# Enantioselective total synthesis of (+)-aureol via a $BF_3$·$Et_2O$-promoted rearrangement/cyclization reaction of (+)-arenarol

**Mari Nakatani,[a] Masahiko Nakamura,[b] Akiyuki Suzuki,[c] Takamasa Fuchikami,[a] Munenori Inoue,[a] and Tadashi Katoh*[a,b]**

*[a] Sagami Chemical Research Center, 2743-1 Hayakawa, Ayase, Kanagawa 252-1193, Japan, [b] Department of Electronic Chemistry, Tokyo Institute of Technology, Nagatsuta, Yokohama 226-8502, Japan, [c] Department of Chemistry, Kitasato University, Kitasato, Sagamihara, Kanagawa 228-0829, Japan*
*E-mail: takatoh@alles.or.jp*

**Dedicated to Professor Keiichiro Fukumoto on his 70th birthday**
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**Abstract**
(+)-Aureol (**1**), a structurally novel and biologically important marine natural product, was efficiently synthesized in an enantiomerically pure form starting from the known *cis*-fused decalin derivative **5**. The synthetic method features a $BF_3$·$Et_2O$-promoted rearrangement/cyclization reaction of (+)-arenarol (**2**) to deliver (+)-aureol (**1**) with complete stereoselectivity in high yield. Arenarol (**2**), a plausible biogenetic precursor of (+)-aureol (**1**), was prepared in an efficient way through; *(i), a* coupling reaction of **5** with 2-lithioanisole to build the requisite carbon framework **6**, and *(ii),* salcomine oxidation of the phenolic derivative **10** to form the quinone system **11** as the crucial steps.

**Keywords:** Aureol, arenarol, marine natural product, total synthesis, rearrangement

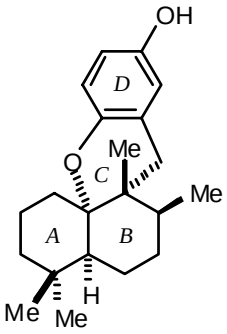
## Introduction

Marine organisms, particularly algae and sponges, have recently yielded a number of clerodane diterpenoids and related compounds.[1] Several of these marine metabolites were reported to exhibit promising biological profiles including antimicrobial, antiviral, cytotoxic, and immunomodulatory activities.[1] In most cases, however, further biological studies of these marine natural products are severely restricted by the scarcity of samples from the marine organisms.[1]

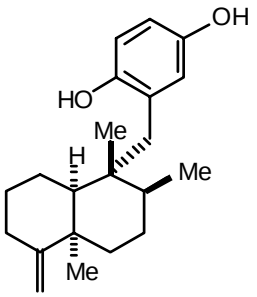
Aureol (**1**, Figure 1) was originally isolated in 1980 by Faulkner and his group[2] from the Caribbean sponge, *Smenospongia aurea*, and subsequently in 2000 by Fattorusso and his

co-workers from a different species of the Caribbean sponge, *Verongula gigantea*.[3] This marine natural product has been shown to exhibit selective cytotoxicity against the A549 human non-small cell lung cancer cells ($IC_{50}$=4.3 μg/mL),[4] and anti-influenza-A virus activity ($IC_{50}$=11.6 μM).[5]




aureol (**1**)



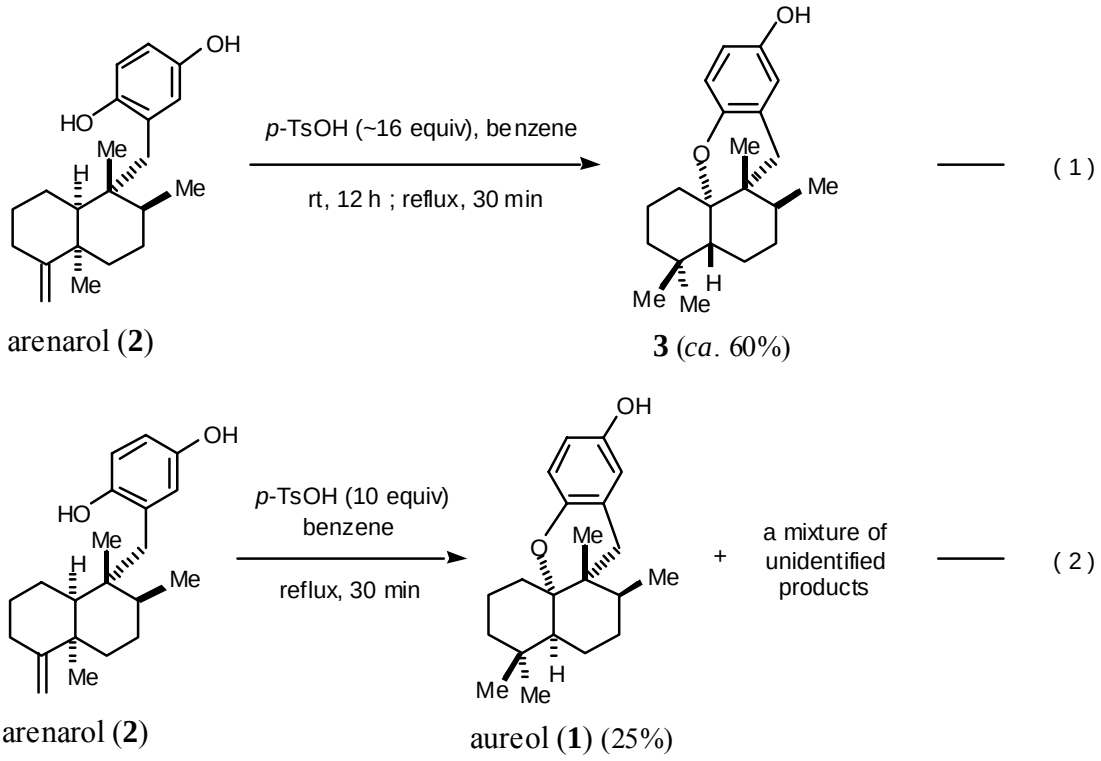

arenarol (**2**)

