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Synthesis of the Cyclohepta[*e*]hydrindane Core of the Marine Homoverrucosane Diterpenoid Gagunin E

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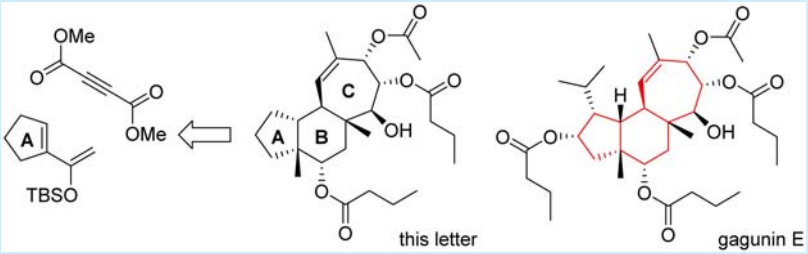
Supporting Information



ABSTRACT: The synthesis of the A−B-*cis* B−C-*trans* annulated cyclohepta[*e*]hydrindane core of gagunin E with a fully elaborated B−C ring segment has been achieved. Using an adaptable A ring building block, the B ring was annulated by (4 + 2)-cycloaddition and the C ring by ring-closing metathesis. The angular methyl groups were attached by electrophilic cyclopropanation−ring opening.

In 2002, Shin and co-workers reported the isolation of a small sample (3.1 mg) of the marine homoverrucosane diterpenoid gagunin E from a sponge (1.8 kg dry weight) of the genus *Phorbas* (Figure 1).[1] The intricate architecture of gagunin E (**1**) poses a significant synthetic challenge and requires an original synthetic design.[2] Furthermore, biological studies demonstrate that gagunin E exhibits a notable LC_{50} (0.03 μg/mL) against the human leukemia cell-line K562. Whereas total syntheses of the structurally related cyathane diterpenoids are well documented,[3] endeavors toward the homoverrucosane scaffold are rare. Piers has reported the first total synthesis of an A−B-*trans* B−C-*trans* annulated homoverrucosanoid which was isolated from the sponge *Axinyssa aplysinoides* by Faulkner.[4,5] Stoltz and co-workers revealed an enantioselective synthesis of the A−B-*cis* B−C-*trans* annulated cyclohepta[*e*]hydrindane core of gagunin E that relied on their Tsuji allylation tactic for construction of the quaternary stereogenic carbon atoms C3a and C5a.[6]

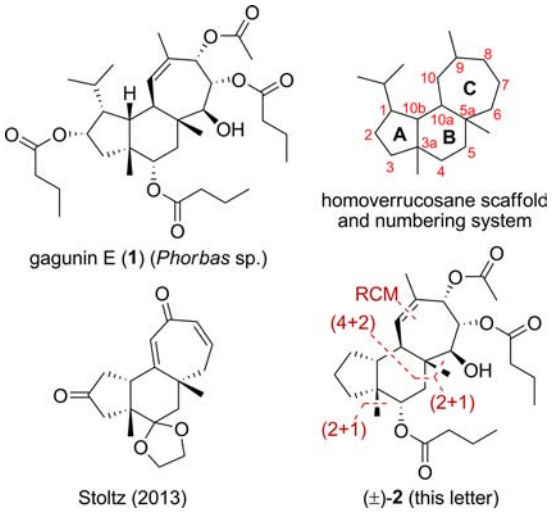


Figure 1. Gagunin E, the homoverrucosane scaffold and numbering system, and the cyclohepta[*e*]hydrindane core structure synthesized by Stoltz and co-workers (2013).

Our synthetic design for the A−B-*cis* B−C-*trans* annulated cyclohepta[*e*]hydrindane core of gagunin E envisioned late-stage construction of the seven-membered C ring by ring-closing metathesis (RCM) and an early stage intramolecular (4 + 2)-cycloaddition for the assemblage of the A−B-*cis* annulated hydrindane segment (Figure 1).[7] The curvature of the *cis*-hydrindane building block would then allow for introduction of the angular 3a- and 5a-methyl groups from the convex diastereoface.

