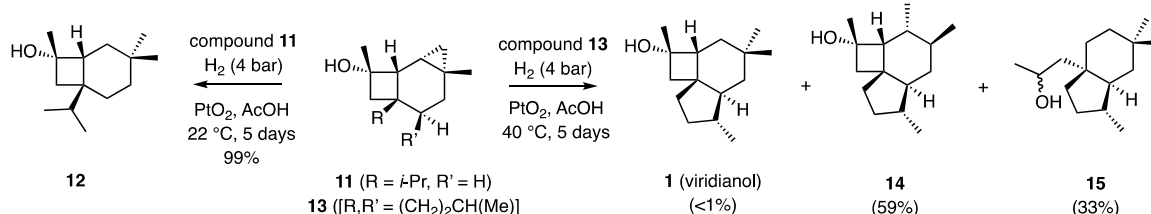


Synthetic Studies on the Marine-Derived Sesquiterpene (+)-Viridianol: Divergent Behaviour of Two Structurally Related, Ring-Fused Cyclopropanes Under the Same Hydrogenolytic Conditions.

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ABSTRACT: Hydrogenolytic cleavage of the ring-fused cyclopropane **11** using hydrogen in the presence of platinum oxide afforded the *gem*-dimethylated cyclohexane **12** in 99% yield. In contrast, analogous treatment of congener **13** afforded only trace amounts of the targeted and *gem*-dimethylated sesquiterpene (+)-viridianol (**1**), the major products of reaction now being the *vic*-dimethylated compound **14** and the two-fold ring-cleavage product **15**.

INTRODUCTION

One subset of the multitude of sesquiterpenoid natural products generated by terrestrial and marine organisms¹ embodies a four- and a five-membered ring fused to a common six-membered one. Among the three possible arrangements of such mutually-fused rings,² the one seen in the red seaweed-derived natural product (+)-viridianol (**1**)³ is the rarest with only one other natural product, (+)-trefolane A,⁴ embodying this ring system that necessarily incorporates a quaternary carbon center at the junction between the constituent rings. Recently,⁵ we detailed a total synthesis of (+)-viridianol **1** that started with the enantiomerically enriched *cis*-1,2-dihydrocatechol **2**,⁶ a compound readily obtained through the whole-cell biotransformation of *p*-iodotoluene.⁷

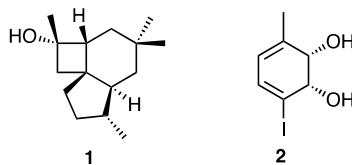
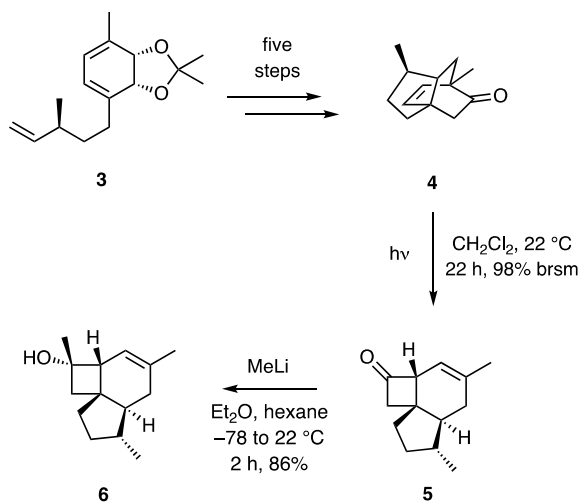


Figure 1: The structure of the sesquiterpene (+)-viridianol (**1**) and the starting material, **2**, used in its recently reported total synthesis.