**Figure 1.** Structures of aureol (1) and arenarol (2).

The gross structure and stereochemistry, including the absolute configuration, were determined by X-ray crystallographic analysis of the brominated *O*-acetyl derivative of **1**, and were shown to have a novel tetracyclic benzo[*d*]xanthene skeleton (ABCD ring system) with four contiguous asymmetric centers and three quaternary carbons,[2] in which *cis*-fused AB rings and BC rings, and an ethereal bond at the bridgehead of the AB ring juncture are particularly characteristic features. Its remarkable biological properties and unique structural features as well as the limited availability from natural resources,[6] make **1** an exceptionally intriguing and timely target for total synthesis. While a synthetic approach toward this type of tetracyclic ring system was reported by Letcher and co-workers in 1998,[7] the total synthesis of **1** has not been achieved to date.

It is envisaged that aureol (**1**) might be produced biogenetically by acid-promoted rearrangement of arenarol (**2**), which was first isolated from the marine sponge, *Dysidea arenaria*, by Schmitz *et al*.[8] in 1984, and subsequently from a *Fenestrasongia* species by Faulkner *et al*.[9] in 1985. This type of acid-promoted rearrangement has been applied successfully to determine the absolute configuration of marine sesquiterpene quinones and hydroquinones.[10,11] To our knowledge, as outlined in Scheme 1, two examples of acid-promoted rearrangement of arenarol (**2**) have appeared in the literature. In these examples, however, the important synthetic chemical issues with respect to stereocontrol and efficiency were not considered. Thus, Schmitz and Helm and their coworkers[12] described in 1990 that treatment of arenarol (**2**) with a large excess (~16 equiv.) of *p*-toluenesulfonic acid (*p*-TsOH) in benzene at room temperature overnight, followed by reflux for 30 minutes, led to the formation of the rearrangement/cyclization product **3** (60%), which corresponds to a stereoisomer of **1** having the *trans*-fused decalin ring system (Equation 1). On the other hand, Urban and Capon[10a] reported in 1994 that treatment of **2** in the same acid solution at reflux for 30 minutes provided **1** in 25 % yield, along with a mixture of unidentified

products (Equation 2). Taking into account the foregoing facts, the development of an efficient and reliable method for preparing aureol (**1**) in high yield is very desirable and useful from the standpoint of medicinal chemistry as well as pharmaceuticals.



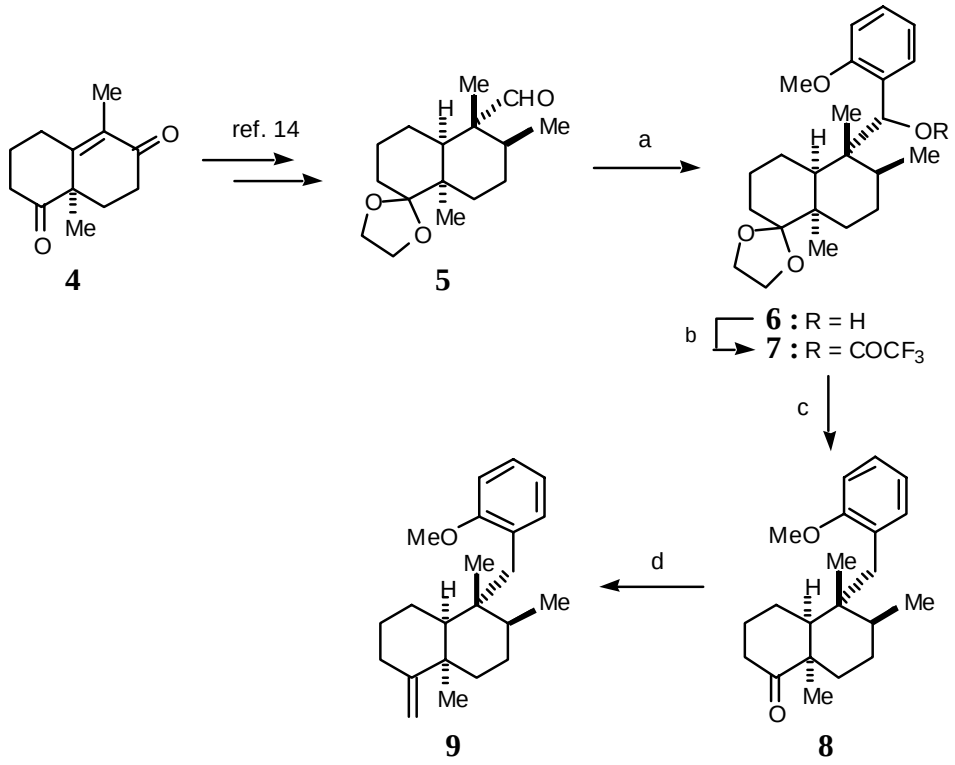

**Scheme 1.** Previous examples of acid-promoted rearrangement of arenarol (**2**).

In 2001, we embarked on a project directed at the total synthesis of aureol (1) in an enantiomerically pure form, with the aim of investigating further the biological activity of **1**. Our earnest endeavors culminated in the completion of the first total synthesis of natural (+)-**1** in 2002.[13] This paper gives details of our first total synthesis of (+)-**1**. The method features, *(i)*, a coupling reaction of the *cis*-fused decalin derivative **5** with 2-lithioanisole to build the requisite carbon framework **6** (**5**→**6**, Scheme 2), *(ii),* salcomine oxidation of the phenolic derivative **10** to form the corresponding quinone **11** (**10**→**11**, Scheme 3), and, *(iii),* $BF_3{\cdot}Et_2O$-promoted rearrangement/ cyclization reaction of (+)-arenarol (**2**) to deliver (+)-aureol (**1**) with complete stereoselectivity, in high yield (**2**→**1**, Scheme 3).

