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Highly Efficient Total Synthesis of the Marine Natural Products (+)-Avarone, (+)-Avarol, (−)-Neoavarone, (−)-Neoavarol and (+)-Aureol

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Abstract: Biologically important and structurally unique marine natural products avarone (**1**), avarol (**2**), neoavarone (**3**), neoavarol (**4**) and aureol (**5**), were efficiently synthesized in a unified manner starting from (+)-5-methyl-Wieland–Miescher ketone **10**. The synthesis involved the following crucial steps: i) Sequential $BF_3{\cdot}Et_2O$-induced rearrangement/cyclization reaction of **2** and **4** to produce **5** with complete stereoselectivity in high yield (**2** → **5** and **4** → **5**); ii) strategic salcomine oxidation of the phenolic compounds **6** and **8** to derive the corresponding quinones **1** and **3** (**6** → **1** and **8** → **3**); and iii) Birch reductive alkylation of **10** with bromide **11** to construct the requisite carbon framework **12** (**10** + **11** → **12**). An in vitro cytotoxicity assay of compounds **1**–**5** against human histiocytic lymphoma cells U937 determined the order of cytotoxic potency (**3** > **1** > **5** > **2** > **4**) and some novel aspects of structure-activity relationships.

Keywords: biomimetic synthesis · natural products · quinones · rearrangement · total synthesis

Introduction

In recent years, a number of clerodane diterpenoids and related compounds have been isolated from marine organisms, particularly from algae and sponges.[1] Several of these marine natural products have been reported to exhibit attractive biological activities such as cytotoxic, antimicrobial, antiviral, and immunomodulatory activities.[1] In most cases, however, further biological studies of these marine natural products are severely restricted, presumably because of the scarcity of samples from the marine organisms.[1] Consequently, the development of an efficient and reliable method for the synthesis of these marine natural products is highly desirable and worthwhile from the viewpoint of medicinal chemistry and pharmaceuticals.

(+)-Avarone (**1**) and (+)-avarol (**2**) (Figure 1), the first examples of naturally occurring sesquiterpenoidal quinones and hydroquinones, were isolated from the Mediterranean sponge *Dysidea avara* by Minale et al. in 1974.[2] These compounds show a wide variety of pharmacological properties including cytotoxic,[3] antimicrobial,[3a,4] antiinflammatory,[5] antioxidant,[6] antiplatelet,[7] antipsoriatic[8] and anti-HIV[9] activities. (−)-Neoavarone (**3**) and (−)-neoavarol (**4**) were isolated from an Okinawan sponge *Dysidea* sp. by Iguchi et al.[10] in 1990. The structures of **3** and **4** were assigned as the C4 *exo*-olefinic isomers of **1** and **2**;[10] however, their biological activity has not been reported to date. (+)-Aureol (**5**) was originally isolated in 1980 by Faulkner et al.[11] from a Caribbean sponge *Smenospogia aurea*, and subsequently in 2000 by Fattorusso et al.[12] from a different species of the Caribbean sponge, *Verongula gigantea*. Compound **5** consists of a novel tetracyclic benzo[*d*]xanthene skeleton (ABCD ring system) in which *cis*-fused AB and BC rings, and an ether bond at the bridgehead of the AB ring junction are the characteristic features. (+)-Aureol exhibits selective cytotoxicity against human tumor cells, including non-small cell lung cancer A549 and colon adenocarcinoma HT-29 cells,[13] and has anti-influenza A virus activity.[14]

The remarkable biological properties and unique structural features of these marine natural products and their limited availability from natural resources have made them intri-

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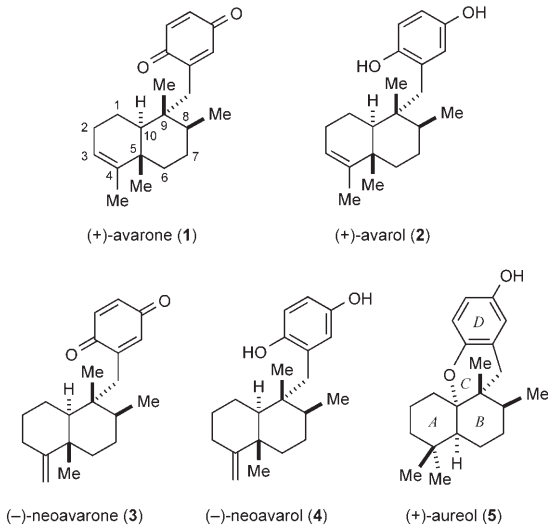
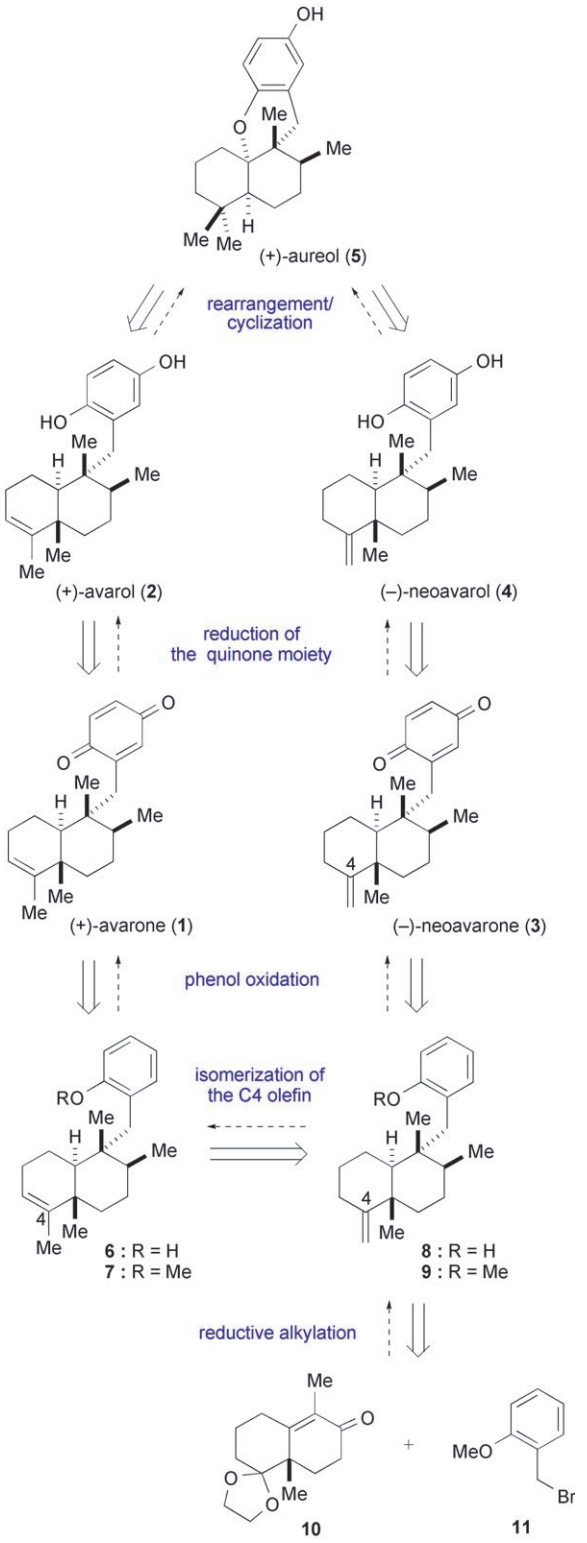


Figure 1. Structures of **1**–**5**.

guing targets for total synthesis. One racemic[15] and three enantioselective[16] total syntheses of avarone (**1**) and avarol (**2**) have been reported. We have already reported our own preliminary results concerning the first total synthesis of (−)-neoavarone (**3**), (−)-neoavarol (**4**) and (+)-aureol (**5**) in enantiomerically pure form.[17] In this paper, we describe the full details of our unified total synthesis of (+)-avarone (**1**), (+)-avarol (**2**), (−)-neoavarone (**3**), (−)-neoavarol (**4**) and (+)-aureol (**5**) in an enantioselective manner. In addition, the in vitro cytotoxic activity of these marine natural products **1**–**5** against a human cancer cell line U937 was evaluated to disclose novel aspects of the structure–activity relationships (SAR).

