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Synthesis of (+)-Lineariifolianone and Related Cyclopropenone-Containing Sesquiterpenoids

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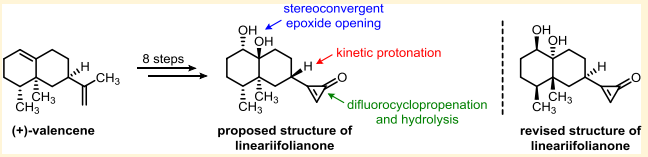
Supporting Information

ABSTRACT: A synthesis of the proposed structure of lineariifolianone has been achieved in eight steps and 9% overall yield starting from (+)-valencene, leading to a reassignment of the absolute configuration of this unusual cyclopropenone-containing natural product. Key steps in the synthetic route include kinetic protonation of an enolate to epimerize the C7 stereocenter and a stereoconvergent epoxide opening to establish the *trans*-diaxial diol functionality. The syntheses of the enantiomers of two other closely related natural products are also reported, confirming that all three compounds belong to the eremophilane class of sesquiterpenoids.



INTRODUCTION

Plants of the genus *Inula* have been widely used in traditional Chinese medicine for their anti-inflammatory properties and to treat bacterial infections.[1] In 2010, Zhang and Jin reported the isolation of the sesquiterpenoid lineariifolianone (**1**), which was obtained from the aerial parts of the flowering plant *Inula lineariifolia* (Figure 1).[2] The structure of this natural product

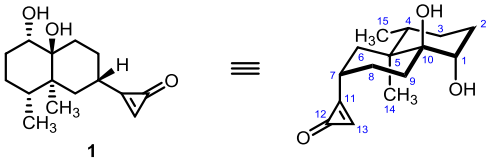


Figure 1. Proposed structure of lineariifolianone (**1**).

was confirmed through X-ray crystallography, and the absolute configuration was assigned based on NMR analysis of Mosher ester derivatives.[3] Structurally, lineariifolianone (**1**) features a *trans*-fused decalin ring system and five stereogenic centers, four of which are contiguous. In addition, **1** contains a *trans*-diaxial vicinal diol and a cyclopropenone substituent, which occupies an axial position on the same face of the decalin ring system as the angular methyl group at C5.

Cyclopropenones are notable for their many unusual properties, including large dipole moments (μ = 4−5 D), high basicity, and significant angle strain.[4] The cyclopropenone ring also exhibits aromatic character,[5] as first investigated by Breslow following his pioneering synthesis of diphenylcyclopropenone in 1959.[6] More recently, cyclopropenones have attracted considerable interest for their biological applications as protease inhibitors[7] and in the chemical ligation of biomolecules under mild conditions.[8] Cyclopropenones have also appeared in topical medications[9] and synthetic steroid derivatives,[10] and the parent compound has even been detected in interstellar space.[11]

Natural products containing the cyclopropenone group are quite rare, and to date only six other examples have been isolated (Figure 2). Penitricin (**2**)[12] and alutacenoic acids A and B (**3** and **4**)[13] are fungal metabolites that exhibit cytotoxicity and inhibit the plasma transglutaminase factor XIIIa. Although the origin of the cyclopropenone ring has not been fully elucidated, studies on penitricin suggest that 4-hydroxycrotonaldehyde serves as the biosynthetic precursor, and an efficient enzymatic conversion requires copper(II) ion as a co-factor.[14] Total syntheses of **2** and **3**−**4** have been reported by Nakamura[15] and Kogen,[13] respectively, and synthetic analogs of these compounds have been examined in structure−activity relationships for enzyme inhibition and cytotoxicity.

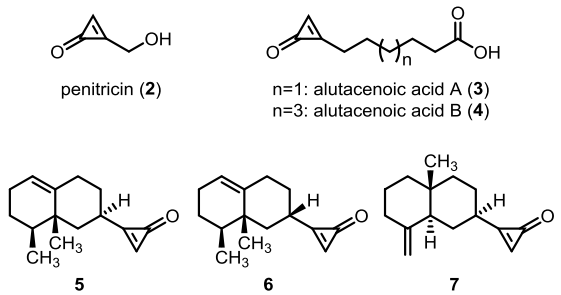


Figure 2. Other cyclopropenone-containing natural products.

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In 1981, Schuster and co-workers isolated three cyclopropenone-containing natural products (**5**–**7**) from the plant *Telekia speciosa*, which belongs to the same tribe as the *Inula* genus.[16] Although the absolute configurations of **5** and its epimer **6** were not rigorously determined, these compounds were classified as eremophilane sesquiterpenoids[17] (**8**, Figure 3) based on analogy to a known acrylate derivative.[18] Compound **7** was similarly classified as a eudesmane (selinane) sesquiterpenoid (**9**).[19]

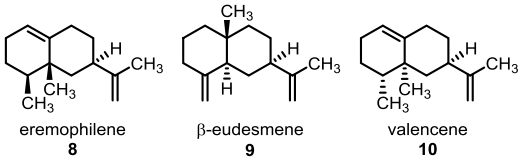


Figure 3. Structurally related sesquiterpenes.

There is a clear structural similarity between linearifolianone (**1**) and natural product **5** since the C1–C10 olefin found in the latter compound has been oxidized to form a *trans*-diol. However, it is also significant that **1** and **5** belong to opposite enantiomeric series, which is highly unusual for natural products isolated from such closely related plant species. Whereas **1** is formally derived from eremophilene (**8**), it appears that **1** is a C7-epi-valencene derivative (**10**).[20] Indeed, the co-isolation of compounds **5** and **6** indicates that the configuration at C7 can vary within this class of natural products. Interestingly, compound **6** and (+)-valencene (**10**) also belong to opposite enantiomeric series.

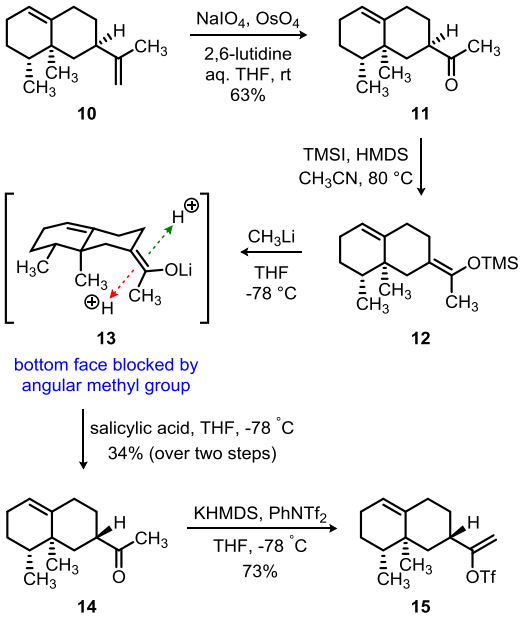
Given the promising biological activity of cyclopropenone derivatives and the stereochemical discrepancies outlined above, we found linearifolianone (**1**) and the related sesquiterpenoids **5** and **6** to be compelling synthetic targets. Although many simple cyclopropenone derivatives are known, there are very few examples in the chemical literature where this sensitive functionality has been introduced in more complex settings. Herein, we report the synthesis of **1**, which ultimately led to the reassignment of the absolute configuration of its naturally occurring enantiomer. We also report the synthesis of the enantiomers of sesquiterpenoids **5** and **6**, confirming the absolute configurations of these natural products.

RESULTS AND DISCUSSION

Our synthesis of **1** started from commercially available (+)-valencene (**10**), which already contains the decalin framework and the two methyl-bearing stereocenters found in the natural product (Scheme 1).[21] Chemoselective oxidative cleavage of the exocyclic isopropenyl group was achieved under Lemieux–Johnson conditions, giving ketone **11** in 63% yield.[22] Notably, no reaction was observed at the C1–C10 alkene, which is consistent with prior studies of the osmium-catalyzed dihydroxylation of **10**.[23] Interestingly, ketone **11** is itself a natural product[24] and has previously been prepared in low yield by ozonolysis of **10**,[25] by microbial oxidation of **10**,[26] and as an intermediate in prior total syntheses of (±)-valencene.[27,28]

To epimerize the stereocenter at C7, we planned to perform a kinetic protonation of the thermodynamic enolate derived from ketone **11**.[29] Although it is often difficult to selectively prepare thermodynamic enolates directly from unsymmetrical