Our assemblage of the tricyclic core of gagunin E commenced with the (4 + 2)-cycloaddition between silyl dienol ether **3**[7] and dimethyl acetylenedicarboxylate **4** to provide bicyclic silyl enol ether **5** (76% isolated yield, 14.8 g isolated mass) (Scheme 1).[8] Regioselective cyclopropanation then delivered siloxy cyclopropane **6**.[9,10] Subsequent ring opening was accomplished with *p*-TsOH under carefully controlled conditions to afford an inseparable mixture (**7**:**8** = 1:9) of the initially expected ketone **7** and its constitutional isomer **8** as a mixture of C10a epimers.[11,12]

With the enone **8** in hand, we initially attempted to introduce the 5a-methyl group by 1,4-addition without success. Facing this setback, we opted for introduction of the 5a-methyl group by electrophilic cyclopropanation. Toward this end, **8** was reduced

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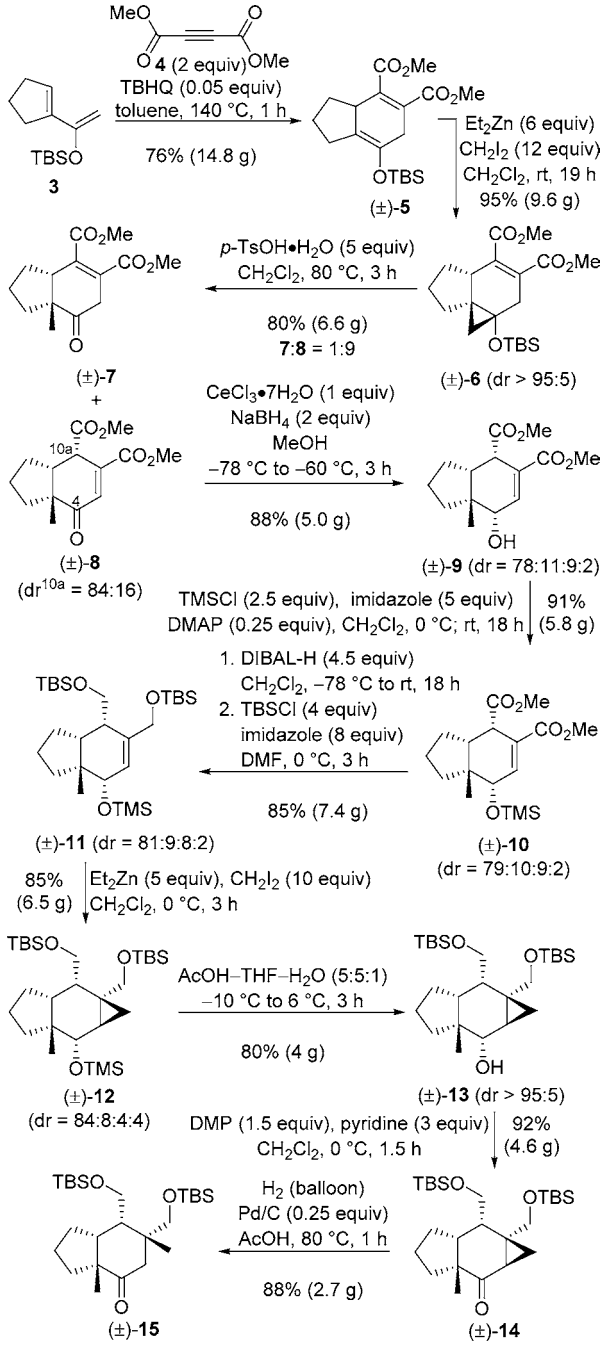
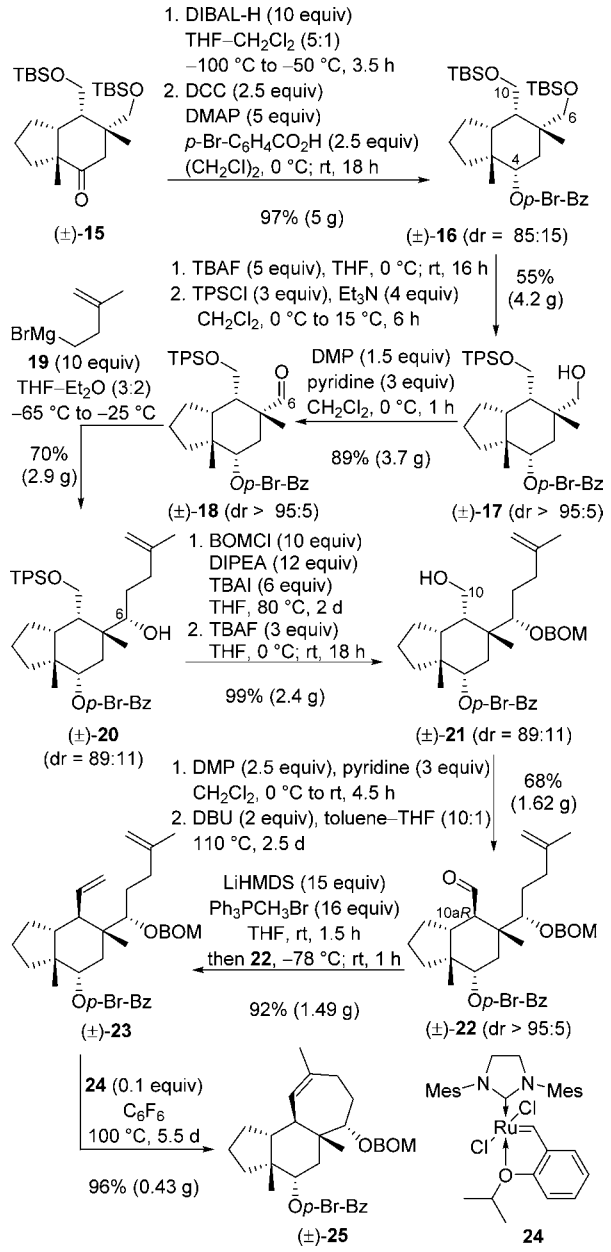
Scheme 1. Synthesis of *cis*-Hydrindanoid 15



