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Novel Synthesis of the C1–C15 Polyether Domain of the Thyrsiferol and Venustatriol Natural Products

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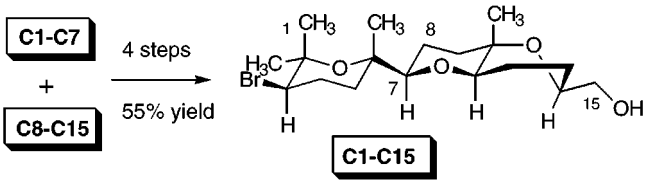
ABSTRACT



A convergent construction of the C1–C15 domain of the thyrsiferol-related natural products has been developed. This involved the separate construction of C1–C7 and C8–C15 fragments, their organochromic-mediated coupling, and subsequent reductive closure of the B ring. This synthetic A–B–C ring construct will be useful for the total synthesis of the biologically active polyether squalenoid natural products, as well as their non-natural analogues.

The marine algae metabolites thyrsiferol (**1**),[1,2] venustatriol (**4**),[2] and congeners[3−7] represent a biogenetically unique class of squalene-derived polyether natural products that display a range of potent biological activities (Figure 1). Chief among these are venustatriol's potent antiviral activity[2] and thyrsiferyl 23-acetate's (**2**) in vitro cytotoxicity toward P388 murine leukemia (ED_{50} = 0.3 ng/mL, 0.5 nM)[4] and selective inhibition of the protein serine/threonine phosphatase 2A (IC_{50} = 4−16 μM).[8] The polyether structures of these squalenoid natural products are characterized by a bromotetrahydropyranyl A ring appended directly to a trans-fused 2,7-dioxabicyclo-[4.4.0]decane B−C ring system and a side chain-linked tetrahydrofuran D ring. X-ray analyses of thyrsiferyl 18-acetate (**3**)[1] and **4**[2] revealed that the B−C rings adopt a chair-twist-boat conformation that is phenotypic of this class, to avoid 1,3-diaxial interactions between the

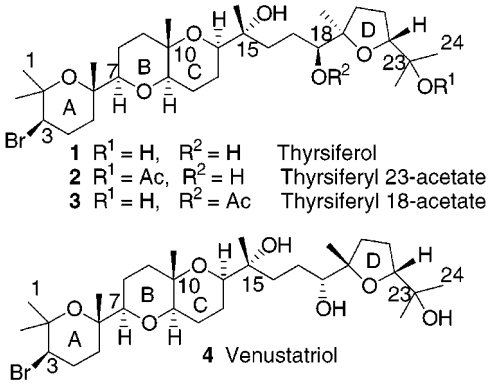


Figure 1. Structures of thyrsiferol and venustatriol.

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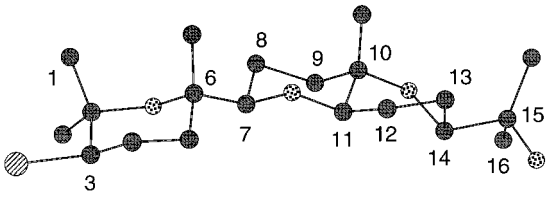
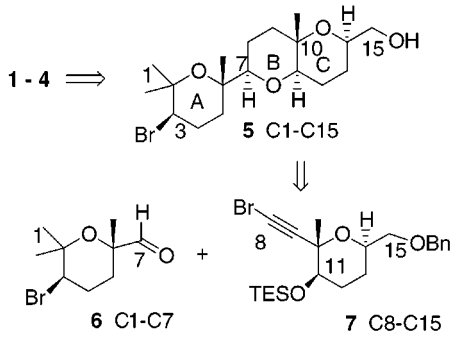


Figure 2. X-ray conformation of the C1−C15 domain of thyrsiferyl 18-acetate, highlighting the C10−C14 twist-boat.[1]

angular methyl group at C10 and the C15 side chain (Figure 2). The distinct structural features of the A−B−C ring system have motivated the synthetic strategies that have been devised toward these natural products.[9−15] Reported here is a novel assembly of the A−B−C ring system of thyrsiferol and venustatriol.