Scheme 1. Epimerization of the C7 Stereocenter via Kinetic Protonation



ketones, good results can often be achieved using a two-step method proceeding through a silyl enol ether intermediate.[30] Thus, treatment of ketone **11** with hexamethyldisilazane (HMDS) and iodotrimethylsilane (generated *in situ* from sodium iodide and TMSCl) in refluxing acetonitrile gave the desired thermodynamic silyl enol ether **12** as an inconsequential mixture of *E*/*Z* isomers. Since **12** proved to be somewhat acid sensitive, it was typically used directly in the next step after filtration through silica gel that had been deactivated with triethylamine. The thermodynamic enolate **13** was then generated by treating **12** with methyllithium;[31] subsequent addition of salicylic acid at low temperature achieved the desired kinetic protonation, forming epimerized ketone **14** in 34% yield over the two-step sequence. It is notable that this kinetic protonation affords **14** as a single diastereomer. Presumably, the bottom face of enolate **13** is blocked by the angular methyl group at C5, resulting in exclusive protonation from the more sterically accessible top face.[27,32]

Having successfully epimerized the stereocenter at C7, our next goal was to convert the methyl ketone into a terminal alkyne.[33] Treating ketone **14** with potassium bis(trimethylsilyl)amide (KHMDS) formed the kinetic enolate, which was trapped with phenyl triflimide to form enol triflate **15**. To perform the subsequent elimination reaction, **15** was treated with excess tetrabutylammonium fluoride (TBAF) at room temperature in *N*,*N*-dimethylformamide (DMF), using conditions originally reported by Mori (Scheme 2).[34] This afforded a mixture of the desired terminal alkyne **16** and a small amount of the isomeric allene **17**, which were separable by column chromatography. At this stage, we decided to epoxidize the C1–C10 alkene in intermediate **16**. Not only would the epoxide serve as a convenient precursor to the *trans*-diol found in the natural product, but we also envisioned that it would minimize competing reactivity when elaborating the terminal alkyne to the cyclopropenone. Thus, treating **16** with buffered 3-chloroperoxybenzoic acid (*m*-CPBA) gave a 2:1 mixture of epoxides **18** and **19** in 82% yield. As observed in the

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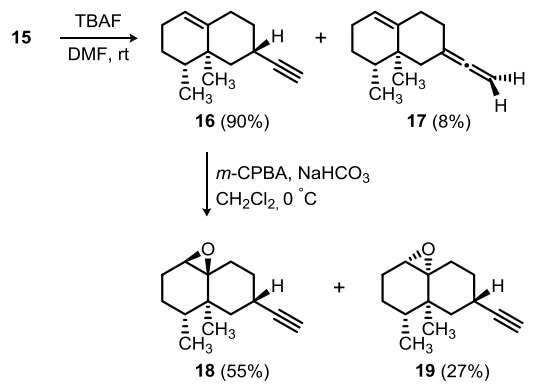
Scheme 2. Elaboration of Vinyl Triflate 15 to Diastereomeric Epoxides 18 and 19



kinetic protonation step, the major diastereomer **18** arises from the epoxidation of the alkene from the less sterically hindered face opposite the angular methyl group at C5.[35]

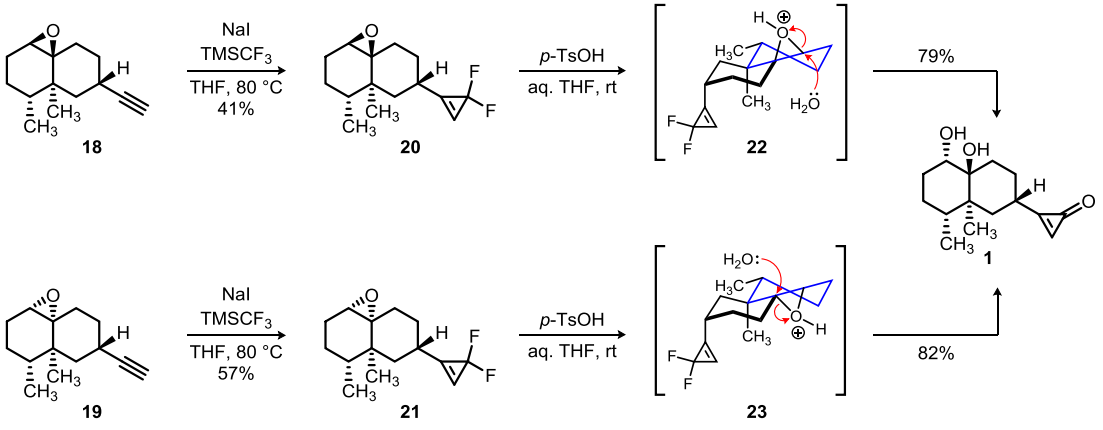
Although epoxides **18** and **19** were similar in polarity, we found that they could be separated by careful column chromatography. We originally anticipated that only the minor diastereomer **19** would lead to the correct diol configuration upon acidic hydrolysis due to the attack of water at the more substituted position. Nevertheless, both diastereomers were elaborated separately to investigate the formation of the key cyclopropenone group (Scheme 3). The most common precursors to cyclopropenones are geminal-dihalocyclopropenes, which are usually prepared from alkynes via the cheletropic cycloaddition of a dihalocarbene.[36] Free carbenes are typically highly reactive intermediates, but difluorocarbene in particular exhibits many desirable characteristics, including greater kinetic stability, and, therefore, enhanced chemoselectivity.[37] Although difluorocarbene can be generated from a wide variety of precursors, we chose to employ the particularly mild method developed by Hu and Prakash[38] utilizing trifluoromethyl trimethylsilane ($TMSCF_3$), which is also known as the Ruppert–Prakash reagent.[39] We were pleased to observe that heating a solution of epoxide **18** or **19** in tetrahydrofuran (THF) with $TMSCF_3$ and sodium iodide in a sealed tube at 80 °C cleanly gave difluorocyclopropenes **20** and **21**. This reaction could also be carried out on the mixture of epoxides obtained in the previous step, giving an inseparable 2:1 mixture of **20** and **21** in 95% yield. Notably, the epoxide functionality survives this transformation despite the high concentration of nucleophilic iodide and the presumed intermediacy of the strong Lewis acid iodotrimethylsilane (TMSI).

At this stage, only two steps remained to complete the synthesis of **1**: (1) perform a nucleophilic opening of the epoxide to form the *trans*-diol and (2) hydrolyze the difluorocyclopropene to form the cyclopropenone. We hoped to achieve both of these transformations in a single step by treating **20** and **21** with *para*-toluenesulfonic acid (*p*-TsOH) in aqueous THF at room temperature. Under these conditions, we observed that epoxide opening occurred first; however, subsequent hydrolysis of the difluorocyclopropene was much slower, requiring additional aliquots of *p*-TsOH and a total reaction time of up to 12 days. Nevertheless, the overall transformation occurred in good yield, and we were surprised to observe that hydrolysis of **20** and **21** resulted in the formation of the same diol **1**, corresponding to our targeted natural product.

This stereoconvergent epoxide opening can be explained using the so-called Fürst–Plattner rule, an effect that was first observed in the reactions of steroid-derived epoxides in 1949.[40] The Fürst–Plattner rule states that there is a strong kinetic preference for the formation of the *trans*-diaxial product in the opening of epoxides (or other three-membered rings such as halonium ions) fused to cyclohexane rings.[41] More specifically, the transition state for *trans*-diaxial ring opening avoids the unfavorable torsional strain arising in the alternative, higher-energy twist-boat transition state.[42] In the context of our system, the Fürst–Plattner rule dictates the regioselectivity of nucleophilic attack of water on the protonated epoxide intermediate. For the major epoxide diastereomer **20**, water attacks at the less substituted position, as depicted in **22**. In contrast, the nucleophilic attack of water occurs at the more substituted position in minor epoxide diastereomer **21**, as shown in **23**. As a result, both diastereomeric epoxides converge to a single diastereomer of the *trans*-diol, ultimately corresponding to the relative configuration found in **1**.

