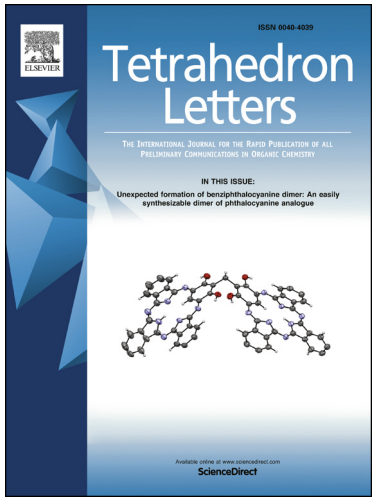

Total synthesis of greensporone C

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Total synthesis of greensporone C

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ABSTRACT

The first total synthesis of greensporone C, a cytotoxic 14-membered resorcylic acid lactone, has been accomplished *via* a longest linear sequence of 16 steps in 3.3% overall yield. The key features of the synthesis include Mitsunobu esterification and ring-closing metathesis to construct the macrocycle and establish the (*E*)-olefin geometry, respectively. Our synthesis also confirmed the absolute stereochemistry of the natural product.

Keywords:

Greensporone C

Resorcylic acid lactone

Total synthesis

Ring-closing metathesis

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Resorcylic macrolides are a group of fungal polyketide metabolites, consisting of 14-membered □-resorcylic acid lactone (RAL) derivatives, that possess diverse biological activities[1] including cytotoxic,[2] antifungal,[3] and antimalarial[2,4] properties as well as inhibitory effects against ATPases and kinases.[5] A subgroup of these RALs are those containing a ketone functional group at the 10-position, which are radicicol[6] derivatives. This group of metabolites has been shown to exhibit significant and promising biological activities.[7-10] Greensporone C (**1**) is a new 14-membered resorcylic acid lactone which was isolated, along with 13 other RALs, from a culture of the freshwater aquatic fungus *Halenospora* sp. by Oberlies and co-workers in 2014 (Fig. 1).[11] This series of metabolites represent rare examples of RALs containing resorcylic acid monomethyl ethers with non-chelated hydroxyl groups. Structurally, greensporone C possesses only one stereogenic center at the 2 position. The absolute configuration of the C2 stereogenic center of **1** and other co-metabolites in the series was proposed to be *S* based on X-ray diffraction analysis of the bromobenzoyl derivative of one of the analogues as well as Mosher's ester analyses of those containing C5 alcohol stereogenic centers. Additionally, greensporone C exhibited potent cytotoxicity against the MDA-MB-435 (melanoma) and HT-29 (colon) cancer cell lines with IC_{50} values of 2.9 and 7.5 □M, respectively. In order to prove the stereochemistry of the natural product and due to potential biological activities of this group of macrolides, we set out a synthetic program aimed at such compounds. Herein, we report the total synthesis of greensporone C.

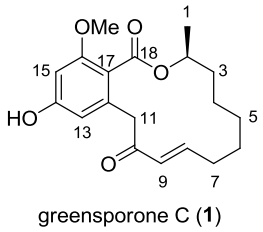
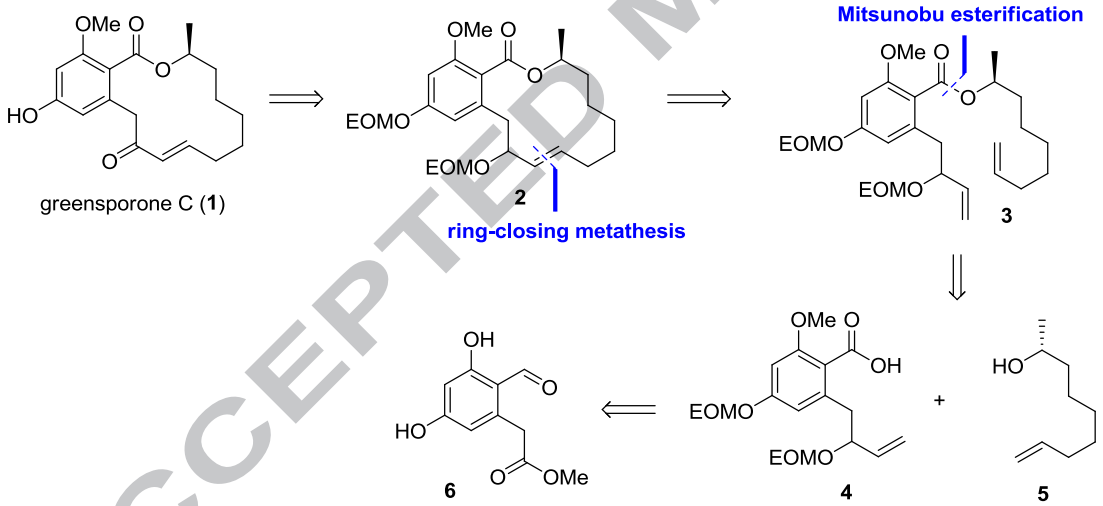


