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An efficient synthesis of (+)-aureol via boron trifluoride etherate-promoted rearrangement of (+)-arenarol

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Abstract—A novel marine natural product, (+)-aureol (**1**), was efficiently synthesized starting from the *cis*-fused decalin derivative **4**. The synthetic method features boron trifluoride etherate-promoted rearrangement/cyclization reaction of (+)-arenarol (**2**) to form (+)-aureol (**1**) with complete stereoselectivity in high yield. (+)-Arenarol (**2**) was prepared in an alternative and more efficient manner employing salcomine oxidation protocol. © 2002 Elsevier Science Ltd. All rights reserved.

Over the past two decades a number of clerodane diterpenoids and related compounds have been isolated from marine algae and sponges.[1] Several of these marine natural products were reported to possess interesting biological properties such as antimicrobial, antiviral, and cytotoxic activities.[1] Aureol (**1**, Fig. 1) was originally isolated from the marine sponge, *Smenospongia aurea*, by Faulkner et al. in 1980, and its structure and stereochemistry including the absolute configuration were determined by X-ray diffraction analysis of the brominated *O*-acetyl derivative of **1** to have a novel tetracyclic benzo[*d*]xanthen skeleton (ABCD ring system).[2] Recently, **1** was found to exhibit selective cytotoxicity against the A549 human non-small cell lung cancer cells[3] and anti-influenza A virus activity.[4] Its unique structural features and promising biological profiles as well as the limited supplies[5] from natural resources, make **1** an attractive target for total synthesis. However, to the best of our knowledge, the total synthesis of **1** has not been disclosed to date.

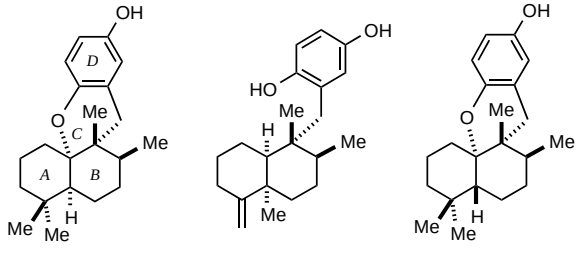

Figure 1. Structures of aureol (**1**), arenarol (**2**), and related compound **3**.

It is envisioned that aureol (**1**) might be produced biogenetically by acid-promoted rearrangement of arenarol (**2**), which was initially isolated from the marine sponge, *Dysidea arenaria*, by Schmitz et al.[6] in 1984. This type of acid-promoted rearrangement has been successfully applied to reveal the absolute stereochemistry of marine sesquiterpene quinones and hydroquinones.[7,8] So far, to our knowledge, two examples of acid-promoted rearrangement of **2** have been recorded in the literature; however, the important synthetic chemical issues of stereocontrol and efficiency were not considered. Thus, Schmitz et al.[9] reported for the first time that treatment of **2** with *p*-toluenesulfonic acid in benzene at room temperature overnight, followed by at reflux for 30 min, resulted in the formation of compound **3**, a stereoisomer of **1** possessing the *trans*-fused decalin system, in approximately 60% yield. On the other hand, Capon et al.[7a] described that reaction of **2** in the same acid solution at reflux for 30 min provided a 25% yield of **1** together with a mixture of unidentified products.

Keywords: aureol; arenarol; marine natural product; rearrangement; domino reaction.