Results and Discussion

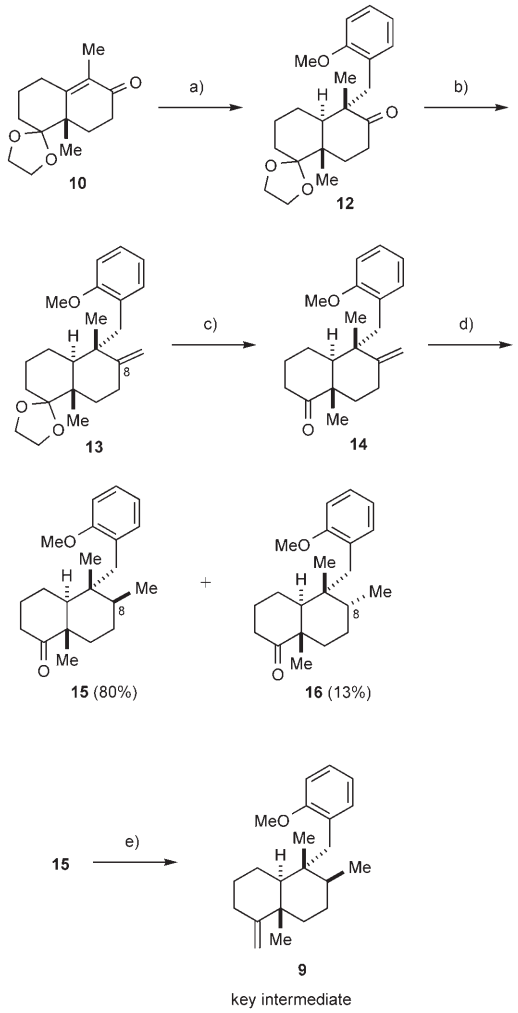
Synthetic plan for (+)-avarone (1), (+)-avarol (2), (−)-neoavarone (3), (−)-neoavarol (4) and (+)-aureol (5): Our synthetic plan for (+)-avarone (**1**), (+)-avarol (**2**), (−)-neoavarone (**3**), (−)-neoavarol (**4**) and (+)-aureol (**5**) is outlined in Scheme 1. The key feature of this plan is a novel biogenetic-type acid-induced rearrangement/cyclization reaction of **2** and **4** to produce the tetracyclic **5** in one step; we envisioned that this rearrangement/cyclization event would proceed stereoselectively to install the requisite *cis*-fused decalin ring junction (cf. **4** → **Ia** → **IIa** → **IIIa** → **5** and **2** → **Ib** → **IIb** → **IIIb** → **5**, see Scheme 6). Compounds **2** and **4** would be readily derived from **1** and **3**, respectively, upon reduction of the quinone moiety. Compounds **1** and **3** would be accessed in a straightforward manner by employing strategic phenol oxidation[18] of intermediates **6** and **8**. To the best of our knowledge, the utilization of the phenol oxidation method for synthesizing sesquiterpenoidal quinones such as **1** and **3** is hitherto unknown, and hence this type of reaction poses a considerable challenge at the synthetic chemistry level. Methyl ethers **7** and **9** would in turn be prepared by stereo-



Scheme 1. Synthetic plan for **1**–**5**.

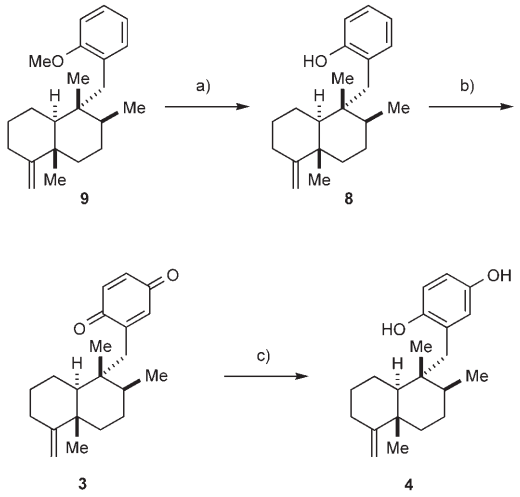
controlled reductive alkylation of the known enone **10**[19] with the known bromide **11**[20] applying previously described protocols from the literature.[21] The *endo*-olefin **7** should be accessible from the *exo*-olefin **9** by isomerization at the C4 olefinic double bond.

Synthesis of the key intermediate 9: We initially pursued the synthesis of the decalin derivative **9**, a common key intermediate for synthesis of **1**–**5**, as shown in Scheme 2. The synthesis commenced with the reductive alkylation of the known enantiomerically pure enone **10**[19] (>99% *ee*) with 2-methoxybenzyl bromide (**11**),[20] readily prepared from commercially available 2-methoxybenzyl alcohol. Thus, treatment of enone **10** with lithium metal (4 equiv) in liquid ammonia followed by reaction of the intermediary lithium enolate with bromide **11** (6 equiv) provided the expected coupling product **12** as the single diastereomer in 74% yield. Subsequent methylenation of the sterically hindered carbonyl group in **12** was achieved by employing a combination of $Ph_3P^+CH_3Br^-$and *t*BuOK in refluxing benzene, furnishing *exo*-olefin **13** in 86% yield. This reagent system was reported to be highly effective for methylenation sterically hindered carbonyl groups.[22] To establish the C8 stereogenic center, the ethylene acetal moiety in **13** was first removed by acid treatment (4 M HCl, THF, RT, 3 h, 97%), and the resulting ketone **14** was subjected to hydrogenation [H_2 (1 atm), 10% Pd/C, Et_3N/MeOH 50:1, RT], which afforded the desired product **15** (80%) and its C8 epimer **16** (13%) (**15**/**16** ca. 6:1) after separation by column chromatography on silica gel. When ethylene acetal **13** was used as a substrate for this hydrogenation under the same reaction conditions, the stereoselectivity at C8 decreased considerably (**15**/**16** ca. 2:1); this is probably due to an unfavorable conformation change of the decalin ring system.[23] Finally, compound **15** was efficiently converted to the desired key intermediate **9** in quantitative yield by Wittig methylenation ($Ph_3P^+CH_3Br^-$, *t*BuOK, benzene, reflux, 12 h).



Scheme 2. Synthesis of the key intermediate **9**. a) Li, liq. NH_3/THF, −78 → −30 °C; at −30 °C, add **11**, −30 °C to RT, 74%; b) $Ph_3P^+CH_3Br^-$, *t*BuOK, benzene, reflux, 86%; c) 4 M HCl, THF, RT, 97%; d) H_2 (1 atm), 10% Pd/C, Et_3N/MeOH 50:1, 80% for **15**, 13% for **16**; e) $Ph_3P^+CH_3Br^-$, *t*BuOK, benzene, reflux, quant.

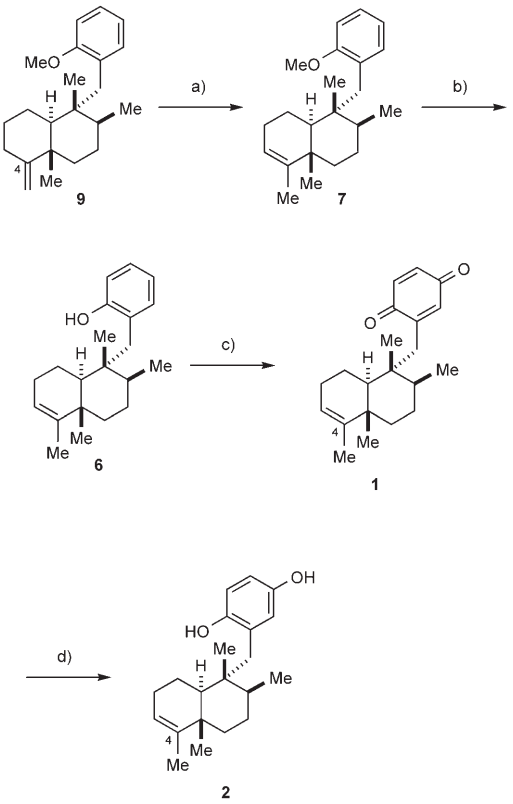
Synthesis of (−)-neoavarone (3) and (−)-neoavarol (4): With the key intermediate **9** synthesized, we next conducted the synthesis of **3** and **4**, as shown in Scheme 3. Thus, treatment of **9** with *n*BuSLi[24] in hexamethylphosphoramide (HMPA) at 110 °C for 3 h deprotected the phenolic *O*-methyl group, leading to the liberated phenol **8** in 92% yield. To construct the quinone system directly, phenol **8** was allowed to react with molecular oxygen (O_2 balloon) in the presence of salcomine [*N*,*N*′-bis(salicylidene)ethylenediaminocobalt(II)][18] in DMF at ambient temperature for 24 h, producing the target compound **3**, m.p. 94–95 °C (lit.[10] m.p. 78–79 °C), $[\alpha]_D^{20} = -62.7$ ($c = 1.02$, $CHCl_3$) {lit.[10] $[\alpha]_D^{20} = -55.2$ ($c = 0.07$, $CHCl_3$)}, in 91% yield. Subsequent conversion of **3** to **4** was first examined using the conventional procedure ($Na_2S_2O_4$, THF/H_2O, RT);[25] however, the yield of the desired product **4** was moderate (≈50%). After several experiments, we found that the requisite conversion proceeded smoothly and cleanly by treating **3** with $NaBH_4$ in THF/H_2O 10:1 at 0 °C for 3 min, producing the desired **4**, m.p. 175–177 °C (lit.[10] m.p. 151–153 °C), $[\alpha]_D^{20} = -41.6$ ($c =$



Scheme 3. Synthesis of (−)-neoavarone (**3**) and (−)-neoavarol (**4**). a) *n*BuSLi, HMPA, 110 °C, 92%; b) O_2 (1 atm), salcomine, DMF, RT, 91% c) $NaBH_4$, THF/H_2O 10:1, 0 °C, 86%. HMPA = hexamethylphosphoramide, salcomine = *N*,*N*′-bis(salicylidene)ethylenediaminocobalt(II).

