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Synthesis and biological analysis of truncated caliculone H

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Abstract

Herein, we report for the first time the design and linear synthesis of a truncated caliculone H (**7**) that lacks the telltale isopropyl/isopropylene groups, whereas the 12-membered macrocycle remains intact. Key steps for the framework of target molecule include allylic oxidation using SeO_2 , Sharpless asymmetric epoxidation, Barbier zinc allylation, and ring-closing metathesis (RCM) reactions. A second truncated “caliculone-like” analogue, **27**, with a different oxidation pattern around the ring was also synthesized following a similar strategy. Screening for in vitro cytotoxicity against a panel of 60 human cancer cell lines revealed that **7** was as potent if not more so (for a few cell lines) than the natural product caliculone A (**2**).

Graphical abstract

Keywords

Cubitanes diterpenes; Caliculones; Synthesis of marine natural products; Hoveyda-Grubbs II catalyst; ring closing metathesis; Sharpless asymmetric epoxidation; Barbier zinc allylation

1. Introduction

The rare cubitane carbon skeleton consists of a 12-membered monocyclic diterpenoid ring system that contains two isopropyl groups (Fig. 1).¹ (+)-Cubitene (**1**), isolated in 1978 from the East African termite *Cubitermes umbratus*, is regarded as the first natural product based on this irregular diterpene skeleton.² Approximately 14 additional cubitane-type

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Supplementary data

Copies of the ^1H NMR and ^{13}C NMR spectra for all new compounds and full 2D-NMR spectroscopic data for truncated cubitanes **7** and **26**. Supplementary data associated with this article can be found in the online version, at <http://dx.doi.org/...>

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diterpenoids have since then been isolated primarily from several gorgonian coral species of the genus *Eunicea* (family Plexauridae).^{3–6}

The first cubitane diterpenes of marine origin, calyculones A–C (**2–4**), were reported by the Fenical group in 1984 from the gorgonian *Eunicea calyculata*.³ The structure of the crystalline metabolite calyculone A (**2**) was solved by single-crystal X-ray diffraction, whereas those of calyculone B (**3**) and calyculone C (**4**) were proposed based on comprehensive spectroscopic analyses.^{3,7} Nearly 30 years later, our group reported the structures of two additional marine cubitanes, named calyculone H (**5**) and calyculone I (**6**), along with known calyculones A–C from a Colombian gorgonian species of the genus *Eunicea*.⁶ These compounds exemplified the rearranged cubitane class of marine diterpenoids.^{1,8}

It is interesting to notice that among the 15 or so cubitane diterpenes known to date only (+)-cubitane (**1**) has been targeted by the synthetic chemists.^{8,9} Still, although a total synthesis of calyculone A (**2**) and its derivatives has remained elusive, thus far only one group has described an approach toward its core ring system.¹⁰ Although calyculone A (**2**) has displayed substantial cytotoxicity,⁶ as it happens with many marine natural products, the lack of an adequate supply of material has impeded research into the biological potential of the calyculones. In light of their potential as anticancer agents coupled with their challenging molecular structures, it is bewildering that the calyculones have not received more attention from the synthetic organic chemistry community. Recently, while contemplating work on the total synthesis of calyculone H (**5**),¹¹ it became apparent to us that a practical total synthesis of a truncated calyculone H analogue that contains the basic core ring system (a compelling pharmacophore) was more enticing.¹² This design was based on our contention that the 12-membered macrocycle of the calyculones may be the key pharmacophore that interacts with cellular target(s), whereas the isopropyl/isopropylene groups could hamper (i.e. partially block) molecular docking thus preventing the molecule from binding tightly to its target.¹³

2. Results and discussion

2.1. Synthesis of truncated calyculone H (**7**)

Our synthetic approach for the synthesis of truncated calyculone H (**7**) was envisioned via the retrosynthetic route as shown in Scheme 1. Because the absolute configuration of the calyculones remains unknown, we sought the synthesis of an enantiopure chemical target from an arbitrary stock of readily available enantiopure substance.

Thus, we first examined the preparation of ester **11** starting from the commercially available (*S*)-citronellol (**10**). Benzoylation of starting material **10** with benzoyl chloride in the presence of pyridine afforded **11** in 88% yield, which was subjected to regioselective allylic oxidation¹⁴ to provide allylic alcohol **12** in 69% yield over two steps (Scheme 2). With enantiomerically pure alcohol **12** in hand, we then subjected it to Sharpless asymmetric epoxidation to give epoxy alcohol **9** as a single diastereomer in 83% yield as evidenced by the NMR spectra (only one set of peaks was detected) and subsequent HPLC analysis.¹⁵ Next, the terminal alcohol underwent a one-pot sequence of oxidation and Wittig olefination

with Py·SO₃ complex and Ph₃P=CHCHO, respectively, to give α,β-unsaturated aldehyde **13** in a 81% yield as a mixture of *E*- and *Z*-isomers (*E*:*Z*, 9:1).¹⁶ Sequential reduction of the mixture of aldehydes with NaBH₄ in MeOH, protection of the ensuing alcohol **14** with TBSCl/imidazole giving **15**, and double bond hydrogenation using diimide¹⁷ in EtOH served to convert the mixture of aldehydes to pure TBS protected alcohol **16** in 56% from **13** (Scheme 3). Chemoselective deprotection of **16** with TBAF in THF afforded alcohol **17** in 87% yield. Attempts were made to synthesize **17** directly from TBS unprotected alcohol **14** using diimide in EtOH, but the product yields were all unsatisfactory in this case due to the formation of unidentified impurities. As shown in Scheme 3, oxidation of alcohol **17** using Dess–Martin periodinane provided a condensation precursor aldehyde, which was used in the next step without purification. Condensation of this aldehyde with methyltriphenylphosphonium iodide and NaHMDS at 0°C afforded olefin **18** in 61% yield for two steps.¹⁸ Saponification of **18** using LiOH in MeOH at 0°C released the expected alcohol **19** in 91% yield. Next, the primary alcohol was converted to the aldehyde with Dess–Martin periodinane, which was then extended to homoallylic alcohol **8** through Barbier zinc allylation reaction¹⁹ in 61% yield for two steps. The conversion to **8** was optimized by the use of this method as it proceeds with good yield and avoids the formation of side products due to ring opening of the epoxide. With product **8** in hand (isolated as a 1:1 mixture of diastereomers which was used without separation in the following step), we focused our efforts on the formation of the skeleton of truncated calyculone H via a ring closing metathesis (RCM) reaction.²⁰ In this fashion, it was discovered that when the Hoveyda-Grubbs II catalyst was used for intramolecular cross-metathesis, diene **8** was successfully converted into *trans*-cyclododecene **20** in 53% yield as a mixture of epimers at C-11. Finally, oxidation of the mixture of alcohols using Dess–Martin periodinane furnished **7** in 89% yield as a single isomer. The stereochemistry (1*S*, 4*R*, 5*R*, 8*E*) and connectivity of compound **7** were determined by 2D NMR (¹H–¹H COSY, HSQC, HMBC, NOESY) analysis (see Supplementary data). The *E* geometry of the ethylenic double bond in **7** was supported by the presence of a strong band near 976 cm^{−1} in the IR spectrum and the large coupling constant (13.6 Hz) observed for the olefinic protons in C₆D₆.²¹ Moreover, comparison of the NMR data for **7** with characterization data provided for calyculone H (**5**) supported the structural relatedness of these compounds (Table 1).⁶

2.2. Synthesis of truncated “calyculone-like” product **27**

In order to demonstrate that our synthetic approach is in fact flexible and can be easily modified for the synthesis of other designed analogues, we tackled the generation of truncated “calyculone-like” product **27** for biological investigation. Whilst not inspired by a natural calyculone, the preparation of **27** was considered important in that it could provide important information regarding the structure–activity relationship and pharmacophore identification.²² The synthesis, which was separately carried on with enantiomerically pure intermediate **12**, began with protection of the hydroxyl group with TBSCl followed by hydrolysis of benzoate ester to yield alcohol **21** in 83% yield over two steps (Scheme 4). Product **21** was swiftly converted to chiral homoallylic alcohol **22** following consecutive oxidation to aldehyde with PCC and Keck asymmetric allylation²³ at −20°C for 3 days in 73% yield for two steps. Acetylation of **22** with acetic anhydride followed by TBS removal

with PTSA in MeOH afforded alcohol **23** in 86% yield for two steps. Once more, under Sharpless asymmetric epoxidation conditions,^{15c} epoxide **24** was obtained from **23** in 71% yield as a single diastereomer. On subjecting primary alcohol **24** to Py·SO₃ oxidation conditions followed by Barbier zinc allylation at 0°C for 30 min furnished diene precursor **25** with moderate diastereoselectivity (dr 7:3) in 67% yield for two steps (Scheme 5). After purification of this material the RCM protocol using Hoveyda-Grubbs II catalyst furnished the *trans*-cyclododecene **26** as a single diastereomer in 43% yield. As with **7**, the stereochemistry (1*S*, 4*R*, 5*R*, 6*R*, 8*E*, 11*S*) and connectivity of compound **26** were swiftly established by 2D NMR (¹H–¹H COSY, HSQC, HMBC, NOESY) analysis (see Supplementary data). Treatment of this alcohol under Dess-Martin oxidation conditions provided the truncated calyculone-like product **27** in 89% yield.

2.3. Attempted synthesis of partially truncated calyculone **30**

To conclude, an additional model study was explored as summarized in Scheme 6 to synthesize a 12-membered macrocycle having the “natural” isopropyl group at C-8 common to all marine cubitanoids.⁸ Toward this end we oxidized alcohol **24** with Py·SO₃ complex as before. Next, the intermediate aldehyde was subjected to zinc mediated allylation with allyl iodide **28** in THF to yield alcohol **29** with moderate diastereoselectivity (dr 7:3) in 46% yield over two steps.²⁴ Disappointingly, but not altogether surprising, the cross-metathesis between the olefin groups in **29** conducted under a variety of conditions (including use of Grubbs II and Hoveyda-Grubbs II catalysts) proved to be quite challenging leading instead to a complex product mixture from which the desired *trans*-cyclododecene **30** was not detected (Table 2).²⁵ We hypothesized that in this case significant steric hindrance from the isopropyl group, perhaps heighten by the *E*-geometry of the trisubstituted epoxide, render the olefins in **29** recalcitrant to formation of the strained *trans*-cyclododecene. To circumvent this effect, we reason it would be necessary to hold off the assembly of the C-4,5 epoxide group until after Hoveyda-Grubbs catalyst-promoted cross-metathesis. Future efforts by investigators aiming at the total synthesis of calyculone H (**5**) should be directed toward advancing this course of action.

