Successive Michael Reaction-Sigmatropic Rearrangement of Naphthodiquinone with *O*-Silylated Ketene Acetals Leading to Synthesis of Cycloshikonin and Structure–Reactivity Relationship for Side Chain of Naphthazarins

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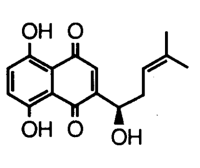
Synthesis of cycloshikonin *via* successive Michael reaction-sigmatropic rearrangement of naphthodiquinone with *O*-silylated ketene acetals is described. The structure dependence of the reactivity of the side chain of intermediary naphthazarin derivatives has also been investigated.

Keywords cycloshikonin; *O*-silyl ketene acetal; naphthazarin; naphthodiquinone; Michael reaction; sigmatropic rearrangement

Shikon, the root of *Lithospermum erythrorhizon*, contains substituted naphthazarin derivatives and has been used as a dyestuff and medicine. Shikonin (**1**)[1] is one of the constituents of shikon and has important biological activities[2] such as antibacterial, and antiulcer activity as does its enantiomer, alkannin. The antitumor activity of shikonin and its derivatives[3] and their structural similarity to anthracycline antibiotics (*peri*-hydroxy quinone skeleton and leaving groups which are easily eliminated after reduction of the quinone nucleus) have attracted much attention and synthetic studies of shikonin have been reported.[4] Introduction of the side chain into the naphthazarin skeleton was accomplished *via* the reaction naphthaldehyde with appropriate nucleophiles, the acid-catalyzed nucleophilic substitution of naphthazarin with acetals, and so on.

On the other hand, cycloshikonin (**2**) is easily formed from shikonin under acidic conditions and has considerable antitumor activity, like shikonin. Shikonin is unstable in acidic conditions, and is obtained from cycloshikonin.[5] Thus, cycloshikonin can be regarded as an intermediate in the synthesis of shikonin.

In the course of our studies on site-selective reactions of polyquinones, we developed a successive Michael reaction-sigmatropic rearrangement sequence, wherein naphthodiquinone (**3**) reacts with silyl ketene acetal (**4a**) to give the substituted naphthazarin **7a** in good yield (Chart 2).[6] The obtained **7a** has a suitable side chain for the synthesis of cycloshikonin.


1: (+)-shikonin

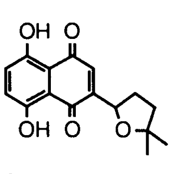

2: cycloshikonin

Chart 1

Here we present the full experimental details of our studies on the synthesis of (±)-cycloshikonin and the chemistry of transformation of the side chain of naphthazarin derivatives such as **7b** and **7c**.

Results and Discussion

Synthesis of Cycloshikonin Based on the retrosynthetic analysis shown in Chart 3, the tertiary alcohol **8** and secondary alcohol **9**, which could be obtained from **7b** and **7c**, respectively, seemed to be promising intermediates for the synthesis of cycloshikonin and shikonin. Thus, silyl ketene acetals **4b** and **4c** were prepared[7,8] for the reaction with **3**.

Conjugate addition of **3** with **4b** proceeded with ease to afford **5b**. After characterization of the structure, heating of **5b** in benzene at reflux caused a [3, 3] sigmatropic rearrangement. The reaction could be monitored by TLC and the formation of **6b** was anticipated by analogy with the reaction of **3** with **4a**. Since **6b** was unstable, rearrangement of **6b** was conducted without confirmation of the structure by NMR spectroscopy. Successive Claisen rearrangement of **6b** under reductive conditions afforded **7b** in 80% yield from **3**, and this confirmed the structure of **6b** (Chart 4). Reaction of **3** with **4c** proceeded with ease to give **5c**, which further rearranged to **7c** *via* **6c** by consecutive [3, 3] sigmatropic rearrangements (68% from **3**). In this manner, successful introduction of a side chain onto the naphthazarin skeleton was effected in a three-step one-pot reaction of **3** with silyl ketene acetals **4**.

The naphthazarin skeletons of **7b** and **7c** were protected as acetates or leucoacetates (masked naphthazarins) for

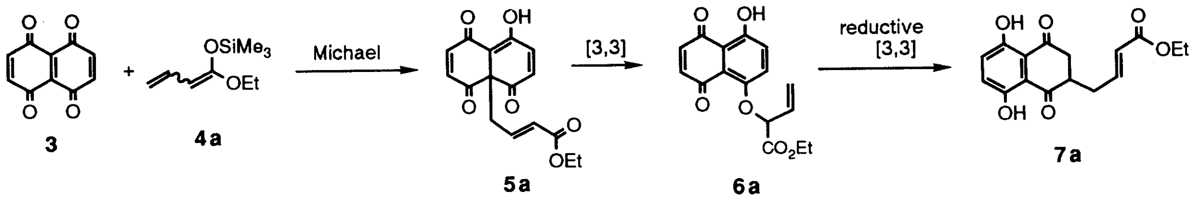


Chart 2

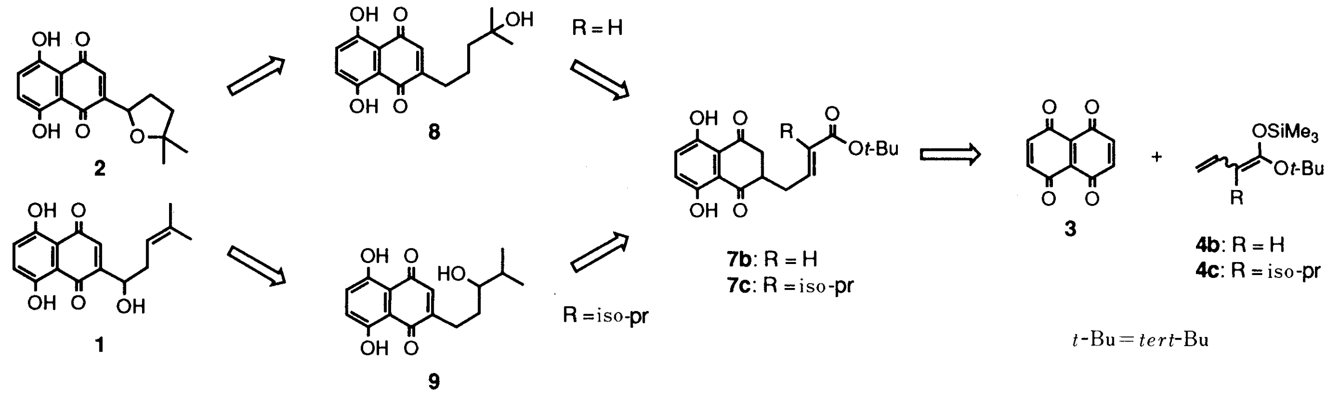
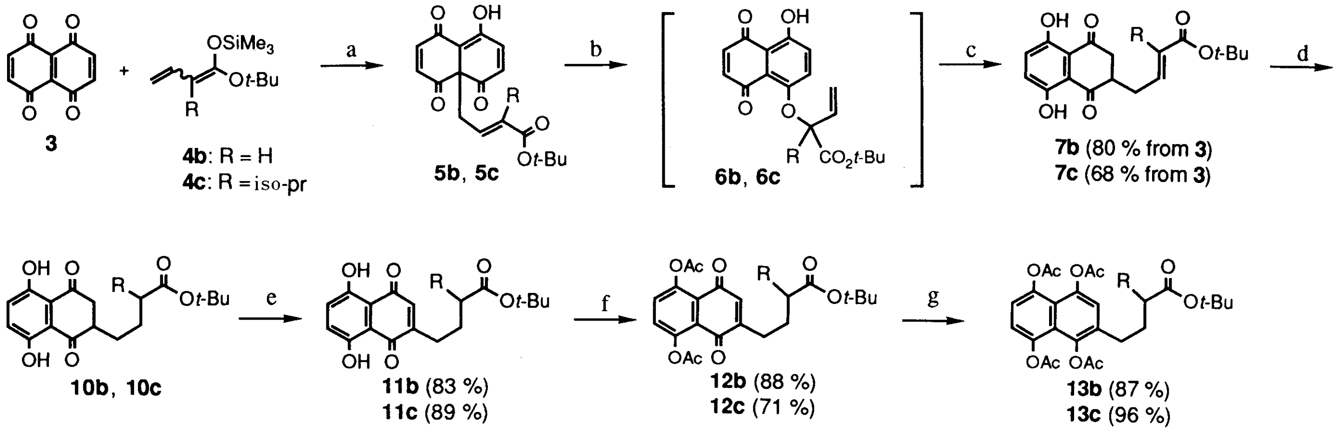
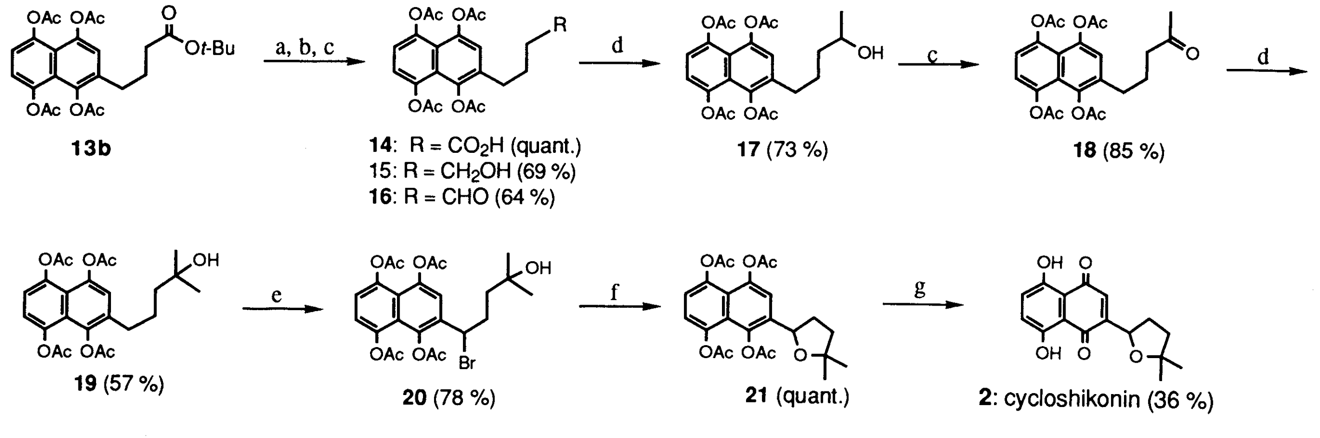