We were pleased to observe that the NMR data for synthetic **1** were in full agreement with those reported for the natural product. However, the specific rotation of our synthetic material was positive instead of negative, suggesting that the absolute configuration of the natural product had been misassigned (Figure 4). Indeed, Mosher ester analysis often gives erroneous results when applied to sterically hindered secondary alcohols.[43] In the case of linearifolianone,

Scheme 3. Stereoconvergent Epoxide Opening Leading to the Synthesis of 1



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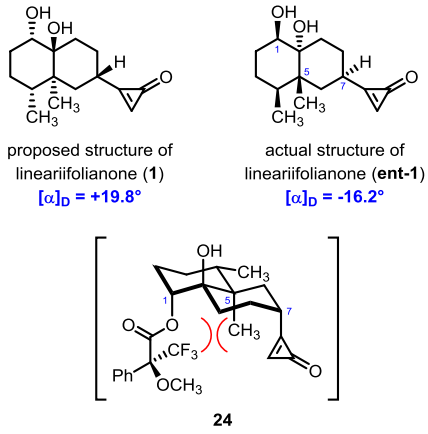
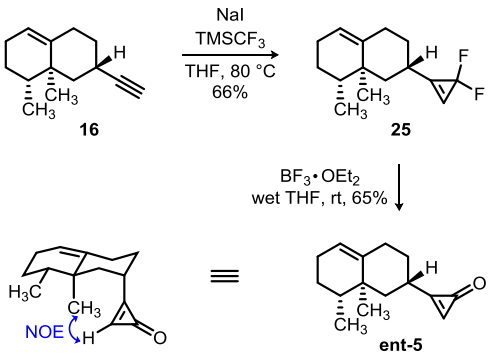


Figure 4. Reassignment of the absolute configuration of lineariifolianone.

esterification of the C1-alcohol would form a Mosher ester that suffers a destabilizing 1,3-diaxial relationship with the angular methyl group at C5 (**24**). This could result in an alternative preferred conformation that minimizes nonbonding interactions, giving an inaccurate Mosher ester analysis.[44] The absolute configuration of lineariifolianone is therefore corrected as shown in Figure 4, establishing that this natural product is in fact an eremophilane sesquiterpenoid.

Based on our successful synthesis of (+)-**1** from valencene, we set out to prepare the enantiomers of sesquiterpenoids **5** and **6** to confirm their absolute configurations. Our synthesis of **ent-5** started from the previously prepared terminal alkyne **16** (Scheme 4). Although difluorocarbene could react with

Scheme 4. Synthesis of ent-5

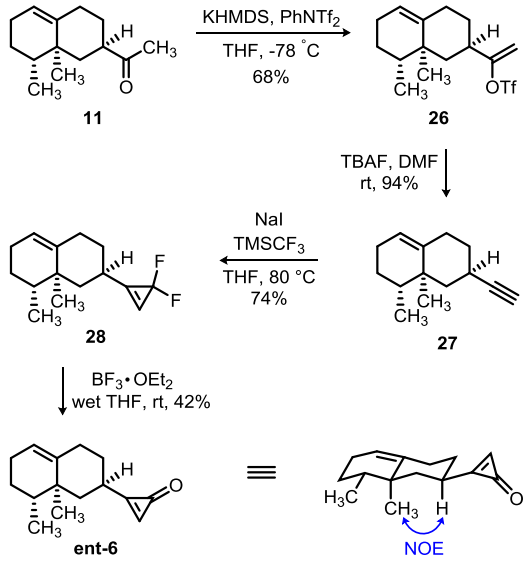


either the alkyne or the trisubstituted alkene, we observed excellent selectivity for the formation of the desired difluorocyclopropene using Prakash's conditions. This result is consistent with previous reports demonstrating that difluorocarbene reacts with alkynes approximately 10 times faster than it does with alkenes.[36c] Nevertheless, when substrate **16** was exposed to excess NaI and $TMSCF_3$ for a prolonged period of time, cyclopropanation of the alkene was also observed, giving a mixture of difluorocyclopropane diastereomers in a 2:1 ratio.

With compound **25** in hand, all that remained to complete the synthesis of **ent-5** was hydrolysis of the difluorocyclopropene to form the cyclopropenone. Interestingly, no reaction was observed when **25** was treated with *p*-TsOH in aqueous THF even though these conditions were successful in the preparation of **1**. Similarly, no reaction was observed using wet silica gel, which is a particularly mild method that has been utilized in the preparation of other cyclopropenones.[8b] Instead, we found that treating **25** with the Lewis acid boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) in wet THF resulted in clean hydrolysis, giving cyclopropenone **ent-5** in 65% yield.[45] The observed specific rotation for synthetic **ent-5** ($[\alpha]_D^{20}$ +105.2°) was indeed opposite in sign to that reported for natural product **5** ($[\alpha]_D^{24}$ −78°), albeit of somewhat larger magnitude. Thus, the absolute configuration of **5** has been confirmed as originally depicted in Figure 2. The structure of **ent-5** was also rigorously confirmed using two-dimensional (2D) NMR, which led to the reassignment of several of the reported ^{13}C NMR chemical shifts (see the Supporting Information for full details).

Our final synthetic target was **ent-6**, an epimer of **ent-5** featuring the opposite configuration at C7 (Scheme 5). Our

Scheme 5. Synthesis of ent-6



route started from ketone **11**, previously prepared in one step from the oxidative cleavage of (+)-valencene. The formation of the kinetic enol triflate occurred in 68% yield using our previous conditions, and subsequent elimination with TBAF gave terminal alkyne **27** in 94% yield. Interestingly, none of the isomeric allene **17** was formed during this reaction, in contrast to the analogous transformation of its diastereomer **15** (Scheme 2). We attribute this difference to a steric effect: in the E2 reaction of **26** to form the allene, the base would need to remove the more hindered axial proton at C7, which is on the same face as the angular methyl group at C5. As before, selective difluorocyclopropenation of the alkyne could be achieved to form **28** in 74% yield, and the final $BF_3{\cdot}OEt_2$-mediated hydrolysis gave cyclopropenone **ent-6** in 42% yield. Although the specific rotation for natural product **6** was not reported, the structure of **ent-6** was again confirmed with extensive 2D NMR. In particular, a prominent nuclear Overhauser effect (NOE) correlation was observed between the angular methyl group at C5 and the axial methine hydrogen at C7, confirming the equatorial orientation of the cyclopropenone group.

To further explore the reactivity of these cyclopropenone-containing compounds, we decided to investigate the nucleophilic addition of methanol to compound **1**. We

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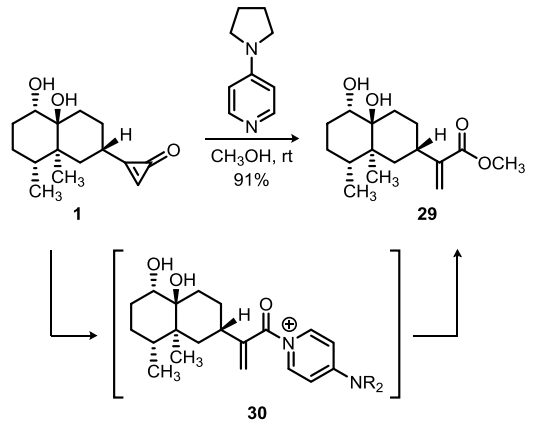
observed that an NMR sample of **1** in methanol-d_4 was stable indefinitely at room temperature, showing no discernable change after 3 months. Similarly, no cyclopropenone ring opening or dimethyl ketal formation was observed in the presence of *p*-TsOH. However, the addition of a small amount of the nucleophilic catalyst 4-(pyrrolidino)pyridine to a solution of **1** in methanol resulted in formation of the corresponding acrylate ester **29** (Scheme 6).[46] Presumably,

Scheme 6. Nucleophilic Opening of Cyclopropenone 1 with Methanol in the Presence of 4-(pyrrolidino)pyridine



this reaction proceeds through an acylpyridinium intermediate such as **30**, which undergoes nucleophilic acyl substitution with methanol to form the ester.[47] The regioselectivity of ring opening (10:1, as determined by ^{1}H NMR) is dictated by the formation of the less substituted vinyl anion, which is consistent with previous reports of cyclopropenone cleavage in aqueous hydroxide solution.[6e] It is notable that this transformation occurs under especially mild conditions (room temperature, no strong acids or bases), and similar reactions could be used to prepare synthetic analogs of **1** (or its naturally occurring enantiomer) for further biological screening.

In summary, we have achieved the synthesis of the reported structure of (+)-linearifolianone (**1**) and reassigned the absolute configuration of the natural product based on optical rotation data. We have also established the structures of the related cyclopropenone-containing sesquiterpenoids **5** and **6** by synthesizing their enantiomers. As a result, all three natural products have been confirmed as eremophilane derivatives. Efforts to further evaluate the biological activity of the cyclopropenones prepared in this study are currently underway in our laboratory.