Figure 1. Structure of greensporone C (**1**).

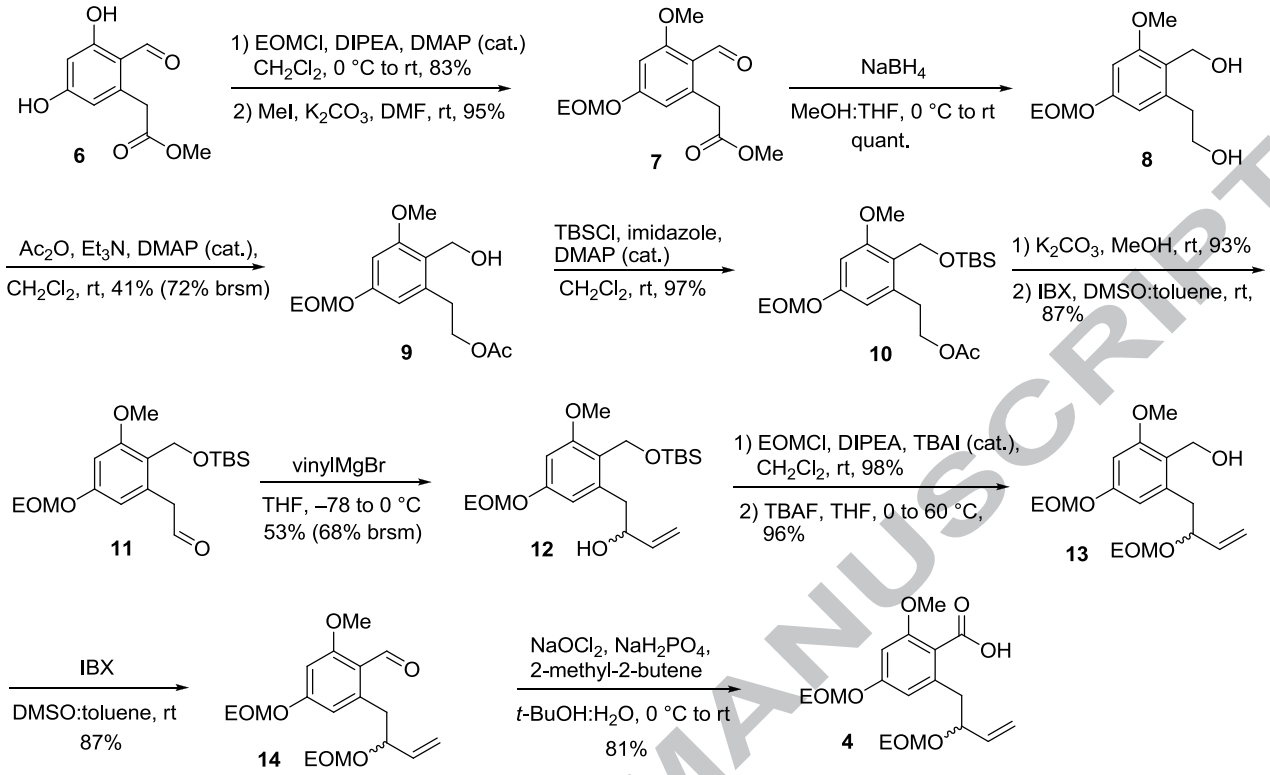
The retrosynthetic approach towards greensporone C is illustrated in Scheme 1. Compound **1** would be derived from macrocycle **2** *via* oxidation. Ring-closing metathesis (RCM) was envisioned as the key macrocyclization strategy to establish the (*E*)-geometry of the C8–C9 olefin. The RCM diene precursor **3** would be united by Mitsunobu esterification of the two key fragments: benzoic acid derivative **4** and (*R*)-non-8-en-2-ol (**5**). The requisite benzoic acid **4** could be elaborated from known phenol **6**.