Chart 3



reagents and conditions : a) CH_2Cl_2, -78 °C . b) benzene reflux. c) $Na_2S_2O_4$, ether–H_2O, 25 °C. d) H_2, Pd-C or PtO_2, EtOH–AcOEt, 25 °C. e) TMSCl, NaBr, DMSO, MeCN, 25 °C. f) Ac_2O, pyridine, DMAP, CH_2Cl_2, 25 °C. g) $Na_2S_2O_4$, ether-H_2O, then Ac_2O, pyridine, DMAP, CH_2Cl_2, 25°C

Chart 4



reagents and conditions : a) CF_3CO_2H, CH_2Cl_2, 0 °C . b) BH_3-THF complex, THF, 0 °C. c) PCC, Celite, CH_2Cl_2, 25 °C. d) MeMgI, THF , -78 °C. e) Br_2, AIBN, CCl_4, 70 °C. f) $AgNO_3$, 50% aqueous acetone, 25 °C . g) 1 N KOH, 0 °C

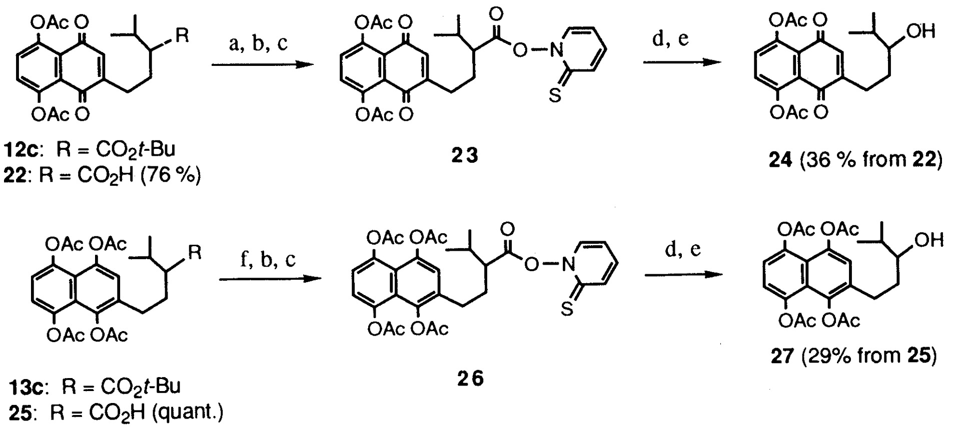
Chart 5

transformation of the side chains. After catalytic hydrogenation of **7b** and **7c**, oxidation of the leuconaphthazarin skeleton of **10b** and **10c** to the naphthazarins **11b** and **11c**[9] followed by acetylation gave **12b** and **12c**, respectively. Further reduction of **12b** and **12c** with $Na_2S_2O_4$ followed by acetylation afforded **13b** and **13c**, respectively.

Compound **13b** was converted to the tertiary alcohol **19**, which is the reduced equivalent of **8**, as shown in Chart 5. Bromination of **19** (Br_2, AIBN) proceeded smoothly to afford the bromide **20**. Treatment of **20** with $AgNO_3$ in 50% aqueous acetone resulted in quantitative formation of the cyclic ether **21** instead of the diol by hydrolysis. Formation of **21** presumably involves the nucleophilic attack of the hydroxyl group in the side chain onto the benzylic cation formed by the treatment of **20** with $AgNO_3$. Compound **21** was easily hydrolyzed to cycloshikonin (**2**) in 1 N KOH solution. Direct hydrolysis of **20** with 1 N KOH also gave cycloshikonin (57%) (Chart 5).

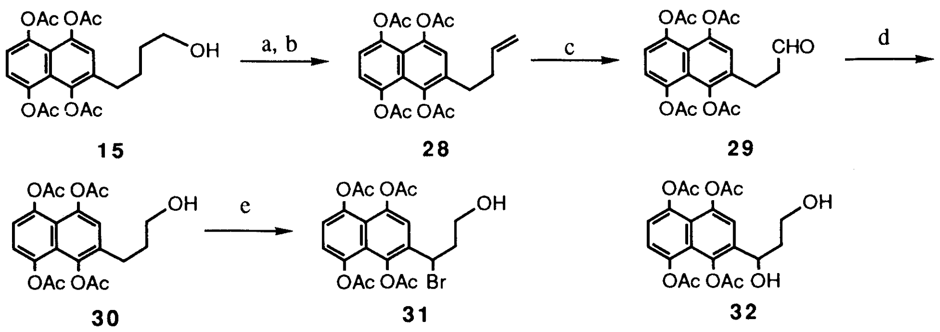
Structure–Reactivity Relationship for Side Chain of Naphthazarins The synthetic approach to shikonin from **7c** requires the conversion of the carbo-*tert*-butoxyl group to a hydroxyl group (*i.e.*, **7c** to **9** in Chart 3). Introduction of the hydroxyl group at the allylic position and selective dehydration complete the synthesis. So, the reactivity of substituted naphthazarins in the side-chain conversion was investigated.

For the functional group transformation from *tert*-butyl ester group to hydroxyl group, **12c** and **13c** were both exposed to the conditions for the Hunsdiecker reaction[10] after hydrolysis. After hydrolysis of the ester group of **12c** under acidic conditions, the resultant **22** was converted to the ester **23**. Photolytic decomposition of **23** in the presence



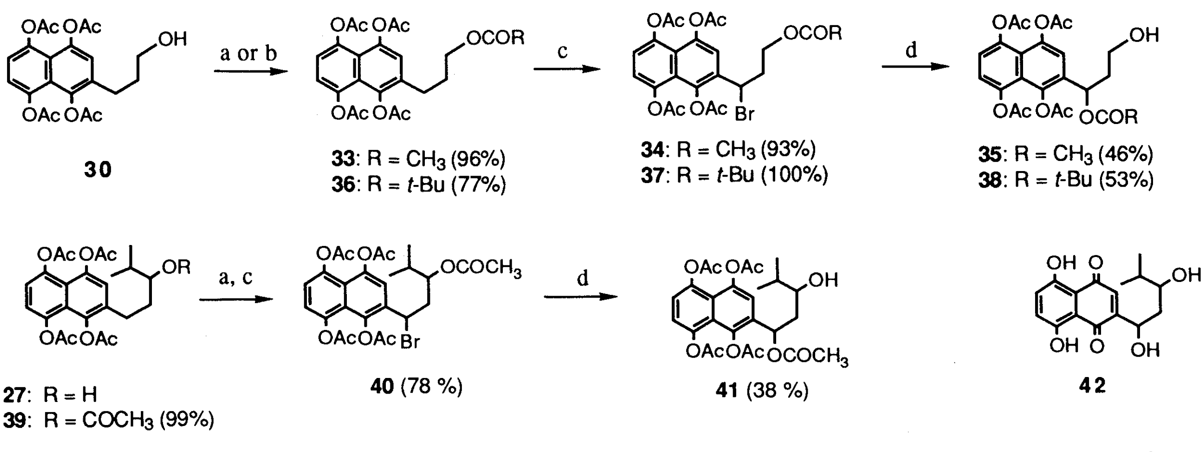
reagents and conditions : a) CF_3CO_2H, CH_2Cl_2, -20 °C. b) $(COCl)_2$, DMF, benzene, 25 °C. c) *N*-hydroxypyridinethione, pyridine, toluene. d) $h\nu$, O_2, *tert*-butylmercaptan, toluene. e) $P(OMe)_3$. f) CF_3CO_2H, CH_2Cl_2, 0 °C.