EXPERIMENTAL SECTION

General Protocols. All reactions were carried out in a flame-dried glassware (unless water was present in the reaction mixture) with magnetic stirring under a positive pressure of argon. ACS reagent grade chloroform ($CHCl_3$), dichloromethane (CH_2Cl_2), *N*,*N*-dimethylformamide (DMF), ethyl acetate (EtOAc), hexanes, methanol (CH_3OH), tetrahydrofuran (THF), and triethylamine (NEt_3) were used without further purification. Anhydrous acetonitrile (CH_3CN) and THF dried over 4 Å molecular sieves were purchased in septum-sealed bottles. Reactions were monitored by thin layer chromatography (TLC) using glass plates precoated with a 0.25 mm layer of silica gel containing a fluorescent indicator. TLC plates were visualized by exposure to ultraviolet light and subsequently stained with acidic ethanolic *para*-anisaldehyde solution followed by heating on a laboratory hot plate. Silica gel for flash column chromatography had a 60 Å pore size, 40−63 μm particle size, and was 230−400 mesh.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were collected at 400 MHz and are calibrated to the residual monoprotio solvent peak ($CHCl_3$: 7.26 ppm; CHD_2OD: 3.31 ppm). Coupling constants were extracted assuming first-order coupling, and peak multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad signal, and app = apparent signal. Proton-decoupled carbon nuclear magnetic resonance (^{13}C{^{1}H} NMR) spectra were collected at 100 MHz and calibrated to the deuterated solvent peak ($CDCl_3$: 77.16 ppm; CD_3OD: 49.00). Fluorine nuclear magnetic resonance (^{19}F NMR) spectra were collected at 376 MHz and are uncalibrated. IR spectra for both solids and oils were recorded using an ATR accessory. High-resolution mass spectral (HRMS) data were obtained using either an electrospray ionization (ESI+) liquid chromatography−mass spectrometer or an electron impact (EI) gas chromatography−mass spectrometer equipped with a time-of-flight mass analyzer.

*1-((2R,8R,8aS)-8,8a-Dimethyl-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl)ethan-1-one (**11**).* Commercial (+)-valencene (≥65% purity, Sigma-Aldrich) was purified by column chromatography (19:1 hexanes/EtOAc) prior to use (15 g scale, 93% recovery). To a solution of purified (+)-valencene (8.00 g, 39.2 mmol, 1.00 equiv) in 415 mL of THF and 208 mL of water was added 2,6-lutidine (9.20 mL, 79.0 mmol, 2.02 equiv). Solid sodium periodate (25.2 g, 118 mmol, 3.01 equiv) was added followed by a 4% aqueous solution of osmium tetroxide (5.00 mL, 0.787 mmol, 0.02 equiv), and the reaction mixture immediately turned brown. The resulting suspension was stirred vigorously at room temperature for 4 days, at which point TLC (19:1 hexanes/EtOAc, anisaldehyde stain) showed partial conversion of valencene (R_f = 0.97, stains dark blue) to the desired ketone of R_f = 0.61 (stains yellow-green). A second portion of the 4% aqueous osmium tetroxide solution (2.50 mL, 0.394 mmol, 0.01 equiv) was added, and the reaction mixture was stirred for an additional 3 days, at which point TLC showed essentially complete consumption of the valencene. The accumulated solids were removed by filtration, and the filtrate was quenched with saturated aqueous Na_2SO_3 and diluted with water and EtOAc. The layers were separated, and the organic phase was washed twice with 1 M aq HCl before drying over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a brown oil that was purified by column chromatography (9:1 hexanes/EtOAc) to afford ketone **11** as a colorless oil (5.10 g, 63%).

$[\alpha]_D^{20}$ +76.0° (*c* 0.53, $CHCl_3$); IR (neat) $\tilde{\nu}$ 2925, 2856, 1709, 1455, 1353, 1172, 808 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.33 (1H, dt, *J* = 4.5 Hz, 2.1 Hz), 2.63 (1H, dddd, *J* = 12.6 Hz, 12.6 Hz, 3.3 Hz, 3.3 Hz), 2.28 (1H, m), 2.13 (3H, s), 2.10 (1H, m), 2.04−1.87 (4H, m), 1.46−1.36 (3H, m), 1.27 (1H, dddd, *J* = 13.9 Hz, 12.5 Hz, 12.5 Hz, 4.3 Hz), 1.07 (1H, m), 0.92 (3H, s), 0.87 (3H, d, *J* = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.3, 141.7, 121.2, 47.8, 41.1, 40.8, 37.6, 31.8, 30.0, 28.1, 27.2, 25.9, 18.3, 15.7; HRMS (ESI+) calcd for $C_{14}H_{23}O$ ($[M + H]^+$): 207.1749, found 207.1750.

*1-((2S,8R,8aS)-8,8a-Dimethyl-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl)ethan-1-one (**14**).* To a solution of ketone **11** (1.50 g, 7.27 mmol, 1.00 equiv) in 30 mL of anhydrous CH_3CN was added neat 1,1,1,3,3,3-hexamethyldisilazane (HMDS, 7.62 mL, 36.35 mmol, 5.00 equiv). Neat chlorotrimethylsilane (2.30 mL, 18.18 mmol, 2.50 equiv) was then added followed by solid sodium iodide (2.80 g, 18.68 mmol, 2.57 equiv), forming an opaque gray suspension. The flask was equipped with a water-cooled condenser, and the reaction mixture was heated at reflux for 15 h. After cooling to room temperature, the reaction was diluted with hexanes and quenched with saturated aqueous $NaHCO_3$ solution that had been prechilled to 0 °C. The layers were separated, and the organic phase was dried over anhydrous Na_2SO_4. TLC (9:1 hexanes/EtOAc, anisaldehyde stain) showed complete consumption of the starting ketone (R_f = 0.60) and formation of the silyl enol ether of R_f = 0.97. The solvent was removed under reduced pressure to give the crude silyl enol ether as a brown oil. This material was dissolved in 25 mL of 19:1 hexanes/NEt_3 and filtered through a plug of silica gel, which was then washed with

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an additional 150 mL of 19:1 hexanes/NEt_3. The solvent was removed under reduced pressure to give silyl enol ether **12** as a pale brown oil that was used directly in the next step.

A solution of silyl enol ether **12** (1.52 g, 5.47 mmol, 1.00 equiv) in 50 mL of freshly distilled THF was cooled to −78 °C in a dry ice/isopropanol bath. A 1.6 M solution of methyllithium in diethyl ether (4.10 mL, 6.57 mmol, 1.20 equiv) was then added dropwise, giving a yellow solution. After 30 min at −78 °C, the flask was transferred to an ice bath and stirred for an additional 30 min before recooling to −78 °C. A solution of salicylic acid (1.13 g, 8.21 mmol, 1.50 equiv) in 5.0 mL of distilled THF was added dropwise, and the reaction mixture was stirred at −78 °C for 30 min before the reaction was quenched at that temperature with saturated aqueous $NaHCO_3$ solution and diluted with EtOAc. After warming to room temperature, the layers were separated, and the organic phase was washed with one additional portion of saturated aqueous $NaHCO_3$ before drying over anhydrous Na_2SO_4. TLC (9:1 hexanes/EtOAc, anisaldehyde stain) showed clean formation of the epimerized ketone **14** of R_f = 0.66. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (9:1 hexanes/EtOAc) to give ketone **14** as a white solid (505 mg, 34% over two steps).

Mp 70.4−71.1 °C; $[\alpha]_D^{20}$ +150.5° (*c* 0.38, $CHCl_3$); IR (solid ATR) $\tilde{\nu}$ 2924, 2856, 1708, 1459, 1435, 1368, 1349, 1187, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.33 (1H, dd, *J* = 4.5 Hz, 2.1 Hz), 2.49 (1H, dddd, *J* = 5.2 Hz, 5.2 Hz, 5.2 Hz, 5.2 Hz), 2.41 (1H, m), 2.22−2.09 (2H, m), 2.19 (3H, s), 2.03−1.88 (3H, m), 1.58 (1H, dd, *J* = 13.9 Hz, 6.1 Hz), 1.46−1.35 (4H, m), 0.88 (3H, d, *J* = 6.4 Hz), 0.81 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.0, 143.1, 120.7, 46.8, 39.8, 39.3, 38.2, 28.9, 28.0, 27.1, 27.0, 25.7, 19.1, 15.9; HRMS (ESI+) calcd for $C_{14}H_{23}O$ ($[M + H]^+$): 207.1749, found 207.1747.

*1-((2S,8R,8aS)-8,8a-Dimethyl-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl)vinyl Trifluoromethanesulfonate (**15**).* A solution of ketone **14** (501 mg, 2.43 mmol, 1.00 equiv) in 30 mL of anhydrous THF was cooled to −78 °C in a dry ice/isopropanol bath. A 0.7 M solution of potassium bis(trimethylsilyl)amide (KHMDS, 4.16 mL, 2.91 mmol, 1.20 equiv) in $PhCH_3$ was added dropwise, and the resulting yellow solution was stirred at −78 °C for 1.5 h. A solution of *N*-phenylbis(trifluoromethanesulfonimide) (1.17 g, 3.28 mmol, 1.35 equiv) in 5 mL of anhydrous THF was then added dropwise, and the reaction mixture was stirred for 1 h at −78 °C before quenching at that temperature with saturated aqueous NH_4Cl solution and diluting with EtOAc. After warming to room temperature, the layers were separated, and the aqueous phase was extracted with one additional portion of EtOAc before the combined organic phases were dried over anhydrous Na_2SO_4. TLC (19:1 hexanes/EtOAc, anisaldehyde stain) showed complete consumption of ketone **14** (R_f = 0.41) and clean formation of the vinyl triflate of R_f = 0.76. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (19:1 hexanes/EtOAc) to give vinyl triflate **15** as a yellow oil (602 mg, 73%).

