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Total Synthesis of (+)-Aureol

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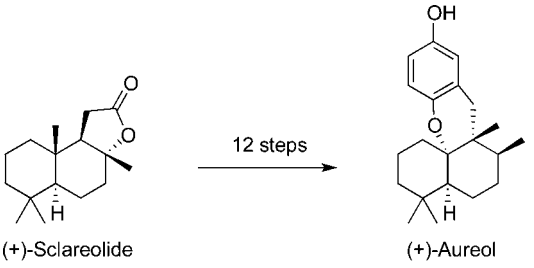
ABSTRACT



A total synthesis of the marine sponge meroterpenoid (+)-aureol has been achieved in 12 steps (6% overall yield) from (+)-sclareolide. Key steps of the synthesis include a biosynthetically inspired sequence of 1,2-hydride and methyl shifts, and a biomimetic cycloetherification reaction.

Marine sponges are a rich source of biologically active hydroquinone sesquiterpenes, such as (+)-aureol (**1**) (Figure 1). (+)-Aureol was first isolated from the Caribbean marine sponge *Smeonspongia aurea* in 1980 by Faulkner,[1] and it was also subsequently isolated from the *Verongula gigantea* marine sponge in 2000.[2] The aureol structure contains a compact tetracyclic ring system, with four contiguous stereocenters and a *cis*-relationship between the two cyclohexane rings of the decalin fragment. (+)-Aureol shows selective cytotoxicity against human tumor cells, including nonsmall cell lung cancer A549 and colon adenocarcinoma HT-29 cells.[3] It has also been shown to possess potent anti-influenza A virus activity.[4] Semisynthetic derivatives of aureol have shown promising activity against Hepa59t/VGH, KB and Hela tumor cell lines.[5] Since the isolation of (+)-aureol, a number of structurally related tetracyclic meroterpenoid natural products with similar antiviral and antitumor activities have been discovered, such as strongylin A (**2**)[6] and stachyflin (**3**).[7] Several related natural products with a *trans*-decalin structure have also been isolated, including cyclosmenospongine (**4**).[8]

(+)-Aureol has previously been synthesized by Katoh from a methyl analogue of the (−)-Wieland−Mischer ketone,[9] and (−)-aureol has recently been synthesized by Marcos from *ent*-halimic acid as a chiral pool starting material.[10] (±)-Stachyflin has been synthesized by the Shionogi research group,[11] and (+)-stachyflin has recently been synthesized by Katoh.[12] An enantioselective approach to the tetracyclic core structure of the aureol family has been reported by Cramer.[13]

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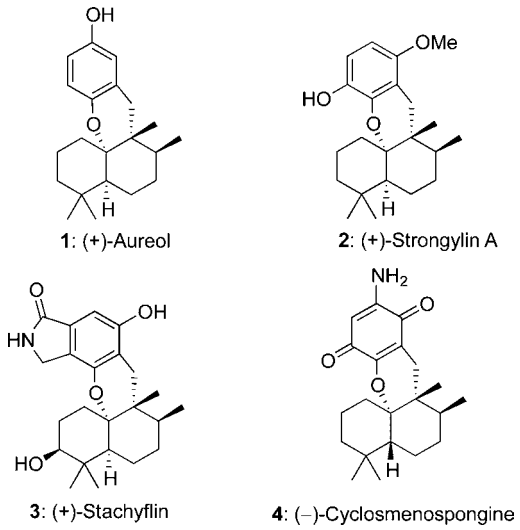
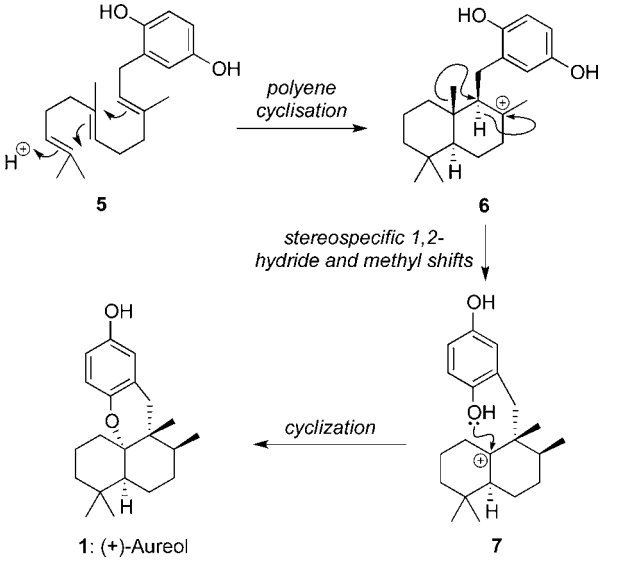


Figure 1. Representative members of the aureol family of sesquiterpenoid natural products.

