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Enantioselective Total Synthesis and Assignment of the Absolute Configuration of the Meroterpenoid (+)-Taondiol

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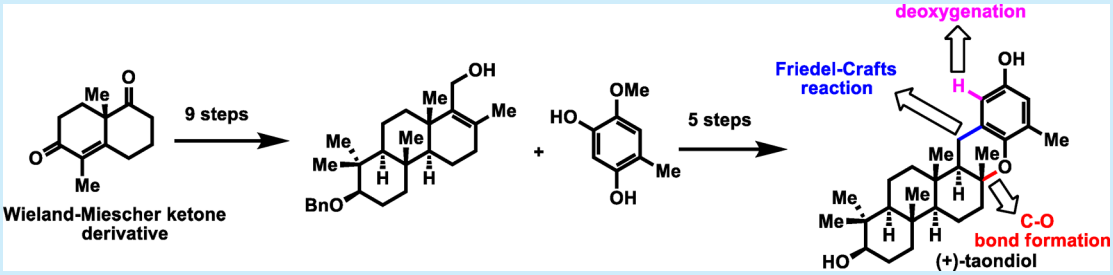
Supporting Information



ABSTRACT: The first enantioselective total synthesis of (+)-taondiol, a pentacyclic marine meroterpenoid, has been achieved, which in addition to confirming the structure also established the absolute configuration of the natural product. The notable points in the synthetic route are synthesis of a highly functionalized tricyclic diterpenoid moiety starting from an enantiopure Wieland−Miescher ketone derivative in concise manner via Robinson-type annulation and an elegant hydrogen atom transfer olefin reduction followed by Lewis acid-catalyzed Friedel−Crafts reaction for one-pot C−C and C−O bond formations resulting in construction of the pentacyclic meroterpenoid skeleton.

Marine algae are microorganisms that act as potential sources of highly bioactive secondary metabolites possessing different skeletal structures and varied biological activities. These algal metabolites represent a class of meroterpenoids owing to their core structure of the fused polycyclic diterpene part with an aromatic ring. *Stypopodium zonale* is one such marine brown algae found abundantly in the Western Caribbean Sea. It acts as a source of various pentacyclic algal metabolites such as stypoldione (**1**), stypodiol (**2**), etc., which constitute a unique and interesting polycyclic diterpene benzoquinone moiety as their backbone. The *Stypopodium* family possesses an unusual spiro-*o*-benzoquinonefuran carbon skeleton. Taondiol (**3**) is a structural congener of the *Stypopodium* family comprising a benzopyran moiety as the only skeletal exception (Figure 1). These marine alkaloids are known to show ichthyotoxic and cytotoxic activities. Taondiol is known to exhibit distinct lethargic behavior and narcosis at 10 μg/mL levels. Taondiol was isolated by Gonzalez et al. from marine alga *Taonia atomaria* in 1971 where upon extensive studies it was found to be (−)-taondiol (**3**).[2] In the year 1980, Fenical and his group, while continuing their research on algal metabolites from *Stypopodium zonale*, also isolated taondiol which was shown to be an optical antipode of that previously reported by the Gonzalez group.[1b] Thus, it was postulated that both the enantiomers (−)-taondiol (**3**) and (+)-taondiol (**4**) are naturally occurring, differing in their source of marine algae. *Stypopodium zonale* also constitutes other stereoisomers of taondiol such as epitaondiol (**5**),[3] isotaondiol (**6**),[4] etc. Although there are a couple of reports in the literature for the total[5] synthesis and a formal[6] synthesis of

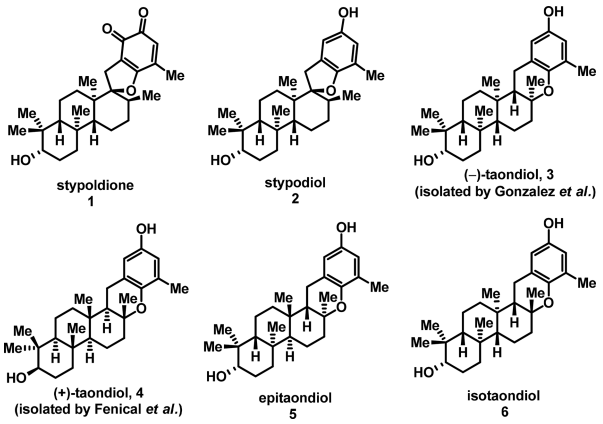


Figure 1. Algal meroterpenoids.