Chart 6



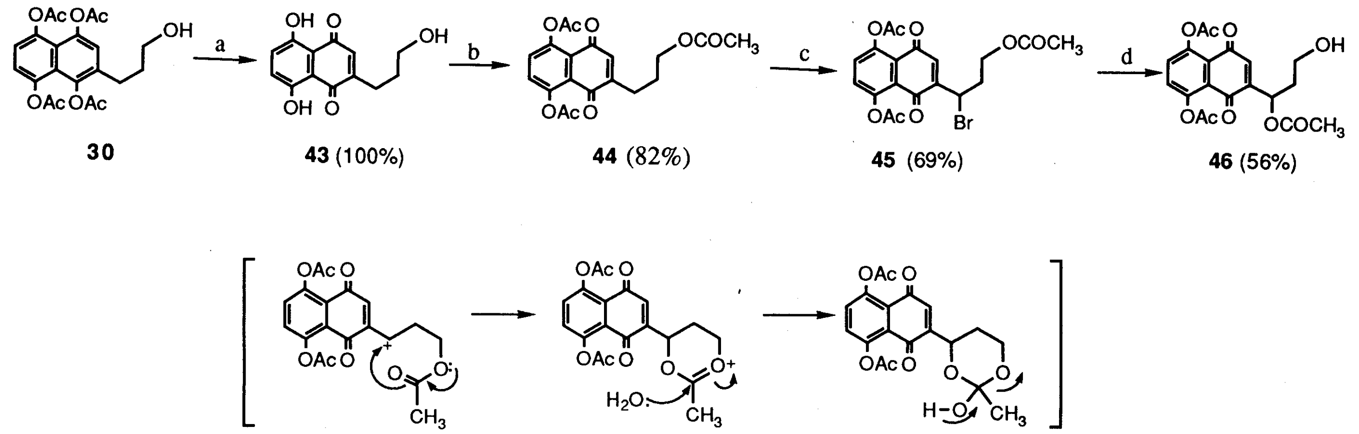
reagents and conditions : a) *o*-nitrophenylselenocyanate, *n*-Bu_3P, THF (77% based on recovery of **15**). b) $NaIO_4$, Et_2O–THF–H_2O (70%). c) OsO_4, $NaIO_4$, THF– H_2O (89%). d) BH_3–THF complex, THF (97%). e) Br_2, AIBN, CCl_4, 70 °C (40 %)

Chart 7



reagents and conditions : a) Ac_2O, pyridine, DMAP, CH_2Cl_2. b) pivaroylchloride, pyridine, CH_2Cl_2.c) Br_2, AIBN, CCl_4, 70 °C. d) $AgNO_3$, 50% aq. acetone

Chart 8



reagents and conditions : a) 1 N KOH, 0 °C. b) Ac_2O, pyridine, DMAP, CH_2Cl_2. c) Br_2, AIBN, CCl_4, 70 °C. d) $AgNO_3$, 50% aq. acetone

Chart 9

of oxygen and *tert*-butylmercaptan in toluene afforded the *nor*-alcohol **24** after reduction with trimethylphosphite (Chart 6). Compound **13c** could be converted into the corresponding *nor*-alcohol **27** in a similar manner.

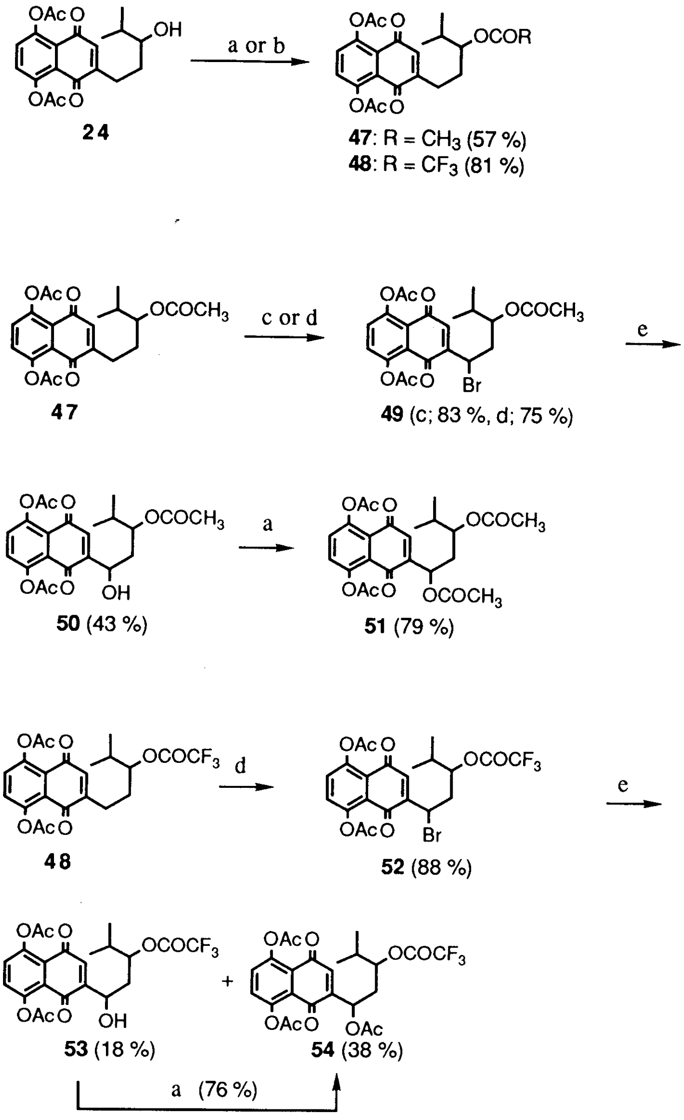
Introduction of a hydroxyl group at the allylic position of the naphthazarin skeleton was attempted by bromination followed by bromination followed by treatment with $AgNO_3$. Compounds **24** and **27** have a secondary hydroxyl group, which is not situated at a favorable position for intramolecular substitution of allylic or benzylic bromide (*i.e.*, 2-carbon remote). It was anticipated that bromination of **24** and **27** followed by treatment with $AgNO_3$ would result in direct introduction of a hydroxyl group at the allylic or benzylic position instead of intramolecular nucleophilic substitution as observed in formation of the cyclic ether **21**.

Bromination of **30**, which was prepared from **15**[11] and has the primary hydroxyl group 2-carbon remote from the benzylic position, proceeded to give **31**. Treatment of **31** with $AgNO_3$, however, resulted in failure, contrary to expectation (Chart 7).

Intramolecular substitution of bromide is an alternative solution for the introduction of an oxygen functionality. If the hydroxyl group is acylated, the carbonyl oxygen atom of the acyl group, which is situated at the 3-atom remote position from the benzylic position would be an appropriate nucleophilic site.

Bromination of **33** under similar conditions proceeded smoothly to give the bromide **34**. Treatment of **34** with an excess of silver nitrate in 50% aqueous acetone led to transfer of the acetyl group from the side chain to the benzylic position to afford **35** in 46% yield. In the ^{1}H-NMR spectrum, a downfield shift of the benzylic proton signal (δ 5.31 to 6.30) through transformation from **34** to **35** confirmed the acetyl group transfer. Similar acyl transfer reaction proceeded more effectively for the pivaloate **37** to give **38** in 53% yield (Chart 8).

Based on these results, introduction of a hydroxyl group at the benzylic position was examined for **27** after acetylation of the hydroxyl group. Bromination of **39** gave **40**, which afforded **41** on treatment with silver nitrate in 50% aqueous acetone. Attempted hydrolysis of **41** under



reagents and conditions : a) Ac_2O, pyridine, DMAP, CH_2Cl_2. b) $(CF_3CO)_2O$, pyridine, CH_2Cl_2. c) NBS, BPO, CCl_4, reflux. d) NBS, $h\nu$, CCl_4, reflux. e) CF_3CO_2Ag, CH_3CO_2H

Chart 10

alkaline conditions, however, resulted in decomposition instead of formation of the diol **42**.

A similar type of acyl group transfer reaction also proceeded for the quinone triacetate **44**, which is easily obtained from **30** by hydrolysis with oxidation and acetylation, to give **46** *via* **45**. This type of acyl group transfer was attributed to a reaction of the allylic or benzylic cation, formed by silver nitrate treatment with the acyl group to give the oxonium cation (Chart 9).[12] This intermediate may react with water to give products such as **46**.

Compound **24** could be converted into the corresponding acetate **47** and trifluoroacetate **48**. Compounds **47** and **48** were exposed to the conditions for introduction of an oxygen functionality at the allylic position. Bromination of **47** and **48** using *N*-bromosuccinimide in the presence of benzoyl peroxide or under photochemical conditions resulted in successful formation of the bromides **49** and **52**. In contrast to the above cases, treatment of **49** and **52** with silver nitrate resulted in failure. Treatment of **49** with silver trifluoroacetate in acetic acid, however, caused replacement of bromide by a hydroxyl group to give **50**. On the other hand, similar treatment of **52** gave a mixture of **53** (18%) and **54** (38%) (Chart 10). From these results, the oxidation level of the quinone skeleton, the steric influence of the side chain, and the electronic properties of the acyl groups used as hydroxyl-protecting groups all influence the substitution reaction.

In summary, successive Michael reaction-sigmatropic rearrangement of naphthodiquinone with *O*-silylated ketene acetals gave naphthazarin derivatives with a side chain, suitable for further conversion. These derivatives serve as important synthetic intermediates for not only cycloshikonin and shikonin, but also shikonin analogues required for development of more biologically active naphthazarin derivatives.

Experimental

The melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. The ^{1}H-NMR spectra were taken with a JEOL GX-270, a JEOL PS-100 spectrometer and a Hitachi R-600 spectrometer with tetramethylsilane as an internal standard, and the chemical shifts are expressed in δ values. The IR spectra were taken with a JASCO A-100 infrared spectrophotometer. Mass spectra were determined on a JEOL JMS-D-300 or DX-300 spectrometer. Elemental analyses were performed on a Yanagimoto MT2 CHN recorder. For thin layer chromatography (TLC) analysis, Merck precoated TLC plates (Kieselgel 60 F_{254}, 0.2 mm) were used. Column chromatography was performed by using Merck Kieselgel 60 (70—200 mesh) as the stationary phase.