## Results and Discussion

As shown in Scheme 2, the synthesis commenced with the crucial coupling reaction of the known *cis*-fused decalin aldehyde **5**,[14] previously prepared from the enantiomerically pure

(–)-Wieland–Miescher ketone analogue **4** (>99% *ee*) in our laboratory,[14] with commercially available 2-bromoanisole. Thus, the aryllithium generated *in situ* by treatment of 2-bromoanisole with *n*-butyllithium in THF at –78°C was allowed to react with **5** at the same temperature, providing an excellent yield (93%) of the desired coupling product **6** as the sole product; the stereochemistry at the benzylic carbon was not determined.

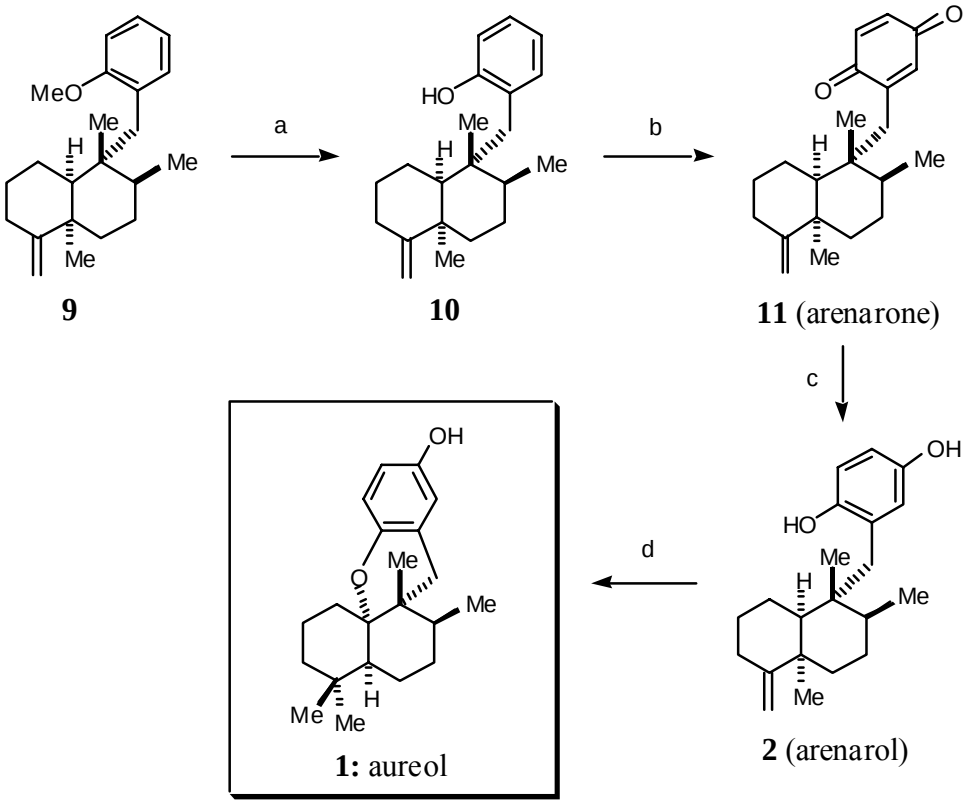



**Scheme 2.** Synthesis of the key intermediate **9**. (a), 2-bromoanisole, *n*-BuLi, THF, –78°C ; at –78°C, add **5**, 93%; (b), $(CF_3CO)_2O$, pyridine, 0°C, 91% (c) $H_2$ (5 atm.), 10% Pd–C, MeOH, rt, 90%, (d), $CH_2Br_2$, Zn, $TiCl_4$, THF, rt, 82%.

Simultaneous removal of both the benzylic hydroxy group and the ethylene acetal moiety in **6** was achieved effectively by initial formation of the corresponding trifluoroacetate **7** followed by reaction under the conditions for hydrogenolysis, which led to the production of the carbonyl compound **8** in 82% yield for the two steps. Subsequent methylenation of the sterically hindered carbonyl group in **8** was best achieved by employing the Takai procedure.[15] Thus, treatment of **8** with a mixture of dibromoethane, zinc powder, and titanium (IV) chloride in THF at room temperature furnished the exo-olefinic compound 9 in 82% yield. The methylenation of **8** by reaction with the Wittig reagent ($Ph_3P^+CH_3Br^-$/t-BuOK), Peterson's reagent ($LiCH_2SiMe_3$), or Tebbe reagent gave none of the desired product **9** and resulted in almost complete recovery of the starting material **8**.

Next, as shown in Scheme 3, deprotection of the methyl ether protecting group was investigated to obtain the phenolic derivative **10**, a key substrate for the following crucial

salcomine oxidation step. The exo-olefin moiety present in this type of decalin system **9** is known to be highly sensitive to acidic conditions:[14,16] therefore, the requisite demethylation of **9** was conducted by the use of a non-acidic alkylthiolate reagent. Thus, treatment of **9** with lithium *n*-butylthiolate[14a,17] in hexamethyl-phosphoramide (HMPA) at 100°C for 2 hours afforded the liberated phenolic compound **10** in 84% yield. The pivotal conversion of the phenolic derivative **10** to the corresponding quinone **11** (arenarone) was effected by reaction of **10** with molecular oxygen ($O_2$ balloon) in the presence of salcomine [N,N-bis(salicylidene)ethylenediiminocobalt (II)][14a,18] (1.0 equiv.) in N,N-dimethylformamide (DMF) at room temperature for 3 hours, which led to the production of **11** in 91% yield. Subsequent reduction of the quinone system in **11** using sodium hydrosulfite[19] proceeded smoothly to give the sub-target arenarol **(2)** in 76% yield.

