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A strategy toward the synthesis of C_{13}-oxidized cembrenolides

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ABSTRACT

An efficient strategy for the construction of C_{13}-oxidized cembrenolides is reported. Central to this strategy is the installation of the C_{13} hydroxyl group prior to cembrane macrocyclization (via formation of the C_1–C_2 bond), allowing access to both C_{13} alcohol epimers. The orientation of the C_{13} alcohol was found to influence the cyclization mode of the cembranolide scaffold upon furan oxidation, leading to motifs reminiscent to bipinnatolide F, bielschowskysin, and verrillin.

Isolated from soft corals and octocorals, cembrenolides constitute a large family of natural products that are typified by a 14-membered cembrane skeleton. Oxidations at the periphery of this framework set the stage for various skeletal rearrangements and transannular cyclizations ultimately producing a wide array of polycyclic metabolites.[1] In addition to their ecological impact,[2] these compounds have been pursued both for their unusual structural motifs and for their biological and pharmacological potential.[1a,3] For instance, oxidation at the C_{13} center of the cembrane motif is found in several structurally intricate and biologically unexplored cembrenolides (Fig. 1).[2a] Among them, bielschowskysin (**1**), a complex hexacyclic cembrane, was shown to exhibit very potent cytotoxicity against nonsmall cell lung cancer (EKVX, GI_{50} ca. 10 nM) and renal cancer (CAKI-1, GI_{50} ca. 0.5 μM).[4,5] Moreover, **1** has demonstrated potent anti-malarial activity against *Plasmodium falciparum* (IC_{50} ca. 10 μg/ml).[4] Lophotoxin (**4**)[6] was found to be a potent nicotinic acetylcholine receptor inhibitor with an LD_{50} of 8 mg/kg[2a] in mice and, since its isolation, it has become a synthetic conundrum.[7] On the other hand, the bioactivities of verrillin (**2**)[8] and bipinnatolide F (**3**)[9] have not yet been fully explored.

Evaluation of the polycyclic motifs of bielschowskysin (**1**) and verrillin (**2**) suggests that both compounds can derive biosynthetically from the same precursor **5a** (R_1 = Me) whose cembrane macrocycle contains a furan in close proximity to a butenolide ring (Fig. 2). Furan oxidation of **5a** could produce intermediate **6** in which the electron rich enol could react with the pendant butenolide to form intermediate **7**. If the C_{13} β-alcohol is modified as an acetate (R_2 = OAc), the resulting C_{12} carbanion could cyclize at the C_6 center creating the strained cyclobutane motif reminiscent to that found in **1**.[1b,c] Both photochemical[5a–c] and Lewis-acid induced conditions[10] could account for the formation of this ring. However, if the C_{13} β-alcohol is available (R_2 = H), it could cyclize at the C_6 center of **7**, forming a more structurally favorable six membered hemiketal ring encountered in the motif of verrillin (**2**).

The combination of structural intricacy and biological potential of these metabolites prompted our studies toward the synthesis of the C_{13} oxidized cembranolide **5b** (R_1 = H). From a synthetic standpoint, **5b** could derive from the union of three components: (a) a C_7–C_{12} fragment containing a masked butenolide; (b) a

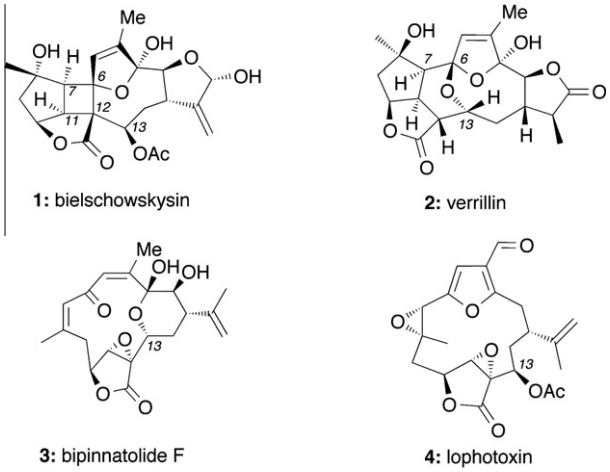

Figure 1. Proposed biosynthetic pathway to bielshowskysin and verrillin.