Materials Naphthodiquinone (**3**) was prepared according to the reported method.[13,14]

Reaction of Naphthodiquinone (3) with 4b Compound **4b** was prepared as follows. Butyllithium (1.56 M in hexane, 18.5 ml, 28.9 mmol) to a solution of diisopropylamine (4.1 ml, 28.9 mmol) in 20 ml of dry THF was added dropwise at −20 °C over 5 min. After cooling to −78 °C, hexamethylphosphoramide (HMPA) (5.05 ml, 29 mmol) was added and the reaction mixture was stirred for 30 min. *tert*-Butyl crotonate (3.73 g, 26.3 mmol) was added dropwise at −78 °C over a 20 min period and the reaction mixture was stirred for 40 min. Chlorotrimethylsilane (TMSCl) (4.1 ml, 32.3 mmol) was added to the reaction mixture and the whole was allowed to warm to room temperature after 30 min. The reaction mixture was diluted with 125 ml of *n*-hexane, washed with 18 ml of saturated aqueous $NaHCO_3$ containing 18 g of ice and H_2O (18 ml × 2) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give **4b**. ^{1}H-NMR ($CDCl_3$) δ: 0.11 (s, 9H), 1.43 (s, 9H), 4.34—4.96 (m, 3H), 6.23—6.85 (m, 1H). A solution of **4b** (5.1 g, 24 mmol) in 50 ml of dry CH_2Cl_2 was added to a solution of **3** (2.3 g, 12 mmol) in 700 ml of dry CH_2Cl_2 at −78 °C under Ar and the reaction mixture was stirred for 30 min. The reaction was quenched with 100 ml of 5% HCl and the resulting mixture was extracted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, H_2O, brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give **5b** as a red oil. IR ($CHCl_3$): 3400, 1715, 1645, 1570 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (s, 9H), 2.92 (d, $J=7.8$ Hz, 2H), 5.67 (d, $J=15.6$ Hz, 1H), 6.54 (dt, $J=15.6$, 7.8 Hz, 1H), 6.59 (d, $J=10.8$ Hz, 2H), 6.99 (d, $J=10.8$ Hz, 2H), 14.07 (s, 1H). MS *m*/*z*: 330 (M$^+$). Compound **5b** was unstable and was subjected to the next reaction without further purification.

Leuconaphthazarin 7b A solution of **5b** obtained above in 700 ml of benzene was heated at reflux for 6 h. After cooling, the solution was concentrated under reduced pressure. The resulting red oil was dissolved in 200 ml of ether and shaken with 300 ml of saturated aqueous $Na_2S_2O_4$ until the color of the solution changed from orange to yellow. To organic layer was washed with 100 ml of H_2O, brine, and dried over Na_2SO_4, and then evaporated under reduced pressure. The residue was chromatographed on silica gel eluting with *n*-hexane–AcOEt (9 : 1) to give **7b** (3.24 g, 80%) as a red oil. IR ($CHCl_3$): 1705, 1635 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.49 (s, 9H), 2.38—3.60 (m, 5H), 5.85 (dt, $J=15.6$, 1.4 Hz, 1H), 6.80 (dt, $J=15.6$, 7.1 Hz, 1H), 7.26 (s, 2H), 11.85 (s, 1H), 11.87 (s, 1H). MS *m*/*z*: 332 (M$^+$). HRMS Calcd for $C_{18}H_{20}O_6$ 332.3565, Found 332.3576.

Hydrogenation of 7b A solution of **7b** (3.24 g, 9.76 mmol) in 30 ml of AcOEt was added to a mixture of 200 mg of 10% palladium on carbon in 30 ml of ethanol. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 8 h. The catalyst was removed by filtration and washed with AcOEt. The combined filtrates were concentrated under reduced pressure to give **10b** (3.26 g, 100%) as a red oil. IR ($CHCl_3$): 1715, 1630, 1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (s, 9H), 1.72—1.89 (m, 4H), 2.12—2.33 (m, 2H), 2.97—3.06 (m, 3H), 7.24 (s, 2H), 11.86 (s, 1H), 11.93 (s, 1H). MS *m*/*z*: 334 (M$^+$). HRMS Calcd for $C_{18}H_{22}O_6$ 334.3724, Found 334.3733.

5,8-Dihydroxy-2-(3′-carbo-*tert*-butoxypropyl)-1,4-naphthoquinone (11b) A mixture of NaBr (2.28 g, 22.1 mmol) and TMSCl (2.8 ml, 22.1 mmol) in 10 ml of CH_3CN was stirred for 15 min at room temperature. Then, dimethylsulfoxide (1.57 ml, 22.1 mmol) was added, followed after 5 min by a solution of **10b** (2.46 g, 7.37 mmol) in 30 ml of CH_3CN. The reaction mixture was stirred for 2 h and washed with 30 ml of H_2O and brine and dried over Na_2SO_4. The solvent was evaporated off and the residue was chromatographed on silica gel with *n*-hexane–AcOEt (4 : 1) to give **11b** (2.02 g, 83%) as red crystals; mp 95—99 °C (CH_2Cl_2–*n*-hexane). IR ($CHCl_3$): 3500, 1720, 1615, 1570 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (s, 9H), 1.73—2.73 (m, 6H), 6.88 (t, $J=1.2$ Hz, 1H), 7.19 (s, 2H), 12.43 (s, 1H), 12.59 (s, 1H). MS *m*/*z*: 332 (M$^+$). *Anal.* Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 64.90; H, 6.08.

5,8-Diacetoxy-2-(3′-Carbo-*tert*-butoxypropyl)-1,4-naphthoquinone (12b) A mixture of **11b** (1.17 g, 3.53 mmol), acetic anhydride (1 ml, 10.6 mmol), pyridine (0.86 ml, 10.6 mmol) and 4-dimethylaminopyridine (DMAP) (13 mg, 1.06 mmol) in 30 ml of CH_2Cl_2 was stirred at room temperature for 4 h. The reaction mixture was washed with 10 ml of aqueous 5% HCl, H_2O and brine, and then dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel with *n*-hexane–AcOEt (9 : 1—4 : 1) to give **12b** (1.29 g, 88%) as yellow crystals; mp 107—108 °C (CH_2Cl_2–*n*-hexane). IR ($CHCl_3$): 1765, 1720, 1665 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (s, 9H), 2.43 (s, 6H), 1.78—2.87 (m, 6H), 6.64 (s, 1H), 7.36 (s, 2H). FDMS *m*/*z*: 416 (M$^+$); HRMS (FAB) Calcd for $C_{22}H_{25}O_8$ 417.4398 (M+H)$^+$, Found 417.4390.

2-(3′-Carbo-*tert*-butoxypropyl)-1,4,5,8-tetraacetoxynaphthalene (13b) A solution of **12b** (2.31 g, 5.55 mmol) in 100 ml of ether was shaken with 200 ml of saturated aqueous $Na_2S_2O_4$ until the solution became colorless. The reaction mixture was washed with 50 ml of H_2O and brine, and dried over Na_2SO_4, and then evaporated to dryness. The residue was chromatographed on silica gel with *n*-hexane–AcOEt (4 : 1—1 : 1) to give **13b** (2.42 g, 87%) as colorless crystals; mp 169—171 °C (CH_2Cl_2–*n*-hexane). IR ($CHCl_3$): 1755, 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (s, 9H), 2.36, 2.41 (each s, 12H), 1.80—2.74 (m, 6H), 7.08 (s, 3H). MS *m*/*z*: 502 (M$^+$). *Anal.* Calcd for $C_{26}H_{30}O_{10}$: C, 62.14; H, 6.02. Found: C, 62.08; H, 5.98.

Preparation of 4c and Reaction of 3 with 4 *n*-Butyllithium (1.56 M in hexane, 94 ml, 147 mmol) was added dropwise to a solution of diisopropylamine (20.6 ml, 147 mmol) in 500 ml of dry THF at −20 °C over 5 min. After cooling to −78 °C, HMPA (25.6 ml, 147 mmol) was added and the resulting mixture was stirred for 30 min. *tert*-Butyl crotonate (20.9 g, 147 mmol) was added dropwise over a 20 min period and 2-iodopropane (25 g, 147 mmol) was added dropwise after 40 min. The reaction mixture was stirred for 2 h, poured into saturated aqueous ammonium chloride, and extracted with ether. The extract was washed with H_2O and brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was chromatographed on silica gel with AcOEt–*n*-hexane (1 : 9) to give *tert*-butyl 2-isopropyl crotonate (19.5 g, 72%) as a colorless oil. IR (neat) 1720 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.82—0.98 (m, 6H), 1.44 (s, 9H), 1.51 (m, 1H), 2.57 (t, $J=8.4$ Hz, 1H), 4.79—6.12 (m, 3H). Compound **4c** was prepared in a similar manner to **4b**. ^1H-NMR ($CDCl_3$) δ: 0.05 (s, 9H), 1.15 (d, $J=7.2$ Hz, 3H), 1.27 (d, $J=7.2$ Hz, 3H), 1.49 (s, 9H), 1.74 (m, 1H), 4.80—5.18 (m, 2H), 6.63 (t, $J=9.6$ Hz, 1H). Further reaction of **3** with **4c** was performed in a similar manner to the reaction of **3** with **4b** to give **5c** (68%) as a red oil. IR ($CHCl_3$): 3400, 1700, 1630, 1555 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.15 (d, $J=6.0$ Hz, 6H), 1.48 (s, 9H), 1.50 (m, 1H), 2.95 (d, $J=8.4$ Hz, 2H), 6.63 (t, $J=8.4$ Hz, 1H), 6.59 (d, $J=10.8$ Hz, 2H), 7.00 (d, $J=10.8$ Hz, 2H), 12.51 (s, 1H). MS *m/z*: 372 (M^+). Compound **5c** was unstable and was subjected to the next reaction without further purification.

