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SYNTHETIC STUDIES ON CLERODANE DITERPENOIDS. 4.[1] THE TOTAL SYNTHESIS OF (±)-6β-ACETOXY-2-OXOKOLAVENOOL

Hsing-Jang Liu* and Kak-Shan Shia

Department of Chemistry, University of Alberta
Edmonton, Alberta, Canada T6G 2G2

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Abstract: The first total synthesis of the title compound in racemic form has been accomplished from ketone **4**, a readily accessible compound via an intermolecular Diels-Alder approach developed previously for the synthesis of clerodane diterpenoids. © 1998 Elsevier Science Ltd. All rights reserved.

Clerodane diterpenoids are widely distributed in nature and constitute one of the largest and, yet, still rapidly growing family of secondary metabolites.[2] Of the relatively few clerodanes tested for biological activity, many were found to possess interesting antifeedant and medicinal properties and are potentially useful as insecticidal, antitumour, antifungal, antibiotic, anti-peptic ulcer and psychotropic agents.[2a] The structural complexity and biological activity associated with this class of natural products have attracted extensive effort towards their total syntheses.[3] In most of the reported syntheses, the synthetic sequence is specific to the target molecule. We have recently developed a versatile synthetic approach[4,5] which is applicable to the synthesis of a large number of target molecules with minor modifications. The key operation of this approach is the face-selective Diels-Alder reaction of an activated 4,4-disubstituted cyclohexenone, whereby the decalin nucleus present in virtually all clerodane diterpenoids can be rapidly assembled with concomitant introduction, in a correct sense, of four contiguous chiral centers often found in the natural clerodanes of the *cis*-series. This approach has been successfully applied to the total synthesis of 2-oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid (**1**)[5] involving, as a key operation, the zinc chloride catalyzed Diels-Alder addition of dienone ester **2** to *trans*-piperylene (Scheme 1). The addition occurred regio- and stereoselectively to give adduct **3** in high yield. This compound was transformed in four steps to ketone **4**[4] which served as an advanced synthetic intermediate leading eventually to the natural acid **1**.[5] To demonstrate the flexibility of this synthetic approach, we have now completed the first total synthesis, in racemic form, of the title compound **5**, a constituent of several Mexican *Stevia* species,[6] making use of ketone **4** as a common intermediate. The synthesis also substantiates the structural assignment of the natural product based mainly on spectroscopic methods.

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e-mail: Hsing-Jang.Liu@ualberta.ca

