Total Synthesis of Thyrsiferyl 23-Acetate, a Specific Inhibitor of Protein Phosphatase 2A and an Anti-Leukemic Inducer of Apoptosis

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Abstract: A convergent synthetic entry to the squalenoid polyether system has been developed and applied to the biologically active marine natural products thyrsiferyl 23-acetate (**1a**), thyrsiferol (**1b**), thyrsiferyl 18-acetate (**1c**), and thyrsiferyl 18,23-diacetate (**1d**). This involved the separate construction of two advanced intermediates representing the C1−C15 (**4**) and C16−C24 (**5**) domains, followed by their organochromium-mediated coupling, installation of the tertiary alcohol at C15, and manipulation of the C18 and C23 acetate moieties. The C1−C15 (**4**) intermediate containing the three tetrahydropyranyl rings (A−B−C) was derived from two preconstructed tetrahydropyran-containing units representing the functionalized A (C2−C6) and C (C10−C14) rings (**6** and **7**, respectively). The bromotetrahydropyranyl A ring was obtained via bromoetherification of the hydroxyalkene **16**, which was synthesized from (2*R*,3*R*)-epoxy geraniol. The C ring was stereoselectively constructed by acid-catalyzed opening of the hydroxy epoxide **32**, derived from D-glutamic acid. Intermediates **6** and **7** were joined using organochromium conditions, and ketone and hydroxyl functionalities were installed at carbons 7 and 11, respectively. Closure of the B ring was accomplished stereoselectively by formation of species derived from a C7, C11 keto-alcohol and in situ reduction of a tetrahydropyranyl oxonium. The complementary tetrahydrofuran D (C19−C22) ring was obtained from a geraniol-derived tertiary hydroxy alkene (**44**) via a stereoselective Re(VII)-induced *syn*-oxidative cyclization. The side chain appended to the D ring was elaborated into *trans*-alkenyl iodide **5** under Takai reaction conditions. $CrCl_2$-mediated coupling of aldehyde **4**, containing the secondary bromide at C3 of the natural products, with iodide **5** bearing acetate moieties at C18 and C23, installed the C15−C16 carbon−carbon bond. The resultant C15 allylic carbinol was converted into an α,β-saturated ketone, and the final methyl group was added stereoselectively using methylmagnesium bromide. Saponification of the C18 acetate yielded **1a**, whereas cleavage of both C18 and C23 acetates gave the triol **1b**. This modular entry into the squalenoid−polyether system may facilitate further evaluation of the antileukemic, apoptosis-inducing, protein serine/threonine phosphatase 2A inhibitory and anti-multidrug resistance activities of the thyrsiferol-derived natural products.

A variety of squalene-derived natural products that present strong cytotoxic properties have been isolated from marine red algae of the genus *Laurencia*.[1] Among this class of compounds, thyrsiferyl 23-acetate (**1a**, Figure 1) appears to elicit the most intriguing array of biological responses.[2] Compound **1a** exhibits superior in vitro cytotoxic activity against P-388 murine leukemia ($IC_{50} = 0.5$ nM)[2] and specific inhibition of protein serine/threonine phosphatase 2A (PP2A) ($IC_{50} = 4-16\ \mu$M),[3] whereas several other phosphatases, including protein phospatases 1 (PP1), 2B (PP2B), and 2C (PP2C) or protein tyrosine phosphatases, are not affected by **1a** at concentrations up to 1 mM. More recently, **1a** and several related analogues[4] induced rapid apoptotic cell death in a variety of human leukemic T- and B-cell lines.[5] However, among these compounds only **1a** also appreciably inhibits PP2A and may be a useful probe for identification of cellular processes reliant upon PP2A activity.[6] Exogenous compounds that induce apoptotic death of cancer cells represent a mechanistically important class of potential therapeutic agents,[7] whereas very few highly specific inhibitors of PP2A are known.[8] Remarkably, the close structural analogue 15(28)-anhydrothyrsiferol (**2b**) was found to circumvent multidrug resistance

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(4) Thyrsiferol (**1b**), 15(28)-anhydrothyrsiferyl-23-acetate (**2a**), thyrsiferyl 18-acetate (**1c**), and thyrsiferyl 15, 18, 23-triacetate.

(5) (a) Matsuzawa, S.-I.; Kawamura, T.; Mitsuhashi, S.; Suzuki, T.; Matsuo, Y.; Suzuki, M.; Mizuno, Y.; Kikuchi, K. *Bioorg. Med. Chem.* **1999**, *7*, 381−387. (b) Kikuchi, K.; Shima, H.; Mitsuhashi, S.; Suzuki, M.; Oikawa, H. *Int. J. Mol. Med.* **1999**, *4*, 395−401.

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(8) Okadaic acid: $IC_{50\ PP1/PP2A} = 10^2-10^3$, $IC_{50\ PP2A} = 32$ pM (Takai, A.; Sasaki, K.; Nagai, H.; Mieskes, G.; Isobe, M.; Isono, K.; Yasumoto, T. *Biochem. J.* **1995**, *306*, 657−665; Bialojan, C.; Takai, A. *Biochem. J.* **1988**, *256*, 283−290). Fostriecin: $IC_{50\ PP1/PP2A} = 10^4-10^5$, $IC_{50\ PP2A} = 3.2-40$ nM (Roberge, M.; Tudan, C.; Hung, S. M. F.; Harder, K. W.; Jirik, F. R.; Anderson, H. *Cancer Res.* **1994**, *54*, 6115−6121; Walsh, A. H.; Cheng, A.; Honkanen, R. E. *FEBS Lett.* **1997**, *416*, 230−234).

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mediated by P-glycoprotein and might therefore be an interesting candidate for detailed future investigations on these grounds.[9] In addition, **2b** has been reported to cause growth inhibition in KB cancer cells without inducing apoptosis.[10]

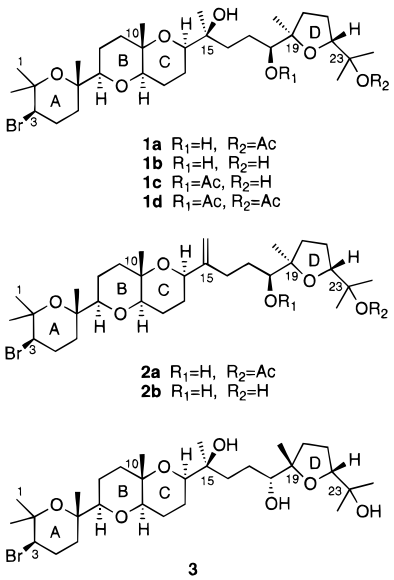
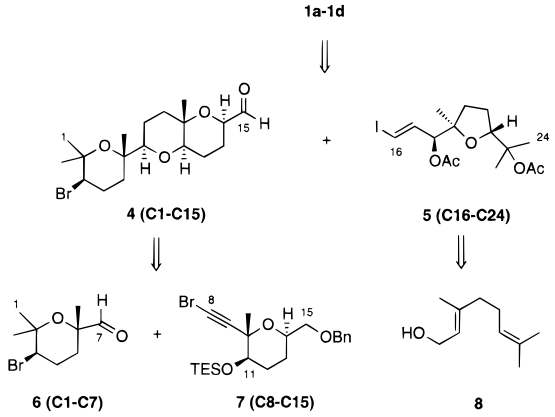


Figure 1.

The unique squalenoid polyether structures of thyrsiferol and its acetate derivatives feature a bromotetrahydropyranyl A ring (C2−C6) appended directly to a trans-fused 2,7-dioxabicyclo-[4.4.0]decane B−C ring system (C7−C14), which in turn is tethered to a distal tetrahydrofuranyl D ring (C19−C22). X-ray analysis of thyrsiferyl 18-acetate[1a] (**1c**) and the related venustatriol[1c] (**3**) revealed that the B−C rings adopt a unique chair-twist boat conformation to avoid 1,3-diaxial interactions in the C ring. The biogenesis of these polyether natural products has been proposed to involve attack by a bromonium ion at the C2−C3 double bond, causing a concerted cyclization of three epoxides at C6−C7, C10−C11, and C14−C15 as a first step and the formation of the furan ring by protonation of either the C18−C19 or the C22−C23 epoxides as a second step.[1c] This hypothesis was reinforced by the identical configuration of the C1−C15 moiety exhibited by most of the squalenoid polyethers isolated from the *Laurencia* species. However, the isolation of additional structural variations of these polyethers, including callicladol,[1e] 10-epidehydrothyrsiferol,[1f] isodehydrothyrsiferol,[1f] thyrsenols A and B,[1g] and predehydrovenustatriol acetate,[1h] may suggest that the polycyclizations are not entirely concerted.

The biological activities of these squalenoid polyethers are exquisitely sensitive to gross as well as minor changes in structure. Degradation studies involving oxidative fragmentation of **1b** and **2b** gave subunits that were devoid of significant cytotoxic activity.[11] Molecular modeling studies have suggested that the presence of the flexible chain around C14 to C19 is one of the fundamental factors related to the cytotoxic activity of these metabolites.[11] Apparently, the hydroxyl at the C15 position is not essential for cytotoxic activity, considering the similar IC_{50} values of **1b** and **2b** against P-388 leukemia cells.[12]

Scheme 1



However, the hydroxyl at C18 may be important in light of the lower cytotoxic activity of **1c**.[12] In addition, recent studies have suggested that the induction of apoptosis by **1a** may require structural features that are different from those involved in the inhibition of PP2A. However, the structural bases for these diverse activities have not been established.

The biogenetic features and classic structures of these polyethers have stimulated considerable synthetic activity,[13−15] which had previously culminated in total syntheses of **1a**[14c,14d] and **1b**,[14b,14d] as well as **3**.[14b,14d,15] The recent recognition of distinct biological activities of thyrsiferyl derivatives, including the induction of apoptosis, selective inhibition of PP2A by **1a**, and anti-multidrug resistance by **2b**, has prompted renewed interest in this class of compounds. However, dissection and exploitation of the manifold activities of the thyrsiferol derivatives will require the emergence of a reliable and general source of these compounds.

Reported here is a modular total synthesis of thyrsiferyl 23-acetate (**1a**) and its derivatives (**1b**, **1c**, and **1d**) that highlights a rapid and convergent entry into the squalenoid/polyether system. This involves the optimal sequencing of distinct etherification processes to construct each of the cyclic ethers and strategic derivatization of hydroxyl groups in concert with chemoselective carbon−carbon bond formation. This novel entry into the thyrsiferol system may provide unique access to natural and unnatural derivatives in support of continued biological evaluation of these remarkable compounds.

