Synthesis and Antitumor Activity of Tropolone Derivatives. 4[1]

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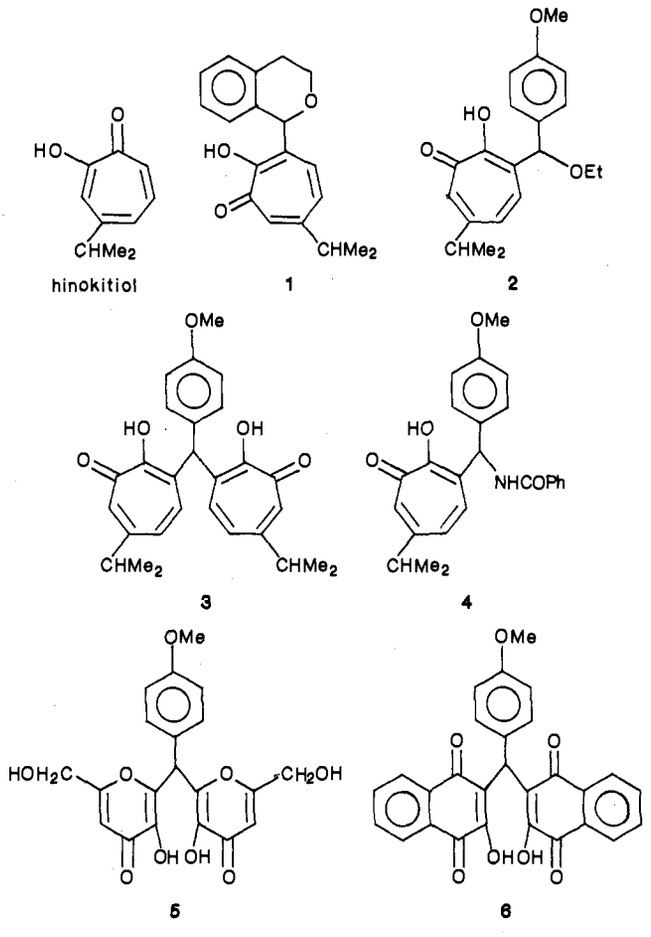
Modifications of monotropolone **2** having poor potency against P388 in mice were studied. The α-ethoxy group of **2**, prepared from hinokitiol and benzaldehyde diethyl acetal, was replaced with a phenolic or heteroaromatic compound by heating **2** with the appropriate nucleophile. Structure–activity relationships indicated that an acidic hydroxyl and a proton-accepting group situated in the neighboring position, which permits the formation of a chelate with a metal ion, contributed to enhanced activity. Among the compounds studied, the 8-hydroxyquinoline analogue **10f** was the most favorable compound.

The syntheses of new tropolone derivatives **1–4** (Chart I), which inhibit the growth of KB cells (in vitro system) and which are active in the survival test of mice with P388 leukemia (in vivo system) have been previously reported.[1-5] Among them, bistropolone α,α-bis(2-hydroxy-6-isopropyltropon-3-yl)-4-methoxytoluene (**3**)[4] is much more potent than monotropolones, such as 3-isochromanyl-6-isopropyltropolone (**1**)[4], 3-(α-ethoxy-4-methoxybenzyl)-6-isopropyltropolone (**2**),[4] or 3-[α-(benzoylamino)-4-methoxybenzyl]-6-isopropyltropolone (**4**) in the in vivo system, although **3** and the monotropolones exhibit nearly equal potency in the in vitro system.[4,5] We[1] have also concluded that bis(non-troponoid) derivatives **5** and **6**, which are designed to have a structure similar to the potently active bistropolone **3**, are all inactive even in the in vitro system. Previous studies on the molecular requirements for such activity showed that the tropolone moiety is essential. However, the reason why two tropolone rings in a molecule are necessary for producing potent activity in the in vivo system remains unknown. These observations have prompted us to design and synthesize new tropone derivatives **7–11** in which the one tropolone ring in **3** is replaced by an aromatic or heteroaromatic compound that contains a hydroxyl and/or a carbonyl group as found in hinokitiol. We have called these new compounds pseudobistropolones.