stypoldione (**1**), there is only a single report directed toward the biomimetic synthesis of DL-taondiol via acid-mediated polyene cyclization of epoxide of the geranylgeranyl derivative of toluquinol by Kitahara et al. in 1973.[7] The major drawback of their synthesis was the reaction yield of only 2% for the final key polyene cyclization step. Therefore, a more efficient method for the total synthesis of taondiol is desirable. Until now, there were no reports on the enantioselective total synthesis of taondiol, and hence its absolute configuration is also unknown.

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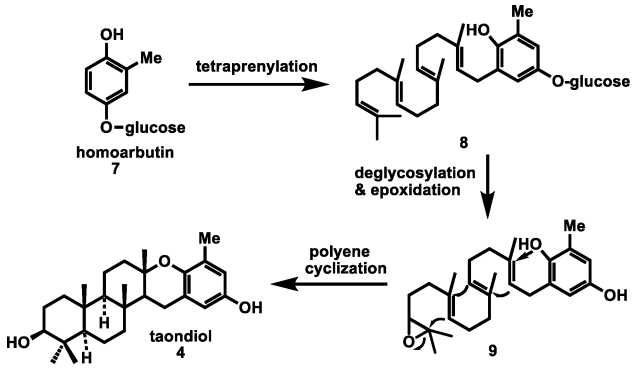
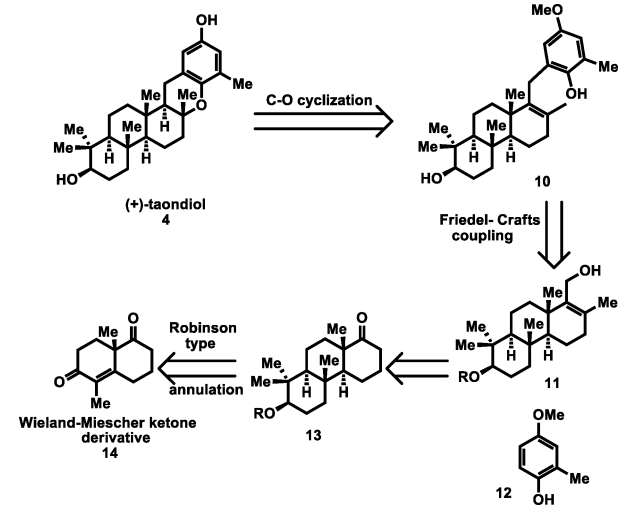
The biosynthesis of taondiol (**4**) has been proposed to occur via tetraprenylation of homoarbutin **7** followed by deglycosylation and selective epoxidation to obtain the deglycosylated intermediate **9**. The taondiol structure was obtained after opening of the epoxide followed by polyene cyclization (Scheme 1).[8]

Scheme 1. Proposed Biosynthesis of Taondiol



Herein, we report the first enantioselective total synthesis of (+)-taondiol (**4**), which not only confirmed the stereostructure but also established the absolute configuration of the meroterpenoid. A quick analysis of the taondiol skeleton revealed a fusion of a polycyclic diterpene moiety with a suitably substituted aromatic ring. Based on our analysis, a synthetic strategy for (+)-taondiol (**4**) was envisaged to happen via C−O cyclizaton of the intermediate **10** to form the pyran ring. Compound **10** could be synthesized by a Friedel−Crafts reaction[9] between terpenoid **11** and quinol derivative **12** (Scheme 2). The terpenoid moiety **11**, the most challenging

Scheme 2. Retrosynthetic Analysis



part of the synthesis, could be obtained from enantiopure Wieland−Miescher ketone derivative **14** by Robinson-type annulation followed by a few functional group transformations.