Various of the key steps employed in this total synthesis⁵ are shown in Scheme 1. The first of these was the formation of the triene **3** through engagement of the acetonide derivative of diol **2** in a metal-for-iodine exchange reaction with the ensuing organozinc species then participating in a Negishi cross-coupling with an ω -unsaturated primary iodide. Triene **3** participated in a thermally-induced, type I intramolecular Diels-Alder cycloaddition reaction and thus yielding an adduct that was elaborated over a further five steps into cyclopentannulated bicyclo[2.2.2]octenone **4**. A photochemically-promoted and highly efficient 1,3-acyl migration (Givens rearrangement)⁸ of compound **4** followed and thus yielding the octahydrocyclobuta[*d*]indene **5** embodying the full carbon framework of (+)-viridianol (**1**). Treatment of cyclobutanone **5** with methyl lithium resulted in a stereoselective addition reaction and thereby providing the tertiary allylic alcohol **6** incorporating a further key structural element of target **1**. In a formal sense, the conversion **6** \rightarrow **1** required to complete the synthesis (through establishment of the *gem*-dimethyl subunit associated with the latter) requires the Markovnikov-type hydromethylation of the unactivated olefinic residue within the former compound, a process for which few direct methods have been reported.⁹ As such we sought to pursue indirect methods involving olefinic cyclopropanation followed by hydrogenolysis of the resulting three-membered ring. This protocol that has been applied with considerable success in a range of settings,¹⁰ although not to any great extent with tri- or more highly-substituted cyclopropanes. Details of our efforts to effect such a transformation are presented in the following section.

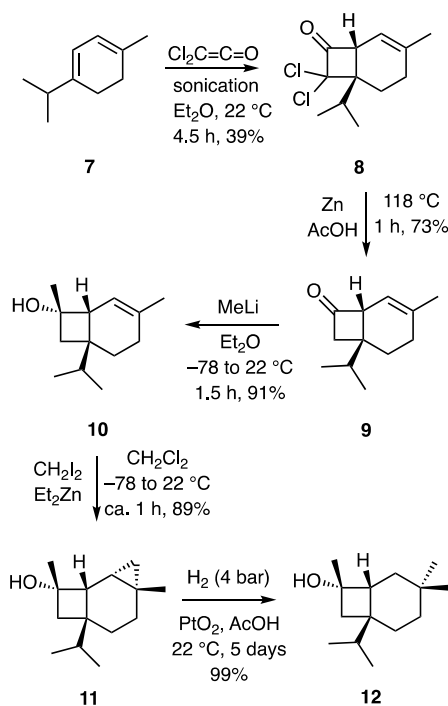
Scheme 1: Key steps associated with the formation of the octahydrocyclobuta[*d*]indene framework of (+)-viridianol and leading to tertiary-alcohol **6**.



RESULTS AND DISCUSSION

The length and complexity of the reaction sequence leading to compound **6** did not lend itself to the accumulation of this material in sufficient quantity for the purposes of conducting the extensive studies of the cyclopropanation/hydrogenolysis protocol it was thought would be necessary in defining a means for introducing the *gem*-dimethyl group associated with target **1**. As such, a model study was pursued in the first instance. Details are presented in Scheme 2.

Scheme 2: The synthesis of tertiary alcohol **10**, an analogue of compound **6**, and its two-step Markownikoff hydromethylation leading to the *gem*-dimethylated cyclohexane **12**



Following protocols established by Greene,¹¹ commercially available α-terpinene (**7**) was treated, under ultrasonication conditions, with *in situ* generated dichloroketene and thereby affording the required [2+2] cycloadduct **8** in 39% yield after chromatographic purification. Treatment of compound **8** with freshly activated zinc powder in acetic acid under reflux for 1 h resulted in two-fold dechlorination and the formation of cyclobutanone **9** that was obtained in 73% yield. At low temperatures, addition of methyllithium to ketone **9** proceeded in an *exo*-fashion and thereby forming the *endo*-configured alcohol **10** in 91% yield. Compound **10** represents a model for congener **6** and

so methods for effecting its two-step hydromethylation, using a two-step cyclopropanation/hydrogenolysis sequence, were explored.

The **hydroxy** group within compound **10** served to direct a low-temperature Furukawa-type cyclopropanation reaction¹² and thus leading to the formation of the crystalline tricyclo[5.2.0.0^{2,4}]nonane **11** in 89% yield. All of the spectral data acquired on cyclopropane **11** were in accord with the assigned structure but final confirmation of this followed from a single-crystal X-ray analysis, details of which are provided in the Experimental Section and the Supporting Information.