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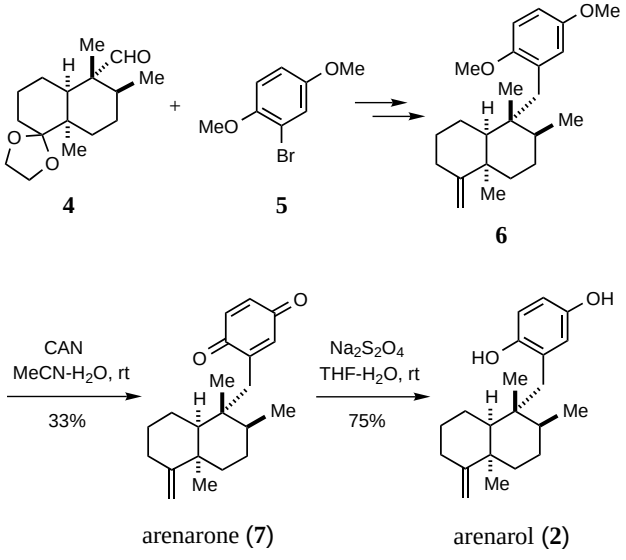
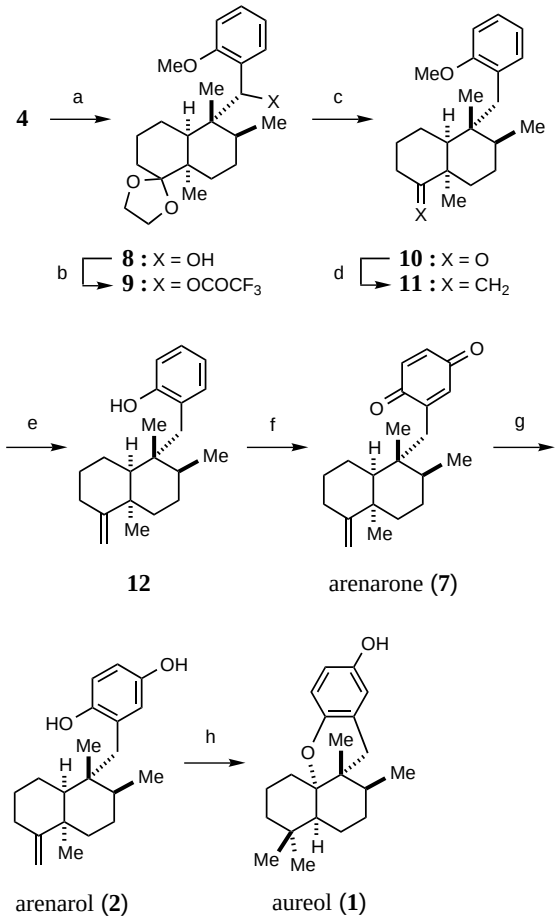
In view of the foregoing facts, development of an efficient and reliable method for obtaining aureol (**1**) in high yield is strongly desirable and useful from a pharmaceutical point of view. We have now found that arenarol (**2**) undergoes a very facile acid-promoted rearrangement in the presence of boron trifluoride etherate at low temperature, which exclusively provided **1** with complete stereoselectivity in an almost quantitative yield. In this communication, we report our preliminary results concerning the enantioselective total synthesis of **1**, which features a biogenetic-type rearrangement (**2**→**1**, Schemes 2 and 3) as the pivotal step. Recently, we have reported the enantioselective total synthesis of **2** starting from the *cis*-fused decalin derivative **4** (10% overall yield from **4** over six steps);[10] an outline of the synthetic route is depicted in Scheme 1. In this synthesis, 1-bromo-2,5-dimethoxybenzene (**5**) was employed as an aromatic synthon, and oxidative cleavage of the two methyl ether protecting groups in the intermediate **6** to deliver the corresponding quinone **7** (arenarone) was carried out by employing ceric ammonium nitrate (CAN); however, the reaction was not clean and the yield of **7** was observed to be poor (~33%).[11] In order to circumvent the problematic CAN oxidation step, we sought a potential alternative synthetic method for **2**. Herein, we also disclose an improved synthetic route to **2** (36% overall yield from **4** over seven steps) which involves salcomine [*N*,*N*′-bis(salicylidene)ethylenediiminocobalt(II)][12] oxidation of the phenolic compound **12** as the strategic step (**12**→**7**, Scheme 2).

As shown in Scheme 2, we initially pursued the synthesis of the anisole derivative **11** by employing a reaction sequence analogous to that reported previously.[10,12a] Thus, the aryllithium generated in situ by treatment of 2-bromoanisole with *n*-butyllithium was allowed to react with the known *cis*-fused decalin **4**,[10,12a] affording the coupling product **8**, mp 188–189°C, $[\alpha]_D^{20}$ −11.1° (*c* 1.01, $CHCl_3$), in 93% yield as the sole product; the stereochemistry at the benzylic carbon was not determined. Removal of both the benzylic hydroxy group and ethylene acetal function in **8** was achieved by initial formation of the corresponding trifluoroacetate **9**, $[\alpha]_D^{20}$ +19.3° (*c* 1.05, $CHCl_3$), followed by treatment under the conditions for hydrogenolysis, providing the ketone **10**, mp 84–86°C, $[\alpha]_D^{20}$ +50.6° (*c* 1.00, $CHCl_3$), in 82% yield for the two steps. Subsequent olefination of the carbonyl group in **10** was carried out by the Takai procedure[13] to furnish the *exo*-olefin **11**, mp 63–64°C, $[\alpha]_D^{20}$ +53.3° (*c* 1.03, $CHCl_3$), in 82% yield.



Scheme 1. Previous synthetic route to arenarol (**2**).



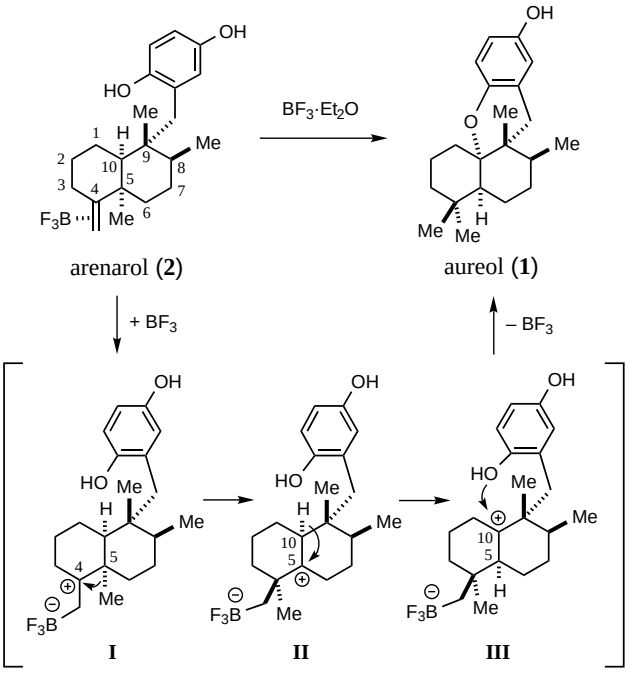
Scheme 2. Synthesis of aureol (**1**) starting from the *cis*-fused decalin **4**. *Reagents and conditions*: (a) 2-bromoanisole, *n*-BuLi, THF, −78°C; **4**, −78°C, 93%; (b) $(CF_3CO)_2O$, pyridine, 0°C, 91%; (c) H_2, 10% Pd–C, MeOH, rt, 90%; (d) CH_2Br_2, Zn, $TiCl_4$, THF, rt, 82%; (e) *n*-BuSLi, HMPA, 100°C, 84%; (f) O_2, salcomine, DMF, rt, 91%; (g) $Na_2S_2O_4$, THF–H_2O, rt, 76%; (h) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −40°C, 97%.