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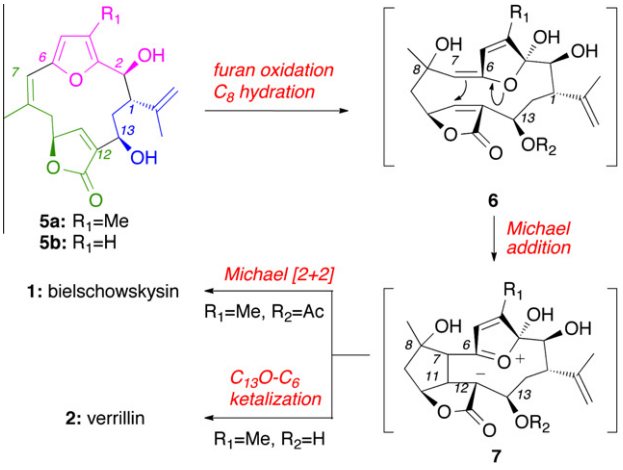
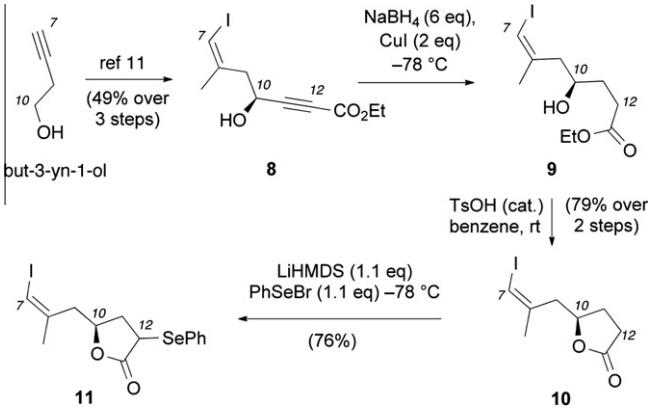


Figure 2. Proposed biosynthetic pathway to bielshowskysin and verrillin.



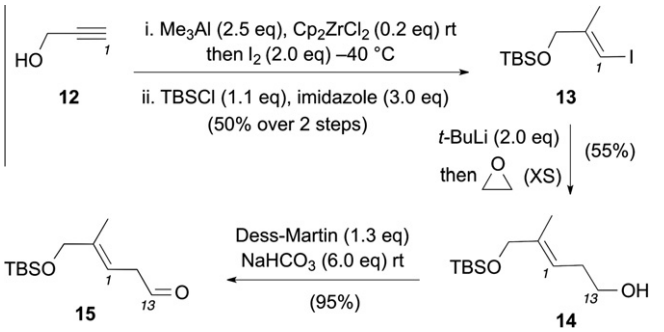
Scheme 1. Reagents and conditions: (a) 6 equiv $NaBH_4$, 2 equiv CuI, MeOH, −78 °C, 15 min; (b) 0.1 equiv TsOH, PhH, 25 °C, 30 min, 79% (over 2 steps); (c) 1.1 equiv LiHMDS, −78 °C, then 1 equiv PhSeBr, THF, −78 to 25 °C, 30 min, 76%.

C_{13}–C_1 aldehyde motif; and (c) a C_2–C_6 framework containing a furan ring.

The synthesis of **5b** began with construction of the C_7–C_{12} fragment **11**, in which the butenolide ring is introduced as an α-selenolactone (Scheme 1).[7d] To this end, propargyl ester **8**, available from but-3-yn-1-ol in 3 steps,[11] was reduced to saturated ester **9** using excess $NaBH_4$ and CuI[12] (Scheme 1). The crude material was then treated with cat. TsOH in benzene to form γ-lactone **10** (79% yield over two steps). It is worth noting that this approach represents a significant improvement over the previously reported synthesis of compound **10**.[13] Treatment of **10** with LiHMDS/PhSeBr then afforded **11** in 76% yield.[7f,13]