A range of catalysts has been employed in the hydrogenolytic cleavage of ring-fused cyclopropanes¹⁰ and among the most conspicuous of these is platinum oxide. Accordingly, and taking leads from the work of Overman¹³ and Jones,¹⁴ an acetic acid solution of cyclopropane **11** was exposed to dihydrogen at 4 bar in the presence of PtO₂ at 22 °C for 5 days and after workup the anticipated *gem*-dimethylated compound **12** was obtained in 99% yield. The spectral data derived from product **12** were in complete accord with the illustrated structure. Notably, in the high field region of the 400 MHz ¹H NMR spectrum, three three-proton singlets and two three-proton doublets were evident, as would be expected for structure **12**. These resonances are only consistent with a product arising from the illustrated mode of cyclopropane ring cleavage and not the other two possibilities that would lead to either a seven-membered ring or a vicinally dimethylated product that would display two, three-proton doublets in the derived ¹H NMR spectrum. In the ¹³C NMR spectrum of compound **12** the expected fourteen resonances were observed with three of these being due to quaternary carbons, a situation that is also only consistent with the illustrated outcome among the three possible modes of cyclopropane ring-cleavage within substrate **11**.

Encouraged by the outcomes of the model study detailed immediately above, compound **6** was subjected to reaction with diiodomethane in the presence of Et₂Zn (Scheme 3) and thus affording the anticipated cyclopropane **13** as a single diastereoisomer in 93% yield. As was the case with the analogous conversion shown in Scheme 2, in this instance it is assumed that the **hydroxy** group associated with substrate **6** directs delivery of the

methylene unit incorporated into product **13** such that the illustrated stereochemical outcome is observed. This is entirely credible given that delivery of the methylene unit to substrate **6** would not only be directed by the hydroxy group but also take place at that face of the olefin opposite the cyclopentane ring that is annulated to opposing side of the six-membered ring.

When compound **13** was exposed to hydrogen under exactly the same conditions as employed for the conversion **11** → **12** then a rather complex product mixture was obtained. Disappointingly, only trace amounts of (+)-viridianol (**1**) were obtained with its *vic*-dimethylated isomer **14** (59%) predominating and the two-fold reductive cleavage product **15** (33% of a *ca.* 3:1 mixture of diastereoisomers) being the other major product of reaction. These three reactions products could be separated from one another by careful flash column chromatography.

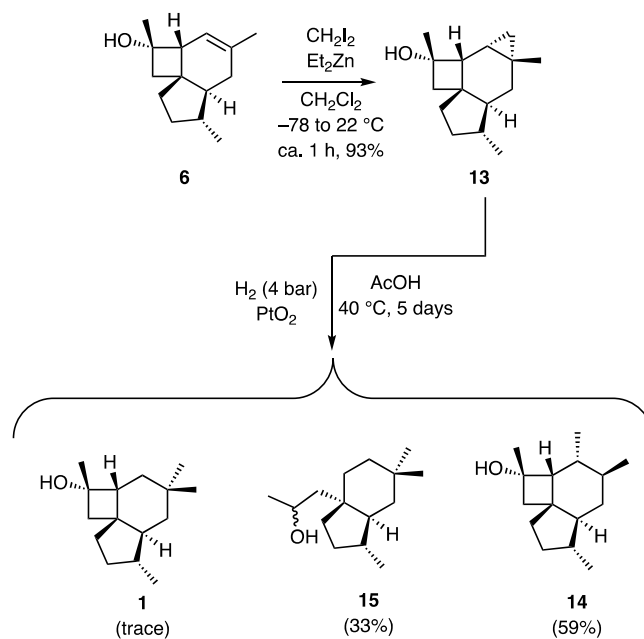
The structure of compound **1** obtained by the pathway shown in Scheme 3 was confirmed through comparison of the derived spectral data with those obtained on an authentic sample prepared by a different hydromethylation route.⁵

In the ¹H NMR spectrum of compound **14** three, three-proton doublets were observed in the high-field region and so suggesting the presence of three methyl groups attached to tertiary rather than quaternary carbon centres. The configurations of the newly established stereogenic centres in product **14** are assigned on the basis that hydrogenolytic cleavage of the cyclopropane ring within substrate would proceed through addition of the elements of dihydrogen from the notionally more accessible *exo*-face of the bicyclo[4.1.0]heptane substrate. Such a pathway would establish the illustrated *trans*-relationship between the methyl groups attached to the six-membered ring. The ¹³C NMR spectrum of product **14** displayed the expected fifteen resonances while the infra-red spectrum showed a strong O-H stretching band at 3342 cm⁻¹. Mass spectral data could not be acquired on this material due to its high volatility.