Results and Discussion

Synthetic Plan. A convergent synthetic approach to these natural products involves the separate construction of two fragments representing C1−C15 (**4**)[16] and C16−C24 (**5**) (Scheme 1). The aldehyde **4** was synthesized from farnesol in Corey's seminal total synthesis of venustratriol.[15] A key feature of our synthetic plan was the independent construction of the

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(10) (a) Pec, M. K.; Hellan, M.; Moser-Their, K.; Fernández, J. J.; Souto, M. L.; Kubista, E. *Anticancer Res.* **1997**, *17*, 4090. (b) Pec, M. K.; Hellan, M.; Moser-Their, K.; Fernández, J. J.; Souto, M. L.; Kubista, E. *Anticancer Res.* **1998**, *18*, 3027−3032.

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(12) $IC_{50\ \mathbf{1b}}$ = 16 nM,[2] $IC_{50\ \mathbf{2b}}$ = 17 nM,[11] $IC_{50\ \mathbf{1c}}$ = 464 nM.[2]

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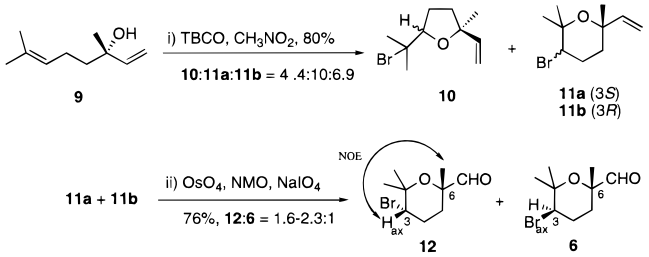
Scheme 2



bromotetrahydropyranyl A ring which was joined in the form of the C1−C7 aldehyde **6** to a fragment containing the preformed C ring, represented by the C8−C15 bromide **7**. In previous studies toward the synthesis of the thyrsiferol and venustatriol natural products, low-yielding intramolecular bromoetherifications (<26%) were employed to prepare the A ring late in the synthetic sequences. This fact detracted from the overall efficiency of former routes. In contrast, the problematic A ring (**6**) was assembled early in the present synthetic sequence and then was joined with alkynyl bromide **7** under organochromium[17,18] conditions. Subsequent reductive closure of the intervening B ring concludes the preparation of the C1−C15 domain of the thyrsiferol- and venustatriol-related natural products.

The tetrahydrofuran D ring-containing fragment (**5**) of thyrsiferyl 23-acetate (**1a)** and derivatives was envisioned to come from geraniol (**8**, Scheme 1) via stereoselective Re(VII)-induced *syn*-oxidative cyclization.[19−21] The utilization of acetates at C18 and C23 in **5** would minimize protection and deprotection manipulations at the end of the synthesis. This, however, would require a fragment coupling under mild and chemoselective conditions that would be unprecedented in the context of squalenoid polyether synthesis. Hence, advanced intermediates **4** and **5** would be coupled under organochromium-mediated conditions en route to the natural products.[22] The synthesis of **1a** and its derivatives thus began with the preparation of aldehyde **6**, alkynyl bromide **7**, and vinyl iodide **5**, and an examination of their sequential couplings.

Synthesis of the C1−C7 Aldehyde (6). Initially, the construction of the A ring of **1a**−**1d** from (*S*)-linalool (**9**) via bromoetherification using 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO)[23] was explored. (*S*)-Linalool was efficiently prepared from geraniol by sequential Sharpless asymmetric epoxidation, tosylation, and Te-assisted reduction (Scheme 2).[24] Thereafter, treatment of **9** with TBCO provided in good yield (∼80%)[25] a mixture of tetrahydrofurans **10** and tetrahydropyrans

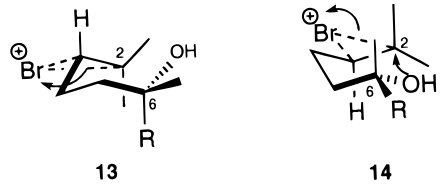
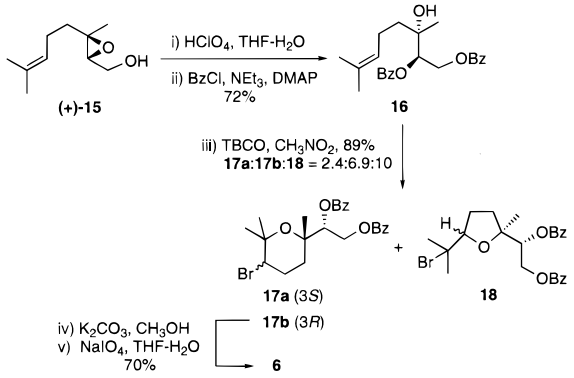


Figure 2.

Scheme 3



11a and **11b** in the **10**/**11a**/**11b** ratio 4.4:10:6.9.[26] After partial separation by MPLC, a mixture (86−90% pure by GC) of tetrahydropyrans **11a** and **11b** (**11a**/**11b** = 1.6−2.3:1)[26] was isolated in ∼56% yield.[25] The resultant mixture of tetrahydropyrans **11** was treated with osmium tetroxide, *N*-methyl morpholine oxide, and sodium periodate to obtain a mixture of aldehydes **12** and **6** (**12**/**6** = 1.6−2.3:1)[26] in ∼76% combined yield.[25] After isolation of each aldehyde by MPLC, the configuration of **12** was assigned by detection of an NOE between the proton at C3 and the methyl group at C6 which was not present in the desired (3*R*)-bromo aldehyde **6** (Scheme 2). Alternatively, oxidative cleavage of the mixture of compounds **10** and **11** provided aldehyde **6** in approximately the same yield (∼12%) from **9** after just one MPLC step at the end of the sequence.

An explanation of the observed stereoselectivity in the bromoetherification cyclization is given in Figure 2. The diaxial interactions in the bromonium ion **13** between the C1 methyl group and the sp^2-hybridized substituent R may be less severe than those between two methyl groups in **14**, leading to the (3*S*)-bromotetrahydropyran **11a** as the major product.[27]

The desired aldehyde **6** was synthesized in a two-step sequence from (*S*)-linalool **9**. However, the low yield caused by the unfavorable stereoselectivity of the bromoetherification step prompted an attempt to synthesize **6** from hydroxy alkene **16** (Scheme 3). In this case, the bulky substituent at C6 may preferentially adopt an equatorial orientation, as in bromonium ion **14**, to favor the formation of the bromotetrahydropyran (3*R*)-**17b**.

The hydroxy alkene **16** was obtained from (2*R*,3*R*)-epoxy geraniol[28] in good yield by regio- and stereoselective epoxide ring hydrolysis using perchloric acid in 6:1 (v/v) THF/H$_2$O[15]

(19) (a) Kennedy, R. M.; Tang, S. *Tetrahedron Lett.* **1992**, *33*, 3729−3732. (b) Tang, S.; Kennedy, R. M. *Tetrahedron Lett*. **1992**, *33*, 5299−5302. (c) Tang, S.; Kennedy, R. M. *Tetrahedron Lett*. **1992**, *33*, 5303−5306. (d) Boyce, R. S.; Kennedy, R. M. *Tetrahedron Lett*. **1994**, *35*, 5133−5136.

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(21) Morimoto, Y.; Iwai, T. *J. Am. Chem. Soc*. **1998**, *120*, 1633−1634. These authors reported the use of 4 equiv of $(CF_3CO_2)ReO_3{\cdot}2CH_3CN$ for efficient oxidative cyclizations of homoallylic tertiary alcohols, although it is not clear whether such an excess of reagent is necessary. In the present case, a considerable excess of $(CF_3CO_2)ReO_3{\cdot}2CH_3CN$ was used without determining the optimal stoichiometry of $(CF_3CO_2)ReO_3{\cdot}2CH_3CN$ to homoallylic alcohol **44**.

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(25) This approximate yield was obtained after purification of the crude mixture through a short silica gel column; further purification using MPLC caused loss of material.

(26) The ratio was determined by GC using a DB5 column (10 m × 0.1 mm × 0.1 μm film thickness).

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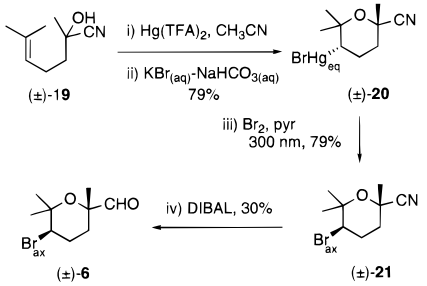
(28) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masumune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

Scheme 4



followed by conversion of the primary and secondary hydroxyls into benzoates. Bromoetherification of **16** with TBCO in nitromethane gave a mixture of tetrahydropyrans **17a** and **17b** and tetrahydrofurans **18** in the ratio **17a**/**17b**/**18** = 2.4:6.9:10. The desired tetrahydropyran **17b** was isolated after chromatography in 32% yield, as the major tetrahydropyran obtained. This reaction was plagued by the competitive formation of tetrahydrofurans **18**, presumably because of the remaining unfavorable diaxial interactions (methyl/methyl) encountered en route to **17b** via bromonium ion **14**. However, the desired bromotetrahydropyran (3*R*)-**17b** was easily isolated after chromatography more conveniently and in higher yield (32%) than was bromotetrahydropyran (3*R*)-**11b** (17−21%), which could only be obtained as a mixture with (3*S*)-**11b** in the previous route, even after MPLC. Thereafter, saponification of both benzoates of **17b** with K_2CO_3 in methanol followed by treatment with sodium periodate yielded aldehyde **6**, with spectroscopic and physical properties that were identical to those of **6** obtained from (*S*)-linalool.

Oxymercuration was also examined in a further attempt to enhance the synthetic access to the bromotetrahydropyran A ring.[29] Treatment of the (*S*)-cyanohydrin of 6-methyl-5-hepten-2-one under mercuric trifluoroacetate-mediated brominative conditions was expected to provide the (3*S*)-bromomercurial tetrahydopyran. Subsequent treatment of the mercurial solution with Br_2 under photolytic conditions[29b] could then provide the desired (3*R*)-bromotetrahydropyran as a result of inversion of the configuration at the C3 position. A preliminary model study was conducted to test the feasibility of this approach (Scheme 4). The racemic cyanohydrin (±)-**19**[30] was obtained by treatment of 6-methyl-5-hepten-2-one with trimethylsilylcyanide and ZnI_2 followed by acidic hydrolysis.[31] Oxymercuration of (±)-**19** with mercuric trifluoroacetate followed by treatment with a saturated aqueous solution of KBr and $NaHCO_3$ provided only organomercurial (±)-**20**. As expected, treatment of (±)-**20** with Br_2 in pyridine under 300 nm irradiation provided bromide (±)-**21**. The axial position of the bromine atom was confirmed by the appearance of an equatorial proton resonance as a doublet of doublets (J = 3.3 and 3.3 Hz) at δ 4.25. Reduction of the cyano group using DIBAL provided aldehyde (±)-**6**, whose ^{1}H NMR signals matched with those of the enantiomerically pure aldehyde **6** prepared previously.