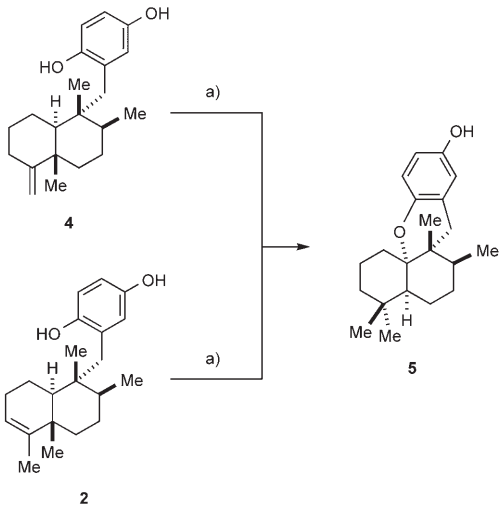
0.10, $CHCl_3$) {lit.[10] $[\alpha]_D^{20}=-38.6$ ($c=0.14$, $CHCl_3$)}, in 86% yield. The spectroscopic properties (^1H and ^{13}C NMR, MS) of the synthetic samples **3** and **4** were identical with those reported[10] for natural (−)-neoavarone and (−)-neoavarol, respectively.

Synthesis of (+)-avarone (1) and (+)-avarol (2): Having established the concise synthetic route to **3** and **4**, we next performed the synthesis of **1** and **2**, both of which possess an *endo*-olefinic double bond at C4, as shown in Scheme 4. Isomerization of the *exo*-olefin moiety in the key intermediate **9** to the desired *endo*-olefinic double bond was efficiently achieved by treatment with $RhCl_3\cdot 3H_2O$[16b,c,18c] (20 mol%) in refluxing EtOH for 24 h, produced *endo*-olefin **7** in quantitative yield. Compound **7** was then converted to **1** and **2** via phenol **6** by employing the same reaction sequence as that described for the synthesis of **3** and **4** from the key intermediate **9** (cf. **9** → **8** → **3** → **4**, Scheme 3). Thus, deprotection of the phenolic *O*-methyl group in **7** by exposure to *n*BuSLi in HMPA followed by salcomine oxidation of the liberated phenol **6** produced the desired **1**, m.p. 61–63 °C, $[\alpha]_D^{25}=+12.5$ ($c=0.94$, CH_2Cl_2) {lit.[16d] $[\alpha]_D^{25}=+13.1$ ($c=0.5$, CH_2Cl_2)}, in 80% yield for the two steps. Reduction of **1** with $NaBH_4$ provided the requisite **2**, m.p. 147–149 °C (lit.[2a] m.p. 148–150 °C), $[\alpha]_D^{20}=+10.8$ ($c=0.74$, CH_2Cl_2) {lit.[2a] $[\alpha]_D=+6.1$, lit.[16d] $[\alpha]_D^{25}=+10.2$ ($c=0.8$, CH_2Cl_2)}, in 85% yield. The spectroscopic properties (^1H and ^{13}C NMR, MS) of the synthetic samples **1** and **2** were identical with those reported[2a,b] for natural (+)-avarone and (+)-avarol, respectively.



Scheme 4. Synthesis of (+)-avarone (**1**) and (+)-avarol (**2**). a) $RhCl_3\cdot 3H_2O$, EtOH, reflux, quant.; b) *n*BuSLi, HMPA, 110 °C, 90%; c) O_2 (1 atm), salcomine, DMF, RT, 89%; d) $NaBH_4$, THF/H_2O 10:1, 0 °C, 85%.

Synthesis of (+)-aureol (5): Having obtained **4** and **2** in an efficient and expeditious way, the stage was set for the most crucial acid-induced rearrangement/cyclization event for the synthesis of the final target compound **5**. As shown in Scheme 5, the desired acid-induced rearrangement/cyclization reaction was successfully achieved by treating **4** with



Scheme 5. Synthesis of (+)-aureol (**5**). a) $BF_3\cdot Et_2O$, CH_2Cl_2, −50 → −5 °C, 93% for **4** → **5**, 91% for **2** → **5**.

$BF_3\cdot Et_2O$ (5.0 equiv) in CH_2Cl_2 at −50 to −5 °C for 5 h, which resulted in the formation of **5**, m.p. 143–144 °C (lit.[11] m.p. 144–145 °C), $[\alpha]_D^{20}=+64.5$ ($c=1.04$, CCl_4) {lit.[11] $[\alpha]_D^{20}=+65$ ($c=2.0$, CCl_4)} in excellent yield (93%). In addition, the same treatment of **2** also provided **5**, m.p. 143–144 °C and $[\alpha]_D^{20}=+64.5$ ($c=1.04$, CCl_4), in 91% yield. It is noteworthy that both of these reactions proceeded smoothly and cleanly in a completely stereocontrolled manner. The spectroscopic properties (IR, ^1H and ^{13}C NMR, MS) of the synthetic sample **5** were identical with those reported[11] for natural (+)-aureol.

The remarkable stereocontrolled $BF_3\cdot Et_2O$-induced rearrangement/cyclization reaction of **4** and **2** can be rationalized by the mechanistic route shown in Scheme 6. Both of the reaction processes would involve tertiary carbocation intermediates, such as **Ia**,**b**, **IIa**,**b**, and **IIIa**,**b**. Thus, the first coordination-activation between the Lewis acid and the C4 olefinic double bond in **4** and **2** would lead to the formation of intermediates **Ia**,**b**, which would further produce intermediates **IIa**,**b** via migration of the C5 methyl group to the C4 carbocation center. Intermediates **IIa**,**b** would undergo a 1,2-hydride shift from the C10 position to the C5 carbocation center on the α-face of the molecules to provide inter-

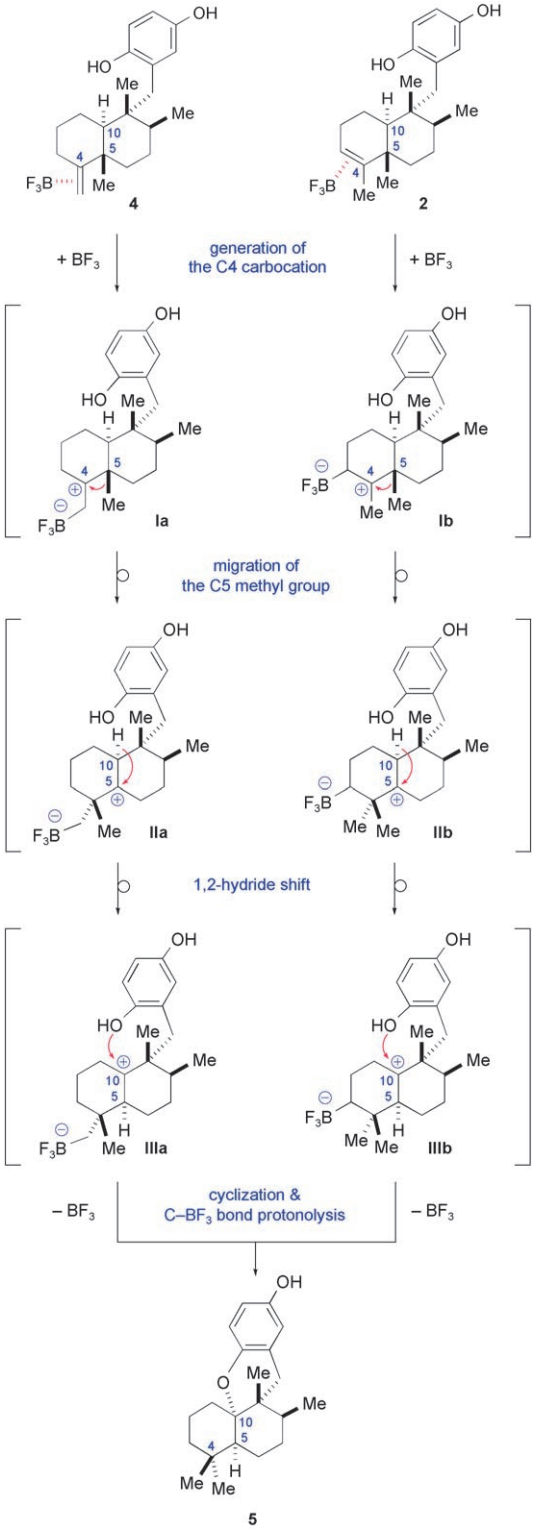
mediates **IIIa**,**b**, wherein the C10 carbocation center would be trapped by the inner phenolic hydroxy group to yield, after protonolysis of the C–BF_3 bond, the desired cyclized product **5**. We believe that this cascade-type rearrangement/cyclization sequence would proceed under kinetically controlled conditions.

