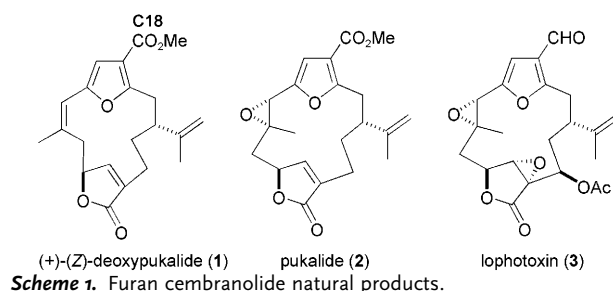


Synthesis of (–)-(Z)-Deoxypukalide**

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The furan cembranolides are an intriguing class of macrocyclic marine natural products, which have been isolated from several soft corals found at various locations around the world.^[1] Members of this family exhibit a wide range of biological activities, from neurotoxicity through to anti-inflammatory and anti-feedant properties (Scheme 1).^[2] It has been suggested that their biosynthetic origin involves the macrocyclization of geranylgeranyl diphosphate to form a 14-



Scheme 1. Furan cembranolide natural products.

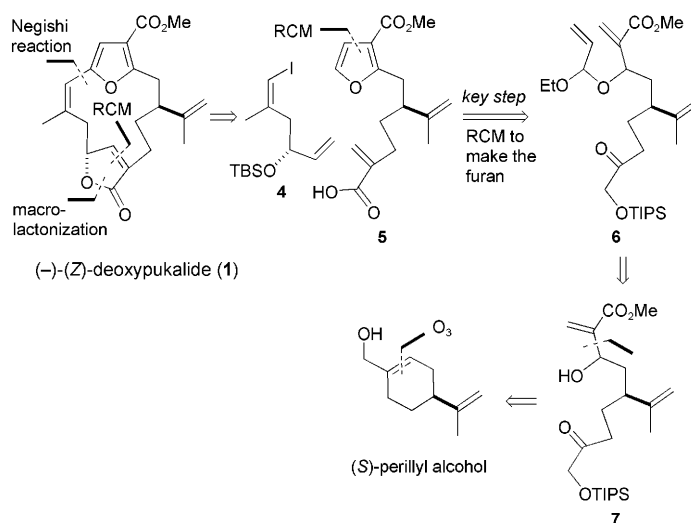
membered carbocycle, which is then subjected to an oxidation cascade leading to the natural products.^[3] Interestingly, it has also been proposed that the oxidation level of the C18 carbon may be correlated to the genus of Octocoral that produces a particular product.^[1]

Several research groups have reported key synthetic studies and elegant biomimetic investigations which have culminated in the syntheses of members of this class of natural product,^[4,5] however, it has been acknowledged that cembranolides are deceptively demanding targets.^[5] Intrigued by its 14-membered carbon macrocycle containing a trisubstituted furan moiety, our interest was drawn to (Z)-deoxypukalide (1) as a worthwhile synthetic target. More specifically, we wanted to test a powerful new methodology that was developed by our research group for the synthesis of furans and which uses ring-closing metathesis as the key step.^[6] Our approach allows for some new and unusual disconnections on the furan nucleus, and if the method

passes this test then an exceptionally short and efficient synthesis of the natural product will be achieved.

Natural product (+)-1 was recently isolated from the Pacific Octocoral *Leptogorgia* sp.^[1] The structure of (+)-1 was easily confirmed because its spectroscopic data was identical to that of a sample prepared independently by Marshall and Devender (through a 28-step synthesis), whose studies were complete before (Z)-deoxypukalide was recognized as a natural product.^[5c]

The retrosynthesis of this molecule involves a late-stage construction of the butenolide by means of ring-closing metathesis (RCM) of a macrocyclic lactone (Scheme 2). The lactone precursor would be prepared from a hydroxy acid that would itself come from a Negishi coupling of functionalized (and protected) vinyl iodide 4 with disubstituted furan 5. The key test of our furan-forming RCM methodology would come from the design of a short and efficient route to compound 5 that would allow the preparation of this precursor and enable completion of the synthesis.