With the *cis*-hydrindanone **15** in hand, we targeted annulation of the C ring (Scheme 2). DIBAL-H was found to effect a

Scheme 2. Synthesis of Cyclohepta[*e*]hydrindanoid 25



to yield the allylic alcohol **9** as a mixture of four diastereomers.[13,14] The diastereomeric mixture was carried downstream until separation by SiO_2 chromatography was possible. Our experience taught us that high-yielding DIBAL-H reduction of the ester groups in **9** required preceding formation of TMS ether **10**. Treatment of **10** with DIBAL-H then delivered the corresponding diol which was converted into the bis-TBS ether **11**. Cyclopropanation of **11** provided **12** as a mixture of four diastereomers.[15] In preparation of the cyclopropane ring opening, the TMS ether was cleaved under carefully optimized conditions to yield the alcohol **13** as a single diastereomer. Oxidation then provided cyclopropyl ketone **14**, and subsequent hydrogenolysis furnished *cis*-hydrindanone **15**.

diastereoselective reduction of the C4 ketone **15** from the convex diastereoface.[16] The resulting alcohol was esterified to deliver **16** as a mixture of diastereomers at C4.[17] The construction of the seven-membered C ring then required differentiation of the primary hydroxyl groups at C6 and C10. Because attempted regioselective desilylation led to a mixture of monosilylated products under various conditions,[18] we turned to site-selective silyl ether formation. Thus, the primary TBS ethers were cleaved and the resulting diol was treated with *tert*-butyldiphenylsilyl chloride (TPSCl) and Et_3N to afford TPS ether **17** as a single diastereomer but contaminated with trace amounts of the C6 TPS ether.[19] Alcohol **17** was exposed to the Dess–Martin periodinane (DMP) to deliver aldehyde **18** as a single diastereomer. Subjecting **18** to an excess of the Grignard reagent **19** at low temperature provided **20** as a mixture of diastereomers and

