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Synthesis of a Highly Functionalized Core of Verrillin

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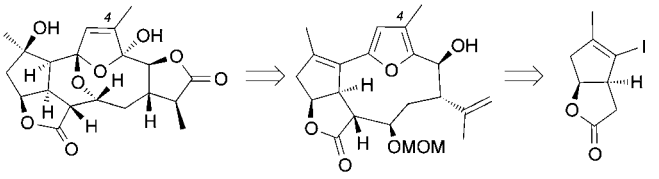
ABSTRACT



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 C_4 methyl group on the furan reactivity is also discussed.

Gorgonian octocorals and soft corals supply a diverse array of diterpenes and C_4-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 cembrenoid, was found to exhibit significant antimalarial activity against *Plasmodium falciparium* (IC_{50} ca. 10 μg/mL). In addition, potent cytotoxicity data regarding **2** have been reported against nonsmall cell lung cancer (EKVX, GI_{50} ca. 0.01 μM) and renal cancer cells (CAKI-1, GI_{50} ca. 0.50 μM).[3] Along these lines, ineleganolide (**3**) displays strong cytoxicity against P-388 cancer cells (ED_{50} 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 μM[5] while the bioactivities of verrillin (**1**)[6] have not yet been studied.

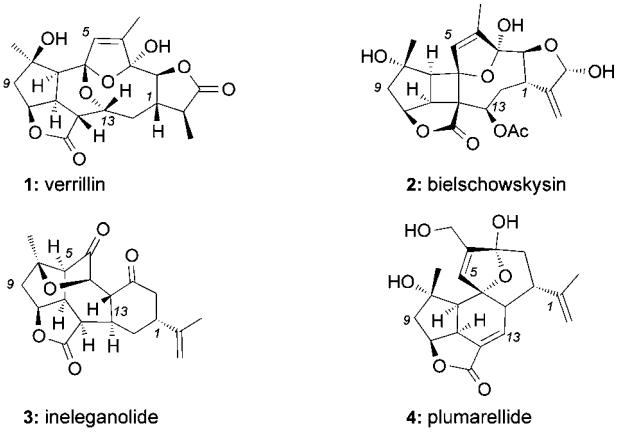


Figure 1. Structures of selected polycyclic cembrenoids.

A commonality shared by these polycyclic cembrenoids is an oxidative ring contraction of the 14-membered cembrane ring across the C_7 and C_{11} carbons thereby producing the verrillane core (**6**) (Figure 2).[3,7] Subsequent ring contractions across the C_6 and C_{12} or the C_6 and C_{14} centers would produce the bielschowskyane (**9**)[1c,3,7] and

(1) (a) Roethle, P. A.; Trauner, D. *Nat. Prod. Rep.* **2008**, *25*, 298–317. (b) Li, Y.; Pattenden, G. *Nat. Prod. Rep.* **2011**, *28*, 429–440. (c) Li, Y.; Pattenden, G. *Nat. Prod. Rep.* **2011**, *28*, 1269–1310.

(2) Lakshmi, V.; Kumar, R. *Nat. Prod. Res.* **2009**, *23*, 801–850.

(3) Marrero, J.; Rodriguez, A. D.; Baran, P.; Raptis, R. G.; Sanchez, J. A.; Ortega-Barria, E.; Capson, T. L. *Org. Lett.* **2004**, *6*, 1661–1664.

(4) Duh, C. Y.; Wang, S. K.; Chia, M. C.; Chiang, M. Y. *Tetrahedron Lett.* **1999**, *40*, 6033–6035.

(5) Stonik, V. A.; Kapustina, I. I.; Kalinovsky, A. I.; Dmitrenok, P. S.; Grebnev, B. B. *Tetrahedron Lett.* **2002**, *43*, 315–317.

(6) Rodriguez, A. D.; Shi, Y. P. *J. Org. Chem.* **2000**, *65*, 5839–5842.

(7) Saitman, A.; Sullivan, S. D. E.; Theodorakis, E. A. *Tetrahedron Lett.* **2013**, *54*, 1612–1615.