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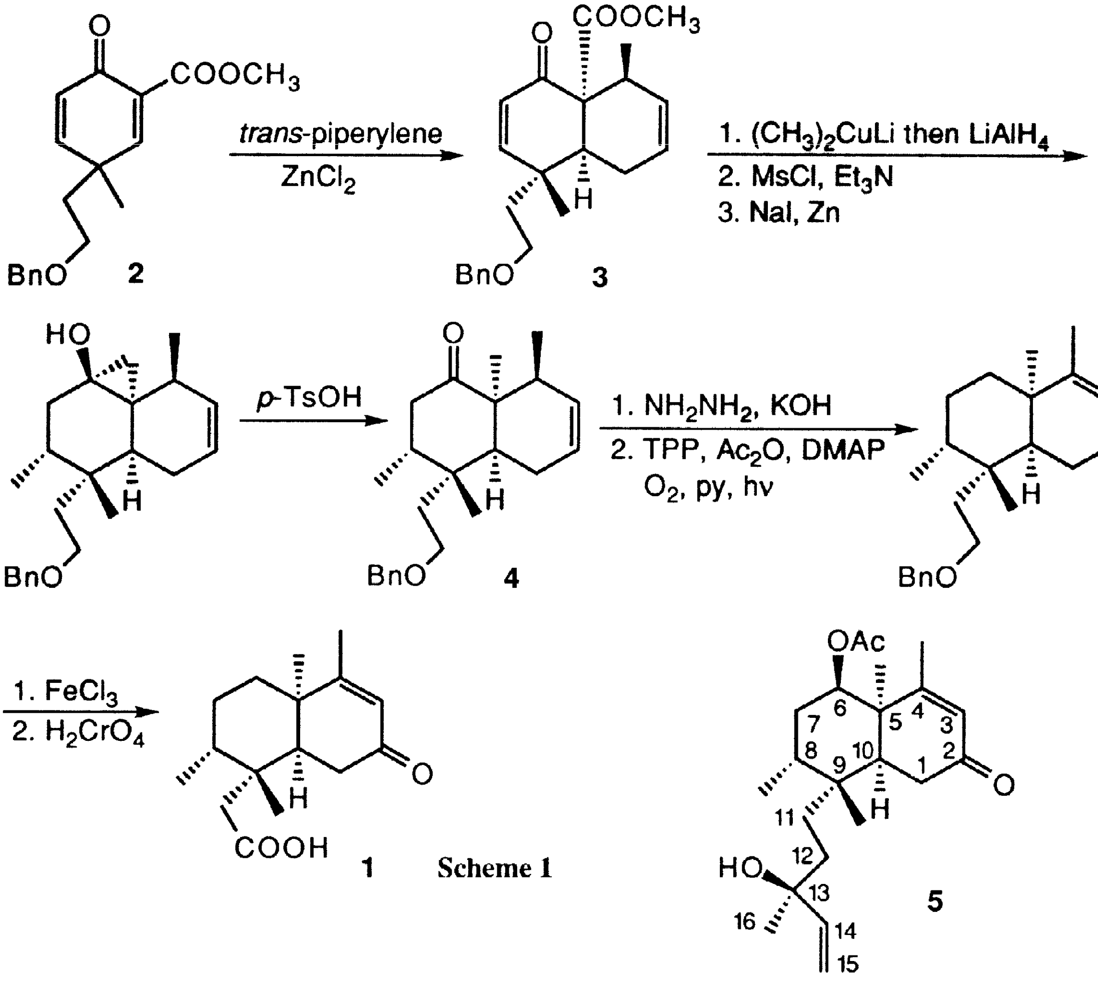
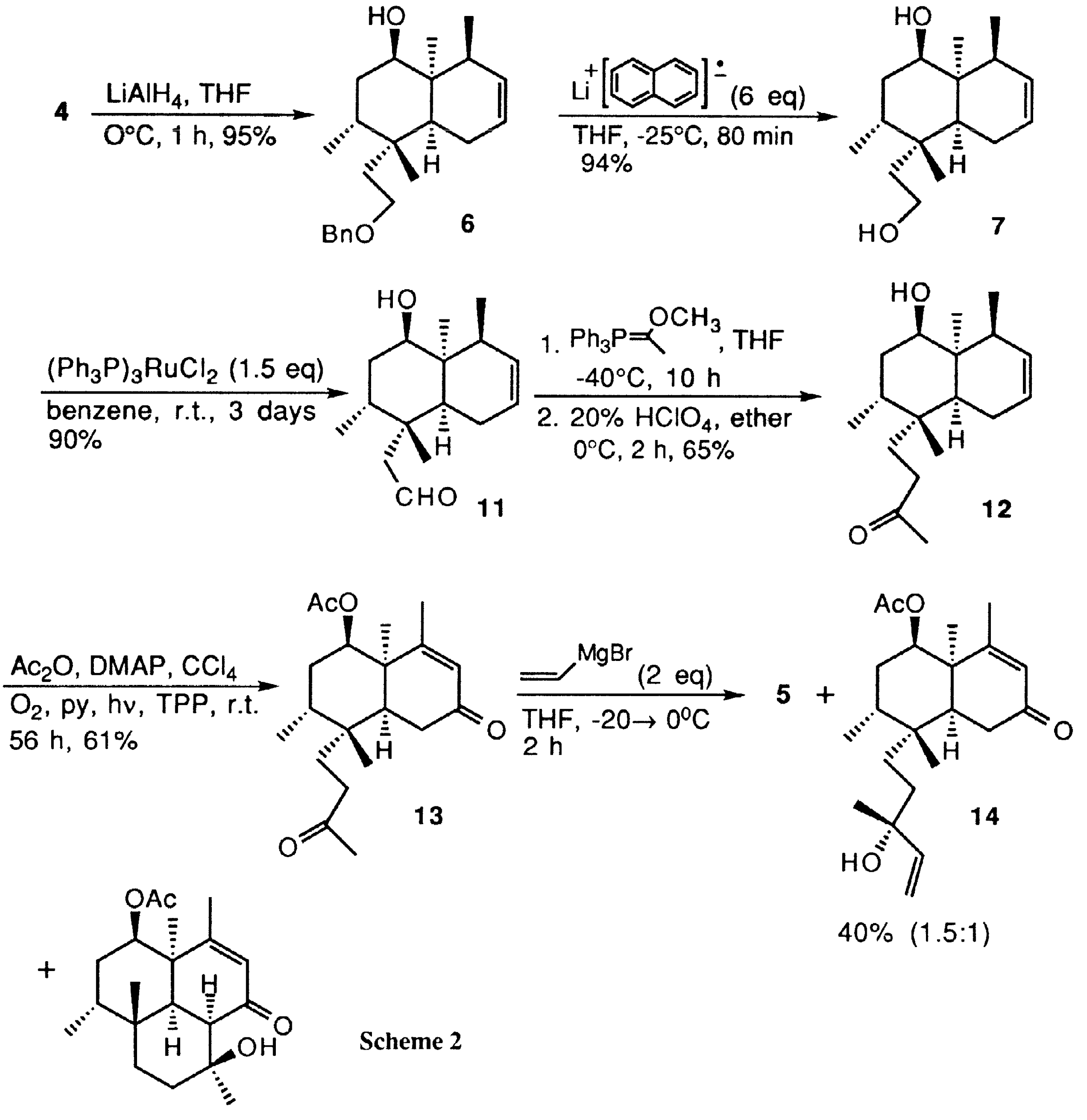