Scheme 1. Retrosynthesis of greensporone C (**1**).

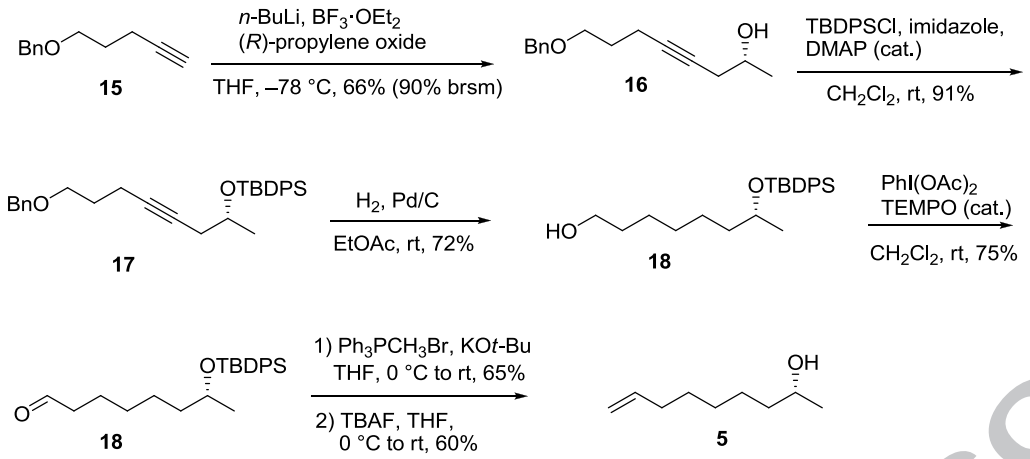
The synthesis of benzoic acid derivative **4** commenced with selective monoprotection of phenol **6**[12] with the ethoxymethyl (EOM) group, followed by methylation of the remaining hydroxyl group using iodomethane and K_2CO_3 in DMF (Scheme 2). Reduction of both the aldehyde and ester functional groups in **7** was accomplished using excess $NaBH_4$ in MeOH to give diol **8**. It should be noted that the

reduction strategy to manipulate the oxidation states of the two carbonyl groups was chosen in order to circumvent facile lactonization during the course of the synthesis. Selective acetylation of the presumably less sterically hindered hydroxyl group of **8** using acetic anhydride (1 equiv.) resulted in the formation of monoacetate **9** in 72% yield based on the recovered diol. Protection of the other hydroxyl group with *t*-butyldimethylsilyl chloride (TBSCl) furnished silyl ether **10** in 97% yield. Conversion of **10** to the corresponding aldehyde **11** was achieved in two high-yielding steps: removal of the acetate group by methanolysis (K_2CO_3, MeOH) to reveal the 1° alcohol, followed by IBX oxidation. Addition of vinylmagnesium bromide to aldehyde **11** gave racemic allylic alcohol **12** in moderate yield (68% based on recovered aldehyde). The stereoselectivity of this step was inconsequential since the newly generated alcohol chiral center would eventually be oxidized to a ketone. Attempts to reduce the number of synthetic steps by removal of the TBS group and simultaneously oxidizing both alcohols failed and resulted in formation of the undesired lactol, possibly due to the higher reactivity of the benzylic alcohol compared to allylic alcohol in this substrate. Thus, we proceeded to protect the allylic alcohol with the EOM group using a large excess of EOMCl and DIPEA in the presence of catalytic tetrabutylammonium iodide (TBAI) to give the corresponding EOM ether in 98% yield.[13] Subsequent removal of the TBS protecting group using TBAF smoothly delivered benzylic alcohol **13** in 96% yield. Finally, IBX oxidation of **13** gave the benzaldehyde derivative **14** in 87% yield. Further oxidation of **14** under Pinnick oxidation conditions afforded the desired benzoic acid **4** in 81% yield after careful acidic workup to avoid undesired deprotection of the EOM groups.