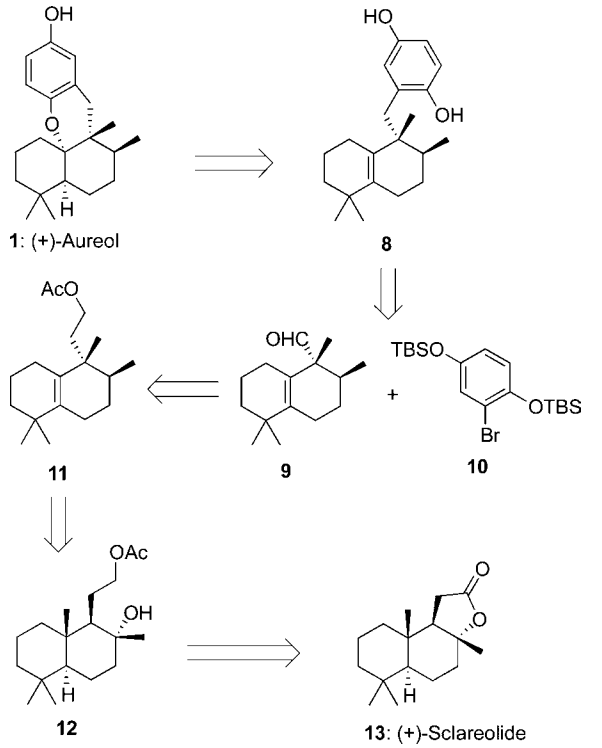
The biosynthesis of (+)-aureol (**1**) presumably involves stereoselective cyclization of polyene **5** (which could be derived from the union of farnesyl pyrophosphate and hydroquinone) to generate the tertiary carbocation **6** (Scheme 1). This carbocation could then undergo a sequence of stereospecific 1,2-hydride and methyl shifts to give a second tertiary carbocation **7**, which could be attacked by the adjacent hydroquinone to give **1**.

Scheme 1. Proposed Biosynthesis of (+)-Aureol



As part of our continuing interest in the synthesis of biologically active meroterpenoids of marine sponge origin,[14] we were interested in developing a concise synthesis of (+)-aureol (**1**). It was our intention to use the proposed biosynthesis of **1** as a guideline for our retrosynthetic analysis, as outlined in Scheme 2. We believed that **1** could be generated from the hydroquinone **8** by a biomimetic acid mediated cyclization, presumably involving the carbocation **7** as an intermediate. Compound **8** could be formed from addition of the aryllithium derived from aryl bromide **10** to aldehyde **9** followed by deoxygenation and deprotection steps. Aldehyde **9** could conceivably be obtained from **11** by a one-carbon dehomologation sequence. Acetate **11** could be derived from the tertiary alcohol **12** via a biomimetic sequence of 1,2-hydride and methyl shifts, and **12** could be formed by reduction and monoprotection of the cheap, enantiopure terpenoid starting material (+)-sclareolide (**13**).[15] Importantly, the late stage introduction of the hydroquinone motif in this strategy should allow easy access to related natural products and synthetic derivatives for further biological evaluation.

Scheme 2. Biosynthetically Inspired Retrosynthesis of (+)-Aureol



We have previously observed a related sequence of stereospecific 1,2-hydride and methyl shifts in the conversion of **14** to **15** as part of a biomimetic study of simplified labdane rearrangements (Scheme 3),[16] so we anticipated