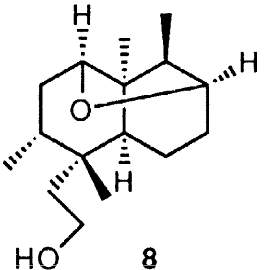
Scheme 1

Towards the synthesis of **5** which contains an acetoxy group at C_6 (clerodane numbering), ketone **4** was subjected to reduction using lithium aluminium hydride in tetrahydrofuran at 0°C (Scheme 2). Alcohol **6** was obtained in virtually quantitative yield as a single diastereomer. The addition of the hydride ion is expected to occur from the sterically less hindered convex face of the starting compound **4**, and the stereochemistry of the resulting alcohol **6** was assigned accordingly. Unfortunately, the available spectral data did not provide conclusive evidence to this assignment due to the conformational flexibility of the *cis*-decalin system. Subsequent formation of the unexpected cyclic ethers **8** and **9** from this alcohol (*vide infra*), however, lends credence to the stereochemical assignment.

Two major operations are necessary for the conversion of alcohol **6** to the target compound **5**: (1) modification of the C_9 side chain involving the incorporation of a 1-hydroxy-1-methyl-2-propenyl unit, and (2) the installation of an enone system using the existing double bond. In order to keep the number of functional groups at a minimun in each synthetic stage, thus avoiding possible complications, the former transformation was first explored. Alcohol **6** was subjected to debenzylation with lithium naphthalenide,[7] prepared *in situ* from lithium and naphthalene, in tetrahydrofuran at -25°C to give diol **7** in 94% yield. This newly developed procedure for debenzylation is far superior to several conventional methods explored. The reaction with ferric chloride in dichloromethane,[5,8] for example, gave only the cyclization products **8** and **9**. Although the desired transformation could also be effected using lithium in ethylamine at 0°C, the reaction was not highly



Scheme 2



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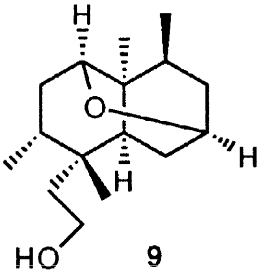

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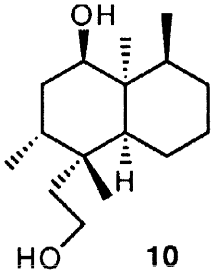

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reproducible; diol **7** was obtained in 87-14% yield along with the over-reduced product **10** in 6-81% yield.