Biological evaluation: Biological evaluation of compounds **1**–**5** is of great interest from the viewpoint of SAR. To this end, the synthesized compounds **1**–**5** were evaluated for their in vitro cytotoxicities against a human histiocytic lymphoma cell line, U937, which has been used extensively in routine screening programs for the development of new anticancer agents. The IC_{50} values of the tested compounds **1**–**5** along with mitomycin C, a reference compound, at three different culture times (24, 48, and 72 h) are shown in Table 1. It was evident that **1**, **3** and **5** exhibited cytotoxic activity in a dose- and culture time-dependent manner; however, **2** and **4** displayed no time-dependent cytotoxicity. Among the tested compounds, **3** was the most cytotoxic (IC_{50} = 6.5 μM at 72 h), while the potency was about $^1/_{40}$ of that of mitomycin C. The order of the potency at 72 h was estimated to be **3** > **1** > **5** > **2** > **4**. Quinone compounds **1** and **3** are more cytotoxic than the corresponding hydroquinone compounds **2** and **4**. This observation is in good agreement with a previous SAR study on naturally occurring **1** and **2** reported by Müller et al.[3a] The effect of *endo*- versus *exo*-olefin function was also investigated. A comparison of the cytotoxicity of the *endo*-olefinic quinone compound **1** (IC_{50} = 33.5 μM) and the *exo*-olefinic quinone compound **3** (IC_{50} = 6.5 μM) showed that the position of the olefinic double bond has a large effect on activity. These results suggest that both the quinone substructure and the C4 *exo*-olefinic double bond in the decalin ring are indispensable for the cytotoxic activity of this class of marine natural products.

Table 1. Inhibitory activity of compounds **1**–**5** against cell growth of U937 human histiocytic lymphoma cells.[a]

	IC_{50}[b] [μM]		
	24 h	48 h	72 h
(+)-avarone (**1**)	95.8	52.9	33.5
	(59.2–154.9)	(24.0–116.4)	(16.6–67.2)
(+)-avarol (**2**)	115.3	124.9	56.4
	(65.1–203.8)	(61.0–255.6)	(27.8–114.7)
(−)-neoavarone (**3**)	34.2	17.7	6.5
	(22.2–52.6)	(9.6–32.3)	(3.1–13.9)
(−)-neoavarol (**4**)	392.6	938.0	537.6
	(195.1–790.2)	(327.0–2691.0)	(282.6–22.0)
(+)-aureol (**5**)	62.0	50.9	42.8
	(27.7–138.4)	(22.9–113.2)	(21.3–86.1)
mitomycin C[c]	9.21	0.50	0.17
	(5.76–14.75)	(0.27–0.92)	(0.14–0.20)

[a] Numbers in parentheses show the 95% confidence limits. [b] Concentration required for 50% inhibition of cell growth after incubation at 37°C, 5% in humidified air. [c] Positive control as a representative anticancer agent.



Scheme 6. Mechanisitic consideration for BF_3·Et_2O-induced rearrangement/cyclization reaction of (−)-neoavarol (**4**) and (+)-avarol (**2**) leading to (+)-aureol (**5**).

Conclusion

In conclusion, we have succeeded in developing a highly efficient synthetic route to the marine natural products **1**–**5** (31–41% overall yields in 7–10 steps). The method explored features i) coupling reaction of the known enone **10** and 2-methylbenzyl bromide (**11**) to construct the requisite carbon framework **12** (**10** + **11**→ **12**), ii) strategic salcomine oxidation of the phenolic compounds **6** and **8** to form **1** and **3**, respectively (**6**→ **1** and **8**→ **3**) and iii) $BF_3{\cdot}Et_2O$-induced rearrangement/cyclization reaction of **4** and **2** to produce **5** with complete stereoselectivity in high yield (**2**→ **5** and **4**→ **5**). Preliminary biological evaluation of the synthesized compounds **1**–**5** disclosed some novel aspects of the SAR of these marine natural products, which would be useful in designing and preparing new anticancer agents.

Experimental Section

General techniques: All reactions involving air- and moisture-sensitive reagents were carried out using oven dried glassware and standard syringe-septum cap techniques. Routine monitoring of reaction were carried out using glass-supported Merck silica gel 60 F_{254} TLC plates. Flash column chromatography was performed on Kanto Chemical Silica Gel 60N (spherical, neutral 40–50 μm) with the solvents indicated.

All solvents and reagents were used as supplied with following exceptions. Tetrahydrofuran (THF) was freshly distilled from Na/benzophenone under argon. MeOH and EtOH were distilled from Na metal under argon. Benzene, hexamethylphosphoramide (HMPA), *N*,*N*-dimethylformamide (DMF), and CH_2Cl_2, were distilled from CaH_2 under argon.

Measurements of optical rotations were performed with a JASCO P-1020 automatic digital polarimeter. Melting points were taken on a Yanaco MP-3 micro melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured with a JEOL JNM-LA500 (500 MHz) spectrometer. Chemical shifts were expressed in ppm using Me_4Si ($\delta=0$) as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). Infrared (IR) spectral measurements were carried out with a JASCO FT/IR-5300 spectrometer. Low-resolution mass (MS) spectra was measured on a Shimadzu GCMS-QP2010. High-resolution mass (HRMS) spectra was measured on a JEOL MStation JMS-700 mass spectrometer. Elemental analyses were performed with a Perkin Elmer 2400II apparatus.

(4a*R*,5*S*,8a*S*)-5-(2-Methoxybenzyl)-5,8a-(dimethyl)hexahydronaphthalen-1,6(2*H*,7*H*)-dione-1-ethyleneacetal (12): (*S*)-5,8a-Dimethyl-3,4,8,8a-tetrahydronaphthalen-1,6(2*H*,7*H*)-dione-1-ethyleneacetal (**10**) (300 mg, 1.3 mmol) in dry THF (3.0 mL) was added dropwise to a stirred solution of lithium (36 mg, 5.2 mmol) in liquid ammonia (35 mL) at −78 °C under argon. The resulting solution was allowed to warm at reflux of liquid ammonia for 1 h. A solution of 2-methoxybenzyl bromide (**11**) (1.30 g, 6.5 mmol) in dry THF (12 mL) was added slowly to the above mixture. The reaction mixture was allowed to stand for 2 h at room temperature in order to evaporate off ammonia. After addition of saturated aqueous NH_4Cl (5.0 mL), the resulting mixture was extracted with Et_2O (3× 30 mL). The combined extracts were washed with brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 20:1) to give **12** (337 mg, 74%) as a colourless viscous liquid. $[\alpha]_D^{25}=+47.9$ ($c=1.48$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.03$ (s, 3H), 1.04 (s, 3H), 1.36–1.53 (m, 3H), 1.57–1.61 (m, 3H), 1.66–1.68 (m, 1H), 1.90 (dt, $J=8.3$, 13.7 Hz, 1H), 2.26 (dd, $J=3.2$, 11.9 Hz, 1H), 2.27–2.33 (m, 1H), 2.51 (ddd, $J=6.3$, 8.7, 15.6 Hz, 1H), 2.82 (d, $J=13.2$ Hz, 1H), 2.92 (d, $J=$ 13.2 Hz, 1H), 3.75 (s, 3H), 3.82–3.94 (m, 4H), 6.8–6.85 (m, 2H), 6.98–7.01 (m, 1H), 7.16–7.20 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=$ 17.3, 20.7, 22.7, 22.8, 28.4, 29.9, 35.2, 39.7, 42.0, 45.1, 51.7, 54.8, 64.7, 65.0, 110.0, 112.8, 120.0, 126.3, 127.7, 132.0, 158.0, 217.2 ppm; IR (neat): $\tilde{\nu}=$ 2945, 2883, 2835, 1699, 1601, 1585, 1493, 1462, 1440, 1381, 1336, 1288, 1244, 1182, 1128, 1099, 1074, 1047, 949, 910, 866, 754, 648, 588, 509, 474 cm^{-1}; HRMS(EI): *m*/*z*: calcd for $C_{22}H_{30}O_4$: 358.2144; found: 358.2155 $[M]^+$.