2.4. Biological analysis

Unfortunately, due to the limited supply for testing biological activity no attempts were made during previous investigations to screen calyculone H (**5**) for cytotoxic activity.⁶ Hence, the cytotoxicity of truncated calyculone H (**7**) was evaluated in vitro at the National Cancer Institute (NCI) Developmental Therapeutics Program²⁶ and compared with data previously available for calyculone A (**2**).⁶ This study was comprised of 60 cell lines from 9 different cancer types: leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer.²⁷ Interestingly, at a concentration of 1.0 X10^{−4} M, both **2** and **7** inhibited growth from 50% to 100% of nearly all of the cancer cells screened. However, at 1.0 × 10^{−5} M, both compounds became significantly less cytotoxic. In this manner, when treated with calyculone A (**2**) the growth inhibition of all the cells ranged from 28% to 0%, whereas truncated calyculone H (**7**) inhibited growth from 15% to 0% in over 90% of the cells treated. In particular, the data shown in Table 3 reveal that for some human tumor cells, compound **7** was actually slightly

more potent in suppressing cell growth than its natural counterpart calyculone A (**2**). In alignment with these results calyculone-like product **27**, which has a slightly different oxidation pattern around the ring, was shown to inhibit the proliferation of several cancer cell lines (SNB-75, UO-31, and MCF7) at a concentration of 1.0×10^{-5} M but only by ~15%. These combined data, albeit preliminary, suggest that the cubitane ring system and the C11 ketone are indispensable for the observed cytotoxicity of the calyculones whereas the isopropyl and isopropylene groups are not.

3. Conclusion

In summary, truncated calyculone H (**7**) was successfully synthesized in 17 steps from commercially available starting material **10** in 2.9% overall yield. In addition, we easily modified our flexible synthetic approach for the synthesis of “unnatural” truncated calyculone-like product **27**. It should be remarked that all stereogenic carbon centers and double bonds present in these target molecules were constructed stereoselectively. Taken together, these results confirm our hypothesis that the functionalized 12-membered core ring system of the calyculones is indeed the pharmacophore that interacts with its putative target(s) in the cells, and that the modification of the cubitane skeleton to a *trans*-cyclododecene ring apparently does not significantly affect its cytotoxic activity. This knowledge is paramount for the design of future calyculone analogues. Moreover, the observation that calyculone H (**5**) and **7** possess nearly identical ^{13}C NMR data (the resonances due to the C-13 secondary methyl, the methine carbon (C-1) and the epoxide functionality were shifted only slightly in compound **7** from their positions in the ^{13}C NMR spectrum of calyculone H) suggests that these compounds have identical relative stereochemistry (Table 1).²⁸ On the other hand, the absolute configuration of **7** is probably the same as that of calyculone H (**5**) given the sign of the optical rotation.

4. Experimental section

4.1. General procedures

Unless otherwise noted, all other reagents, drying agents, solvents, and inorganic salts were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried by passage through two columns of activated neutral alumina. Methanol (MeOH) and dimethylsulfoxide (DMSO) were dried by passage through two columns of activated 4 Å molecular sieves. Dichloromethane (CH_2Cl_2) and triethylamine (Et_3N) were distilled from calcium hydride. The combined organic layers were typically washed with brine, dried over anhydrous Na_2SO_4 , filtered, and evaporated under vacuum. Removal of solvent or concentration under reduced pressure was performed using a rotary evaporator. Unless otherwise indicated, all ^1H and ^{13}C NMR spectra were recorded at room temperature in CDCl_3 . Chemical shifts were reported in parts per million (ppm) downfield from TMS ($\delta = 0.00$ ppm) and referenced relative to CDCl_3 (7.26 ppm for ^1H and 77.0 ppm for ^{13}C). Coupling constants were reported in hertz (Hz). Splitting patterns were designated as: s = singlet; d = doublet; dd = doublet of doublet; ddd = doublet of doublet of doublets; dddd = doublet of doublet of doublet of doublets; dp = doublet of pentuplet; t = triplet; q = quartet; p = pentuplet; hep = heptet; m = multiplet; comp = overlapping

multiplets of non-magnetically equivalent protons; br = broad. Infrared (IR) spectra were obtained as thin films on NaCl plates and reported in wavenumbers (cm^{-1}). Optical rotations were measured in CHCl_3 at 589 nm using a 10-cm microcell. Mass spectrometric analyses were performed on a single quadrupole liquid chromatograph–mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Column chromatography was performed on normal-phase silica gel (35–75 mesh) with the indicated solvents. Analytical thin-layer chromatography (TLC) was performed on glass pre-coated silica gel plates with the indicated solvents. Visualization was accomplished by UV light or by staining with I_2 vapors or KMnO_4 solution. Systematic IUPAC names for all the compounds synthesized were created with the ChemDraw's Structure-to-Name conversion tool.

4.2. (S)-3,7-Dimethyloct-6-en-1-yl benzoate (11)

To a solution of (*S*)-citronellol (**10**) (5.5 g, 30 mmol) in dry CH₂Cl₂ (80 mL) at 0 °C was added pyridine (12 mL, 150 mmol) and benzoyl chloride (5.1 mL, 45.0 mmol). After stirring for 4 h, the reaction mixture was quenched with saturated NaHCO₃ and extracted with CH₂Cl₂ (2 × 50 mL). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product obtained was subsequently purified by column chromatography (silica gel, hexane–EtOAc, 9:1) to yield known compound **11** (6.9 g, 88%);¹⁴ pale yellow liquid; [α]_D²³ = –92.0 (*c* 1.0, CHCl₃); IR (film) ν_{max} 3064, 2963, 2916, 2855, 1721, 1603, 1452, 1314, 1274, 1176, 1113, 1070, 1027, 711 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 8.04 (2H, m), 7.54 (1H, m), 7.42 (2H, m), 5.10 (1H, br t, *J* = 7.5 Hz), 4.37 (2H, br t, *J* = 7.5 Hz), 2.02 (2H, m), 1.82 (1H, m), 1.67 (3H, s), 1.61 (3H, s), 1.41 (m, 2H), 1.25 (2H, m), 0.98 (3H, d, *J* = 6.3 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 17.6, 19.5, 25.4, 25.6, 29.6, 35.5, 37.0, 63.4, 124.5, 128.3 (2 × CH), 129.5 (2 × CH), 130.6, 131.3, 132.7, 166.6; MS (ESI⁺) *m/z* 283.1 [M+Na]⁺, 261.2 [M+H]⁺.

4.3. (S,E)-8-Hydroxy-3,7-dimethyloct-6-en-1-yl benzoate (12)

To a mixture of compound **11** (6.8 g, 26.1 mmol) and salicylic acid (0.4 g, 2.6 mmol, 10 mol %) in dry CH₂Cl₂ (80 mL) kept at 25 °C under N₂ was added *t*-BuOOH (10.5 mL, 31.4 mmol) and powdered SeO₂ (0.14 g, 1.3 mmol, 5 mol %). After stirring for 6 h at r.t. the reaction mixture was diluted with CH₂Cl₂ (2 × 50 mL) and washed successively with saturated Na₂S₂O₃ (2 × 100 mL) and brine (1 × 100 mL). After the combined organic layer was dried over Na₂SO₄ the solvent was removed by rotary evaporation to yield a mixture of alcohol **12** and its corresponding aldehyde. The crude product was dissolved in MeOH (50 mL), cooled to 0 °C and treated with NaBH₄ (1.1 g, 28.7 mmol). Thereafter, the solvent was evaporated, the residue left taken up with Et₂O (200 mL), and the ensuing solution washed with H₂O (100 mL) and brine (100 mL). The dried organic layer (Na₂SO₄) was concentrated and the crude product subjected to column chromatography (silica gel, hexane–EtOAc, 8:2) to afford pure alcohol **12** (5.0 g, 69% for two steps): colorless liquid; [α]_D²³ = –99.0 (*c* 1.0, CHCl₃); IR (film) ν_{max} 3421, 3065, 2924, 1717, 1602, 1456, 1386, 1275, 1177, 1114, 1071, 1026, 952, 712 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 8.03 (2H, m), 7.54 (1H, m), 7.47 (2H, m), 5.40 (1H, br t, *J* = 7.5 Hz), 4.34 (2H, m), 3.97 (2H, br s), 2.06 (2H, m), 2.0–1.70 (2H, comp), 1.66 (3H, s), 1.64–1.20 (3H, comp), 0.96 (3H, d, *J* = 6.3 Hz), 0.90 (1H, m); ¹³C NMR (75 MHz, CDCl₃) δ 13.6, 19.5, 24.9, 29.6, 35.5, 36.5, 63.4, 68.9, 126.2, 128.3 (2 ×

CH), 129.5 (2 × CH), 130.5, 132.8, 134.8, 166.7; MS (ESI⁺) m/z 299.1 [M+Na]⁺, 259.1 [M+H-H₂O]⁺; HRMS (ESI⁺) m/z C₁₇H₂₄O₃Na [M+Na]⁺ calcd 299.1623, found 299.1625.