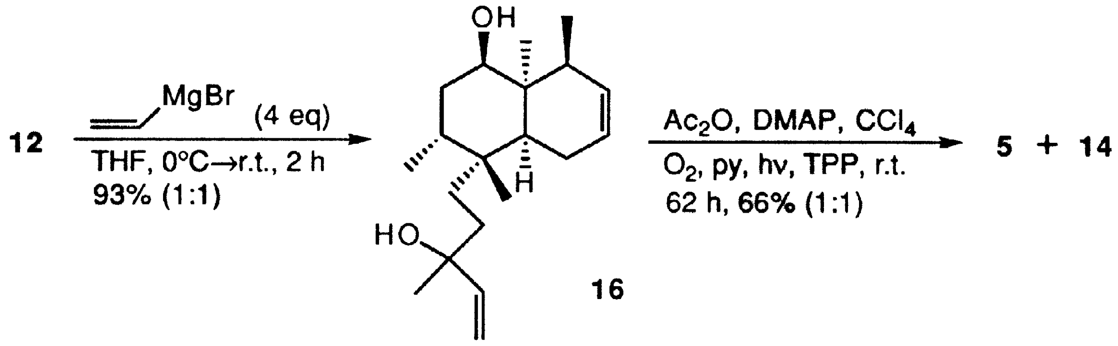
The next crucial step according to the synthetic scheme was to oxidize the primary hydroxyl of diol **7** selectively to form an aldehyde. Most of the commonly applied reagents oxidize the primary and secondary alcohols at comparable rates with preference for the secondary one. Several methods have been reported that permit the oxidation of secondary alcohols[9] in the presence of primary ones. There are only few efficient methods available for the preferential oxidation of primary alcohol over a secondary one.[10] Among these, $RuCl_2(PPh_3)_3$-benzene system[10c] has been reported to be highly effective for the selective oxidation of primary hydroxyls. Thus, diol **7** was subjected to oxidation with dichlorotris(triphenylphosphine)ruthenium (1.5 eq) in dry benzene at room temperature. The reaction was found to be very clean but quite slow. After 72 h, only 65% conversion took place. However, the desired hydroxy aldehyde **11** was produced virtually as the only product in 90% yield based on the consumed starting material. The reaction rate did not show any significant improvement over an extended period of reaction time (4 days) with additional $RuCl_2(PPh_3)_3$ (2 eq).

The introduction of the required "butenol" unit began with a Wittig reaction. α-Methoxyethyltriphenylphosphonium chloride[11] was deprotonated with *n*-butyllithium in tetrahydrofuran at -78°C to form the corresponding ylide, resulting in a blood-red solution. Upon treatment with this Wittig reagent at -40°C for 10 h, hydroxy aldehyde **11** was converted to an unstable enol ether which, without purification, was hydrolyzed in a mixture of aqueous 20% perchloric acid and ether (1:1) at 0°C. After 2 h, the desired product **12** was formed in 65% yield.

At this stage, the incorporation of the enone moiety present in the target molecule **5** was carried out via a photochemical process. Photooxygenation of **12** with oxygen and 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine in carbon tetrachloride in the presence of acetic anhydride, pyridine, and 4-dimethylaminopyridine[12] gave the desired enedione **13** in 61% yield. The regioselectivity observed for the photooxygenation reaction was somewhat unusual. Instead of forming an enone system with a less substituted double bond following the "normal" regiochemical course of photooxygenation, the double bond moved towards the carbon center possessing a greater number of substituents. The unusual regiochemistry in the present case was nevertheless quite expectable based on the studies on several structurally closely related compounds in this series.[4,5] However, exactly what controls the regiochemistry is not fully understood.

The final step of the synthesis was to introduce a vinyl group to the saturated ketone carbonyl. Vinylmagnesium bromide was used to effect this transformation. Treatment of enedione **13** with vinylmagnesium bromide (2 eq) in tetrahydrofuran at -20°C for 30 min and then at 0°C for 1.5 h gave a mixture of two epimeric products. This mixture could not be separated by flash chromatography on silica gel. Its ^1H nmr spectrum showed two sets of signals in 1.5:1 ratio and the ratio was enhanced from 1.5:1 to 4:1 by a single preparative thin layer chromatography. The major signals were found to be in good agreement with those reported for the natural clerodanoid **5**.[6] By inference, the minor set of signals could be readily attributed to its epimer **14**. Due to the limited quantity of the material, a further separation of these two epimers could not be carried out. Although there was a very modest control of the stereochemistry at a remote center, the yield of the addition products was quite low (40% in total), due to the highly competitive intramolecular aldol reaction leading to the undesired tricyclic hydroxy enone **15**, which was obtained in 35% yield.