Leuconaphthazarin 7c Compound **7c** was prepared in a similar manner to **7b** as an oil. IR ($CHCl_3$): 1720, 1710, 1640 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.96 (d, $J=6.6$ Hz, 6H), 1.41 (s, 9H), 1.50 (m, 1H), 1.96—2.96 (m, 5H), 5.47 (t, $J=7.2$ Hz, 1H), 7.16 (s, 2H), 11.85 (br s, 2H) MS *m/z*: 374 (M^+). HRMS Calcd for $C_{21}H_{26}O_6$ 374.4378, Found 374.4391.

Hydrogenation of 7c Compound **10c** was obtained in a similar manner to **10b** using platinum oxide; oil. IR ($CHCl_3$): 1715, 1635 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.92 (d, $J=6.0$ Hz, 6H), 1.43 (s, 9H), 1.40—2.97 (m, 5H), 3.00 (m, 4H), 7.16 (s, 2H), 11.88 (s, 1H), 11.95 (s, 1H). MS *m/z*: 376 (M^+). HRMS Calcd for $C_{21}H_{28}O_6$ 376.4537, Found 376.4547.

Preparation of 11c, 12c and 13c Compounds **11c**, **12c** and **13c** were prepared in similar manners to **11b**, **12b** and **13b**, respectively.

11c: mp 115—117 °C (CH_2Cl_2–*n*-hexane). IR ($CHCl_3$): 1710, 1605, 1565 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.94 (d, $J=6.6$ Hz, 6H), 1.49 (s, 9H), 1.68—2.21, 2.45—2.77 (m, 6H), 6.88 (s, 1H), 7.21 (s, 2H), 12.46 (s, 1H), 12.62 (s, 1H). *Anal.* Calcd for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.30; H, 7.08.

12c: oily compound. IR ($CHCl_3$): 1760, 1700, 1650 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.92 (d, $J=6.0$ Hz, 6H), 1.47 (s, 9H), 1.47—2.42 (m, 6H), 2.42 (s, 6H), 6.63 (s, 1H), 7.35 (s, 2H). FDMS *m/z*: 458 (M^+). HRMS (FAB) Calcd for $C_{25}H_{31}O_8$ 459.5210 $(M+H)^+$, Found 459.5204.

13c: mp 150—151 °C (CH_2Cl_2–*n*-hexane). IR ($CHCl_3$): 1760, 1720 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.91 (d, $J=6.0$ Hz, 6H), 1.48 (s, 9H), 1.50—2.42 (m, 6H), 2.35, 2.40 (each s, 12H), 7.08 (s, 3H). MS *m/z*: 544 (M^+). *Anal.* Calcd for $C_{29}H_{36}O_{10}$: C, 63.96; H, 6.66. Found: C, 63.79; H, 6.64.

2-(3′-Carboxypropyl)-1,4,5,8-tetraacetoxynaphthalene (14) A solution of **13b** (1.17 g, 2.33 mmol) in 50 ml of CH_2Cl_2 at 0 °C under Ar was treated with 10 ml of CF_3CO_2H and the reaction mixture was stirred at 0 °C for 12 h, then concentrated under reduced pressure to give **14** (1.04 g, quantitative). Recrystallization from CH_2Cl_2–*n*-hexane afforded **14** as colorless crystals; mp 190—192 °C. IR ($CHCl_3$): 1755, 1705 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.76—2.86 (m, 6H), 2.38 (s, 12H), 3.64 (br s, 1H, D_2O exchangeable), 7.10 (s, 3H), 7.92 (br s, 1H). MS *m/z*: 446 (M^+). *Anal.* Calcd for $C_{22}H_{22}O_{10}$: C, 59.19; H, 4.97. Found: C, 59.07; H, 4.98.

2-(4′-Hydroxybutyl)-1,4,5,8-tetraacetoxynaphthalene (15) Borane–THF complex (1.0 M solution in THF, 3.5 ml, 3.5 mmol) was added to a solution of **14** (1.03 g, 2.33 mmol) in 60 ml of dry THF at 0 °C under Ar. After 6 h, the reaction was quenched by cautious addition of EtOH followed by removal of volatiles under reduced pressure. The residue was chromatographed on silica gel with *n*-hexane–AcOEt (2 : 1) to give **15** (695 mg, 69%) as colorless crystals; mp 185—186 °C. (CH_2Cl_2–*n*-hexane). IR ($CHCl_3$): 3500, 1760 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.55—1.74 (m, 4H), 1.74 (br s, 1H, D_2O-exchangeable), 2.36, 2.38 (each s, 12H), 2.60 (m, 2H), 3.60 (t, $J=6.0$ Hz, 2H), 7.08 (s, 3H). MS *m/z*: 432 (M^+). *Anal.* Calcd for $C_{22}H_{24}O_9$: C, 61.11; H, 5.59. Found: C, 61.10; H, 5.60.

2-(4′-Oxobutyl)-1,4,5,8-tetraacetoxynaphthalene (16) A solution of **15** (359 mg, 0.83 mmol) in 10 ml of dry CH_2Cl_2 was added to a mixture of pyridinium chlorochromate (232 mg, 1.08 mmol) and 460 mg of Celite in 10 ml of dry CH_2Cl_2 at room temperature. After 3 h, the reaction mixture was filtered through Celite and the Celite was washed with CH_2Cl_2. The combined filtrates were concentrated under reduced pressure and the residue was chromatographed on silica gel with *n*-hexane–AcOEt (1 : 1) to give **16** (228 mg, 64%) as colorless crystals. IR ($CHCl_3$): 1760, 1720 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.38, 2.42 (each s, 12H), 2.40—2.64 (m, 6H), 7.06 (s, 1H), 7.10 (s, 2H), 9.79 (s, 1H). MS *m/z*: 430 (M^+). Compound **16** was not stable and was subjected to the next reaction without further purification.

2-(4′-Hydroxypentyl)-1,4,5,8-tetraacetoxynaphthalene (17) Methylmagnesium iodide (1.29 M solution in ether, 13.6 ml, 17.6 mmol) was added dropwise to a solution of **16** (758 mg, 1.76 mmol) in 60 ml of dry THF at −78 °C under Ar. After 2 h, the reaction mixture was poured into 50 ml of 5% HCl and extracted with AcOEt (20 ml × 5). The extract was washed with H_2O and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel with *n*-hexane–AcOEt (1 : 1)–AcOEt to give **17** as an oily compound (361 mg, 46%; 73% based on recovery of **16**) and recovered **16** (301 mg, 0.7 mmol). IR ($CHCl_3$): 3500, 1755 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.06 (d, $J=6.0$ Hz, 3H), 1.54—1.71 (m, 4H), 2.36, 2.38 (each s, 12H), 2.63 (m, 1H, D_2O-exchangeable), 2.48—2.70 (m, 2H), 3.69 (m, 1H), 7.08 (s, 3H). MS *m/z*: 446 (M^+). HRMS (FAB) Calcd for $C_{23}H_{27}O_9$ 447.4662 $(M+H)^+$, Found 447.4671.

2-(4′-Oxopentyl)-1,4,5,8-tetraacetoxynaphthalene (18) A solution of **17** (131 mg, 0.29 mmol) in 10 ml of dry CH_2Cl_2 was added to a mixture of pyridinium chlorochromate (90 mg, 0.42 mmol) and 175 mg of Celite in 10 ml of dry CH_2Cl_2 at room temperature. After 3 h, the reaction mixture was filtered through Celite and the Celite was washed with CH_2Cl_2. The combined filtrates were concentrated under reduced pressure and the residue was chromatographed on silica gel with *n*-hexane–AcOEt (1 : 1) to give **18** (111 mg, 85%) as colorless crystals; mp 165—166 °C (CH_2Cl_2–*n*-hexane). IR ($CHCl_3$): 1750, 1700 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.71—2.00 (m, 4H), 2.12 (s, 3H), 2.37, 2.42 (each s, 12H), 2.61 (t, $J=7.4$ Hz, 2H), 7.05 (s, 1H), 7.09 (s, 2H). MS *m/z*: 444 (M^+). *Anal.* Calcd for $C_{23}H_{24}O_9$: C, 62.16; H, 5.44. Found: C, 62.26; H, 5.48.

2-(4′-Hydroxy-4′-methylpentyl)-1,4,5,8-tetraacetoxynaphthalene (19) Methylmagnesium iodide (1.25 M solution in ether, 6.0 ml, 7.5 mmol) was added dropwise to a solution of **18** (335 mg, 0.75 mmol) in 25 ml of dry THF at −78 °C under Ar. After 2 h, the reaction mixture was poured into 10 ml of 5% HCl and extracted with AcOEt (10 ml × 5). The combined extracts were washed with H_2O, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel with *n*-hexane–AcOEt (2 : 1)–AcOEt to give **19** (119 mg, 34%; 57% based on recovery of **18**) and recovered **18** (132 mg, 0.3 mmol); mp 184—186 °C (CH_2Cl_2–*n*-hexane). IR ($CHCl_3$): 3500, 1760 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.16 (s, 6H), 1.23—1.79 (m, 5H; 1H, D_2O-exchangeable), 2.35, 2.38 (each s, 12H), 2.58 (t, $J=7.2$ Hz, 2H), 7.08 (s, 3H). MS *m/z*: 460 (M^+). *Anal.* Calcd for $C_{24}H_{28}O_9$: C, 62.60; H, 6.13. Found: C, 62.81; H, 6.23.