The most notable features in the ¹H NMR spectrum of compound **15** were a one-proton oxymethine resonance at δ 3.97 and, in the higher field region, two, three-proton singlets

together with two, three-proton doublets. The former pair of signals arise from the *gem*-dimethyl moiety associated with the six-membered ring while the latter derive from the methyl groups attached to methine carbons including, in one case, an oxymethine carbon and thus resonating at notably lower field than the other (δ 1.25 vs 1.00 ppm). The ^{13}C NMR spectrum of alcohol **15** displayed two sets of fifteen resonances and thus indicating it is a *ca.* 3:1 mixture of diastereoisomers due to the presence of both the *R*- and *S*-epimeric forms at the hydroxy-bearing carbon. The IR spectrum of compound **15** displayed a prominent OH stretching band at 3363 cm^{-1} but no molecular ion could be observed in the mass spectrum due to its volatility. Clearly, compound **15** arises through successive and regio-selective hydrogenolyses of the three and the four-membered rings in substrate **13** but the ordering of these events remains unclear. In particular, due to a lack of material, (+)-viridianol could not be re-subjected to the reaction conditions so as to determine if it serves as a precursor to alcohol **15**.

Scheme 3:



The regio-selective but non-stereoselective nature of the hydrogenolytic cleavage of the cyclobutane ring necessarily involved in the conversion **13** \rightarrow **15** is noteworthy and it might be argued that this process is influenced by the ability of the flanking cyclopropane

to stabilize developing positive charge at the closest of the cyclobutane ring carbons and this ring is, therefore, cleaved first. If this were the case then (+)-viridianol would not be a precursor to compound **15**.

CONCLUSION

Given the divergent behaviors of substrates **11** and **13** under the same hydrogenolytic reaction conditions it is evident that the cyclopentannulated nature the latter compound impacts significantly on its reactivity. While the precise origins of this effect remain unclear, the selectivities associated the reductive ring-cleavage of three- and four-membered carbocycles would seem to be delicately balanced. As such, substrates incorporating two or more such moieties seem likely to engage in competitive processes and thus making synthetic planning involving such conversions rather challenging. The present work, when considered alongside our recently reported⁵ total synthesis of (+)-viridianol (**1**), clearly demonstrate that the development of direct, broadly applicable and high-yielding means for effecting the Markovnikov hydromethylation of unsymmetric alkenes remains an important objective.

EXPERIMENTAL SECTION

General Experimental Procedures.

Unless otherwise specified, proton (¹H) and carbon (¹³C) NMR spectra were recorded at room temperature in base-filtered CDCl₃ on a spectrometer operating at 400 MHz for proton and 101 MHz for carbon nuclei. The signal due to residual CHCl₃ appearing at δ_{H} 7.26 and the central resonance of the CDCl₃ “triplet” appearing at δ_{C} 77.0 were used to reference ¹H and ¹³C NMR spectra, respectively. ¹H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. Infrared spectra (ν_{max}) were recorded on a FTIR spectrometer. Samples were analyzed as thin films on KBr plates. Optical rotations were recorded in the indicated solvent at 20 °C. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph-mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Analytical thin layer chromatography

(TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F₂₅₄ plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g : 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still *et al.*¹⁵ with silica gel 60 (40–63 μ m) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents, drying agents, and other inorganic salts were generally commercially available and used as supplied. Tetrahydrofuran (THF), methanol and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs *et al.*¹⁶ Where necessary, reactions were performed under an atmosphere of nitrogen.

