

Synthesis of a Highly Functionalized Core of Verrillin

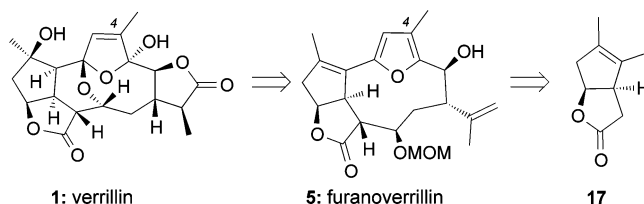
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ABSTRACT



An efficient stereoselective synthesis of furanoverrillin (**5**), a highly functionalized core of verrillin (**1**), is reported. The synthetic strategy is based on constructing bicyclic lactone **17** prior to the 10-membered ring macrocyclization. The effect of the C₄ methyl group on the furan reactivity is also discussed.

Gorgonian octocorals and soft corals supply a diverse array of diterpenes and C₄-norditerpenes that biosynthetically derive from a 14-membered cembrane skeleton.¹ Among them, verrillin (**1**), bielschowskysin (**2**), ineleganolide (**3**) and plumarellide (**4**) are highlighted by a combination of intricate structural density and potent bioactivity (Figure 1).^{1a,2} For example, bielschowskysin (**2**),³ a multifarious hexacyclic cembranoid, was found to exhibit significant antimalarial activity against *Plasmodium falciparum* (IC₅₀ ca. 10 μg/mL). In addition, potent cytotoxicity data regarding **2** have been reported against nonsmall cell lung cancer (EKVX, GI₅₀ ca. 0.01 μM) and renal cancer cells (CAKI-1, GI₅₀ ca. 0.50 μM).³ Along these lines, ineleganolide (**3**) displays strong cytotoxicity against P-388 cancer cells (ED₅₀ 3.82 μg/mL).⁴ On the other hand, plumarellide (**4**) exhibits moderate hemolytic activity in mice with 50% hemolysis of mouse blood erythrocytes at 140 μM⁵ while the bioactivities of verrillin (**1**)⁶ have not yet been studied.

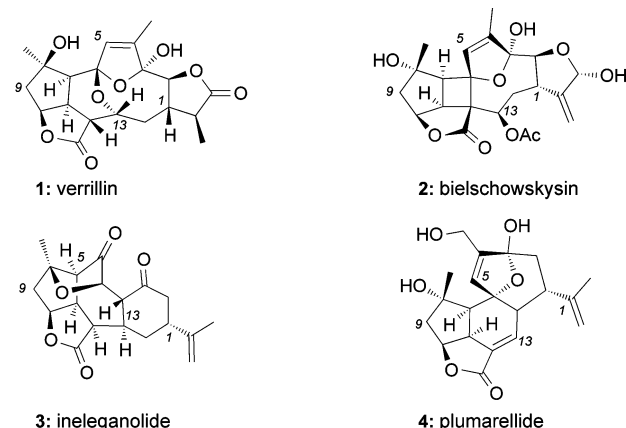


Figure 1. Structures of selected polycyclic cembranoids.

A commonality shared by these polycyclic cembranoids is an oxidative ring contraction of the 14-membered cembrane ring across the C₇ and C₁₁ carbons thereby producing the verrillane core (**6**) (Figure 2).^{3,7} Subsequent ring contractions across the C₆ and C₁₂ or the C₆ and C₁₄ centers would produce the bielschowskyane (**9**)^{1c,3,7} and

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the plumarane core (**7**),^{1c} respectively. On the other hand, oxidative demethylation followed by nucleophilic ring contraction at the C₄ and C₁₃ centers could assemble the inelegane core (**8**).^{1c}