2-(1′-Bromo-4′-hydroxy-4′-methylpentyl)-1,4,5,8-tetraacetoxynaphthalene (20) A solution of Br_2 in CCl_4 (0.5 M, 0.086 ml, 0.043 mmol) and azobisisobutylonitrile (3 mg, 0.017 mmol) was added to a solution of **19** (20 mg, 0.043 mmol) in 10 ml of CCl_4, through which Ar gas had been bubbled for 15 min before the reaction, and the mixture was heated at 70 °C. After 1 h, a solution of Br_2 in CCl_4 (0.5 M, 0.086 ml, 0.043 mmol) was added, and the reaction mixture was further heated at 70 °C for 1 h, then cooled to room temperature. The mixture was washed with aqueous 10% sodium thiosulfate solution, H_2O, and brine, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on silica gel with *n*-hexane–AcOEt (1 : 1) to give **20** as an oily compound (18 mg, 78%). IR ($CHCl_3$): 3500, 1760 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.20 (s, 6H), 1.20—1.80 (m, 5H; 1H D_2O-exchangeable), 2.38, 2.43 (each s, 12H), 5.22 (t, $J=7.2$ Hz, 1H), 7.16 (s, 2H), 7.36 (s, 1H). Compound **20** was unstable and was subjected to the next reaction without further purification.

2-(5′,5′-Dimethyl-2′-tetrahydrofuranyl)-1,4,5,8-tetraacetoxynaphthalene (21) A mixture of **20** (6 mg, 0.011 mmol) and silver nitrate (5 mg, 0.03 mmol) in 1 ml of 50% aqueous acetone was stirred at room temperature for 2 h. The reaction mixture was diluted with ether, washed with H_2O, and dried over Na_2SO_4. The solvent was evaporated to dryness and the residue was chromatographed on silica gel with *n*-hexane–AcOEt (2 : 1) to give **21** (5 mg, 99%); mp 230—239 °C (MeOH). IR ($CHCl_3$): 1765 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.33 (s, 3H), 1.38 (s, 3H), 1.60—1.95 (m, 4H), 2.36 (s, 12H), 5.13 (t, $J=7.2$ Hz, 1H), 7.10 (s, 2H), 7.41 (s, 1H). MS *m/z*: 458 (M^+). *Anal.* Calcd for $C_{24}H_{26}O_9$: C, 62.88; H, 5.72. Found: C, 62.73; H, 5.69.

Preparation of Cycloshikonin (2) Compound **20** (18 mg, 0.033 mmol) in 10 ml of 1 N KOH was stirred at 0 °C for 2 h. The reaction mixture was acidified with aqueous 10% HCl and extracted with CH_2Cl_2. The solvent was evaporated under reduced pressure and the residual solid was chromatographed on silica gel with $CHCl_3$ to give cycloshikonin (5 mg, 57%); mp 79—83 °C (MeOH). IR ($CHCl_3$): 1610, 1570 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.36 (s, 6H), 1.77—1.88, 2.30—2.80 (m, 4H), 5.14 (m, 1H), 7.20 (s, 3H), 12.52 (s, 2H). MS *m/z*: 288 (M^+). *Anal.* Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.82; H, 5.75. Compound **21** was hydrolyzed to cycloshikonin in a similar manner.[5)]

5,8-Diacetoxy-2-(3′-carboxy-4′-methylpentyl)-1,4-naphthoquinone (22)

Trifluoroacetic acid (6 ml) was added dropwise to a solution of **12c** (470 mg, 1.03 mmol) in 10 ml of dry CH_2Cl_2 at -20 °C. The reaction mixture was stirred at -20 °C for 2 d and was poured into diluted aqueous $NaHCO_3$ and the pH value of the aqueous layer was adjusted to around neutrality. The mixture was extracted with CH_2Cl_2 and the extract was washed with H_2O, and brine, and dried over Na_2SO_4, and then evaporated to dryness. The crude product was chromatographed on silica gel with *n*-hexane–AcOEt (2 : 1)–AcOEt to give **22** (314 mg, 76%) as a yellow oil. IR (neat): 1790, 1720, 1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (d, J=6.0 Hz, 6H), 2.42 (s, 6H), 1.52—2.70 (m, 6H), 6.65 (br s, 1H), 7.35 (s, 2H); FDMS m/z: 403 (M^++1). HRMS (FAB) Calcd for $C_{21}H_{23}O_8$ 403.4127 $(M+H)^+$, Found 403.4132.

5,8-Diacetoxy-2-(3′-hydroxy-4′-methylpentyl)-1,4-naphthoquinone (24) Two drops of DMF were added to a mixture of **22** (236 mg, 0.59 mmol) and oxalyl chloride (1.5 ml in 5 ml of dry benzene), and the reaction mixture was stirred at room temperature for 3 h. After removal of volatiles under reduced pressure, the crude acid chloride was diluted in 4 ml of dry toluene and added to a stirred solution of *N*-hydroxypyridinethione (73 mg, 0.65 mmol) and pyridine (0.1 ml) in toluene (6 ml). After 15 min, the precipitated pyridinium chloride was removed by filtration and **23** was added dropwise over 15 min under irradiation with a 300 W tungsten lamp to a stirred solution of *tert*-butylmercaptan (0.6 ml, 5.3 mmol) in 6 ml of toluene that was being continually saturated with oxygen at a rate of approximately 0.33 l/min. After 1 h, the crude reaction mixture was reduced with trimethylphosphite (0.15 ml) at room temperature. After 1 h, the reaction mixture was thoroughly washed with water (3 × 10 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residual solid was chromatographed on silica gel with *n*-hexane–AcOEt (1 : 4—1 : 1) to give **24** as an oily compound (79 mg, 36%). IR ($CHCl_3$): 3500, 1770, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (d, J=6.2 Hz, 6H), 1.50—2.00 (m, 6H; 1H D_2O-exchangeable), 2.43 (s, 6H), 3.33 (m, 1H), 6.65 (br s, 1H), 7.36 (s, 2H). FDMS m/z: 375 (M^++1). HRMS (FAB) Calcd for $C_{20}H_{23}O_7$ 375.4021 $(M+H)^+$, Found 375.4033.

2-(3′-Carboxy-4′-methylpentyl)-1,4,5,8-tetraacetoxynaphthalene (25) Compound **25** was prepared in a similar manner to **22** at room temperature; oily compound; IR ($CHCl_3$): 1770, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (d, J=6.6 Hz, 6H), 1.50—2.50 (m, 6H), 2.38 (s, 12H), 7.08 (s, 2H), 7.10 (s, 1H). MS m/z: 488 (M^+). HRMS Calcd for $C_{25}H_{28}O_{10}$ 488.4959, Found 488.4965.

2-(3′-Hydroxy-4′-methylpentyl)-1,4,5-8-tetraacetoxynaphthalene (27) Compound **27** was prepared in a similar manner to **24**; oily compound. IR ($CHCl_3$): 1770 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (d, J=6.6 Hz, 6H), 1.47—1.90 (m, 4H), 2.36 (s, 12H), 2.86—2.96 (m, 3H; 1H D_2O-exchangeable), 7.09 (s, 3H). MS m/z: 458 (M^+). HRMS Calcd for $C_{24}H_{26}O_9$ 458.4694, Found 458.4707.

2-(3′-Butenyl)-1,4,5,8-tetraacetoxynaphthalene (28) A suspension of **15** (2.73 g, 6.32 mmol) and *o*-nitrophenylselenocyanate (2.15 g, 9.48 mmol) in 40 ml of dry THF was treated dropwise with *n*-Bu_3P (2.4 ml, 9.48 mmol) and the reaction mixture was sonicated for 1 h. The solvent was removed under reduced pressure and chromatography of the residue on silica gel using AcOEt–*n*-hexane (1 : 9—1 : 1) gave the corresponding selenide (2.59 g, 66%; 73% based on recovery of **15**) and **15** (241 mg). IR ($CHCl_3$): 1763, 1510, 1330 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.51—1.97 (m, 4H), 2.61 (m, 2H), 2.37 (s, 12H), 2.91 (t, J=6.6 Hz, 2H), 7.06—7.50 (m, 6H), 8.30 (d, J=6.6 Hz, 1H). A solution of the obtained selenide (2.59 g, 4.20 mmol) in 120 ml of THF–H_2O (3 : 1) was treated with $NaIO_4$ (7.11 g, 33.6 mmol) and the reaction mixture was stirred for 12 h. The mixture was washed with H_2O and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residual solid was chromatographed on silica gel with *n*-hexane–AcOEt (1 : 1) to give **28** (1.50 g, 86%) as colorless crystals; mp 175—176 °C (CH_2Cl_2–*n*-hexane). IR ($CHCl_3$): 1760 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.36, 2.38 (each s, 12H), 2.49—2.68 (m, 4H), 4.83—5.20, 5.55—6.09 (m, 3H), 7.08 (s, 3H). FDMS m/z: 414 (M^+). *Anal.* Calcd for $C_{22}H_{22}O_8$; C, 63.76; H, 5.35. Found: C, 63.57; H, 5.32.

2-(3′-Oxopropyl)-1,4,5,8-tetraacetoxynaphthalene (29) A solution of **28** (33 mg, 0.08 mmol) in 16 ml of ether–THF–H_2O (4 : 3 : 1) was treated with $NaIO_4$ (34 mg, 0.16 mmol) and the reaction mixture was sonicated for 8 h. The reaction mixture was extracted with AcOEt, washed with H_2O and brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residual solid was chromatographed on silica gel with *n*-hexane–AcOEt (1 : 1) to give **29** (26 mg, 89%) as colorless crystals. IR ($CHCl_3$); 1763, 1723 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.38 (s, 12H), 2.70—2.91 (m, 4H), 7.09 (s, 3H), 9.81 (br s, 1H). MS m/z: 416 (M^+). Compound **29** was not stable and was subjected to the next reaction without further purification.

