.

Results and Discussion

Cyclization of 5,8-dihydroxy-2-(1,4-hydroxy-4-methylpentyl)-1,4-naphthoquinone (**4**)[2] with *p*-toluenesulfonic acid in acetone gave **2** in good yield. Also 2-(1,4-dihydroxy-4-methylpentyl)-1,4,5,8-tetramethoxynaphthalene (**5**)[2] cyclized to 2-(5,5-dimethyl-2-tetrahydrofuranyl)-1,4,5,8-tetramethoxynaphthalene (**6**) in a similar manner. This **6** was also prepared as follows. Treatment of 2-formyl-1,4,5,8-tetramethoxynaphthalene (**8**)[2] with the Grignard reagent prepared from 4-chloro-2-methyl-1-butene gave 2-(1-hydroxy-4-methyl-4-pentenyl)-1,4,5,8-tetramethoxynaphthalene (**9**) in 95% yield. The cyclization of **9** with *p*-toluenesulfonic acid in benzene gave **6**.



4

shikonin (α-hydroxyl is *R*)
alkannin (α-hydroxyl is *S*)

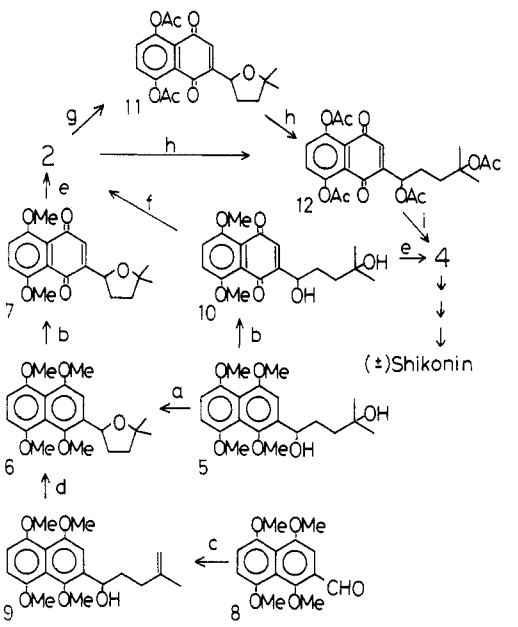
Demethylation of **6** by oxidation with cerium(IV) ammonium nitrate[5] (CAN is used as the abbreviation hereafter) in acetonitrile afforded 5,8-dimethoxy-2-(5,5-dimethyl-2-tetrahydrofuranyl)-1,4-naphthoquinone (**7**) in 40% yield as a major product.[6] Also, the miner product, 5,8-dimethoxy-6-(5,5-dimethyl-2-tetrahydrofuranyl)-1,4-naphthoquinone, was obtained in 24% yield. The further demethylation of **7** with AgO–40% HNO_3[7] gave **2**.

On the other hand, demethylation of **5** with CAN provided 5,8-dimethoxy-2-(1,4-dihydroxy-4-methylpentyl)-1,4-naphthoquinone (**10**)[2] as a main product, and the further demethylation with aluminum chloride afforded **2**. However, the demethylation of **10** with AgO–40% HNO_3 gave **4**[2] instead of **2** (Scheme I).

Opening of the furanyl ring of **2** was carried out as follows. Acetylation of **2** with acetic anhydride in pyridine gave 5,8-diacetoxy-2-(5,5-dimethyl-2-tetrahydrofuranyl)-1,4-naphthoquinone (**11**) in an almost quantative yield. Treatment of **11** with *p*-toluenesulfonic acid in acetic anhydride gave 5,8-diacetoxy-2-(1,4-diacetoxy-4-methylpentyl)-1,4-naphthoquinone (**12**) in 47% yield. Also **12** was prepared directly by reaction of **2** with *p*-toluenesulfonic acid in acetic anhydride.