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the plumarane core (**7**),[1c] respectively. On the other hand, oxidative demethylation followed by nucleophilic ring contraction at the C_4 and C_{13} centers could assemble the inelegane core (**8**).[1c]

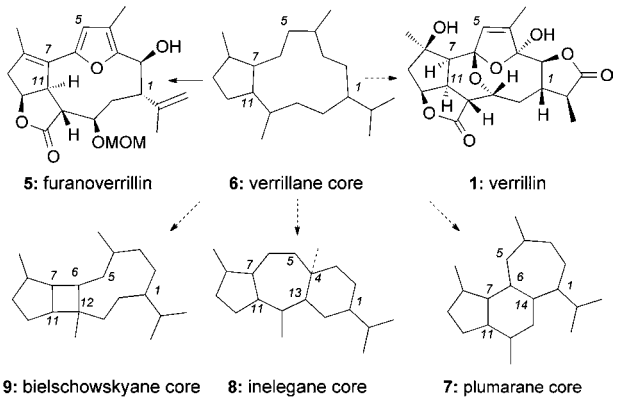


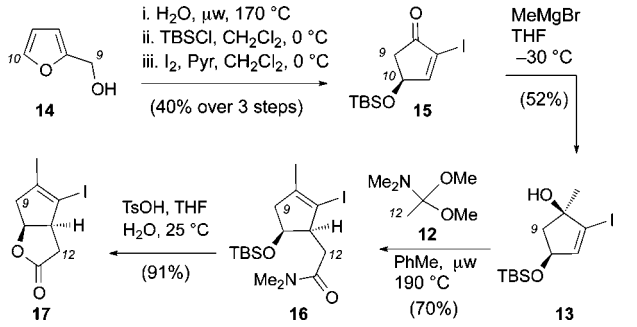
Figure 2. Carbocyclic scaffolds related to verrillane core **6**.

Although several strategies toward the synthesis of bielschowskysin[8] (**2**) and plumarellide[9] (**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 $C_{12}-C_{13}$ connection as well as provide the important C_{13} oxidation present in this family of compounds.[7] Pd(0)-coupling could then be used to join furan derivative **10** by creating the C_6-C_7 bond, while macrocylization under Nozaki–Hiyama–Kishi (NHK) conditions[12] could afford the final C_1-C_2 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 irradiation[13] 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 rearrangement[15] 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 C_{13}

(8) (a) Doroh, B.; Sulikowski, G. A. *Org. Lett.* **2006**, *8*, 903–906. (b) Miao, R.; Gramani, S. G.; Lear, M. J. *Tetrahedron Lett.* **2009**, *50*, 1731–1733. (c) Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Angew. Chem., Int. Ed.* **2011**, *50*, 5149–5152. (d) Farcet, J.; Himmelbauer, M.; Mulzer, J. *Org. Lett.* **2012**, *14*, 2195–2197. (e) Jana, A.; Mondal, S.; Hossain, M. F.; Ghosh, S. *Tetrahedron Lett.* **2012**, *53*, 6830–6833.

(9) (a) Li, Y.; Pattenden, G. *Tetrahedron Lett.* **2011**, *52*, 2088–2092. (b) Palframan, M.; Pattenden, G. *Tetrahedron Lett.* **2013**, *54*, 324–328.

(10) Saitman, A.; Rulliere, P.; Sullivan, S. D. E.; Theodorakis, E. A. *Org. Lett.* **2011**, *13*, 5854–5857.

(11) (a) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, *47*, 2425–2429. (b) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939–3002.

(12) (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1979**, *99*, 3179–3181. (b) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, T. *Tetrahedron Lett.* **1983**, *24*, 5281–5284. (c) Fürster, A. *Chem. Rev.* **1999**, *99*, 991–1045.