$[\alpha]_D^{20}$ +86.1° (*c* 0.41, $CHCl_3$); IR (neat) $\tilde{\nu}$ 2925, 2861, 1663, 1466, 1417, 1250, 1209, 1147, 1093, 911, 801 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.38 (1H, dt, *J* = 4.2 Hz, 2.0 Hz), 5.14 (1H, dd, *J* = 3.9 Hz, 1.3 Hz), 5.03 (1H, dd, *J* = 3.9 Hz, 1.7 Hz), 2.53 (1H, m), 2.41 (1H, ddddd, *J* = 13.6 Hz, 10.6 Hz, 7.5 Hz, 4.6 Hz, 2.3 Hz), 2.08−1.91 (3H, m), 1.83−1.76 (3H, m), 1.57 (1H, dd, *J* = 13.6 Hz, 4.6 Hz), 1.46−1.40 (3H, m), 0.94 (3H, s), 0.88 (3H, d, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 142.2, 121.9, 118.6 (q, $^1J_{C-F}$ = 319.8 Hz), 102.9, 38.6, 38.5, 38.0, 36.5, 28.8, 27.6, 26.9, 25.6, 19.9, 15.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.2; HRMS (ESI+) calcd for $C_{15}H_{22}F_3O_3S$ ($[M + H]^+$): 339.1242, found 339.1241.

*(3S,4aS,5R)-3-Ethynyl-4a,5-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalene (**16**) and (4aS,5R)-4a,5-Dimethyl-3-vinylidene-1,2,3,4,4a,5,6,7-octahydronaphthalene (**17**).* To a solution of vinyl triflate **15** (602 mg, 1.78 mmol, 1.00 equiv) in 13 mL of DMF was added a 1.0 M solution of tetrabutylammonium fluoride (TBAF, 5.33 mL, 5.33 mmol, 3.00 equiv) in THF. The reaction mixture immediately changed from colorless to orange, and stirring was continued at room temperature for 1.5 h. After this time, the reaction mixture was diluted with hexanes and water. The layers were separated, and the organic phase was washed twice with water before drying over anhydrous Na_2SO_4. TLC (19:1 hexanes/EtOAc, anisaldehyde stain) showed complete consumption of the vinyl triflate (R_f = 0.76), the formation of the desired alkyne **16** (R_f = 0.69, stains green), and a small amount of the isomeric allene **17** (R_f = 0.81, stains blue). The solvent was removed under reduced pressure, and the crude product mixture was purified by column chromatography (19:1 hexanes/EtOAc) to give alkyne **16** as a colorless oil (303 mg, 90%). A small amount of allene **17** was also isolated as a colorless oil (27 mg, 8%). Depending on the scale of the reaction, allene **17** was formed in 0−22% yield.

Alkyne **16**: $[\alpha]_D^{20}$ +97.1° (*c* 0.24, $CHCl_3$); IR (neat) $\tilde{\nu}$ 3308, 2963, 2923, 1463, 1435, 1355, 1061, 1002, 978, 844, 819 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.34 (1H, m), 2.85 (1H, m), 2.63 (1H, m), 2.07−1.85 (5H, m), 2.05 (1H, d, *J* = 2.7 Hz), 1.55−1.25 (5H, m), 1.17 (3H, s), 0.86 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 120.5, 89.5, 68.9, 42.7, 41.5, 38.3, 32.7, 29.0, 26.8, 25.9, 25.5, 20.2, 15.8; HRMS (EI) calcd for $C_{14}H_{20}$ ($M^{+\bullet}$): 188.1560, found 188.1560.

Allene **17**: $[\alpha]_D^{20}$ +83.6° (*c* 0.78, $CHCl_3$); IR (neat) $\tilde{\nu}$ 2964, 2925, 1963, 1711, 1655, 1461, 1435, 1382, 1356, 1286, 1207, 1180, 1063, 1000, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.37 (1H, dt, *J* = 4.4 Hz, 2.0 Hz), 4.59 (1H, dddd, *J* = 9.2 Hz, 9.2 Hz, 4.1 Hz, 4.1 Hz), 4.57 (1H, dddd, *J* = 9.2 Hz, 9.2 Hz, 4.8 Hz, 4.8 Hz), 2.45−2.29 (3H, m), 2.12 (1H, ddd, *J* = 13.4 Hz, 5.0 Hz, 1.6 Hz), 2.08−1.90 (3H, m), 1.77 (1H, m), 1.52−1.38 (3H, m), 0.93 (3H, s), 0.89 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.7, 142.3, 121.2, 99.0, 72.6, 44.0, 40.6, 39.6, 33.1, 32.1, 27.6, 26.1, 18.2, 15.9; HRMS (EI) calcd for $C_{14}H_{20}$ ($M^{+\bullet}$): 188.1560, found 188.1557.

*(1aR,4R,4aS,6S,8aS)-6-Ethynyl-4,4a-dimethyloctahydro-3H-naphtho[1,8a-b]oxirene (**18**) and (1aS,4R,4aS,6S,8aR)-6-Ethynyl-4,4a-dimethyloctahydro-3H-naphtho[1,8a-b]oxirene (**19**).* A solution of alkyne **16** (522 mg, 2.77 mmol, 1.00 equiv) in 43 mL of CH_2Cl_2 was cooled to 0 °C in an ice bath. Solid $NaHCO_3$ (466 mg, 5.55 mmol, 2.00 equiv) was added followed by the addition of 3-chloroperoxybenzoic acid (*m*-CPBA, 70−75% pure, 718 mg, 2.91 mmol, 1.05 equiv) in small portions over the course of 2 min. After 30 min, TLC (19:1 hexanes/EtOAc, anisaldehyde stain) showed complete consumption of the alkyne (R_f = 0.69) and clean formation of the major epoxide of R_f = 0.44 and the minor epoxide of R_f = 0.37. The reaction was diluted with CH_2Cl_2 and quenched by the addition of saturated aqueous Na_2SO_3 solution and saturated aqueous $NaHCO_3$ solution. The layers were separated, and the aqueous phase was extracted with one additional portion of CH_2Cl_2 before the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (19:1 hexanes/EtOAc to 9:1 hexanes/EtOAc) to give a mixture of epoxides **18** and **19** as a colorless oil (467 mg, 82%). ^1H NMR showed that diastereomers **18** and **19** were formed in a 2:1 ratio, favoring epoxidation on the side opposite the angular methyl group. Although it was possible to isolate the individual diastereomers by repeated column chromatography (19:1 hexanes/EtOAc), the mixture could also be taken on without prior separation due to the stereoconvergent epoxide opening later in the route.

*Major Epoxide **18**.* $[\alpha]_D^{20}$ +110.0° (*c* 0.65, $CHCl_3$); IR (neat) $\tilde{\nu}$ 3306, 2940, 2879, 2110, 1435, 1360, 1234, 1123, 1008, 983, 961, 895 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.95 (1H, m), 2.93 (1H, d, *J* = 3.6 Hz), 2.46 (1H, ddd, *J* = 13.5 Hz, 13.5 Hz, 4.3 Hz), 2.09 (1H, d, *J* = 2.3 Hz), 1.99−1.79 (5H, m), 1.68 (1H, m), 1.49 (1H, dd, *J* = 13.5 Hz, 6.0 Hz), 1.31−1.11 (2H, m), 1.24 (3H, s), 0.92 (1H, m), 0.68 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 89.9, 69.2, 66.0, 61.0, 38.1, 36.3, 34.1, 28.2, 27.4, 25.0, 24.1, 22.3, 16.1, 15.1; HRMS (ESI+) calcd for $C_{14}H_{21}O$ ($[M + H]^+$): 205.1592, found 205.1598.