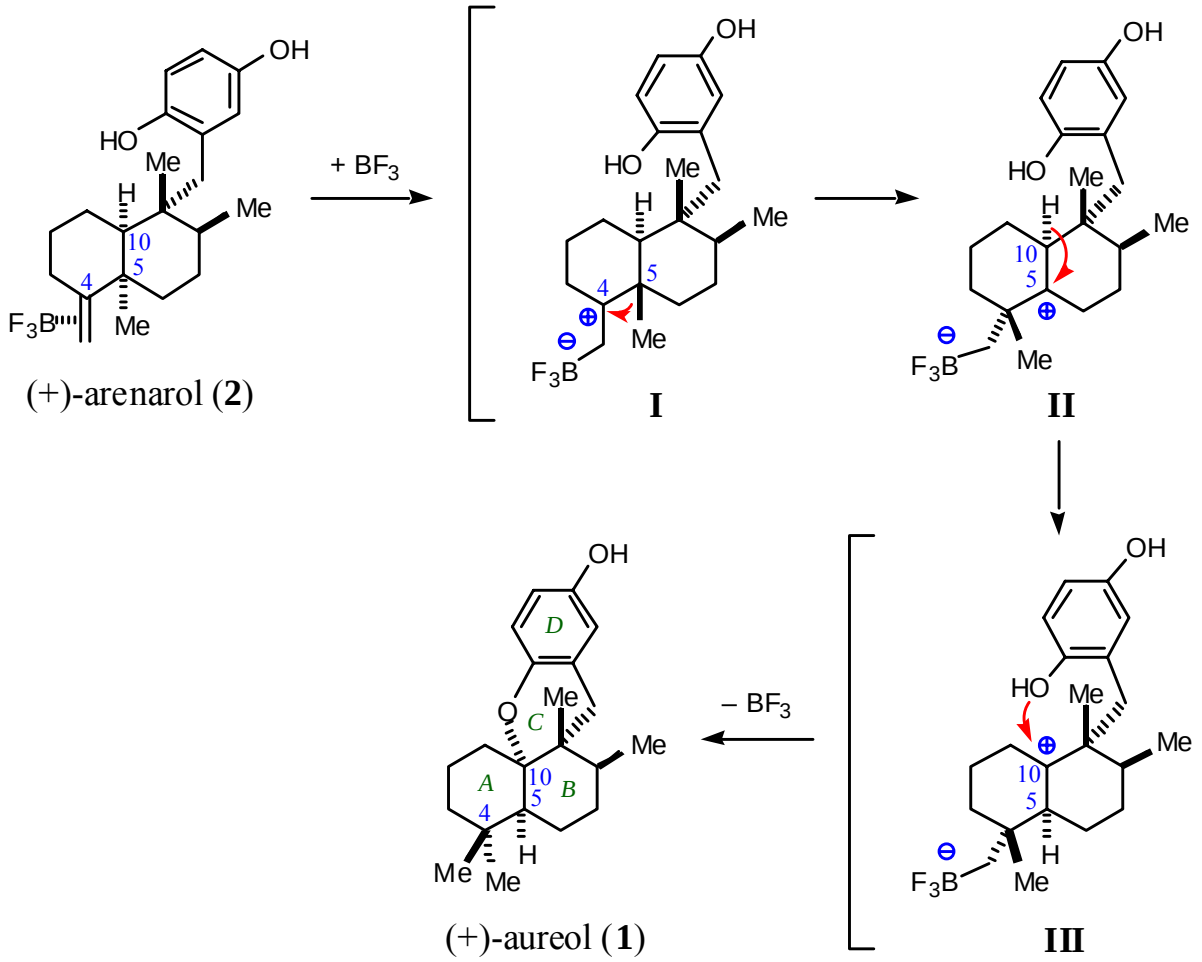



**Scheme 3.** Completion of the total synthesis of aureol **(1)** (a) n-BuSLi, HMPA, 100°C, 84% (b) $O_2$, salcomine, DMF, rt, 91% (c) $Na_2S_2O_4$, THF-$H_2O$, rt, 76% (d) $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, –40°C, 97%.

Having obtained arenarol **(2)** in an efficient way, we then set the stage for the most crucial acid-promoted rearrangement/cyclization event for completing the synthesis of the targeted (+)-aureol (1). To our delight, the desired acid-promoted rearrangement/cyclization reaction was found to proceed effectively by treating **2** with $BF_3{\cdot}Et_2O$ (5.0 equiv.) in dichloromethane at –40°C for 3 hours, which led to the formation of aureol (1), m.p 141-142°C [lit.[2] m.p 144-145°C], $[\alpha]D_{20}$ +65.6° (c 0.20, $CCl_4$) [lit.,[2] [α ]D +65° (c 2.0, $CCl_4$)], with perfect stereoselectively in excellent

yield (97%). The spectroscopic properties (IR, 1H and $^{13}$C NMR, MS) of synthetic material **1** were identical with those reported[2] for natural aureol (**1**). It is noteworthy that no isomeric products (e.g., trans-fused decalin isomer **3**, Scheme 1) were generated in this rearrangement/cyclization reaction.

The remarkable stereocontrolled $BF_3{\cdot}Et_2O$-promoted rearrangement/cyclization reaction of arenarol **(2)** leading to aureol **(1)** can be rationalized by the mechanistic route shown in Scheme 4.




**Scheme 4.** Reaction mechanism for the $BF_3{\cdot}Et_2O$-promoted rearrangement/cyclization reaction of (+)-arenarol **(2)** leading to (+)-aureol **(1)**. (Possible coordinations between the Lewis acid and the phenolic hydroxy groups are omitted for clarity.