Compounds **7a** and **7b** were prepared as typical examples having one phenolic hydroxyl group on a benzene ring and compounds **8a–c** were synthesized as examples of those with two phenolic hydroxyl groups. On the other hand, **9a–c** were prepared as typical compounds having one or two carbonyl groups. Compounds **10a–e** were designed to have a hydroxyl and a carbonyl group on a ring. The 8-hydroxyquinoline analogue **10f** was synthesized on the basis of the consideration that it has a potent ability to form a chelate with a metal ion similar to bistropolone **3**. Compounds **11a** and **11b** were obtained by the heating of **2** with 1,4-naphthalenediols.

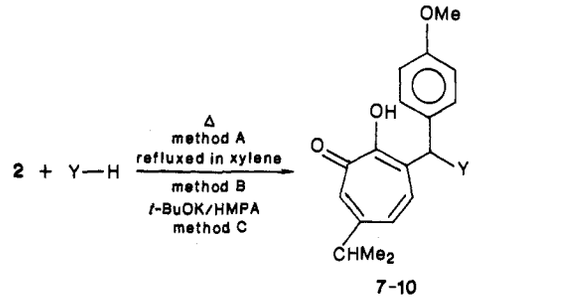
Chart I



Chemistry

Pseudobistropolones **7–11** were prepared by the reaction of **2**[6] synthesized from hinokitiol[7] and benzaldehyde acetal with appropriate the nucleophiles, as shown in Scheme I. During the preparation, it was necessary to vary the reaction conditions according to the nucleophilicities of the reagents. Three methods were used to synthesize the needed compounds. One was the heating of **2** with a nucleophile in the absence of catalyst without solvent (method A) while another was reflux with xylene (method B). The third method was the heating of **2** with a nucleophile in the presence of potassium *tert*-butoxide and hexamethylphosphoric triamide (HMPA) in refluxing xylene[1] (method C).

Scheme I



† Okayama University.
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(1) Part 3: Yamato, M.; Hashigaki, K.; Kokubu, N.; Tashiro, T.; Tsuruo, T. *J. Med. Chem.* **1986**, *29*, 1202.
(2) Yamato, M.; Ishikawa, T.; Ishikawa, S.; Hashigaki, K. *Chem. Pharm. Bull.* **1983**, *31*, 2952.

0022-2623/87/1830-0117$01.50/0

Table I. Preparations of 7–11

compd	molar[a] ratio	method	reactn time, h	reactn temp, °C	chromatography[b]	recrystn solvent	yield, %	mp, °C	formula[c]
7a	4 eq	A	14	100	20% AH	EtOH	30	88–90	$C_{28}H_{32}O_4$
7b	1.5 eq	A	1	160	10% AH	Et_2O	27	141–143	$C_{28}H_{26}O_4$
8a	1.2 eq	A	2	160	25% AH	Et_2O	60	96–99	$C_{28}H_{32}O_5$
8b	1.2 eq	A	4	110	25% AH	Et_2O–hexane	28	108–113	$C_{24}H_{24}O_5$
8c	1.2 eq	A	2	130	25% AH	Et_2O–hexane	15	145–150	$C_{24}H_{24}O_5$
9a	1.2 eq	B	6	ref[d]	10% AH	MeOH–CH_2Cl_2	12	160–162	$C_{28}H_{24}O_5$
9b	1 eq	B	2	ref	10% AH	hexane–AcOEt	20	82–83	$C_{29}H_{26}O_5$
9c	1 eq	C	8	ref	60% AH	CH_2Cl_2	11	207–209	$C_{28}H_{26}ClO_7$
10a	1.2 eq	A	0.5	120	*e*	CH_2Cl_2	89	195–198	$C_{29}H_{26}O_6$
10b	1.2 eq	B	0.5	ref	25% AH	CH_2Cl_2–MeOH	21	183–185	$C_{33}H_{28}O_7$
10c	1.1 eq	A	4	140	10% AH	CH_2Cl_2–MeOH	27	185–187	$C_{28}H_{24}O_6$
10d	1.2 eq	A	4	120	*e*	CH_2Cl_2	44	203–204	$C_{27}H_{24}O_6$
10e	1.2 eq	A	3	140	*e*	CH_2Cl_2–MeOH	31	143–145	$C_{24}H_{24}O_7$
10f	1.2 eq	C	5	ref	10% AH	AcOEt–$CHCl_3$	29	212–214	$C_{27}H_{25}NO_4$
11a	1 eq	A	1	160	10% AH	MeOH–$CHCl_3$	17	228–232	$C_{28}H_{24}O_4$
11b	1 eq	A	2	160	10% AH	MeOH–$CHCl_3$	12	205–207	$C_{29}H_{26}O_4$