2-(3′-Hydroxypropyl)-1,4,5,8-tetraacetoxynaphthalene (30) Borane–THF complex (1 M solution, 0.22 ml, 0.22 mmol) was added dropwise to a solution of **29** (183 mg, 0.44 mmol) in 10 ml of dry THF at 0 °C. After 2 h, the reaction was quenched by cautious addition of EtOH followed by removal of volatiles under reduced pressure. The residue was chromatographed on silica gel with *n*-hexane–AcOEt(1 : 2) to give **30** (180 mg, 98%) as colorless crystals; mp 156—158 °C (CH_2Cl_2–*n*-hexane). IR ($CHCl_3$): 3530, 1760 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.71—1.95 (m, 2H), 2.37, 2.40 (each s, 12H), 2.57—2.83 (m, 3H; 1H D_2O-exchangeable), 3.62 (t, J=6.0 Hz, 2H), 7.09 (s, 3H). MS m/z: 418 (M^+). *Anal.* Calcd for $C_{21}H_{22}O_9$: C, 60.28; H, 5.30. Found: C, 60.19; H, 5.31.

2-(1′-Bromo-3′-hydroxypropyl)-1,4,5,8-tetraacetoxynaphthalene (31) Compound **31** was obtained in a similar manner to **20**. IR ($CHCl_3$): 3550, 1770 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.45—1.64 (m, 2H), 2.38, 2.44 (each s, 12H), 3.53—3.85 (m, 3H; 1H D_2O-exchangeable), 5.52 (t, J=7.2 Hz, 1H), 7.16 (s, 2H), 7.35 (s, 1H). Compound **31** was subjected to the next reaction with further purification.

2-(3′-Acetoxypropyl)-1,4,5,8-tetraacetoxynaphthalene (33) Acetic anhydride (0.025 ml, 0.27 mmol), pyridine (0.02 ml, 0.27 mmol) and DMAP (2 mg, 0.014 mmol) were added to a solution of **30** (57 mg, 0.14 mmol) in 5 ml of CH_2Cl_2 and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was washed with 5% aqueous HCl, H_2O, brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel with *n*-hexane–AcOEt (1 : 1) to give **33** (60 mg, 96%) as an oily compound: IR ($CHCl_3$): 1760, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.83—2.00 (m, 2H), 2.04 (s, 3H), 2.38, 2.41 (each s, 12H), 2.68—2.88 (m, 2H), 4.12 (t, J=6.0 Hz, 2H), 7.07 (s, 2H), 7.10 (s, 1H). MS m/z: 460 (M^+). HRMS Calcd for $C_{23}H_{24}O_{10}$ 460.4417, Found 460.4411.

2-(3′-Acetoxy-1′-bromopropyl)-1,4,5,8-tetraacetoxynaphthalene (34) Compound **34** was obtained in a similar manner to **20**. IR ($CHCl_3$): 1765, 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.44—1.82 (m, 2H), 2.02 (s, 3H), 2.38, 2.44 (each s, 12H), 4.22 (t, J=6.0 Hz, 2H), 5.31 (t, J=7.2 Hz, 1H), 7.16 (s, 2H), 7.36 (s, 1H). Compound **34** was subjected to the next reaction without further purification.

2-(1′-Acetoxy-3′-hydroxypropyl)-1,4,5,8-tetraacetoxynaphthalene (35) Compound **35** was obtained in a similar manner to **21**; mp 82—85 °C (CH_2Cl_2–*n*-hexane). IR ($CHCl_3$): 3550, 1765, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.45—1.80 (m, 3H; 1H D_2O-exchangeable), 2.08 (s, 3H), 2.38, 2.45 (each s, 12H), 3.63 (t, J=6.0 Hz, 2H), 6.30 (t, J=6.6 Hz, 1H), 7.14 (s, 3H). MS m/z: 476 (M^+). *Anal.* Calcd for $C_{23}H_{24}O_{11}$: C, 57.98; H, 5.08. Found: C, 57.87; H, 5.04.

2-(3′-Pivaloxypropyl)-1,4,5,8-tetraacetoxynaphthalene (36) Pivaloyl chloride (0.006 ml, 0.05 mmol) and pyridine (0.004 ml, 0.05 mmol) were added to a solution of **30** (14 mg, 0.03 mmol) in 2 ml of CH_2Cl_2, and the reaction mixture was stirred for 1 h, then washed with 5% aqueous HCl, H_2O, and brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel with *n*-hexane–AcOEt (1 : 1) to give **36** (12 mg, 77%) as an oily compound. IR ($CHCl_3$): 1760, 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (s, 9H), 1.90—2.04 (m, 2H), 2.36, 2.40 (each s, 12H), 2.61—2.88 (m, 2H), 4.12 (t, J=6.0 Hz, 2H), 7.07 (s, 2H), 7.10 (s, 1H). MS m/z: 502 (M^+). HRMS Calcd for $C_{26}H_{30}O_{10}$ 502.5230, Found 502.5224.

2-(1′-Bromo-3′-pivaloxypropyl)-1,4,5,8-tetraacetoxynaphthalene (37) Bromination of **36** was done in a similar manner to that of **20**. IR ($CHCl_3$): 1765, 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (s, 9H), 1.56—1.67 (m, 2H), 2.38, 2.43 (each s, 12H), 4.23 (t, J=6.0 Hz, 2H), 5.35 (t, J=7.2 Hz, 1H), 7.16 (s, 2H), 7.33 (s, 1H). Compound **37** was subjected to the next reaction without further purification.

2-(3′-Hydroxy-1′-pivaloxypropyl)-1,4,5,8-tetraacetoxynaphthalene (38) Compound **38** was obtained in a similar manner to **21**; mp 196—197 °C (CH_2Cl_2–*n*-hexane). IR ($CHCl_3$): 3540, 1765, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.52—1.64 (m, 2H), 2.38, 2.46 (each s, 12H), 3.41—3.80 (m, 3H; 1H D_2O-exchangeable), 6.30 (t, J=6.6 Hz, 1H), 7.15 (s, 3H). FDMS m/z: 518 (M^+). *Anal.* Calcd for $C_{26}H_{30}O_{11}$: C, 60.23; H, 5.83. Found: C, 60.21; H, 5.80.

2-(3′-Acetoxy-4′-methylpentyl)-1,4,5,8-tetraacetoxynaphthalene (39) Compound **39** was obtained in a similar manner to **33**; mp 101—103 °C (CH_2Cl_2–*n*-hexane). IR ($CHCl_3$): 1765, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (d, J=6.6 Hz, 6H), 1.45—1.95 (m, 3H), 2.07 (s, 3H), 2.37, 2.40 (each s, 12H), 2.45—2.90 (m, 2H), 4.70—4.80 (m, 1H), 7.06 (s, 2H), 7.09 (s, 1H). FDMS m/z: 502 (M^+). *Anal.* Calcd for $C_{26}H_{30}O_{10}$: C, 62.14; H, 6.02. Found: C, 62.03; H, 5.98.

2-(3′-Acetoxy-1′-bromo-4′-methylpentyl)-1,4,5,8-tetraacetoxynaphthalene (40) Compound **40** was obtained in a similar manner to **20**. IR

(CHCl$_3$): 1765, 1730 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 0.93 (d, $J=6.6$ Hz, 6H), 1.57—1.82 (m, 3H), 2.02 (s, 3H), 2.38, 2.42 (each s, 12H), 5.27 (t, $J=7.2$ Hz, 1H), 7.16—7.35 (m, 3H). Compound **40** was subjected to the next reaction without further purification.

2-(1′-Acetoxy-3′-hydroxy-4′-methylpentyl)-1,4,5,8-tetraacetoxynaphthalene (41) Compound **41** was obtained in a similar manner to **21** as an oily compound. IR (CHCl$_3$): 3530, 1760, 1735 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 0.86 (d, $J=6.6$ Hz, 6H), 1.57—1.84 (m, 4H; 1H D$_2$O-exchangeable), 2.02 (s, 3H), 2.38, 2.44 (each s, 12H), 3.01—3.48 (m, 1H), 6.31 (t, $J=7.2$ Hz, 1H), 7.14 (s, 2H), 7.23 (s, 1H). FDMS *m/z*: 518 (M$^+$). HRMS (FAB) Calcd for $C_{26}H_{31}O_{11}$ 519.5304 $(M+H)^+$, Found 519.5313.

5,8-Dihydroxy-2-(3′-hydroxypropyl)-1,4-naphthoquinone (43) Compound **43** was obtained in a similar manner to **2**; mp 115—116 °C (CH$_2$Cl$_2$–*n*-hexane). IR (CHCl$_3$): 1605, 1565 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 1.61—2.09 (m, 3H; 1H D$_2$O-exchangeable), 2.75 (t, $J=7.2$ Hz, 2H), 3.74 (t, $J=6.0$ Hz, 2H), 6.92 (s, 1H), 7.19 (s, 2H), 12.45 (s, 1H), 12.61 (s, 1H). FDMS *m/z*: 248 (M$^+$). *Anal.* Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.85; H, 4.86.