Encouraged by the success of this model study, attempts to prepare the (*S*)-cyanohydrin of 6-methyl-5-hepten-2-one were made. The (*S*)-oxynitrilase [EC 4.1.2.37] isolated from *Manihot esculenta* catalyzes the formation of (*S*)-ketone cyanohydrins (≤90% ee); unfortunately, the enzyme preparation is not commercially available.[32] On the other hand, the commercial (*S*)-oxynitrilase [EC 4.1.2.11] from *Sorghum bicolor* does not readily accept ketones as substrates.[33b] However, (*S*)-ketone cyanohydrins have been obtained by transcyanation of aldehydes with racemic ketone cyanohydrins using almond meal as a source of (*R*)-oxynitrilase.[33,34] Thus, the cyanohydrin (±)-**19** was treated with almond meal in diisopropyl ether and citrate buffer (0.02 M, pH 5.5) or tartrate buffer (0.1 M, pH 5.4) in the presence of a variety of aldehydes. Unfortunately, significant conversion of the aldehydes into their corresponding (*R*)-cyanohydrins and subsequent optical enrichment of (*S*)-cyanohydrin was not observed, results that are attributable to the steric hindrance of the ketone cyanohydrin.[33c] Alternative syntheses of the (*S*)-cyanohydrin of 6-methyl-5-hepten-2-one have yet to be explored.

In summary, the most convenient route to aldehyde **6** was found to be that illustrated in Scheme 3, which spanned five steps from (2*R*,3*R*)-epoxy geraniol in 16% overall yield. The yield of the bromoetherification obtained here was comparable to those in previous total syntheses. However, the early execution of this task, together with the possibility of recycling the undesired isomers using Zn in acetic acid/ethanol,[13−15] diminishes its impact on the overall efficiency of the present total synthesis.

Synthesis of the C8−C15 Alkynyl Bromide (7). With reasonable synthetic access to the A ring precursor, focus was turned to the generation of the complementary C ring intermediate as a prelude to their convergent joining and closure of the B ring. Regio- and stereoselective 6-*endo* ring opening of an epoxide by an internal hydroxyl group would provide a straightforward approach to the C ring of **1a** and derivatives. Three major successful tactics have been developed in line with this strategy: activation of *trans*-epoxides by an adjacent vinyl moiety leading to vinyltetrahydropyran derivatives,[35,36] palladium-catalyzed cyclizations of hydroxy epoxides containing an α,β-unsaturated ester vicinal to the epoxide,[37] and ring closure of hydroxy epoxides possessing an acetylenic moiety adjacent to the epoxide.[38]

Initially, the synthesis of the C ring of thyrsiferol and venustatriol-related derivatives was envisioned to occur via acid-catalyzed ring opening of the vinyl hydroxyepoxide **29** (Scheme 5). The requisite epoxy alcohol **29** could be obtained from lactone **22**,[39] which in turn was prepared from D-glutamic acid in two steps (Scheme 5). Acid-catalyzed benzylation of **22** followed by reduction with diisobutyl aluminum hydride (DIBAL) and direct treatment of the lactol with (carboethoxyethylene)−triphenylphosphorane afforded the α,β-unsaturated ester **24** in 85% yield. Silylation of the free hydroxyl group of **24** and subsequent reduction of the ester with DIBAL afforded the allylic alcohol **26**. Sharpless asymmetric epoxidation[28] provided the epoxy alcohol **27**, which upon oxidation with SO_3·

(29) (a) Hoye, T. R.; Kurth, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 5065−5067. (b) Hoye, T. R.; Kurth, M. *J. Org. Chem.* **1979**, *44*, 3461−3467.
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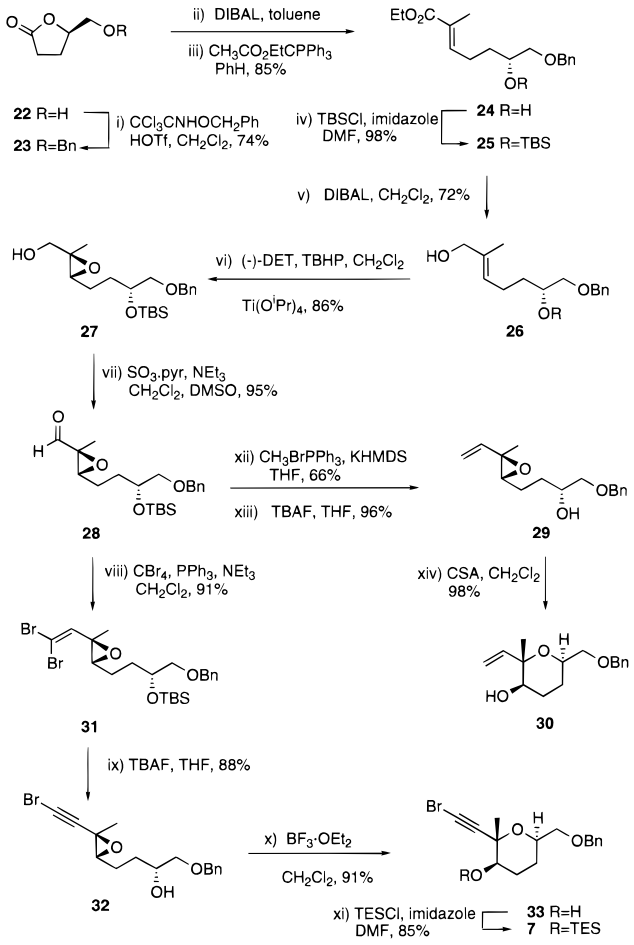
(32) Förster, S.; Roos, J.; Effenberger, F.; Wajant, H.; Sprauer, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 437−439.
(33) (a) Huuhtanen, T. T.; Kanerva, L. T. *Tetrahedron: Asymmetry* **1992**, *3*, 1223−1226. (b) Kiljunen, E.; Kanerva, L. T. *Tetrahedron: Asymmetry* **1996**, *7*, 1105−1116. (c) Kiljunen, E.; Kanerva, L. T. *Tetrahedron: Asymmetry* **1997**, *8*, 1551−1557.
(34) Menéndez, E.; Brieva, R.; Rebolledo, F.; Gotor, V. *J. Chem. Soc., Chem. Commun.* **1995**, 989−990.
(35) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330−5334.
(36) The corresponding cis epoxides have been shown to disfavor the 6-*endo* mode of ring closure.
(37) Suzuki, T.; Sato, O.; Hirama, M. *Tetrahedron Lett.* **1990**, *31*, 4747−4750.
(38) (a) Mukai, C.; Sugimoto, Y.-I.; Ikeda, Y.; Hanaoka, M. *Tetrahedron Lett.* **1994**, *35*, 2183-2186. (b) Mukai, C.; Ikeda, Y.; Sugimoto, Y.; Hanaoka, M. *Tetrahedron Lett.* **1994**, *35*, 2179−2182.
(39) (a) Ravid, U.; Silverstein, R. M.; Smith, L. R. *Tetrahedron* **1978**, *34*, 1449−1452. (b) Herdeis, C. *Synthesis* **1986**, 232−233.

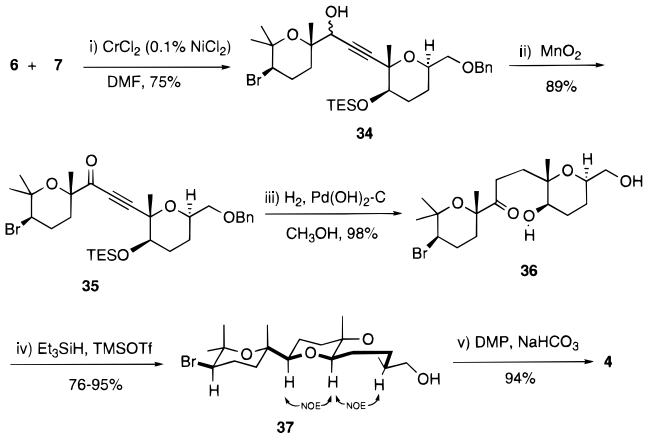
Scheme 5



pyridine gave the epoxy aldehyde **28**.[40] Treatment of **28** with methyltriphenylphosphonium bromide generated the vinyl epoxide that was desilylated to the epoxy alcohol **29**. Upon treatment of **29** with catalytic camphorsulfonic acid (CSA), the tetrahydropyran **30** was regio- and stereoselectively formed in high yield (98%). Conversion of the vinyl tetrahydropyran **30** into the required alkynyl bromide **7** may be achievable in four additional steps. For example, this might involve hydroxyl silylation, oxidative cleavage of the alkene to give the corresponding aldehyde, and a two-step conversion of the aldehyde into the alkynyl bromide.

Alternatively, acid-catalyzed rearrangement of bromoalkynyl epoxide **32** would provide **7** in a shorter synthetic sequence. Acid-catalyzed cyclizations of adjacent acetylenic *trans*-epoxides possessing electron-withdrawing substituents at the alkyne terminus were reported to favor 5-*exo* etherification.[38a] However, in the present case, further alkyl substitution at the propargylic position of the *trans*-epoxide was anticipated to direct regioselective 6-*endo* ring formation. Initial attempts to synthesize **31** from aldehyde **28** using Corey−Fuchs[41] conditions provided a mixture of products derived from epoxide opening. However, **31** was efficiently obtained (91%) from **28** when the reaction was conducted in the presence of triethylamine.[42] Interestingly, treatment of **31** with an excess of TBAF (4 equiv) induced both desilylation and monodebromination to yield the hydroxy

Scheme 6



alkynyl epoxide **32**,[43] bearing the required alkynyl bromide functionality. Subsequent cyclization of **32** catalyzed by CSA in CH_2Cl_2 at 0 to 25 °C afforded a 3:1 mixture of THP/THF isomers in 98% yield. The selectivity of the reaction was improved by using $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −78 to −10 °C to obtain regio- and stereoselectively the tetrahydropyran **33** (91%). As expected, the presence of the methyl substituent at the δ position of the *trans*-epoxy alcohol successfully stabilizes incipient positive charge, leading to 6-*endo* etherification. Finally, silylation of the hydroxyl at **33** completed the synthesis of the alkynyl bromide **7**.

