A six-step synthetic approach to marine natural product (+)-aureol

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A six-step synthetic approach to marine natural product (+)-aureol

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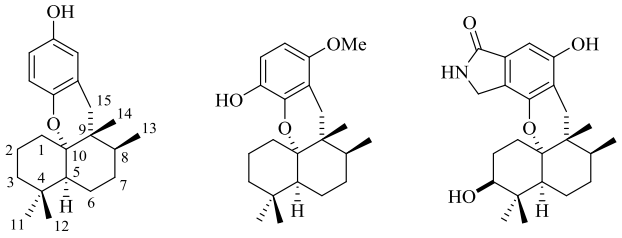
ABSTRACT

A concise synthetic approach to the marine natural product (+)-aureol has been achieved from readily available starting materials using obviously fewer steps in comparison to the related report in literature (6 steps versus 12 steps from (+)-sclareolide). Key steps of this protocol include a boron trifluoride-catalyzed domino 1,2-H and 1,2-methyl shifts and a nickel(II)-catalyzed cross-coupling reaction between an alkyl iodide and an aryl Grignard reagent.

In recent decades, more and more natural products, owing to their special chemical structures and interesting biological activities, have been isolated from marine organisms. (+)-Aureol (**1**, Figure 1) was isolated from the marine sponge *Smenospongia aurea* in 1980 by Faulkner,[1] and subsequently isolated from sponge *Verongula gigantean*[2] and *Smenospongia* sp.[3] The structure of this marine natural product has been revealed by means of extensive spectroscopic studies as well as X-ray crystallographic analysis to have a novel tetracyclic skeleton with four asymmetric carbon stereocenters. (+)-Aureol shows selective cytotoxicity against human tumor cells, including nonsmall cell lung cancer A549 and colon adenocarcinoma HT-29 cells.[4] The derivatives of (+)-aureol have shown promising activity against Hepa59t/VGH, KB and Hela tumor cell lines.[3] Besides, the structurally related (+)-strangylin A[5] (**2**, Figure 1) and (+)-stachyflin[6] (**3**, Figure 1) were reported to display similar antiviral and antitumor activities.



(+)-aureol (**1**) (+)-strongylin A (**2**) (+)-stachyflin (**3**)

Figure 1. Structures of (+)-aureol and related natural products.

The unique structural features and important biological profile of aureol-type natural products have attracted significant attention from the synthetic community.[7–11] The pioneering work on the synthesis of the marine natural product (+)-aureol (**1**) was carried out by the group of Katoh using various Wieland-Miescher ketone derivatives as the starting materials,[8] such as (+)-Wieland-Miescher ketone analogue **4** (Scheme 1a).[8a] George reported an elegant twelve-step synthesis of (+)-aureol (**1**) via the key aldehyde intermediate **7**, which was prepared from the cheap, enantiopure terpenoid starting material (+)-sclareolide (**6**) in 8 steps (Scheme 1b).[9] Marcos described a seminal synthesis of the enantiomer of the natural (+)-aureol (**1**) in 15 steps with the use of *ent*-halimic acid (**8**) as a chiral pool starting material (Scheme 1c).[10] Recently, Rosales and Oltra reported an impressive eight-step synthesis of (±)-aureol (**1**) via the key tetrasubstituted olefin intermediate **11**, which was prepared from epoxy-farnesol in 6 steps (Scheme 1d).[11] Various skeletal rearrangement reactions were involved in these synthetic protocols owing to their unrivalled power to form multiple bonds in a single operation. However, it is still a challenge to develop a facile and efficient skeletal rearrangement reaction for a step-economical synthesis of (+)-aureol (**1**) from commercially available starting materials. In connection with our consistent interest towards the development of concise strategies for the synthesis of bioactive compounds,[12] herein we report a six-step synthetic approach to the marine natural product (+)-aureol (**1**) from readily available and inexpensive starting material (+)-sclareolide (**6**) via the key intermediate **12** (Scheme 1e). The concise synthetic approach could be used for the preparation of sufficient quantity of this marine natural product for biological and medical studies.