Hydrolysis of the ester **12** by alkali produced easily the tetraol **4**, which was our key intermediate to (±)-shikonin.[2]

Scheme I[a]



[a] (a) $TsOH·H_2O$ in acetone; (b) CAN in CH_3CN; (c) (3-methyl-3-butenyl)magnesium chloride; (d) $TsOH·H_2O$ in benzene; (e) AgO–40% HNO_3 in acetone; (f) $AlCl_3$ in CH_2Cl_2; (g) Ac_2O in pyridine; (h) $TsOH·H_2O$, Ac_2O; (i) OH^-.

In summary, we have found a new synthetic route of shikonin via cycloshikonin.

Experimental Section

Melting points were determined with a Yanagimoto micromelting point apparatus and uncorrected. ^1H NMR spectra were taken on a JEOL JNM-FX60 spectrometer using tetramethylsilane as an internal standard and the chemical shifts were reported in δ values. Mass spectral data were obtained with a JEOL DX-300. Infrared spectra were recorded on a Hitachi 260-30 infrared spectrometer. Analytical high-performance liquid chromatography (HPLC) was done with a EYELA PLC-10 using a TC-ODS1171 column. Column chromatography was performed on silica gel (Wakogel C-200) and alumina (Sumitomo activated alumina, KCG-30).

5,8-Dihydroxy-2-(5,5-dimethyl-2-tetrahydrofuranyl)-1,4-naphthoquinone, (±)-Cycloshikonin (2). A. Cycloshikonin from Shikonin. Shikonin was extracted from the commercially available "Ko-shikon" by the method[8] reported previously. The cycloshikonin (**2**) was prepared from this shikonin according to the method reported by Brockmann.[3b] Recrystallization from methanol gave red needles, mp 75–76 °C (lit.[3b] mp 79–80 °C); IR (KBr) 1610 (C=O), 1570, and 1065 cm^{-1}; MS, *m/e* 288 (M^+), 255, 232, 219, 217, and 190; NMR ($CDCl_3$) δ 1.36 (s, 6 H, 2 CH_3), 1.80–1.85, 2.39–2.81 (m, 4 H, 2 CH_2), 5.14 (m, 1 H, CH), 7.19 (s, 3 H, Ar H), and 12.51 (s, 2 H, ArOH). Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.80; H, 5.74.

B. 2 from 5,8-Dihydroxy-2-(1,4-dihydroxy-4-methylpentyl)-1,4-naphthoquinone (4). A solution of **4**[2] (10 mg, 0.033 mmol) and *p*-toluenesulfonic acid monohydrate (62 mg, 0.33 mmol) in acetone (3 mL) was allowed to stand overnight at room temperature with occasional shaking, then diluted with water, and extracted with chloroform. The chloroform solution was washed with brine and dried over anhydrous sodium sulfate, and the solvent was evaporated. The crude product was chromatographed on silica gel with chloroform as eluant and gave 9 mg (95%) of **2**, mp 72–75 °C. The IR, NMR, and MS spectra agreed well with those of the sample obtained by method A.

C. 2 from 5,8-Dimethoxy-2-(5,5-dimethyl-2-tetrahydrofuranyl)-1,4-naphthoquinone (7). To a mixture of the quinone **7** (72 mg, 0.228 mmol) and AgO (280 mg, 2.28 mmol) in acetone

(5) (a) Jacob, P., III.; Callery, P. S.; Shulgin, A. T.; Castagnolic, N., Jr. *J. Org. Chem.* **1976**, *41*, 3627. (b) Li, T.-t.; Ellison, R. H. *J. Am. Chem. Soc.* **1978**, *100*, 6263. (c) Kometani, T.; Yoshii, E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1191; (d) *J. Chem. Soc., Perkin Trans. 1* **1981**, 1197.

(6) Demethylation of monosubstituted-1,4,5,8-tetramethoxynaphthalenes with CAN usually gave two kinds of 1,4-naphtoquinones, namely, 2-substituted- and 6-substituted-5,8-dimethoxy-1,4-naphthoquinones. The report is to be published and in preparation (Tanoue, Y.; Terada, A.)