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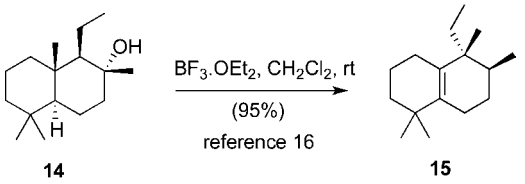
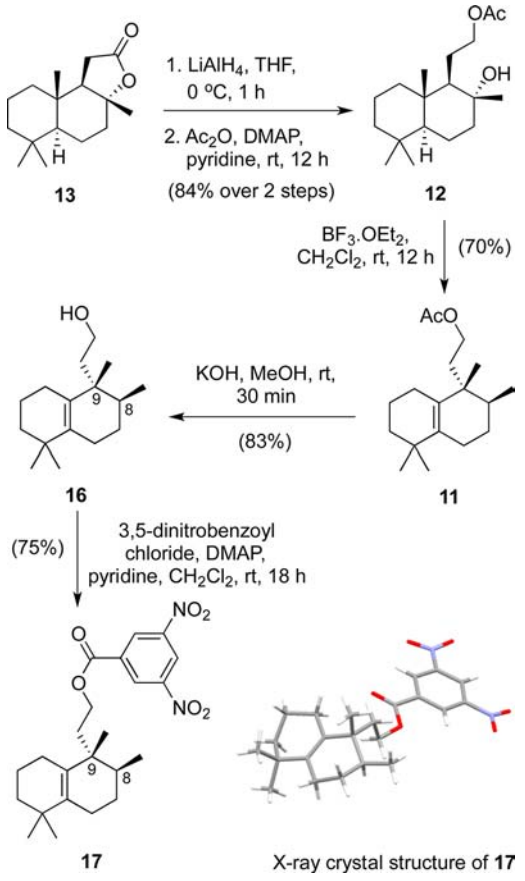
that the conversion of **12** to **11** would be possible by treatment with a strong Lewis acid.

Scheme 3. Conversion of **14** to **15** via Stereospecific 1,2-Hydride and Methyl Shifts



Our synthesis of (+)-aureol (**1**) commenced with reduction of (+)-sclareolide **13** using $LiAlH_4$ to give a diol, which was selectively protected at the primary alcohol using Ac_2O in pyridine to give the acetate ester **12** in good yield (Scheme 4).

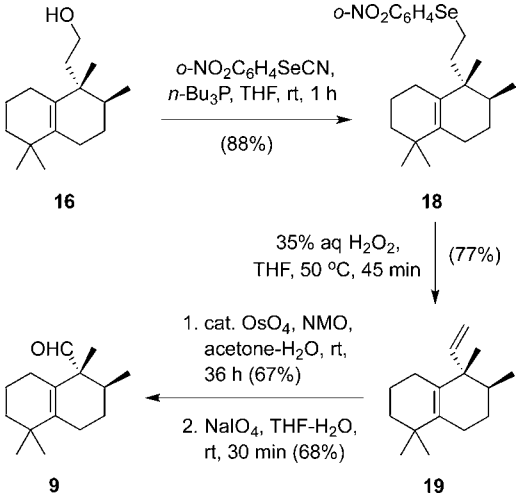
Scheme 4. Synthesis of Alcohol **16** via Stereospecific 1,2-Hydride and Methyl Shifts



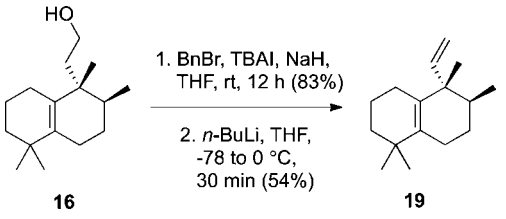
The first key step in the overall synthesis was the BF_3-mediated rearrangement of **12** to give **11**, which occurred via stereospecific 1,2-hydride and methyl shifts to generate the desired product as a single stereoisomer in 70% yield. Basic hydrolysis of acetate **11** then gave alcohol **16**. The relative stereochemistry of **16** at C-8 and C-9 was determined by single crystal X-ray crystallography of the 3,5-dinitrobenzoate derivative **17**.[17]

Synthesis of the key aldehyde intermediate **9** from **16** required the excision of one carbon atom, accomplished using a Grieco–Sharpless elimination protocol[18] followed by oxidative cleavage of the resultant terminal alkene (Scheme 5). Thus, treatment of alcohol **16** with *o*-$NO_2C_6H_4SeCN$ and *n*-Bu_3P gave **18** in 88% yield, which underwent oxidative *syn*-elimination on exposure to H_2O_2 to give alkene **19** in 77% yield. Dihydroxylation of **19** with OsO_4/NMO then gave a diol as a mixture of diastereomers that underwent oxidative cleavage with $NaIO_4$ to give aldehyde **9**. Yields for these latter two steps were modest, presumably due to the relatively hindered nature of the terminal alkene of **19**.

