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Synthesis of Shikalkin (±Shikonin) and Related Compounds[1)]

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The key intermediate, 2-formyl-1,4,5,8-tetramethoxynaphthalene, was prepared through 1,4,5,8-tetramethoxynaphthalene, which was obtained from 1,5-naphthalenediol via three steps or from naphthazarin via one step. A total synthesis of shikalkin and dihydroshikalkin have been accomplished with this aldehyde via a side-chain introductions with Grignard reactions and the following demethylations.

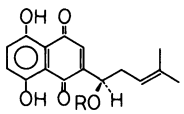
A root of *Lithospermum erythrorhizon* Sieb. et Zucc. found in Japan, China, and Korea is called Shikon and contains purple pigments (about 1 wt%) under the bark. Two kinds of Shikon are available in the market. One is called "Ko-shikon," which is the root of the above, and the other is "Nan-shikon," which is the root of *Macrotomia euchroma* Pauls. From ancient times the purple pigments have been used as dyes, which are well known as Kodaimurasaki. They can be represented by shikonin and its esters as Fig. 1.

These compounds have antiinflammatory,[4)] antibacterial,[5)] and antitumor actions,[6)] and are also used as raw materials for dyes[7)] and cosmetics.[8)]

Alkanna tinctoria in Europe contains alkannin,[9)] an enantiomer of shikonin. According to a proposal of R. Kuhn, Brockmann named the racemate shikalkin, an equimolar mixture of shikonin and alkannin. Japanese shikonin also contains 20% shikalkin.[10)]

Kuroda[11)] and Brockmann[9)] reported on shikonin's structure and a synthesis of its derivatives, but there was no report concerning the total synthesis of shikonin itself. First, Kuroda had proposed that all three hydroxyl groups in shikonin were bonded to the naphthazarin skeleton; finally, however, formula **1-a** was established by Brockmann.[9a)] Arakawa et al.[12)] showed that the absolute configuration of the α-hydroxyl group in shikonin is *R*.

Shikonin and alkannin are so labile that they must be delicately handled during their extraction.[9b,11)] The fact that shikonin cyclizes easily by Lewis acid[13)] to cycloshikonin has posed difficulties in attempts toward its total synthesis. Until recently, cycloshikonin and cycloalkannin had been considered to possess structure **2**, but Sankawa et al.[14)] proved that the real structure was the ether **3** Fig. 2.



1a—f

(**a**) Shikonin R : H. (**b**) Acetylshikonin R : $COCH_3$. (**c**) 3-Methyl-2-butenoylshikonin R : $COCH{=}C(CH_3)_2$.[2)] (**d**) Isobutyrylshikonin R : $COCH(CH_3)_2$.[2)] (**e**) 3,4-Dimethyl-3-pentenoylshikonin R : $COCH_2C(CH_3){=}C(CH_3)_2$.[3)] (**f**) β-Hydroxyisovalerylshikonin R : $COCH_2C(OH)(CH_3)_2$.[3)]

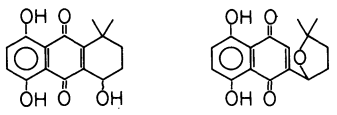
Fig. 1.

In a recent communication we reported on the total synthesis of shikalkin[(±)shikonin].[15)] The present paper describes the total synthesis in detail in addition to related compounds of shikalkin, and a new synthetic method of 1,4,5,8-tetramethoxynaphthalene.

Results and Discussion

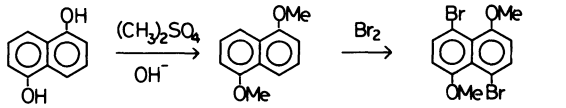
Methylation of 1,5-naphthalenediol with dimethyl sulfate provided 1,5-dimethoxynaphthalene (**4**).[16)] Bromination of **4** gave 4,8-dibromo-1,5-dimethoxynaphthalene (**5**).[17)] Zweig et al.[18)] reported that the compound **5** gave 1,4,5,8-tetramethoxynaphthalene (**6**) (19%) when treated with sodium methoxide and copper(I) oxide in DMF. By using copper(I) iodide[19)] instead of copper(I) oxide we were able to obtain **6** in a good yield (84%). The treatment of **6** with Vilsmeier reagent ($POCl_3$, DMF)[20)] gave 2-formyl-1,4,5,8-tetramethoxynaphthalene (**7**) in 99% yield.

Compound **6** was also synthesized from naphthazarin, which was easily prepared by a treatment of

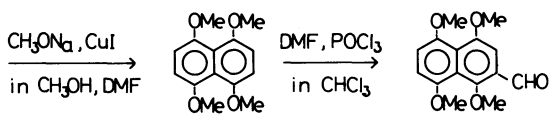


2 3

Fig. 2.



4 5



6 7

Fig. 3.

maleic anhydride with hydroquinone in a molten mixture of aluminum chloride and sodium chloride.[11b] According to Thomson's procedure, methylation of naphthazarin with methyl *p*-toluenesulfonate gave 5,8-dimethoxy-1,4-naphthoquinone (**8**) in 44% yield.[21] Reduction of the quinone **8** and methylation were simultaneously accomplished with sodium dithionite and dimethyl sulfate to give the tetramethyl ether **6** (48%). The ether **6** was also directly prepared in 44% yield from naphthazarin without the isolation of the quinone **8**.

First, the synthesis of dihydroshikalkin was tried. A treatment of the aldehyde **7** with isopentylmagnesium bromide gave 2-(1-hydroxy-4-methylpentyl)-1,4,5,8-tetramethoxynaphthalene (**9**) (95%). Methylation of **9** with methyl iodide gave 2-(1-methoxy-4-methylpentyl)-1,4,5,8-tetramethoxynaphthalene (**10**) (81%), which was transformed into a 1,4-naphthoquinone derivative **11** (42%)[22] by oxidation using cerium(IV) ammonium nitrate [$Ce(NH_4)_2(NO_3)_6$, CAN].[23]

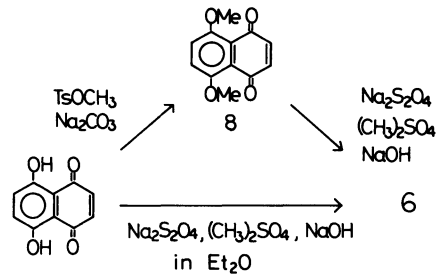


Fig. 4.

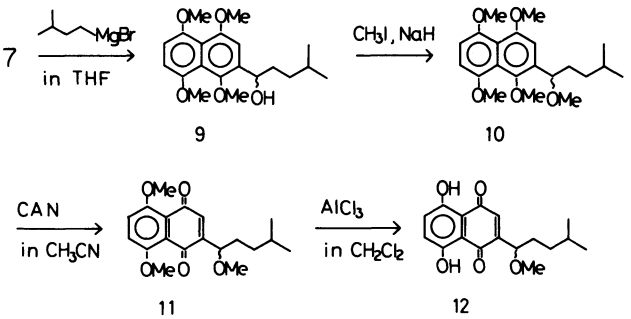


Fig. 5.