Lewis acid-catalyzed cyclization of the hydroxy bromoalkynyl epoxide **32** provided an efficient and stereoselective procedure for the synthesis of the C ring of the thyrsiferol and venustatriol natural products. The synthesis of the alkynyl bromide **7** from lactone **22** was accomplished in 11 steps, with an overall yield of 22%.

Synthesis of the C1−C15 Aldehyde (4). Conjoining the A and C ring intermediates and formation of the B ring would complete the synthesis of the tris-oxane domain of the thyrsiferol and venustatriol natural products. For this, both the C8 carbon and C11 oxygen of **7** would have to become covalently attached to C7 of bromotetrahydropyran **6**. This was initiated by formation of the C7−C8 bond by organochromium-mediated coupling[17,18] of the C1−C7 aldehyde **6** and C8−C15 alkynyl bromide **7** (Scheme 6). Treatment of **6** and **7** with $CrCl_2$[17] in DMF afforded propargylic alcohols **34** in moderate yield (66%) after 22 h of reaction. In contrast, the use of $CrCl_2$ doped with $NiCl_2$ (0.1%)[18] provided propargylic alcohols **34** in better yield (75%) after only 5 h of reaction. Importantly, the secondary alkyl bromide of **6** withstands this mild carbon−carbon bond-forming process. Initial attempts to saturate the alkyne of **34** by hydrogenation using Pd on C afforded complex mixtures of products of complete and semihydrogenation with concomitant removal of either the benzyl group or both the benzyl and the triethylsilyl groups. Semihydrogenation of **34** with Lindlar's catalyst ($Pd/CaCO_3/Pb$) gave the corresponding allylic alcohols without cleavage of the benzyl or TES ethers, but the allylic alcohol product was surprisingly unreactive toward treatment with MnO_2. In contrast, oxidation of propargyl alcohols **34** using MnO_2 provided the ynone **35** efficiently (89%). Subsequent hydrogenation mediated by $Pd(OH)_2$ or Pd on C in methanol successfully yielded dihydroxy ketone **36**, as a result of alkyne saturation and liberation of both silyl and benzyl groups. The next task was the reduction of the hemiketal tautomer of **36** to

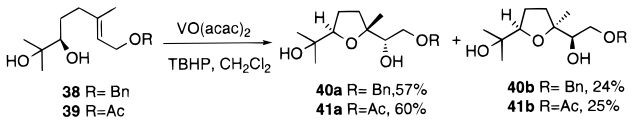
(40) A diastereomer of the aldehyde **28** was prepared previously from L-glutamic acid: Nicolaou, K. C.; Reddy, K. J.; Skokotas, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.-K. *J. Am. Chem. Soc.* **1993**, *115*, 3558−3575.

(41) Corey, E. J.; Fuchs, P. *Tetrahedron Lett.* **1972**, 3769−3772.

(42) McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4823−4832.

(43) For a precedent of this reaction in a *cis* dibromoalkenyl epoxide, see ref 35.

Scheme 7

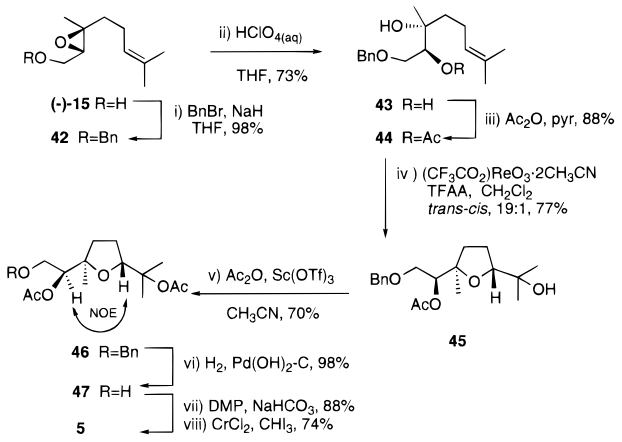


permanently close the B ring. Dihydroxyketone **36** remained unreacted upon treatment with triethylsilane and $BF_3{\cdot}OEt_2$.[44] However, using triethylsilane and trimethylsilyltriflate (TMSOTf)[45] in CH_3CN at −10 °C, fused ether **37** was afforded stereoselectively and in generally high, although variable yield. NOESY experiments performed on compound **37** and summarized in Scheme 6 showed that the relative configuration at C7 was as expected from the axial delivery of hydride to the oxonium intermediate derived from **36**. Thereafter, oxidation of **37** with Dess−Martin reagent (DMP)[46] buffered with $NaHCO_3$ provided aldehyde **4** (94%).

After successfully joining the two preconstructed tetrahydropyran-containing units representing the functionalized A and C rings (**6** and **7**, respectively), the synthesis of the C1−C5 tricycle **(4)** was completed after four additional steps with minimum protecting group manipulations and an overall yield of 53%. Hence, an efficient and convergent construction of the A−B−C ring system of thyrsiferol, venustatriol, and derivatives was developed. This features a separate etherification method for the closure of each oxane ring and provides aldehyde **4** from the D-glutamic acid derivative **22** in 16 steps in the longest linear sequence and 12% overall yield. Notably, the problematic bromoetherification process does not impact the longest linear sequence.

Synthesis of C16−C24 Alkenyl Iodide (5). In contrast to the tris-oxane system **4**, the remaining fragment of **1a**−**1d** contains a solitary tetrahydrofuran ring. The stereoselective construction of this cyclic ether[47] is the key event in the construction of the C16−C24 side chain of **1a** and its derivatives. Accordingly, the formation of the *trans*-tetrahydrofuran ring via vanadium(V)-catalyzed epoxidation and spontaneous cyclization,[48] as suggested by the work of Shirahama,[14] was first explored (Scheme 7). Diol **38**[49] was delivered from benzyl geraniol ether by Sharpless asymmetric dihydroxylation[50] using AD-mix β and methylsulfonamide in moderate yield (41%) but excellent stereoselectivity (>98% ee). Treatment of **38** with $VO(acac)_2$ and *tert*-butylhydroperoxide provided a mixture of tetrahydrofurans **40** (trans/cis = 2.4:1) in good yield (81%).[51] Unfortunately, compounds **40a** and **40b** were not readily separable by simple silica gel column chromatography. On the other hand, treatment of **39**,[52] similarly obtained from geraniol acetate (52% yield, >98% ee), with $VO(acac)_2$ and *tert*-butylhydroperoxide produced a separable mixture of tetrahydrofurans **41** (trans/cis = 2.4:1) in high yield (85%).[53] Acetylation of **41a** with acetic anhydride catalyzed by $Sc(OTf)_3$[54] afforded the triacetate derivative, but selective cleavage of the primary acetate failed because of concomitant saponification of the secondary ester. The low stereoselectivity of the vanadyl-induced tetrahydrofuran formation and the difficulty in the early incorporation of acetates at the C18 and C13 hydroxyls in this route prompted the development of an alternative route toward the D ring. However, the C18 and C23 hydroxyls of the *cis*-tetrahydrofuran **41b** could be protected (MOM or TBS) in one step to provide intermediates that may be useful for the synthesis of venustatriol and its derivatives.

Scheme 8



The possibility of constructing the *trans*-tetrahydrofuran via the hydroxyl-directed Re(VII)-promoted *syn*-oxidative cyclization of bis-homoallylic alcohols seemed an attractive alternative (Scheme 8).[19−21] In particular, the recent use of $(CF_3CO_2)ReO_3{\cdot}2CH_3CN$[58] in the presence of trifluoroacetic anhydride (TFAA) for *trans*-tetrahydrofuran formation from tertiary bis-homoallylic alcohols[21] inspired the direct conversion of hydroxy alkene **44** into the functionalized D ring. The trans-diastereoselectivity in Re(VII)-induced *syn*-oxidative cyclizations has been attributed to steric interaction in an alkoxyrhenium intermediate,[20b,21] although cis-diastereoselectivity may be favored by chelation control.[21,55,56] In the case of **44**, the electron-withdrawing character of the neighboring acetate at C18 was expected to diminish any metal chelation and thereby contribute to trans selectivity in the *syn*-oxidative cyclization.

The synthesis of **5** began with (2*S*,3*S*)-epoxy geraniol.[28] Regio- and stereoselective hydrolysis[15] of the derived benzyl ether provided diol **43**, which was monoacetylated[57] to give **44** (Scheme 8). Treatment of **44** with $(CF_3CO_2)ReO_3{\cdot}2CH_3CN$[58] in the presence of TFAA[21] efficiently provided (77%) the *trans*-tetrahydrofuran **45** with excellent stereoselectivity (trans/cis =

(44) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976−4978.

(45) Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136−137.

(46) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

(47) (a) Harmange, J.-C.; Figadère, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711−1754. (b) Koert, U. *Synthesis* **1995**, 115−132.

(48) (a) Fukuyama, T.; Vranesic, B.; Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1978**, *31*, 2741−2744. (b) Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933−2935.

(49) Hoeman, M. Z.; Agrios, K. A.; Aubé, J. *Tetrahedron* **1997**, *53*, 11087−11098.

(50) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768−2771.

(51) The stereochemistry of tetrahydrofurans **40** was determined at the stage of the diacetate derivatives. The diacetate **46**, derived from **40a**, showed an NOE between protons at the C18 and C22 positions (Scheme 8).

(52) Vidari, G.; Dapiaggi, A.; Zanoni, G.; Garlaschelli, L. *Tetrahedron Lett.* **1993**, *34*, 6485−6488.

(53) The stereochemistry of the *trans*-tetrahydrofuran **41a** was determined after protecting the two free hydroxyls with MOM groups, by detection of an NOE between protons at the C18 and C22 positions.

(54) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 4413−4414.

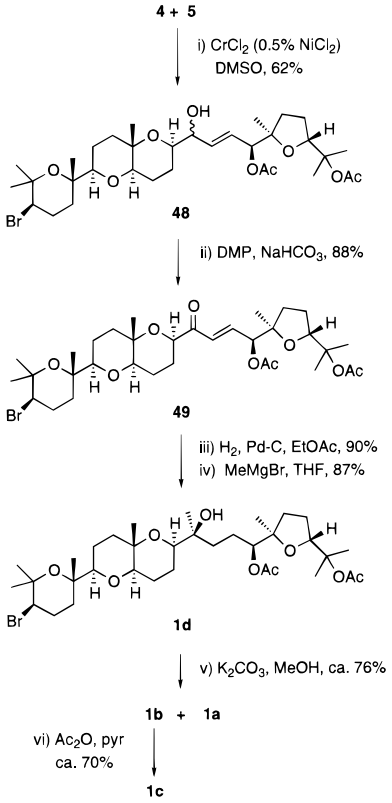
(55) Sinha, S. C.; Keinan, E.; Sinha, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9076−9077.