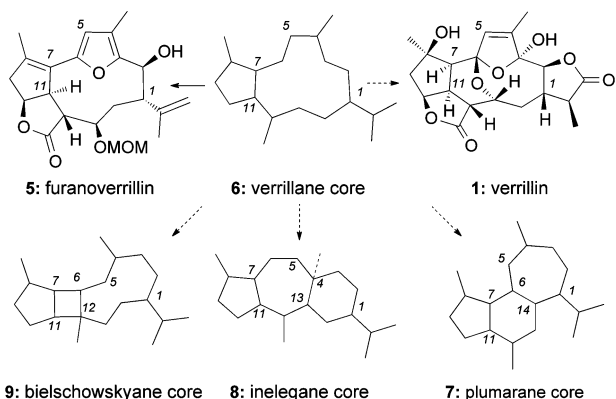


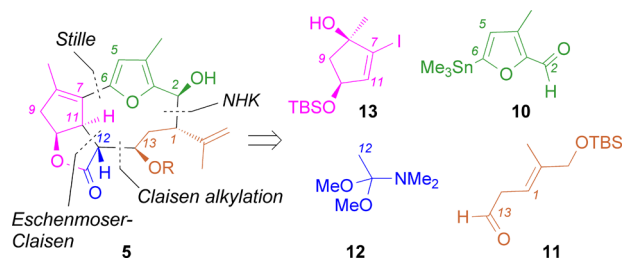
Figure 2. Carbocyclic scaffolds related to verrillane core **6**.

Although several strategies toward the synthesis of bielschowskysin⁸ (**2**) and plumarellide⁹ (**4**) have been reported, none have generated a true cembrane scaffold with relevant carbon connections and oxidation patterns. Inspired by the challenge, we directed our efforts^{7,10} toward the synthesis of motif **5** that contains an appropriately functionalized verrillane core (Figure 2). Referred to herein as furanoverrillin, compound **5** represents a branching node toward the synthesis of verrillin (**1**) and its more intricate brethren.

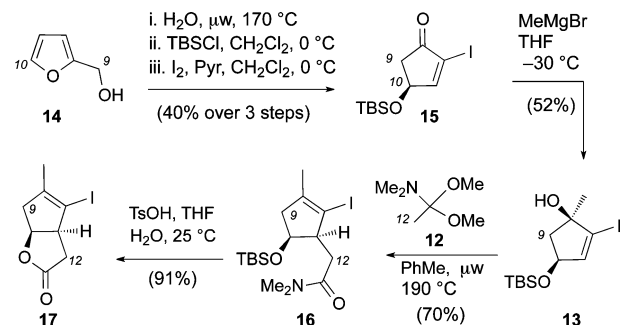
Scheme 1 highlights the key disconnections of furanoverrillin (**5**) and identifies the essential synthetic fragments. We envisioned that construction of the fused bicyclic lactone, present in our target, could be furnished via an Eschenmoser-Claisen rearrangement.¹¹ This disconnection reveals allylic alcohol **13** and commercially available amide acetal **12** as the coupling partners. Claisen alkylation of this adduct with aldehyde **11** could then create the desired C₁₂–C₁₃ connection as well as provide the important C₁₃ oxidation present in this family of compounds.⁷ Pd(0)-coupling could then be used to join furan derivative **10** by creating the C₆–C₇ bond, while macrocyclization

under Nozaki–Hiyama–Kishi (NHK) conditions¹² could afford the final C₁–C₂ linkage.

Scheme 1. Retrosynthetic Analysis of Furanoverrillin (**5**)



Scheme 2. Synthesis of Fragment **17**



The synthesis of furanoverrillin (**5**) commenced with the formation of lactone **17** (Scheme 2). Furfuryl alcohol **14** was rearranged to a cyclopentenone derivative under microwave irradiation¹³ that, after TBS protection and regioselective iodination,¹⁴ gave rise to iodo enone **15** (3 steps, 40% overall yield). Nucleophilic addition onto the carbonyl with methyl magnesium bromide yielded tertiary alcohol **13** as a single diastereomer in good yield (52%). To our satisfaction, the key Eschenmoser-Claisen rearrangement¹⁵ of **13** with **12** proceeded smoothly and in a diastereoselective manner, to afford amide **16** (70% yield). Treatment of the crude amide **16** with excess acid led to rapid cleavage of the TBS group and cyclization of the resulting alcohol at the amide carbonyl center to produce lactone **17** in 91% yield (Scheme 2).

Deprotonation of **17** with freshly prepared LiHMDS followed by quick addition of the previously described aldehyde **11**⁷ supplied alcohol **18** as a 1:1.7 mixture of C₁₃