Demethylation of **11** with aluminum chloride[24] gave 5,8-dihydroxy-2-(1-methoxy-4-methylpentyl)-1,4-naphthoquinone (**12**) in 49% yield. The ^1H NMR spectrum showed signals at δ 12.49 (1H), 12.59 (1H) due to phenolic hydroxyl groups whose protons form strong hydrogen bonds. The presence of a signal at δ 3.32 (3H) due to the methoxyl group suggested that no demethylation in the side chain had occurred. Therefore, a similar reaction was carried out without the protection of the hydroxyl group (shown in the scheme of Fig. 6).

Oxidation of **9** with CAN gave 2-(1-hydroxy-4-methylpentyl)-5,8-dimethoxy-1,4-naphthoquinone (**13**) (52%) as a major product. Further demethylation of the quinone **13** with aluminum chloride gave crude products, which were purified by silica-gel chromatography to afford two products.

The IR of the product eluted first barely showed a broad absorption at 3100—3700 cm^{-1}, which is similar to the spectrum of naphthazarin. The lack of a secondary alcoholic hydroxyl group was also proved by the IR spectrum which showed no C–O stretching band at 1060 cm^{-1}. The ^1H NMR spectrum showed signals at δ 12.47 (1H), 12.61 (1H) due to the phenolic hydroxyl groups; however, no signal was found at δ 3—6. Therefore, it was thought that there was no other hydroxyl group present. The mass spectrum (*m/z*, 274, M^+)[25] and the above spectral data revealed that the structure was **15**. Kyogoku et al.[26] had obtained this from the natural product. The formation mechanism of **15** will be investigated more and reported in the near future.

The product eluted next (in 48% yield) was similar to shikonin under an IR comparison. The presence of a secondary alcoholic hydroxyl group was confirmed by a broad absorption at 3050—3700 cm^{-1} and a C–O band at 1060 cm^{-1}. The ^1H NMR spectrum showed

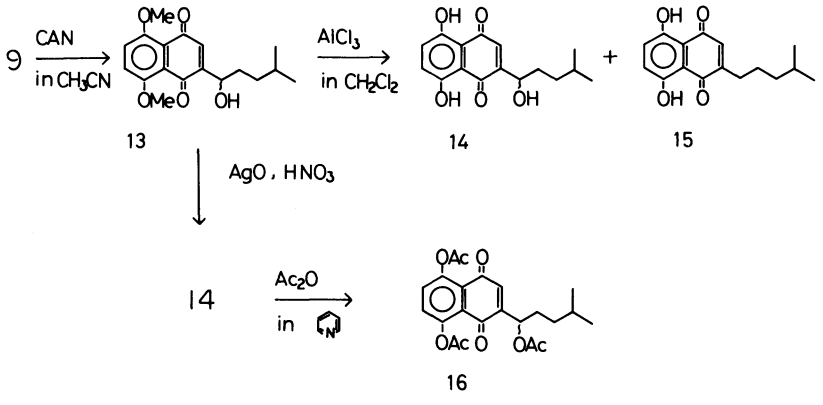


Fig. 6.

signals at δ 12.46 (1H), 12.58 (1H) due to hydrogen-bonded phenolic hydroxyl groups, and at δ 4.87 (1H) due to a proton of the methine attached to the secondary hydroxyl group. The mass spectrum of the product clearly exhibited a molecular ion peak at *m/z* 290. These data as well as an elemental analysis clearly indicated that this was the proposed dihydroshikalkin, 5,8-dihydroxy-2-(1-hydroxy-4-methylpentyl)-1,4-naphthoquinone (**14**). Sankawa et al.[6] had obtained this from the natural product.

Since demethylation using aluminum chloride is accompanied by various side reactions; Parker et al. used AgO–HNO_3[27] as a demethylation reagent. In an analogous way, demethylation of **13** with AgO–HNO_3 gave **14** in 28% yield. Treatment of **14** with acetic anhydride in pyridine afforded triacetate **16**.

The total synthesis of shikalkin is described below.

Treatment of methyl vinyl ketone with hydrogen bromide by the procedure of Gerlach et al.[28]; and acetalization with ethylene glycol in the presence of an acid catalyst gave 4-bromo-2-butanone ethylene acetal **17**. The treatment of the aldehyde **7** with the Grignard reagent of **17** afforded 2-[4,4-(ethylenedioxy)-1-hydroxypentyl]-1,4,5,8-tetramethoxynaphthalene (**18**) in 96% yield. Methylation of **18** with methyl iodide gave an ether, which was converted into 2-(1-methoxy-4-oxopentyl)-1,4,5,8-tetramethoxynaphthalene (**19**) by deacetalization in the presence of an acid. The ketone **19** was treated with methylmagnesium iodide to give 2-(1-methoxy-4-hydroxy-4-methylpentyl)-1,4,5,8-tetramethoxynaphthalene (**20**) in 86% yield. Dehydration of the alcohol **20** with thionyl chloride in pyridine at −18 °C gave 2-(1-methoxy-4-methyl-4-pentenyl)-1,4,5,8-tetramethoxynaphthalene (**22**) and 2-(1-methoxy-4-methyl-3-pentenyl)-1,4,5,8-tetramethoxynaphthalene (**21**). The ratio of these two isomers was about 3:5 as judged by gas chromatography.

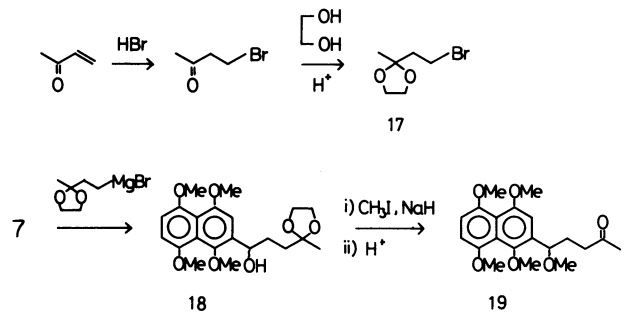


Fig. 7.

A variety of reagents such as HBr, $AlCl_3$, $(CH_3)_3SiI$, BBr_3, etc.,[29,30] are available for the demethylation of methyl ethers; however, hard reaction conditions are usually required except for BBr_3 and $(CH_3)_3SiI$. Our preliminary attempt to treat 1,4,5,8-tetramethoxynaphthalene **6** with BBr_3 at −78 °C gave the naphthazarin (**23**) in 68% yield. Then, a demethylation of **21** with BBr_3 in CH_2Cl_2 at −70—−80 °C afforded the cyclic ether **3** in 5% yield instead of the desired shikalkin **24**. A cleavage of the ether **21** with $AlCl_3$ or $(CH_3)_3SiI$ was unsuccessful.

A synthesis of shikalkin was attempted while considering the following two points: 1) that the carbon–carbon double bond of the side chain should be introduced as late as possible, and 2) the selection of a protecting group for the secondary alcoholic hydroxyl group which could be easily removed under mild conditions.