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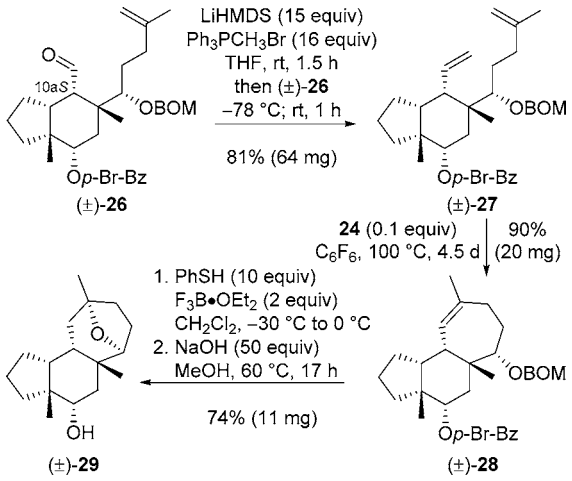
without cleavage of the benzoate. The alcohol **20** was converted into the corresponding benzyloxymethyl (BOM) acetal, and ensuing desilylation afforded **21**.[20] Alcohol **21** was oxidized to the corresponding 10a*S*-configured aldehyde **26** (Scheme 3).

Scheme 3. Transannular Etherification



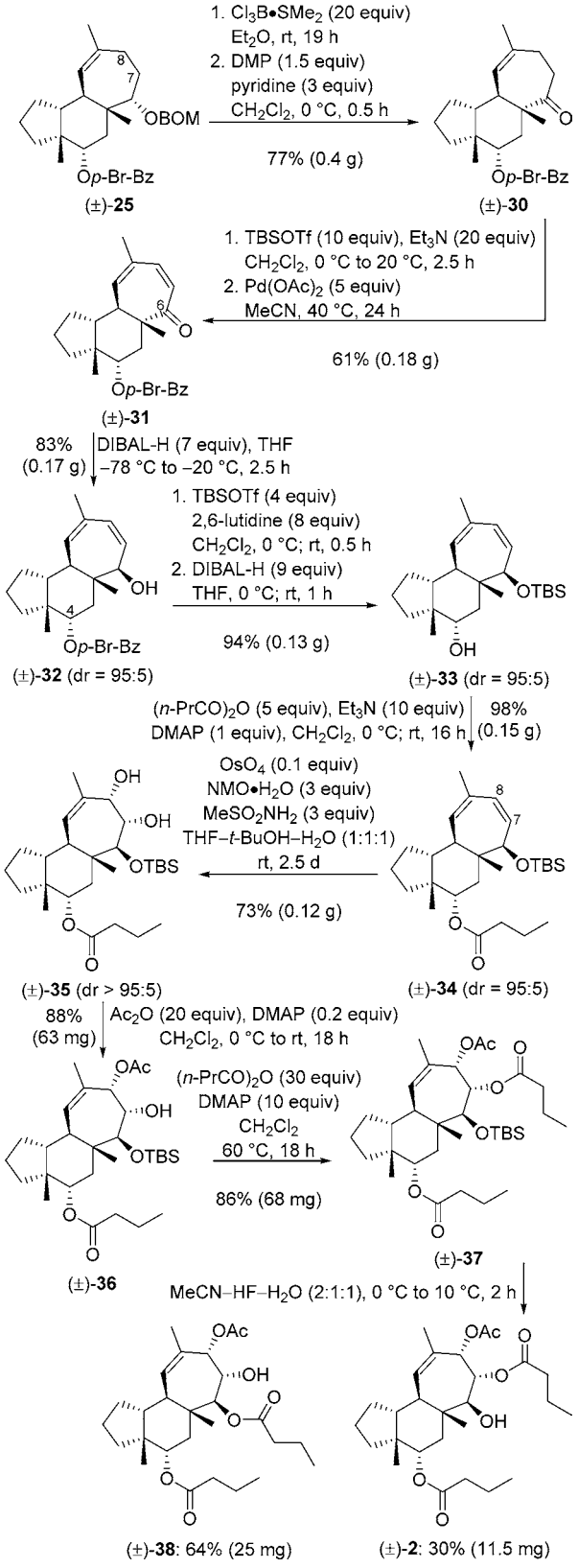
Subsequent 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-mediated epimerization of **26** delivered the required 10a*R*-configured **22** as a single diastereomer.[21] Wittig methylenation of aldehyde **22** furnished **23** and enabled the *trans* annulation of the seven-membered C ring by RCM.[22] RCM of diene **23** was best accomplished using the Hoveyda–Grubbs catalyst II **24** in C_6F_6 (100 °C) to deliver the A–B-*cis* B–C-*trans* annulated cyclohepta[*e*]hydrindane core **25** of gagunin E in excellent yield.[23]

