

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

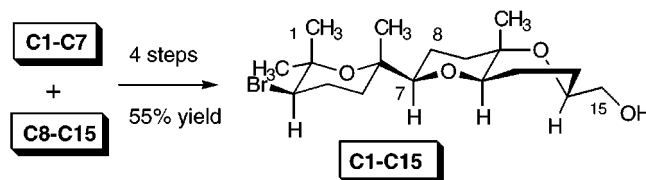
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ABSTRACT



A convergent construction of the C1–C15 domain of the thyrseferol-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 thyrseferol (**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 activity² and thyrseferyl 23-acetate's (**2**) in vitro cytotoxicity toward P388 murine leukemia ($ED_{50} = 0.3 \text{ ng/mL}$, 0.5 nM)⁴ and selective inhibition of the protein serine/threonine phosphatase 2A ($IC_{50} = 4\text{--}16 \text{ }\mu\text{M}$).⁸ The polyether structures of these squalenoid natural products are characterized by a bromotet-

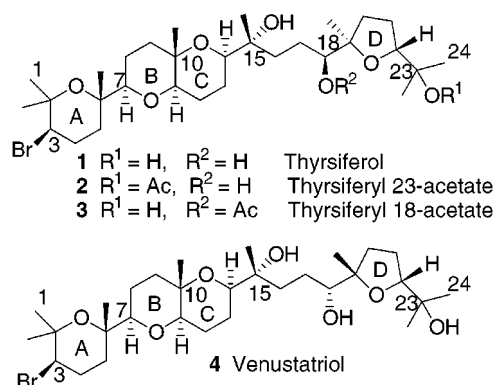


Figure 1. Structures of thyrseferol and venustatriol.

rahydropyranyl 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 thyrseferyl 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

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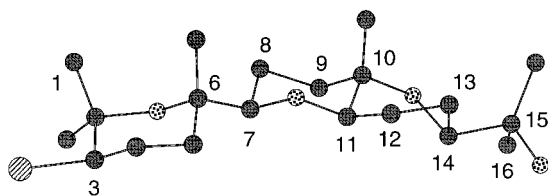
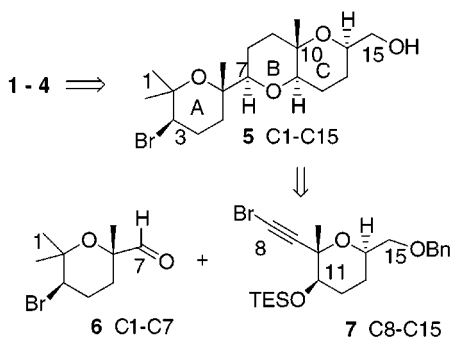


Figure 2. X-ray conformation of the C1–C15 domain of thyransferyl 18-acetate, highlighting the C10–C14 twist-boat.¹

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 thyransferol 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 Thyransferol and Venustatriol Natural Products

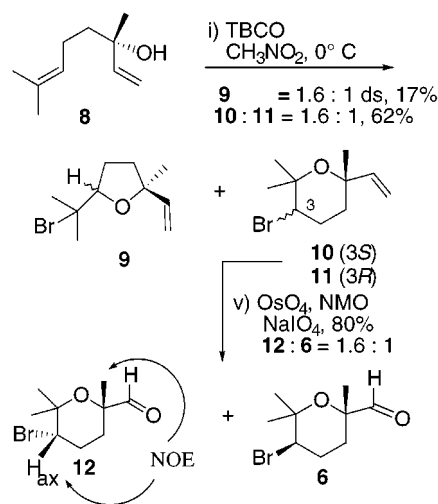


The aldehyde corresponding to **5** was an advanced intermediate used in Corey's total synthesis of **4**,¹⁴ whereas Shirahama⁹ and Broka¹⁵ have also prepared A–B–C ring constructs related to **5**. In the total syntheses of **1**, **2**, and **4**, Shirahama assembled these rings in the order B–C–A, 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 oxymercuration 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 TBCO¹⁸ in CH₃NO₂ 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. Subjecting the mixture of **10** and **11** to alkene oxidation allowed facile chromatographic separation to provide epimeric bromo