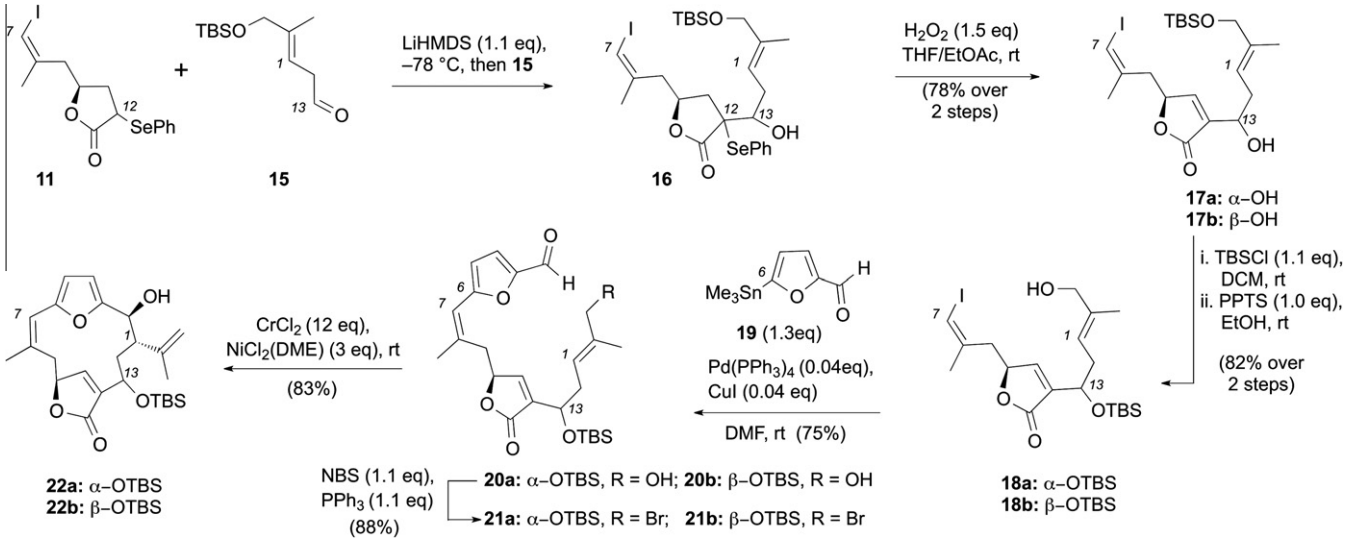
Aldehyde **15**, representing the C_{13}–C_1 component, was prepared beginning from propargyl alcohol **12** (Scheme 2). Methyl zirconation/iodination[14] of **12** followed by protection of the pendant allylic alcohol afforded **13** in 50% combined yield. Lithiation of the resulting vinyl iodide and quenching of the reaction with oxirane yielded **14** in 55% yield.[15] Oxidation of **14** with Dess–Martin periodinane[16] cleanly afforded β,γ-unsaturated aldehyde **15** that was used without further purification.

The construction of the C_{13}-hydroxylated cembrenolide motif via sequential coupling of the three components is described in