(4a*S*,5*S*,8a*S*)-5-(2-Methoxybenzyl)-5,8a-dimethyl-6-(methylene)octahydronaphthalen-1(2*H*)-one-1-ethyleneacetal (13): A stirred suspension of *t*BuOK (0.77 g, 6.9 mmol) and methyltriphenylphosphonium bromide (2.45 g, 6.9 mmol) in dry benzene (30 mL) was heated at reflux for 3 h under argon, and then roughly half volume of the solvent was evaporated off. A solution of **12** (245 mg, 0.69 mmol) in dry benzene (7.5 mL) was added to the above mixture. The resulting solution was refluxed for 24 h under argon. After cooling, the reaction was quenched with H_2O (5.0 mL) at 0 °C, and the mixture was extracted with Et_2O (2×30 mL). The combined extracts were washed with brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 100:1) to give **13** (209 mg, 86%) as a colourless viscous liquid. $[\alpha]_D^{25}=+60$ ($c=1.35$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.90$ (s, 3H), 1.05 (s, 3H), 1.17 (ddd, $J=7.4$, 11.7, 12.8 Hz, 1H), 1.38–1.71 (m, 6H), 1.97 (dd, $J=3.4$, 12.2 Hz, 1H), 2.03–2.15 (m, 2H), 2.29–2.38 (m, 1H), 2.63 (d, $J=13.2$ Hz, 1H), 2.77 (d, $J=13.2$ Hz, 1H), 3.74 (s, 3H), 3.87–4.04 (m, 4H), 4.18 (d, $J=1.5$ Hz, 1H), 4.69 (d, $J=1.5$ Hz, 1H), 6.77–6.83 (m, 2H), 6.95–6.99 (m, 1H), 7.12–7.17 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=19.9$, 21.0, 22.9, 23.1, 29.5, 29.7, 32.1, 39.9, 42.9, 43.5, 46.6, 54.9, 64.5, 64.9, 107.2, 109.8, 113.7, 119.2, 126.9, 127.3, 132.6, 153.8, 158.5 ppm; IR (neat): $\tilde{\nu}=$ 2934, 2878, 1722, 1639, 1601, 1493, 1462, 1383, 1340, 1246, 1180, 1124, 1099, 1080, 1049, 1028, 947, 906, 883, 752, 605, 532 cm^{-1}; HRMS(EI): *m*/*z*: calcd for $C_{23}H_{32}O_3$: 356.2351; found: 356.2356 $[M]^+$.

(4a*S*,5*S*,8a*S*)-5-(2-Methoxybenzyl)-5,8a-dimethyl-6-(methylene)octahydronaphthalen-1(2*H*)-one (14): 4.0 M HCl (8.80 mL, 36 mmol) was added to a stirred solution of **13** (133 mg, 0.38 mmol) in THF (7.0 mL) at room temperature. After 3 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (4.0 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (3×30 mL). The combined extracts were washed with brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 10:1) to give **14** (113 mg, 97%) as a white solid. Recrystallization from hexane afforded colourless prisms. M.p. 94–95 °C; $[\alpha]_D^{25}=+175.3$ ($c=1.04$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.07$ (s, 3H), 1.13 (s, 3H), 1.31–1.50 (m, 2H), 1.71–1.87 (m, 3H), 2.03–2.08 (m, 1H), 2.18–2.27 (m, 3H), 2.32–2.39 (m, 1H), 2.47–2.56 (m, 1H), 2.72 (s, 2H), 3.74 (s, 3H), 4.43 (s, 1H), 4.80 (s, 1H), 6.79–6.83 (m, 2H), 7.02–7.04 (m, 1H), 7.14–7.18 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=21.4$, 22.6, 23.3, 25.5, 28.8, 31.5, 38.1, 40.3, 44.1, 49.0, 49.2, 54.9, 108.3, 109.9, 119.5, 126.7, 127.3, 132.4, 152.7, 158.2, 215.4 ppm; IR (KBr): $\tilde{\nu}=$ 2951, 2870, 1693, 1495, 1458, 1248, 1132, 1053, 1034, 885, 754 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{28}O_2$: C 80.73, H 9.03; found: C 80.74, H 9.15.

(4a*S*,5*R*,6*S*,8a*S*)-5-(2-Methoxybenzyl)-5,6,8a-(trimethyl)octahydronaphthalen-1(2*H*)-one (15) and its (4a*S*,5*R*,6*R*,8a*S*)-isomer (16): 10% Pd/C (89.0 mg) was added to a solution of **14** (53.0 mg, 0.17 mmol) in Et_3N (1.5 mL) containing MeOH (0.03 mL), and the mixture was stirred for 17 h under H_2 (1 atm) at room temperature. The reaction mixture was diluted with EtOAc (30 mL), and the catalyst was filtered off through a small pad of Celite. Concentration of the filtrate in vacuo afforded a residue, which was purified by column chromatography (Et_2O/EtOAc 100:1) to give **15** (42.6 mg, 80%) (more polar) and its C8 epimer **16** (6.9 mg, 13%) (less polar).

Compound 15: Colourless needles (recrystallization from hexane); M.p. 127–128 °C; $[\alpha]_D^{25}=-43.6$ ($c=0.97$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.92$ (s, 3H), 1.01 (d, $J=5.9$ Hz, 3H), 1.11 (dd, $J=12.0$, 2.0 Hz, 1H), 1.15 (s, 3H), 1.19–1.43 (m, 4H), 1.43–1.47 (m, 1H), 1.50 (dt, $J=4.7$, 17.9 Hz, 1H), 1.75 (dq, $J=3.4$, 13.2 Hz, 1H), 2.07–2.08 (m, 1H), 2.13–2.19 (m, 1H), 2.23–2.26 (m, 1H), 2.58 (td, $J=7.3$, 14.1 Hz, 1H), 2.72 (s, 2H), 3.75 (s, 3H), 6.806.85 (m, 2H), 7.00–7.03 (m, 1H), 7.15–7.19 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=17.4$, 18.0, 18.9, 22.0, 25.6, 26.8, 32.3, 35.6, 37.0, 37.5, 42.3, 47.6, 49.3, 54.8, 110.3, 119.8, 126.7, 127.4,

132.3, 158.2, 216.3 ppm; IR (KBr): $\tilde{\nu}$ = 2953, 2932, 2864, 1705, 1494, 1456, 1317, 1288, 1244, 1176, 1130, 1099, 1030, 954, 752, 709, 598, 538 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{30}O_2$: C 80.21, H 9.62; found: C 80.11, H 9.64.

Compound 16: Colourless prisms (recrystallization from hexane); M.p. 122–124 °C; $[\alpha]_D^{25} = -25.5$ ($c = 0.68$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.94$ (s, 3H), 1.12 (d, $J = 7.0$ Hz, 3H), 1.21 (s, 3H), 1.26 (dt, $J = 3.9$, 14.0 Hz, 1H), 1.37 (dq, $J = 4.0$, 13.8 Hz, 1H), 1.50–1.71 (m, 4H), 1.80–1.87 (m, 2H), 1.99–2.05 (m, 2H), 2.20–2.24 (m, 1H), 2.29 (d, $J = 13.7$ Hz, 1H), 2.58 (dt, $J = 7.1$, 13.9 Hz, 1H), 3.06 (d, $J = 13.7$ Hz, 1H), 3.79 (s, 3H), 6.83–6.88 (m, 2H), 7.17 (dt, $J = 1.7$, 8.1 Hz, 1H), 7.24 ppm (dd, $J = 1.7$, 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 16.0$, 20.5, 20.7, 21.1, 24.8, 26.0, 26.4, 35.2, 36.0, 37.4, 41.1, 46.7, 49.7, 55.2, 110.4, 120.0, 127.0, 128.4, 131.0, 158.3, 215.9 ppm; IR (KBr): $\tilde{\nu}$ = 2940, 2870, 1701, 1493, 1460, 1385, 1242, 1127, 1028, 756 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{30}O_2$: C 80.21, H 9.62; found: C 80.53, H 9.78.

(1*R*,2*S*,4a*S*,8a*S*)-1-(2-Methoxybenzyl)-1,2,4a-trimethyl-5-(methylene)decahydronaphthalene (9): A stirred suspension of *t*BuOK (106 mg, 0.92 mmol) and methyltriphenylphosphonium bromide (340 mg, 0.92 mmol) in dry benzene (7.0 mL) was heated at reflux for 3 h under argon, and then the roughly half volume of the solvent was evaporated off. A solution of **15** (44.0 mg, 0.14 mmol) in dry benzene (7.0 mL) was added to the above mixture, and the resulting solution was then refluxed for 12 h under argon. After the reaction was quenched with H_2O (4.0 mL) at 0 °C, and the mixture was extracted with Et_2O (2 × 40 mL). The combined extracts were washed with brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 100:1) to give **9** (43.2 mg, 100%) as a colourless viscous liquid. $[\alpha]_D^{25} = -48.1$ ($c = 1.05$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.85$ (s, 3H), 0.93 (dd, $J = 12.0$, Hz, 1H), 1.00 (d, $J = 5.9$ Hz, 3H), 1.05 (s, 3H), 1.17–1.41 (m, 5H), 1.41–1.47 (m, 1H), 1.47–1.54 (m, 1H), 1.86–1.93 (m, 1H), 2.04–2.14 (m, 2H), 2.29–2.38 (m, 1H), 2.60 (d, $J = 13.7$ Hz, 1H), 2.69 (d, $J = 13.7$ Hz, 1H), 3.74 (s, 3H), 4.34–4.36 (m, 1H), 4.39–4.40 (m, 1H), 6.79–6.86 (m, 2H), 7.02–7.05 (m, 1H), 7.13–7.17 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 17.6$, 17.7, 20.6, 23.1, 27.8, 28.3, 33.1, 36.2, 36.6, 36.9, 40.2, 42.0, 48.0, 54.8, 102.5, 110.1, 119.6, 127.0, 127.5, 132.5, 158.4, 160.3 ppm; IR (neat): $\tilde{\nu}$ = 3078, 3030, 2916, 2856, 1633, 1599, 1583, 1494, 1454, 1381, 1323, 1290, 1244, 1178, 1136, 1095, 1030, 991, 962, 927, 893, 752, 706, 540 cm^{-1}; HRMS (EI): m/z: calcd for $C_{22}H_{32}O$: 312.2453; found: 312.2443 $[M]^+$.