*Minor Epoxide **19**.* $[\alpha]_D^{20}$ +76.2° (*c* 0.82, $CHCl_3$); IR (neat) $\tilde{\nu}$ 3306, 2930, 2870, 1451, 1382, 1265, 1222, 1128, 1096, 973, 948, 915, 883 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.96 (1H, s), 2.67 (1H, dddd, *J* = 11.2 Hz, 7.1 Hz, 4.9 Hz, 2.8 Hz), 2.31 (1H, ddd, *J* = 13.4 Hz, 11.7 Hz, 7.9 Hz), 2.07 (1H, d, *J* = 2.5 Hz), 2.02 (1H, m), 1.94−1.81 (2H, m), 1.78 (1H, dd, *J* = 13.9 Hz, 8.8 Hz), 1.71 (1H, m), 1.66

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(1H, dd, J = 13.9 Hz, 3.9 Hz), 1.34 (1H, m), 1.20 (1H, dddd, J = 13.7 Hz, 11.7 Hz, 6.1 Hz, 2.9 Hz), 1.10 (1H, dddd, J = 13.0 Hz, 5.1 Hz, 2.5 Hz, 2.5 Hz), 1.01 (3H, s), 0.96 (1H, ddd, J = 13.6 Hz, 5.9 Hz, 2.7 Hz), 0.79 (3H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 88.7, 68.8, 63.6, 62.0, 41.4, 37.4, 36.3, 28.9, 28.3, 26.2, 24.1, 23.0, 17.3, 15.9; HRMS (ESI+) calcd for $C_{14}H_{21}O$ ($[M + H]^+$): 205.1592, found 205.1597.

*(1aR,4R,4aS,6S,8aS)-6-(3,3-Difluorocycloprop-1-en-1-yl)-4,4a-dimethyloctahydro-3H-naphtho[1,8a-b]oxirene (**20**) and (1aS,4R,4aS,6S,8aR)-6-(3,3-Difluorocycloprop-1-en-1-yl)-4,4a-dimethyloctahydro-3H-naphtho[1,8a-b]oxirene (**21**).* A 2:1 mixture of epoxide diastereomers **18** and **19** (140.0 mg, 0.69 mmol, 1.00 equiv) in 4.0 mL of anhydrous THF was added to a flame-dried 8 mL vial under argon equipped with a magnetic stirring bar. Neat trifluoromethyl trimethylsilane (405 μL, 2.74 mmol, 4.00 equiv) was added followed by solid sodium iodide (452 mg, 3.01 mmol, 4.40 equiv), and the reaction mixture immediately turned yellow. The vial was tightly capped and then heated at 80 °C on an aluminum block. After 2 h, the reaction mixture was allowed to cool to room temperature, and the internal pressure was released by loosening the cap. TLC (19:1 hexanes/EtOAc, anisaldehyde stain) showed partial consumption of the starting alkyne (R_f = 0.40, stains blue) and formation of the corresponding difluorocyclopropene (R_f = 0.23). An additional portion of trifluoromethyl trimethylsilane (405 μL, 2.74 mmol, 4.00 equiv) was added followed by additional sodium iodide (452 mg, 3.01 mmol, 4.40 equiv), and heating was continued at 80 °C for 2 h. After this time, TLC of the orange reaction mixture showed complete consumption of the starting material and clean formation of the product. The reaction was diluted with EtOAc and quenched with saturated aqueous K_2CO_3 solution. The layers were separated, and the aqueous phase was extracted with one additional portion of EtOAc before the combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel deactivated with 10:1 hexanes/NEt_3 and then eluted with 40:1 hexanes/NEt_3) to give an inseparable 2:1 mixture of difluorocyclopropenes **20** and **21** (165 mg, 95%) as a colorless oil. For characterization purposes, the same procedure was carried out using the individual epoxide diastereomers **18** and **19** that had been previously separated by column chromatography, giving difluorocyclopropenes **20** and **21** in 41% yield (200 mg scale) and 57% yield (9 mg scale), respectively.

*Major Difluorocyclopropene **20**.* $[\alpha]_D^{20}$ +77.0° (c 0.29, $CHCl_3$); IR (neat) $\tilde{\nu}$ 2935, 1712, 1459, 1436, 1388, 1301, 1280, 1015, 961, 895, 823, 798 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27−7.25 (1H, m), 3.08 (1H, m), 2.94 (1H, d, J = 3.7 Hz), 2.22 (1H, m), 2.11−1.92 (4H, m), 1.86 (1H, m), 1.77−1.68 (2H, m), 1.29−1.44 (2H, m), 1.00 (1H, m), 0.90 (3H, s), 0.70 (3H, d, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2 (dd, $^2J_{C-F}$ = 10.4 Hz, $^2J_{C-F}$ = 10.4 Hz), 116.6 (dd, $^2J_{C-F}$ = 12.0 Hz, $^2J_{C-F}$ = 12.0 Hz), 103.6 (dd, $^1J_{C-F}$ = 270 Hz, $^1J_{C-F}$ = 270 Hz), 65.5, 60.9, 37.0, 35.8, 34.1, 29.9, 27.5, 25.5, 24.1, 22.2, 16.1, 15.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ −103.4 (ddd, $^2J_{F-F}$ = 123.5 Hz, $^3J_{H-F}$ = 3.2 Hz, $^4J_{H-F}$ = 1.7 Hz), −104.3 (d, $^2J_{F-F}$ = 123.5 Hz); HRMS (ESI+) calcd for $C_{15}H_{20}F_2NaO$ ($[M + Na]^+$): 277.1380, found 277.1387.

*Minor Difluorocyclopropene **21**.* $[\alpha]_D^{20}$ +74.0° (c 0.54, $CHCl_3$); IR (neat) $\tilde{\nu}$ 3010, 1607, 1508, 1459, 1297, 1234, 1181, 1118, 1039, 827, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (1H, m), 2.99 (1H, s), 2.90 (1H, m), 2.20 (1H, m), 2.09−1.96 (2H, m), 1.88 (1H, dddd, J = 13.6 Hz, 8.0 Hz, 8.0 Hz, 2.3 Hz), 1.80−1.68 (3H, m), 1.38−1.24 (2H, m), 1.14 (1H, dddd, J = 10.7 Hz, 5.1 Hz, 2.4 Hz, 2.4 Hz), 1.05 (1H, ddd, J = 13.6 Hz, 6.8 Hz, 2.3 Hz), 0.93 (3H, s), 0.81 (3H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7 (dd, $^2J_{C-F}$ = 10.4 Hz, $^2J_{C-F}$ = 10.4 Hz), 116.0 (dd, $^2J_{C-F}$ = 12.0 Hz, $^2J_{C-F}$ = 12.0 Hz), 103.2 (dd, $^1J_{C-F}$ = 268 Hz, $^1J_{C-F}$ = 270 Hz), 63.5, 61.5, 38.5, 36.3, 36.2, 28.2, 27.4, 26.1, 25.9, 24.1, 17.2, 15.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ −103.5 (d, $^2J_{F-F}$ = 123.1 Hz), −104.1 (d, $^2J_{F-F}$ = 123.1 Hz); HRMS (ESI+) calcd for $C_{15}H_{20}F_2NaO$ ($[M + Na]^+$): 277.1380, found 277.1398.

*(+)-Lineariifolianone (**1**).* A 2:1 mixture of difluorocyclopropene epoxide diastereomers **20** and **21** (164.7 mg, 0.648 mmol, 1.00 equiv) was dissolved in 9 mL of THF and 3 mL of water, and solid p-toluenesulfonic acid monohydrate (10 mg, 0.053 mmol, 0.08 equiv) was added. The reaction was stirred at room temperature and periodically monitored by TLC (100% EtOAc, anisaldehyde stain). After 5 days, TLC showed roughly equal amounts of unreacted starting material (R_f = 0.79), the diol derived from epoxide opening (R_f = 0.66), and the cyclopropenone diol **1** (R_f = 0.16). Additional portions of p-toluenesulfonic acid monohydrate (15 mg, 0.080 mmol, 0.12 equiv) were added at 48 h intervals until TLC showed complete conversion to **1** after 12 days. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and diluted with EtOAc. The layers were separated, and the aqueous phase was extracted with one additional portion of EtOAc before the combined organic phases were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (100% EtOAc to 9:1 EtOAc/CH_3OH) to give **1** as a white solid (135.2 mg, 83%). The same procedure was carried out using the individual epoxide diastereomers **20** and **21** [79% yield (105.5 mg scale) and 82% yield (14.7 mg scale), respectively] to demonstrate that they converged to the same product **1**.

Mp 184 °C (decomp.); $[\alpha]_D^{20}$ +19.8° (c 1.2, CH_3OH); IR (solid ATR) $\tilde{\nu}$ 3448, 3266, 3028, 3003, 2990, 2925, 2868, 1851, 1797, 1559, 1433, 1370, 1323, 1086, 1049, 1028, 946 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ 8.75 (1H, d, J = 1.4 Hz), 3.42 (1H, m), 3.35 (1H, s), 3.05 (1H, m), 2.37−2.26 (2H, m), 2.19 (1H, m), 2.12−2.02 (2H, m), 1.95−1.85 (2H, m), 1.65−1.48 (2H, m), 1.32−1.19 (3H, m), 0.92 (3H, s), 0.77 (3H, d, J = 6.9 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ 176.6, 162.0, 147.9, 76.5, 74.3, 40.4, 36.8, 36.0, 34.3, 29.8, 29.5, 26.7, 23.1, 17.0, 15.5; HRMS (ESI+) calcd for $C_{15}H_{22}NaO_3$ ($[M + Na]^+$): 273.1467, found 273.1467.