4.4. (S)-5-((2R,3R)-3-(Hydroxymethyl)-3-methyloxiran-2-yl)-3-methylpentyl benzoate (9)

A dried two neck round bottom flask containing activated molecular sieves (5 g, 4 Å) in dry CH₂Cl₂ (50 mL) kept at -20 °C under N₂ was loaded with (-)-diisopropyl D-tartrate (0.5 mL, 2.3 mmol, 13 mol %) and Ti(O^{*i*}Pr)₄ (0.5 mL, 1.8 mmol, 10 mol %). After stirring for 10 min the resulting mixture was cooled to -48 °C before adding *t*-BuOOH (7.5 mL, 26.4 mmol). Thereafter, the solution was stirred for 30 min before a solution of **12** (4.8 g, 17.6 mmol) in dry CH₂Cl₂ (10 mL) was added and left stirring at -20 °C for 24 h. Thereafter, the reaction mixture was allowed to warm up to 0 °C, H₂O (50 mL) added, and stirring continued for 30 min. Upon reaching r.t. the reaction was treated with 30% NaOH (50 mL) and brine (50 mL) and stirred until a biphasic solution appeared. The organic layer was separated and the aqueous phase extracted with CH₂Cl₂ (2 × 100 mL). The combined organic layer was dried (Na₂SO₄), concentrated, and the residue left over purified by column chromatography (silica gel, hexane-EtOAc, 7:3) to furnish pure compound **9** (4.3 g, 83%): colorless oil; [α]_D²⁰ = -15.0 (*c* 1.0, CHCl₃); IR (film) ν_{max} 3444, 3065, 2960, 1715, 1602, 1602, 1585, 1453, 1385, 1276, 1177, 1114, 952, 868, 714 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.02 (2H, m), 7.53 (1H, m), 7.42 (2H, m), 4.36 (2H, m), 3.59 (2H, ddd, *J* = 6.0, 9.0, 12.0 Hz), 3.00 (1H, br t, *J* = 4.5 Hz), 2.11 (1H, m), 1.93 (1H, br s), 1.9–1.50 (5H, comp), 1.28 (3H, s), 0.97 (3H, d, *J* = 6.3 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 14.1, 19.3, 25.7, 29.8, 33.5, 35.6, 60.3, 60.9, 63.2, 65.5, 128.3 (2 × CH), 129.5 (2 × CH), 130.4, 132.8, 166.6; MS (ESI⁺) m/z 315.3 [M+Na]⁺, 293.3 [M+H]⁺, 275.3 [M+H-H₂O]⁺.

4.5. (S)-3-Methyl-5-((R)-3-methyl-3-(3-oxoprop-1-en-1-yl)oxiran-2-yl)pentyl benzoate (13)

To a stirred solution of **9** (4.2 g, 14.4 mmol) and Et₃N (12.1 mL, 86.4 mmol) dissolved in a 1:1 mixture of dry CH₂Cl₂-DMSO (60 mL) kept at 0 °C under N₂ was added Py·SO₃ complex (9.2 g, 57.6 mmol). After stirring for 2 h the reaction was quenched with H₂O (3 × 50 mL) and the mixture extracted with Et₂O (2 × 100 mL). After the combined organic layer was dried over Na₂SO₄ and concentrated the crude product was purified by flash column chromatography (silica gel, hexane-EtOAc, 7:3) to afford the intermediate aldehyde as a yellowish oil. A solution of the latter compound (3.7 g, 12.8 mmol) and Ph₃P=CHCHO (4.3 g, 14.1 mmol) in dry CH₂Cl₂ (40 mL) kept at r.t. under N₂ was heated to 50 °C for 6 h. *In vacuo* solvent removal followed by purification of the oil obtained by column chromatography (silica gel, hexane-EtOAc, 8:2) gave pure aldehyde **13** (3.7 g, 81% for two steps) as a mixture of isomers (*E:Z*, 9:1): pale yellowish oil; [α]_D²² = -26.0 (*c* 0.5, CHCl₃); IR (film) ν_{max} 3064, 2962, 2873, 2735, 1716, 1636, 1602, 1453, 1385, 1275, 1177, 1115, 1071, 1027, 975, 714, 688 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.53 (1H, d, *J* = 9.0 Hz), 8.03 (2H, m), 7.55 (1H, m), 7.43 (2H, m), 6.54 (1H, d, *J* = 18.0 Hz), 6.27 (1H, dd, *J* = 9.0, 18.0 Hz), 4.37 (2H, m), 2.89 (1H, br t, *J* = 6.0 Hz), 1.90–1.58 (5H, comp), 1.37 (3H, m), 1.42–1.21 (2H, comp), 1.01 (3H, d, *J* = 6.3 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 14.9, 19.3, 26.1, 29.8, 33.3, 35.5, 58.4, 63.1, 66.0, 128.3 (2 × CH), 129.5 (2 × CH), 130.4, 131.9, 132.9, 158.4, 166.6, 192.8; MS (ESI⁺) m/z 355.3 [M+K]⁺, 317.4 [M+H]⁺; HRMS (ESI⁺) m/z C₁₉H₂₅O₄ [M+H]⁺ calcd 317.1753, found 317.1755.

4.6. (S)-5-((R)-3-(3-Hydroxyprop-1-en-1-yl)-3-methyloxiran-2-yl)-3-methylpentyl benzoate (14)

To a 0 °C solution of **13** (3.6 g, 11.4 mmol) in MeOH (50 mL) was added NaBH₄ (0.9 g, 22.8 mmol) in one portion. After stirring the mixture for 1 h at 0 °C the solvent was rotoevaporated, the residue obtained taken up with H₂O (50 mL), extracted with EtOAc (2 × 50 mL) and then washed with brine (50 mL). Solvent removal followed by purification of the crude product by column chromatography (silica gel, hexane–EtOAc, 6:4) yielded pure alcohol **14** (3.3 g, 92%): colorless liquid; $[\alpha]_D^{23} = -17.5$ (*c* 0.4, CHCl₃); IR (film) $\nu_{\max}$ 3422, 2961, 2927, 2871, 1717, 1602, 1455, 1386, 1275, 1177, 1113, 1071, 970, 714 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.02 (2H, m), 7.54 (1H, m), 7.43 (2H, m), 5.89 (1H, dt, *J* = 6.0, 15.0 Hz), 5.53 (1H, d, *J* = 15.0 Hz), 4.36 (2H, m), 4.13 (2H, t, *J* = 6.0 Hz), 2.78 (1H, t, *J* = 6.0 Hz), 1.90–1.50 (5H, comp), 1.39 (3H, s), 1.28 (2H, m), 0.98 (3H, d, *J* = 6.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 15.5, 19.3, 26.2, 29.8, 33.4, 35.5, 58.8, 62.8, 63.2, 65.5, 128.3 (2 × CH), 129.5 (2 × CH), 130.4, 130.6, 132.8, 134.0, 166.6; MS (ESI⁺) *m/z* 341.3 [M + Na]⁺.

4.7. (S)-5-((R)-3-(3-((tert-Butyldimethylsilyl)oxy)prop-1-en-1-yl)-3-methyloxiran-2-yl)-3-methylpentyl benzoate (15)

To a mixture of **14** (3.3 g, 10.4 mmol) and imidazole (2.1 g, 31.1 mmol) in dry CH₂Cl₂ (32 mL) kept at 0 °C under N₂ was added TBSCl (2.0 g, 13.5 mmol) in one portion. The mixture was stirred for 6 h while allowing the temperature to slowly rise to r.t. Thereafter, the reaction was quenched with cold H₂O (10 mL), extracted with EtOAc (2 × 100 mL) and washed with brine (100 mL). After solvent removal column chromatography of the crude product (silica gel, hexane–EtOAc, 9:1) gave pure compound **15** (4.0 g, 89%): colorless liquid; $[\alpha]_D^{23} = -34.3$ (*c* 0.7, CHCl₃); IR (film) $\nu_{\max}$ 2956, 2929, 2857, 1721, 1462, 1275, 1113, 1071, 837, 777, 712 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.03 (2H, m), 7.54 (1H, m), 7.43 (2H, m), 5.80 (1H, dt, *J* = 6.0, 15.0 Hz), 5.52 (1H, d, *J* = 15.0 Hz), 4.37 (2H, m), 4.17 (2H, br d, *J* = 6.0 Hz), 2.77 (1H, t, *J* = 6.0 Hz), 1.90–1.53 (5H, comp), 1.39 (3H, s), 1.33 (2H, m), 0.99 (3H, d, *J* = 6.3 Hz), 0.90 (9H, s), 0.06 (6H, s); ¹³C NMR (75 MHz, CDCl₃) δ -5.3 (2 × CH₃), 15.6, 18.4, 19.3, 25.9 (3 × CH₃), 26.3, 29.9, 33.5, 35.6, 58.9, 63.1, 63.2, 65.4, 128.3 (2 × CH), 129.5 (2 × CH), 130.4, 130.9, 132.5, 132.8, 166.6; MS (ESI⁺) *m/z* 433.4 [M + H]⁺, 301.3 [M + H – TBSOH]⁺.

4.8. (S)-5-((2R,3R)-3-(3-((tert-Butyldimethylsilyl)oxy)propyl)-3-methyloxiran-2-yl)-3-methylpentyl benzoate (16)

To a stirred solution of **15** (3.9 g, 9.0 mmol) in MeOH (30 mL) was added freshly prepared dipotassium azodicarboxylate (8.8 g, 45.1 mmol). Thereafter, a 4 M solution of AcOH in MeOH (22.5 mL, 90.2 mmol) was slowly added over 36 h using a syringe pump at r.t. under N₂. After the reaction was complete the solvent was evaporated *in vacuo*, H₂O (2 × 20 mL) added, and the aqueous layer extracted with CH₂Cl₂ (2 × 50 mL). The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography (silica gel, hexane–EtOAc, 9.5:0.5) to afford pure compound **16** (2.5 g, 63%): colorless liquid; $[\alpha]_D^{20} = -15.5$ (*c* 2.0, CHCl₃); IR (film) $\nu_{\max}$ 2956, 2929, 2857, 1721, 1462, 1385, 1274, 1110, 1027, 837, 777, 712 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.02 (2H, m), 7.53 (1H, m), 7.42 (2H, m), 4.36 (2H, t, *J* = 6.6 Hz), 3.58

(2H, m), 2.68 (1H, t, $J = 5.8$ Hz), 1.90–1.28 (11H, comp), 1.24 (3H, s), 0.98 (3H, d, $J = 6.3$ Hz), 0.87 (9H, s), 0.03 (6H, s); ^{13}C NMR (75 MHz, CDCl_3) δ –5.3 ($2 \times \text{CH}_3$), 16.5, 18.3, 19.3, 25.9 ($3 \times \text{CH}_3$), 26.2, 28.5, 29.9, 33.6, 35.0, 35.6, 60.6, 62.8, 63.2, 63.5, 128.3 ($2 \times \text{CH}$), 129.5 ($2 \times \text{CH}$), 130.4, 132.8, 166.5; MS (ESI $^+$) m/z 457.4 $[\text{M}+\text{Na}]^+$, 435.5 $[\text{M}+\text{H}]^+$, 303.3 $[\text{M}+\text{H}-\text{TBSOH}]^+$; HRMS (ESI $^+$) m/z $\text{C}_{25}\text{H}_{42}\text{SiO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ calcd 457.2750, found 457.2755.