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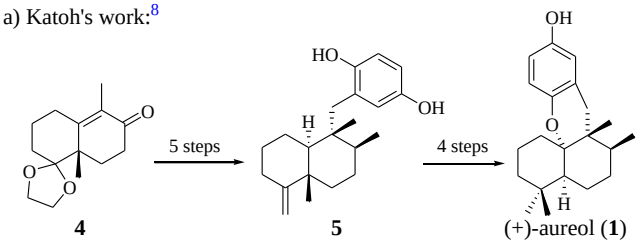
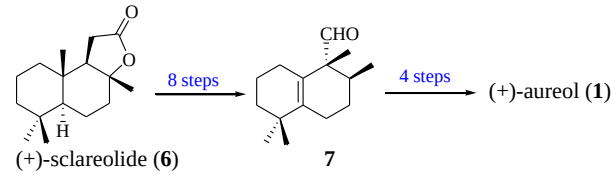
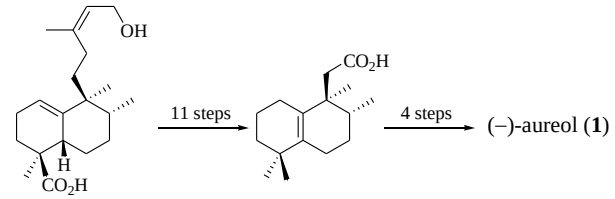
a) Katoh's work:[8]



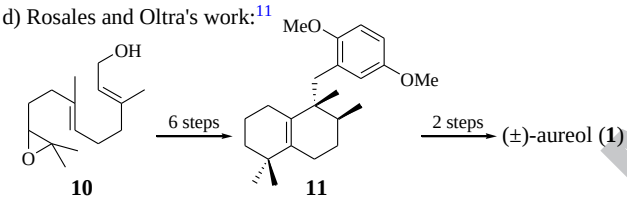
b) George's work:[9]



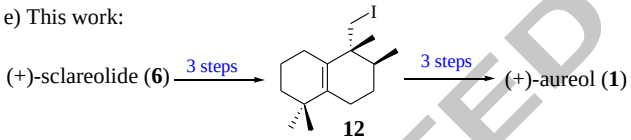
c) Marcos' work:[10]



d) Rosales and Oltra's work:[11]

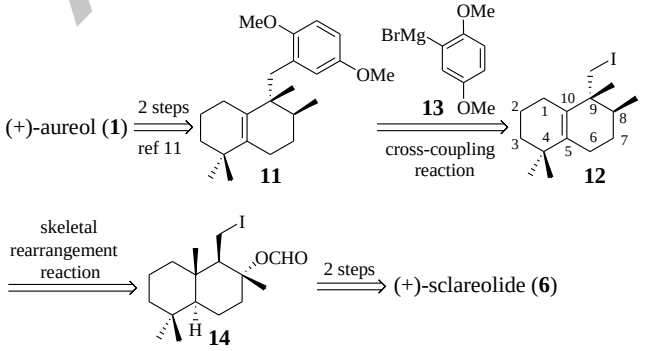


e) This work:



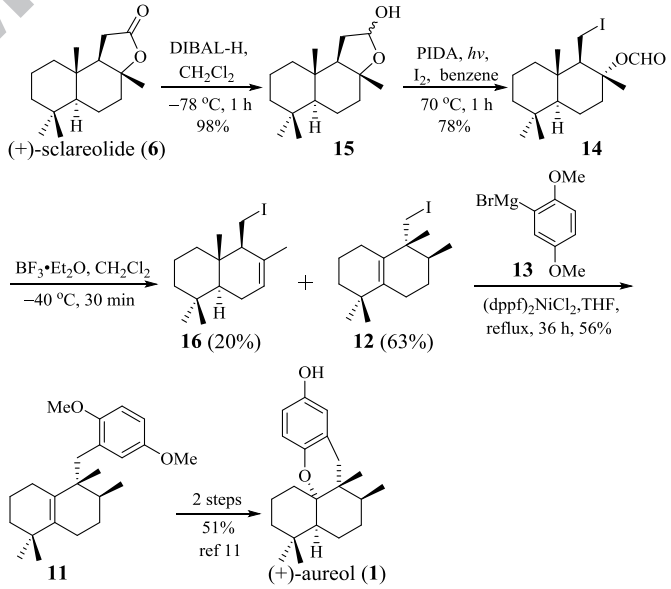
Scheme 1. Synthesis of aureol (**1**).

Our retrosynthesis of (+)-aureol (**1**) is outlined in Scheme 2. (+)-Aureol (**1**) could be synthesized from olefin **11** in two known steps.[11] Olefin **11** was thought to be prepared by the cross-coupling reaction between alkyl iodide **12** and aryl Grignard reagent **13**.[13] The key intermediate **12** was planned to be constructed by the skeletal rearrangement reaction of drimanal iodoformate **14** via regioselective and stereoselective 1,2-H and 1,2-methyl shifts. Drimanal iodoformate **14** would be prepared from readily available (+)-sclareolide (**6**) in two known steps.[14] We report herein the realization of this strategy by developing a six-step synthetic approach to (+)-aureol (**1**).