Deacetalization of **18** with an acid afforded the ketone **25** and a treatment of **25** with methylmagnesium iodide gave 2-(1,4-dihydroxy-4-methylpentyl)-1,4,5,8-tetramethoxynaphthalene (**26**). Oxidation of **26** with CAN afforded 5,8-dimethoxy-2-(1,4-dihydroxy-4-methylpentyl)-1,4-naphthoquinone (**27**) as a major product, and further demethylation of **27** with AgO–HNO_3 yielded 5,8-dihydroxy-2-(1,4-dihydroxy-4-methylpentyl)-1,4-naphthoquinone (**28**). Acetylation of **28** with acetic anhydride in pyridine gave the

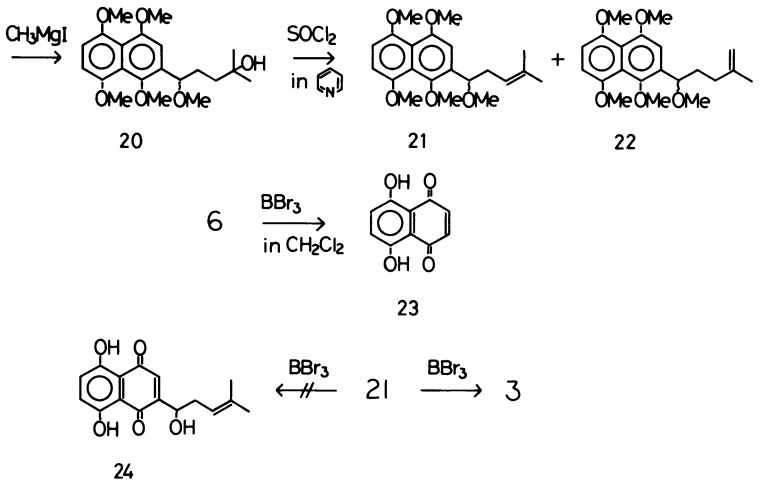


Fig. 8.

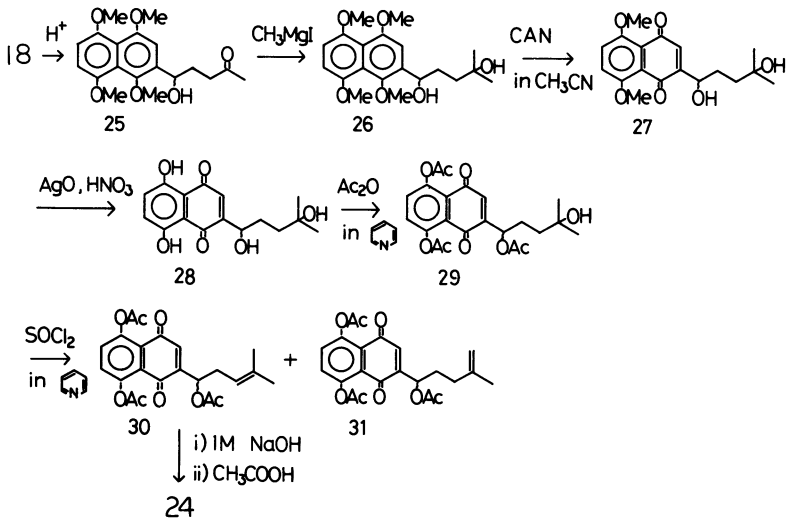


Fig. 9.

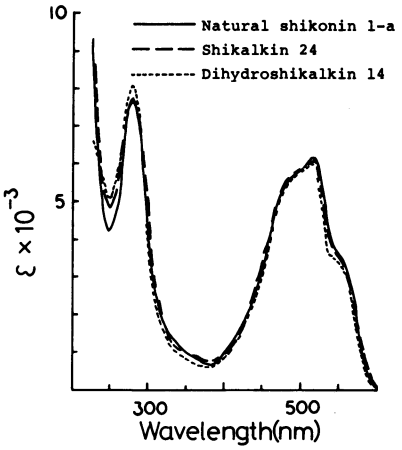


Fig. 10.

triacetate **29**. The secondary hydroxyl group of **28** was acetylated, but tertiary one was not because of a steric hindrance. The treatment of **29** with thionyl chloride in pyridine at −38 °C afforded a mixture of dehydrated compounds, **30** and **31**, in 46% yield. The ratio of these two isomers **30**:**31** was ca. 3:1 as judged by the ^{1}H NMR. Compound **30** was separated by chromatography on silica-gel and was then hydrolyzed by an alkali; and neutralization with acetic acid gave shikalkin **24** in 37% yield.

The ultraviolet spectra of natural shikonin extracted from shikon, synthetic shikalkin **24**, and dihydroshikalkin **14** are shown in Fig. 10. In the spectra of all compounds the benzenoid and quinonoid electron-transfer (E.T.) bands appear at 278 nm, and the benzenoid E.T. band at 515 nm.

Experimental

^{1}H 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 and the UV spectra on a Shimadzu recording spectrometer UV-200S. Analytical GLC was performed on a Shimadzu GC-6A gas chromatography using Silicone SE-30. High-performance liquid chromatography (HPLC) was performed with a EYELA PLC-10 using TC-ODS 1171. Column chromatography was performed on silica gel (Wakogel C-200) and alumina (Sumitomo activated alumina, KCG-30). Melting points were determined with a Yanagimoto micromelting point apparatus and were uncorrected.

1,5-Dimethoxynaphthalene **4**, mp 181—182 °C (lit,[16] 183—184 °C) was prepared by the method of Benthey.[16]

4,8-Dibromo-1,5-dimethoxynaphthalene (5). Bromine (49.3 g, 0.32 mol) in carbon tetrachloride (50 ml) was added to a solution of 1,5-dimethoxynaphthalene (30.3 g, 0.16 mol) *in carbon tetrachloride (600 ml) at 70—71 °C. After stirring* at 70 °C for 30 min, the solution was concentrated and the residue was recrystallized from carbon tetrachloride to give 32.4 g (58%) of **5**, mp 187—189 °C (lit,[17] 187 °C). Found: C, 41.64; H, 2.93%. Calcd for $C_{12}H_{10}O_2Br_2$: C, 41.65; H, 2.91%.

1,4,5,8-Tetramethoxynaphthalene (6). A 6 from 5. A mixture of 4,8-dibromo-1,5-dimethoxynaphthalene (11 g, 32 mmol), sodium methoxide (5.7 g, 106 mmol), copper(I) iodide (20 g, 106 mmol), *N,N*-dimethylformamide (360 ml) and methanol (360 ml) was refluxed for 30 h. The cooled mixture was poured into ice water and the resulting precipitate was filtered, washed with water and dried. It was extracted with chloroform, and evaporation of the solvent gave a solid residue which was chromatographed on alumina. The fractions taken from the column were recrystallized from ligroin to give 6.66 g (84%) of **6** as white needles, mp 168.5—169 °C (lit.,[17] 167—168 °C). Found: C, 67.53; H, 6.58%. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50%.