Scheme 2. Synthesis of benzoic acid **4**.

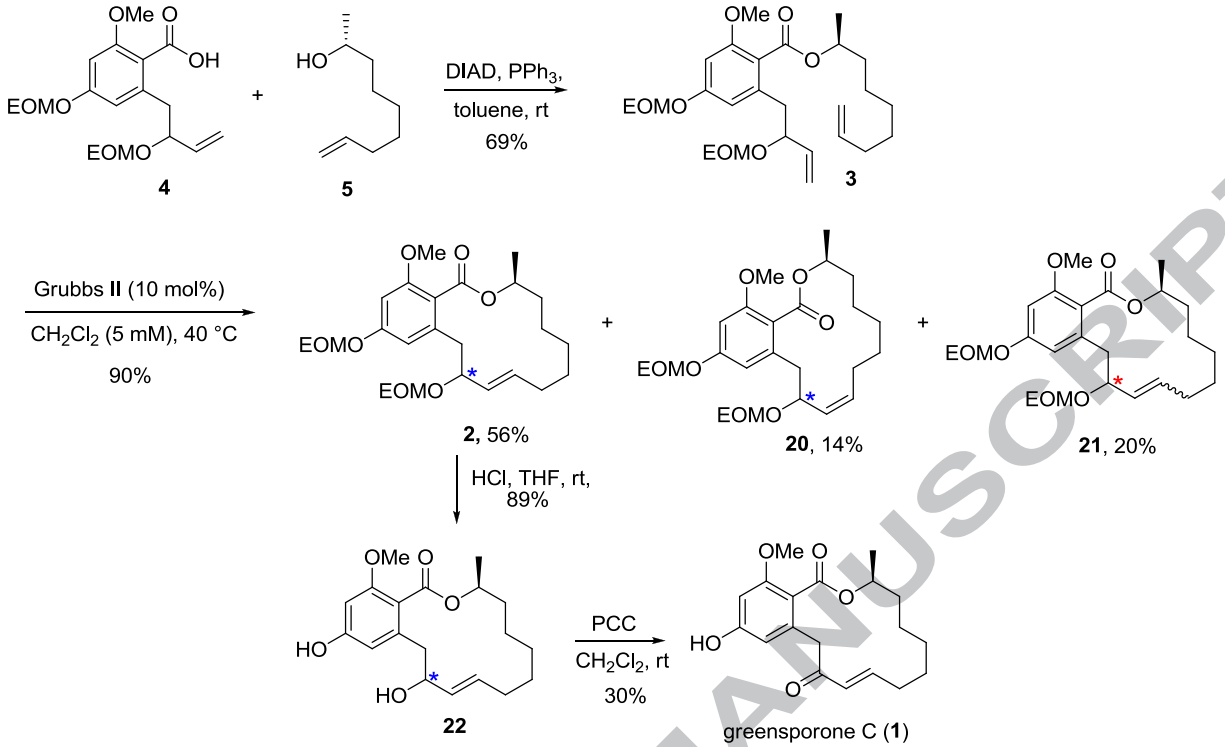
Synthesis of the requisite chiral alcohol fragment, (*R*)-non-8-en-2-ol (**5**), is outlined in Scheme 3. Regioselective opening of commercially available, optically pure (*R*)-propylene oxide with the acetylide generated *in situ* by deprotonation of 5-(benzyloxy)pentyne (**15**) with *n*-BuLi in the presence of $BF_3 \cdot OEt_2$ gave (*R*)-propargylic alcohol **16** in good yield and >99% ee.[14] The newly generated alcohol was then masked as the *t*-butyldiphenylsilyl (TBDPS) ether **17**. Alkyne reduction and concomitant removal of the benzyl protection group of **17** *via* catalytic hydrogenation in EtOAc provided alcohol **18** in 72% yield. To install the last carbon of this fragment, the 1° alcohol was oxidized using iodobenzene diacetate in the presence of catalytic TEMPO to deliver aldehyde **19** in 75% yield. Wittig olefination of **19** using methyltriphenylphosphonium bromide and KO*t*-Bu gave the desired alkene, which after TBDPS deprotection using TBAF furnished (*R*)-non-8-en-2-ol (**5**) in 60% yield. The NMR spectroscopic data and specific rotation of **5** matched those previously described in the literature.[15]



Scheme 3. Synthesis of (*R*)-non-8-en-2-ol (**5**).