The next task was deprotection of the methyl ether protecting group in **11** to obtain the phenolic compound **12**, a key substrate for the following critical salcomine oxidation event. Since the *exo*-olefin moiety present in this type of decalin system is known to be labile under acidic conditions,[14] demethylation of **11** was performed by the use of a non-acidic alkylthiolate reagent. Thus, treatment of **11** with lithium *n*-butylthiolate[15] (10 equiv.) in hexamethylphosphoramide (HMPA) at 100°C for 2 h, led to the formation of **12**, $[\alpha]_D^{20}$ +49.7° (*c* 1.02, $CHCl_3$), in 84% yield.

Having obtained the phenolic compound **12** in an efficient way, our next effort was devoted to the critical construction of the quinone system to produce arenarone (**7**). Toward this end, **12** was reacted with molecular oxygen (O_2 balloon) in the presence of salcomine[12] (1.0 equiv.) in *N*,*N*-dimethylformamide (DMF) at room temperature for 2 h, which successfully gave rise to the corresponding quinone **7** (arenarone), $[\alpha]_D^{20}$ +32.0° (*c* 0.21, $CHCl_3$) [lit.,[10] $[\alpha]_D^{20}$ +31.8° (*c* 0.21, $CHCl_3$)], in 91% yield. Subsequent reaction of **7** with sodium hydrosulfite afforded the subtarget arenarol (**2**), $[\alpha]_D^{20}$ +17.1° (*c* 0.10, $CHCl_3$) [lit.,[6] $[\alpha]_D$ +19° (*c* 0.1, $CHCl_3$)], in 76% yield.

With an improved process for the synthesis of arenarol (**2**) developed, we next focused our attention on the crucial acid-promoted rearrangement of **2** to complete the synthesis of the targeted aureol (**1**). After several experiments, to our delight, the desired acid-promoted rearrangement was found to proceed effectively by treating **2** with boron trifluoride etherate (1.0 equiv.) in dichloromethane at −40°C for 3 h, which led to the formation of aureol (**1**), mp 141–142°C [lit.,[2] mp 144–145°C], $[\alpha]_D^{20}$ +65.6° (*c* 0.20, CCl_4) [lit.,[2] $[\alpha]_D$ +65° (*c* 2.0, CCl_4)], in 97% yield. The IR, ^1H and ^{13}C NMR, and MS spectra of the 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**, Fig. 1) were obtained in this rearrangement/cyclization reaction.

The remarkable stereocontrolled rearrangement/cyclization reaction of **2** leading to **1** can be rationalized by the mechanistic route shown in Scheme 3, which is essentially based on the proposed mechanism for a similar acid-catalyzed rearrangement.[7a] The reaction process would involve three possible tertiary carbocation intermediates such as **I**, **II**, and **III**. Initial coordination–activation between the Lewis acid and the *exo*-olefin functionality in **2** would lead to the intermediate **I**, which then would furnish the intermediate **II** via migration of the C-5 methyl group to the C-4 carbocation center. The intermediate **II** would undergo a 1,2-hydride shift from the C-10 position to the C-5 center at the α-face of the molecule to furnish the intermediate **III**, in which the C-10 carbocation center would be trapped by the inner phenolic hydroxy group to provide the requisite cyclized product **1** after protonolysis of the C–BF_3 bond. We believe that the sequence of this domino-type rearrangement/cyclization reaction would proceed under kinetically controlled conditions.[16]



Scheme 3. Possible reaction mechanism for the acid-promoted rearrangement of arenarol (**2**) leading to aureol (**1**).

In summary, we have succeeded in developing a facile and efficient synthetic pathway to (+)-aureol (**1**) starting from the known *cis*-fused decalin derivative **4**. The explored synthetic method features a highly stereocontrolled Lewis acid-promoted rearrangement/cyclization reaction of (+)-arenarol (**2**) as the key step. In addition, we have achieved an alternative and more efficient synthesis of (+)-arenarol (**2**) by means of salcomine oxidation methodology. Further applications of the rearrangement/cyclization strategy to the synthesis of biologically significant natural products that possess a tetracyclic benzo[*d*]xanthen skeleton containing a *cis*-fused decalin system are currently under investigation and will be reported in due course.

Acknowledgements

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