[a] Molar ratio of Y-H to **2**. [b] % AH = percent ethyl acetate in hexane. [c] All compounds were analyzed for C, H, and N. [d] ref = reflux. [e] Column chromatography was not run.

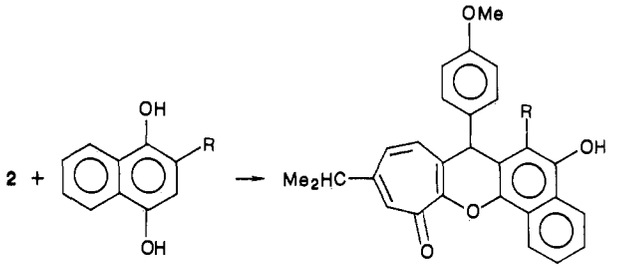
When the nucleophiles were phenolic compounds, most pseudobistropolones were prepared without the use of a catalyst. In practice, monohydroxy (**7a**, **7b**, and **10a**) and dihydroxy (**8a–8c**) analogues were prepared by method A. On the other hand, **10b** was prepared by method B, because chrysin is reactive with **2**. Compound **10f**[8] was the exception. It could only be prepared when potassium *tert*-butoxide was used as a catalyst (method C). For this reason, the nucleophilicity of 8-hydroxyquinoline was considered to be relatively weaker than the others.

In the preparation of the quinone analogues **9a** and **9b**, the reaction of 1,4-naphthoquinones with **2** did not occur under any of the conditions examined. Consequently, **9a** and **9b** were prepared by the reaction of 1,4-naphthalenediols with **2** via method B followed by autoxidation. The benzofuranone analogue **9c** was prepared by method C.

Compounds **10c–e**, which have an enolic hydroxy group, were prepared by method A, in a manner similar to the preparation of the phenolic analogues **7** and **8**.

Compound **11a** was obtained by treating 1,4-naphthalenediol with **2** at 160 °C for 1 h (method A). Under the above conditions, 3-[α-(1,4-dihydroxy-2-naphthyl)-4-methoxybenzyl]-6-isopropyltropolone (**8d**), formed by the reaction of 1,4-naphthalenediol and **2**, underwent further dehydration to yield the cyclized compound **11a**. A similar result was observed during the reaction of 2-methyl-1,4-naphthalenediol with **2**, from which **11b** was synthesized.

Scheme II



11a: R = H
11b: R = Me

Biological Results and Discussion

The compounds listed in Table II were evaluated for antitumor activity against leukemia P388 in mice. As previously reported,[1,3-5] all but a few tropolone derivatives were found to be very active in tests of inhibitory activity against the growth of KB cells (in the in vitro system). Therefore, two typical compounds, **10c** and **10e**, were tested. Their resulting ID_{50} values were 1.83 and 0.51 μg/mL, respectively.

Compounds **7** and **8**, having one or two hydroxyl groups on the benzene ring, improved the activity of the parent compound **2**. Among them, **8a** and **8c** were more active than **2**, suggesting that the presence of two hydroxyl groups is desirable for enhancement of activity. Compounds **9a–c** did not improve the activity of the parent compound **2**, implying that the presence of only a carbonyl group in the ring has no significant effect on improvement of the activity of **2**.