A convergent synthetic approach to these natural products involves the separate construction of two fragments representing C1−C15 (**5**) and C16−C24 domains (Scheme 1).

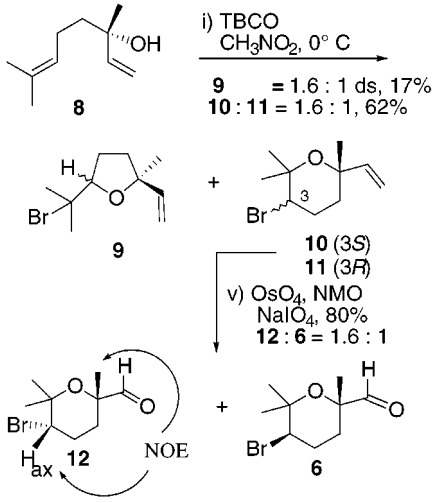
Scheme 1. Retrosynthesis of the C1−C15 Domain of the Thyrsiferol and Venustatriol Natural Products



The aldehyde corresponding to **5** was an advanced intermediate used in Corey's total synthesis of **4**,[14] whereas Shirahama[9] and Broka[15] have also prepared A−B−C ring constructs related to **5**. In the total syntheses of **1**, **2**, and **4**, Shirahama assembled these rings in the order B−C−A, highlighting the use of epoxy alcohol opening/ring expansion strategies for the B and C rings, and a brominative cyclization to close the A ring. Corey's concise synthesis of **4** featured a C−B−A ring closure sequence involving cyanohydrin formation, distal hydroxyl-directed asymmetric epoxidation−epoxy alcohol opening, and brominative cyclization, respectively. Broka innovated the use of intramolecular oxymercurations to sequentially close the C and B rings, followed by bromoetherification to access the A ring. The combined yields for the three key etherification steps in each of these approaches range from 4 to 16%. This is largely due to the low yielding formation of the desired bromotetrahydropyranyl A ring via intramolecular bromoetherification (22−36% yield).[13−15] Here, the problematic A ring is constructed independently and at the outset, and then joined in the form of C1−C7 aldehyde **6** to a fragment containing the preformed C ring and representing C8−C15 (**7**). Subsequent annulation to close the B ring completes the synthetic sequence.

The synthesis of aldehyde **6** began with (*S*)-(+)-linalool (**8**) which was prepared from geraniol in 95% ee (Mosher ester analysis) by sequential Sharpless asymmetric epoxidation,[16] tosylation, and Te-assisted reduction (Scheme 2).[17]

Scheme 2. Synthesis of the C1−C7 A-Ring (**6**)



Tertiary alcohol **8** was treated with TBCO[18] in CH_3NO_2 at 0 °C to give a mixture of bromotetrahydrofurans **9** (17% yield) and tetrahydropyrans **10** (38%) and **11** (24%).[19] Although the direct yield of the desired tetrahydropyran **11** was comparable to those reported for similar bromoetherifications,[13−15] far less of the 5-exo tetrahydrofuran products (**9**) were obtained. The mild diastereoselectivity reflects the preferential axial orientation of the terminal alkene in the transition state leading to **10**. Isomers **9** and **10** could be reverted to **8** by treatment with Zn in AcOH−EtOH,[14,15] but separation of **10** and **11** was difficult. Subjection of the mixture of **10** and **11** to alkene oxidation allowed facile chromatographic separation to provide epimeric bromo