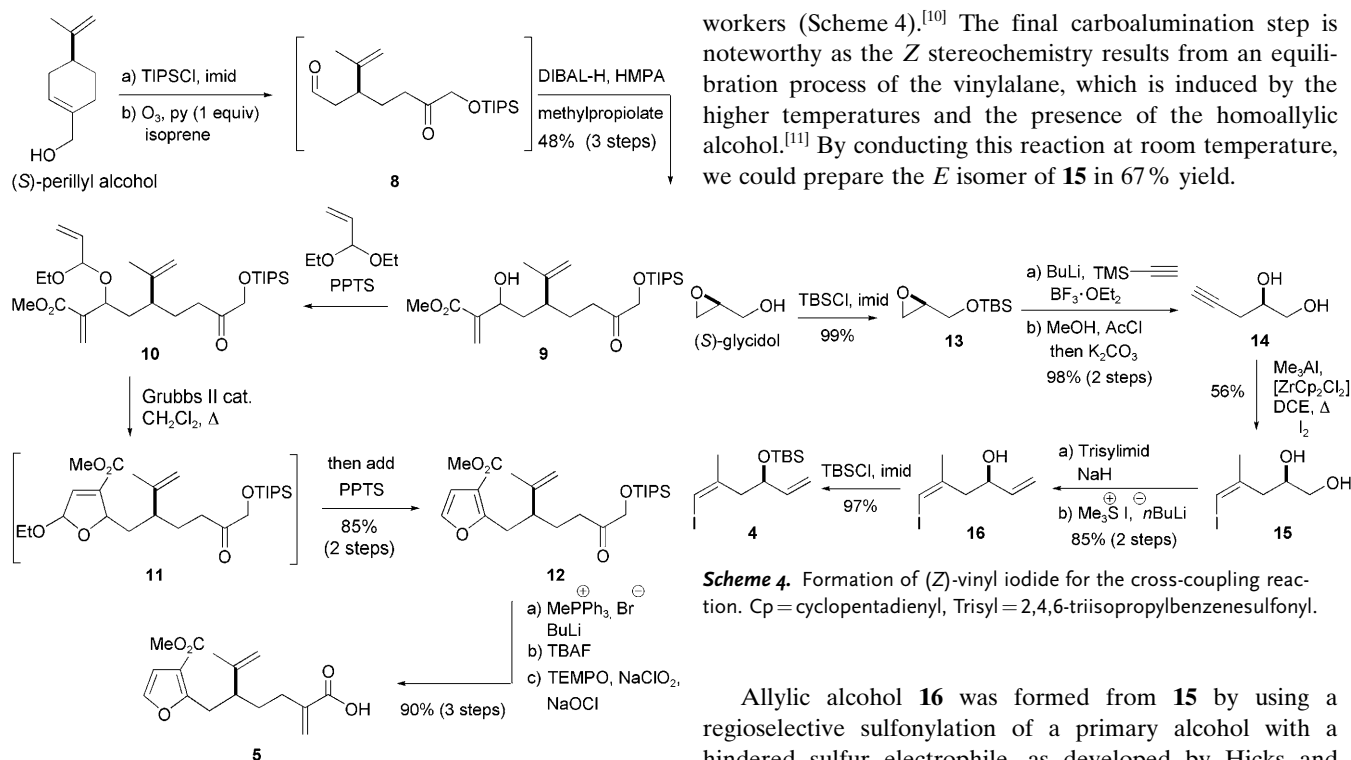
Scheme 2. Retrosynthetic analysis of (Z)-deoxypukalide. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

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Our synthesis began with (*S*)-perillyl alcohol, which is commercially available and is inexpensive (Scheme 3). The sequence shown will result in the formation of the enantiomer of the natural product. (*R*)-Perillyl alcohol is commercially available but reasonably expensive; however, it can be obtained by the enzymatic oxidation of (+)-limonene.^[7] Silyl protection of the primary hydroxy group and then selective ozonolysis of the trisubstituted alkene ensued. Success for the regioselective ozonolysis (the trisubstituted alkene reacts faster than a 1,1-disubstituted alkene) was only achieved in the presence of a stoichiometric amount of



Scheme 3. RCM route to the furan segment. DIBAL-H = diisobutylaluminum hydride, HMPA = hexamethyl phosphoramide, imid = imidazole, PPTS = pyridinium *p*-toluenesulfonate, py = pyridine, TBAF = tetra-*n*-butylammonium fluoride, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical.

pyridine and excess isoprene, both of which attenuated the amount of over-oxidation of the 1,1-disubstituted alkene. The use of pyridine to reduce the reactivity of ozone has been reported by Slomp and Johnson.^[8] In addition, we added isoprene to act as a buffer that would be cleaved in preference to the 1,1-disubstituted alkene in the substrate; to the best of our knowledge, this is the first time that such a tactic has been used in this context.