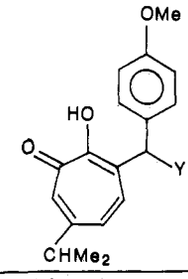
Compounds **10a–e**, except for the coumarin analogue **10d**, share the ring moiety of having the carbonyl and hydroxyl groups situated in the neighboring position. Among them, the potency of **10a** was equal with **2** at 100 mg/kg. On the other hand, **10b–e** showed activity at low doses (5–25 mg/kg) when compared with **2**. Compound **10e** has relative potent activity at low doses. From these results, we concluded that the ability of the two carbonyl–hydroxyl pairs to form a chelate with a metal ion in **3** or **10** is closely related to the potent antitumor activities of these compounds. Consequently, **10f**, in which one tropolone was replaced by 8-hydroxyquinoline, well-known as a potent chelating agent, was synthesized and found to be remarkably more potent than monotropolone **2**.

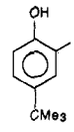
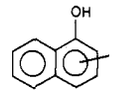
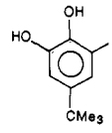
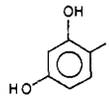
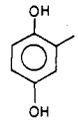
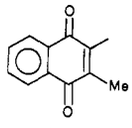
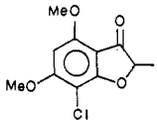
Compounds **11a** and **11b** were inactive, implying that methylation of the hydroxyl group of **1** results in loss of activity.

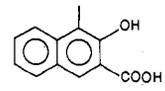
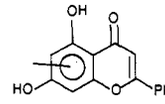
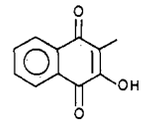
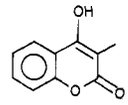
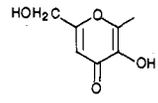
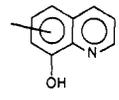
In summary, several new types of potent antitumor-active compounds were developed. Present findings led us to conclude that antitumor-active tropolone derivatives **3** or **10**, which could act as a chelator, are inhibitors of a metal-dependent enzyme such as ribonucleoside diphosphate reductase[9,10] and hence the synthesis of DNA.

(3) Yamato, M.; Hashigaki, K.; Kokubu, N.; Nakato, Y. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1301.
(4) Yamato, M.; Hashigaki, K.; Kokubu, N.; Tsuruo, T.; Tashiro, T. *J. Med. Chem.* **1984**, *27*, 1749.
(5) Yamato, M.; Hashigaki, K.; Ishikawa, S.; Kokubu, N.; Inoue, Y.; Tsuruo, T.; Tashiro, T. *J. Med. Chem.* **1985**, *28*, 1026.
(6) The preparation of **2** was reported previously (see ref 3). Presently, the improved method described in the Experimental Section was achieved.
(7) Nozoe, T. *Bull. Chem. Soc. Jpn.* **1936**, *11*, 295.
(8) Study on the establishment of the structure is in progress.
(9) Moor, E. C. In *Methods in Enzymology*, Colowick, S. P., Kaplan, N. D., Eds.; Academic: New York, 1967; Vol. 12, Part A, pp 155–164.

Table II. Antitumor Activities of Pseudobistropolones



compd	Y	antitumor act. P388 in mice: dose, mg/kg ip[a]	T/C,[b] %
7a		100	120
		50	116
		25	116
7b		50	108
		25	125
		12.5	105
8a		50	168
		25	127
		12.5	110
8b		200	136
		100	104
		50	98
8c		50	128
		25	142
		12.5	128
9b		400	72
		200	131
		100	114
9c		100	130
		50	109
		25	117

compd	Y	antitumor act. P388 in mice: dose, mg/kg ip[a]	T/C,[b] %
10a		200	0
		100	141
		20	106
10b		200	148
		100	136
		25	127
10c		50	0
		20	129
		5	108
10d		20	127
		10	117
		5	128
10e		50	152
		25	146
		12.5	128
10f		12.5	141
		6.3	151
		3.1	144
2		400	140
		200	128
		100	148
		50	119
3		5	173
		2.5	134
		0.6	127

[a] The doses listed were given once a day for 1 and 5 days. [b] Compounds **9a**, **11a**, and **11b** are inactive at 400 mg/kg.