The reaction process would involve three possible tertiary carbocation intermediates such as **I**, **II**, and **III**. Thus, the first coordination-activation between the Lewis acid and the C4 *exo*-olefin moiety in **2** would lead to the formation of the intermediate **I**, which would further furnish the intermediate **II** via migration of the C-5 methyl group to the C-4 carbocation center. The

intermediate **II** would suffer a 1,2-hydride shift from the C-10 position to the C-5 carbocation center on the α-face of the molecule to provide the intermediate **III**, wherein the C-10 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, namely, (+)-aureol (**1**). We believe that the sequence of this domino-type rearrangement/cyclization reaction would proceed under kinetically controlled conditions. In contrast, the previously reported reactions illustrated in Scheme 1 would take place under thermodynamically controlled conditions. In order to obtain theoretical support for this rearrangement/cyclization event, we carried out computational studies with the Gaussian 98 program.[20] The structural optimizations of compounds **1** and **3** were performed by the B3LYP DFT (Density Functional Theory) using 6-31G(D) as a basis set. The calculations estimate that the *trans*-fused decalin compound **3** is 6.67 kcal/mol more stable than aureol (**1**) possessing the *cis*-fused decalin system.

## Conclusions

We have succeeded in developing an efficient synthetic pathway to (+)-aureol **(1)** starting with the known *cis*-fused decalin derivative **5**, accessible from the (–)-Wieland Miescher ketone analogue **4** (>99% *ee*), by way of arenarone (**11**) and arenarol (**2**). The explored method features; *(i), a* coupling reaction of **5** with 2-lithioanisole to construct the requisite carbon framework **6** (**5**→**6**, Scheme 2); *(ii),* salcomine oxidation of the phenolic compound **10** to deliver the quinone **11** (**10**→**11**, Scheme 3), and *(iii),* $BF_3$·$Et_2O$-promoted rearrangement/cyclization reaction of **2** to produce **1** (**2**→**1**, Scheme 3). Further applications of the rearrangement/cyclization strategy to the synthesis of biologically important natural products possessing a tetracyclic benzo[*d*]xanthen skeleton are currently under investigation, and will be reported in due course.

## Experimental Section

**General Procedures.** All reactions involving air- and moisture-sensitive reagents were carried out using oven-dried glassware and standard syringe-septum cap techniques. Routine monitoring of the reaction was 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 the following exceptions. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone under argon. Dichloromethane, *N*,*N*-dimethylformamide (DMF), and hexamethylphosphoramide (HMPA) were distilled from calcium hydride 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 Bruker AM-400 (400 MHz) or Bruker DRX-500 (500 MHz) spectrometers.

Chemical shifts are expressed in ppm using tetramethylsilane (δ=0) as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Infrared (IR) spectral measurements were carried out with a JASCO FT/IR-5300 spectrometer. Low-resolution mass (MS) spectra and high resolution mass (HRMS) spectra were measured on a Hitachi M-80B spectrometer.

**(1*R*,2*S*,4a*R*,8a*S*)-*cis*-Decahydro-1α-[1-hydroxy-(2-methoxyphenyl)methyl]-1β,2β,4aα-trimethyl-5-(1,3-dioxolan-2-yl)-naphthalene (6).** *n*-Butyllithium in hexane (1.52 *M* solution, 2.40 ml, 3.6 mmol) was added dropwise to a stirred solution of 2-bromoanisole (0.45 ml, 3.6 mmol) in dry THF (5 ml) at –78°C under argon. The resulting solution was gradually warmed to –15°C during 1 h, and then a solution of (1*R*,2*S*,4a*R*,8a*R*)-*cis*-decahydro-1β,2β,4aα-trimethyl-5-(1,3-dioxolan-2-yl)-naphthalene-1-carbox ald- ehyde (**5**) (95.0 mg, 0.36 mmol) in dry THF (5 ml) was added slowly at –78°C. After 1 h, the reaction was quenched with water (3 ml), and the mixture was extracted with ethyl acetate (3 x 20 ml). The combined extracts were washed with saturated aqueous sodium hydrogencarbonate and brine, then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane–ethyl acetate, 9:1) to give **6** (124 mg, 93%) as a white solid. Recrystallization from ether and hexane afforded white needles, mp 188–189°C: $[\alpha]_D^{20} = -11.1°$ (*c* 1.01, $CHCl_3$); $^1$H- NMR (500 MHz, $CDCl_3$) δ 0.50 (3H, br d, J = 4.3 Hz), 0.95 (3H, s), 1.19–1.24 (1H, m), 1.29 (3H, s), 1.31–1.42 (1H, m), 1.42–1.51 (3H, m), 1.57–1.72 (4H, m), 1.85 (1H, td, J = 5.7, 14.1 Hz), 1.89–1.99 (1H, m), 2.05–2.13 (1H, m), 2.15–2.69 (1H, br s), 3.82 (3H, s), 3.90–3.99 (4H, m), 5.29–5.35 (1H, m), 6.82–6.88 (1H, m), 6.95 (1H, dt, J = 0.9, 7.5 Hz), 7.19–7.25 (1H, m ), 7.41 (1H, br d, J = 7.3 Hz); $^{13}$C NMR (125 MHz, DMSO) δ 13.1, 18.3, 22.1, 24.9, 26.1, 27.4, 28.1, 29.4, 30.3, 41.9, 43.4, 44.7, 55.1, 64.0, 64.1, 69.7, 110.2, 113.3, 119.4, 127.2, 129.6, 133.2, 156.5; IR (KBr) 3447, 2961, 2935, 2891, 2868, 1722, 1597, 1489, 1469, 1379, 1290, 1275, 1240, 1178, 1145, 1086, 1030, 951, 900, 887, 758, 663, 623, 509, 437 $cm^{-1}$; HREIMS *m/z* calcd for $C_{23}H_{34}O_4$ ($M^+$), 374.2457, found 374.2435.