4.9.(S)-5-((2R,3R)-3-(3-Hydroxypropyl)-3-methyloxiran-2-yl)-3-methylpentyl benzoate (17)

To a 0 °C solution of **16** (2.4 g, 5.5 mmol) in dry THF (17 mL) was added dropwise 1.0 M TBAF in THF (6.6 mL, 6.6 mmol). The reaction mixture was stirred and allowed to warm up to r.t. for the next 12 h. Upon completion, the reaction was quenched with saturated NaHCO_3 (20 mL), extracted with EtOAc (4×25 mL), and concentrated leaving a residue that was subsequently purified by column chromatography (silica gel, hexane–EtOAc, 7:3) to afford pure alcohol **17** (1.5 g, 87%): pale yellowish liquid; $[\alpha]_{\text{D}}^{20} = -50.3$ (c 1.0, CHCl_3); IR (film) ν_{max} 3430, 3065, 2958, 1717, 1602, 1455, 1386, 1275, 1177, 1113, 1070, 1027, 953, 714 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.01 (2H, m), 7.51 (1H, m), 7.41 (2H, m), 4.35 (2H, m), 3.60 (2H, t, $J = 5.8$ Hz), 2.72 (1H, t, $J = 6.0$ Hz), 2.25 (1H, br s), 1.86–1.49 (9H, m), 1.26 (2H, m), 1.23 (3H, s), 0.97 (3H, d, $J = 6.3$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 16.3, 19.3, 26.1, 28.0, 29.8, 33.5, 34.9, 35.5, 60.6, 62.3, 63.2, 63.8, 128.3 ($2 \times \text{CH}$), 129.5 ($2 \times \text{CH}$), 130.4, 132.8, 166.6; MS (ESI $^+$) m/z 343.4 $[\text{M}+\text{Na}]^+$, 321.4 $[\text{M}+\text{H}]^+$, 303.3 $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$.

4.10.(S)-5-((2R,3R)-3-(But-3-en-1-yl)-3-methyloxiran-2-yl)-3-methylpentyl benzoate (18)

A mixture of **17** (1.5 g, 4.7 mmol), NaHCO_3 (2.0 g, 23.4 mmol) and Dess–Martin periodinane (3.0 g, 7.0 mmol) in dry CH_2Cl_2 (30 mL) was stirred at 0 °C for 1 h while the temperature slowly rose to r.t. The reaction mixture was concentrated *in vacuo* and the residue obtained purified quickly by flash column chromatography over silica gel (hexane–EtOAc, 8:2) affording the intermediate aldehyde (1.2 g). A solution of the latter in dry THF (10 mL) was added dropwise to a dry round neck flask containing a cooled mixture (0 °C) of methyltriphenylphosphonium iodide (3.8 g, 9.4 mmol) and NaHMDS (1.7 g, 9.4 mmol) in dry THF (20 mL) under N_2 , which had been previously stirred for 1 h. The resulting reaction mixture was stirred for 2 h, quenched with H_2O (2×10 mL), and extracted with Et $_2\text{O}$ (2×25 mL). The organic layer was washed with brine (2×25 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The crude product was then purified by column chromatography (silica gel, hexane–EtOAc, 9:1) furnishing pure **18** (0.9 g, 61% for two steps): colorless liquid; $[\alpha]_{\text{D}}^{19} = -154.5$ (c 0.4, CHCl_3); IR (film) ν_{max} 3073, 2960, 2927, 2856, 1720, 1642, 1602, 1453, 1384, 1274, 1176, 1112, 1027, 911, 713 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.03 (2H, m), 7.55 (1H, m), 7.44 (2H, m), 5.79 (1H, m), 5.0 (2H, m), 4.38 (2H, m), 2.70 (1H, t, $J = 6.0$ Hz), 2.15 (2H, m), 1.80–1.48 (9H, comp), 1.26 (3H, s), 0.99 (3H, d, $J = 6.8$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 16.5, 19.3, 26.2, 29.5, 29.9, 33.5, 35.6, 38.0, 60.4, 63.3, 63.6, 114.8, 128.3 ($2 \times \text{CH}$), 129.5 ($2 \times \text{CH}$), 130.4, 132.8, 138.0, 166.6; MS (ESI $^+$) m/z 339.4 $[\text{M}+\text{Na}]^+$, 317.4 $[\text{M}+\text{H}]^+$.

4.11. (S)-5-((2R,3R)-3-(But-3-en-1-yl)-3-methyloxiran-2-yl)-3-methylpentan-1-ol (19)

A 0 °C solution of benzoate ester **18** (850 mg, 2.7 mmol) in 1:1 MeOH–THF (10 mL) was treated with LiOH·H₂O (169 mg, 4.3 mmol) in H₂O (5 mL). The reaction mixture was stirred for 1 h while the temperature slowly warmed to r.t. Thereafter, the organic solvent was evaporated and the aqueous layer remaining extracted with EtOAc (2 × 20 mL). The combined organic layer was dried over Na₂SO₄, evaporated *in vacuo*, and the product obtained purified by column chromatography (silica gel, hexane–EtOAc, 7:3) to furnish pure alcohol **19** (519 mg, 91%): colorless liquid; $[\alpha]_D^{19} = -74.0$ (*c* 1.0, CHCl₃); IR (film) $\nu_{\max}$ 3418, 3078, 2928, 1642, 1460, 1384, 1254, 1062, 1004, 911 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.82 (1H, m), 5.02 (2H, m), 3.71 (2H, m), 2.72 (1H, br t, *J* = 6.0 Hz), 2.17 (2H, m), 1.78–1.38 (9H, comp), 1.27 (3H, s), 0.94 (3H, d, *J* = 6.5 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 16.5, 19.5, 26.2, 29.4, 29.5, 33.7, 38.0, 39.8, 60.6, 60.9, 63.8, 114.8, 138.0; MS (ESI⁺) *m/z* 235.3 [M+Na]⁺, 213.4 [M+H]⁺, 195.5 [M+H–H₂O]⁺; HRMS (ESI⁺) *m/z* C₁₃H₂₅O₂ [M+H]⁺ calcd 213.1854, found 213.1855.

4.12. (6S)-8-((2R,3R)-3-(But-3-en-1-yl)-3-methyloxiran-2-yl)-6-methyloct-1-en-4-ol (8)

A mixture of **19** (500 mg, 2.4 mmol), NaHCO₃ (990 mg, 11.8 mmol), and Dess–Martin periodinane (1.5 g, 3.5 mmol) in dry CH₂Cl₂ (15 mL) kept at 0 °C was stirred for 1 h while allowing the temperature to slowly rise to r.t. After concentration *in vacuo* the liquid residue obtained was purified by flash column chromatography over silica gel (hexane–EtOAc, 7.5:2.5) to yield the intermediate aldehyde (439 mg) as a colorless oil. To a cooled mixture (0 °C) of the aldehyde (400 mg, 1.9 mmol), activated zinc dust (619 mg, 9.5 mmol) and allyl bromide (0.32 mL, 3.8 mmol) in dry THF (15 mL) was added saturated NH₄Cl (5 mL) over 15 min and the resulting mixture stirred for 30 min. Thereafter, the mixture was filtered through Celite® and extracted with Et₂O (3 × 25 mL). After the combined organic layer was dried (Na₂SO₄) the solvent was evaporated *in vacuo* and the product obtained purified by column chromatography (silica gel, hexane–EtOAc, 9:1) to furnish **8** (363 mg, 61% for two steps) as a 1:1 mixture of inseparable epimers: colorless liquid; IR (film) $\nu_{\max}$ 3447, 3077, 2927, 1642, 1457, 1437, 1385, 1252, 1068, 997, 912 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.80 (2H, m), 5.05 (4H, m), 3.74 (1H, m), 2.69 (1H, br t, *J* = 6.0 Hz), 2.20 (4H, comp), 1.78–1.35 (9H, comp), 1.25 (3H, s), 0.94/0.92 (3H, d, *J* = 6.5 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 16.5, 19.1, 20.1, 25.9/26.2, 29.2/29.5, 33.1/34.3, 38.0, 42.2/42.8, 44.2/44.3, 60.4, 63.7, 68.3/68.6, 114.7, 118.1/118.2, 134.7/134.8, 138.0; MS (ESI⁺) *m/z* 275.4 [M+Na]⁺, 253.4 [M+H]⁺, 235.4 [M+H–H₂O]⁺.

4.13. (1R,4S,12R,Z)-4,12-Dimethyl-13-oxabicyclo[10.1.0]tridec-8-en-6-ol (20)

A stirred mixture of diene precursor **8** (252 mg, 1.0 mmol) and Hoveyda–Grubbs II catalyst (63 mg, 10 mol %) in dry CH₂Cl₂ (120 mL) was refluxed under N₂ for 8 h. After the solvent was rotoevaporated the crude product obtained was purified by flash column chromatography (silica gel, hexane–EtOAc, 7:3) to furnish **20** (118 mg, 53%) as a 1:1 mixture of C-11 epimers: light brown oil; IR (film) $\nu_{\max}$ 3444, 2924, 2853, 1456, 1383, 1262, 1095, 1025, 975, 856 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.43 (2H, comp), 3.96 (1H, m), 2.64/2.54 (1H, m), 2.47–1.80 (5H, comp), 1.77–1.35 (5H, m), 1.25/1.22 (3H, s), 1.20–1.00 (3H, comp), 0.97/0.86 (3H, d *J* = 6.5 Hz); ¹³C NMR (75 MHz, CDCl₃) δ

15.7/16.6, 20.5/20.7, 23.5/24.7, 25.8/26.2, 29.7/29.9, 31.4, 35.5, 37.5, 37.9/38.0, 38.4, 42.4, 46.9, 60.2/61.3, 63.1/64.7, 68.2/68.8, 125.1/128.8, 130.6/132.9; MS (ESI⁺) *m/z* 247.3 [M + Na]⁺, 225.3 [M + H]⁺.