In order to clarify the antitumor action, further studies will be done.

Experimental Section

Melting points were determined on a Yanagimoto micromelting apparatus and are uncorrected. NMR spectra were run on a Hitachi R-24 spectrometer at 60 MHz, with Me_4Si as an internal standard. Mass spectra were recorded on a Shimadzu LKB-9000 spectrometer. The elemental analysis were within 0.4% of the theoretical values. Column chromatographic separations were performed by flash technique on 200–300-mesh silica gel (Wako C-300).

3-(α-Ethoxy-4-methoxybenzyl)-6-isopropyltropolone (2). A solution of hinokitiol[7] (5 g, 30 mmol) and *p*-anisaldehyde diethyl acetal (25.2 g, 120 mmol) in toluene (50 ml) was allowed to reflux for 20 h with removal of ethanol that formed. The solvent and excess acetal were removed in vacuo, and the resulting oil was chromatographed on silica gel with hexane–AcOEt (10:1) to give **2** (7.22 g, 72%, based on hinokitiol), mp[11] 66–67 °C (from hexane–Et_2O).

3-(5-*tert*-Butyl-2-hydroxy-4′-methoxybenzhydryl)-6-isopropyltropolone (7a). Method A. A mixture of **2** (0.5 g, 1.5 mmol) and 4-*tert*-butylphenol (0.85 g, 5.7 mmol) was heated at 100 °C for 14 h. The reaction mixture was chromatographed on silica gel with hexane–AcOEt (4:1) to give **7a** (0.2 g, 30%): mp 88–90 °C (from EtOH); IR (Nujol) 3170, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (s, 9 H, CMe_3), 1.40 (d, J = 7 Hz, 6 H, $CHMe_2$), 2.5–3.3 (m, 1 H, $CHMe_2$), 3.80 (s, 3 H, OMe), 6.35 (s, 1 H, CH), 6.5–7.7 (m) and 7.7–8.2 (br) (12 H, aromatic H, tropolone H, OH); MS, m/z 432 (M^+).

Compounds **7b**, **8a–c**, **10a**, and **10c–e** were prepared in a similar manner.

2- or 4-[α-(2-Hydroxy-6-isopropyltropon-3-yl)-4-methoxybenzyl]-1-naphthol (7b): IR (Nujol) 3200, 1625, 1595 cm^{-1}; NMR ($CDCl_3$) δ 1.20 (d, J = 7 Hz, 6 H, $CHMe_2$), 2.5–3.4 (m, 1 H, $CHMe_2$), 3.78 (s, 3 H, OMe), 6.70 (s, 1 H, CH), 6.9–8.1 (m, 12 H, aromatic H, tropolone H), 8.3–8.7 (m, 1 H, aromatic H), 9.22 (br, 1 H, OH); MS, m/z 426 (M^+).

(10) French, F. A.; Blanz, E. J., Jr.; Shaddix, S. C.; Brockman R. W. *J. Med. Chem.* **1974**, *17*, 172.

(11) Compound **2** was reported previously to be an oil (see ref 2).

3-(5-*tert*-Butyl-2,3-dihydroxy-4′-methoxybenzhydryl)-6-isopropyltropolone (8a): IR (Nujol) 3500, 3175, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (s, 9 H, CMe_3), 1.30 (d, J = 7 Hz, 6 H, $CHMe_2$), 2.6–3.3 (m, 1 H, $CHMe_2$), 3.82 (s, 3 H, OMe), 6.41 (s, 1 H, CH), 6.7–7.9 (m, 9 H, aromatic H, tropolone H); MS, m/z 448 (M^+).