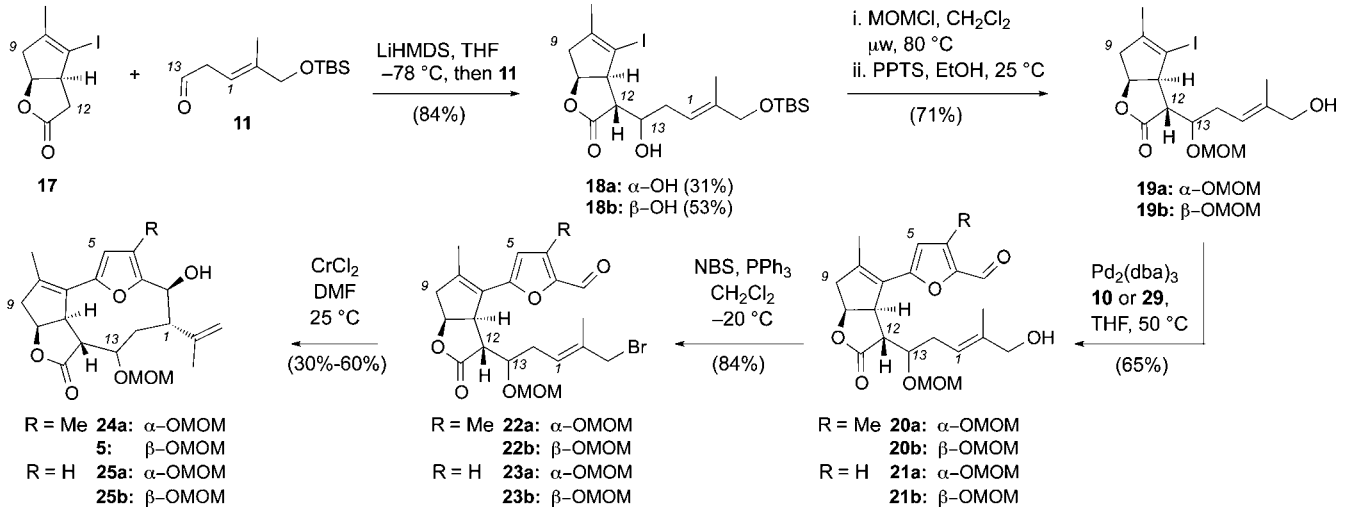
(13) Kruger, G.; Harde, C.; Bohlmann, F. *Tetrahedron Lett.* **1985**, *49*, 6027–6030.

(14) Otero, M. P.; Santin, E. P.; Rodriguez-Barrios, F.; Vaz, B.; De Lera, A. R. *Biorg. Med. Chem. Lett* **2009**, *19*, 1883–1886.

(15) Mulzer, J.; Giester, G.; Gilbert, M. *Helv. Chim. Acta* **2005**, *88*, 1560–1579.

(16) (a) Lautens, M.; Paquin, J.-F. *Org. Lett.* **2003**, *5*, 3391–3394. (b) Bourcet, E.; Fache, F.; Piva, O. *Tetrahedron* **2010**, *66*, 1319–1326. (c) The stereochemistry of the C_{13} hydroxyl group was unambiguously determined after macrocyclization via single crystal X-ray diffraction analysis of compounds **25a** and **33b**.

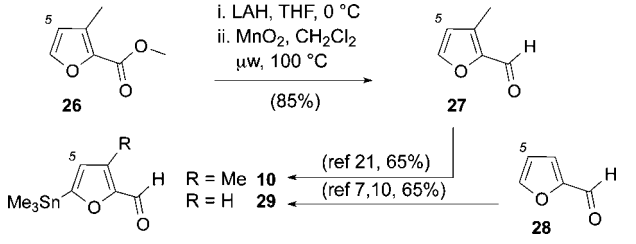
Scheme 3. Synthesis of Furanoverrillin **5** and Derivatives



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 MOMCl[17] 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 alcohol[19] that, after oxidation with manganese dioxide[20] 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**



To our chagrin, coupling of stannane **10** with primary alcohols **19a** and **19b** under the previously established Stille conditions ($Pd(PPh_3)_4/CuI$)[7,10,21] was not successful. However, switching of reagents to catalytic $Pd_2(dba)_3$ and triphenylarsine[22] cleanly afforded compounds **20a** and **20b** in 65% average yield (Scheme 3). Appel bromination conditions[23] were employed to convert alcohols **20a** and **20b** to their corresponding bromides **22a** and **22b** (ca. 84% yield).

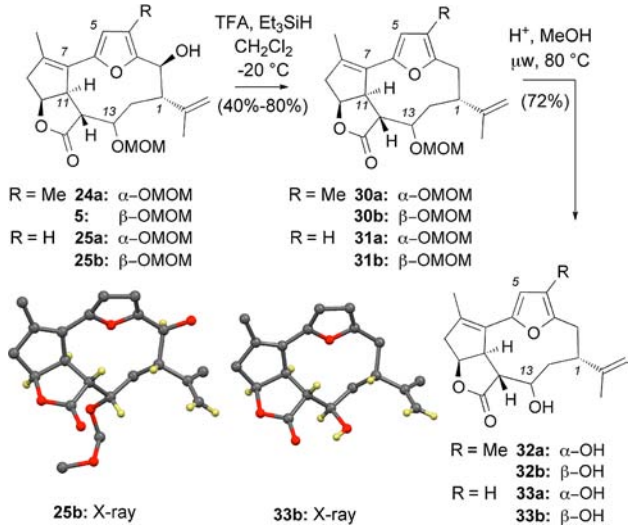
The final macrocyclization event that would create the 10-membered macrocycle[24] also proved to be more problematic than previously described[7,10,21] leading to a complex mixture of products. Changing the solvent from THF to DMF[25] greatly improved the reaction outcome to afford furanoverrillin (**5**), containing the desired verrillin stereochemistry at C_{13}, together with its C_{13} α-isomer **24a** in 30% combined yield. The diastereoselectivity of the macrocyclization was 4/1 anti/syn with respect to the orientation of the C_2 alcohol and the C_1 isopropene.[24a]