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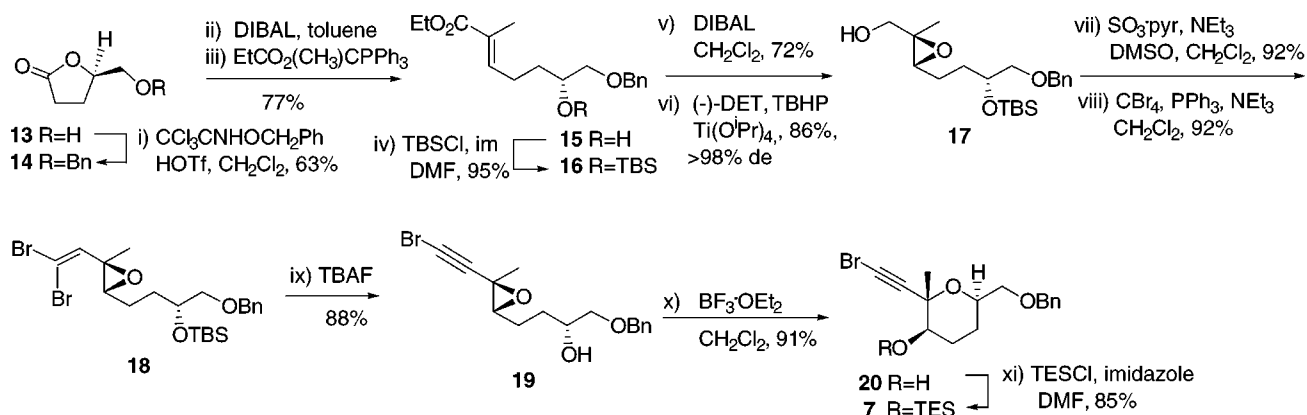
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Scheme 3. Synthesis of the C8–C15 C-Ring (7)



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 $\text{BF}_3\cdot\text{OEt}_2$.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 benzoylation 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 epoxidation¹⁶ using D-(-)-diethyl tartrate provided the epoxy alcohol **17**.²⁴ Subsequent oxidation with $\text{SO}_3\cdot\text{pyr}$ 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 monodehydrode-bromination 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 $\text{BF}_3\cdot\text{OEt}_2$ 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/CaCO₃/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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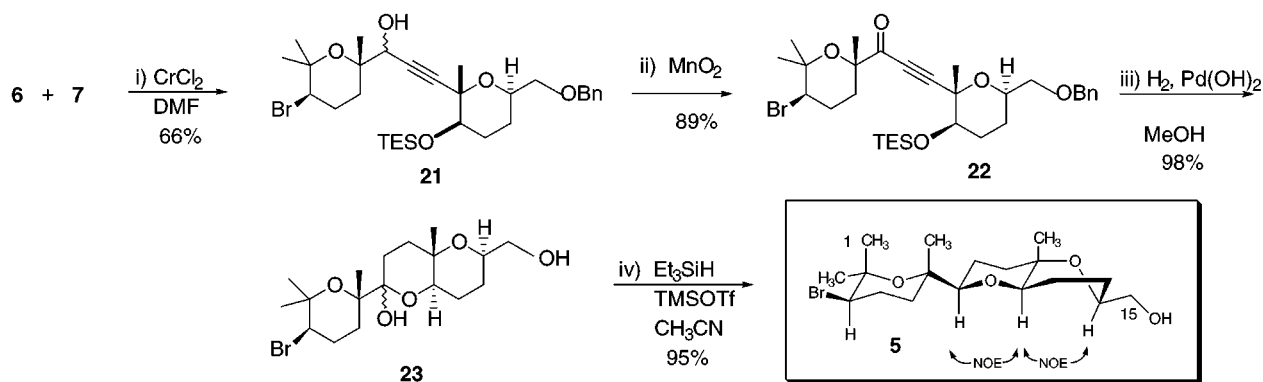
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Scheme 4. Synthesis of the C1–C15 Domain (**5**) of the Thysiferol and Venustatriol Natural Products



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 thysiferol 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 thysiferol-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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