3-(2,4-Dihydroxy-4′-methoxybenzhydryl)-6-isopropyltropolone–ethanol (8b·EtOH): IR (Nujol) 3200, 1589 cm^{-1}; NMR ($CDCl_3$) δ 1.19 (t, J = 7 Hz, 3 H, CH_3CH_2OH), 1.22 (d, J = 6 Hz, 6 H, $CHMe_2$), 2.5–3.3 (m, 1 H, $CHMe_2$), 3.54 (q, J = 7 Hz, 2 H, CH_3CH_2OH), 3.80 (s, 3 H, OMe), 6.40 (d, J = 6 Hz, 2 H, aromatic H), 6.5–7.7 (m) and 7.7–9.0 (br) (13 H, aromatic H, tropolone H, CH, OH).

3-(2,5-Dihydroxy-4′-methoxybenzhydryl)-6-isopropyltropolone (8c): IR (Nujol) 3450, 3200, 1605 cm^{-1}; NMR (Me_2SO-d_6) δ 1.27 (d, J = 7 Hz, 6 H, $CHMe_2$), 2.6–3.1 (m, 1 H, $CHMe_2$), 3.80 (s, 3 H, OMe), 6.2–7.6 (m) and 7.6–8.6 (br) (14 H, aromatic H, tropolone H, CH, OH).

2-Hydroxy-1-[α-(2-hydroxy-6-isopropyltropon-3-yl)-4-methoxybenzyl]-3-naphthoic acid (10a): IR (Nujol) 3200, 3150, 1670, 1610 cm^{-1}; NMR (Me_2SO-d_6) δ 1.15 (d, J = 7 Hz, 6 H, $CHMe_2$), 2.4–3.2 (m, 1 H, $CHMe_2$), 3.65 (s, 3 H, OMe), 6.70 (s, 1 H, CH), 6.8–8.3 (m, 11 H, aromatic H, tropolone H), 8.60 (s, 1 H, 4-H); MS, m/z 470 (M^+).

2-Hydroxy-3-[α-(2-hydroxy-6-isopropyltropon-3-yl)-4-methoxybenzyl]-1,4-naphthoquinone (10c): a yellow crystal; IR (Nujol) 3300, 3200, 1665, 1640, 1590 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (d, J = 7 Hz, 6 H, $CHMe_2$), 2.6–3.3 (m, 1 H, $CHMe_2$), 3.79 (s, 3 H, OMe), 6.74 (s, 1 H, CH), 6.7–8.3 (m, 11 H, aromatic H, tropolone H), 8.7 (br, 2 H, OH).

4-Hydroxy-3-[α-(2-hydroxy-6-isopropyltropon-3-yl)-4-methoxybenzyl]coumarin (10d): IR (Nujol) 3200, 1690, 1610 cm^{-1}; NMR (Me_2SO-d_6) δ 1.25 (d, J = 7 Hz, 6 H, $CHMe_2$), 2.6–3.3 (m, 1 H, $CHMe_2$), 3.77 (s, 3 H, OMe), 6.22 (s, 1 H, CH), 6.7–8.2 (m, 11 H, aromatic H, tropolone H); MS, m/z 444 (M^+).

3-Hydroxy-2-[α-(2-hydroxy-6-isopropyltropon-3-yl)-4-methoxybenzyl]-6-(hydroxymethyl)-4*H*-pyran-4-one (10e): IR (Nujol) 3300, 3200, 1650, 1610 cm^{-1}; NMR (Me_2SO-d_6) δ 1.21 (d, J = 7 Hz, 6 H, $CHMe_2$), 2.6–3.3 (m, 1 H, $CHMe_2$), 3.79 (s, 3 H, OMe), 4.32 (s, 2 H, CH_2OH), 5.7 (br, 1 H, CH_2OH), 6.46 (s, 1 H, 5-H), 6.9–7.5 (m, 8 H, aromatic H, tropolone H, CH), 8.7–9.5 (br, 1 H, OH); MS, m/z 424 (M^+).