*(3S,4aS,5R)-3-(3,3-Difluorocycloprop-1-en-1-yl)-4a,5-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalene (**25**).* A solution of alkyne **16** (120 mg, 0.64 mmol, 1.00 equiv) in 4.0 mL of anhydrous THF was added to a flame-dried 8 mL vial under argon equipped with a magnetic stirring bar. Neat trifluoromethyl trimethylsilane (377 μL, 2.55 mmol, 4.00 equiv) was added followed by solid sodium iodide (420 mg, 2.80 mmol, 4.40 equiv), and the vial was tightly capped and heated at 80 °C on an aluminum block. After 2 h, the reaction mixture was allowed to cool to room temperature, and the internal pressure was released by loosening the cap. TLC (19:1 hexanes/EtOAc, anisaldehyde stain) showed complete consumption of the starting alkyne (R_f = 0.40) and formation of the corresponding difluorocyclopropene (R_f = 0.37). The reaction was diluted with EtOAc and quenched with saturated aqueous K_2CO_3 solution. The layers were separated, and the aqueous phase was extracted with one additional portion of EtOAc before the combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel deactivated with 10:1 hexanes/NEt_3 and then eluted with 40:1 hexanes/NEt_3) to give difluorocyclopropene **25** (102 mg, 66%) as a colorless oil.

$[\alpha]_D^{20}$ +88.8° (c 0.65, $CHCl_3$); IR (neat) $\tilde{\nu}$ 2964, 2927, 2859, 1713, 1464, 1435, 1305, 1282, 1017, 844, 800 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (1H, m), 5.37 (1H, m), 2.97 (1H, m), 2.35 (1H, m), 2.16 (1H, ddd, J = 13.8 Hz, 2.4 Hz, 2.4 Hz), 2.08−1.90 (4H, m), 1.67 (1H, dddd, J = 14.1 Hz, 14.1 Hz, 4.9 Hz, 4.9 Hz), 1.52 (1H, dd, J = 13.8 Hz, 6.1 Hz), 1.44−1.37 (3H, m), 0.879 (3H, s), 0.877 (3H, d, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.7 (dd, $^2J_{C-F}$ = 10.5 Hz, $^2J_{C-F}$ = 10.5 Hz), 142.2, 121.3, 116.6 (dd, $^2J_{C-F}$ = 12.0 Hz, $^2J_{C-F}$ = 12.0 Hz), 103.6 (dd, $^1J_{C-F}$ = 270 Hz, $^1J_{C-F}$ = 270 Hz), 41.3, 41.3, 37.8, 30.4, 30.2, 29.1, 26.8, 25.8, 20.1, 15.7 (note that a methylene and a methine carbon were coincident at 41.3 ppm); ^{19}F NMR (376 MHz, $CDCl_3$): δ −103.4 (d, $^2J_{F-F}$ = 123.5 Hz), −104.3 (d, $^2J_{F-F}$ = 123.5 Hz); HRMS (EI) calcd for $C_{14}H_{20}$ ($[M-CF_2]^{+\bullet}$): 188.1560, found 188.1559.

*2-((2S,8R,8aS)-8,8a-Dimethyl-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl)cycloprop-2-en-1-one (**ent-5**).* A solution of difluorocyclopropene **25** (75.0 mg, 0.31 mmol, 1.00 equiv) in 6 mL of wet THF was cooled to 0 °C in an ice bath, and neat boron trifluoride diethyl etherate (45 μL, 0.358 mmol, 1.14 equiv) was added. After 20 min,

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TLC (1:1 hexanes/EtOAc, anisaldehyde stain) showed a mixture of unreacted starting material (R_f = 0.79) and the desired cyclopropenone **13** (R_f = 0.33). Additional 45 μL portions of boron trifluoride diethyl etherate were added at 15 min intervals until TLC showed that the reaction was complete (450 μL total, 3.58 mmol, 11.4 equiv). The reaction was quenched with saturated aqueous $NaHCO_3$ solution and diluted with EtOAc. The layers were separated, and the organic phase was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (2:1 hexanes/EtOAc to 1:1) to give cyclopropenone **ent-5** (44.4 mg, 65%) as a colorless oil.

$[\alpha]_D^{20}$ +105.2° (*c* 0.67, $CHCl_3$); IR (neat) $\tilde{\nu}$ 3040, 2924, 2858, 1835, 1580, 1456, 1357, 1061, 1044, 996, 878, 842, 808 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.45 (1H, m), 5.38 (1H, m), 3.04 (1H, m), 2.36 (1H, m), 2.32 (1H, ddd, *J* = 13.8 Hz, 2.3 Hz, 2.3 Hz), 2.18 (1H, m), 2.05 (1H, m), 2.00−1.89 (2H, m), 1.69 (1H, dddd, *J* = 13.2 Hz, 13.2 Hz, 4.8 Hz, 4.8 Hz), 1.54 (1H, dd, *J* = 13.8 Hz, 6.1 Hz), 1.45−1.35 (3H, m), 0.87 (3H, d, *J* = 6.3 Hz), 0.85 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 158.3, 147.3, 141.4, 121.9, 41.23, 41.19, 37.8, 34.2, 29.3, 29.1, 26.8, 25.7, 19.7, 15.7; HRMS (ESI+) calcd for $C_{15}H_{20}NaO$ ($[M + Na]^+$): 239.1412, found 239.1422.

*1-((2R,8R,8aS)-8,8a-Dimethyl-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl)vinyl Trifluoromethanesulfonate (**26**).* A solution of ketone **11** (500 mg, 2.42 mmol, 1.00 equiv) and *N*-phenylbis(trifluoromethanesulfonimide) (865 mg, 2.42 mmol, 1.0 equiv) in 12 mL of anhydrous THF was cooled to −78 °C in a dry ice/isopropanol bath. A 0.7 M solution of potassium bis(trimethylsilyl)amide (KHMDS, 3.81 mL, 2.67 mmol, 1.10 equiv) was added dropwise, and the resulting yellow solution was stirred at −78 °C for 1 h. TLC (19:1 hexanes/EtOAc, anisaldehyde stain) showed complete consumption of ketone **11** (R_f = 0.61) and clean formation of the vinyl triflate of R_f = 0.80. The reaction was quenched at −78 °C with saturated aqueous NH_4Cl solution and diluted with EtOAc. After warming to room temperature, the layers were separated, and the aqueous phase was extracted with one additional portion of EtOAc before the combined organic phases were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (49:1 hexanes/EtOAc) to give vinyl triflate **26** as a yellow oil (560 mg, 68%).

$[\alpha]_D^{20}$ +72.9° (*c* 0.28, $CHCl_3$); IR (neat) $\tilde{\nu}$ 2928, 2858, 1665, 1418, 1250, 1208, 1148, 933, 910, 884 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.37 (1H, dt, *J* = 4.5 Hz, 2.0 Hz), 5.07 (1H, d, *J* = 3.8 Hz), 4.89 (1H, d, *J* = 3.8 Hz), 2.53 (1H, dddd, *J* = 12.2 Hz, 12.2 Hz, 3.1 Hz, 3.1 Hz), 2.32 (1H, m), 2.13 (1H, ddd, *J* = 14.1 Hz, 4.2 Hz, 2.5 Hz), 2.08 (1H, ddd, *J* = 12.6 Hz, 2.7 Hz, 2.7 Hz), 2.04−1.91 (3H, m), 1.45−1.40 (3H, m), 1.21 (1H, m), 0.99 (1H, dd, *J* = 12.6 Hz, 12.6 Hz), 0.94 (3H, s), 0.89 (3H, d, *J* = 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 141.4, 121.5, 118.6 (q, $^1J_{C-F}$ = 319.8 Hz), 102.2, 43.1, 40.9, 38.6, 37.7, 31.8, 31.6, 27.1, 25.9, 18.2, 15.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.3; HRMS (ESI+) calcd for $C_{15}H_{21}F_3NaO_3S$ ($[M + Na]^+$): 361.1061, found 361.1087.

*(3R,4aS,5R)-3-Ethynyl-4a,5-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalene (**27**).* To a solution of vinyl triflate **26** (431 mg, 1.27 mmol, 1.00 equiv) in 9 mL of DMF was added a 1.0 M solution of tetrabutylammonium fluoride (TBAF, 3.82 mL, 3.82 mmol, 3.00 equiv) in THF. The reaction mixture immediately changed from colorless to orange, and stirring was continued at room temperature for 2 h. After this time, the reaction mixture was diluted with hexanes and water. The layers were separated, and the organic phase was washed twice with water before drying over anhydrous Na_2SO_4. TLC (19:1 hexanes/EtOAc, anisaldehyde stain) showed complete consumption of the vinyl triflate (R_f = 0.80, stains blue) and formation of the desired alkyne (R_f = 0.88, stains green). The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (49:1 hexanes/EtOAc) to give alkyne **27** as a colorless oil (225 mg, 94%).