To consummate the total synthesis of (+)-taondiol (**4**), synthesis of the polycyclic diterpene moiety (**11**) was taken as a preliminary target. As per retrosynthetic analysis, it was envisaged that tricyclic compound **13** could be a viable intermediate to obtain the tricyclic terpenoid moiety **11** after sequential functionalizations, and hence we focused majorly on devising an elegant route to synthesize the tricyclic ketone **13**. The synthetic sequence was commenced by a selective ketal protection of the Wieland−Miescher ketone derivative **14** using ethylene glycol. A Robinson-type annulation was then effected on the bicyclic part to attain the tricyclic diterpene structure. Thermodynamically controlled alkylation using 1-chloro-3-pentanone/KO^{t}Bu followed by an intramolecular aldol condensation delivered enone **15**[10] in 83% yield (over 2 steps). To carry forward with functionalizations on the tricyclic compound, reductive methylation on enone **15** was carried out using Li/NH_3 and MeI to furnish ketone **16** in 80% yield. LAH reduction on **16** followed by benzylation of the alcohol, thus generated, provided the tricyclic benzyl compound **17** which was further subjected to acid-mediated deketalization to generate **18** in 90% yield. The next motive was to achieve the desired compound **13** by reduction of the olefinic part in **18**. The usual hydrogenation procedure using a H_2 balloon and Pd/C rendered reduction of olefin, but not surprisingly an unwanted debenzylation was also observed. Hence, a different method was foreseen to affect olefin reduction without undergoing debenzylation. A thorough literature study revealed Shenvi's elegant method of hydrogen atom transfer (HAT) using Mn catalyst and phenylsilane as an efficient route for olefin reduction providing trans stereochemistry at the decalin ring junction,[11] which was quintessential for our total synthesis. Henceforth, the requisite ketone **13** was attained in 80% yield by following Shenvi's protocol using $Mn(dpm)_3$, TBHP, and phenylsilane with delightfully no trace of debenzylated product. Advancing further, α-methylation of the ketone **13** was then carried out using LDA/MeI, followed by epimerization at the newly generated stereocenter by treatment with NaOMe in methanol to get the single diastereomer of **19** in 80% yield. The penultimate step was Nozaki−Yamamoto homologation[12] on ketone **19** to obtain the unsaturated aldehyde **20** which upon Luche reduction[13] furnished the required tricyclic alcohol **11** in 57% yield (over 2 steps) (Scheme 3).

After acquiring the diterpene compound **11** in gram quantity, we proceeded further toward the total synthesis of taondiol.

In our prior discussion, taondiol **4** was envisioned to be achievable after C−O cyclization of the intermediate **10**. Therefore, to generate the intermediate **10**, Lewis acid catalyzed Friedel−Crafts reaction between the diterpene moiety **11** and quinol **12** was executed using $BF_3{\cdot}OEt_2$. Unfortunately, the coupling reaction did not happen as expected, and rather elimination of allylic alcohol was observed as the only product. Herein, we reasoned the failure of the Friedel−Crafts coupling reaction might be due to inadequate nucleophilicity at the required position on the aromatic ring. It was anticipated that introduction of an extraneous hydroxy group onto the aromatic ring might enhance the nucleophilicity at the required carbon. Later, deoxygenation of the extra hydroxy group would deliver the required pentacyclic taondiol skeleton. The considered aromatic ring **23** with rightful substitutions was thus obtained via sequential functionalization and deprotection on trimethoxybenzene **21** (Scheme 4). Therefore, the synthesis of **23** was initiated with Vilsmeir−Haack reaction on trimethoxybenzene **21** that provided the trimethoxy benzaldehyde **22** in 80% yield. Next, selective demethylation of **22** was performed using $AlCl_3$ which was followed by reduction of the aldehyde group by $NaCNBH_3$ to render **23** in 75% yield (over 2 steps).