4.14. (1*R*,4*S*,12*R*,*E*)-4,12-Dimethyl-13-oxabicyclo[10.1.0]tridec-8-en-6-one (**7**) (truncated calyculone H)

A cooled (0 °C) mixture of alcohols **20** (90 mg, 0.40 mmol), NaHCO₃ (168 mg, 2.0 mmol), and Dess–Martin periodinane (254 mg, 0.60 mmol) in dry CH₂Cl₂ (120 mL) was stirred for 1 h while allowing the reaction temperature to rise to r.t. After rotoevaporation the crude oil obtained was subjected to flash column chromatography to afford ketone **7** (79 mg, 89%) as a single diastereomer: colorless oil; [α]_D²¹ = −307.3 (*c* 1.8, CHCl₃); IR (film) ν_{max} 2936, 2871, 2854, 1708, 1665, 1454, 1384, 1251, 1124, 1105, 976, 927, 860, 845, 787, 687 cm^{−1}; ¹H NMR (500 MHz, CDCl₃) and ¹³C NMR (125 MHz, CDCl₃) (Table 1); HRMS (ESI⁺) *m/z* C₁₄H₂₃O₂ [M + H]⁺ calcd 223.1698, found 223.1695.

4.15. (*S*,*E*)-8-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethyloct-6-en-1-ol (**21**)

To a stirred solution of **12** (4.0 g, 14.5 mmol) in dry CH₂Cl₂ (50 mL) at 0 °C was added imidazole (2.1 g, 31.1 mmol) and TBSCl (2.0 g, 13.5 mmol). The reaction was stirred for 6 h while allowing the temperature to rise to r.t. Upon completion the reaction mixture was quenched with cold H₂O (20 mL), extracted with EtOAc (4 × 50 mL), and washed with brine (2 × 50 mL). The combined organic phase was dried over Na₂SO₄, rotoevaporated, and the residue left purified by column chromatography (silica gel, hexane–EtOAc, 9:1) to afford the TBS protected intermediate as a colorless liquid. To a cold (0 °C) solution of the latter compound (3.9 g) in 1:1 MeOH–THF (50 mL) was added aqueous LiOH·H₂O (690.6 mg, 29.0 mmol) (20 mL). After stirring for 1 h the solvent was rotoevaporated and the aqueous suspension extracted with EtOAc (2 × 50 mL). The combined organic layer was dried over Na₂SO₄, concentrated, and the residue left behind subjected to column chromatography (silica gel, hexane–EtOAc, 7:3) to furnish pure **21** (3.5 g, 83% for two steps): colorless liquid; [α]_D²² = −29.50 (*c* 1.0, CHCl₃); IR (film) ν_{max} 3347, 2929, 2857, 1462, 1362, 1254, 1113, 1065, 837, 776 cm^{−1}; ¹H NMR (300 MHz, CDCl₃) δ 5.37 (1H, br t, *J* = 6.0 Hz), 3.99 (2H, br s), 3.66 (2H, m), 2.02 (2H, m), 1.63 (3H, s), 1.45–1.30 (4H, comp), 1.21 (1H, m), 0.90 (3H, d, *J* = 6.5 Hz), 0.88 (9H, s), 0.06 (6H, s); ¹³C NMR (75 MHz, CDCl₃) δ −5.3 (2 × CH₃), 13.4, 18.4, 19.5, 24.9, 25.9 (3 × CH₃), 29.2, 36.8, 39.9, 61.1, 68.7, 124.8, 134.2; MS (ESI⁺) *m/z* 309.5 [M + Na]⁺.

4.16. (4*S*,6*S*,*E*)-11-((*tert*-Butyldimethylsilyl)oxy)-6,10-dimethylundeca-1,9-dien-4-ol (**22**)

A 0 °C mixture of **21** (3.4 g, 11.8 mmol), Celite® (40 g), and PCC (5.1 g, 23.6 mmol) in dry CH₂Cl₂ (80 mL) was stirred for 3 h while allowing the temperature to rise to r.t. Thereafter, the mixture was diluted with Et₂O (50 mL), and passed through a short column of silica gel (hexane–EtOAc, 8:2) to afford the intermediate aldehyde (3.1 g). Meanwhile, a mixture of (*S*)-BINOL (0.5 g, 1.7 mmol), Ti(OiPr)₄ (0.35 mL, 1.2 mmol), and dry molecular sieves (6 g, 4 Å) in CH₂Cl₂ (60 mL) was refluxed for 1 h and allowed to cool to r.t. before adding the aldehyde in dry CH₂Cl₂ (15 mL) and stirring the mixture for 10 min. The reaction mixture was cooled to −78 °C, allyl tributylstannane (5.5 g, 17.8 mmol) added, and the resulting

solution stirred at $-20\text{ }^{\circ}\text{C}$ for 72 h. Upon completion (as noticed by TLC), the reaction was quenched with saturated NaHCO_3 (30 mL) and the mixture stirred for another 30 min before extracting it with CH_2Cl_2 ($1 \times 50\text{ mL}$). The organic layer was washed with brine (30 mL), dried over Na_2SO_4 , and concentrated *in vacuo* to leave a residue that was purified by column chromatography (silica gel, hexane–EtOAc, 9:1) to afford pure **22** as a single isomer (2.8 g, 73% for two steps): colorless liquid; $[\alpha]_{\text{D}}^{20} = -11.0$ ($c\ 1.0$, CHCl_3); IR (film) ν_{max} 3374, 3076, 2956, 2929, 2857, 1641, 1463, 1361, 1254, 1068, 914, 837, 776 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.83 (1H, m), 5.36 (1H, br t, $J = 6.0\text{ Hz}$), 5.12 (2H, br d, $J = 12.0\text{ Hz}$), 3.99 (2H, br s), 3.74 (1H, m), 2.32–1.95 (4H, comp), 1.59 (3H, s), 1.57–1.14 (5H, comp), 0.92 (3H, d, $J = 6.5\text{ Hz}$), 0.90 (9H, s), 0.05 (6H, s); ^{13}C NMR (75 MHz, CDCl_3) δ -5.3 ($2 \times \text{CH}_3$), 13.4, 19.1, 25.0, 25.9 ($3 \times \text{CH}_3$), 29.0, 37.5, 42.8, 44.2, 68.4, 68.7, 117.9, 124.8, 134.2, 134.9; MS (ESI $^{+}$) m/z 349.4 $[\text{M}+\text{Na}]^{+}$, 327.3 $[\text{M}+\text{H}]^{+}$, 195.3 $[\text{M}+\text{H}-\text{TBSOH}]^{+}$; HRMS (ESI $^{+}$) m/z $\text{C}_{19}\text{H}_{38}\text{SiO}_2\text{Na}$ $[\text{M}+\text{Na}]^{+}$ calcd 349.2539, found 349.2535.

4.17. (4S,6S,E)-11-Hydroxy-6,10-dimethylundeca-1,9-dien-4-yl acetate (23)

A mixture of **22** (2.8 g, 8.4 mmol), Ac_2O (2.7 mL, 25 mmol), Et_3N (6.0 mL, 42 mmol), and catalytic DMAP in CH_2Cl_2 (50 mL) was stirred at $0\text{ }^{\circ}\text{C}$ for 4 h. After the reaction was quenched with cold H_2O (10 mL) and extracted with CH_2Cl_2 ($4 \times 25\text{ mL}$), the solvent was rotoevaporated to leave a residue that was purified by column chromatography (silica gel, hexane–EtOAc, 7.5:2.5) to furnish the expected acetate as a light yellowish liquid. To a $0\text{ }^{\circ}\text{C}$ solution of the latter compound (3.0 g, 8.2 mmol) in MeOH (30 mL) was added PTSA (272 mg, 10 mol %) and the solution obtained stirred for 3 h while the temperature rose to $25\text{ }^{\circ}\text{C}$. After addition of saturated NaHCO_3 (50 mL), extraction with EtOAc ($3 \times 50\text{ mL}$) and washing the combined organic layer with brine ($2 \times 50\text{ mL}$), *in vacuo* concentration gave a residue that was subjected to column chromatography (silica gel, hexane–EtOAc, 7.5:2.5) to yield pure **23** (1.8 g, 86% for two steps): light yellowish liquid; $[\alpha]_{\text{D}}^{19} = -4.0$ ($c\ 1.0$, CHCl_3); IR (film) ν_{max} 3406, 2957, 2924, 2855, 1737, 1643, 1458, 1436, 1375, 1241, 1078, 1022, 917 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.72 (1H, m), 5.34 (1H, br t, $J = 6.0\text{ Hz}$), 5.08–4.97 (3H, comp), 3.96 (2H, br s), 2.27 (2H, m), 2.02 (2H, m), 2.0 (3H, s), 1.64 (3H, s), 1.62–1.15 (5H, comp), 0.87 (3H, d, $J = 6.5\text{ Hz}$); ^{13}C NMR (75 MHz, CDCl_3) δ 13.6, 19.3, 21.1, 24.9, 28.9, 37.1, 39.5, 40.9, 68.8, 71.4, 117.6, 126.2, 133.7, 134.7, 170.8; MS (ESI $^{+}$) m/z 277.4 $[\text{M}+\text{Na}]^{+}$, 237.3 $[\text{M}+\text{H}-\text{H}_2\text{O}]^{+}$, 177.4 $[\text{M}+\text{H}-\text{AcOH}-\text{H}_2\text{O}]^{+}$.