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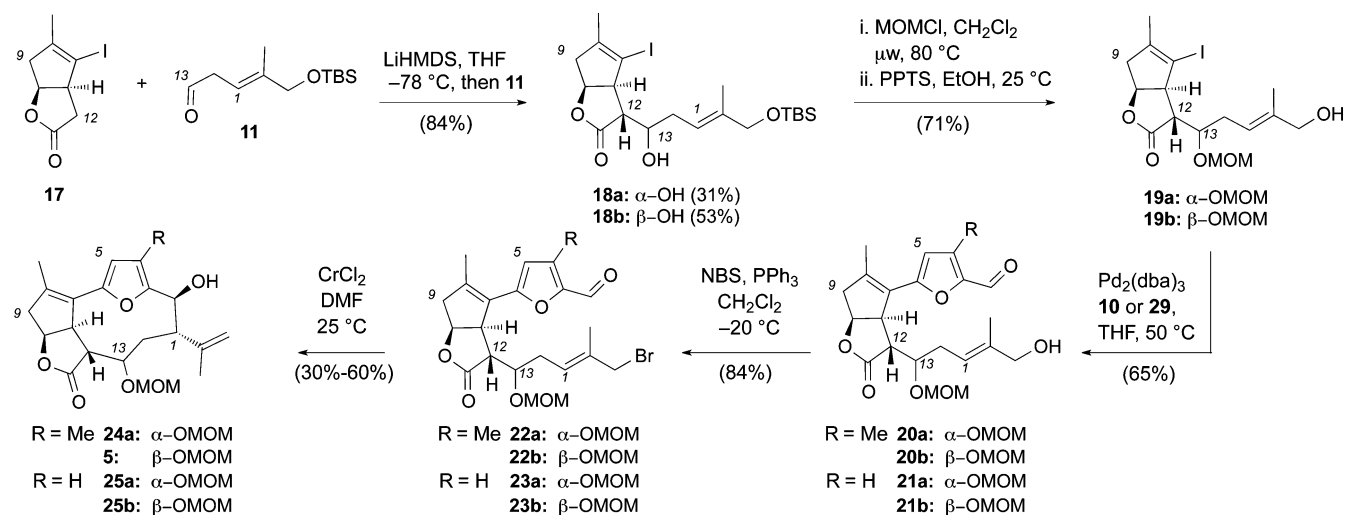
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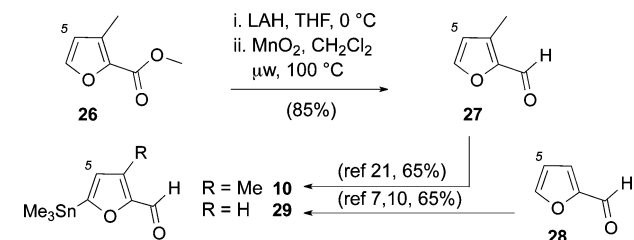
Scheme 3. Synthesis of Furanoverrillin **5** and Derivatives



diastereomers (Scheme 3).⁷ These isomers, **18a** and **18b**, were separated by column chromatography and used separately in subsequent manipulations.¹⁶ TBS protection of the newly installed alcohol functionality was markedly slow and low yielding. Protection of the secondary alcohols **18a** and **18b** with MOMCl¹⁷ was also slow at room temperature. Microwave irradiation conditions at 80 °C for 10 min, however, successfully yielded the desired MOM protected alcohols. Selective TBS deprotection of this crude material using PPTS in ethanol afforded primary alcohols **19a** and **19b** (ca. 71% yield over 2 steps).¹⁸

The synthesis of methyl furfuryl stannane **10** was accomplished as shown in Scheme 4. Commercially available furan derivative **26** was reduced to the corresponding primary alcohol¹⁹ that, after oxidation with manganese dioxide²⁰ under microwave irradiation produced aldehyde **27** (2 steps, 85% yield). Stannylation of a transiently protected aldehyde **27** with trimethyltin chloride afforded stannane **10** in 65% yield.²¹ In a similar fashion, aldehyde **28** was converted to stannane **29**.^{7,21}

Scheme 4. Synthesis of Furfuryl Stannanes **10** and **29**



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To our chagrin, coupling of stannane **10** with primary alcohols **19a** and **19b** under the previously established Stille conditions (Pd(PPh₃)₄/CuI)^{7,10,21} was not successful. However, switching of reagents to catalytic Pd₂(dba)₃ and triphenylarsine²² cleanly afforded compounds **20a** and **20b** in 65% average yield (Scheme 3). Appel bromination conditions²³ were employed to convert alcohols **20a** and **20b** to their corresponding bromides **22a** and **22b** (ca. 84% yield).