(7) (a) Parker, K. A.; Kallmerten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5881. (b) Synder, C. D.; Rapoport, H. *Ibid.* **1972**, *94*, 227.

(8) Toribara, T. Y.; Underwood, A. L. *Anal. Chem.* **1949**, *21*, 1352.

(10 mL) was added 40% HNO_3 (6 mL) with stirring at room temperature. After 15 min, the reaction mixture was diluted with water and extracted with dichloromethane. The dichloromethane solution was washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent and chromatographic purification (silica gel, chloroform) of the product gave **2** (20 mg, 30%). Recrystallization from hexane gave an analytical sample of **2**, mp 79–81 °C. The IR, NMR, and MS spectra were identical with those of the authentic sample obtained by method A.

D. 2 from 5,8-Dimethoxy-2-(1,4-dihydroxy-4-methylpentyl)-1,4-naphthoquinone (10). A solution of the quinone **10**[2] (100 mg, 0.299 mmol) in dichloromethane (5 mL) was cooled in an ice bath. To this solution was added anhydrous aluminum chloride (398 mg, 2.99 mmol), and the reaction mixture was stirred at room temperature for 1 h. The system was decomposed by addition of ice water (50 mL) and 5% aqueous oxalic acid (100 mL) and extracted with chloroform. The usual workup and purification of the crude product by silica gel chromatography with chloroform as eluant gave 21 mg (24%) of **2**, mp 79–80.5 °C. The IR, NMR, and MS spectra agreed well with those of the sample prepared by method A.

E. 6 from 2-(1,4-Dihydroxy-4-methylpentyl)-1,4,5,8-tetramethoxynaphthalene (5). A solution of **5**[2] (101 mg, 0.277 mmol) and *p*-toluenesulfonic acid monohydrate (530 mg, 2.77 mmol) in acetone (10 mL) was allowed to react overnight at room temperature, then diluted with water, and extracted with chloroform. The usual workup and chromatographic purification (silica gel, chloroform) of the product gave 79 mg (82%) of **6**. Recrystallization from hexane gave an analytical sample: mp 75–77 °C; IR (KBr) 1600, 1340, 1260, and 1070 cm^{-1}; NMR ($CDCl_3$) δ 1.40, 1.46 (each s, 3 H, CH_3), 1.7–2.6 (m, 4 H, 2 CH_2), 3.75, 3.88, 3.92, 3.95 (each s, 3 H, OCH_3), 5.49 (t, 1 H, J = 6.6 Hz, CH), 6.79 (s, 2 H, Ar H), and 7.13 (s, 1 H, Ar H). Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 69.18; H, 7.64.

F. 6 from 2-(1-Hydroxy-4-methyl-4-pentenyl)-1,4,5,8-tetramethoxynaphthalene (9). A solution of **9** (125 mg, 0.36 mmol) and *p*-toluenesulfonic acid monohydrate (69 mg, 0.36 mmol) in benzene (5 mL) was stirred in the dark at room temperature for 12 h. The reaction mixture was diluted with brine and extracted with chloroform. The chloroform solution was worked up in the usual manner, and purification of the crude product by chromatography on alumina with ether as eluant gave 64 mg (51%) of **6**. Recrystallization from hexane gave an analytical sample, mp 75.5–77 °C. The IR, NMR, and MS spectra and HPLC analysis agreed with those of the sample prepared by method E.