In order to circumvent the formation of **15**, an alternative approach was explored. This approach furnished eventually an equal amount of the target compound **5** and its epimer **14**. Nevertheless, the overall yield of **5** could be improved considerably. In this approach (Scheme 3), keto alcohol **12** was first treated with an excess of vinylmagnesium bromide in tetrahydrofuran at room temperature for 2 h. The resulting inseparable mixture of diols **16** (1:1 93% yield) was then subjected to photooxygenation under similar conditions used previously for the transformation of **12** to **13**. In this way, the natural keto alcohol **5** and its C_{13} epimer **14** were obtained in 1:1 ratio and in 66% yield. High performance liquid chromatography (HPLC) of this mixture resulted in the isolation of (±)-**5** in pure form.



Scheme 3

In conclusion, the first total synthesis of (±)-6β-acetoxy-2-oxokolavenool (**5**) has been accomplished in seven steps from ketone **4** which also served as an advanced intermediate previously in the total synthesis of the natural acid **1**. The present work lends support to the structure assigned to the natural clerodanoid **5** and demonstrates the flexibility of our approach to the synthetic challenge presented by the large family of clerodane diterpenoids.

Experimental

General

Fourier transform infrared spectra (ir) were recorded on a Nicolet 7199 or Nicolet MX-1 FTIR spectrophotometer. Proton nuclear magnetic resonance (^1H nmr) spectra were recorded on a Bruker WH-200, Bruker WH-300, Bruker WH-400 or Bruker AM-400 spectrometer using deuterochloroform as solvent unless otherwise stated. Carbon-13 nuclear magnetic resonance (^{13}C nmr) spectra were recorded on a Bruker WH-300 (75 MHz) NMR spectrometer, and were obtained as solutions in deuterochloroform as the internal standard setting the central peak at 77.00 ppm. Carbon-13 multiplicities were derived from Carr-Purcell-Meiboom-Gill spin echo *J*-modulated experiments (APT or Attached Proton Test).[13] Methyl and methine groups are shown as signals possessing an antiphase (a) with respect to the deuterochloroform signal, whereas methylene groups and quaternary carbons appear in phase (p) with it. High resolution electron impact mass spectra (hrms) were recorded using an A.E.I. model MS-50 mass spectrometer. Chemical ionization mass spectra (cims) were recorded on an A.E.I. model MS-12 mass spectrometer, using ammonia as the reagent gas. A Hitachi L-6200 system was used for HPLC. Solvents were distilled under argon from appropriate drying agents before use. Tetrahydrofuran (THF), benzene and diethyl ether were freshly distilled from a blue or purple solution of sodium benzophenone ketyl. Pyridine and carbon tetrachloride were distilled from calcium hydride. Flash chromatography was used routinely for purification and separation of product mixtures, using silica gel (Merck) of 230-400 mesh. All solvents were distilled prior to use for chromatography, and concentrations of solvent systems are given by volumes.

(1S*, 2R*, 4R*, 5R*, 6S*, 10S*)-5-(2-Benzyloxyethyl)-1,4,5,10-tetramethylbicyclo-[4.4.0]dec-8-en-2-ol (6)

To a suspension of lithium aluminum hydride (9.2 mg, 0.23 mmol) in THF (10 mL) at 0°C under an atmosphere of argon, was added a solution of compound **4** (40 mg, 0.12 mmol) in THF (3 mL) dropwise. The reaction mixture was stirred for 1 h at 0°C. Water (3 mL) was then added to quench the reaction and the resulting mixture acidified with 1 M aqueous hydrochloric acid. The aqueous solution was extracted with ether (2 x 10 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography of the resulting residue with ethyl acetate and hexane (10:90) gave **6** (38 mg, 95% yield) as a colorless oil: ir (CH_2Cl_2 cast) 3579 (OH, sharp) and 3487 (OH, broad), 735 and 697 cm^{-1} (C-H bending, aromatic); ^{1}H nmr (300 MHz) δ 7.33 (m, 5 H, aromatic H), 5.79 (dm, J = 10 Hz, 1 H, -CH=CH-), 5.56 (ddd, J = 10, 5, 2 Hz, 1 H, -CH=CH-), 4.55 (d, J = 12 Hz, 1 H, -OCHHPh), 4.49 (d, J = 12 Hz, 1 H, -OCHHPh), 3.71 (br s, 1 H, -CHOH), 3.67 (ddd, J = 11, 9, 5 Hz, 1 H, -CHHOBn), 3.56 (ddd, J = 11, 9, 5 Hz, 1 H, -CHHOBn), 2.30-2.50 (m, 2 H), 1.98-2.21 (complex, 4 H), 1.47-1.75 (complex, 4 H), 1.15 (d, J = 7.5 Hz, 3 H, C-10 CH_3), 1.12 (s, 3 H, C-1 CH_3), 1.03 (s, 3 H, C-5 CH_3), 0.87 (d, J = 7 Hz, 3 H, C-4 CH_3); ^{13}C nmr (APT) δ 138.6 (p), 132.3 (a), 128.7 (a), 128.4 (a, 2 x aromatic C), 127.7 (a, 2 x aromatic C), 127.6 (a), 73.3 (a), 73.2 (p), 67.7 (p), 41.9 (a), 40.7 (a), 39.6 (p), 38.7 (p), 35.8 (p), 35.3 (p), 30.5 (a), 28.4 (p), 27.5 (a), 26.4 (a), 15.6 (a), 15.1 (a); hrms $[M-C_5H_8]^+$ 274.1927 (calcd. for $C_{18}H_{26}O_2$: 274.1932); cims $[M+NH_4]^+$ 360.