B 6 from 8. 5,8-Dimethoxy-1,4-naphthoquinone (**8**) was prepared according to the method described in the literature.[20] To a solution of the quinone **8** (2.19 g, 10 mmol) in methanol (10 ml) was added 40% aqueous sodium hydroxide (5 ml). The solution was alternatively

treated with sodium dithionite (8.5 g, 49 mmol) in water (10 ml), and dimethyl sulfate (6 g, 49 mmol) under reflux for 8 h. After cooling, the reaction mixture was diluted with water and extracted with chloroform. The chloroform solution was washed with brine, dried, and evaporated. The residue was chromatographed on alumina and recrystallized from ligroin to give 1.20 g (48%) of **6**, mp 168—169 °C.

C. 6 from Naphthazarin. To a solution of naphthazarin (0.19 g, 1 mmol) in ether (40 ml) was added sodium dithionite (0.53 g, 3 mmol) in water (10 ml) with stirring. After 30 min, the solution was alternatively treated with sodium hydroxide (5 g) in water (10 ml) and dimethyl sulfate (7.5 g, 60 mmol) at room temperature for 3 h. To the solution was again added the above-mentioned amounts of aqueous sodium hydroxide, dimethyl sulfate and aqueous sodium dithionite; and the mixture was then stirred at room temperature for 12 h. The reaction mixture was acidified by the addition of hydrochloric acid and extracted with chloroform. After the usual work-up, column chromatography on alumina gave 0.11 g (44%) of **6**, mp 167—168 °C.

2-Formyl-1,4,5,8-tetramethoxynaphthalene (7). A solution of **6** (6.0 g, 25 mmol) in chloroform (50 ml) was added to a mixture of phosphoryl chloride (19.0 g, 125 mmol) and *N,N*-dimethylformamide (9.0 g, 125 mmol) and the mixture was refluxed for 6 h. It was then decomposed with ice water and extracted with chloroform. The chloroform solution was washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a residue which could be recrystallized from hexane–benzene to afford 6.72 g (99%) of **7** as yellow crystals, mp 124—125.5 °C. IR (KBr) 1673 (C=O), 2845, and 1067 cm^{-1} (OCH_3); MS *m/z* 276 (M^+) and 248 (M^+-CO); ^1H NMR ($CDCl_3$) δ=3.91, 3.92, 3.98, 3.99 (each s, 3H, OCH_3), 6.96, 7.00, 7.20 (3H, ArH), and 10.56 (s, 1H, CHO). Found: C, 65.44; H, 5.94%. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84%.

2-(1-Hydroxy-4-methylpentyl)-1,4,5,8-tetramethoxynaphthalene (9). The aldehyde **7** (2.0 g, 7.3 mmol) was added to the Grignard solution of isopentylmagnesium bromide (21.9 mmol) in tetrahydrofuran (40 ml) and the mixture was stirred at room temperature for 3 h, decomposed with aqueous ammonium chloride and extracted with chloroform. The chloroform solution was treated as usual and left a crude oil. This oil was purified by alumina chromatography to give 2.4 g (95%) of **9**. IR (neat) 3470 (OH) and 1065 cm^{-1} (OCH_3); MS *m/z* 348 (M^+) and 330 (M^+-H_2O); ^1H NMR ($CDCl_3$) δ=0.83, 0.92 (6H, $2CH_3$) 1.1—1.9 (5H, $2CH_2$, CH), 2.22 (1H, OH), 3.74 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.93 (s, 6H, $2OCH_3$), 5.20 (t, 1H, -C<u>H</u>(OH)-), 6.81 (s, 2H, ArH), and 6.97 (s, 1H, ArH).

2-(1-Methoxy-4-methylpentyl)-1,4,5,8-tetramethoxynaphthalene (10). A solution of the alcohol **9** (0.61 g, 1.76 mmol) in dry tetrahydrofuran (15 ml) was chilled to 0—5 °C, and sodium hydride (ca. 60% in oil, 0.35 g, 8.8 mmol) was added. Methyl iodide (1.25 g, 8.8 mmol) was added to this solution at 0—5 °C with strring. The mixture was allowed to stand overnight at room temperature, then poured into ice water, and extracted with chloroform. The chloroform solution was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed by a rotary evaporator to give an oil. Chromatography on alumina with chloroform as an eluent gave a purified oil of **10** (0.51 g, 81%). IR (neat) 2840 and 1060 cm^{-1} (OCH_3); MS *m/z* 362 (M^+), 330, and 291; ^1H NMR ($CDCl_3$) δ=0.83, 0.91 (6H, $2CH_3$), 1.1—1.9 (m, 5H, $2CH_2$ and CH), 3.24 (s, 3H, -CH($OC\underline{H}_3$)-), 3.76, 3.90 (each s, 3H, OCH_3), 3.94 (s, 6H, $2OCH_3$), 4.78 (t, 1H, -C<u>H</u>(OCH_3)-), 6.83 (s, 2H, ArH), 6.92 (s, 1H, ArH). Found: C, 69.00; H, 8.22%. Calcd for $C_{21}H_{30}O_5$: C, 69.59; H, 8.34%.

2-(1-Methoxy-4-methylpentyl)-5,8-dimethoxy-1,4-naphthoquinone (11). A solution of the ester **10** (1.34 g, 3.7 mmol) in acetonitrile (30 ml) was cooled in an ice bath. To this solution was added a solution of cerium(IV) ammonium nitrate (6 g, 11.1 mmol) in water (10 ml). The mixture was stirred for 30 min, diluted with water, and extracted with chloroform. After working up as usual, the crude product was purified by silica-gel chromatography to yield 0.52 g (42%) of **11**, mp 97—99 °C. IR (KBr) 1655(C=O) and 1060 cm^{-1} (OCH_3); MS *m/z* 332 (M^+), 317, and 216; ^1H NMR($CDCl_3$) δ=0.82, 0.90 (6H, $2CH_3$), 1.1—2.0 (m, 5H, $2CH_2$ and CH), 3.29 (s, 3H, OCH_3), 3.97 (s, 6H, $2OCH_3$), 4.43 (t, 1H, -C<u>H</u>(OCH_3)-), 6.78 (s, 1H, quinonoid ring H), 7.32 (s, 2H, benzenoid ring H).

5,8-Dihydroxy-2-(1-methoxy-4-methylpentyl)-1,4-naphthoquinone (12). A solution of 1,4-naphthoquinone **11** (0.18 g, 0.54 mmol) in dichloromethane (8 ml) was cooled in an ice bath. Aluminum chloride (1 g, 5.4 mmol) was added to this solution and the mixture was stirred at room temperature for 1 h. The reaction mixture was decomposed by the addition of ice water and extracted with ether. The usual work-up and purification of the crude product by silica-gel chromatography gave 80 mg (49%) of **12** as a viscous oil. IR (KBr) 1610 (C=O), 1570, and 1100 cm^{-1}; MS *m/z* 304 (M^+), 277, 232, and 229; ^1H NMR ($CDCl_3$) δ=0.83, 0.92 (6H, $2CH_3$), 1.1—1.9 (m, 5H, $2CH_2$ and CH), 3.32 (s, 3H, OCH_3), 4.50 (t, 1H, -C<u>H</u>(OCH_3)-), 7.12 (s, 1H, quinonoid ring H), 7.17 (s, 2H, benzenoid ring H), 12.49 and 12.59 (each s, 1H, ArOH).