**(1*R*,2*S*,4a*R*,8a*S*)-*cis*-Decahydro-1α-[2-methoxyphenyl-1-(trifluoroacetoxy)methyl]-1β,2β,4aα-trimethyl-5-(1,3-dioxolan-2-yl)-naphthalene (7).** Trifluoroacetic anhydride (85 μl 0.60 mmol) was added dropwise to a stirred solution of (1*R*,2*S*,4a*R*,8a*S*)-*cis*-decahydro-1α-[1-hydroxy-(2-methoxyphenyl) methyl] -1β,2β,4aα-trimethyl-5-(1,3-dioxolan-2-yl)-naphthalene (**6**) (105 mg, 0.30 mmol) in dry pyridine (4.5 ml) at 0°C under argon. After 1 h, the reaction mixture was diluted with ethyl acetate (30 ml). The resulting solution was washed with 1% aqueous hydrochloric acid (2 x 5 ml) and brine, then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane–ethyl acetate, 8:1) to give **7** (120 mg, 91%) as a colorless oil: $[\alpha]_D^{20} = +19.3°$ (*c* 1.05, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 0.68–0.80 (3H, br s), 0.94–1.04 (1H, m), 1.12 (3H, s), 1.14 (3H, s), 1.26–1.34 (1H, m), 1.46–1.63 (5H, m), 1.66–1.77 (3H, m), 1.77–1.83 (1H, m), 1.83–1.89 (1H, m), 3.85 (3H, s), 3.88–3.95 (4H, m), 6.68 (1H, s), 6.86–6.91 (1H, m), 6.95 (1H, dt, J = 0.9, 7.5 Hz), 7.26–7.34 (2H, m); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 13.3, 18.6, 22.3, 25.1, 27.2, 28.3, 30.3, 30.4, 32.2, 41.5,

44.9, 45.5, 55.6, 64.6, 64.7, 79.9, 110.9, 113.8, 114.7 (q, $^1J_{c,f}$ = 284.6 Hz), 120.4, 125.8, 128.8, 129.4, 156.6 (q, $^2J_{c,f}$ = 41.5 Hz), 157.6; IR (neat): 2941, 2879, 2287, 1782, 1602, 1493, 1466, 1383, 1356, 1288, 1249, 1221, 1161, 1089, 1051, 1030, 925, 758 cm$^{-1}$; HREIMS *m/z* calcd for $C_{25}H_{33}F_3O_5$ ($M^+$), 470.2280, found 470.2270.

**(1*R*,2*S*,4a*R*,8a*S*)-*cis*-Decahydro-1α-[(2-methoxyphenyl)methyl]-1β,2β,4aα-trimethyl-naphthalen-5-one (8).** 10% Pd/C (160 mg) was added to a solution of (1*R*,2*S*,4a*R*,8a*S*) -*cis*-decahydro-1α-[2-methoxyphenyl-1-(trifluoroacetoxy)methyl]-1β,2β,4aα-trimethyl-5-(1,3-dioxolan-2-yl)-naphthalene (**7**) (80.0 mg, 0.17 mmol) in methanol (5 ml), and the mixture was stirred for 25 h under hydrogen (5 atm) at room temperature. The reaction mixture was diluted with ethyl acetate (50 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 (hexane–ethyl acetate, 20:1) to give **8** (48.1 mg, 90 %) as a white solid. Recrystallization from hexane afforded colorless needles, mp 84–86°C: $[\alpha]_D^{20}$ = +50.6° (*c* 1.00, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 0.60–0.69 (1H, m), 0.82 (3H, s), 0.98 (3H, d, J = 6.2 Hz), 1.15 (3H, s), 1.19–1.41 (3H, m), 1.69 (1H, d, J = 6.3 Hz), 2.01–2.10 (1H, m), 2.10–2.26 (4H, m), 2.26–2.35 (1H, m), 2.59–2.72 (1H, m), 2.63 (1H, d, J = 14.1 Hz), 2.83 (1H, d, J = 14.1 Hz), 3.79 (3H, s), 6.82–6.91 (2H, m), 7.12 (1H, dd, J = 1.6, 7.5 Hz), 7.16–7.23 (1H, m); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 17.7, 18.3, 20.5, 24.3, 27.8, 30.5, 34.6, 36.2, 36.6, 36.7, 43.1, 47.9, 49.7, 54.8, 110.4, 119.8, 127.1, 127.2, 132.4, 158.3, 217.4; IR (KBr): 2947, 2856, 1701, 1599, 1493, 1460, 1439, 1383, 1288, 1246, 1163, 1120, 1097, 1053, 1030, 987, 933, 862, 839, 760, 601, 584, 513 cm$^{-1}$; HREIMS *m/z* calcd for $C_{21}H_{30}O_2$ ($M^+$), 314.2246, found 314.2261.