2-[[(1*R*,2*S*,4a*S*,8a*S*)-1,2,4a-Trimethyl-5-(methylene)decahydronaphthalen-1-yl]methyl]phenol (8): *n*BuSLi in HMPA (1.68 M solution, 5.0 mL, 8.4 mmol) was added to a stirred solution of **9** (86.0 mg, 0.28 mmol) in HMPA (6.0 mL) at room temperature, and the mixture was heated at 110 °C for 3 h. After cooling, the reaction was quenched with saturated aqueous NH_4Cl (1.0 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (3 × 30 mL). The combined extracts were washed with brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 100:1) to give **8** (75.5 mg, 92%) as a white solid. Recrystallization from hexane/Et_2O afforded colorless needles. M.p. 106–108 °C; $[\alpha]_D^{25} = -5.8$ ($c = 1.09$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.87$ (s, 3H), 0.98–1.03 (m, 1H), 1.02 (d, $J = 5.8$ Hz, 3H), 1.06 (s, 3H), 1.18–1.44 (m, 5H), 1.45–1.49 (m, 1H), 1.50–1.62 (m, 1H), 1.87–1.95 (m, 1H), 2.05–2.11 (m, 2H), 2.03–2.39 (m, 1H), 2.56 (d, $J = 14.6$ Hz, 1H), 2.68 (d, $J = 14.6$ Hz, 1H), 4.35–4.38 (s, 1H), 4.41–4.45 (m, 1H), 4.61–4.66 (br s, 1H), 6.69–6.71 (m, 1H), 6.80–6.86 (m, 1H), 6.99–7.06 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 17.6$, 17.7, 20.6, 23.2, 27.7, 28.2, 33.0, 36.2, 36.5, 37.4, 40.2, 42.0, 48.0, 102.7, 115.5, 120.2, 125.1, 127.2, 133.0, 154.5, 160.1 ppm; IR (KBr): $\tilde{\nu}$ = 3547, 3439, 2957, 2858, 1720, 1631, 1587, 1452, 1383, 1332, 1255, 1170, 1122, 1086, 1049, 1022, 991, 927, 891, 864, 754 cm^{-1}; HRMS(EI):m/z: calcd for $C_{21}H_{30}O$: 298.2297; found: 298.2294 $[M]^+$.

2-[[(1*R*,2*S*,4a*S*,8a*S*)-1,2,4a-Trimethyl-5-(methylene)decahydronaphthalen-1-yl]methyl]cyclohexa-2,5-diene-1,4-dione [(−)-neoavarone (3)]: Salcomine [*N*,*N*′-bis(salicylidene)ethylenediaminocobalt(II)] (96.4 mg, 0.30 mmol) was added to a stirred solution of **8** (44.4 mg, 0.15 mmol) in dry DMF (6.0 mL) at room temperature. The suspension was stirred under oxygen atmosphere (O_2 balloon) for 24 h at room temperature. The reaction mixture was concentrated in vacuo to afford a residue, which was purified by column chromatography (hexane/EtOAc 30:1) to give **3** (42.2 mg, 91%) as a yellow solid. Recrystallization from hexane/Et_2O afforded pale yellow prisms. M.p. 94–95 °C; $[\alpha]_D^{25} = -62.7$ ($c = 1.02$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.76$ (d, $J = 10.2$ Hz, 1H), 0.86 (s, 3H), 0.94 (d, $J = 6.3$ Hz, 3H), 1.05 (s, 3H), 1.11–1.21 (m, 2H), 1.32–1.38 (m, 1H), 1.42–1.57 (m, 4H), 1.86–1.89 (m, 2H), 2.08–2.11 (m, 1H), 2.28–2.34 (m, 1H), 2.40 (d, $J = 13.7$ Hz, 1H), 2.57 (d, $J = 13.7$ Hz, 1H), 4.45 (d, $J = 8.3$ Hz, 1H), 6.46 (s, 1H), 6.68–6.76 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 16.8$, 17.6, 20.6, 22.6, 27.4, 28.1, 32.8, 35.3, 36.7, 37.2, 40.3, 43.0, 49.3, 103.2, 135.9, 136.0, 137.1, 147.3, 159.6 187.3, 187.4 ppm; IR (KBr): $\tilde{\nu}$ = 3418, 3084, 2928, 2858, 1658, 1596, 1449, 1385, 1354, 1289, 1069, 891 cm^{-1}; HRMS(EI): m/z: calcd for $C_{21}H_{28}O_2$: 312.2090; found: 312.2090 $[M]^+$.

2-[[(1*R*,2*S*,4a*S*,8a*S*)-1,2,4a-Trimethyl-5-(methylene)decahydronaphthalen-1-yl]methyl]benzene-1,4-diol [(−)-neoavarol (4)]: $NaBH_4$ (9.70 mg, 0.26 mmol) was added in small portion to a stirred solution of **3** (40.0 mg, 0.13 mmol) in THF/H_2O 10:1 (4 mL) at 0 °C. After 3 min, the reaction was quenched with saturated NH_4Cl (1.0 mL) at 0 °C. The resulting mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 10:1) to give **4** (34.6 mg, 86%) as a white solid. Recrystallization from Et_2O afforded colorless needles. M.p. 175–177 °C; $[\alpha]_D^{25} = -41.6$ ($c = 0.10$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.86$ (s, 3H), 0.93–0.98 (m, 1H), 1.00 (d, $J = 5.9$ Hz, 3H), 0.98–1.02 (m, 1H), 1.06 (s, 3H), 1.21–1.33 (m, 2H), 1.41–1.47 (m, 3H), 1.46–1.61 (m, 2H), 1.87–1.92 (m, 1H), 1.99–2.06 (m, 1H), 2.07–2.12 (m, 1H), 2.33–2.36 (m, 1H), 2.51 (d, $J = 14.1$ Hz, 1H), 2.62 (d, $J = 14.1$ Hz, 1H), 4.35 (s, 2H), 4.40 (s, 1H), 4.43 (s, 1H), 6.52–6.60 ppm (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 17.6$, 17.6, 20.6, 23.2, 27.7, 28.3, 33.0, 36.3, 36.5, 37.5, 40.3, 42.1, 48.2, 102.9, 113.9, 116.2, 119.4, 126.5, 148.6, 148.7 160.0 ppm; IR (KBr): $\tilde{\nu}$ = 3381, 2971, 2917, 2857, 1634, 1501, 1453, 1397, 1186, 1154, 889, 808, 750 cm^{-1}; HRMS(EI): m/z: calcd for $C_{21}H_{30}O_2$: 314.2246; found: 314.2254 $[M]^+$.

(1*R*,2*S*,4a*S*,8a*S*)-1-(2-Methoxybenzyl)-1,2,4a,5-tetramethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene (7): A mixture of **9** (34.0 mg, 0.11 mmol) and $RhCl_3 \cdot 3H_2O$ (4.80 mg, 20 mmol) in EtOH (5 mL) was heated at reflux for 24 h. After cooling, the reaction mixture was concentrated in vacuo. The resulting residue was purified by column chromatography (hexane/EtOAc 10:1) to give **7** (33.9 mg, 100%) as a colorless viscous liquid. $[\alpha]_D^{25} = +1.1$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.85$ (s, 3H), 0.87–0.95 (m, 1H), 1.00 (d, $J = 5.8$ Hz, 3H), 1.01 (s, 3H), 1.15–1.17 (m, 1H), 1.32–1.40 (m, 3H),1.49 (d, $J = 1.5$ Hz, 3H), 1.50–1.58 (m, 2H), 2.00–2.08 (m, 3H), 2.70 (s, 2H), 3.76 (s, 3H), 5.10–5.14 (s, 1H), 6.80–6.86 (m, 2H), 7.08–7.11 (m, 1H), 7.13–7.18 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 17.4$, 17.8, 18.1, 19.7, 20.1, 26.5, 27.8, 35.8, 36.0, 37.0, 38.3, 41.7, 45.7,54.8, 110.2, 119.7, 120.4, 127.0, 127.6, 132.7, 144.4, 158.4 ppm; IR (neat): $\tilde{\nu}$ = 2928, 2833, 1599,1493, 1460, 1437, 1381, 1290, 1244, 1176, 1134, 1099, 1032, 929, 896, 796, 750, 638, 528 cm^{-1}; HRMS(EI): m/z: calcd for $C_{22}H_{32}O$: 312.2453; found: 312.2432 $[M]^+$.