(56) Sinha, S. C.; Sinha, A.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1997**, *119*, 12014−12015.

(57) Zhdanov, R. I.; Zhenodarova, S. M. *Synthesis* **1975**, 222−245.

(58) (a) Herrmann, W. A.; Thiel, W. R.; Kühn, F. E.; Fischer, R. W.; Kleine, M.; Herdtweck, E.; Scherer, W. *Inorg. Chem.* **1993**, *32*, 5188−5194. (b) Edwards, P.; Wilkinson, G. J. *J. Chem. Soc., Dalton Trans.* **1984**, 2695−2702.

Scheme 9



19:1). Prior to extension of the side chain appended to the D ring, acetylation of the tertiary alcohol of tetrahydrofuran **45** with acetic anhydride catalyzed by $Sc(OTf)_3$[54] provided diacetate **46**. The detection of an NOE between protons at C22 and C18 of **46** (Scheme 8) confirmed the *trans* selectivity in the formation of **45**. Hydrogenolytic removal of the benzyl group followed by alcohol oxidation with buffered Dess−Martin periodinane[46] gave the corresponding aldehyde, which was immediately converted into the *trans*-alkenyl iodide **5** under Takai reaction conditions.[59] Overall, the *trans*-tetrahydrofuran **5** was stereoselectively obtained from (2*S*,3*S*)-epoxy geraniol in an eight-step sequence and an overall yield of 22%. This approach provided the C16−C24 fragment of **1a** and derivatives with acetates strategically incorporated at both the C18 and C23 hydroxyl positions to facilitate the anticipated strategic end-game manipulations.

Synthesis of Thyrsiferyl 23-Acetate (1a) and Its Derivatives (1b, 1c, and 1d). Only two major tasks remained to complete the assembly of thyrsiferol natural products: coupling the tris-oxane and tetrahydrofuran-containing fragments and installation of the tertiary hydroxyl group at C15. Mild and chemoselective organochromium-mediated conditions were selected for the formation of the C15−C16 bond of **1a** and derivatives.[22] Preliminary attempts to join **4** and **5** using $CrCl_2$ doped with $NiCl_2$ (0.1%) in DMF provided, after 24 h, the mixture of allylic alcohols **48** in low yield (<40%, Scheme 9). Under these conditions, significant elimination of the bromide and tetrahydropyran opening were observed. The yield of the reaction was improved using $CrCl_2$ doped with $NiCl_2$ (0.5%) in DMSO to provide a mixture of allylic alcohols **48**[60] in 62% yield. Although the efficiency of this organochromium-mediated coupling was moderate, it was possible to minimize the bromide elimination, the acetates at C18 and C23 remained intact, and unreacted aldehyde **4** could be recovered.

Oxidation of alcohols **48** with buffered Dess−Martin periodinane reagent[46] satisfactorily gave the enone **49**. Fortunately, at this point it was possible to separate the *cis*-tetrahydrofuran diastereomer from intermediate **5** by simple chromatography. Catalytic hydrogenation of **49** with $Pd(OH)_2$ on carbon in methanol failed to produce the desired saturated derivative cleanly. However, Pd on carbon-mediated hydrogenation in ethyl acetate provided the α,β-saturated ketone. The tertiary hydroxyl at C15 was installed following Corey's precedent, using methylmagnesium bromide.[15] Alternatively, chemoselective methylenation[61,62] of the α,β-saturated ketone from **49** could provide access to **2a** and **2b**. Selective cleavage of the secondary acetate at C18 in the presence of the tertiary ester at C23 might be expected to occur upon methyl installation. However, treatment of the α,β-saturated ketone with methylmagnesium bromide at −78 °C gave efficiently and stereoselectively **1d** (87%). Upon allowing the reaction mixture to warm to 0 °C, minor amounts of thyrsiferol (**1b)** and thyrsiferyl 23-acetate (**1a)** were also detected. This observation is not surprising in light of the simultaneous functionalization of the hydroxyls at C18 and C23 at the stage of **41b**, which may be explained by their similar steric environments. Partial saponification of **1d** with K_2CO_3 in methanol for 9 h occurred in 76% yield to provide thyrsiferyl 23-acetate (**1a**) and thyrsiferol (**1b**).[63] However, saponification of both acetates at the C18 and C23 positions was achieved by prolonged treatment of **1d** with an excess of K_2CO_3 in methanol, to obtain exclusively **1b**. Finally, monoacetylation of **1b**, as described previously,[1a] afforded thyrsiferyl 18-acetate (**1c)** (70%).[64] After joining the two halves of the thyrsiferol derivatives, represented by fragments **4** and **5**, the synthesis of thyrsiferyl 18,23-diacetate (**1d**) was accomplished in four additional steps without protecting group manipulations, with an overall yield of 43%. At last, partial or complete saponification of the acetates at C18 and C23 successfully gave thyrsiferyl 23-acetate **(1a**) or thyrsiferol (**1b**), respectively.

Conclusions

This modular total synthesis delivers thyrsiferyl 23-acetate (**1a**) and thyrsiferol (**1b**) in 21 steps in the longest linear sequence. In addition to providing the scarce and uniquely biologically active natural product **1a**, a variety of other natural and non-natural congeners may also be accessed by minor modifications of the synthetic route. The early joining of intermediates containing the A and C rings followed by an efficient annulation of the B ring, convergent attachment of the D ring intermediate, and minimal manipulation of hydroxyl-protecting groups characterizes the flexibility and efficiency of the synthesis. Furthermore, the tetrahydrofuranyl D ring was constructed by a highly stereoselective Re(VII)-promoted *syn*-oxidative cyclization of bis-homoallylic alcohol **44**. Also noteworthy is the use of mild and chemoselective organochromium reactions for the coupling of highly functionalized intermediates,[65] which allowed the early incorporation of a

(59) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc*. **1986**, *108*, 7408−7410.

(60) By ^{1}H NMR determination of the crude mixture it was possible to distinguish the two possible isomers in the ratio 3:1; however, the stereochemistry at the C15 was not assigned.

(61) Lombardo, L. *Tetrahedron Lett*. **1982**, *23*, 4293.

(62) Huang, H.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 5746−5757.

(63) The ratios of **1a**/**1b**/**1c** were dependent upon the amount of K_2CO_3 and varied from ∼1:0.5−1:1−0.7. The ^{1}H NMR and HRMS data of **1b** and **1a** matched those previously reported: Blunt, J. W.; McCombs, J. D.; Munro, M. H. G.; Thomas, F. N. *Magn. Reson. Chem.* **1989**, *27*, 792−795 and ref 14d.

(64) HRMS and ^{1}H NMR data of **1c** were consistent with the assignment, and a 300 MHz ^{1}H NMR spectrum of totally synthetic **1c** was identical to a 300 MHz ^{1}H NMR spectrum of semisynthetic **1c** obtained from a natural sample of **1b**, which was kindly provided by Prof. J. W. Blunt.

secondary bromide at C3 and acetates at C18 and C23 and an expedient completion of the total synthesis. This work should not only help to alleviate the problem of limited supply of **1a** but may also be instrumental for dissecting the structural bases for the novel combination of anti-leukemic, apoptotic-inducing, PP2A inhibitory, and anti-multidrug resistance activities of the thyrsiferol-derived natural products.

Experimental Section[66]

Tetrahydrobromofurans (10) and Tetrahydrobromopyrans (11a and 11b). To a stirred 0 °C solution of (*S*)-(+)-linalool[24] (0.91 g, 5.9 mmol) in CH_3NO_2 (80 mL) was added TBCO (2.66 g, 6.51 mol) in the dark. After 5 h, the reaction mixture was poured into a 1 M aqueous NaOH solution (250 mL), diluted with ether (150 mL), and stirred for 10 min. The organic phase was separated and washed with additional 1 M NaOH solution (70 mL). The combined aqueous phases were extracted with ether (3 × 100 mL). The combined organic phases were washed with saturated aqueous NaCl (50 mL), dried over $MgSO_4$, filtered, and concentrated. Silica gel chromatography (hexanes/ethyl acetate, 99:1, v/v) gave a mixture of tetrahydrofurans and tetrahydropyrans (**10**/**11a**/**11b** = 4.4:10:6.9) (1.1 g, 4.7 mmol, 80%). An analytical sample was purified by MPLC to obtain a mixture of **11a** and **11b**: R_f 0.11 (hexanes); IR (neat) 2956, 2919, 2815, 1462, 1377, 1260; ^{1}H NMR ($CDCl_3$, 500 MHz) **11a** δ 5.98 (dd, J = 11, 18 Hz, 1H), 4.97−5.09 (m, 2H), 3.95 (dd, J = 4, 12 Hz, 1H), 2.24 (dddd, J = 4, 13, 13, 13 Hz, 1H), 2.11−2.16 (m, 2H), 1.64 (dddd, J = 1.5, 4, 14, 14 Hz, 1H), 1.38 (s, 3H), 1.33 (s, 3H), 1.15 (s, 3H), **11b** δ 5.92 (dd, J = 11, 18 Hz, 1H), 4.97−5.09 (m, 2H), 4.10 (dd, J = 3.5, 7.5 Hz, 1H), 2.28 (dddd, J = 4, 4, 9, 9 Hz, 1H), 2.05−2.11 (m, 1H), 1.92 (dddd, J = 4, 7, 9, 9 Hz, 1H), 1.82 (ddd, J = 4, 7.5, 14 Hz, 1H), 1.40 (s, 3H), 1.37 (s, 3H), 1.30 (s, 3H); HRMS (CI) calcd for $C_{10}H_{21}O^{79}BrN$ $[M + NH_4]^+$ 250.0802, found 250.0832, calcd for $C_{10}H_{18}O^{79}Br$ $[M + H]^+$ 233.0537, found 233.0531.