4-Chloro-2-methyl-1-butene. A solution of a commercially available 3-methyl-3-buten-1-ol (102 g, 1.18 mol) in pyridine (103 g, 1.30 mol) was cooled to −5 °C in an ice bath, and then thionyl chloride (155 g, 1.30 mol) was added dropwise at −5 to +3 °C for 3 h, stirred at 0 °C for another 6 h, and allowed to stand overnight at room temperature. To this solution was added water (200 mL) and then it was steam-distilled. The organic portion obtained was washed with brine and dried over calcium chloride. Fractional distillation gave 21.4 g (20%) of isoprene, bp 34.5 °C, and 24.5 g (20%) of 4-chloro-2-methyl-1-butene: bp 102.5 °C (lit.[9] bp 102 °C); IR (neat) 1650, 1455, 1380, and 893 cm^{-1}; NMR ($CDCl_3$) δ 1.75 (s, 3 H, CH_3), 2.47 (t, 2 H, J = 7.2 Hz, CH_2CH_2Cl), 3.61 (t, 2 H, J = 7.2 Hz, CH_2Cl), and 4.83 (m, 2 H, $C=CH_2$).

2-(1-Hydroxy-4-methyl-4-pentenyl)-1,4,5,8-tetramethoxynaphthalene (9). A solution of 2-formyl-1,4,5,8-tetramethoxynaphthalene (**8**)[2] (0.77 g, 2.8 mmol) in tetrahydrofuran (5 mL) was added to the Grignard reagent, prepared from the above obtained 4-chloro-2-methyl-1-butene (1.04 g, 0.01 mol) and magnesium (0.244 g, 0.01 mol) in ether (2 mL) and tetrahydrofuran (10 mL), at 0 °C and stirred at room temperature for 1 h. The reaction mixture was decomposed by a cautious addition of aqueous ammonium chloride and extracted with chloroform. The chloroform solution was washed with aqueous sodium hydrogencarbonate and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent and chromatographic purification of the product on alumina with chloroform as eluant gave 0.96 g (95%) of **9** as a viscous oil: IR (neat) 3480 (OH), 1645 (C=C), and 885 cm^{-1} (C=C); MS, m/e 346 (M^+), 328 ($M^+ - H_2O$), 313, 258, 243, and 234; NMR ($CDCl_3$) δ 1.75 (s, 3 H, CH_3), 1.8–2.4 (m, 5 H, 2 CH_2 and OH), 4.74 (m, 2 H, $C=CH_2$), 5.22 (t, 1 H, J = 6.4 Hz, $-CH(OH)-$), 6.81 (s, 2 H, Ar H), and 6.98 (s, 1 H, Ar H). Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 68.87; H, 7.54.

5,8-Dimethoxy-2-(5,5-dimethyl-2-tetrahydrofuranyl)-1,4-naphthoquinone (7). To a solution of **6** (460 mg, 1.33 mmol) in acetonitrile (7 mL) and chloroform (5 mL) was added cerium ammonium nitrate (1.82 g, 3.33 mmol) in water (10 mL) over 5 min. After being stirred at room temperature for 30 min, the reaction mixture was extracted with chloroform. The usual workup and purification of the crude product by chromatography on alumina with chloroform as eluant gave two products as viscous oils. The first eluate gave 103 mg (24%) of an isomer of **7**, 5,8-dimethoxy-6-(5,5-dimethyl-2-tetrahydrofuranyl)-1,4-naphthoquinone: NMR ($CDCl_3$) δ 1.41, 1.43 (each s, 3 H, CH_3), 1.6–2.7 (m, 4 H, 2 CH_2), 3.82, 4.00 (each s, 3 H, OCH_3), 5.31 (t, 1 H, J = 7.3 Hz, CH), 6.77 (s, 2 H, quinonoid ring H), and 7.62 (s, 1 H, benzenoid ring H). The second eluate gave 183 mg (44%) of **7**: IR (neat) 1650 (C=O), 1582, 1560, and 1060 cm^{-1}; MS, m/e 316 (M^+), 301, 283, 260, and 247; calcd for $C_{18}H_{20}O_5$ m/e 316.1310, found m/e 316.1307; NMR ($CDCl_3$) δ 1.32, 1.34 (each s, 3 H, CH_3), 1.6–2.7 (m, 4 H, 2 CH_2), 3.95 (s, 6 H, 2 OCH_3), 5.04 (m, 1 H, CH), 6.91 (d, J = 1.6 Hz, 1 H, quinonoid ring H), and 7.30 (s, 2 H, benzenoid ring H).