2-(1-Hydroxy-4-methylpentyl)-5,8-dimethoxy-1,4-naphthoquinone (13). A solution of the alcohol **9** (1.3 g, 3.7 mmol) in acetonitrile (15 ml) was cooled to 10—20 °C. To this solution was added dropwise a solution of cerium(IV) ammonium nitrate(5.1 g, 9.25 mmol) in water (15 ml) under stirring. The reaction mixture was stirred at room temperature for 30 min, diluted with water and extracted with chloroform. Usual work-up and chromatography on silica-gel gave two products as viscous oils. The first eluate gave 0.20 g (17%) of an isomer of **13**, 6-(1-hydroxy-4-methylpentyl)-5,8-dimethoxy-1,4-naphthoquinone. IR (KBr) 3500 (OH), 1650 (C=O), 1580, 1560, and 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.84, 0.93 (6H, $2CH_3$), 1—2 (m, 5H, $2CH_2$ and CH), 2.60 (broad, 1H, OH), 3.82 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 5.16 (m, 1H, -C<u>H</u>(OH)-), 6.77 (2H, quinonoid ring 2H), and 7.51 (s, 1H, benzenoid ring H).

The second eluate gave 0.62 g (52%) of **13**. IR (KBr) 3500 (OH), 1650 (C=O), 1580, 1560, and 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.84, 0.93 (6H, $2CH_3$), 1—2 (m, 5H, $2CH_2$ and CH), 2.60 (broad, 1H, OH), 3.96 (s, 6H, $2OCH_3$), 4.70 (m, 1H, -C<u>H</u>(OH)-), 6.77 (1H, quinonoid ring H), and 7.31 (s, 2H, benzenoid ring H).

5,8-Dihydroxy-2-(1-hydroxy-4-methylpentyl)-1,4-naphthoquinone (14) and 5,8-Dihydroxy-2-(4-methylpentyl)-1,4-naphthoquinone (15). A, Demethylation with $AlCl_3$. Aluminum chloride (41 mg, 3.1 mmol) was added to a solution of the quinone **13** (98 mg, 0.31 mmol) in dichloromethane (5 ml) cooled in an ice bath. The reaction

mixture was stirred at room temperature for 1 h, decomposed by the addition of water (50 ml) and 5% aqueous oxalic acid (100 ml), and extracted with chloroform. After the usual work-up, the crude product was purified by silica-gel chromatography to yield two crystalline products: 22 mg (26%) of **15** from the first eluate, mp 55—70 °C (lit,[26] 99 °C). IR (KBr) 1609 (C=O) and 1570 cm^{-1}; MS *m/z* 274 (M^+), 205, and 204. Calcd for $C_{16}H_{18}O_4$: *m/z* 274.1205, Found: 274.1210. ^1H NMR ($CDCl_3$) δ=0.85, 0.94 (6H, $2CH_3$), 1.1—1.9 (m, 5H, $2CH_2$ and CH), 2.60 (t, 2H, *J*=7 Hz, $ArCH_2$–), 6.85 (s, 1H, quinonoid ring H), 7.20 (s, 2H, benzenoid ring H), 12.47 and 12.62 (each s, 1H, ArOH).

The second eluate gave 43 mg (48%) of **14**, mp 78—81 °C (lit,[6] 100—107 °C). IR (KBr) 3600—3100 (broad, OH), 1610 (C=O), 1570, and 1065 cm^{-1} (OH); MS Found: *m/z* 290.1143. Calcd: 290.1154. ^1H NMR ($CDCl_3$) δ=0.85, 0.95 (6H, $2CH_3$), 1.1—2.0 (m, 5H, $2CH_2$ and CH), 2.24 (broad, 1H, -CH(O<u>H</u>)-), 4.87 (t, 1H, -C<u>H</u>(OH)-), 7.14 (s, 1H, quinonoid ring H), 7.19 (s, 2H, benzenoid ring H), 12.46 and 12.58 (each s, 1H, ArOH). Found: C, 65.95; H, 6.45%. Calcd for $C_{16}H_{18}O_5$: C, 66.20; H, 6.25%.

B Demethylation with AgO-HNO_3. To a solution of the quinone **13** (1.10 g, 3.5 mmol) and AgO (4.27 g, 35 mmol) in acetone (50 ml), was added dropwise 40% HNO_3 (45 ml) at 15—20 °C over 5 min. The mixture was stirred at room temperature for 5 min and extracted with dichloromethane (100 ml). The dichloromethane solution was washed with brine and dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by silica-gel chromatography to afford 0.21 g (28%) of **14**, mp 79.5—81.5 °C.

5,8-Diacetoxy-(1-acetoxy-4-methylpentyl)-1,4-naphthoquinone (16). Acetic anhydride (1 ml) was added to a solution of dihydroshikalkin **14** (65 mg, 0.224 mmol) in pyridine (2.5 ml) at 0—5 °C, and stirred at 0—5 °C for 2 h. After concentration under reduced pressure at room temperature, the crude product was chromatographed on silica-gel to give 85 mg (91%) of **16**, mp 98—100 °C. IR (KBr) 1775 (ester C=O), 1745 (ester C=O), 1667 (quinone C=O), and 1188 cm^{-1}; MS *m/z* 374, 332, 272, 229, and 43 (CH_3CO^+), and no parent peak was observed. ^1H NMR ($CDCl_3$) δ=0.83, 0.92 (6H, $2CH_3$), 1.1—1.9 (m, 5H, $2CH_2$ and CH), 2.11 (s, 3H, -CH(OCOC<u>H</u>$_3$)-), 2.43 (s, 6H, ArOAc), 5.82 (t, 1H, -C<u>H</u>(OCOCH$_3$)-), 6.65 (s, 1H, quinonoid ring H), and 7.37 (s, 2H, benzenoid ring H).

4-Bromo-2-butanone Ethylene Acetal (17). Hydrogen bromide was bubbled into a freshly distilled methyl vinyl ketone (192 g, 2.74 mol) to saturate for 5 h at −80 °C; then the solution gradually solidified. To this solution was added ethylene glycol (340 g, 5.48 mol) and *p*-toluenesulfonic acid monohydrate (10 g, 0.052 mol) at −80 °C; the mixture was then stirred at −80—−40 °C for 3 h. Acetonitrile (250 ml) was added to the mixture and the solvent was evaporated at room temperature under reduced pressure; this procedure was repeated 3 times. The solution was combined with 1 M† KOH (1000 ml) and the product was extracted with hexane. After the usual work-up, the crude product was distilled under reduced pressure to yield 143 g (28%) of **17**, bp 55—56 °C/1.5 mmHg (lit,[28] 64—68 °C/9 mmHg). Found: C, 37.06; H, 5.78%. Calcd for $C_6H_{11}O_2Br$: C, 36.95; H, 5.68%.