4.18. (4S,6S)-8-((2R,3R)-3-(Hydroxymethyl)-3-methyloxiran-2-yl)-6-methyloct-1-en-4-yl acetate (24)

A mixture of freshly activated molecular sieves (3 g, 4 Å), (–)-diisopropyl D-tartrate (0.2 mL, 0.92 mmol, 13 mol %) and $\text{Ti}(\text{O}^i\text{Pr})_4$ (0.2 mL, 0.7 mmol, 10 mol %) in dry CH_2Cl_2 (30 mL) was stirred under N_2 for 10 min at $-20\text{ }^{\circ}\text{C}$. The reaction mixture was then cooled to $-48\text{ }^{\circ}\text{C}$ before adding *t*-BuOOH (3.5 M solution in toluene, 3.0 mL, 10.6 mmol). After stirring for 30 min, a solution of allyl alcohol **23** (1.8 g, 7.1 mmol) in dry CH_2Cl_2 (50 mL) was added and the resulting mixture left stirring for 24 h at $-20\text{ }^{\circ}\text{C}$. Thereafter, the mixture was warmed to $0\text{ }^{\circ}\text{C}$, H_2O added (50 mL), and the stirring continued for 30 min. Upon reaching r.t. the reaction was treated with 30% NaOH (20 mL) and brine (20 mL) and stirred until a biphasic solution appeared. The organic layer was separated, the aqueous phase extracted with CH_2Cl_2 ($2 \times 50\text{ mL}$), and the combined organic layer dried over Na_2SO_4 and

concentrated *in vacuo*. The crude product obtained was purified by column chromatography (silica gel, hexane–EtOAc, 7:3) to furnish pure **24** (1.4 g, 71%): colorless oil; $[\alpha]_D^{19} = +3.0$ (*c* 1.0, CHCl₃); IR (film) $\nu_{\max}$ 3453, 3078, 2929, 1737, 1643, 1462, 1435, 1376, 1242, 1134, 1105, 1027, 919 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.73 (1H, m), 5.12–4.98 (3H, comp), 3.61 (2H, m), 2.99 (1H, t, *J* = 6.0 Hz), 2.29 (2H, m), 2.02 (3H, s), 1.81 (1H, m), 1.71–1.40 (6H, comp), 1.28 (3H, s), 0.90 (3H, d, *J* = 6.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 14.2, 19.1, 21.2, 25.7, 29.1, 34.0, 39.4, 40.9, 60.2, 60.8, 65.4, 71.2, 117.7, 133.6, 170.7; MS (ESI⁺) *m/z* 293.3 [M+Na]⁺, 271.4 [M+H]⁺, 211.2 [M+H–AcOH]⁺, 193.5 [M+H–AcOH–H₂O]⁺.

4.19. (4S,6S)-8-((2R,3R)-3-((R)-1-Hydroxybut-3-en-1-yl)-3-methyloxiran-2-yl)-6-methyloct-1-en-4-yl acetate (25)

A mixture of **24** (600 mg, 2.2 mmol), Et₃N (1.8 mL, 13.2 mmol), and Py·SO₃ complex (1.4 g, 8.8 mmol) in a 1:1 mixture of dry CH₂Cl₂–DMSO (30 mL) was stirred at 0 °C under N₂ for 1 h. After quenching the reaction with H₂O (3 × 50 mL) and extracting with Et₂O (2 × 50 mL), the combined organic layer was dried over Na₂SO₄ and concentrated *in vacuo* to give a crude product that was purified by flash column chromatography (silica gel, hexane–EtOAc, 7:3) to yield the expected aldehyde (510 mg). After a mixture of the intermediate aldehyde, allyl bromide (575 mg, 6.6 mmol) and activated zinc dust (572 mg, 8.8 mmol) stirred in dry THF (10 mL) at 0 °C was treated with saturated NH₄Cl (3 mL, added portionwise over 10 min), the resulting solution was stirred for 30 min. Upon completion, the reaction mixture was filtered through Celite® and washed with saturated NaHCO₃ (2 × 50 mL). The combined organic layer was dried over Na₂SO₄, concentrated *in vacuo* and the product mixture obtained purified by column chromatography (silica gel, hexane–EtOAc, 8:2) to afford pure **25** (452 mg, 67% for two steps, 7:3 dr): light yellowish oil; $[\alpha]_D^{20} = +4.0$ (*c* 1.5, CHCl₃); IR (film) $\nu_{\max}$ 3467, 3077, 2961, 2929, 2874, 1737, 1642, 1434, 1376, 1241, 1056, 1025, 916 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.77 (2H, comp), 5.18–4.98 (5H, comp), 3.64 (1H, dd, *J* = 3.0, 9.0 Hz), 2.97 (1H, t, *J* = 6.0 Hz), 2.47–2.11 (4H, comp), 2.01 (3H, s), 1.76–1.40 (7H, comp), 1.26 (3H, s), 0.89 (3H, d, *J* = 6.3 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 14.2 (CH₃), 19.0 (CH₃), 21.1 (CH₃), 25.6 (CH), 29.1 (CH₂), 33.9 (CH₂), 37.3 (CH₂), 39.5 (CH₂), 40.9 (CH₂), 59.7 (CH), 62.3 (C), 71.2 (CH), 72.3 (CH), 117.4 (CH₂), 117.7 (CH₂), 133.6 (CH), 134.4 (CH), 170.7 (C); HRMS (ESI⁺) *m/z* C₁₈H₃₀O₄Na [M+Na]⁺ calcd 333.2042, found 333.2047.

4.20. (1R,4S,6S,11R,12R,E)-11-Hydroxy-4,12-dimethyl-13-oxabicyclo[10.1.0]tridec-8-en-6-yl acetate (26)

A stirred mixture of diene precursor **25** (220 mg, 0.70 mmol) and Hoveyda-Grubbs II catalyst (43 mg, 10 mol %) in dry CH₂Cl₂ (120 mL) was refluxed under N₂ for 8 h. After cooling, the solvent was evaporated *in vacuo* and the residue left subjected to column chromatography (silica gel, hexane–EtOAc, 7:3) to yield pure **26** (84 mg, 43%) as a single stereoisomer: light brown liquid; $[\alpha]_D^{20} = -126.0$ (*c* 1.0, CHCl₃); IR (film) $\nu_{\max}$ 3480, 2955, 2931, 2854, 1733, 1457, 1433, 1371, 1248, 1077, 1023, 977, 704 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.60 (1H, m, H-8), 5.48 (1H, m, H-9), 4.87 (1H, m, H-11), 3.88 (1H, t, *J* = 5.0 Hz, H-6), 3.11 (1H, dd, *J* = 5.0, 10.0 Hz, H-4), 2.57 (1H, m, H-7), 2.33 (2H, m, H-10), 2.25 (1H, m, H-7'), 2.03 (1H, m, H-3), 1.98 (3H, s, -OCOC(=O)H₃), 1.86 (1H, m, H-1), 1.62–1.45 (3H, comp, H-2, H-12, H-12'), 1.33 (1H, m, H-3'), 1.24 (3H, s, H₃-14), 1.14 (1H, m,

H-2'), 0.95 (3H, d, J = 6.6 Hz, H₃-13); ¹³C NMR (125 MHz, CDCl₃) δ 14.6 (CH₃, C-14), 20.4 (CH₃, C-13), 21.4 (CH₃, OCOCH₃), 23.9 (CH₂, C-3), 25.2 (CH, C-1), 31.2 (CH₂, C-2), 35.1 (CH₂, C-7), 39.2 (CH₂, C-10), 42.1 (CH₂, C-12) 56.8 (CH, C-4), 62.2 (C, C-5), 70.6 (CH, C-6), 71.3 (CH, C-11), 126.8 (CH, C-8), 129.2 (CH, C-9), 170.4 (C, OCOCH₃); MS (ESI⁺) m/z 303.2 [M+Na-H₂]⁺, 223.2 [M+H-AcOH]⁺, 205.2 [M+H-AcOH-H₂O]⁺; HRMS (ESI⁺) m/z C₁₆H₂₄O₄Na [M+Na-H₂]⁺ calcd 303.1572, found 303.1570.

4.21. (1*R*,4*S*,6*S*,12*S*,*E*)-4,12-Dimethyl-11-oxo-13-oxabicyclo[10.1.0]tridec-8-en-6-yl acetate (27)

To a 0 °C solution of **26** (75 mg, 0.26 mmol) in dry CH₂Cl₂ (10 mL) was added NaHCO₃ (87.0 mg, 1.0 mmol) and Dess–Martin periodinane (179.0 mg, 0.4 mmol). The ensuing mixture was stirred for 1 h while allowing the temperature to rise to r.t. After removing the solvent by rotoevaporation the residue obtained was subjected to flash column chromatography (silica gel, hexane–EtOAc, 6.5:3.5) to furnish pure ketone **27** (64 mg, 89%): colorless oil; [α]_D²⁰ = –232.0 (c 0.5, CHCl₃); IR (film) ν_{max} 2958, 2929, 2856, 1731, 1458, 1432, 1372, 1247, 1068, 1023, 977 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 5.78 (1H, dddd, J = 3.0, 6.0, 9.0, 12.0 Hz, H-8), 5.43 (1H, dddd, J = 3.0, 6.0, 9.0, 12.0 Hz, H-9), 4.99 (1H, m, H-11), 3.50 (1H, dd, J = 9.0, 12.0 Hz, H-7), 3.04 (1H, dp, J = 3.0, 12.0 Hz, H-7'), 2.75 (1H, dd, J = 3.0, 9.0 Hz, H-4), 2.49 (1H, m, H-10), 2.34 (1H, dt, J = 9.0, 15.0 Hz, H-10'), 2.07 (1H, m, H-3), 2.02 (3H, s, –OCOCH₃), 1.77 (1H, m, H-1), 1.68–1.15 (5H, comp, H-2, H-2', H-3', H-12, H-12'), 1.62 (3H, s, H₃-14), 0.96 (3H, d, J = 6.4 Hz, H₃-13); ¹³C NMR (75 MHz, CDCl₃) δ 14.0 (CH₃, C-14), 20.6 (CH₃, C-13), 21.3 (CH₃, OCOCH₃), 23.9 (CH₂, C-3), 25.7 (CH, C-1), 31.4 (CH₂, C-2), 38.7 (CH₂, C-10), 41.6 (CH₂, C-12), 45.2 (CH₂, C-7), 62.0 (CH, C-4), 62.5 (C, C-5), 70.8 (CH, C-11), 124.8 (CH, C-8), 132.8 (CH, C-9), 170.3 (C, OCOCH₃), 205.3 (C, C-6); HRMS (ESI⁺) m/z C₁₆H₂₄O₄Na [M+Na]⁺ calcd 303.1572, found 303.1564.