Compounds **5** and **24a** were subjected to standard C_2 deoxygenation conditions using triethylsilane and trifluoroacetic acid[26] to produce deoxygenated products **30a** and **30b** in lower than expected yields (ca. 40% yield) (Scheme 5).[7,10,21]

(17) Maegawa, T.; Otake, K.; Hirosawa, K.; Goto, A.; Fujioka, H. *Org. Lett.* **2012**, *14*, 4798–4801.
(18) Crouch, R. D. *Tetrahedron* **2004**, *60*, 5833–5871.
(19) Aldington, R. M.; Baldwin, J. E.; Mayweg, A. V. W.; Pritchard, G. J. *Org. Lett.* **2002**, *4*, 3009–3011.
(20) Hashami, A. S. K.; Haffner, T.; Yang, W.; Pankajakshan, S.; Schafer, S.; Schultes, L.; Rominger, F.; Frey, W. *Chem.—Eur. J.* **2012**, *18*, 10480–10486.
(21) Roethle, P.; Trauner, D. *Org. Lett.* **2006**, *8*, 345–347.
(22) (a) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595. (b) Farina, V.; Kapadia, S.; Krishman, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **2000**, *65*, 3192–3199. (c) Roth, G. P.; Farina, V. *Tetrahedron Lett.* **1995**, *36*, 2191–2194.
(23) Appel, R. *Angew. Chem., Int. Ed.* **1975**, *14*, 801–811.
(24) (a) Huang, Q. H.; Rawal, V. H. *Org. Lett.* **2006**, *8*, 543–545. (b) Paquette, L. A.; Astles, P. C. *J. Org. Chem.* **1993**, *58*, 165–169. (c) Rayner, C. M.; Astles, P. C.; Paquette, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 3926–3936.
(25) Maguire, R. J.; Mulzer, J.; Bats, J. W. *Tetrahedron Lett.* **1996**, *37*, 5487–5490.
(26) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, *9*, 633–651.
(27) Yadav, J. S.; Premalatha, K.; Harshavardhan, S. J.; Reddy, B. V. S. *Tetrahedron Lett.* **2008**, *49*, 6765–6767.

Acid-induced MOM deprotection under microwave conditions[27] 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 C_2 center, as previously reported for certain C_2 hydroxyfuranocembrenolides 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 NHK[12] conditions were then applied using DMF as a solvent,[25] a clean conversion to the desired nor-furanoverrillin intermediates **25a** and **25b** was observed in good yields (ca. 60% yield). Deoxygenation at the C_2 center using triethylsilane and trifluoroacetic acid[26] also cleanly produced deoxygenated intermediates **31a** and **31b** in noticeably increased yields. Finally, acidic removal of the MOM group[27] 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 cembrenoids. Our approach relies on introduction of the C_7-C_{11} cyclopentene ring prior to the macrocyclization of the fully functionalized verrillin core. We observed that the presence of a C_4 methyl group at the furan ring increases its susceptibility toward oxidative decomposition. In turn, this attests to the role of the C_4 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 ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

(28) (a) Hyde, E. G.; Thornhill, S. M.; Boyer, A. J.; Abramson, S. N. *J. Med. Chem.* **1995**, *38*, 4704–4709. (b) Rodriguez, A. D.; Shi, J.-G.; Shi, Y.-P. *J. Org. Chem.* **2000**, *65*, 3192–3199.

(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.

(30) (a) Roethle, P. A.; Hernandez, P. T.; Trauner, D. *Org. Lett.* **2006**, *8*, 5901–5904. (b) Tang, B.; Bray, C. D.; Pattenden, G. *Tetrahedron Lett.* **2008**, *47*, 6401–6404. (c) Kimbrough, T. J.; Roethle, P. A.; Mayer, P.; Trauner, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 1–4. (d) Marshall, J. A.; Griot, C. A.; Chobanian, H. R.; Myers, W. H. *Org. Lett.* **2010**, *12*, 4328–4331. (e) Li, Y.; Pattenden, G. *Tetrahedron* **2011**, *67*, 10045–10052.

The authors declare no competing financial interest.