Scheme 2. Retrosynthesis of (+)-aureol (**1**).

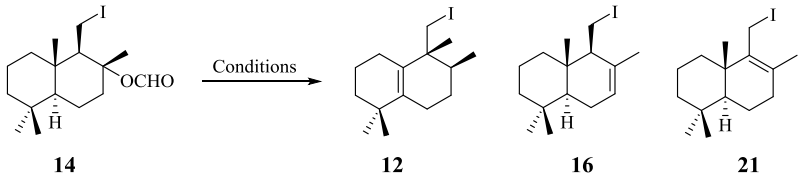
As shown in Scheme 3, the synthesis of (+)-aureol (**1**) commenced with commercially available sclareolide (**6**). Reduction of (+)-sclareolide (**6**) using diisobutylaluminium hydride (DIBAL-H) gave the sclaral **15**, which upon exposure to the hypoiodite-mediated C−C bond cleavage conditions of Suárez (PIDA/I_2/*hv*) delivered drimanal iodoformate **14** in 76% overall yield.[14] We envisaged then to achieve the skeletal rearrangement reaction of drimanal iodoformate **14** mentioned in Scheme 2. After much experimentation (Table 1), this tandem reaction was realized by treatment of drimanal iodoformate **14** with 200 mol % of BF_3·Et_2O in dichloromethane at –40 °C for 30 minutes to afford the desired alkyl iodide **12** and by-product **16** in 63% and 20% yields, respectively (Scheme 3). Subsequently, the potential skeletal rearrangement reaction of by-product **16** to alkyl iodide **12** has been extensively studied but failed nevertheless.[15] With alkyl iodide **12** in hand, the cross-coupling reaction between alkyl iodide **12** and aryl Grignard reagent **13** was subsequently investigated. The optimization of reaction parameters by varying the catalysts [(dppf)$NiCl_2$, (dppf)$NiCl_2$/$ZnCl_2$, $Pd_2(dba)_3$, $Pd(PPh_3)_4$], the temperature (r.t., 40 °C, 60 °C, 68 °C) and the solvents (THF, dioxane, toluene) allowed us to identify the optimum reaction conditions. Thus, the cross-coupling reaction of alkyl iodide **12** and aryl Grignard reagent **13** was realized in the presence of (dppf)$NiCl_2$ (10 mol %) in THF under reflux for 36 hours to afford the key tetrasubstituted olefin intermediate **11** in 56% yield (Scheme 3). As olefin **11** is an advanced intermediate in the Rosales and Oltra's total synthesis of aureol,[11] our work described herein constitutes a formal synthesis of (+)-aureol (**1**, Scheme 3).



Scheme 3. Synthesis of (+)-aureol (**1**) from (+)-sclareolide (**6**).

The BF_3·Et_2O-promoted stereospecific skeletal rearrangement reaction of drimanal iodoformate **14** to alkyl iodide **12** as well as the formation of by-products **16** and **21** could be understood by the possible reaction mechanisms shown in Scheme 4. Intermediate **17** was likely to be formed when drimanal iodoformate **14** was treated with 200 mol % of BF_3·Et_2O. The HCOO group of drimanal iodoformate **14** was activated by the Lewis acid BF_3·Et_2O, and thereby left to form carbocation intermediate **18**. Since the cleavage of a C-H bond is usually easier than that of a C-C bond, the 9-hydrogen, in this case, had a higher migratory aptitude than the 9-alkyl group. The configuration of C9 facilitated a 1,2-H shift on the α-face of the carbocation intermediate **18** to form carbocation intermediate **19** (rout *a*, Scheme 4). Subsequently, the configuration of C10