4.22. 2-(Iodomethyl)-3-methylbut-1-ene (28)

A 0 °C mixture of 3-methyl-2-methylene-1-butanol (6.0 g, 60.0 mmol), Ph₃P (15.7 g, 60.0 mmol) and imidazole (12.2 g, 180.0 mmol) in dry CH₂Cl₂ (100 mL) was stirred for 10 min before adding iodine (22.9 g, 90.0 mmol). After stirring for 2 h the reaction mixture was quenched with saturated Na₂S₂O₃ (60 mL), extracted with Et₂O (4 × 100 mL), washed with brine (2 × 100 mL), and the combined organic layer dried with Na₂SO₄. Solvent removal *in vacuo* (the water bath temperature should not exceed 15 °C) gave a crude product that was carefully filtered through a short plug of silica gel (petroleum ether) to afford allyl iodide **28** (5.4 g, 43%): colorless liquid; ¹H NMR (300 MHz, CDCl₃) δ 5.18 (1H, br s), 5.00 (1H, br s), 4.06 (2H, s), 2.58 (1H, hep), 1.12 (3H, d, J = 6.5 Hz), 1.08 (3H, d, J = 6.5 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 21.6 (2 × CH₃), 30.9 (CH), 36.1 (CH₂), 113.1 (CH₂), 151.6 (C).^{24d}

4.23. (4*S*,6*S*)-8-((2*R*,3*R*)-3-((*R*)-1-Hydroxy-4-methyl-3-methylenepentyl)-3-methyloxiran-2-yl)-6-methyloct-1-en-4-yl acetate (29)

A solution of **24** (600 mg, 2.2 mmol) in a 1:1 mixture of dry CH₂Cl₂–DMSO (30 mL) under N₂ at 0 °C was treated with Et₃N (1.8 mL, 13.2 mmol) and Py·SO₃ complex (1.4 g, 8.8 mmol). After stirring for 1 h the reaction mixture was quenched with H₂O (3 × 50 mL),

extracted with Et₂O (3 × 50 mL), the combined organic layer dried over Na₂SO₄ and concentrated *in vacuo*. The crude product obtained was purified by flash column chromatography (silica gel, hexane–EtOAc, 7:3) to furnish the intermediate aldehyde (515 mg). A –20 °C solution of allyl iodide **28** (1.8 g, 8.8 mmol) in dry THF (20 mL) was carefully degassed before adding activated zinc dust (1.1 g, 17.6 mmol). After stirring the mixture for 1 h the aldehyde was added and the resulting solution stirred for 12 h while allowing the dry-ice bath to melt. Upon completion (established by TLC) the reaction mixture was filtered through Celite®, washed with saturated NaHCO₃ (2 × 50 mL), the combined organic layer dried (Na₂SO₄), and the clear extract concentrated *in vacuo*. The crude product mixture was purified by flash column chromatography (silica gel, hexane–EtOAc, 8:2) to yield pure alcohol **29** (358 mg, 46% for 2 steps, 7:3 dr): pale yellow oil; [α]_D²⁰ = +17.6 (*c* 1.5, CHCl₃); IR (film) $\nu_{\max}$ 3470, 3081, 2962, 2930, 2873, 1738, 1643, 1463, 1376, 1241, 1105, 1025, 916, 893 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.74 (1H, m), 5.05 (3H, comp), 4.88 (2H, dt, *J* = 3.0, 15.0 Hz), 3.62 (1H, dd, *J* = 2.8, 9.6 Hz), 2.95 (1H, t, *J* = 6.0 Hz), 2.43–2.22 (4H, comp), 2.10 (2H, m), 2.02 (3H, s), 1.69–1.41 (6H, comp), 1.29 (3H, s), 1.28 (1H, m), 1.06 (3H, d, *J* = 6.5 Hz), 1.04 (3H, *J* = 6.5 Hz), 0.91 (3H, d, *J* = 6.3 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 13.7 (CH₃), 19.1 (CH₃), 21.2 (CH₃), 21.6 (CH₃), 21.9 (CH₃), 25.7 (CH), 29.1 (CH), 33.2 (CH₂), 34.0 (CH₂), 38.4 (CH₂), 39.5 (CH₂), 41.0 (CH₂), 60.5 (CH), 62.4 (C), 71.2 (CH), 71.8 (CH), 109.5 (CH₂), 117.7 (CH₂), 133.6 (CH), 152.2 (C), 170.7 (C); HRMS (ESI⁺) *m/z* C₂₁H₃₆O₄Na [M+Na]⁺ calcd 375.2511, found 375.2508.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References and notes

- (a) Rodríguez AD. Tetrahedron. 1995; 51:4571–4618.(b) Berrue F, Kerr RG. Nat Prod Rep. 2009; 26:681–710. [PubMed: 19387501] (c) Marrero, J., Rodríguez, IL., Rodríguez, AD. The Natural Products Chemistry of the Gorgonian Genus Pseudopterogorgia (Octocorallia: Gorgoniidae). In: Mander, L., Lui, H-W., editors. In Comprehensive Natural Products II Chemistry and Biology. Vol. 2. Elsevier; Oxford: 2010. p. 363-428.
- Prestwich GD, Weimer DF, Meinwald J, Clardy J. J Am Chem Soc. 1978; 100:2560–2561.
- Look SA, Fenical W, Qi-tai Z, Clardy J. J Org Chem. 1984; 49:1417–1423.
- Shin J, Fenical W. J Org Chem. 1991; 56:3392–3398.
- (a) Marville KI, Reynolds WF, Sealy RI, Tinto WF. Heterocycles. 2004; 63:107–113.(b) Cheng CH, Lin YS, Wen ZH, Su JH. Molecules. 2012; 17:10072–10078. [PubMed: 22922278]
- Wei X, Nieves K, Rodríguez AD. Pure Appl Chem. 2012; 84:1847–1855.
- Subsequent work from the Fenical group led to the isolation of caliculones D–G as minor constituents (<0.5%) from nonpolar extracts of the same gorgonian species (see ref. 4).
- Wefer J, Simon K, Lindel T. Phytochem Rev. 2013; 12:95–105.
- (a) Vig OP, Bari SS, Trehan IR, Vig R. Indian J Chem Sect B: Org Chem Incl Med Chem. 1980; 19B:446–449.(b) Kodama M, Takahashi T, Kojima T, Ito S. Tetrahedron Lett. 1982; 23:3397–3400.

- (c) Kodama M, Takahashi T, Kojima T, Ito S. *Tetrahedron*. 1988; 44:7055–7062.(d) Kodama M, Maeda H, Hioki H. *Chem Lett*. 1996; 25:809–810.(e) Simon K, Wefer J, Schöttner E, Lindel T. *Angew Chem*. 2012; 124:11047–11050.
10. Schöttner E, Wiechoczek M, Jones PG, Lindel T. *Org Lett*. 2010; 12:784–787. [PubMed: 20085310]
11. Initially, it was the lure of the substituted twelve-membered ring of the marine cubitanoids, our interest to provide materials for more extensive biological evaluation, and our desire to determine the absolute configuration of its stereogenic centers, what rendered the total synthesis of calyculone H (**5**) irresistible to us.
12. The cytotoxicity (and tubulin-binding ability) of some naturally occurring diterpenes useful in cancer chemotherapy, such as taxol (paclitaxel) and the eleutherobins/sarcodictyins, show high sensitivity to the size and flexibility of the macrocycle as well as the presence of heteroatom(s) in the surface of the macrocycle, see: Giannakakou P, Gussio R, Nogales E, Downings KH, Zaharevitz D, Bollbuck B, Poy G, Sackett D, Nicolaou KC, Fojo T. *Proc Natl Acad Sci USA*. 1999; 97:2904–2909. Ganesh T, Guza RC, Bane S, Ravindra R, Shanker N, Lakdawala AS, Snyder JP, Kingston DGI. *Proc Natl Acad Sci USA*. 2004; 101:10006–10011. [PubMed: 15226503] Maier ME. *Org Biomol Chem*. 2015; 13:5302–5343. [PubMed: 25829247]
13. Ojima I, Chakravarty S, Inoue T, Lin S, He L, Horwitz S-B, Kuduk SD, Danishefsky SJ. *Proc Natl Acad Sci USA*. 1999; 96:4256–4261. [PubMed: 10200249]
14. (a) Fischman C, Alder S, Hofferberth JE. *J Org Chem*. 2013; 78:7318–7323. [PubMed: 23790053] (b) Stoekl J, Hofferberth J, Pritschet M, Brummer M, Ruther J. *J Chem Ecol*. 2012; 38:331–339. [PubMed: 22477024] (c) Beckett JS, Beckett JD, Hofferberth JE. *Org Lett*. 2010; 12:1408–1411. [PubMed: 20222691]
15. (a) Katsuki T, Sharpless KB. *J Am Chem Soc*. 1980; 102:5974–5976.(b) Martin VS, Woodard SS, Katsuki T, Yamada Y, Ikeda M, Sharpless KB. *J Am Chem Soc*. 1981; 103:6237–6240.(c) Boruwa J, Gogoi N, Barua NC. *Org Biomol Chem*. 2006; 4:3521–3525. [PubMed: 17036149] (d) Tanuwidjaja J, Ng SS, Jamison TF. *J Am Chem Soc*. 2009; 131:12084–12085. [PubMed: 19663441] (e) Kanto M, Sasaki M. *Org Lett*. 2016; 18:112–115. [PubMed: 26654463]
16. Nagamitsu T, Takano D, Fukuda T, Otoguro K, Kuwajima I, Harigaya Y, Ohmura S. *Org Lett*. 2004; 6:1865–1867. [PubMed: 15151434]
17. (a) Biswas K, Lin H, Njardarson JT, Chappell MD, Chou TC, Guan Y, Tong WP, He L, Horwitz SB, Danishefsky SJ. *J Am Chem Soc*. 2002; 124:9825–9832. [PubMed: 12175242] (b) Morimoto Y, Takeuchi E, Kambara H, Kodama T, Tachi Y, Nishikawa K. *Org Lett*. 2013; 15:2966–2969. [PubMed: 23721415]
18. Kawai N, Fujikura Y, Takita J, Uenishi J. *Tetrahedron*. 2013; 69:11017–11024.
19. (a) Keltjens R, Vadivel SK, Gelder RD, Klunder AJH, Zwanenburg B. *Eur J Org Chem*. 2003:1749–1758.(b) Gao Y, Wang X, Sun L, Xie L, Xu X. *Org Biomol Chem*. 2012; 10:3991–3998. [PubMed: 22526727]
20. (a) Maier M. *Angew Chem Int Ed*. 2000; 39:2073–2077.(b) Chatterjee AK, Choi TL, Sanders DPH, Grubbs RH. *J Am Chem Soc*. 2003; 125:11360–11370. [PubMed: 16220959] (c) Nicolaou KC, Bulger PG, Sarlah D. *Angew Chem Int Ed*. 2005; 44:4490–4527.(d) Gradillas A, Perez-Castells J. *Angew Chem Int Ed*. 2006; 45:6086–6101.(e) Radtke L, Willot M, Sun H, Ziegler S, Sauerland S, Strohmman C, Frohlich R, Habenberger P, Waldmann H, Christmann M. *Angew Chem Int Ed*. 2011; 50:3998–4002.
21. Overlap of the signals ascribed to H-8 and H-9 in the ^1H NMR (500 MHz, CDCl_3) spectrum of **7** made it necessary to conduct the coupling constant measurements in C_6D_6 : ^1H NMR (700 MHz, C_6D_6) δ 5.21 (1H, dddd, J = 2.0, 4.1, 10.9, 13.0 Hz, H-9), 4.85 (1H, dddd, J = 2.5, 5.4, 11.1, 13.6 Hz, H-8).
22. In addition to the isopropylene and isopropyl groups at C8 and C10, respectively, each marine cubitanoid has a ketone moiety at C11, with most having a trisubstituted epoxy group between C5 and C6. When compared to **7**, analogue **27** has the same structural features except for the oxidation pattern at C6 and C11. Thus, its synthesis could help us ascertain whether the ketone functionality of the calyculones at C11 is essential for the observed activity.