As conceptualized, to our delight, Friedel−Crafts reaction of hydroxyquinol **23** with diterpenoid **11** using $BF_3{\cdot}OEt_2$ directly furnished a pentacyclic meroterpenoid core **24** by sequential

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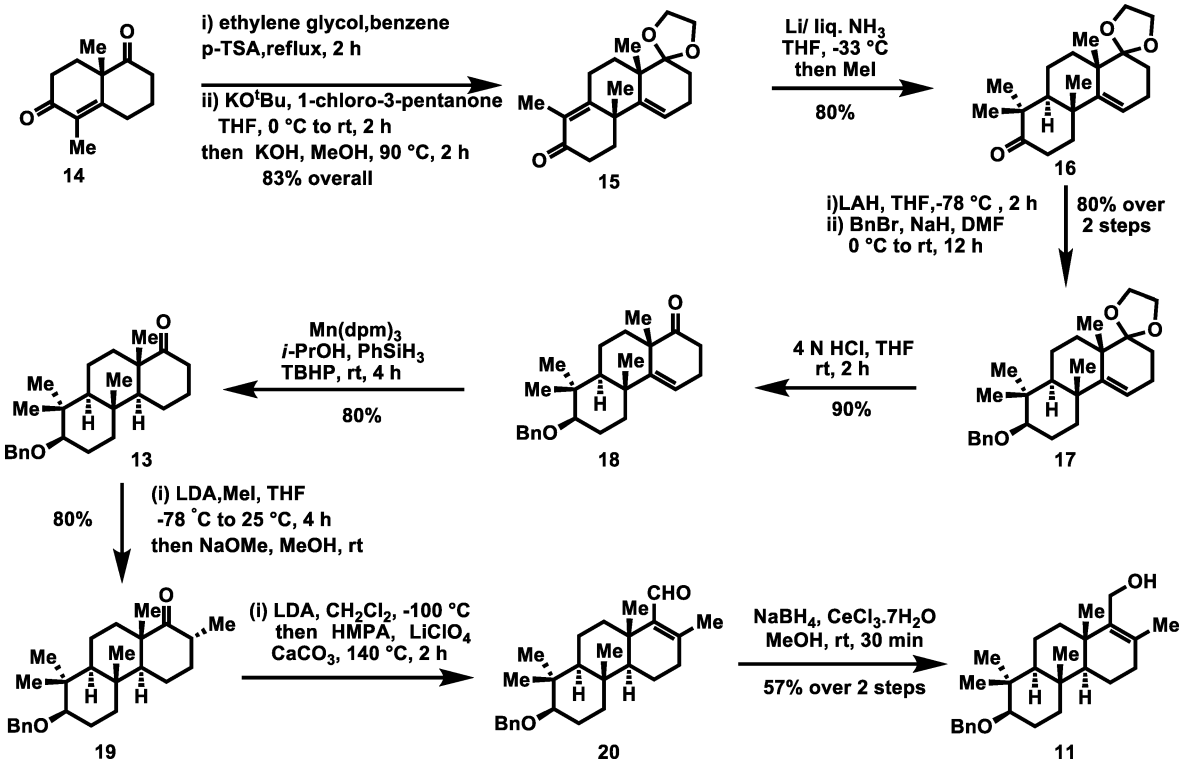
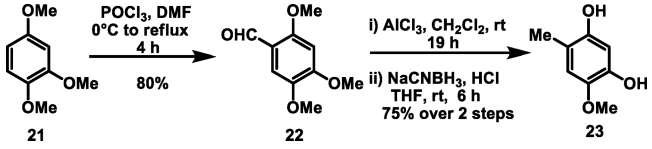
Scheme 3. Synthesis of Tricyclic Alcohol (11)