Aldehydes (12 and 6). To a stirred, room temperature solution of the mixture of **10**, **11a**, and **11b** (**10**/**11a**/**11b** = 4.4:10:6.9, 1.1 g, 4.7 mmol) in THF (12 mL) was added a solution of NMO (0.87 g, 6.4 mmol) in H_2O (3 mL) and OsO_4 (1.4 mL of a 0.15 M solution in H_2O, 0.21 mmol). After the solution was stirred at room temperature for 24 h, it was cooled to 0 °C and $NaIO_4$ (1.4 g, 6.4 mmol) and H_2O (3 mL) were added. The mixture was allowed to warm to room temperature, and after 4 h it was diluted with H_2O (75 mL) and extracted with ether (3 × 50 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by MPLC to obtain **12** (0.28 g, 1.2 mmol, 25%) and **6** (0.15 g, 0.6 mmol, 13%). Data for **12**: R_f 0.51 (hexanes/ethyl acetate, 8:2, v/v); IR (neat) 2980, 2960, 1730, 1450, 1380, 1260, 1000; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.59 (s, 1H), 3.92 (dd, J = 4.5, 12.5, 1H), 2.33 (ddd, J = 3, 3, 14 Hz, 1H), 1.97−2.10 (m, 2H), 1.46−1.54 (m, 1H), 1.42 (s, 3H), 1.30 (s, 3H), 1.11 (s, 3H). Data for **6**: R_f 0.43 (hexanes/ethyl acetate, 8:2, v/v); $[\alpha]^{22}_D$ +18 (*c* 0.44, $CHCl_3$); IR (neat) 2980, 2960, 1730, 1450, 1380, 1260, 1000; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.55 (s, 1H), 4.13 (dd, J = 2.2, 3 Hz, 1H), 2.14−2.20 (m, 1H), 2.00−2.09 (m, 2H), 1.87−1.92 (m, 1H), 1.43 (s, 3H), 1.30 (s, 3H), 1.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.51, 58.27, 30.91, 26.55, 26.29, 24.45, 23.85; HRMS (CI) calcd for $C_9H_{19}O_2{}^{79}BrN$ $[M + NH_4]^+$ 252.0593, found 252.0598.

Tetrahydrobromopyran (17b). To a stirred, 0 °C solution of **16** (0.58 g, 1.5 mmol) in CH_3NO_2 (29 mL) was added TBCO (0.66 g, 1.6 mmol) in the dark. After 20 h at 4 °C, the reaction mixture was poured into a 1 M aqueous NaOH solution (100 mL), diluted with ether (50 mL), and stirred for 10 min. The organic phase was separated and washed with additional 1 M NaOH solution (25 mL). The combined aqueous phases were extracted with ether (3 × 50 mL). The combined organic phases were washed with saturated aqueous NaCl (10 mL), dried over $MgSO_4$, filtered, and concentrated. Silica gel chromatography (hexanes/ethyl acetate, 98:2, v/v) gave **17b** (0.23 g, 0.47 mmol, 32%) as a colorless oil: R_f 0.35 (hexanes/ethyl acetate, 9:1, v/v); $[\alpha]^{22}_D$ +31 (*c* 1.0, $CHCl_3$); IR (neat) 2961, 2923, 1710, 1250, 1231; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.05 (dd, J = 1, 8.2 Hz, 2H), 7.95 (dd, J = 1, 8.2 Hz, 2H), 7.27−7.60 (m, 5H), 5.45 (dd, J = 2.5, 9 Hz, 1H), 4.80 (dd, J = 2.5, 11.5 Hz, 1H), 4.52 (dd, J = 9, 11.5 Hz, 1H), 3.94 (dd, J = 4, 12.2 Hz, 1H), 2.27 (dddd, J = 4, 13, 13, 13 Hz, 1H), 2.16 (dddd, J = 4, 4, 4, 13.2 Hz, 1H), 1.81 (ddd, J = 4, 13.2, 13.2 Hz, 1H), 1.71 (ddd, J = 4, 4, 13.5 Hz, 1H), 1.47 (s, 6H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.56, 165.85, 133.22, 132.97, 129.70, 129.65, 128.47, 128.34, 77.82, 75.76, 74.22, 63.63, 57.50, 35.24, 30.77, 27.50, 23.82, 21.35; HRMS (CI) calcd for $C_{24}H_{31}O_5N^{79}Br$ $[M + NH_4]^+$ 492.1378, found 492.1345, calcd for $C_{24}H_{28}O_5{}^{79}Br$ $[M + H]^+$ 475.1113, found 475.1085.

Tetrahydropyran (33). To a stirred, −78 °C solution of **32** (1.0 g, 2.9 mmol) in CH_2Cl_2 (85 mL) under Ar was added a borontrifluoride etherate (2.9 mL of a 0.1 M solution in CH_2Cl_2, 0.29 mmol) dropwise. After 30 min, the mixture was warmed to −10 °C. After the reaction mixture was stirred at −10 °C for 6 h, it was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 75 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 8:2, v/v) gave **33** as a colorless oil (0.89 g, 2.6 mmol, 91%): R_f 0.32 (hexanes/ethyl acetate, 7:3, v/v); $[\alpha]^{22}_D$ −6.3 (*c* 0.29, $CHCl_3$); IR (neat) 3436, 3030−2867, 2203, 1496, 1452, 1367, 1262, 1202, 1124, 1094, 1071; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35−7.36 (m, 5H), 4.59 (AB, J = 12.5 Hz, 2H), 4.11−4.16 (m, 1H), 3.58−3.62 (m, 1H), 3.54 (dd, J = 5, 10 Hz, 1H), 3.45 (dd, J = 5, 10 Hz, 1H), 2.21 (dddd, J = 2.5, 5.2, 14, 14 Hz, 1H), 1.95 (d, J = 10 Hz, 1H), 1.86 (ddd, J = 2.5, 6.7, 14 Hz, 1H), 1.48−1.64 (m, 2H), 1.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.23, 128.39, 127.76, 127.65, 80.20, 74.35, 73.43, 73.05, 73.57, 72.57, 69.80, 47.61, 27.21, 25.29, 21.18; HRMS (CI) calcd for $C_{16}H_{23}{}^{79}BrNO_3$ $[M + NH_4]^+$ 356.0856, found 356.0859, calcd for $C_{16}H_{20}{}^{79}BrO_3$ $[M + H]^+$ 339.0591, found 339.0548, calcd for $C_{16}H_{18}{}^{79}BrO_2$ $[M - OH]^+$ 321.0486, found 321.0459.

Propargylic Alcohols (34). To a room temperature mixture of $CrCl_2$ containing 0.1% by wt $NiCl_2$ (0.15 g, 1.2 mmol) in DMF (0.9 mL) was added dropwise a solution of the aldehyde **6** (0.11 g, 0.47 mmol) and alkynyl bromide **7** (0.27 g, 0.61 mmol) in DMF (0.3 mL) in a glovebox under nitrogen. The reaction mixture was stirred at room temperature for 5 h. Ethyl acetate (3 mL) and a 1 M solution of potassium serinate (3 mL) were added, and the mixture was stirred for 20 min. The separated aqueous phase was washed with ethyl acetate (3 × 10 mL), acidified to ∼pH 3 with a 1 M solution of HCl, and extracted again with ethyl acetate (10 mL). The combined organic phases were washed with saturated aqueous NaCl (5 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 8:2, v/v) gave a mixture of the two propargylic alcohols **34** as a colorless oil (0.21 g, 0.35 mmol, 75%): R_f 0.29 (hexanes/ethyl acetate, 85:15, v/v); IR (neat) 3400, 2951, 2878, 1454, 1376, 1208, 1122, 1074, 1020; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (m, 5H), 4.54−4.56 (m, 2H), 4.14 (d, J = 3 Hz, 1H), 4.04−4.08 (m, 1H), 3.85 (dd, J = 4, 12.7 Hz, 1H), 3.63 (dd, J = 2.5, 2.5 Hz, 1H), 3.57 (dd, J = 5, 10 Hz, 1H), 3.41 (dd, J = 5, 10 Hz, 1H), 2.75 (d, J = 3 Hz, 1H), 2.25 (dddd, J = 4, 13, 13.3, 13.3 Hz, 1H), 2.11−2.19 (m, 2H), 2.03 (ddd, J = 4.5, 13.7, 13.7 Hz, 1H), 1.57−1.73 (m, 4H), 1.46 (s, 3H), 1.45 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 0.97 (t, J = 8 Hz, 9H), 0.62 (q, J = 8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.56, 128.29, 127.71, 127.49, 86.65, 84.06, 76.62, 76.39, 73.47, 73.23, 72.65, 70.29, 69.89, 57.27, 30.92, 30.72, 28.58, 27.77, 25.86, 23.06, 23.01, 21.84, 6.92, 4.90; HRMS (CI) calcd for $C_{31}H_{53}NO_5Si^{79}Br$ $[M + NH_4]^+$ 626.2863, found 626.2873.

Tricycle (37). To a stirred, −35 °C solution of **36** (52 mg, 0.13 mmol) in CH_2Cl_2 (4 mL) under Ar was added $HSiEt_3$ (0.20 mL, 1.3 mmol) and TMSOTf (28 μL, 0.15 mmol). After the reaction mixture was stirred for 30 min, it was diluted with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 10 mL). The organic phase was washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexanes/ethyl acetate, 75:25, v/v) to give **37** (38 mg, 0.10 mmol, 76%): R_f 0.28 (hexanes/ethyl acetate, 6:4, v/v); $[\alpha]^{22}_D$ +6.4 (*c* 0.73, $CHCl_3$); IR (neat) 3444, 2951, 2867, 1456, 1379, 1122, 1102; ^{1}H

(65) (a) Kishi, Y. *Pure Appl. Chem.* **1992**, *64*, 343−350. (b) Cintas, P. *Synthesis* **1992**, 248−257. (c) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1−36. (d) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991−1045.

(66) A complete set of experimental details is included in the Supporting Information.

NMR ($CDCl_3$, 500 MHz) δ 3.93−3.98 (m, 1H), 3.89 (dd, J = 4, 13 Hz, 1H), 3.52 (d, J = 5.5 Hz, 1H), 3.43 (dd, J = 5.5, 11.2 Hz, 1H), 3.09 (dd, J = 2, 11.2 Hz, 1H), 2.25 (dddd, J = 4, 13, 13, 13 Hz, 1H), 2.12 (dddd, J = 4, 4, 8.5, 8.5 Hz, 1H), 1.73−1.88 (m, 6H), 1.67 (bs, 1H), 1.42−1.59 (m, 4H), 1.41 (s, 3H), 1.28 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 86.69, 78.24, 74.99, 74.35, 72.25, 70.73, 65.90, 58.97, 38.39, 37.08, 31.03, 28.23, 23.76, 23.65, 23.05, 21.09, 20.65, 20.07; HRMS (CI) calcd for $C_{18}H_{35}O_4N^{79}Br$ [M + NH_4]$^+$ 408.1741, found 408.1724, calcd for $C_{18}H_{32}O_4{}^{79}Br$ [M + H]$^+$ 391.1476, found 391.1484.