To substantiate our structural assignment, the 10a*S*-configured aldehyde **26** was also subjected to the C ring annulation sequence (Scheme 3). Thus, methylenation of **26** afforded **27** and RCM of **27** delivered BOM acetal **28**. Attempts to cleave the BOM acetal under acidic conditions unveiled a pronounced susceptibility of the B–C-*cis* annulated tricarbocycle for transannular etherification. Subsequent saponification of the benzoate provided the crystalline 6,9-epoxycyclohepta[*e*]hydrindan-4-ol **29** whose relative configuration was assigned by X-ray crystallography.[24]

With the cyclohepta[*e*]hydrindanoid **25** in hand, we were in the position to explore opportunities for the gagunin E-like functionalization of the B–C ring segment (Scheme 4). We considered the tricarbocyclic dienone **32** a key intermediate and envisioned its synthesis from **25** by Saegusa oxidation. Thus, removal of the BOM protecting group was followed by oxidation to afford **30**.[25] The ketone **30** was subjected to TBSOTf and Et_3N to deliver the corresponding silyl enol ether. After screening numerous conditions, Saegusa oxidation was performed using an excess of $Pd(OAc)_2$ in CH_3CN at 40 °C to furnish **31**.[26,27] Diastereoselective DIBAL-H reduction of dienone **31** at low temperature delivered 6*R*-configured **32**.[28] Alcohol **32** was converted to the corresponding silyl ether, and the C4 benzoate was reductively degraded by DIBAL-H at ambient temperature to provide **33**. Alcohol **33** was transformed to the butyrate **34** to set the stage for a nondirected dihydroxylation.

Notably, OsO_4-catalyzed dihydroxylation of the diene **34** proceeded regio- and diastereoselectively to deliver **35** as a single diastereomer.[29] Having made accessible diol **35**, site-selective esterification was required. Gratifyingly, completely regioselective acetylation of the allylic hydroxyl group was achieved by subjecting **35** to an excess of acetic anhydride and catalytic

Scheme 4. Functionalization of the Cyclohepta[*e*]hydrindanoid 25



amounts of 4-(dimethylamino)pyridine (DMAP) at ambient temperature to afford **36**. Formation of the butyric ester at the remaining C7 hydroxyl group of the bis-ester **36** required a large excess of butyric anhydride and DMAP at increased temperature

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to deliver the tris-ester **37**. A seemingly simple degradation of the C6 TBS ether was needed in order to finalize the gagunin E-like functionalization of the B−C ring segment. However, this protecting group operation turned out to be much more challenging than anticipated: Depending on the conditions employed for silyl ether cleavage, we noticed no conversion, decomposition, or a pronounced propensity of the C7 butyric ester for transesterification to deliver the tris-ester **38**.[30] Even using carefully controlled settings, we only isolated a separable mixture of the two tris-esters **2** and **38**.[31]

In summary, we have synthesized the cyclohepta[*e*]hydrindane core of gagunin E **2** with a fully functionalized B−C ring segment. Thereby, we have delineated principles for the functionalization of the homoverrucosane scaffold that could guide future synthetic efforts. On paper, using a suitably substituted nonracemic diene for the initiating (4 + 2)-cycloaddition could enable the total synthesis of the reported structure of gagunin E. However, our current linear strategy requires more than 30 steps and, thus, operates to our disadvantage. Consequently, future efforts toward gagunin E must be guided by a more efficient synthetic design.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03799.