23. (a) Keck GE, Tarbet KH, Geraci LS. *J Am Chem Soc.* 1993; 115:8467–8468. (b) Keck GE, Geraci LS. *Tetrahedron Lett.* 1993; 49:7827–7828. (c) Basubramanyam P, Reddy GC, Salvanna N, Das B. *Synthesis.* 2011:3706–3710.
24. (a) Liu H, Qiao Z, Jiang X. *Org Biomol Chem.* 2012; 10:7274–7277. [PubMed: 22886029] (b) Zhao Y, Xiaojian JX, Yeung YY. *Angew Chem Int Ed.* 2013; 52:8597–8601. (c) Ganguly AK, Alluri SS, Wang CH, Antropow A, White A, Carocchia D, Biswas D, Kang E, Zhang LK, Carroll SS, Burlein C, Fay J, Orth P, Strickland C. *Tetrahedron.* 2014; 70:2894–2904. (d) Cheng B, Sunderhaus JD, Martin SF. *Org Lett.* 2010; 12:3622–3625. [PubMed: 20704405]
25. It has been noticed that the RCM is strongly substrate-dependant mainly due to steric hindrance, complexation and conformational effects. In most cases, the success of the cyclization results from a favorable conformational preorganization of the acyclic dienic precursor and the absence of bulky groups in the vicinity of the reactive centers. The course of the reaction also depends on the nature of the catalyst.
26. https://home.ncifcrf.gov/mtdp/catalog/full_text/paper309/paper309.pdf
27. In ref. 6 the NCI cytotoxicity data provided for calyculone A (**2**) needs to be rectified. The revised averaged GI₅₀ values (the concentration of compound required for 50% growth inhibition) against SR leukemia, melanoma UACC-62, and RXF 393 renal cancer are 2.44×10^{-5} , $>1.00 \times 10^{-4}$, and 3.85×10^{-5} μ M, respectively.
28. Partial data for truncated calyculone H (**7**): $[\alpha]_D -307.3^\circ$, c 1.8 in CHCl_3 ; ^{13}C NMR (CDCl_3) δ 27.0 (C-1), 62.8 (C-4), 60.1 (C-5), 19.8 (C-13), 15.5 (C-14). Partial data for natural calyculone H (**5**) (from ref. 6): $[\alpha]_D -69.0^\circ$, c 1.3 in CHCl_3 ; ^{13}C NMR (CDCl_3) δ 27.7 (C-1), 62.5 (C-4), 59.9 (C-5), 20.0 (C-13), 16.6 (C-14).

Fig. 1.
Carbon backbone for the cubitane class of irregular diterpenes and the structures of some representative cubitane diterpenes.

Scheme 1.

Retrosynthetic analysis for truncated calyculone H (7).

Scheme 2.
Synthesis of fragment **15**.

Scheme 3.

Synthesis of truncated calyculone H (**7**) and ring-closing metathesis (RCM) catalysts.

Scheme 4.

Preparation of pivotal fragment **24**.

Scheme 5. Synthesis of truncated “calyculone-like” product **27**.

Scheme 6. Attempted preparation of partially truncated calyculone **30**.

Table 1

Side-by-side comparison of the ^1H NMR and ^{13}C NMR spectroscopic data for calyculone H (**5**) and truncated calyculone H derivative (**7**).^a

position	Calyculone H (5) ^b		Truncated Calyculone H (7) ^c	
	δ_{H} , mult, intgr (<i>J</i> in Hz)	δ_{C} , type ^d	δ_{H} , mult, intgr (<i>J</i> in Hz)	δ_{C} , type ^d
1	2.17, m, 1H	27.7, CH	2.30, m, 1H	27.0, CH
2 α	1.22, m, 1H	31.9, CH ₂	1.26, m, 1H	32.2, CH ₂
2 β	1.35, m, 1H		1.36, m, 1H	
3 α	2.01, m, 1H	25.0, CH ₂	2.03, m, 1H	24.9, CH ₂
3 β	1.27, m, 1H		1.28, m, 1H	
4	2.73, dd, 1H (3.5, 9.8)	62.5, CH	2.69, dd, 1H (5.0, 10.0)	62.8, CH
5		59.9, C		60.1, C
6 α	2.07, m, 1H	37.1, CH ₂	2.16, m, 1H	38.1, CH ₂
6 β	1.43, m, 1H		1.17, m, 1H	
7 α	2.08, m, 1H	28.0, CH ₂	2.13, m, 1H	29.7, CH ₂
7 β	2.28, m, 1H		2.34, m, 1H	
8		146.4, C	5.47, m, 1H	133.8, CH
9	5.03, br d, 1H (9.3)	122.6, CH	5.47, m, 1H	124.9, CH
10 α	4.29, br d, 1H (9.3)	57.1, CH	3.32, dd, 1H (10.0, 15.0)	46.4, CH ₂
10 β			2.89, dt, 1H (5.0, 15.0)	
11		211.3, C		209.6, C
12 α	2.16, m, 1H	55.0, CH ₂	2.37, dd, 1H (5.0, 10.0)	54.2, CH ₂
12 β	2.55, d, 1H (7.9)		2.20, dd, 1H (8.5, 10.0)	
13	1.05, d, 3H (5.8)	20.0, CH ₃	1.02, d, 3H (6.4)	19.8, CH ₃
14	1.30, s, 3H	16.6 CH ₃	1.23, s, 3H	15.5, CH ₃
15	2.75, m, 1H	29.7, CH		
16	0.97, d, 3H (7.0)	21.6, CH ₃		
17	1.06, d, 3H (7.0)	21.4, CH ₃		
18		143.3, C		
19	1.72, br s, 3H	21.5, CH ₃		
20 α	4.88, br s, 1H	113.3, CH ₂		
20 β	4.77, br s, 1H			

^aSpectra were recorded in CDCl₃ at 25 °C. Chemical shift values are in ppm relative to the residual CHCl₃ (7.26 ppm) or CDCl₃ (77.0 ppm) signals. Assignments were aided by 2D NMR experiments, spin-splitting patterns, the number of attached protons, and chemical shift values.

^bData taken from ref. 6: ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz).

^cData from this work: ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz).

^d ^{13}C NMR types were obtained from DEPTQ NMR experiments.

Table 2Attempts to transform **29** into **30** via a ring-closing metathesis reaction (RCM).^a

Entry	Catalyst (mol%)	Temp in °C	Solvent	Time (hours)	Yield (%)
1	Grubbs 2 nd catalyst (10)	50	DCM	30	0
2	Grubbs 2 nd catalyst (25)	50	DCM	30	0
3	Hoveyda-Grubbs catalyst (20)	50	DCM	24	0
4	Grubbs 2 nd catalyst (20)	80	Toluene	12	0
5	Hoveyda-Grubbs (20)	80	Toluene	12	0

^aOur efforts were characterized by the recovery of starting material, formation of complex product mixtures, and formation of the intermolecular cross-metathesis (acyclic dimer) product.

Table 3Growth percent inhibition of compounds **2** and **7** on various malignant human tumor cells.^a

Entry	NCI Cell Line	Growth % Inhibition	
		2	7
1	NCI-H460	3.0%	33.8%
2	COLO 205	8.0%	26.0%
3	SW-620	0%	19.8%
4	LOX IMVI	13.0%	22.4%
5	MALME-3M	0%	11.6%
6	MCF7	0%	33.4%
7	T-47D	4.0%	24.7%

^aPercentages of growth inhibition measured at a concentration of 1.0×10^{-5} M.