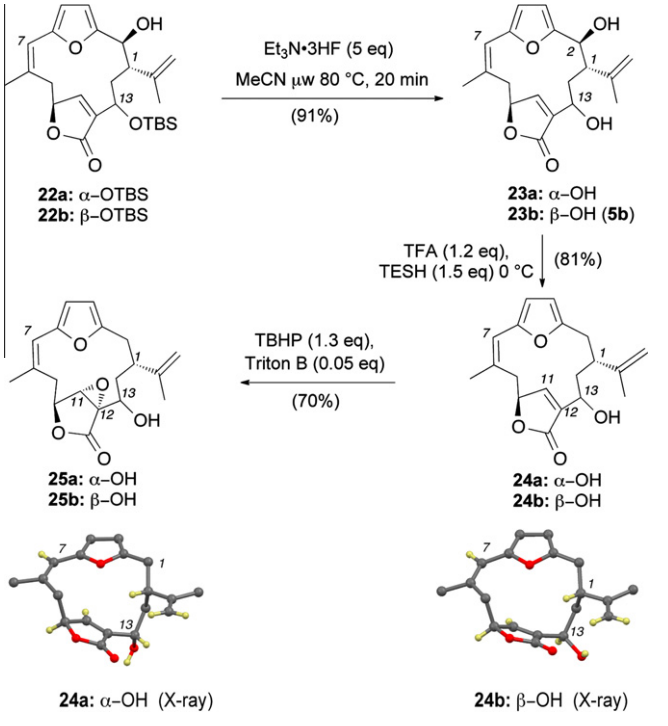


Scheme 2. Reagents and conditions: (a) (i) 2.5 equiv Me_3Al, 0.2 equiv Cp_2ZrCl_2, DCE, 25 °C, 24 h, then 2.0 equiv I_2, −40 °C, 30 min, (ii) 1.1 equiv TBSCl, 3.0 equiv imid, DCM, 0 °C, 1 h, 50% (over 2 steps); (b) 2.0 equiv *t*-BuLi, PhMe, −78 °C, 30 min, then oxirane (excess), −78 to 25 °C over 30 min, 55%; (c) 1.3 equiv Dess–Martin [O], 6.0 equiv $NaHCO_3$, 25 °C, 20 min, 95%.

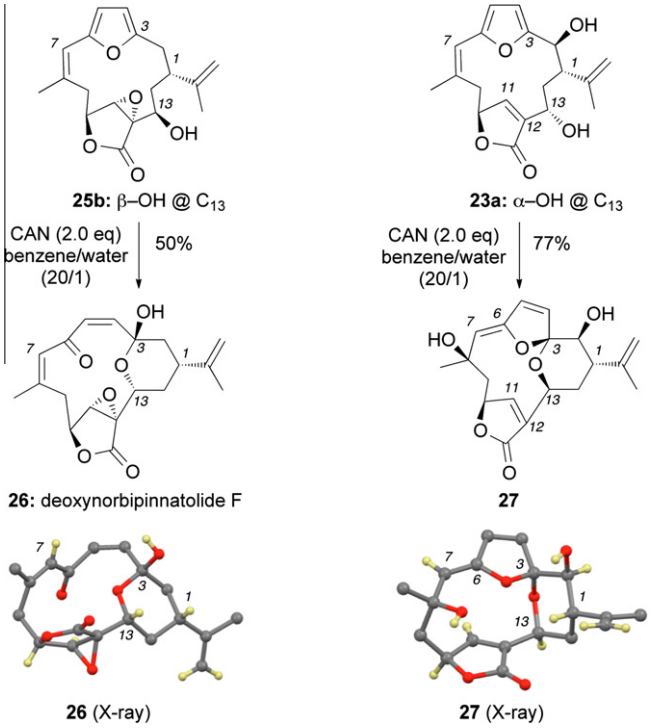
Scheme 3. Compound **11** was lithiated at the C_{12} center (LiHMDS, −78 °C) and alkylated with aldehyde **15** to produce **16** as a mixture of 4 diastereomers. The crude mixture was oxidatively de-



Scheme 3. Reagents and conditions: (a) 1.1 equiv LiHMDS, THF, −78 °C, 1 h, then **15**, −78 °C, 20 min; (b) 1.5 equiv H_2O_2, 10 equiv $NaHCO_3$, THF/EtOAc 1:1, 25 °C, 10 min, 78% (over 2 steps); (c) (i) 1.1 equiv TBSCl, 3.0 equiv imid, DCM, 25 °C, 12 h; (ii) 1.0 equiv PPTS, EtOH, 25 °C, 12 h, 82% (over 2 steps); (d) 4 mol % $Pd(PPh_3)_4$, 4 mol % CuI, then **19**, DMF, 25 °C, 2 h, 75%; (e) 1.1 equiv NBS, 1.1 equiv PPh_3, DCM, −20 °C, 30 min, 88%; (f) 12.0 equiv $CrCl_2$, 3.0 equiv $NiCl_2$(DME), THF, 25 °C, 12 h, 83%.



Scheme 4. Reagents and conditions: (a) 5.0 equiv $Et_3N{\cdot}3HF$, MeCN, mw 80 °C, 20 min, 91%; (b) 1.2 equiv TFA, 1.5 equiv TESH, DCM, 0 °C, 15 min, 81%; (c) 1.3 equiv TBHP, 0.05 equiv Triton B, THF, 0 °C, 70%.