With the key benzoic acid derivative **4** and chiral alcohol **5** in hand, we proceeded to complete the synthesis of greensporone C (Scheme 4). Union of the two key fragments **4** and **5** under Mitsunobu esterification conditions using diisopropyl azodicarboxylate (DIAD) and PPh_3 in toluene smoothly gave the ester RCM diene precursor **3** in 69% yield. This step should also provide the correct stereochemistry of the stereogenic center at the 2-position. The stage was then set for the key RCM to assemble the macrocyclic core of **1**. Thirupathi and Mohapatra recently reported a similar RCM protocol in the synthesis of cryptosporiopsin A and, to the best of our knowledge, their synthesis is the only example of RCM to assemble the C8–C9 olefin for this subgroup of RALs containing a ketone group at the 10-position.[16] The RCM precursor in their synthesis was slightly different from ours by the protecting group choices. Their key RCM proceeded smoothly to give the desired (*E*)-macrocycle in 74% yield using the second-generation Grubbs catalyst. Gratifyingly, RCM of diene **3** using the second-generation Grubbs catalyst (10 mol%) in CH_2Cl_2 at reflux with high dilution (5 mM) proceeded to completion within 4.5 h and furnished the RCM products in 90% combined yield with the (*E*)-olefin isomers identified as the major product. Although we could not separate all four diastereomers of the RCM products, we were able to separate the major diastereomers of macrolactones (*E*)-(**2**) (56% yield) and (*Z*)-(**20**) (14% yield) in an

approximately 4:1 ratio; their structures were confirmed by 1D, 2D NMR spectroscopic and HRMS data. The inseparable minor diastereomers of the (*E*)- and (*Z*)-macrocyclic adducts **21** (20% yield) were confirmed by HRMS data. No attempts were made to assign the absolute configuration of the alcohol stereogenic center of each macrocylic product because it would be oxidized to the ketone functional group in subsequent steps. Removal of both EOM protecting groups of **2** using HCl in THF at ambient temperature furnished diol **22** in 89% yield. Attempts to oxidize the resultant allylic alcohol of **22** with Dess-Martin periodinane was unsuccessful and unreacted diol was recovered. Gratifyingly, the use of pyridinium chlorochromate (PCC) in CH_2Cl_2 at room temperature resulted in the formation of greensporone C (**1**) in 30% yield. The ^{1}H and ^{13}C NMR spectroscopic data as well as HRMS data of synthetic greensporone C were nearly identical to those reported for the natural product. Additionally, the specific rotation of synthetic **1** ($[\square]_D^{27}$ +53.9, *c* 0.56, MeOH) was in accordance with and had the same sign as the natural product **1** ($[\square]_D^{20}$ +112, *c* 0.33, MeOH). The CD spectrum of synthetic **1** showed a negative Cotton effect at 234 nm, which indicated the *S* absolute configuration of C2 analogous to that of *E*-dehydrocurvularin reported by Marsaiolia and co-workers.[17] Thus, our synthesis confirmed the absolute configuration of the natural product greensporone C as proposed by Oberlies and co-workers.



Scheme 4. Completion of the synthesis of greensporone C (**1**). The absolute stereochemistry of the * stereogenic center was not determined.

Conclusion

In summary, the first total synthesis of greensporone C (**1**) has been accomplished *via* a longest linear sequence of 16 steps in 3.3% overall yield from phenol **6**. The key features of the synthesis include Mitsunobu esterification and ring-closing metathesis to construct the macrocycle and establish the (*E*)-olefin geometry, respectively. Our synthesis also confirmed the absolute stereochemistry of the natural product.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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Highlights

- The first total synthesis of greensporone C has been achieved.
- The key steps include Mitsunobu esterification and ring-closing metathesis.
- The synthesis confirmed the absolute stereochemistry of the natural product.

Graphical Abstract

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