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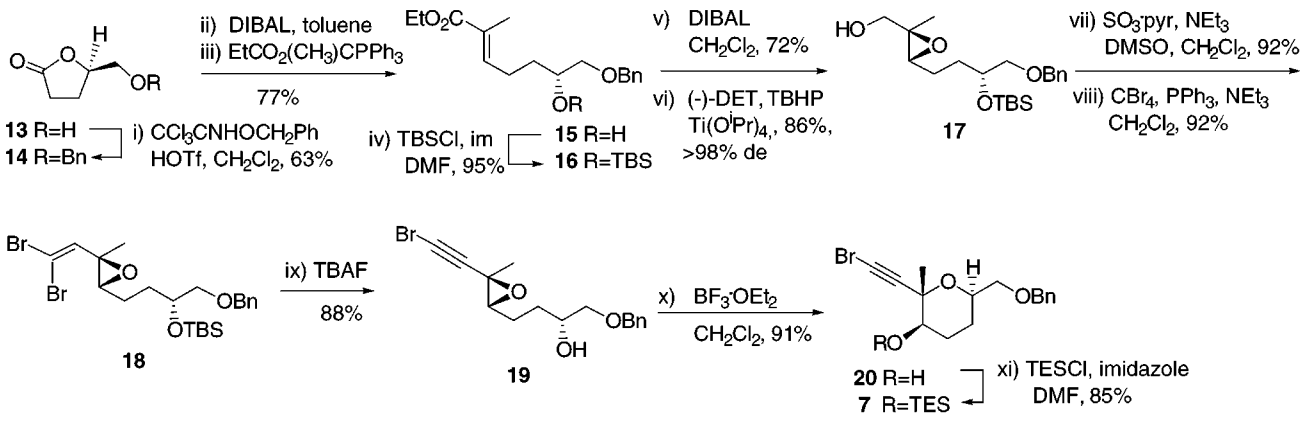
Scheme 3. Synthesis of the C8−C15 C-Ring (**7**)



aldehydes **12** and **6**. Bromooxane **12** showed unique NOEs that were absent in **6** (Scheme 2). Executing the bromoetherification early in the synthesis and the opportunity to revert the undesired bromo ether isomers to **8** ameliorates the low yield.

The bromoalkyne **7** was targeted to serve as a C-ring coupling partner to the A-ring aldehyde **6**. The strategy for the synthesis of **7** was to perform an intramolecular epoxide opening of a trisubstituted, trans γ,δ-epoxy alcohol. Hanaoka and co-workers had found that trans propargylic epoxides bearing electron-withdrawing substituents at the alkyne terminus favored 5-exo etherification upon treatment with $BF_3{\cdot}OEt_2$.[20] A δ-hydroxy disubstituted acetylenic cis-epoxide was reported to also give nearly exclusively the 5-exo ring-opening product upon treatment with catalytic CSA.[21] The presence of both a methyl and an alkyne substituent on the distal position of the trans epoxide was anticipated to direct regioselective 6-endo ring formation. To test this hypothesis the requisite epoxy alcohol was prepared from lactone **13**, which in turn was obtained from D-glutamic acid in two steps (Scheme 3).[22,23] Acid-catalyzed benzylation of **13** followed by reduction with DIBAL and direct treatment of the lactol with (carbethoxyethylene)triphenylphosphorane afforded the α,β-unsaturated ester **15**. The resulting free hydroxyl group was silylated, and the ester was reduced with DIBAL to furnish the corresponding allylic alcohol. A Sharpless asymmetric epoxidation[16] using D-(−)-diethyl tartrate provided the epoxy alcohol **17**.[24] Subsequent oxidation with $SO_3{\cdot}$pyr gave the epoxy aldehyde, which was converted[25,26] into dibromoalkene **18** in high yield. Treatment of **18** with TBAF conveniently induced both desilylation and monodehydrobromination to yield the hydroxyalkynyl epoxide **19**.

Upon treatment of **19** with catalytic CSA, a 76:24 ratio of THP:THF isomers was obtained in 98% combined yield. In contrast, a highly regio- and stereoselective etherification was effected by treatment of the propargylic epoxide with $BF_3{\cdot}OEt_2$ at −10 °C, which resulted in tetrahydropyran **20** as the essentially exclusive product. Hence, the presence of the methyl substituent at the propargylic position stabilizes incipient positive charge destiny leading to 6-endo etherification. The secondary hydroxyl at C11, which would soon serve as the B ring heteroatom, was temporarily masked as a TES ether to complete the synthesis of the C-ring intermediate **7**.