Table 1 Conditions of rearangement of compound **14**

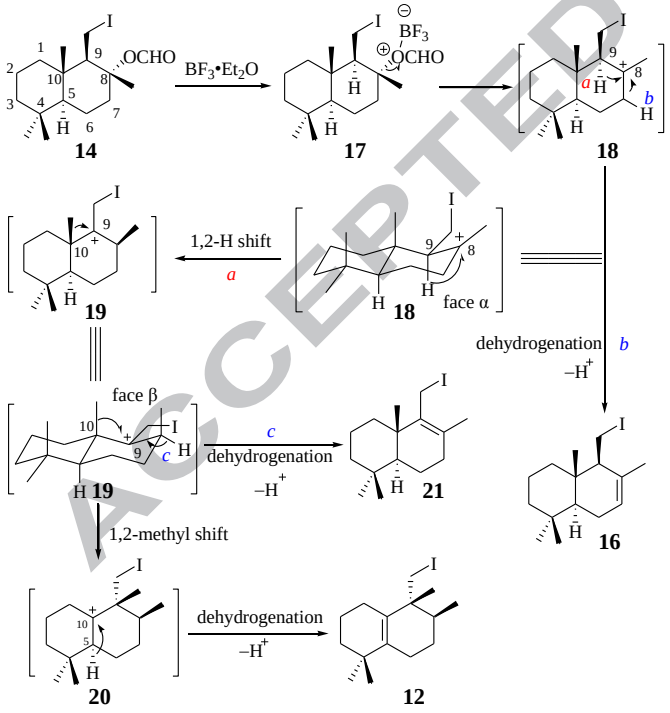


14 **12** **16** **21**

Entry	**14**	Conditions	Yied (%)[a]		
			12	**16**	**21**
1	1.0 equiv	BF_3•Et_2O (2.0 equiv), DCM, -78 °C, 2 h	--	--	85
2	1.0 equiv	BF_3•Et_2O (2.0 equiv), DCM, -60 °C, 2 h	--	13	73
3	1.0 equiv	BF_3•Et_2O (2.0 equiv), DCM, -40 °C, 0.5 h	63	20	--
4[b]	1.0 equiv	BF_3•Et_2O (2.0 equiv), DCM, -20 °C, 0.5 h	18	7	--
5	1.0 equiv	BF_3•Et_2O (2.0 equiv), DCM, 0 °C, 0.5 h	9	4	--
6	1.0 equiv	$SnCl_4$ (2.0 equiv), DCM, -40 °C, 0.5 h	--	--	57
7	1.0 equiv	$AlCl_3$ (2.0 equiv), DCM, -40 °C, 0.5 h	21	--	15
8[c]	1.0 equiv	$TiCl_4$ (2.0 equiv), DCM, -40 °C, 0.5 h	--	--	--
9	1.0 equiv	$FeCl_3$ (2.0 equiv), DCM, -40 °C, 0.5 h	--	78	--
10	1.0 equiv	HCl (2.0 equiv), DCM, -40 °C, 0.5 h	--	72	--

[a] Isolation yeild. [b] Most of the reagent degraded. [c] The reagent degraded.

facilitated a 1,2-methyl shift on the β-face of the carbocation intermediate **19** to form carbocation intermediate **20**, which underwent a dehydrogenation process to afford the desirable alkyl iodide **12** (Scheme 4). On the other hand, the carbocation intermediates **18** and **19** underwent a dehydrogenation process to generate by-products **16** and **21**, respectively (routs *b* and *c*, Scheme 4).



Scheme 4. Proposed reaction mechanisms for the formation of alkyl iodide **12**, and by-products **16** and **21**.

In summary, we described a newly developed BF_3·Et_2O-promoted highly selective skeletal rearrangement reaction of drimanal iodoformate to the corresponding alkyl iodide, which is employed to a facile and step-economical formal synthesis of the marine natural product (+)-aureol from readily available and inexpensive starting materials using obviously fewer steps in comparison to the related report in literature (6 steps versus 12 steps from (+)-sclareolide). This highly regioselective and stereoselective skeletal rearrangement reaction, as well as a nickel(II)-catalyzed cross-coupling reaction between an alkyl iodide and an aryl Grignard reagent could facilitate the preparation of sufficient quantity of this marine natural product for biological and medical studies. Further applications of these strategies for the synthesis of other bioactive natural products with related skeletons are under investigation, and will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.xxx. These data include experimental procedures, characterization data, and copies of NMR spectra (^{1}H NMR and ^{13}C NMR) of the most important compounds described in this article.

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Graphical Abstract

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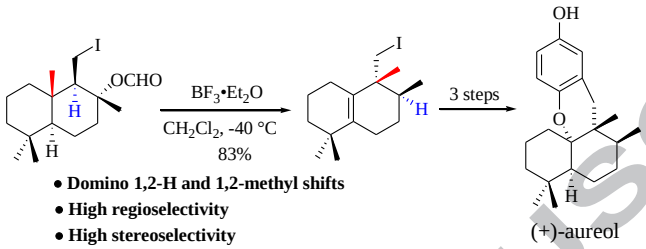

1. Highly regioselective and stereoselective skeletal rearrangement reaction;
2. Readily available and inexpensive starting material;
3. Step-economical synthetic approach to the marine natural product (+)-aureol.