2-[4,4-(Ethylenedioxy)-1-hydroxypentyl]-1,4,5,8-tetramethoxynaphthalene 18. The Grignard solution of the ethylene acetal **17** (26.3 mmol) in tetrahydrofuran (30 ml) was added to the aldehyde **7** (2.4 g, 8.76 mmol) and the reaction mixture was stirred at room temperature for 3 h. After a decomposition with aqueous ammonium chloride, extraction with chloroform, and usual procedures, the crude product was purified by chromatography on alumina with chloroform to give 3.28 g (96%) of **18** as an oil. IR (neat) 3480 (OH), 2850 (OCH_3), and 1060 cm^{-1} (OCH_3); MS *m/z* 392 (M^+), 374 (M^+-H_2O), and 330; ^1H NMR ($CDCl_3$) δ=1.34 (s, 3H, CH_3), 1.6—2.2 (m, 5H, $2CH_2$ and OH), 3.76 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.94 (s, 4H, $2CH_2$), 3.96 (s, 6H, $2OCH_3$), 5.20 (t, 1H, CH), 6.82 (s, 2H, ArH), and 7.01 (s, 1H, ArH).

2-(1-Methoxy-4-oxopentyl)-1,4,5,8-tetramethoxynaphthalene (19). A solution of the alcohol **18** (3.28 g, 8.4 mmol) in dry tetrahydrofuran (30 ml) was cooled to 0—5 °C, and sodium hydride (ca. 60% in oil, 1 g, 25.2 mmol) was added. Methyl iodide (5.94 g, 25.2 mmol) was added at 0—5 °C, and the mixture was allowed to stand at room temperature overnight; then it was poured into ice water and extracted with chloroform. The chloroform solution was washed with brine and dried over Na_2SO_4. After removing the solvent an oil was obtained. To the solution of this oily product in acetone (10 ml) was added *p*-toluenesulfonic acid monohydrate (100 mg). The solution was kept in a freezer for 3 h, diluted with ice water, and extracted with chloroform. After the usual work-up, the crude product was purified by silica-gel chromatography to yield **19** (1.73 g, 57%) as an oil. IR (neat) 2850 (OCH_3), 1710 (C=O), and 1060 cm^{-1} (OCH_3); MS *m/z* 362 (M^+), and 315; ^1H NMR ($CDCl_3$) δ=2.14 (s, 3H, $COCH_3$), 2.0—2.8 (m, 4H, $2CH_2$), 3.23 (s, 3H, -CH(OC<u>H</u>$_3$)-), 3.76 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.94 (s, 6H, $2OCH_3$), 4.78 (t, 1H, CH), 6.84 (s, 2H, ArH), 6.89 (s, 1H, ArH). Found: C, 65.66; H, 7.40%. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23%.

2-(4-Hydroxy-1-methoxy-4-methylpentyl)-1,4,5,8-tetramethoxynaphthalene (20). Methylmagnesium iodide (6.5 mmol) in ether (10 ml) was added to a solution of the ketone **19** (0.47 g, 1.3 mmol) in tetrahydrofuran (20 ml) at 0—5 °C and the mixture was stirred at room temperature for 3 h. After decomposition with aqueous ammonium chloride, extraction with chloroform, and usual procedure, a crude oil was chromatographed on alumina to afford 0.42 g (86%) of **20**. IR (neat) 3470 (OH), 2845, and 1075 cm^{-1}; MS *m/z* 378 (M^+), 360 (M^+-H_2O), and 291; ^1H NMR ($CDCl_3$) δ=1.20 (s, 6H, $2CH_3$), 1.4—2.0 (m, 4H, $2CH_2$), 2.21 (s, 1H, OH), 3.25 (s, 3H, -CH(OC<u>H</u>$_3$)-), 3.76 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.94 (s, 6H, $2OCH_3$), 4.81 (t, 1H, -C<u>H</u>(OCH_3)-), 6.83 (s, 2H, ArH), and 6.92 (s, 1H, ArH).

2-(1-Methoxy-4-methyl-3-pentenyl)-1,4,5,8-tetramethoxynaphthalene (21) and 2-(1-Methoxy-4-methyl-4-pentenyl)-1,4,5,8-tetramethoxynaphthalene (22). Alcohol **20** (191 mg, 0.51 mmol) in dry pyridine (1 ml) was treated with thionyl chloride (70 mg, 0.61 mmol) at 0—5 °C. This mixture was kept in a freezer for 17 h, diluted with ice water and extracted with chloroform. The chloroform solution was washed with dil hydrochloric acid, aqueous sodium hydrogencarbonate, brine, and dried over Na_2SO_4. The solvent removal provided a crude oil which was shown by GLC analysis to be a mixture of **21** and **22** (5:3). The chromatographic separation using alumina succeeded in giving two pure oils. The former eluate gave 62 mg of **22**. IR (neat) 1648 (C=CH_2),

† 1 M=1 mol dm^{-3}.

885 ($C=CH_2$), 1602, and 1073 cm^{-1}; MS *m/z* 306 (M^+); ^1H NMR ($CDCl_3$) δ=1.55 (s, 3H, $CH_2=C(C\underline{H}_3)$-), 1.8—2.2 (m, 4H, $2CH_2$), 3.25 (s, 3H, $CH(OC\underline{H}_3)$), 3.76 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.95 (s, 6H, $2OCH_3$), 4.73 (s, 2H, $C\underline{H}_2=C(CH_3)$-), 6.83 (s, 2H, ArH), and 6.94 (s, 1H, ArH).

The latter eluate afforded 104 mg of **21**. IR (neat) 1602, and 1073 cm^{-1}; MS *m/z* 360 (M^+), 328, and 291; ^1H NMR ($CDCl_3$) δ=1.55, 1.69 (6H, $2CH_3$), 2.50 (t, 2H, CH_2), 3.24 (s, 3H, -$CH(OC\underline{H}_3)$-), 3.75 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.95 (s, 6H, $2OCH_3$), 4.85 (t, 1H, *J*=6.6 Hz, -$C\underline{H}(OCH_3)$-), 5.26 (t, 1H, *J*=7.1 Hz, $(CH_3)_2C=C\underline{H}$-), 6.83 (s, 2H, ArH), and 6.95 (s, 1H, ArH). Found: C, 69.73; H, 7.85%. Calcd for $C_{21}H_{28}O_5$: C, 69.98; 7.83%.

5,8-Dihydroxy-1,4-naphthoquinone (Naphthazarin) (23). To a solution of 1,4,5,8-tetramethoxynaphthalene (**6**) (124 mg, 5 mmol) in dichloromethane (6 ml) was added dropwise BBr_3 (0.5 g, 20 mmol) in dichloromethane (6 ml) at −70 °C. After stirring at −70 °C for 2 h, the solution was allowed to warm to room temperature and to stand overnight. It was then poured into ice water and extracted with ether. After the usual work-up, sublimation of the crude product afforded 65 mg (68%) of pure **23**, mp 200—202 °C (lit,[31] 201—202 °C). IR (KBr) 1610 (C=O), 1565, and 1225 cm^{-1}; MS *m/z* 190 (M^+), 136, 134, and 108; ^1H NMR ($CDCl_3$) δ= 7.14 (s, 4H, ArH), and 12.39 (s, 2H, ArOH).