5,8-Dihydroxy-2-(3′-acetoxypropyl)-1,4-naphthoquinone (44) Acetic anhydride (0.015 ml, 0.16 mmol), and pyridine (0.013 ml, 0.16 mmol) and DMAP (1 mg, 0.008 mmol) were added to a solution of **43** (9 mg, 0.036 mmol) in 1 ml of CH$_2$Cl$_2$, and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was washed with 5% aqueous HCl, H$_2$O, and brine and dried over Na$_2$SO$_4$. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel with *n*-hexane–AcOEt (1 : 1) to give **44**. IR (CHCl$_3$) 1770, 1735, 1660, 1580 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 1.80—1.98 (m, 2H), 2.03 (s, 3H), 2.42 (s, 3H), 2.44 (s, 3H), 2.33—2.70 (m, 2H), 4.13 (t, $J=6.0$ Hz, 2H), 6.64 (t, $J=1.2$ Hz, 1H), 7.37 (s, 2H). FDMS *m/z*: 374 (M$^+$). HRMS (FAB) Calcd for $C_{19}H_{19}O_8$ 375.3585 $(M+H)^+$, Found 375.3580.

5,8-Diacetoxy-2-(3′-acetoxy-1′-bromopropyl)-1,4-naphthoquinone (45) Compound **45** was obtained in a similar manner to **20**. IR (CHCl$_3$): 1770, 1735, 1660, 1580 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 1.44—1.67 (m, 2H), 2.03 (s, 3H), 2.43 (s, 6H), 4.27 (t, $J=6.0$ Hz, 2H), 5.26 (t, $J=7.2$ Hz, 1H), 6.92 (s, 1H), 7.41 (s, 2H). Compound **45** was subjected to the next reaction without further purification.

5,8-Diacetoxy-2-(1′-acetoxy-3′-hydroxypropyl)-1,4-naphthoquinone (46) Compound **46** was obtained in a similar manner to **21** as an oily compound. IR (CHCl$_3$): 1760, 1730, 1680 cm^{-1}. ^{1}H-NMR (CHCl$_3$) δ: 1.50—1.85 (m, 3H; 1H D$_2$O-exchangeable), 2.11 (s, 3H), 2.40, 2.43 (each s, 6H), 4.35—4.57 (m, 2H), 5.97 (t, $J=7.2$ Hz, 1H), 6.78 (s, 1H), 7.38 (s, 2H). FDMS *m/z*: 390 (M$^+$). HRMS (FAB) Calcd for $C_{19}H_{19}O_9$ 391.3579 $(M+H)^+$, Found 391.3585.

5,8-Diacetoxy-2-(3′-acetoxy-4′-methylpentyl)-1,4-naphthoquinone (47) Compound **47** was obtained in a similar manner to **33** as an oily compound. IR (CHCl$_3$): 1770, 1725, 1660 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 0.89 (d, $J=6.6$ Hz, 6H), 1.50—1.95 (m, 3H), 2.05 (s, 3H), 2.41 (s, 3H), 2.42 (s, 3H), 2.43—2.68 (m, 2H), 4.79 (q, $J=6.0$ Hz, 1H), 6.62 (br s, 1H), 7.35 (s, 2H). FDMS *m/z*: 416 (M$^+$). HRMS (FAB) Calcd for $C_{22}H_{25}O_8$ 417.4398 $(M+H)^+$, Found 417.4394.

5,8-Diacetoxy-2-(4′-methyl-3′-trifluoroacetoxypentyl)-1,4-naphthoquinone (48) Trifluoroacetic anhydride (0.3 ml) and pyridine (0.2 ml) were added to a solution of **24** (28 mg, 0.075 mmol) in 1 ml of dry CH$_2$Cl$_2$, and the reaction mixture was stirred at room temperature. After 30 min, the reaction mixture was poured into H$_2$O, and extracted with CH$_2$Cl$_2$. The extract was washed with H$_2$O and brine. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel with *n*-hexane–AcOEt (2 : 1) to give **48** (29 mg, 81%); oily compound. IR (CHCl$_2$): 1775, 1665 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 0.96 (d, $J=7.1$ Hz, 6H), 1.65—2.20 (m, 5H), 2.43 (s, 6H), 4.92 (m, 1H), 6.63 (s, 1H), 7.37 (s, 2H). FDMS. *m/z*: 470 (M$^+$). HRMS (FAB) Calcd for $C_{22}H_{22}F_3O_8$ 471.4110 $(M+H)^+$, Found 471.4116.

5,8-Diacetoxy-2-(3′-acetoxy-1′-bromo-4′-methylpentyl)-1,4-naphthoquinone (49) *N*-Bromosuccinimide (11 mg, 0.06 mmol) and benzoyl peroxide (3 mg, 0.012 mmol) was added to a solution of **47** (17 mg, 0.041 mmol) in 10 ml of CCl$_4$, through which Ar gas had been bubbled for 15 min before the reaction, and the mixture was heated at reflux. After 10 h, the reaction mixture was cooled to room temperature and evaporated to dryness. The residue was chromatographed on silica gel with *n*-hexane–AcOEt (4 : 1) to give **49** (17 mg, 83%). IR (CHCl$_3$): 1770, 1735, 1660, 1580 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 0.93 (d, $J=5.6$ Hz, 6H), 1.50—1.90 (m, 3H), 2.00, 2.08 (each s, 3H), 2.44 (s, 6H), 5.18 (m, 2H), 6.93 (m, 1H), 7.41 (s, 2H). Compound **49** was unstable and was subjected to the next reaction without further purification. Photochemical bromination was done under irradiation with a 300 W tungsten lamp.

5,8-Diacetoxy-2-(3′-acetoxy-1′-hydroxy-4′-methylpentyl)-1,4-naphthoquinone (50) Silver trifluoroacetate (80 mg, 0.36 mmol) was added to a solution of **49** (45 mg, 0.09 mmol) in 1 ml of acetic acid, and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with CH$_2$Cl$_2$ and the precipitates were removed by filtration through Celite. The filtrate was washed with diluted aqueous NaHCO$_3$, H$_2$O, and brine and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel with *n*-hexane–AcOEt (2 : 1) to give **50** (17 mg, 43%) as an oily compound. IR (CHCl$_3$): 3400, 1765, 1725, 1660 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 0.94 (d, $J=6.4$ Hz, 6H), 1.99 (s, 3H), 1.60—2.20 (m, 3H), 2.42 (s, 6H), 3.60 (m, 1H D$_2$O-exchangeable), 4.70—5.04 (m, 2H), 6.92 (br s, 1H), 7.36 (s, 2H). FDMS *m/z*: 433 (M$^+$+1). HRMS (FAB) Calcd for $C_{22}H_{25}O_9$ 433.4392 $(M+H)^+$, Found 433.4401.

5,8-Diacetoxy-2-(1′,3′-diacetoxy-4′-methylpentyl)-1,4-naphthoquinone (51) Compound **51** was obtained in a similar manner to **35** as an oily compound. IR (CHCl$_3$): 1760, 1735, 1725, 1655 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 0.90 (d, $J=6.4$ Hz, 6H), 1.60—2.00 (m, 3H), 1.88 (s, 3H), 2.12 (s, 3H), 2.43 (s, 6H), 4.93 (m, 1H), 5.96 (t, $J=6.4$ Hz, 1H), 6.68 (br s, 1H), 7.38 (s, 2H). FDMS *m/z*: 474 (M$^+$). HRMS (FAB) Calcd for $C_{24}H_{27}O_{10}$ 475.4768 $(M+H)^+$, Found 475.4761.

5,8-Diacetoxy-2-(1′-bromo-4′-methyl-3′-trifluoroacetoxypentyl)-1,4-naphthoquinone (52) Compound **52** was obtained in a similar manner to **49**. IR (CHCl$_3$): 1780, 1655 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 0.98 (d, $J=6.7$ Hz, 6H), 1.18—1.60 (m, 3H), 2.44 (s, 6H), 4.72—5.47 (m, 2H), 6.97 (br s, 1H), 7.41 (s, 2H). Compound **52** was subjected to the next reaction without further purification.

5,8-Diacetoxy-2-(1′-hydroxy-4′-methyl-3′-trifluoroacetoxypentyl)-1,4-naphthoquinone (53) and 5,8-Diacetoxy-2-(1′-acetoxy-4′-methyl-3′-trifluoroacetoxypentyl)-1,4-naphthoquinone (54) Compounds **53** and **54** were obtained in a similar manner to **51** (room temperature, 8 h).

53: oily compound. IR (CHCl$_3$): 1780, 1670 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 0.98 (d, $J=7.0$ Hz, 6H), 1.60—1.85 (m, 4H; 1H D$_2$O-exchangeable), 2.43 (s, 6H), 5.13 (m, 2H), 6.88 (s, 1H), 7.38 (s, 2H). FDMS *m/z*: 486 (M$^+$). HRMS (FAB) Calcd for $C_{22}H_{22}F_3O_9$ 487.4104 $(M+H)^+$, Found 487.4114.

54: oily compound. IR (CHCl$_3$): 1775, 1750, 1655 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 0.98 (d, $J=6.4$ Hz, 6H), 1.50—1.70 (m, 3H), 2.10 (s, 3H), 2.43 (s, 6H), 5.03 (m, 1H), 5.90 (t, $J=6.2$ Hz, 1H), 6.68 (br s, 1H), 7.39 (s, 2H). FDMS *m/z*: 528 (M$^+$). HRMS (FAB) Calcd for $C_{24}H_{24}F_3O_{10}$ 529.4481 $(M+H)^+$, Found 529.4488,

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