Specific Chemical Transformations

(rel-1R,6R)-8,8-Dichloro-1-isopropyl-4-methylbicyclo[4.2.0]oct-4-en-7-one (8). A magnetically stirred suspension of α -terpinene (**7**) (8.10 mL, 50 mmol) and zinc dust (9.80 g, 150 mmol) in diethyl ether (150 mL) maintained under nitrogen at 22 °C and contained in a 500 mL round-bottomed flask equipped with a Liebig condenser was treated, dropwise over 0.5 h and under sonication, with trichloroacetyl chloride (5.60 mL, 100 mmol). Sonication was continued for a further 4 h then the reaction mixture was cooled and concentrated under reduced pressure to *ca.* 50 mL. The residue thus obtained was diluted with hexane (200 mL) and the resulting mixture filtered through a short pad of TLC-grade silica gel and the solids thus retained washed with hexane/diethyl ether (500 mL of a *ca.* 4:1 v/v mixture). The combined filtrates were concentrated under reduced pressure and the ensuing dark-brown residue subjected to flash column chromatography (silica gel, 9:1 v/v 40-60 petroleum spirits/dichloromethane) to give, after concentration of the appropriate fractions ($R_f = 0.4$), compound **8** (3.60 g, 39%) as a clear, light-yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ 5.51 (d, $J = 6.7$ Hz, 1H), 3.79 (d, $J = 6.7$ Hz, 1H), 2.54 (hept, $J = 6.9$ Hz, 1H), 2.13 (m, 1H), 1.95-1.83 (complex m, 3H), 1.75 (s, 3H), 1.08 (d, $J = 6.9$ Hz, 3H), 0.96 (d, $J = 6.9$ Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 194.7, 140.2, 114.1, 92.5, 59.1, 49.9, 34.3, 27.7, 23.3, 18.4, 17.9 (one signal obscured or overlapping); IR (neat) ν_{\max} 2965, 2935, 1803, 1463, 1445, 1389, 1370, 1232, 890, 836, 797, 716 cm⁻¹; MS (EI, 70 eV) m/z 250, 248 and 246 (M⁺, 10, 65 and 95%), 222, 220 and 218 (10, 50

and 80), 213 and 211 (40 and 100); HRMS Calcd for C₁₂H₁₆O³⁵Cl₂: 246.0578. Found: 246.0576.

(rel-1R,6R)-1-Isopropyl-4-methylbicyclo[4.2.0]oct-4-en-7-one (9). A magnetically stirred mixture of compound **8** (3.60 g, 14.6 mmol) and zinc dust (5.00 g, 77 mmol) in acetic acid (50 mL) was heated under reflux for 1 h then cooled to 22 °C and the resulting suspension concentrated under reduced pressure. The residue so obtained was diluted with dichloromethane (100 mL) and the mixture thus formed filtered through a short pad of Celite™. The pad was washed with additional dichloromethane (100 mL) and the combined filtrates washed with NaHCO₃ (3 x 50 mL of a saturated solution), water (1 x 100 mL) and brine (1 x 50 mL) before being dried (MgSO₄), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 1:1 v/v 40-60 petroleum spirits/dichloromethane elution) to give, after concentration of the appropriate fractions (*R_f* = 0.3), compound **9** (1.91 g, 73%) as a clear, pale-yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ 5.40 (m, 1H), 3.33 (m, 1H), 2.70 (ABq, *J* = 17.3 Hz, 2H), 2.12 (m, 1H), 1.96 (m, 1H), 1.79 (hept, *J* = 6.8 Hz, 1H), 1.75 (s, 3H), 1.60 (m, 1H), 1.49 (m, 1H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 207.1, 137.5, 115.1, 62.1, 51.1, 35.4, 34.7, 26.4, 23.7, 22.6, 17.1, 17.0; IR (neat) ν_{max} 2962, 2931, 2876, 1778, 1464, 1446, 1387, 1369, 1130, 1107, 1073, 820 cm⁻¹; MS (ESI, +ve) *m/z* 201 [(M+ Na)⁺, 100%]; HRMS (ESI, +ve) Calcd for C₁₂H₁₈ONa: 201.1255. Found: 201.1256.

(rel-1R,6R,7S)-1-Isopropyl-4,7-dimethylbicyclo[4.2.0]oct-4-en-7-ol (10). A magnetically stirred solution of compound **9** (1.80 g, 10.0 mmol) in diethyl ether (50 mL) maintained under a nitrogen atmosphere was cooled to -78 °C then treated with MeLi (12.5 mL of a 1.6 M solution in diethyl ether, 20 mmol). The resulting mixture was kept at -78 °C for 1 h then allowed to warm to 22 °C over 0.5 h before being treated with NH₄Cl (25 mL of a saturated aqueous solution) and water (25 mL) then extracted with diethyl ether (3 x 50 mL). The combined organic phases were washed with water (1 x 50 mL) and brine (1 x 50 mL) then dried (MgSO₄), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 9:1 v/v 40-60 petroleum spirits/dichloromethane elution) to give, after concentration of the appropriate fractions (*R_f* = 0.25), compound **10** (1.87 g, 91%) as clear, colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 5.43 (d, *J* = 6.5 Hz, 1H), 2.47 (d, *J* = 6.5 Hz, 1H), 2.16