$[\alpha]_D^{20}$ +94.9° (*c* 0.39, $CHCl_3$); IR (neat) $\tilde{\nu}$ 3311, 2967, 2931, 2858, 2116, 1456, 1436, 1382, 1260, 1205, 1046, 982, 883, 845, 809 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.3 (1H, dt, *J* = 4.5 Hz, 2.1 Hz, 2.1 Hz), 2.55 (1H, m), 2.24 (1H, m), 2.10 (1H, ddd, *J* = 13.0 Hz, 3.3 Hz, 2.2 Hz), 2.04 (1H, m), 2.02 (1H, d, *J* = 2.3 Hz), 2.02−1.89 (3H, m), 1.42−1.39 (3H, m), 1.33 (1H, m), 1.16 (1H, dd, *J* = 12.8 Hz, 12.8 Hz), 0.91 (3H, s), 0.88 (3H, d, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.6, 121.2, 89.1, 67.5, 45.8, 40.7, 37.7, 34.3, 32.0, 27.1, 25.9, 25.8, 18.1, 15.7; HRMS (EI) calcd for $C_{14}H_{20}$ ($M^{+\bullet}$): 188.1560, found 188.1561.

*(3R,4aS,5R)-3-(3,3-Difluorocycloprop-1-en-1-yl)-4a,5-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalene (**28**).* A solution of alkyne **27** (120 mg, 0.64 mmol, 1.00 equiv) in 5.0 mL of anhydrous THF was added to a flame-dried 8 mL vial under argon equipped with a magnetic stirring bar. Neat trifluoromethyl trimethylsilane (375 μL, 2.54 mmol, 4.00 equiv) was added followed by solid sodium iodide (419 mg, 2.79 mmol, 4.40 equiv), and the vial was tightly capped and heated at 80 °C on an aluminum block. After 2 h, the reaction mixture was allowed to cool to room temperature, and the internal pressure was released by loosening the cap. TLC (19:1 hexanes/EtOAc, anisaldehyde stain) showed complete consumption of the starting alkyne (R_f = 0.40) and formation of the corresponding difluorocyclopropene (R_f = 0.35). The reaction was diluted with EtOAc and quenched with saturated aqueous K_2CO_3 solution. The layers were separated, and the aqueous phase was extracted with one additional portion of EtOAc before the combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel deactivated with 10:1 hexanes/NEt_3 and then eluted with 40:1 hexanes/NEt_3) to give difluorocyclopropene **28** (112 mg, 74%) as a colorless oil.

$[\alpha]_D^{20}$ +55.6° (*c* 0.32, $CHCl_3$); IR (neat) $\tilde{\nu}$ 2927, 2857, 1718, 1457, 1436, 1384, 1310, 263, 1206, 1021, 899, 846, 792 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.15 (1H, m), 5.38 (1H, dt, *J* = 4.5 Hz, 2.0 Hz), 2.86 (1H, m), 2.34 (1H, m), 2.15−1.95 (5H, m), 1.44−1.41 (2H, m), 1.38−1.25 (2H, m), 1.12 (1H, m), 0.98 (3H, s), 0.89 (3H, d, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7 (dd, $^2J_{C-F}$ = 10.5 Hz, $^2J_{C-F}$ = 10.5 Hz), 141.3, 121.6, 115.4 (dd, $^2J_{C-F}$ = 11.9 Hz, $^2J_{C-F}$ = 11.9 Hz), 103.2 (dd, $^1J_{C-F}$ = 270 Hz, $^1J_{C-F}$ = 270 Hz), 43.0, 40.8, 37.8, 31.8, 31.6, 30.6, 27.1, 25.9, 18.2, 15.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ −103.4 (the two fluorine signals were coincident); HRMS (EI) calcd for $C_{15}H_{20}F_2$ ($M^{+\bullet}$): 238.1528, found 238.1528.

*2-((2R,8R,8aS)-8,8a-Dimethyl-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl)cycloprop-2-en-1-one (**ent-6**).* A solution of difluorocyclopropene **28** (107 mg, 0.45 mmol, 1.00 equiv) in 6 mL of wet THF was cooled to 0 °C in an ice bath, and neat boron trifluoride diethyl etherate (100 μL, 0.796 mmol, 1.77 equiv) was added. After 20 min, TLC (1:1 hexanes/EtOAc, anisaldehyde stain) showed a mixture of unreacted starting material (R_f = 0.82) and the desired cyclopropenone **ent-6** (R_f = 0.30). Additional 100 μL portions of boron trifluoride diethyl etherate were added at 15 min intervals until TLC showed that the reaction was complete (500 μL total, 3.98 mmol, 8.88 equiv). The reaction was quenched with saturated aqueous $NaHCO_3$ solution and diluted with EtOAc. The layers were separated, and the organic phase was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (2:1 hexanes/EtOAc to 1:1) to give cyclopropenone **ent-6** (40.4 mg, 42%) as a colorless oil.

$[\alpha]_D^{20}$ +78.7° (*c* 0.30, $CHCl_3$); IR (neat) $\tilde{\nu}$ 2926, 2855, 1823, 1582, 1457, 1436, 844, 807 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.35 (1H, s), 5.38 (1H, m), 3.01 (1H, dddd, *J* = 12.6 Hz, 12.6 Hz, 3.3 Hz, 3.3 Hz), 2.35 (1H, m), 2.20−2.07 (3H, m), 2.04−1.90 (2H, m), 1.44−1.33 (4H, m), 1.15 (1H, m), 0.97 (3H, s), 0.88 (3H, d, *J* = 6.1 Hz), ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 157.6, 146.7, 140.7, 122.0, 42.0, 40.8, 37.8, 33.8, 31.5, 30.7, 27.1, 25.9, 18.1, 15.7; HRMS (ESI+) calcd for $C_{15}H_{20}NaO$ ($[M + Na]^+$): 239.1412, found 239.1423.

*Methyl 2-((2S,4aS,5S,8R,8aS)-4a,5-dihydroxy-8,8a-dimethyldecahydronaphthalen-2-yl)acrylate (**29**).* To a solution of **1** (23.6 mg, 94 μmol, 1.00 equiv) in 3 mL of methanol was added 4-pyrrolidinopyridine (1.34 mg, 9.4 μmol, 0.10 equiv). After 5 days at room temperature, TLC (100% EtOAc, UV/anisaldehyde stain) showed partial conversion of the starting material (R_f = 0.16) to the

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product of R_f = 0.81. An additional portion of 4-pyrrolidinopyridine (1.34 mg, 9.4 μmol, 0.10 equiv) was added, and the reaction mixture was stirred for 7 days, at which point TLC showed complete consumption of the starting material. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (2:1 hexanes/EtOAc to 1:1 hexanes/EtOAc) to give acrylate **29** as a colorless oil (24.3 mg, 91%). ^{1}H NMR analysis of the product showed that it had been formed as a 10:1 mixture of inseparable acrylate isomers derived from the differential bond cleavage of the cyclopropenone.

$[\alpha]_D^{20}$ +12.3° (*c* 0.30, $CHCl_3$); IR (neat) $\tilde{\nu}$ 3429, 2926, 2860, 1705, 1666, 1623, 1460, 1438, 1383, 1280, 1198, 1142, 1094, 1049, 990, 951, 938 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10 (1H, s), 5.64 (1H, s), 3.76 (3H, s), 3.50 (1H, m), 3.02 (1H, m), 2.40 (1H, m), 2.18−2.02 (2H, m), 1.90−1.78 (2H, m), 1.72 (1H, m), 1.58−1.50 (3H, m), 1.44 (2H, br s), 1.28−1.19 (2H, m), 0.96 (3H, s), 0.72 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 147.2, 122.1, 75.8, 74.7, 51.9, 39.6, 37.9, 36.2, 32.9, 29.4, 29.1, 25.1, 22.6, 17.8, 15.3; HRMS (ESI+) calcd for $C_{16}H_{26}NaO_4$ ([M + Na]$^+$): 305.1729, found 305.1737.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b00478.

^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra for all new compounds; selected 2D NMR spectra; full spectral assignments for **1**, **ent-5**, and **ent-6**; and a spectral comparison of these synthetic compounds to the corresponding natural products (PDF)

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Notes

The authors declare no competing financial interest.

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