The resulting aldehyde **8** proved to be relatively unreactive under Baylis–Hillman reaction conditions. Therefore it was treated with a vinylalane, itself derived by addition of DIBAL-H to methylpropiolate.^[9] This sequence, which is a useful alternative to the Baylis–Hillman reaction, resulted in the formation of allylic alcohol **9** as an inconsequential (1:1) mixture of diastereoisomers.

The pivotal furan-forming reaction sequence was then examined, starting with the formation of the mixed acetal **10**, by exchange with commercially available acrolein diethyl acetal. Subsequent ring-closing metathesis with the second-generation Grubbs catalyst formed cyclic olefin **11**, which was immediately aromatized in situ with mild acid^[6] to produce disubstituted furan **12** in 85% overall yield (over two steps from **9**). This protocol was followed by a three-step functional group manipulation to prepare furan **5**, which was now ready for the cross-coupling reaction.

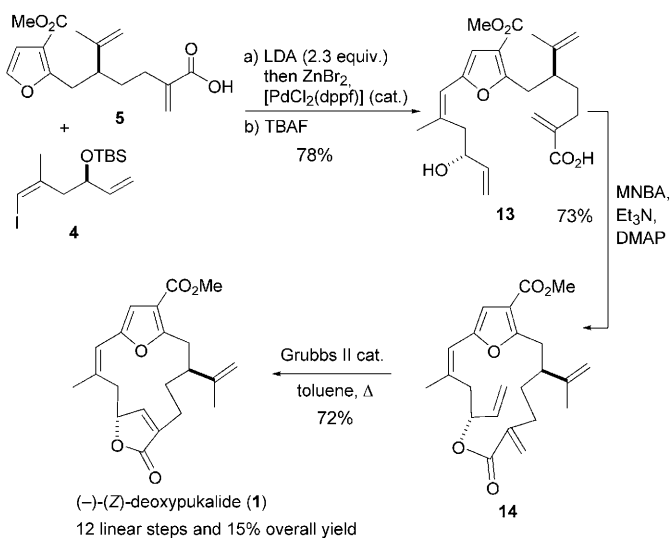
To enable the proposed Negishi cross-coupling reaction, we prepared (*Z*)-vinyl iodide **15** starting from (*S*)-glycidol using a four-step sequence reported by Pattenden and co-

workers (Scheme 4).^[10] The final carboalumination step is noteworthy as the *Z* stereochemistry results from an equilibration process of the vinylalane, which is induced by the higher temperatures and the presence of the homoallylic alcohol.^[11] By conducting this reaction at room temperature, we could prepare the *E* isomer of **15** in 67% yield.

Scheme 4. Formation of (*Z*)-vinyl iodide for the cross-coupling reaction. Cp = cyclopentadienyl, Trisyl = 2,4,6-triisopropylbenzenesulfonyl.

Allylic alcohol **16** was formed from **15** by using a regioselective sulfonylation of a primary alcohol with a hindered sulfur electrophile, as developed by Hicks and Fraser-Reid.^[12] This transformation was followed by opening of the epoxide and olefin formation using trimethylsulfonium iodide and strong base, as reported by Alcaraz et al.^[13] Finally, silyl protection of the free alcohol gave (*Z*)-vinyl iodide **4**.

Completion of this sequence required joining of the two fragments by using a Negishi cross-coupling reaction as shown in Scheme 5.^[14,51] Double deprotonation of **5** with LDA and then in situ transmetalation with zinc bromide was followed by palladium-catalyzed coupling with **4**; after removal of the TBS group with TBAF, this sequence provided trisubstituted furan **13** in 78% yield over two steps.



The final sequence required the implementation of the macrolactonization procedure developed by Shiina et al. to give lactone **14** in 73 % yield (Scheme 5).^[15] This remarkable set of reaction conditions gave a much higher yield than the macrolactonization protocol of Yamaguchi and co-workers,^[16] which failed to give more than about 5 % of **14**. Finally, formation of the butenolide unit was completed by using RCM with the second-generation Grubbs catalyst^[17] in toluene at reflux which proceeded smoothly in 72 % yield (with the remaining mass recovered as starting material). The (–)-(Z)-deoxypukolide (**1**) that was synthesized by this sequence had spectroscopic data identical to that reported for the natural product.

In conclusion, we have completed the synthesis of (–)-(Z)-deoxypukalide (**1**) by a sequence that is noteworthy for its brevity and efficiency: just 12 linear steps and an overall yield of 15 %. The key features in the synthesis were the successful RCM/aromatization protocol used to prepare a disubstituted furan, and a regioselective Negishi cross-coupling reaction to construct the fully substituted aromatic core of the target. Finally, macrolactonization and subsequent RCM enabled us to complete the synthesis.

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