(broad s, 1H), 2.05-1.98 (complex m, 2H), 1.87 (dd, $J = 13.0$ and 2.0 Hz, 1H), 1.81 (s, 3H), 1.78 (hept, $J = 7.0$ Hz, 1H), 1.65 (d, $J = 12.9$ Hz, 1H), 1.37 (s, 3H), 1.30-1.20 (complex m, 2H), 0.81 (d, $J = 7.0$ Hz, 3H), 0.78 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 140.5, 119.2, 70.1, 49.3, 44.3, 36.6, 34.2, 30.0, 27.1, 24.1, 22.9, 16.6, 16.4; IR (neat) ν_{max} 3543, 3469, 2959, 2925, 2874, 1447, 1383, 1367, 1343, 1238, 1159, 1089, 953, 885, 860 cm^{-1} ; Due to its volatility, satisfactory MS and HRMS data could not be obtained on this material.

(rel-1R,2S,4S,7R,9S)-7-Isopropyl-4,9-dimethyltricyclo[5.2.0.0^{2,4}]nonan-9-ol (11). A magnetically stirred solution of compound **10** (333 mg, 1.70 mmol) in dry dichloromethane (5 mL) maintained under nitrogen was cooled to -78 °C then treated with CH_2I_2 (560 μL , 6.8 mmol) and Et_2Zn (3.4 mL of a 1.0 M solution in hexane, 3.4 mmol). The ensuing mixture was allowed to warm to 22 °C over 1 h then quenched with NH_4Cl (10 mL of a saturated solution) and extracted with dichloromethane (3×10 mL). The combined organic phases were washed with brine (1×10 mL) and water (1×10 mL) before being dried (MgSO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 1:9 v/v diethyl ether/pentane elution) to give, after concentration of the appropriate fractions ($R_f = 0.4$), compound **11** (332 mg, 89%) as a clear, colorless solid. ^1H NMR (400 MHz, CDCl_3) δ 2.89 (broad s, 1H), 2.37 (dd, $J = 7.0$ and 2.4 Hz, 1H), 2.00 (dd, $J = 12.8$ and 2.4 Hz, 1H), 1.70-1.45 (complex m, 3H), 1.40-1.30 (complex m, 2H), 1.28 (s, 3H), 1.03 (s, 3H), 0.92 (m, 1H), 0.76 (d, $J = 6.8$ Hz, 3H), 0.74 (d, $J = 6.8$ Hz, 3H), 0.64 (m, 1H), 0.32 (dd, $J = 8.6$ and 4.2 Hz, 1H) (resonance due to one proton obscured or overlapping); ^{13}C NMR (101 MHz, CDCl_3) δ 70.4, 50.7, 46.2, 36.3, 31.5, 30.5, 28.6, 26.4, 26.0, 17.7, 16.6, 16.3, 13.2, 12.6; IR (neat) ν_{max} 3592, 3459, 2954, 1468, 1448, 1383, 1367, 1234, 1208, 1172, 1102, 1090, 1050, 953, 909, 890 cm^{-1} . Due to its volatility, satisfactory MS and HRMS data could not be obtained on this material.

A sample of this material was subjected to sublimation (40 °C/400 mm Hg) to give compound **11** as colorless needles, m.p. = 66 - 69 °C, one of which proved suitable for single-crystal X-ray analysis.

(rel-1R,6R,7S)-1-Isopropyl-4,4,7-trimethylbicyclo[4.2.0]octan-7-ol (12). A Parr hydrogenator was charged with mixture of compound **11** (250 mg, 1.20 mmol), PtO_2 (250 mg, 100% w/w) and glacial acetic acid (20 mL) and then pressurized with hydrogen gas (4