2-[[(1*R*,2*S*,4a*S*,8a*S*)-1,2,4a,5-Tetramethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-yl]methyl]phenol (6): *n*BuSLi in HMPA (2.0 M solution, 6.3 mL, 12.4 mmol) was added to a stirred solution of **7** (77.3 mg, 0.25 mmol) in HMPA (6.0 mL) at room temperature, and the mixture was heated at 110 °C for 2 h. After cooling, the reaction was quenched with saturated aqueous NH_4Cl (1.0 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (3 × 30 mL). The combined extracts were washed with brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 100:1) to give **6** (66.4 mg, 90%) as a colorless viscous liquid. $[\alpha]_D^{25} = +4.6$ ($c = 1.07$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.87$ (s, 3H), 0.91–0.97 (m, 1H), 1.02 (d, $J = 4.9$ Hz, 3H), 1.02 (s, 3H), 1.20–1.23 (m, 1H), 1.33–1.39 (m, 2H), 1.40–1.48 (m, 1H), 1.48–1.53 (m, 3H), 1.55–1.64 (m, 2H), 1.99–2.09 (m, 3H), 2.62 (d, $J = 14.1$ Hz, 1H), 2.73 (d, $J = 14.1$ Hz, 1H), 4.79 (s, 1H), 5.13 (s, 1H), 6.71 (d, $J = 8.3$ Hz, 1H), 6.81–6.84 (m, 1H), 7.04–7.09 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 17.5$, 17.7,

18.1, 19.8, 20.1, 26.6, 27.7, 35.8, 36.0, 37.4, 38.3, 41.7, 45.7, 115.5, 120.1, 120.4, 125.1, 127.2, 133.1, 144.3, 154.6 ppm; IR (neat): $\tilde{\nu}$ = 3398, 2932, 1705, 1589, 1452, 1381, 1327, 1261, 1236, 1170, 1126, 1086, 1046, 854, 798, 754 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{21}H_{30}O$: 298.2297, found: 298.2299 $[M]^+$.

2-[[(1*R*,2*S*,4a*S*,8a*S*)-1,2,4a,5-Tetramethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-yl]methyl]cyclohexa-2,5-diene-1,4-dione [(+)-avarone (1)]: Salcomine (38.5 mg, 0.14 mmol) was added to a stirred solution of **6** (42.0 mg, 0.14 mmol) in dry DMF (4.0 mL) at room temperature. The suspension was stirred under oxygen atmosphere (O_2 balloon) for 24 h at room temperature. The reaction mixture was concentrated in vacuo to afford a residue, which was purified by column chromatography (hexane/EtOAc 30:1) to give **1** (39.1 mg, 89%) as a yellow solid. Recrystallization from hexane/Et_2O afforded pale yellow prisms. M.p. 61–63 °C; $[\alpha]_D^{25}$ = +12.5 (*c* = 0.94, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (s, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 1.00 (s, 3H), 1.01–1.08 (m, 2H), 1.15–1.26 (m, 1H), 1.34-.43 (m, 2H), 1.49–1.58 (m, 4H), 1.65 (td, *J* = 3.3, 12.8 Hz, 1H), 1.80–1.90 (m, 2H), 2.00–2.07 (m, 1H), 2.44 (d, *J* = 13.4 Hz, 1H), 2.65 (d, *J* = 13.4 Hz, 1H), 5.12–5.17 (m, 1H), 6.50–6.52 (m, 1H), 6.71 (dd, *J* = 2.3, 10.1 Hz, 1H), 6.76 ppm (d, *J* = 10.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.7, 17.7, 18.0, 19.3, 20.0, 26.4, 27.4 35.4, 36.1 36.9, 38.5, 42.7, 47.0, 120.6, 136.0, 136.1, 137.1, 144.0, 147.4, 187.3, 187.4; IR (KBr): $\tilde{\nu}$ = 3449, 2930, 1657, 1597, 1454, 1383, 1290, 1070, 912 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{21}H_{28}O_2$: 312.2090; found: 312.2072 $[M]^+$.

2-[[(1*R*,2*S*,4a*S*,8a*S*)-1,2,4a,5-Tetramethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-yl]methyl]benzene-1,4-diol [(+)-avarol (2)]: $NaBH_4$ (9.70 mg, 0.24 mmol) was added in small portion to a stirred solution of **1** (40.0 mg, 0.12 mmol) in THF/H_2O 10:1 (4 mL) at 0 °C. After 5 min, the reaction was quenched with saturated NH_4Cl (2.0 mL) at 0 °C. The resulting mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 10:1) to give **2** (34.2 mg, 85%) as a white solid. Recrystallization from Et_2O afforded colorless needles. M.p. 147–149 °C; $[\alpha]_D^{25}$ = +10.8 (*c* = 0.74, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (s, 3H), 0.93–0.98 (m, 1H), 1.00 (d, *J* = 6.3 Hz, 3H), 1.02 (s, 3H), 1.23 (dd, *J* = 1.4, 12.1 Hz, 1H), 1.34–1.39 (m, 2H), 1.41–1.49 (m, 1H), 1.51–1.53 (m, 3H), 1.55–1.61 (m, 2H), 1.96–2.01 (m, 1H), 2.04–2.06 (m, 2H), 2.57 (d, *J* = 14.1 Hz, 1H), 2.68 (d, *J* = 14.1 Hz, 1H), 4.41 (br s, 1H), 5.14 (s, 1H), 6.52–6.61 ppm (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.5, 17.7, 18.1, 19.8, 20.1, 26.6, 27.7 35.8, 36.0 37.6, 38.3, 41.8, 45.8, 113.8, 116.2, 119.6, 120.4, 126.5, 144.3, 148.6, 148.7 ppm; IR (KBr): $\tilde{\nu}$ = 3371, 2926, 2859, 1705, 1651, 1601, 1502, 1450, 1381, 1309, 1195, 1124, 877, 806, 754 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{21}H_{30}O_2$: 314.2246; found: 314.2252 $[M]^+$.

(4a*S*,7*S*,7a*R*,13a*S*)-4,4,7,7a-Tetramethyl-1,2,3,4,4a,5,6,7,7a,8-decahydrobenzo[*d*]xanthen-10-ol [(+)-aureol (5)]

a) (−)-Neoavarol (4): $BF_3{\cdot}Et_2O$ (0.1 mL, 0.75 mmol) was added to a stirred solution of **4** (47.0 mg, 0.15 mmol) in CH_2Cl_2 (15 mL) at −50 °C, and the resulting mixture was gradually warmed to −5 °C over 5 h. The reaction was quenched with saturated aqueous NH_4Cl (1.0 mL) at −5 °C, and the mixture was extracted with dichloromethane (3 × 10 mL). The combined extracts were washed with brine, then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 10:1) to give **5** (43.7 mg, 93%) as a white solid. Recrystallization from Et_2O afforded colorless needles. M.p. 143–144 °C; $[\alpha]_D^{25}$ = +64.5 (*c* = 1.04, CCl_4); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.78 (s, 3H), 0.92 (s, 3H), 1.07 (s, 3H), 1.10 (d, *J* = 7.8 Hz, 3H), 1.18–1.20 (m, 1H), 1.33–1.39 (m, 1H), 1.41–1.47 (m, 3H), 1.52–1.61 (m, 1H), 1.64–1.71 (m, 2H), 1.78–1.85 (m, 2H), 1.97 (d, *J* = 17.1 Hz, 1H), 2.01–2.08 (m, 2H), 3.37 (d, *J* = 17.1 Hz, 1H), 4.27 (br s, 1H), 6.49 (d, *J* = 2.4 Hz, 1H), 6.54–6.62 ppm (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.3, 18.3, 20.2, 22.2, 27.9, 29.3, 29.8, 31.9, 33.8, 33.9, 37.4, 38.1, 39.3, 44.0, 82.4, 114.0, 115.0, 117.2, 122.2, 145.8, 148.3 ppm; IR (KBr): $\tilde{\nu}$ = 3394, 2924, 2853, 1717, 1625, 1496, 1458, 1384, 1261, 1231, 1186, 1106, 955, 899, 862, 805, 754 cm^{-1}; HRMS(EI): *m/z*: calcd for $C_{21}H_{31}O_2$: 314.2246; found: 314.2234 $[M]^+$.

b) (+)-Avarol (2): The same treatment of **2** (43.0 mg, 0.14 mmol) as described above under a) gave **5** (39.2 mg, 91%) as colorless needles. M.p. 143–144 °C; $[\alpha]_D^{25}$ = +64.9 (*c* = 1.08, CCl_4). The 500 MHz ^{1}H NMR spectrum of this sample was identical with that recorded in a).

Cell-growth inhibition assay:[26] Human histiocytic lymphoma cell line U937 (obtained from the Cell Resource Center for Biomedical Research, Tohoku University, Sendai) was maintained in suspension in RPMI culture medium (RPMI-1640 medium supplemented with 10% FCS, 2 mM L-glutamine and penicillin/streptomycin solution, all from Sigma, St. Louis, MO) at 37 °C, 5% in humidified air. Test compounds were dissolved in DMSO. The in vitro cytotoxicity was assessed by triplicate assays for the reduction of [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] (MTT) following 24, 48 and 72 h incubation of cells with compounds. The IC_{50} (concentration of the test compounds showing 50% cell growth inhibition) value was determined by using PRISM software (GrapPad Software, Inc., CA, USA).