2-[α-(2-Hydroxy-6-isopropyltropon-3-yl)-4-methoxybenzyl]-1,4-naphthoquinone (9a). Method B. A solution of **2** (2 g, 61 mmol) and 1,4-naphthalenediol (1.2 g, 7.3 mmol) in xylene (20 mL) was allowed to reflux for 6 h. After removal of the solvent in vacuo, column chromatography of the residue on silica gel with hexane–AcOEt (10:1) gave **9a** (0.32 g, 12%) as a yellow crystal: mp 160–162 °C (from MeOH–CH_2Cl_2); IR (Nujol) 3150, 1650, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.08 (d, J = 7 Hz, 6 H, $CHMe_2$), 2.4–3.2 (m, 1 H, $CHMe_2$), 3.62 (s, 3 H, OMe), 6.1–8.1 (m, 13 H, aromatic H, tropolone H, CH), 8.8 (br, 1 H, OH); MS, m/z 440 (M^+).

Compound **9b** and **10b** were prepared in a similar manner.

2-[α-(2-Hydroxy-6-isopropyltropon-3-yl)-4-methoxybenzyl]-3-methyl-1,4-naphthoquinone (9b): yellow crystal; IR (Nujol) 3200, 1650, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (d, J = 7 Hz, 6 H, $CHMe_2$), 2.20 (s, 3 H, 3-Me), 2.5–3.3 (m, 1 H, $CHMe_2$), 3.74 (s, 3 H, OMe), 6.00 (s, 1 H, CH), 6.6–8.2 (m, 11 H, aromatic H, tropolone H), 8.90 (br, 1 H, OH); MS, m/z 454 (M^+).

5,7-Dihydroxy-6- or -8-[α-(2-hydroxy-6-isopropyltropon-3-yl)-4-methoxybenzyl]-2-phenyl-4*H*-chromen-4-one (10b): IR (Nujol) 3200, 1650, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (d, J = 7 Hz, 6 H, $CHMe_2$), 2.5–3.3 (m, 1 H, $CHMe_2$), 3.75 (s, 3 H, OMe), 6.3–7.8 (m, 13 H, aromatic H, tropolone H, CH), 8.2 (d, J = 10 Hz, 1 H, aromatic H), 8.9 (br, 1 H, OH), 10.7 (br, 1 H, OH), 13.62 (s, 1 H, OH); MS, m/z 536 (M^+).

7-Chloro-4,6-dimethoxy-2-[α-(2-hydroxy-6-isopropyltropon-3-yl)-4-methoxybenzyl]-2*H*-benzofuran-3-one (9c). Method C. A solution of **2** (1.44 g, 4.4 mmol), 7-chloro-4,6-dimethoxy-2*H*-benzofuran-3-one[12] (1 g, 4.4 mmol), *t*-BuOK (45 mg, 0.4 mmol), and HMPA (0.4 g, 2 mmol) in xylene (15 ml) was allowed to reflux for 8 h. After the solvent was removed in vacuo, the residue was made acidic with 10% HCl and extracted with CH_2Cl_2. The extract was washed with H_2O, dried ($MgSO_4$), and concentrated. The residue was column chromatographed on silica gel with hexane–AcOEt (2:3) to give **9c** (0.25 g, 11%): mp 207–209 °C (from benzene–CH_2Cl_2); IR (Nujol) 3200, 1700, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (d, J = 7 Hz, 6 H, $CHMe_2$), 2.6–3.3 (m, 1 H, $CHMe_2$), 3.71 (s, 3 H, OMe), 3.92 (s, 3 H, OMe), 4.00 (s, 3 H, OMe), 5,31 (d, J = 3.5 Hz, 1 H, 2-H), 5.44 (d, J = 3.5 Hz, 1 H, CH), 6.08 (s, 1 H, 5-H), 6.7–7.5 (m, 6 H, aromatic H, tropolone H), 8.32 (d, J = 10 Hz, 1 H, aromatic H); MS, m/z 509 (M^+), 511 ($M^+ + 2$).

Compound **10f** was prepared in a similar manner.