Scheme 5. Reagents and conditions: (a) 2.0 equiv CAN, PhH/H_2O 20:1, 0 °C, 15 min, 50%; (b) 2.0 equiv CAN, PhH/H_2O 20:1, 0 °C, 20 min, 77%.

selenated[7d,17] to afford butenolide **17** as a 1:1 mixture of C_{13} diastereomers (**17a**, **17b**) that were easily separated by column chromatography (78% combined yield). The stereochemistry of the C_{13} hydroxyl group was determined after macrocyclization (see Scheme 4). Protection of **17a** and **17b** with TBSCl produced the di-silylated compounds that, after selective deprotection of the primary TBS group using PPTS in ethanol,[18] produced primary alcohols **18a** and **18b** (ca. 82% yield over 2 steps).

Coupling of compounds **18a** and **18b** with stannylated furfural **19** was performed via a modified Stille reaction[19] (Scheme 3) to afford **20a** and **20b** in 75% average yield. Bromination of the allylic alcohol using Appel conditions[20] produced allylic bromides **21a** and **21b** in 88% yield. We were concerned that the presence of the new C_{13} stereocenter, containing a bulky TBS ether on a linear uncyclized motif, might disrupt the high diastereoselectivity of the macrocylization that has been observed in previous systems.[21] However, to our satisfaction, this macrocylization proceeded smoothly using $CrCl_2/NiCl_2$(DME) and formed compound **22a** and **22b** in 83% average yield. As was previously observed,[21] the diastereoselectivity of this reaction is controlled by the chirality of the butenolide motif.

Removal of the extraneous silyl group was achieved using TEA-buffered HF reagent[22] under microwave irradiation conditions. This treatment afforded cleanly diols **23a** and **23b** in 91% average yield. (Scheme 4). Reduction of the furylic C_2 alcohol of **23a** and **23b** with TFA and TESH gave rise to **24a** and **24b** respectively, the stereochemistry of which was determined via a single crystal X-ray analysis.[23] Epoxidation across the C_{11}–C_{12} alkene proceeded selectively under TBHP/Triton B conditions,[24] to create, irrespectively of the orientation of the adjacent C_{13} alcohol, α-epoxides **25a** and **25b** (70% average yield).

We then explored the effect of the C_{13} hydroxyl functionality during oxidative cyclizations of furanocembrenolides (Scheme 5).[25] With an eye toward the scaffold of bipinnatolide F (**3**), we treated **23b** under oxidative conditions mediated by CAN[5c,26] (benzene/water: 20/1 at 10 °C). Unfortunately, only a complex mixture of products was observed. On the other hand, when identical oxidative conditions were applied to **23a**, containing the C_{13}-hydroxyl group at the α-face of the cembranolide scaffold, we observed the formation of 5,6-spiro ketal **27**.[23] This spiroketal motif is presumably stabilized by the diaxial orientation of the ketal oxygens (anomeric effect), despite the axial orientation of the C_{13} butenolide side chain. Motif **27** is similar to **6**, a proposed intermediate in the biosynthesis of bielschowskysin (**1**) and verrillin (**2**),[1b,c] where the C_6–C_7 enol ether is proposed to undergo cyclization with the C_{11}–C_{12} butenolide to furnish the strained cyclobutane motif. Interestingly, CAN-mediated oxidation[5c,26] of **25b** (benzene/water: 20/1 at 10 °C) led to isolation of compound **26**[23] in which an intermediate ene-dione, produced upon furan oxidation, underwent hemiketalization at the C_3 center by the pendant C_{13} β-hydroxyl group. Hemiketal **26** is stabilized by the diaxial orientation of the oxygen substituents (anomeric effect)[27] and by the equatorial orientation of the C_1 and C_{13} side-chains. As projected, the structure of **26** is reminiscent to that of bipinnatolide F (**3**).[6]

In conclusion, we present here an efficient strategy toward C_{13}-oxidized cembrane scaffolds that paves the way for the synthesis of complex cembrenolides. The developed approach allows construction of such scaffolds in 13 steps from readily available starting materials. Our studies suggest that the stereochemistry of the C_{13} hydroxyl group affects the mode of cyclization upon oxidation of the furan-containing starting materials. The resulting polycyclic motifs bear structural similarities to more intricate natural products. These studies could set the stage for a divergent, biomimetic synthesis of various bioactive natural products of the cembrenolide family.

Acknowledgments

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Supplementary data

Supplementary data (detailed experimental procedures, spectral characterization, and copies of ^{1}H and ^{13}C NMR data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.085.

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