Procedures, characterization data (PDF)
NMR spectra (PDF)
Elemental analyses, MS and IR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(8) Rigorous exclusion of oxygen and the presence of *tert*-butylhydroquinone (TBHQ) is required to suppress aromatization of **5**. Prolonged reaction times (>1 h) promote double bond isomerization and formation of the corresponding 1,3-diene: Stirring at 140 °C for 24 h enforced complete double bond isomerization. Storing **5** in solution at ambient temperature also triggered double bond isomerization.

(9) (a) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, *7*, 3353−3354. (b) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53−58.

(10) The outcome of the cyclopropanation is strongly dependent on the preparation of the reagent; see the Supporting Information for details.

(11) In general, diastereoselectivities were determined by integration of diagnostic ^{1}H NMR signals. Because NOE studies were inconclusive, the relative configuration of C10a was tentatively assigned and later corroborated by X-ray crystallography (Scheme 3).

(12) Somewhat unexpected, the C10a ester group of the major diastereomer of **8** is directed toward the concave diastereoface and, hence, features the undesired relative configuration at C10a.

(13) (a) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226−2227. (b) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454−5459.

(14) Interestingly, **7** isomerized to **8** prior to reduction.

(15) Cyclopropanation of diastereomerically pure **11** delivered **12** as a single diastereomer.

(16) Assignment of the relative configuration rests on the interpretation of NOE experiments of **25**.

(17) Neises, B.; Steglich, W. *Angew. Chem.* **1978**, *90*, 556−557.

(18) Various sets of conditions were screened for site-selective monodesilylation without success: TBAF, TBAF−AcOH, NH_4F, HF−MeCN, HF·pyridine, PPTS, CSA, PTSA, $ClCH_2CO_2H$, TFA, HCO_2H.

(19) An excess of TPSCl and Et_3N is required to achieve complete conversion. Subjecting the product mixture to Et_3N did not alter the original product ratio. TBSCl, TIPSCl, TIPSOTf, and TrCl led to an inferior ratio of monosilylation products.

(20) A large excess of TBAI is required to achieve complete conversion.

(21) THF was required to ensure solubility of the substrate.

(22) High dilution conditions (5 mM) are required to avoid cleavage of the benzoate.

(23) Performing the RCM in benzene (100 °C) or toluene (100 °C) led to incomplete conversion.

(24) Schäfer, A.; Golz, C.; Preut, H.; Strohmann, C.; Hiersemann, M. *Acta Crystallogr. E Cryst. Commun.* **2015**, *71*, o690−o691.

(25) Brønsted acidic conditions must be avoided to prevent transannular etherification.

(26) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011−1013.

(27) In our hands, the effectiveness of the protocol was very much dependent on the nature and the source of the Pd(II) reagent. For instance, using $Pd(tfa)_2$−DMSO in THF at 40 °C initially led to promising yields (67−78%). However, using $Pd(tfa)_2$ from a newly acquired packaging unit led to diminished yields because of competing silyl enol ether hydrolysis.

(28) Assignment of the relative configuration is based on the interpretation of NOESY experiments of **32**.

(29) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973−1976. The assignment of the relative configuration rests on the interpretation of NOESY experiments of **35** and **36**.

(30) No conversion: HF·pyridine, THF; TBAF−AcOH, THF; TASF, THF; $CeCl_3{\cdot}7H_2O$, MeCN; NH_4F, HFIP; NH_4F−HF, DMF, NMP. Low conversion with the propensity for transesterification: TBAF−NH_4F, THF; TBAF−HF, THF; THF−HCO_2H−H_2O (2:1:1). TBAF in THF indeed affected silyl ether cleavage but led to a mixture of four products. Nonspecific decomposition: HCl, MeOH. Interestingly, the ratio of gagunin E-like **2** (11.5 mg) to gagunin F-like **38** (25.0 mg) corresponds to the ratio of gagunin E (3.1 mg) to gagunin F (5.8 mg) isolated from *Phorbas* sp. by Shin and co-workers.

(31) The assignment of the relative configuration rests on the interpretation of NOESY experiments of **2** and **38**.

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