The final B ring could be assembled in four steps via the convergent coupling of A and C rings. An organochromic-mediated coupling[27,28] of the C8−C15 alkynyl bromide **7** with the C1−C7 aldehyde **6** provided a moderate yield of propargylic alcohols **21** nonstereoselectively (Scheme 4). It is noteworthy that the secondary alkyl bromide of **6** withstands this mild carbon−carbon bond-forming process, as well as the subsequent chemistry en route to **5**. Initial attempts to saturate the alkyne of **21** were accompanied by premature liberation of the primary and secondary hydroxyl groups. Semi-hydrogenation (H_2, $Pd/CaCO_3/Pb$) of alkyne **21** gave the corresponding (*Z*)-allylic alcohols without cleavage of the benzyl or TES ethers, but subsequent oxidation to the enone was problematic. However, **21** was converted efficiently into ynone **22**, which upon $Pd(OH)_2$-mediated hydrogenation yielded hemiketal **23**, as a result of triple bond saturation and liberation of both silyl- and benzyl-masked hydroxyls at C11 and C15, respectively.[29] Efficient and stereoselective axial delivery of hydride to the oxonium

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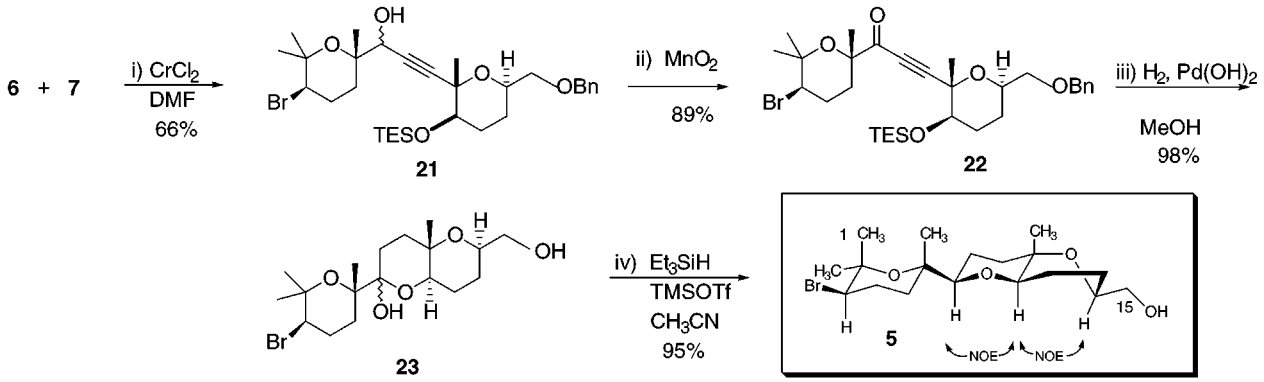
Scheme 4. Synthesis of the C1−C15 Domain (**5**) of the Thyrsiferol and Venustatriol Natural Products



species generated from **23** upon treatment with TMSOTf and Et_3SiH[30] then completed the synthesis of the B ring, as well as the entire C1−C15 system **5**. The stereochemistry of **5** was confirmed by NOE studies, summarized in Scheme 4.

This novel and convergent construction of the A−B−C system of the thyrsiferol natural products provides the C1−C15 domain in 15 steps in the longest linear sequence from the glutamic acid derivative **13**. The combined yield is 21% for the bromoetherification, hydroxy epoxide opening, and hemiketal reductive ring-forming steps. Application of this convergent approach to the total synthesis of thyrsiferol-type natural and unique non-natural products will be reported in due course.

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Supporting Information Available: Experimental procedures for the preparation of compounds **5**−**7** and **9**−**23** and their full characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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