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[1] For recent excellent reviews on the clerodane diterpenoids and related compounds including marine natural products; see: a) R. J. Capon, in *Studies in Natural Products Chemistry, Vol. 15* (Ed.: Atta-ur-Rahman), Elsevier, Amsterdam, **1995**, p. 289–326; b) T. Tokoroyama, *Synthesis* **2000**, 611–633; c) R. J. Capon, *Eur. J. Org. Chem.* **2001**, 633–645; d) D. J. Faulkner, *Nat. Prod. Rep.* **2002**, *19*, 1–48; e) S. De Rosa, in *Natural Products in the New Millennium: Prospects and Industrial Application* (Eds.: A. P. Rauter, F. B. Palma, J. Justino, M. E. Araújo, S. P. Santos), Kluwer, Dordrecht, **2002**, p. 441–461; f) M. T. Hamann, *Curr. Pharm. Des.* **2003**, *9*, 879–889.

[2] a) L. Minale, R. Riccio, G. Sodano, *Tetrahedron Lett.* **1974**, *15*, 3401–3404; b) S. De Rosa, L. Minale, R. Riccio, G. Sodano, *J. Chem. Soc. Perkin Trans. 1* **1976**, 1408–1414; c) R. Puliti, S. De Rosa, C. A. Mattia, *Acta Crystallogr. Sect. C* **1994**, *50*, 830–833.

[3] a) W. E. G. Müller, A. Maidhof, R. K. Zahn, H. C. M. Schröeder, M. J. Gasic, D. Heidemann, A. Bernd, B. Kurelec, E. Eich, G. Seibert, *Cancer Res.* **1985**, *45*, 4822–4826; b) J. M. Miguel del Corral, M. Gordaliza, M. A. Castro, M. M. Mahiques, P. Chamorro, A. Molinari, M. D. García-Grávalos, H. B. Broughton, A. San Feliciano, *J. Med. Chem.* **2001**, *44*, 1257–1267.

[4] M. Stewart, P. M. Fell, J. W. Blunt, M. H. G. Munro, *Aust. J. Chem.* **1997**, *50*, 341–347.

[5] M. L. Ferráandiz, M. J. Sanz, G. Bustos, M. Payá, M. J. Alcaraz, S. De Rosa, *Eur. J. Pharmacol.* **1994**, *253*, 75–82.

[6] M. A. Belisario, M. Maturo, R. Pecce, S. De Rosa, G. R. Villiani, *Toxicology* **1992**, *72*, 221–233.

[7] M. A. Belisario, M. Maturo, G. Avagnale, S. De Rosa, F. Scopacasa, M. De Caterina, *Pharmacol. Toxicol.* **1996**, *79*, 300–304.

[8] M. Amigo, M. C. Terencio, M. Mitova, C. Iodice, M. Paya, S. De Rosa, *J. Nat. Prod.* **2004**, *67*, 1459–1463.

[9] a) W. E. G. Müller, D. Stadic, R. K. Zahn, K.-H. Bässler, N. Dogovic, H. Gerner, M. J. Gasic, H. C. Schröder, *Cancer Res.* **1987**, *47*, 6565–6571; b) S. Loya, A. Hizi, *FEBS Lett.* **1990**, *269*, 131–134; c) H. C. Schröder, M. E. Begin, R. Klöcking, E. Matthes, A. S. Sarma, M. Gasic, W. E. G. Müller, *Virus Res.* **1991**, *21*, 213–223; d) E. De Clercq, *Med. Res. Rev.* **2000**, *20*, 323–349; e) L.-A. Tziveleka, C. Vagias, V. Roussis, *Curr. Top. Med. Chem.* **2003**, *3*, 1512–1535.

[10] K. Iguchi, A. Sahashi, J. Kohno, Y. Yamada, *Chem. Pharm. Bull.* **1990**, *38*, 1121–1123.

[11] P. Djura, D. B. Stierle, D. B. Sullivan, D. J. Faulkner, E. Arnold, J. Clardy, *J. Org. Chem.* **1980**, *45*, 1435–1441.

[12] P. Ciminiello, C. Dell′Aversano, E. Fattorusso, S. Magno, M. Pansini, *J. Nat. Prod.* **2000**, *63*, 263–266.
[13] R. E. Longley, O. J. McConnel, E. Essich, D. Harmody, *J. Nat. Prod.* **1993**, *56*, 915–920.
[14] A. E. Wright, S. S. Cross, N. S. Burres, F. Koehn (Harbor Branch Oceanographics Institution, Inc., USA), PCT WO 9112250A1, August 22, **1991**.
[15] A. S. Sarma, P. Chattopadhyay, *J. Org. Chem.* **1982**, *47*, 1727–1731.
[16] a) J. An, D. F. Wiemer, *J. Org. Chem.* **1996**, *61*, 8775–8779; b) E. P. Locke, S. M. Hecht, *Chem. Commun.* **1996**, 2717–2718; c) T. Ling, A. X. Xiang, E. A. Theodorakis, *Angew. Chem.* **1999**, *111*, 3277–3279; *Angew. Chem. Int. Ed.* **1999**, *38*, 3089–3091; d) T. Ling, E. Poupon, E. J. Rueden, S. H. Kim, E. A. Theodorakis, *J. Am. Chem. Soc.* **2002**, *124*, 12261–12267.
[17] A. Suzuki, M. Nakatani, M. Nakamura, K. Kawaguchi, M. Inoue, T. Katoh, *Synlett* **2003**, 329–332.
[18] a) K. Yoshida, S. Nakajima, T. Ohnuma, Y. Ban, M. Shibasaki, K. Aoe, T. Date, *J. Org. Chem.* **1988**, *53*, 5355–5359; b) F. Miyata, S. Yoshida, T. Yamori, T. Katoh, *Heterocycles* **2001**, *54*, 619–622; c) T. Katoh, M. Nakatani, S. Shikita, R. Sampe, A. Ishiwata, M. Nakamura, S. Terashima, *Org. Lett.* **2001**, *3*, 2701–2704.
[19] H. Hagiwara, H. Uda, *J. Org. Chem.* **1988**, *53*, 2308–2311.
[20] J. L. Kelly, J. A. Linn, J. W. T. Selway, *J. Med. Chem.* **1989**, *32*, 1757–1763.
[21] This type of reductive alkylation, originally explored by Stork et al. in the 1960s (a representative work; see: G. Stork, P. Rosen, N. Goldman, R. V. Coombs, J. Tsuji, *J. Am. Chem. Soc.* **1965**, *87*, 275–286), has been widely used as a critical step in the total synthesis of marine sesquiterpenoidal quinones and hydroquinones. For recent examples; see: a) S. D. Bruner, H. S. Radeke, J. A. Tallarico, M. L. Snapper, *J. Org. Chem.* **1995**, *60*, 1114–1115; b) S. Poigny, M. Guyot, M. Samadi, *J. Org. Chem.* **1998**, *63*, 5890–5894; c) P. Stahl, L. Kissau, R. Mazitschek, A. Huwe, P. Furet, A. Giannis, H. Waldmann, *J. Am. Chem. Soc.* **2001**, *123*, 11586–11593.
[22] L. Fitjer, U. Quabeck, *Synth. Commun.* **1985**, *15*, 855–864.
[23] A similar phenomenon has been previously reported in the total synthesis of **1** and **2**.[15]
[24] a) P. A. Bartlett, W. S. Johnson, *Tetrahedron Lett.* **1970**, *11*, 4459–nnn; b) G. I. Feutrill, R. N. Mirrington, *Aust. J. Chem.* **1972**, *25*, 1719–1729; c) S. C. Welch, A. S. C. P. Pao, *Tetrahedron Lett.* **1977**, *18*, 505–508; d) P. A. Aristoff, A. W. Harrison, A. M. Huber, *Tetrahedron Lett.* **1984**, *25*, 3955–3958; e) T. Taishi, S. Takechi, S. Mori, *Tetrahedron Lett.* **1998**, *39*, 4347–4350; f) M. Nakatani, M. Nakamura, A. Suzuki, M. Inoue, T. Katoh, *Org. Lett.* **2002**, *4*, 4483–4486.
[25] The reducing reagent $Na_2S_2O_4$ has been widely used for the conversion of sesquiterpenoidal quinones to the corresponding hydroquinones. For examples, see: a) N. Harada, T. Sugioka, Y. Ando, H. Uda, T. Kuriki, *J. Am. Chem. Soc.* **1988**, *110*, 8483–8487; b) A. T. Watson, K. Park, D. F. Wiemer, *J. Org. Chem.* **1995**, *60*, 5102–5106; c) N. Kawai, Y. Fujibayashi, S. Kuwabara, K. Takao, Y. Ijuin, S. Kobayashi, *Tetrahedron* **2000**, *56*, 6467–6478.
[26] Mosmann, T. *J. Immunol. Methods* **1983**, *65*, 55–63.

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