***trans*-Tetrahydrofuran (45).** Rhenium heptoxide (2.5 g, 5.2 mmol) was dissolved in CH_3CN (30 mL) in a Schlenk flask, trifluoroacetic anhydride (0.75 mL, 5.2 mmol) was added, and the resulting mixture was stirred under Ar at room temperature for 1 h. The solution was cooled to 0 °C and concentrated in vacuo to produce $(CF_3CO_2)ReO_3 \cdot 2CH_3CN$ as a white solid.[58] To this solid were added CH_2Cl_2 (27 mL) and trifluoroacetic anhydride (0.75 mL, 5.2 mmol) under Ar.[21] After the mixture was cooled to −40 °C, a solution of **44** (0.42 g, 1.3 mmol) in CH_2Cl_2 (3 mL) was added via syringe. After 2 h, the reaction mixture was allowed to warm to −20 °C and stir for an additional 2 h. The resulting dark purple solution was filtered through silica gel with ethyl acetate (50 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ (20 mL) and saturated NaCl (20 mL). The aqueous phase was washed with ethyl acetate (20 mL), and the combined organic phase was dried over $MgSO_4$, filtered, and concentrated to obtain a clear oil. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate, 7:3, v/v) to give **45** and its *cis*-isomer in a 19:1 ratio (*trans/cis*), respectively (0.34 g, 1.0 mmol, 77%), that was not separated but characterized as a mixture after further purification by reverse-phase HPLC (C-18, CH_3OH/H_2O, 99:1, v/v): R_f 0.4 (hexanes/ethyl acetate, 6:4, v/v); $[\alpha]^{22}_D$ −14 (*c* 2.3, $CHCl_3$); IR (neat) 3482, 3029, 2974, 2871, 1740, 1496, 1455, 1373, 1236, 1126, 1057; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29−7.37 (m, 5H), 5.20 (dd, J = 3, 7.8 Hz, 1H), 4.53 (AB, J = 12 Hz, 2H), 3.72−3.77 (m, 2H), 3.59 (dd, J = 7.8, 11 Hz, 1H), 2.11 (s, 3H), 2.01−2.08 (m, 1H), 1.81−1.86 (m, 2H), 1.64−1.76 (m, 2H), 1.19 (s, 6H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.54, 138.08, 128.36, 127.53, 127.59, 87.04, 82.88, 76.08, 72.86, 70.42, 69.15, 35.11, 27.43, 26.02, 24.11, 23.34, 21.20; HRMS (FAB) calcd for $C_{19}H_{29}O_5$ [M + H]$^+$ 337.2007, found 337.2028, calcd for $C_{19}H_{27}O_4$ [M − OH]$^+$ 319.1902, found 319.1899.

Vinyl Iodide (5). To a stirred, room temperature solution of **47** (19:1 mixture (*trans/cis*), 0.11 g, 0.35 mmol) in CH_2Cl_2 (5 mL) was added $NaHCO_3$ (0.29 g, 3.5 mmol) followed by the Dess−Martin periodinane reagent (0.29 g, 0.69 mmol). The resultant mixture was stirred for 45 min. Ethyl acetate (5 mL), saturated aqueous $NaHCO_3$ (5 mL), and 10% aqueous $Na_2S_2O_3$ (5 mL) were added, and the mixture was stirred until the organic layer became clear. The aqueous phase was extracted with ethyl acetate (3 × 10 mL), and the combined organic phase was washed with saturated aqueous NaCl (5 mL), dried over $MgSO_4$, filtered, and concentrated to give an oil. The residue was filtered through a pad of silica gel with hexanes/ethyl acetate (8:2, v/v) to obtain the corresponding aldehyde **47a** and its *cis*-isomer in a 19:1 ratio (*trans/cis*), respectively, as an oil (90 mg, 0.31 mmol, 88%): R_f 0.28 (hexanes/ethyl acetate, 8:2, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.68 (s, 1H), 5.04 (s, 1H), 4.18 (dd, J = 6.6, 8 Hz, 1H), 2.20 (s, 3H), 2.00 (s, 3H), 1.40−2.00 (m, 4H), 1.49 (s, 3H), 1.47 (s, 3H), 1.28 (s, 3H). To a room temperature mixture of $CrCl_2$ (0.43 g, 3.5 mmol) in THF (4.5 mL) was added dropwise a solution of the aldehyde **47a** (19:1 mixture, 84 mg, 0.29 mmol) and CHI_3 (0.46 g, 1.2 mmol) in THF (2 mL) in a glovebox under nitrogen. After 16 h, ethyl acetate (5 mL) and H_2O (5 mL) were added, and the resulting mixture was stirred for 20 min. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, washed with saturated aqueous NaCl (5 mL), dried over $MgSO_4$, filtered, and concentrated. Silica gel column chromatography (hexanes/ethyl acetate, 93:7−90:10, v/v) of the residue gave **5** and its *cis*-isomer in a 19:1 ratio (*trans/cis*), respectively, as a colorless oil (88 mg, 0.21 mmol, 74%). Further purification by reverse-phase HPLC (C-18, CH_3CN-H_2O, 96:4, v/v) afforded an analytical sample: R_f 0.25 (hexanes/ethyl acetate, 9:1, v/v); $[\alpha]^{22}_D$ +21 (*c* 0.61, $CHCl_3$); IR (neat) 2976, 2920, 1732, 1459, 1363, 1237; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.55 (dd, J = 6.3, 14.6 Hz, 1H), 6.42 (dd, J = 1, 14.6 Hz), 5.21 (dd, J = 1, 6.3 Hz, 1H), 4.07 (dd, J = 6, 8.5 Hz, 1H), 2.11 (s, 3H), 1.99 (s, 3H), 1.78−2.00 (m, 3H), 1.64−1.70 (m, 1H), 1.47 (s, 3H), 1.44 (s, 3H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.44, 169.87, 140.94, 85.41, 83.48, 82.50, 80.69, 79.50, 33.94, 26.44, 23.54, 22.49, 22.29, 21.77, 21.08; HRMS (FAB) calcd for $C_{15}H_{24}O_5I$ [M + H]$^+$ 411.0661, found 411.0655.

Ketone (49). To a room temperature solution of **4** (17 mg, 44 μmol) and **5** (19:1 mixture (*trans/cis*), 45 mg, 110 μmol) in DMSO (1.2 mL) was added $CrCl_2$ containing 0.5% by wt $NiCl_2$ (27 mg, 220 μmol) in a glovebox under nitrogen. The mixture was stirred for 21 h before a 1 M potassium serinate solution (2 mL) and ethyl acetate (2 mL) were added. The resulting mixture was stirred for 30 min, the phases were separated, and the aqueous phase was extracted with ethyl acetate (3 × 3 mL). The aqueous phase was acidified with 1 M HCl to ∼3 pH and extracted again with ethyl acetate (3 mL). The combined organic phase was washed with saturated aqueous NaCl (2 mL), dried over $MgSO_4$, filtered, and concentrated. Silica gel column chromatography (hexanes/ethyl acetate, 3:1, v/v) of the residue gave **48** (18 mg, 27 μmol, 62%) as a 3:1 mixture of C15 epimers and a colorless oil: R_f 0.26 (hexanes/ethyl acetate, 7:3, v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.60−5.78 (m, 2H), 5.27−5.31 (m, 1H), 4.07−4.17 (m, 2H), 3.89−4.00 (m, 2H), 3.53 (dd, J = 7, 11.5 Hz, 1H, major isomer), 3.41 (dd, J = 5, 11.2 Hz, 1H, minor isomer), 3.04−3.11 (m, 1H), 2.35 (bs, 1H), 2.24 (dddd, J = 4, 13, 13, 13 Hz, 1H), 2.09 (s, 3H, major isomer), 2.05 (s, 3H, minor isomer), 1.98 (s, 3H), 1.46 (s, 3H), 1.43 (s, 3H), 1.40 (s, 3H), 1.40−2.12 (m, 15H), 1.27 (s, 3H, major isomer), 1.24 (s, 3H, minor isomer), 1.20 (s, 3H), 1.90 (s, 3H), 1.18 (s, 3H); HRMS (FAB) calcd for $C_{33}H_{54}O_9{}^{79}Br$ [M + H]$^+$ 673.2937, found 673.2972. To a stirred, room temperature solution of alcohols **48** (14 mg, 21 μmol) in CH_2Cl_2 (1 mL) was added $NaHCO_3$ (27 mg, 315 μmol) followed by the Dess−Martin periodinane reagent (27 mg, 63 μmol). The resultant mixture was stirred for 1 h. Ethyl acetate (2 mL), saturated aqueous $NaHCO_3$ (2 mL), and 10% aqueous $Na_2S_2O_3$ (2 mL) were added, and the mixture was stirred until the organic layer became clear. The aqueous phase was extracted with ethyl acetate (3 × 2 mL), and the combined organic phase was washed with saturated aqueous NaCl (2 mL), dried over $MgSO_4$, filtered, and concentrated to give an oil. Silica gel column chromatography (hexanes/ethyl acetate/ether/CH_2Cl_2, 75:5:15:5, v/v) of the residue gave **49** (12 mg, 18 μmol, 88%) as a colorless oil. Further purification by reverse-phase HPLC (C-18, CH_3CN/H_2O, 96:4, v/v) afforded an analytical sample: R_f 0.25 (hexanes/ethyl acetate/CH_2Cl_2, 6.5:1.5:1.5, v/v); $[\alpha]^{22}_D$ +11 (*c* 0.88, $CHCl_3$); IR (neat) 2963, 1702, 1678, 1631, 1548, 1529, 1461, 1443, 1413, 1371, 1261, 1102; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.98 (dd, J = 5, 16 Hz, 1H), 6.73 (dd, J = 1.5, 16 Hz, 1H), 5.42 (dd, J = 1.5, 5 Hz, 1H), 4.17 (d, J = 6.3 Hz, 1H), 4.10 (dd, J = 6.5, 8.5 Hz, 1H), 3.89 (dd, J = 4, 12.7 Hz, 1H), 3.14 (dd, J = 4.5, 11.5 Hz, 1H), 3.10 (dd, J = 2.5, 11 Hz, 1H), 2.51−2.56 (m, 1H), 2.24 (dddd, J = 4, 13, 13, 13 Hz, 1H), 2.15 (s, 3H), 1.99 (s, 3H), 1.65−2.15 (m, 11H), 1.40−1.60 (m, 4H), 1.47 (s, 3H), 1.45 (s, 3H), 1.40 (s, 3H), 1.27 (s, 3H), 1.21 (s, 3H), 1.18 (s, 3H), 0.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.57, 170.40, 169.87, 141.34, 127.02, 86.81, 85.45, 84.13, 82.51, 80.52, 75.93, 75.00, 74.54, 74.30, 70.00, 58.95, 37.83, 37.15, 34.42, 31.03, 28.21, 26.44, 23.60, 23.53, 23.08, 22.91, 22.46, 21.70, 21.02, 19.99, 16.92; HRMS (FAB) calcd for $C_{33}H_{51}O_9{}^{79}BrNa$ [M + Na]$^+$ 693.2553, found 693.2609.