5,8-Diacetoxy-2-(5,5-dimethyl-2-tetrahydrofuranyl)-1,4-naphthoquinone (11). Acetic anhydride (2 mL) was added to a solution of **2** (201 mg, 0.70 mmol) in pyridine (3 mL) at 0–5 °C and stirred at 0–5 °C for 2.5 h. After excess of reagents were evaporated under reduced pressure at room temperature, chromatographic purification of the product on silica gel with chloroform as eluant gave 249 mg (96%) of **11**. Recrystallization from hexane gave an analytical sample: mp 149.5–151 °C; IR (KBr) 1755 (ester C=O), 1655 (quinone C=O), 1635, 1590, and 1190 cm^{-1}; MS, m/e 372 (M^+), 330, 288, 232, and 219; NMR ($CDCl_3$) δ 1.31 (s, 6 H, 2 CH_3), 2.42, 2.43 (each s, 3 H, $COCH_3$), 4.99 (m, 1 H, CH), 6.92 (d, 1 H, J = 1.8 Hz, quinonoid ring H), and 7.35 (s, 2 H, benzenoid ring H). Anal. Calcd for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41. Found: C, 64.35; H, 5.52.

5,8-Diacetoxy-2-(1,4-diacetoxy-4-methylpentyl)-1,4-naphthoquinone (12). G. 12 from 5,8-Diacetoxy-2-(5,5-dimethyl-2-tetrahydrofuranyl)-1,4-naphthoquinone (11). A mixture of **11** (127 mg, 0.37 mmol) and *p*-toluenesulfonic acid monohydrate (64 mg, 0.34 mmol) in acetic anhydride (3 mL) was allowed to stand overnight at room temperature with occasional shaking, then was diluted with water, and extracted with ethyl acetate. After the usual workup, chromatogaphy on silica gel with chloroform as eluant gave 83 mg (47%) of **12**: mp 62–65 °C; IR (KBr) 1770, 1730 (each ester C=O), 1665 (quinone C=O), 1370, and 1180 cm^{-1}; MS, m/e 372, 330, 312, 288, 270, and no parent peak was observed; NMR ($CDCl_3$) δ 1.42 (s, 6 H, CH_3), 1.95 (s, 3 H, $COCH_3$), 2.12 (s, 3 H, $-CH(OCOCH_3)-$), 2.43 (s, 6 H, ArO$COCH_3$), 5.83 (m, 1 H, CH), 6.67 (d, 1 H, J = 1.2 Hz, quinonoid ring H), and 7.38 (s, 2 H, benzenoid ring H).

H. 12 from (±)-Cycloshikonin (2). Acetylation of **2** (104 mg, 0.36 mmol) in acetic anhydride (2 mL) with *p*-toluenesulfonic acid monohydrate (69 mg, 0.36 mmol) was carried out as in method G from **11** and gave 44 mg (26%) of **12**, 65–67 °C. The HPLC analysis showed that this product agreed with the authentic sample prepared from **11**.

5,8-Dihydroxy-2-(1,4-dihydroxy-4-methylpentyl)-1,4-naphthoquinone (4). Hydrolysis of **12** (16 mg, 0.034 mmol) in 1 M sodium hydroxide (10 mL) was carried out with stirring at 0–5 °C for 5 h under a nitrogen atmosphere, acidified with acetic acid until the color changed to red, and extracted with dichloromethane. The usual workup and chromatography on silica gel with chloroform as eluant gave 8 mg (78%) of **4**, mp 148–150 °C (lit.[2] mp 151–152 °C). This did not depressed the melting point of an authentic sample of **4** on admixture, and all the spectra agreed well with those of the authentic sample.[2]

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