(1S*, 2R*, 4R*, 5R*, 6S*, 10S*)-5-(2-Hydroxyethyl)-1,4,5,10-tetramethylbicyclo[4.4.0]-dec-8-en-2-ol (7)

To a solution of naphthalene (0.49 g, 3.84 mmol) in THF (14 mL), was added lithium metal (23 mg, 3.29 mmol) in small pieces. The reaction mixture was stirred at room temperature under an argon atmosphere until lithium metal was completely dissolved (~3 h). The resulting dark green solution of lithium naphthalenide was then cooled to -25°C, followed by addition of a solution of alcohol **6** (188 mg, 0.55 mmol) in THF (5 mL) dropwise over 5 min. The resulting mixture was stirred at -25°C for 80 min. Saturated aqueous ammonium chloride (3 mL) and water (4 mL) were then added. The resulting solution was extracted with ether (3 x 20 mL). The combined extracts were washed with water and brine, dried over magnesium sulfate, filtered and concentrated. The crude product was then purified by flash chromatography with ethyl acetate in hexane (8-15%) to give product **7** (130 mg, 94% yield) as a colorless oil: ir (CH_2Cl_2 cast) 3387 cm^{-1} (OH broad); ^{1}H nmr (300 MHz) δ 5.80 (dm, J = 10 Hz, 1 H, -CH=CH-), 5.75 (ddd, J = 10, 4, 2 Hz, 1 H, -CH=CH-), 3.87 (ddd, J = 11, 11, 5.5 Hz, 1 H, -CHHOH), 3.75 (ddd, J = 11, 11, 5.5 Hz, 1 H, -CHHOH), 3.74 (dd, J = 4.5, 3 Hz, 1 H, C-2 H), 2.38 (m, 1 H), 1.99-2.24 (complex, 4 H), 1.47-1.76 (complex, 6 H), 1.17 (s, 3 H, C-1 CH_3), 1.15 (d, J = 7.5 Hz, 3 H, C-10 CH_3), 1.02 (s, 3 H, C-5 CH_3), 0.87 (d, J = 7 Hz, 3 H, C-4 CH_3); ^{13}C nmr (APT) δ 132.3 (a), 128.7 (a), 73.3 (a), 60.2 (p), 42.0 (a), 40.7 (a), 39.7 (p), 39.2 (p), 38.9 (p), 35.2 (p), 30.5 (a), 28.4 (p), 27.6 (a), 26.4 (a), 15.6 (a), 15.1 (a); hrms M^+ 252.2089 (calcd. for $C_{16}H_{28}O_2$: 252.2089), $[M-H_2O]^+$ 234.1983 (calcd. for $C_{16}H_{26}O$: 234.1983).