Thyrsiferyl 18,23-Diacetate (1d). To a −78 °C solution of **49a** (8 mg, 12 μmol) in THF (0.8 mL) was added methylmagnesium bromide (47 μL of a 3 M solution in ether, 143 μmol). After the solution was stirred at −78 °C for 5 h, saturated aqueous NH_4Cl (3 mL) and ethyl acetate (3 mL) were added. The mixture was allowed to warm to room temperature, and the aqueous phase was extracted with ethyl acetate (3 × 3 mL). The combined organic phase was washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate/$CHCl_3$, 75:20:5, v/v) to give **1d** (7 mg, 10 μmol, 87%) as a colorless oil. Further purification by reverse-phase HPLC (C-18, CH_3CN/H_2O, 96:4, v/v) afforded an analytical sample: R_f 0.31 (hexanes/ethyl acetate/CH_2Cl_2, 6.5:3:0.5, v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.90 (dd, J = 4, 9.7 Hz, 1H), 4.03 (dd, J = 5.5, 8.7 Hz, 1H), 3.90 (dd, J = 4, 12.2 Hz, 1H), 3.70 (dd, J = 3, 12.7 Hz, 1H), 3.56 (dd, J = 7.5, 11 Hz, 1H), 3.05 (dd, J = 2.5, 11.5, 1H), 2.45 (bs, 1H), 2.25 (dddd, J

= 4, 13, 13, 13 Hz, 1H), 1.14−2.14 (m, 19 H), 2.08 (s, 3H), 1.98 (s, 3H), 1.46 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H), 1.27 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 1.16 (s, 3H), 1.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.83, 170.45, 86.51, 84.97, 84.39, 82.58, 78.32, 76.26, 75.86, 74.96, 74.36, 72.97, 71.89, 59.01, 38.56, 37.08, 34.25, 32.08, 31.01, 28.23, 26.47, 23.80, 23.68, 23.12, 22.98, 22.48, 22.40, 21.74, 21.41, 21.17, 21.08, 20.60, 20.04; HRMS (FAB) calcd for $C_{34}H_{58}O_9{}^{79}Br$ $[M + H]^+$ 689.3249, found 689.3231, calcd for $C_{34}H_{56}O_8{}^{79}Br$ $[M - OH]^+$ 671.3144, found 671.3148.

Thyrsiferyl 23-Acetate (1a) and Thyrsiferol (1b). To a room temperature solution of **1d** (3.3 mg, 4.8 μmol) in methanol (360 μL) was added K_2CO_3 (~1.3 mg, 9.4 μmol). The mixture was stirred for ~9 h before the pH was adjusted to ~7 with a solution of acetic acid in ethyl acetate. The resultant mixture was concentrated, and the residue was purified by silica gel column chromatography ($CHCl_3$/acetone, 95:5−80:20, v/v) to obtain **1a** (1.1 mg, 1.7 μmol, 35%) and **1b** (1.2 mg, 2.0 μmol, 42%) as colorless oils. Further purification by reverse-phase HPLC (C-18, CH_3CN/H_2O, 96:4, v/v) afforded analytical samples.

Data for **1a**: R_f 0.26 ($CHCl_3$/acetone, 9:1, v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.02 (dd, J = 6.5, 9.5 Hz, 1H), 3.89 (dd, J = 4, 12.2 Hz, 1H), 3.72 (dd, J = 3, 13 Hz, 1H), 3.58 (dd, J = 7.5, 11.2 Hz, 1H), 3.46 (dd, J = 2, 10.5 Hz, 1H), 3.05 (dd, J = 2.5, 12 Hz, 1H), 2.91 (bs, 1H), 2.81 (bs, 1H), 2.25 (dddd, J = 4, 13, 13, 13 Hz, 1H), 1.34−2.10 (m, 19H), 2.00 (s, 3H), 1.49 (s, 3H), 1.45 (s, 3H), 1.40 (s, 3H), 1.27 (s, 3H), 1.20 (s, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 1.10 (s, 3H); HRMS (FAB) calcd for $C_{32}H_{56}O_8{}^{79}Br$ $[M + H]^+$ 647.3144, found 647.3163, calcd for $C_{32}H_{54}O_7{}^{79}Br$ $[M - OH]^+$ 629.3039, found 629.3074. [Lit.[14d] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.00 (dd, J = 6.1, 9.5 Hz, 1H), 3.89 (dd, J = 3.9, 12.2 Hz, 1H), 3.70 (dd, J = 2.4, 12.7 Hz, 1H), 3.57 (dd, J = 7.6, 10.9 Hz, 1H), 3.45 (dd, J = 2.0, 10.3 Hz, 1H), 3.04 (dd, J = 2.7, 11.5 Hz, 1H), 1.99 (s, 3H), 1.48 (s, 3H), 1.44 (s, 3H), 1.40 (s, 3H), 1.27 (s, 3H), 1.20 (s, 3H), 1.18 (s, 3H), 1.16 (s, 3H), 1.09 (s, 3H)].

Data for **1b**. R_f 0.30 ($CHCl_3$/acetone, 7:3, v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.90 (dd, J = 4, 12.5 Hz, 1H), 3.76 (dd, J = 6, 10 Hz, 1H), 3.72 (dd, J = 3, 13 Hz, 1H), 3.57 (dd, J = 7.5, 11 Hz, 1H), 3.46 (dd, J = 2.5, 10.5 Hz, 1H), 3.05 (dd, J = 2.5, 12 Hz, 1H), 2.96 (bs, 1H), 2.81 (bs, 1H), 2.25 (dddd, J = 4, 13, 13, 13 Hz, 1H), 2.06−2.16 (m, 1H), 1.32−1.94 (m, 18H), 1.40 (s, 3H), 1.27 (s, 3H), 1.22 (s, 3H), 1.20 (s, 3H), 1.19 (s, 3H), 1.16 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H); HRMS (FAB) calcd for $C_{30}H_{53}O_7{}^{79}BrNa$ $[M + Na]^+$ 627.2811, found 627.2876, calcd for $C_{30}H_{54}O_7{}^{79}Br$ $[M + H]^+$ 605.3039, found 605.3031. [Lit.[14d] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.89 (dd, J = 3.9, 12.2 Hz, 1H), 3.76 (dd, J = 6.3, 9.8 Hz, 1H), 3.72 (dd, J = 2.9, 13.2 Hz, 1H), 3.57 (dd, J = 7.3, 11.2 Hz, 1H), 3.46 (dd, J = 2.0, 10.3 Hz, 1H), 3.05 (dd, J = 2.4, 11.9 Hz, 1H), 2.25 (dq, J = 3.4, 12.7 Hz, 1H), 1.40 (s, 3H), 1.27 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 1.18 (s, 3H), 1.16 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H); HRMS (FI) found for $C_{30}H_{54}O_7{}^{79}Br$ $[M + H]^+$ 605.3097]. [Lit.[63] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.89 (dd, J = 4.3, 12.2 Hz, 1H), 3.76 (dd, J = 6.5, 9.3 Hz, 1H), 3.73 (dd, J = 3.1, 12.3 Hz, 1H), 3.56 (dd, J = 7.0, 11.3 Hz, 1H), 3.45 (dd, J = 2.2, 9.8 Hz, 1H), 3.04 (dd, J = 2.3, 9.6 Hz, 1H), 1.40 (s, 3H), 1.27 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 1.20 (s, 3H), 1.18 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H), 1.09 (s, 3H)].

Thyrsiferyl 18-Acetate (1c). To a room temperature solution of **1b** (1.2 mg, 2 μmol) in pyridine (80 μL, 1 mmol) was added acetic anhydride (23 μL, 0.2 mmol). The mixture was stirred for 18 h before it was concentrated. Silica gel column chromatography of the residue gave **1c** (0.8 mg, 1.3 μmol, 70%) as a colorless solid. Further purification by reverse-phase HPLC (C-18, CH_3CN/H_2O, 96:4, v/v) afforded an analytical sample: R_f 0.24 (chloroform/acetone, 9:1, v/v); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.91 (dd, J = 4, 9.5 Hz, 1H), 3.89 (dd, J = 4, 12.2 Hz, 1H), 3.69−3.73 (m, 2H), 3.56 (dd, J = 7, 11 Hz, 1H), 3.66 (bs, 1H), 3.05 (dd, J = 2, 12 Hz, 1H), 2.45 (bs, 1H), 2.25 (dddd, J = 4, 13, 13, 13 Hz, 1H), 1.20−2.14 (m, 19H), 2.08 (s, 3H), 1.40 (s, 3H), 1.27 (s, 3H), 1.20 (s, 9H), 1.16 (s, 3H), 1.19 (s, 3H), 1.09 (s, 3H); HRMS (FAB) calcd for $C_{32}H_{56}O_8{}^{79}Br$ $[M + H]^+$ 647.3144, found 647.3131, calcd for $C_{32}H_{54}O_7{}^{79}Br$ $[M - OH]^+$ 629.3039, found 629.3096. Comparison spectra of synthetic **1c** and **1c** derived from naturally occurring **1b** are included in the Supporting Information.

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Supporting Information Available: Experimental procedures and characterization data for compounds **1a**, **1b**, **1c**, **1d**, **4**, **5**, **6**, **6a**, **7**, **10**, **11a**, **11b**, **12**, **16**, **17b**, **23**−**28**, **31**−**37**, **40a**, **40b**, **41a**, **41b**, **42**−**49**, and **49a**; copies of ^{1}H NMR spectra of compounds **1a**−**d**, **4**−**6**, **6a**, **7**, **11a**, **11b**, **12**, **16**, **17b**, **23**−**28**, **31**−**37**, **40a**, **40b**, **41a**, **41b**, **42**−**47**, **47a**, **48**, **49**, and **49a**; NOE data of compounds **12**, **37**, and **46**; and an HMQC spectrum of **1a** (PDF). This information is available free via the Internet at http://pubs.acs.org.

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