5- or 7-[α-(2-Hydroxy-6-isopropyltropon-3-yl)-4-methoxybenzyl]-8-hydroxyquinoline (10f): IR (Nujol) 3350, 3200, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (d, J = 7 Hz, 6 H, $CHMe_2$), 2.4–3.2 (m, 1 H, $CHMe_2$), 3.75 (s, 3 H, OMe), 6.5–7.5 (m, 11 H, aromatic H, tropolone H, CH), 8.05 (dd, J = 9 and 2 Hz, 2-H), 8.67 (dd, J = 4 and 2 Hz, 1 H, 4-H), 9.05 (br, 2 H, OH); MS, m/z 427 (M^+).

7-(4-Anisyl)-5-hydroxy-10-isopropyl-12-oxonaphtho[1,2-*b*]-1*H*-cyclohexa[2,3-*e*]-4*H*-pyran (11a). A mixture of **2** (3.0 g, 9 mmol) and 1,4-naphthalenediol (1.46 g, 9 mmol) was heated at 160 °C for 1 h. Column chromatography of the reaction mixture on a silica gel with hexane–AcOEt (9:1) gave **11a** (0.67 g, 17%): mp 228–232 °C (from MeOH–$CHCl_3$); IR (Nujol) 3300, 1610 cm^{-1}; NMR (CF_3COOD) δ 1.50 (d, J = 7 Hz, 6 H, $CHMe_2$), 2.9–3.8 (m, 1 H, $CHMe_2$), 3.96 (s, 3 H, OMe), 6.65 (s, 1 H, CH), 6.8–8.7 (m, 12 H, aromatic H, tropolone H); MS, m/z 424 (M^+).

Compound **11b** was prepared in a similar manner.

7-(4-Anisyl)-5-hydroxy-10-isopropyl-6-methyl-12-oxonaphtho[1,2-*b*]-1*H*-cyclohexa[2,3-*e*]-4*H*-pyran (11b): IR (Nujol) 3200, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.18 (d, J = 7 Hz, 6 H, $CHMe_2$), 2.20 (s, 3 H, 6-Me), 2.4–3.3 (m, 1 H, $CHMe_2$), 3.70 (s, 3 H, OMe), 4.96 (s, 1 H, CH), 6.7–8.7 (m, 11 H, aromatic H); MS, m/z 438 (M^+).

Biological Assays. Assays of antitumor activity were carried out as described previously.[4]

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Registry No. **2**, 92832-11-6; **7a**, 104598-43-8; **7b** (isomer 1), 104598-44-9; **7b** (isomer 2), 104619-14-9; **8a**, 104598-45-0; **8b**·EtOH, 104598-47-2; **8c**, 104598-48-3; **9a**, 104598-53-0; **9b**, 104598-54-1; **9c**, 104598-56-3; **10a**, 104598-49-4; **10b** (isomer 1), 104598-55-2; **10b** (isomer 2), 104598-61-0; **10c**, 104598-50-7; **10d**, 104598-51-8; **10e**, 104598-52-9; **10f** (isomer 1), 104598-57-4; **10f** (isomer 2), 104598-60-9; **11a**, 104598-58-5; **11b**, 104598-59-6; $(CH_3)_3C$-*p*-C_6H_4OH, 98-54-4; HO-*p*-C_6H_4OH, 123-31-9; hinokitiol, 499-44-5; *p*-anisaldehyde diethyl acetal, 2403-58-9; 1-naphthol, 90-15-3; 2-hydroxy-4-*tert*-butylphenol, 98-29-3; resorcinol, 108-46-3; 2-hydroxy-3-naphthalene carboxylic acid, 92-70-6; 2-hydroxy-1,4-naphthalenediol, 13302-67-5; 4-hydroxycoumarin, 1076-38-6; 3-hydroxy-6-(hydroxymethyl)-4*H*-pyran-4-one, 501-30-4; 1,4-naphthalenediol, 571-60-8; 2-methyl-1,4-naphthalenediol, 481-85-6; chrysin, 480-400; 7-chloro-4,6-dimethoxy-2*H*-benzofuran-3-one, 3261-06-1; 8-hydroxyquinoline, 148-24-3.

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