(1S*, 2R*, 4R*, 5R*, 6S*, 10S*)-5-(2-Oxoethyl)-1,4,5,10-tetramethylbicyclo[4.4.0]dec-8-en-2-ol (11)

To a solution of **7** (70 mg, 0.28 mmol) in dry benzene (8 mL) under argon, was added $RuCl_2(PPh_3)_3$ (0.40 g, 0.42 mmol) in one portion. After being stirred for 3 days at room temperature, the solution turned black and precipitation occurred. The resulting mixture was diluted with ether and passed through a short silica gel column to remove black solids. Concentration gave the crude product, which was subjected to flash chromatography with ethyl acetate (5%) in hexane to furnish the aldehyde **11** (41 mg, 90% yield based on consumed starting material) as a colorless oil: ir (CH_2Cl_2 cast) 3572 (OH sharp), 3488 (OH broad), 2734 (C-H aldehyde) and 1717 cm^{-1} (C=O aldehyde); ^1H nmr (300 MHz) δ 9.98 (dd, J = 4, 1.5 Hz, 1 H, -CH=O), 5.81 (dm, J = 10 Hz, 1 H, -CH=CH-), 5.58 (ddd, J = 10, 4, 2, Hz, 1 H, -CH=CH-), 3.75 (dd, J = 4.5, 3 Hz, 1 H, -CHOH), 2.93 (ddd, J = 16.5, 4, 1.5 Hz, 1 H, -CHHCH=O), 2.31-2.51 (complex, 2 H, mixed with -OH), 2.29 (dd, J = 16.5, 1.5 Hz, 1 H, -CHHCH=O), 2.11-2.25 (complex, 3 H), 1.94 (ddd, J = 11, 6.5, 1 Hz, 1 H), 1.66 (ddd, J = 14, 2, 2 Hz, 1 H), 1.59 (dd, J = 6, 3 Hz, 1 H), 1.27 (d, J = 0.5 Hz, 3 H, C-1 CH_3), 1.16 (d, J = 7.5 Hz, 3 H, C-10 CH_3), 1.08 (s, 3 H, C-5 CH_3), 0.87 (d, J = 7 Hz, 3 H, C-4 CH_3); ^{13}C nmr (APT) δ 204.5 (a), 132.3 (a), 128.3 (a), 72.7 (a), 50.5 (p), 43.5 (a), 40.2 (a), 39.7 (p), 39.1 (p), 35.1 (p), 30.2 (a), 28.4 (p), 27.4 (a), 27.4 (a), 15.6 (a), 15.0 (a); hrms $[M-H_2O]^+$ 232.1823 (calcd. for $C_{16}H_{24}O$: 232.1827), $[M-CH_3CHO]^+$ 206.1673 (calcd. for $C_{14}H_{22}O$: 206.1670); cims $[M+NH_4]^+$ 268.2, $[M+H]^+$ 251.1.

Further elution with 15% ethyl acetate in hexane gave starting material **7** (25 mg, 35%).

(1S*, 2R*, 4R*, 5R*, 6S*, 10S*)-5-(3-Oxobutyl)-1,4,5,10-tetramethylbicyclo[4.4.0]dec-8-en-2-ol (12)

n-Butyllithium (0.32 mL, 1.6 M in hexanes, 0.5 mmol) was added to a solution of 1-methoxyethyltriphenylphosphonium chloride (0.19 g, 0.54 mmol) in THF (8 mL) at -42°C. After stirring at -40°C for 20 min (solution turned homogeneous with a blood-red color), a solution of aldehyde **11** (30 mg, 0.12 mmol) in THF (3 mL) was added slowly. The resulting mixture was stirred at -40°C for 10 h, and then water was added to quench the reaction. The aqueous solution was extracted with ether (3 x15 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated. Without purification the crude Wittig product was dissolved in a solution of aqueous 20% perchloric acid and distilled ether (1:1, 8 mL) and stirred at 0°C for 2 h. The reaction was quenched by addition of 0.5 N NaOH (2 mL) and diluted with ether (8 mL). The aqueous layer was extracted with ether (3 x 15 mL) and the combined extracts were washed with water, dried over $MgSO_4$, and concentrated. Flash chromatography (5-8% ethyl acetate in hexane) of the residue afforded ketone **12** (22 mg, 65% yield) as a colorless oil: ir (CH_2Cl_2 cast) 3572 (OH) and 1714 cm^{-1} (C=O, ketone); ^1H nmr (300 MHz) δ 5.80 (dm, J = 10.5 Hz, 1 H, -CH=CH-), 5.56 (ddd, J = 10.5, 5, 2 Hz, 1 H, -CH=CH-), 3.70 (br s, 1 H, -CHOH), 2.31-2.57 (complex, 3 H), 2.14 (s, 3 H, CH_3C=O), 1.95-2.24 (complex, 3 H), 1.62-1.77 (m, 2 H), 1.45-1.58 (m, 4 H), 1.13 (d, J = 7.5 Hz, 3 H, C-10 CH_3), 1.06 (s, 3 H, C-1 CH_3), 0.92 (s, 3 H, C-5 CH_3), 0.83 (d, J = 7 Hz, 3 H, C-4 CH_3); ^{13}C nmr (APT) δ 209.3 (p), 132.2 (a), 128.6 (a), 73.2 (a), 41.2 (a), 40.7 (a), 39.6 (p), 38.9 (p), 35.2 (p), 30.4 (a), 30.2 (a), 29.7 (p), 28.4 (p), 27.0 (a), 26.2 (a), 15.4 (a), 15.0 (a); hrms M^+ 278.2235 (calcd. for $C_{18}H_{30}O_2$: 278.2245), $[M-H_2O]^+$ 260.2134 (calcd. for $C_{18}H_{28}O$: 260.2140).