bar). The reaction vessel and its contents were shaken at 22 °C for 5 days and after this time the residual hydrogen was displaced with nitrogen and the ensuing mixture diluted with diethyl ether (50 mL) before being washed with NaHCO₃ (3 × 50 mL of a saturated solution), brine (1 × 50 mL) and water (3 × 50 mL) then dried (Na₂SO₄), filtered and concentrated under reduced pressure. The black residue thus obtained was subjected to flash column chromatography (silica gel, 1:4 v/v diethyl ether/pentane elution) to give, after concentration of the appropriate fractions ($R_f = 0.3$), compound **12** (248 mg, 99%) as a clear, colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 2.05 (m, 1H), 1.92 (dd, $J = 12.6$ and 2.7 Hz, 1H), 1.85-1.75 (complex m, 2H), 1.64 (dd, $J = 14.3$ and 7.0 Hz, 1H), 1.51-1.08 (complex m, 6H), 1.35 (s, 3H), 0.95 (s, 3H), 0.85 (d, $J = 6.8$ Hz, 3H), 0.81 (s, 3H), 0.79 (d, $J = 6.8$ Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 69.1, 44.6, 44.5, 36.1, 34.5, 33.9, 33.1, 33.0, 31.4, 27.9, 27.5, 24.5, 17.1, 16.6; IR (neat) ν_{\max} 3284, 2953, 2924, 2863, 1460, 1384, 1376, 1361, 1243, 1219, 1162, 1146, 1077, 961, 738, 711 cm⁻¹. Due to its volatility, satisfactory MS and HRMS data could not be obtained on this material.

(1S,2aS,5R,5aS,6aR,7aS,7bR)-1,5,6a-Trimethyldecahydro-2Hcyclobuta[d]cyclopropa[f]inden-1-ol (13). A magnetically stirred solution of compound **6**⁵ (150 mg, 0.73 mmol) in dry dichloromethane (7 mL) and maintained under nitrogen was cooled to -78 °C then treated with CH₂I₂ (0.23 mL, 2.91 mmol) and Et₂Zn (1.5 mL of a 1.0 M solution in hexane, 1.50 mmol). The ensuing mixture was allowed to warm to 22 °C over 1 h then quenched with NH₄Cl (10 mL of a saturated solution) before being extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with brine (1 × 20 mL) and water (1 × 20 mL) then dried (MgSO₄), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 1:4 v/v diethyl ether/pentane elution) to give, after concentration of the appropriate fractions (R_f 0.3), compound **13** (139 mg, 93%) as a clear, colorless oil, $[\alpha]_D^{20} = -23$ ($c = 4.0$, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 2.84 (broad s, 1H), 2.50 (s, 1H), 1.95 (dd, $J = 12.3$ and 3.2 Hz, 1H), 1.85-1.75 (complex m, 2H), 1.68-1.59 (complex m, 2H), 1.54-1.39 (complex m, 2H), 1.38 (s, 3H), 1.20-1.00 (complex m, 2H), 1.10 (s, 3H), 0.94 (d, $J = 6.8$ Hz, 3H), 0.90 (m, 1H), 0.70-0.63 (complex m, 2H), 0.40 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 70.6, 55.5, 51.4, 50.8, 41.7, 40.7, 35.7, 35.5, 32.7, 28.6, 25.8, 20.9, 16.3, 16.1, 12.8; IR (neat) ν_{\max} 3591, 3464, 2947, 2919, 2866, 1452, 1375, 1351, 1225, 1155, 964, 942 cm⁻¹; MS (ESI, +ve) m/z 463 [(2M+Na)⁺,

6%], 275 [(M+Na+MeOH)⁺, 40%], 243 [(M+Na)⁺, 100], 221 [(M+H)⁺, <1]; HRMS Calcd for (M+H)⁺, C₁₅H₂₅O: 221.1905. Found: 221.1908.

Hydrogenolytic Cleavage of Cyclopropane 13. Formation of Compounds 1, 14, 15. A Parr hydrogenator containing a mixture of compound **13** (100 mg, 0.45 mmol), PtO₂ (100 mg, 100% w/w) and glacial acetic acid (10 mL) was charged with hydrogen (4 bar) then stirred magnetically at 40 °C for 5 days. The cooled reaction mixture was flushed with nitrogen then diluted with diethyl ether (50 mL) before being washed with NaHCO₃ (3 x 50 mL of a saturated solution), brine (1 × 50 mL) and water (1 × 50 mL) then dried (Na₂SO₄) filtered and concentrated under reduced pressure. The ensuing black residue was subjected to flash column chromatography (silica gel, 9:1 → 4:1 v/v pentane/diethyl ether gradient elution) to give four fractions, A-D.

Concentration of fraction A [*R_f* = 0.2(8) in 9:1 v/v pentane/diethyl ether] gave compound **13** (2 mg, 2% recovery) as a clear, colorless film. This material was identical, in all respects, with an authentic sample.