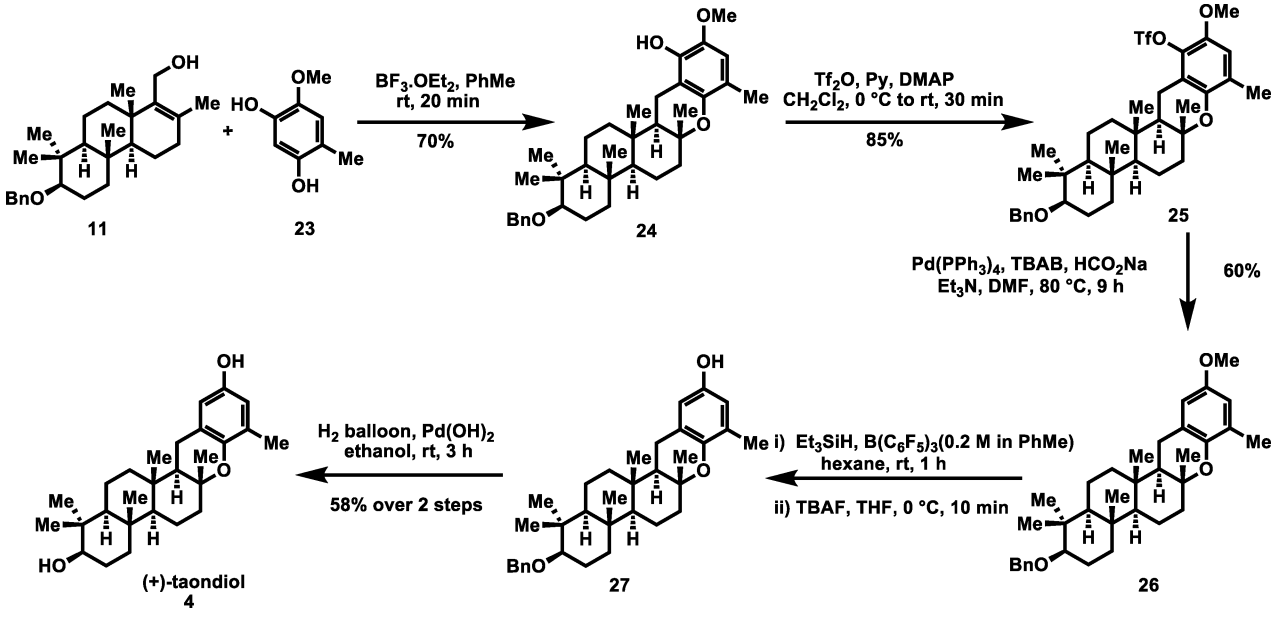


Scheme 4. Synthesis of the Aromatic Ring



C−C and C−O bond formation in 70% yield (Scheme 5). A notable observation of the reaction was the selective cyclization at the olefin through the desired hydroxy group. This could be attributed to the intramolecular hydrogen bonding between the other hydroxy and its adjacent methoxy group that averts its participation in the cyclization reaction. Deoxygenation of **24** was carried out by converting the hydroxy into triflate using triflic anhydride to get the triflate **25** in 85% yield, followed by $Pd(PPh_3)_4$-catalyzed reduction of triflate to obtain **26** in 60% yield. The next step was demethylation of the methoxy in **26**. Unfortunately, the usual methods of demethylation by BBr_3, BCl_3, and EtSH/NaH failed to provide the required demethylated product. Gratifyingly, after a literature survey

Scheme 5. Total Synthesis of (+)-Taondiol (4)



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for other methods, we achieved demethylation upon implementing Yamamoto's method by using $B(C_6F_5)_3$ and triethylsilane[14] to get the silyl ether and then deprotection of the silyl ether with TBAF to generate the desired demethylated product **27**. Finally, hydrogenolysis of **27** using H_2 and $Pd(OH)_2$ delivered (+)-taondiol (**4**) in 58% yield (over 2 steps) whose physical and spectral data were in agreement to those previously reported by isolation groups.[1b−d,2]

In conclusion, the first enantioselective total synthesis of (+)-taondiol (**4**) has been achieved in 14 steps as the longest linear sequence with 3.1% overall yield along with confirmation of the stereostructure and absolute configuration. The key features of the synthesis include the concise method for attaining the polycyclic diterpene moiety from the enantiopure Wieland−Miescher ketone derivative and the Lewis acid-catalyzed Friedel−Crafts coupling to create a pentacyclic core structure, which we anticipate will provide a gateway to deliver several natural products with similar polycyclic skeleton.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00997.

Experimental procedures and spectral data for all the compounds (PDF)

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Notes

The authors declare no competing financial interest.

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