**(1*R*,2*S*,4a*R*,8a*S*)-*cis*-Decahydro-1α-[(2-methoxyphenyl)methyl]-1β,2β,4aα-trimethyl-5-methylene naphthalene (9).** Titanium tetrachloride in dichloromethane (1.0 *M* solution, 1.40 ml, 1.4 mmol) was added dropwise to a suspension of (1*R*,2*S*,4a*R*,8a*S*)-*cis*-decahydro-1α-[(2-methoxyphenyl)methyl] -1β,2β,4aα-trimethyl-naphthalen-5-one (**8**) (40.0 mg, 0.13 mmol) in dry THF (6 ml) containing zinc dust (360 mg, 5.8 mmol) and dibromomethane (0.13 ml, 1.9 mmol) at 0°C, and the mixture was stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (2 ml) and diluted with ethyl acetate (100 ml). The resulting solution was filtered through a small pad of Celite® to remove the rest of the zinc dust. The filtrate was washed with brine, then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane–ethyl acetate, 20:1) to give **9** (32.6 mg, 82%) as a white solid. Recrystallization from hexane afforded colorless needles, mp 63–64°C: $[\alpha]_D^{20}$ = +53.3°(*c* 1.02, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 0.90 (3H, s), 0.91–0.97 (1H, m), 0.98 (3H, d, J = 6.5 Hz), 1.00 (3H, s), 1.18 (1H, qd, J = 3.5, 13.2 Hz), 1.28–1.35 (2H, m), 1.47–1.60 (1H, m), 1.66–1.72 (1H, m), 1.79–1.98 (3H, m), 2.11–2.16 (1H, m), 2.19–2.24 (1H, m), 2.42–2.51 (1H, m), 2.59 (1H, d, J = 14.0 Hz), 2.78 (1H, d, J = 14.0 Hz), 3.77 (3H, s), 4.68–4.73 (2H, m), 6.82–6.89 (2H, m), 7.10 (1H, dd, J = 1.7, 7.5 Hz), 7.17 (1H, ddd, J = 1.7, 7.4, 7.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 18.0, 19.1, 22.3, 25.0, 27.7, 32.0, 32.9, 37.1, 37.4, 37.8, 39.3, 43.5, 46.3, 54.8, 105.6, 110.3, 119.6, 127.0, 127.7, 132.6, 153.8, 158.4; IR (KBr): 2984,

2932, 2866, 1637, 1599, 1583, 1493, 1462, 1383, 1288, 1246, 1176, 1097, 1053, 1033, 889, 752 $cm^{-1}$; HREIMS *m/z* calcd for $C_{22}H_{32}O$ ($M^+$), 312.2453, found 312.2436.

**2-[(1*R*,2*S*,4a*R*,8a*S*)-*cis*-Decahydro-1β,2β,4aα-trimethyl-5-methylene-naphthalen-1-yl-methyl]-phenol (10).** Lithium *n*-butylthiolate in HMPA (0.5*M* solution, 4.80 ml, 2.40 mmol) was added to a stirred solution of (1*R*,2*S*,4a*R*,8a*S*)-*cis*-decahydro-1α-[(2-methoxyphenyl)methyl]-1β,2β,4aα-trimethyl-5-methylenenaphthalene (**9**) (51.0 mg, 0.16 mmol) in HMPA (0.6 ml) at room temperature, and the mixture was heated at 90°C for 2 h. After cooling, the reaction was quenched with saturated aqueous ammonium chloride (1 ml), and the resulting mixture was extracted with ethyl acetate (3 x 15 ml). The combined extracts were washed with brine, then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane–ethyl acetate, 100:1→50:1) to give **10** (40.4 mg, 84%) as a colorless oil: $[\alpha]_D^{20}$ +49.7° (*c* 1.02, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 0.93 (3H, s), 0.98–1.03 (1H, m), 1.00 (3H, d, J = 6.5 Hz), 1.03 (3H, s), 1.20–1.24 (1H, m), 1.36–1.43 (2H, m), 1.49–1.58 (1H, m), 1.68–1.73 (1H, m), 1.84 (1H, tq, J = 5.5, 13.8 Hz), 1.92–2.02 (2H, m), 2.12–2.18 (2H, m), 2.45 (1H, tt, J = 1.9, 13.7 Hz), 2.58 (1H, d, J = 14.5 Hz), 2.74 (1H, d, J = 14.5 Hz), 4.63 (1H, s), 4.71 (2H, td, J = 1.8, 10.6 Hz), 6.73–6.75 (1H, m), 6.84 (1H, dt, J = 1.7, 7.5 Hz), 7.07–7.10 (2H, m); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 18.0, 19.1, 22.5, 24.9, 27.6, 31.9, 32.9, 37.4, 37.4, 37.7, 39.3, 43.4, 46.3, 105.8, 115.6, 120.1, 125.0, 127.2, 133.0, 153.5, 154.6; IR (KBr) 3447, 2930, 1636, 1607, 1503, 1453, 1383, 1260, 1233, 1171, 1125, 891, 752 $cm^{-1}$; HREIMS *m/z* calcd for $C_{21}H_{30}O$ ($M^+$), 298.2297, found 298.2304.

**2-[(1*R*,2*S*,4a*R*,8a*S*)-*cis*-Decahydro-1β,2β,4aα-trimethyl-5-methylene-naphthalen-1-yl-methyl]-[1,4]benzoquinone (11) (arenarone).** *N*,*N*-Bis(salicylidene)ethylenediiminocobalt(II) (35.0 mg, 0.10 mmol) was added to a stirred solution of 2-[(1*R*,2*S*,4a*R*,8a*S*)-*cis*-decahydro-1β,2β,4aα-trimethyl-5-methylene-naphthalen-1-yl-methyl]-phenol (**10**) (30.0 mg, 0.10 mmol) in dry DMF (8.0 ml) at room temperature. The suspension was stirred under an oxygen atmosphere ($O_2$ balloon) for 1 h at room temperature. The mixture was concentrated *in vacuo* to afford a residue, which was purified by column chromatography (hexane–ethyl acetate, 20:1) to give **11** (28.6 mg, 91%) as an orange viscous oil; $[\alpha]_D^{25}$ = +31.8° (*c* 0.21, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, d, J = 5.5 Hz), 0.93 (3H, s), 1.06 (3H, s), 1.04–1.15 (1H, m), 1.20–1.34 (3H, m), 1.48–1.62 (1H, m), 1.64–1.90 (3H, m), 1.93–2.20 (3H, m), 2.38–2.52 (1H, m), 2.41 (1H, dd, J = 0.9, 13.6 Hz), 2.67 (1H, d, J = 13.6 Hz), 4.68–4.76 (2H, m), 6.51–6.55 (1H, m), 6.73 (1H, dd, J = 2.4, 10.0 Hz), 6.77 (1H, d, J = 10.0 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 17.2, 19.1, 21.8, 24.5, 27.4, 31.7, 33.0, 35.3, 37.9, 38.4, 39.4, 44.6, 47.5, 106.1, 135.9, 136.0, 137.2, 147.4, 153.1, 187.2, 187.5; IR (neat): 3310, 3268, 3083, 2932, 2868, 2361, 1784, 1726, 1659, 1595, 1460, 1385, 1352, 1290, 1217, 1117, 1071, 1015, 910, 891, 829, 756, 646, 575, 434 $cm^{-1}$; HREIMS *m/z* calcd for $C_{21}H_{28}O_2$ ($M^+$), 312.2089, found 312.2092.