5,8-Dihydroxy-2-(5,5-dimethyl-2-tetrahydrofuranyl)-1,4-naphthoquinone (3). To the above obtained olefin **21** (119 mg, 0.33 mmol) dissolved in dichloromethane (2.5 ml) was added dropwise BBr_3 (248 mg, 0.99 mmol) in dichloromethane (2.5 ml) at −78 °C. After stirring at −78 °C for 2 h, the solution was allowed to warm to room temperature and to stand overnight. The solution was then poured into aqueous 1 M sodium hydroxide (30 ml) cooled in an ice bath, stirred for 1 h, and centrifuged to settle the precipitate. To the clean layer was added aqueous ammonium chloride (300 ml) and extracted with ether. After the usual work-up, column chromatography of the residue on silica gel afforded 5 mg (5%) of **3**, mp 79—80.5 °C (lit,[9a] 79—80 °C). IR (KBr) 1610 (C=O), 1570, and 1065 cm^{-1}; MS *m/z* 288 (M^+), and 219; ^1H NMR ($CDCl_3$) δ=1.36 (s, 6H, $2CH_3$), 1.80—1.85 and 2.39—2.81 (m, 4H, $2CH_2$), 5.14 (t, 1H, CH), 7.19 (s, 3H, ArH), and 12.51 (s, 2H, ArOH).

2-(1-Hydroxy-4-oxopentyl)-1,4,5,8-tetramethoxynaphthalene (25). A solution of the acetal **18** (7.53 g, 19.2 mmol) in acetone (30 ml) was cooled to 0—5 °C and *p*-toluenesulfonic acid monohydrate (250 mg) was added. The solution was kept in a refrigerator for 3 h with occasional shaking, diluted with ice water, and extracted with chloroform. After the usual work-up, the crude product was purified by chromatography of alumina to give 5.8 g (87%) of **25** as an oil. IR (neat) 3450 (OH), 1705 (C=O), 1600, and 1062 cm^{-1}; MS Found: *m/z* 348.1577. Calcd for $C_{19}H_{24}O_6$: *m/z* 348.1573. ^1H NMR ($CDCl_3$) δ=2.15 (s, 3H, $COCH_3$), 1.8—2.8 (m, 5H, $2CH_2$ and OH), 3.74 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.93 (s, 6H, $2OCH_3$), 5.21 (t, 1H, *J*=6.6 Hz, -$C\underline{H}(OH)$-), 6.81 (s, 2H, ArH), and 6.98 (s, 1H, ArH).

2-(1,4-Dihydroxy-4-methylpentyl)-1,4,5,8-tetramethoxynaphthalene (26). Methylmagnesium iodide (0.15 mol) in ether (30 ml) was added to a solution of ketone **25** (6.26 g, 0.018 mol) in tetrahydrofuran (120 ml) at 0—5 °C, and the mixture was stirred at room temperature for 3 h. After the usual procedures, the crude product was purified by alumina chromatography to afford 5.62 g (86%) of **26**. Recrystallization from ligroin–benzene (4:1) gave crystals, mp 114—115 °C. IR (KBr) 3400 (broad, OH), 1600, and 1070 cm^{-1}; MS Found: *m/z* 364.1900; Calcd: 364.1884. ^1H NMR ($CDCl_3$) δ=1.25 (s, 6H, $2CH_3$), 1.6—2.2 (m, 6H, $2CH_2$ and 2OH), 3.76, 3.89, 3.94, 3.95 (each s, 3H, OCH_3), 5.25 (t, 1H, -$C\underline{H}(OH)$-), 6.82 (s, 2H, ArH), and 7.01 (s, 1H, ArH). Found: C, 65.23; H, 7.73%. Calcd for $C_{20}H_{28}O_6$: C, 65.92; H, 7.74%.

2-(1,4-Dihydroxy-4-methylpentyl)-5,8-dimethoxy-1,4-naphthoquinone (27). A solution of cerium(IV) ammonium nitrate (7.57 g, 14 mmol) in water (25 ml) was added dropwise to a solution of the ether **26** (2.01 g, 6 mmol) in a mixed solvent of chloroform (5 ml) and acetonitrile (25 ml) at room temperature for 5 min. The mixture was stirred at room temperature for 10 min, diluted with ice water, and extracted with chloroform. After the usual work-up, the chromatography on alumina gave two products. The first eluate gave 0.28 g (15%) of an isomer of **27**, 6-(1,4-dihydroxy-4-methylpentyl)-5,8-dimethoxy-1,4-naphthoquinone, as a viscous oil. IR (KBr) 3430, 1650, 1588, and 1052 cm^{-1}; MS Found: *m/z* 334.1429. Calcd for $C_{18}H_{22}O_6$: 334.1417. ^1H NMR ($CDCl_3$) δ=1.24 (s, 6H, $2CH_3$), 1.5—2.1 (m, 4H, $2CH_2$), 2.2—2.6 (broad, 2H, OH), 3.81 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 5.15 (m, 1H, CH), 6.76 (s, 2H, quinonoid ring H), and 7.58 (s, 1H, benzenoid ring H).

The second eluate gave 1.29 g (70%) of **27**. Recrystallization from ligroin–benzene–chloroform mixture gave crystals, mp 127.5—130.5 °C. IR (KBr) 3430 (broad, OH), 1650 (C=O), 1588, and 1052 cm^{-1}; MS *m/z* 334 (M^+); ^1H NMR ($CDCl_3$) δ=1.24 (s, 6H, $2CH_3$), 1.5—2.1 (m, 4H, $2CH_2$), 2.2—2.6 (broad, 2H, 2OH), 3.94 (s, 6H, $2OCH_3$), 4.77 (m, 1H, CH), 6.84 (d, 1H, quinonoid ring H), and 7.29 (s, 2H, benzenoid ring H). Found: C, 64.06; H, 6.73%. Calcd for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63%.

2-(1,4-Dihydroxy-4-methylpentyl)-5,8-dihydroxy-1,4-naphthoquinone (28). To a mixture of the 1,4-naphthoquinone **27** (503 mg, 1.51 mmol) and AgO (1.86 g, 15.1 mmol) in acetone (35 ml) was added 40% HNO_3 (28 ml) at 15—20 °C over 10 min. The reaction mixture was stirred at room temperature for 10 min and extracted with chloroform. The chloroform solution was washed with brine and dried over Na_2SO_4. The solvent was removed to give a crude product; this was purified by silica-gel chromatography to afford 124 mg (27%) of **28**, mp 151—152 °C. IR (KBr) 3300, 3200 (each broad, OH), 1610 (C=O), 1570, 1210, and 1080 cm^{-1}; MS Found: *m/z* 306.1079; Calcd: 306.1103. ^1H NMR ($CDCl_3$) δ=1.25 (s, 6H, $2CH_3$), 1.5—2.7 (m, 6H, $2CH_2$ and 2OH), 4.93 (t, 1H, -$C\underline{H}(OH)$-), 7.19 (s, 3H, ArH), 12.49 and 12.59 (each s, 1H, ArOH). Found: C, 62.43; H, 6.00%. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92%.