The final macrocyclization event that would create the 10-membered macrocycle²⁴ also proved to be more problematic than previously described^{7,10,21} leading to a complex mixture of products. Changing the solvent from THF to DMF²⁵ greatly improved the reaction outcome to afford furanoverrillin (**5**), containing the desired verrillin stereochemistry at C₁₃, together with its C₁₃ α -isomer **24a** in 30% combined yield. The diastereoselectivity of the macrocyclization was 4/1 anti/syn with respect to the orientation of the C₂ alcohol and the C₁ isopropene.^{24a}

Compounds **5** and **24a** were subjected to standard C₂ deoxygenation conditions using triethylsilane and trifluoroacetic acid²⁶ to produce deoxygenated products **30a** and **30b** in lower than expected yields (ca. 40% yield) (Scheme 5).^{7,10,21}

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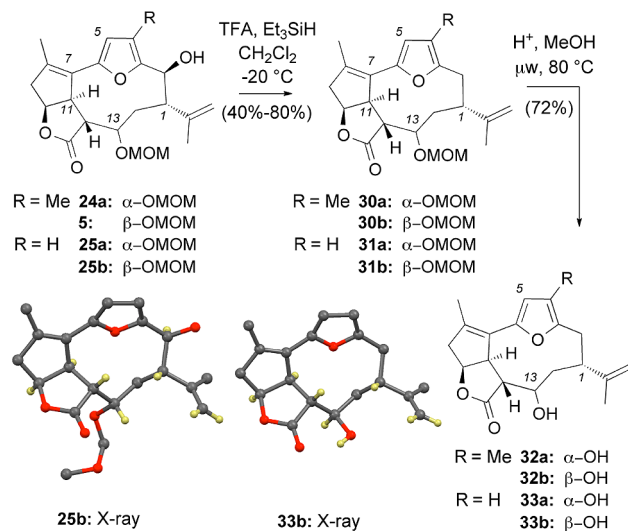
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Acid-induced MOM deprotection under microwave conditions²⁷ afforded the corresponding alcohols **32a** and **32b** in an average yield of 72%.

Scheme 5. Synthesis of **32** and **33**



During this study, we observed modest yields in converting **22a** and **22b** to **24a** and **5**, respectively (Scheme 3). This may be due to the inherent tendency of these compounds to undergo carbocationic rearrangements at the C₂ center, as previously reported for certain C₂ hydroxy-furanocembranolides and pseudottedanolides.²⁸ An alternative explanation is to consider that, due to its high electronic density, the furan ring becomes sensitive to oxidative decomposition. To test this hypothesis we repeated the aforementioned sequence using the nonmethylated furfuraldehyde **28** instead of its methylated analogue **27**. To this end, we coupled the previously synthesized furfural stannane **29**^{7,10} with alcohols **19a** and **19b** to afford **21a** and **21b** in comparable yields (ca. 65% yield). Appel conditions^{7,10,21,23} also smoothly afforded bromides **23a** and **23b** again, in nearly identical yields (ca. 84% yield). When optimized NHK¹² conditions were then applied using DMF as a solvent,²⁵ a clean conversion to the desired

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(29) CCDC 929062 (**25a**) and 929063 (**33b**) contain the supplementary crystallographic data. This information can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/products/csd/request/. In the figures, some hydrogen atoms have been removed for clarity.

nor-furanoverrillin intermediates **25a** and **25b** was observed in good yields (ca. 60% yield). Deoxygenation at the C₂ center using triethylsilane and trifluoroacetic acid²⁶ also cleanly produced deoxygenated intermediates **31a** and **31b** in noticeably increased yields. Finally, acidic removal of the MOM group²⁷ created alcohols **33a** and **33b** in similar yields (ca. 72% yield). Along with a striking improvement in reaction yields of the nor-furanoverrillin derivatives was the ability to then obtain X-ray structures for compounds **25b** and **33b** which confirmed the proposed stereochemical assignments.²⁹

In conclusion, we present herein a stereoselective synthesis of furanoverrillin (**5**), a branching node toward the synthesis of verrillin (**1**) and related polycyclic cembranoids. Our approach relies on introduction of the C₇–C₁₁ cyclopentene ring prior to the macrocyclization of the fully functionalized verrillin core. We observed that the presence of a C₄ methyl group at the furan ring increases its susceptibility toward oxidative decomposition. In turn, this attests to the role of the C₄ methyl group in oxidative rearrangements that account for the plethora of polycyclic cembranes isolated thus far. The described strategy produces, for the first time, the entire carbon framework of verrillin and allows for further functionalization toward verrillin (**1**) and structurally related natural products.³⁰

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Supporting Information Available. Detailed experimental procedures, spectral characterization and copies of ¹H and ¹³C NMR data. 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.