Concentration of fraction B [*R_f* = 0.2(5) in 9:1 v/v pentane/diethyl ether] gave compound **14** (59 mg, 59%) as a clear, colorless oil, [*α*]_D²⁰ = +42 (*c* = 1.1, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 2.03-1.91 (complex m, 1H), 1.93 (dd, *J* = 12.0 and 1.6 Hz, 1H), 1.87-1.35 (complex m, 8H), 1.34 (s, 3H), 1.25 (m, 1H), 1.09-0.95 (complex m, 2H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.90-0.70 (m, 1H), 0.85 (d, *J* = 7.3 Hz, 3H), 0.83 (d, *J* = 7.3 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 72.6, 56.1, 53.1, 52.3, 42.8, 42.0, 39.4, 33.5, 33.3, 31.8, 31.1, 30.2, 21.0, 18.3, 16.9; IR (neat) *v*_{max} 3442, 2949, 2924, 2855, 1456, 1374, 1220 1179, 944, 809 cm⁻¹. Due to its volatility, satisfactory MS and HRMS data could not be obtained on this material.

Concentration of fraction C [*R_f* = 0.2(3) 9:1 v/v pentane/diethyl ether] gave a clear, colorless film tentatively as compound **1** (< 1 mg, <1%). A comparison of the ¹H and ¹³C NMR spectra derived from this material with these derived from an authentic sample of viridianol⁵ clearly established that present fraction contained the natural product as the major component.

Concentration of fraction D (*R_f* = 0.3 in 7:3 v/v pentane/diethyl ether) gave a pale-yellow oil tentatively identified as a *ca.* 3:1 mixture of the diastereoisomeric forms of compound **15** (33 mg, 33%). ¹H NMR (400 MHz, CDCl₃) δ (major isomer) 3.97 (m, 1H), 1.87 (m, 2H), 1.67 (complex m, 1H), 1.55-1.00 (complex m, 12H), 1.21 (d, *J* = 6.1 Hz,

3H), 0.96 (d, $J = 6.4$ Hz, 3H), 0.94 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ (major isomer) 65.8, 52.5, 47.7, 42.8, 38.0, 37.6, 37.1, 34.8, 32.2, 32.1, 29.9, 29.4, 28.9, 25.8, 20.8; IR (neat) ν_{max} 3363, 2949, 2865, 1459, 1373, 1124, 1072, 1022, 938 cm^{-1} . Due to its volatility, satisfactory MS and HRMS data could not be obtained on this material.

Crystallographic Study on Compound 11

Crystal data

Compound 11: $\text{C}_{14}\text{H}_{24}\text{O}$, $M = 208.34$, $T = 150$ K, monoclinic, space group $\text{P}2_1$, $Z = 2$, $a = 8.7607(2)$, $b = 5.6817(1)$, $c = 13.1703(4)$ Å, $\beta = 106.551(3)^\circ$, $V = 628.40(3)$ Å³, $D_x = 1.101$ g.cm⁻³, 1364 unique data ($2\theta_{\text{max}} = 144.4^\circ$), 1332 with $I > 2.0\sigma(I)$; $R = 0.033$, $R_w = 0.086$, $S = 1.00$.

Structure Determination

Images were measured on a Nonius Kappa CCD diffractometer (MoK λ , graphite monochromator, $\lambda = 0.71073$ Å) and data extracted using the DENZO package.¹⁷ Structure solution was by direct methods (SIR92).¹⁸ The structure of compound **11** was refined using the CRYSTALS program package.¹⁹ Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC Deposition number 1863886). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

ASSOCIATED CONTENT

Supporting Information

Anisotropic displacement ellipsoid plot from the single-crystal X-ray analysis of compound **11**. ^1H and ^{13}C NMR spectra of compounds **8-15**. This material is available free-of-charge via the Internet at <http://ajc.....>

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Notes

The authors declare no competing financial interest

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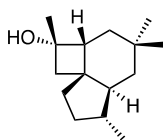
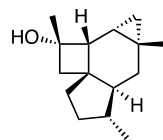
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Graphical Abstract Text:

Contrary to expectations engendered by a model study, the target sesquiterpene (+)-viridianol (**1**) is only the minor product arising from the hydrogenolysis of the ring-fused cyclopropane **13**.

Graphical Abstract:**1****13**