5,8-Diacetoxy-2-(1-acetoxy-4-hydroxy-4-methylpentyl)-1,4-naphthoquinone (29). Acetic anhydride (1 ml) was added to a solution of the tetraol **28** (69 mg, 0.225 mmol) in pyridine (2 ml) at 0—5 °C, and the mixture was stirred at 0—5 °C for 2 h. Excess of the reagent was removed under reduced pressure at room temperature, and the crude product was chromatographed on silica-gel to give 86 mg (88%) of the triacetate **29**. Recrystallization from ligroine–benzene gave crystals, mp 156.5—158.5 °C. IR (KBr) 3500 (broad, OH), 1770 (ester C=O), 1740 (ester C=O), 1660 (quinone C=O), and 1185 cm^{-1}; MS *m/z* 372, 371 (M^+−61),

288, 232, 219, and 43 (CH_3CO^+), and no parent peak was observed. ^1H NMR ($CDCl_3$) δ=1.20 (s, 6H, $2CH_3$), 1.4—2.4 (m, 5H, $2CH_2$ and OH), 2.12 (s, 3H, CH(OCOC$\underline{H}_3$)), 2.43 (s, 6H, ArOCOC$\underline{H}_3$), 5.87 (t, 1H, CH), 6.66 (s, 1H, ArH), and 7.37 (s, 2H, ArH). Found: C, 61.04; H, 5.57%. Calcd for $C_{22}H_{24}O_9$: C, 61.11; H, 5.59%.

5,8-Diacetoxy-2-(1-acetoxy-4-methyl-3-pentenyl)-1,4-naphthoquinone (30) and 5,8-Diacetoxy-2-(1-acetoxy-4-methyl-4-pentenyl)-1,4-naphthoquinone (31). The triacetate **29** (213 mg, 0.49 mmol) in dry pyridine (1.5 ml) was chilled to −38 °C, and thionyl chloride (70.4 mg, 0.59 mmol) was added. The mixture was stirred at −38 °C for 7 min and then poured into ice water. The reaction mixture was extracted with dichloromethane, and washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography of the residue on silica-gel brought two viscous oils of **30** and **31** (3:1). The former eluate gave 23 mg (12%) of **31**. IR (KBr) 1770 (ester C=O), 1750 (ester C=O), 1665 (quinone C=O), and 888 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ=1.56 (s, 3H, CH_2=C($C\underline{H}_3$)-), 1.9—2.5 (m, 4H, $2CH_2$), 2.09 (s, 3H, -CH(OCOC$\underline{H}_3$)-), 2.43 (s, 6H, ArOCOCH_3), 4.69 (s, 2H, C$\underline{H}_2$=C(CH_3)-), 5.87 (t, 1H, CH), 6.65 (s, 1H, ArH), and 7.37 (s, 2H, ArH).

The latter eluate afforded 70 mg (34%) of **30**. IR (KBr) 1770, 1750 (each ester C=O), and 1665 cm^{-1} (quinone C=O); ^1H NMR ($CDCl_3$) δ=1.56, 1.67 (6H, $2CH_3$), 1.9—2.5 (m, 4H, $2CH_2$), 2.09 (s, 3H, -CH(OCOC$\underline{H}_3$)-), 2.43 (s, 6H, ArOCOCH_3), 5.07 (t, 1H, $(CH_3)_2$C=C$\underline{H}$-), 5.87 (t, 1H, -C$\underline{H}$(OAc)-), 6.65 (s, 1H, ArH), and 7.37 (s, 2H, ArH).

5,8-Dihydroxy-(1-hydroxy-4-methyl-3-pentenyl)-1,4-naphthoquinone (24). The triacetate of the internal olefin **30** (63 mg, 0.15 mmol) was dissolved in aqueous 1 M sodium hydroxide (50 ml) and stirred during 3 h. The solution was filtered and the filtrate was acidified by addition of acetic acid until the solution turned red. The product was extracted with dichloromethane, washed with aqueous sodium hydrogencarbonate, brine, and dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by silica-gel chromatography to afford 16 mg (37%) of **24**, mp 146—148 °C (lit,[9a] 148 °C). IR (KBr) 3400, 3100 (each broad, OH), 1613 (C=O), 1570, and 1075 cm^{-1}; MS Found: *m/z* 288.0999. Calcd: *m/z* 288.0997. ^1H NMR ($CDCl_3$) δ=1.66, 1.76 (6H, $2CH_3$), 2.1—2.9 (m, 3H, CH_2 and OH), 4.97 (t, 1H, -C$\underline{H}$(OH)-), 5.19 (t, 1H, (CH_3)C=C$\underline{H}$-), 7.20 (s, 3H, ArH), 12.49 and 12.59 (each s, 1H, ArOH). Found C, 66.34; H, 5.60%. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59%.

Isolation of Shikonin 1-a. Shikonin **1-a** was isolated from "Ko-shikon" according to the procedure described by Toribara,[9b] mp 146—147.5 °C (lit,[13] 147—149 °C). Found: C, 66.32; H, 5.66%. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59%.

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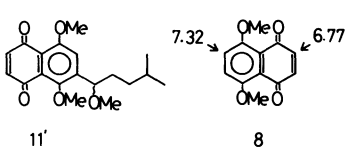
22) The ^1H NMR spectrum of **11** showed signals at δ 6.78 (1H) due to quinonoid ring proton and 7.32 (2H) due to benzenoid ring proton. Because signals of quinonoid ring protons are usually observed at upper field than those of benzenoid ring protons.



11' 8

Fig. 11.

The structure 11′ was excluded because of these two protons being in the quinonoid ring. These are also supported with the NMR spectrum of dimethoxynaphthazarin **8**, whose spectrum showed signals at δ 6.77 due to the quinonoid ring protons and δ 7.32 the benzenoid ring protons.

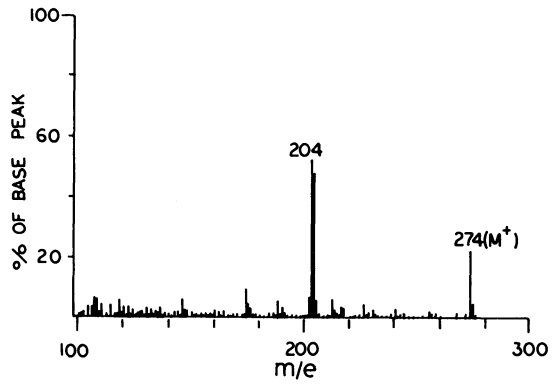


Fig. 12.

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