**2-[(1*R*,2*S*,4a*R*,8a*S*)-*cis*-Decahydro-1β,2β,4aα-trimethyl-5-methylene-naphthalen-1-yl-methyl]-benzene-1,4-diol (2) (arenarol).** Sodium hydrosulfite (159 mg, 0.92 mmol) was added to a stirred solution of 2-[(1*R*,2*S*,4a*R*,8a*S*)-*cis*-decahydro-1β,2β,4aα-trimethyl-5-methylenenaphthalen-1-yl-methyl]-[1,4]benzoquinone (**11**) (arenarone) (28.6 mg, 92 μmol) in THF (3.2 ml) containing water

(1.6 ml) at 0°C. After 35 min, the reaction was quenched with saturated aqueous sodium hydrogencarbonate (2 ml), and the mixture was extracted with ethyl acetate (3 x 15 ml). The combined extracts were washed with brine, then dried over $MgSO_4$. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane–ethyl acetate, 10:1) to give **2** (21.8 mg, 76%) as a colorless viscous liquid: $[\alpha]_D^{25}$ +17.1° (*c* 0.13, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, s), 0.99 (3H, d, J = 6.4 Hz), 1.01–1.08 (1H, m), 1.04 (3H, s), 1.18–1.30 (1H, m), 1.36 (1H, d, J = 6.4 Hz), 1.38–1.48 (1H, m), 1.48–1.62 (1H, m), 1.63–1.74 (1H, m), 1.76–2.03 (3H, m), 2.09–2.19 (2H, m), 2.42–2.54 (1H, m), 2.52 (1H, d, J = 14.3 Hz), 2.70 (1H, d, J = 14.3 Hz), 4.38 (2H, br), 4.68–4.74 (2H, m), 6.55–6.66 (3H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 18.0, 19.1, 22.5, 24.9, 27.6, 31.9, 32.9, 37.4, 37.5, 37.7, 39.3, 43.5, 46.4, 105.8, 113.8, 116.3, 119.3, 126.5, 148.6, 148.7, 153.5.; IR (neat): 3592, 3364, 3083, 2932, 1707, 1634, 1503, 1449, 1381, 1350, 1196, 1123, 1090, 1053, 1015, 968, 891, 810, 758, 667, 538 cm$^{-1}$; HREIMS *m/z* calcd for $C_{21}H_{30}O_2$ ($M^+$), 314.2246, found 312.2220.

**(4a*S*,7*S*,7a*R*,13a*S*)-1,2,3,4,4aα,5,6,7,7a,8-Decahydro-4,4,7β,7aβ-tetramethyl-benzo[*d*]xanthen-10-ol (1) (aureol).** Boron trifluoride etherate (12 μl, 92 μmol) was added to a stirred solution of 2-[(1*R*,2*S*,4a*R*,8a*S*)-*cis*-decahydro-1β,2β,4aα-trimethyl-5-methylene-naphthalen-1-yl-methyl]-benzene-1,4-diol (**2**) (arenarol) (5.8 mg, 18 μmol) in dichloromethane (1.8 ml) at –40°C. After 3 h, the reaction was quenched with saturated aqueous sodium hydrogencarbonate (0.6 ml), and the mixture was extracted with ethyl acetate (4 x 8 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–ethyl acetate, 10:1) to give **1** (5.6 mg, 97%) as a white solid. Recrystallization from ether and hexane afforded white needles, mp 141–142°C [lit.,[2] mp 144–145°C]: $[\alpha]_D^{20}$ +65.6° (*c* 0.2, $CCl_4$) [lit.,[2] $[\alpha]_D$ +65° (*c* 2.0, $CCl_4$)]; $^1$H NMR (500 MHz, $CDCl_3$) δ 0.78 (3H, s), 0.92 (3H, s), 1.06 (3H, s), 1.11 (3H, d, *J* = 7.6 Hz), 1.16–1.21 (1H, m), 1.32–1.38 (1H, m), 1.41–1.50 (3H, m), 1.52–1.61 (1H, m), 1.63–1.72 (2H, m), 1.74–1.87 (2H, m), 1.96 (1H, d, *J* = 17.4 Hz), 1.99–2.11 (2H, m), 3.37 (1H, d, *J* = 17.4 Hz), 4.29 (1H, br s), 6.49 (1H, d, *J* = 2.7 Hz), 6.54–6.63 (2H, m); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 17.3, 18.4, 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, 115.1, 117.3, 122.2, 145.8, 148.3; IR (neat) 3373, 2934, 2872, 1722, 1622, 1496, 1454, 1385, 1263, 1232, 1186, 1118, 953, 904, 864, 806, 733 cm$^{-1}$; HREIMS *m/z* calcd for $C_{21}H_{30}O_2$ ($M^+$), 314.2246, found 314.2241. These spectral data were identical with those reported for natural (+)-aureol (**1**).[2]

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## References and Notes


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