Scheme 5. Synthesis of Aldehyde **9** via a One-Carbon Dehomologation Pathway



Scheme 6. Alternative Synthesis of Alkene **19** via Elimination of a Benzyl Ether



The dehydration of primary alcohol **16** to give terminal alkene **19** could alternatively be achieved via a [2,3]-Wittig type fragmentation of a benzyl ether (Scheme 6). In this

(17) Crystallographic data for the structures of **17** (CCDC 881566) and **22** (CCDC 895904) have been deposited with the Cambridge Crystallographic Data Centre. Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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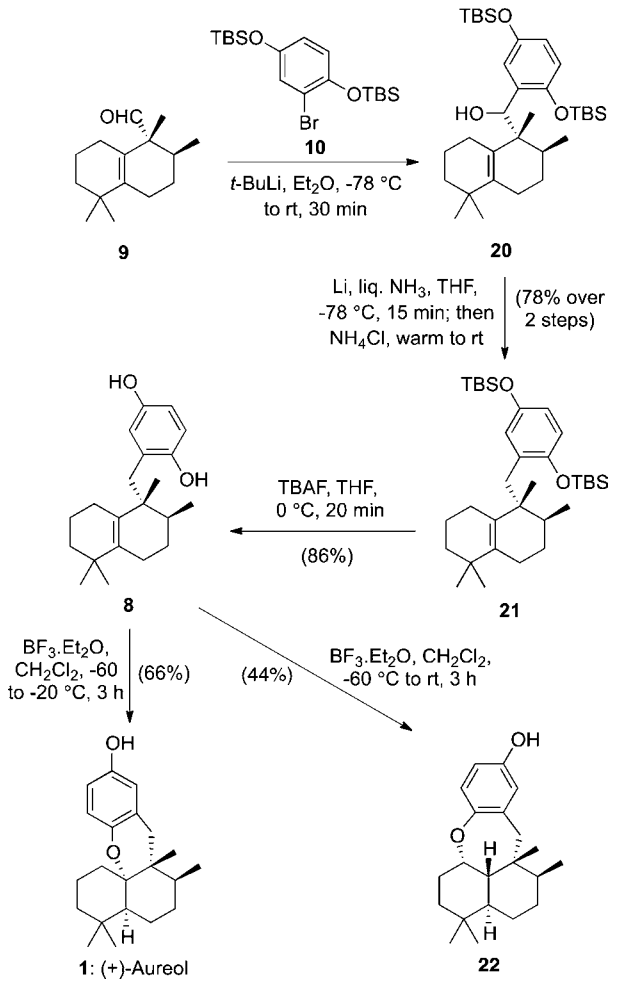
Scheme 7. Synthesis of (+)-Aureol



case, alcohol **16** was benzylated under standard conditions to give the corresponding benzyl ether in 83% yield. Treatment of this compound with 3 equiv of *n*-BuLi at −78 °C according to the procedure of Kodama furnished the terminal alkene **19** in 54% yield via sigmatropic rearrangement of a benzylic anion.[19] Although lower yielding than the Grieco−Sharpless protocol, the Komada reaction is perhaps preferable on a larger scale as it avoids the generation of stoichiometric selenium and phosphorus waste products.

Treatment of aryl bromide **10**[20] with *t*-BuLi formed an aryllithium species that was added to aldehyde **9** to give secondary alcohol **20** as a mixture of diastereomers (Scheme 7). Deoxygenation of **20** under Birch reduction conditions then gave **21** in 78% yield over the two steps. Removal of the TBS protecting groups with TBAF then gave hydroquinone **8**, which was treated with $BF_3 \cdot Et_2O$ at −60 to −20 °C to give (+)-aureol (**1**) in 66% yield for the key cyclization step. This cyclization reaction has previously been reported by Marcos for the synthesis of (−)-aureol.[10] Spectroscopic data for synthetic (+)-aureol (**1**) were identical to those of the natural compound.[1] Interestingly, when the reaction mixture was allowed to warm to room temperature, we found the rearranged 7-membered cyclic ether **22** was the major product. The structure of **22** (as proven by X-ray crystallography[17]) is similar to that of the natural product dactyloquinone C[21] and is presumably formed from carbocation **7** via a 1,2-hydride shift.

In conclusion, we have completed an efficient synthesis of (+)-aureol (**1**) in 12 steps and 6% overall yield from (+)-sclareolide (**10**). Key steps of the synthesis include a biomimetic sequence of 1,2-hydride and methyl shifts, and a biomimetic cycloetherification reaction. The overall strategy involves late stage addition of the aromatic ring system, potentially allowing access to related natural products, such as strongylin A and stachyflin, and synthetic derivatives thereof for further analysis as antiviral and antitumor agents.

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Supporting Information Available. Synthetic procedures and analytical data for compounds **1**, **8**, **9**, **11**, **12**, and **16**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.