(1S*, 6R*, 7R*, 9R*, 10R*)-7-Acetoxy-10-(3-Oxobutyl)-5,6,9,10-tetramethylbicyclo-[4.4.0]dec-4-en-3-one (13)

A solution of compound **12** (20 mg, 0.07 mmol), 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (5 mg), acetic anhydride (0.07 mL, 0.35 mmol), pyridine (0.06 mL, 0.35 mmol), and 4-dimethylaminopyridine (3 mg) in carbon tetrachloride (40 mL) was placed in a photooxygenation apparatus and irradiated with two 200 W tungsten lamps for 56 h. During this period of time a gentle stream of oxygen was bubbled through the reaction mixture. After stopping the irradiation, bubbling was continued for another 18 h. The solution was then concentrated and the residue redissolved in ether (30 mL). The ethereal solution was washed with 1 M aqueous HCl (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to give the crude product, which was purified by flash chromatography on silica gel (35% ethyl acetate in hexane) to afford enone ester **13** (15 mg, 61% yield) as a colorless oil: ir (CCl_4 solution) 1742 (C=O, ester), 1721 (C=O, ketone) and 1671 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz) δ 5.95 (br s, 1 H, -C=CHC=O), 5.08 (br s, 1 H, -CHOAc), 2.72 (dd, *J* = 16.5, 12.5 Hz, 1 H, $-CH_{\beta}HC=O$), 2.42 (m, 3 H), 2.19 (s, 3 H, $CH_3C=O$, ketone), 1.85-2.07 (complex, 4 H), 1.96 (br s, 3 H, CH_3COO-), 1.93 (br s, 3 H, $CH_3C=CHC=O$), 1.51-1.70 (complex, 2 H), 1.33 (s, 3 H, C-6 CH_3), 0.96 (br s, 6 H, C-9 CH_3 and C-10 CH_3); hrms M$^+$ 334.2134 (calcd. for $C_{20}H_{30}O_4$: 334.2144), [M-CH_3COOH]$^+$ 274.1925 (calcd. for $C_{18}H_{26}O_2$: 274.1932).

(±)-6β-Acetoxy-2-oxokolavenool (5), (5R*, 6R*, 8R*, 9R*, 10S*, 13R*)-6-Acetoxy-13-hydroxy-2-oxocleroda-3,14-diene (14) and (1R*, 5R*, 6R*, 8S*, 9R*, 12S*, 13S*)-6-Acetoxy-12-hydroxy-4,5,8,9,12-pentamethyltricyclo[7.3.1.0^{5,13}]tridec-3-en-2-one (15) from Enedione 13

To a solution of compound **13** (4.1 mg, 0.012 mmol) in THF (3 mL) at -20°C under an atmosphere of argon, was added vinylmagnesium bromide (24 μL, 1 M in THF, 0.024 mmol). The mixture was stirred at -20°C for 30 min and then at 0°C for an additional 1.5 h. Water (1 mL) and saturated aqueous NH_4Cl (1 mL) were added followed by extraction with ether (3 x 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was subjected to flash chromatography with 20% ethyl acetate in hexane to afford **15** (1.4 mg, 35% yield) as a white solid: ir (CH_2Cl_2 cast) 3423 (OH, broad), 1737 (C=O, ester) and 1643 cm^{-1} (C=O, enone); ^{1}H nmr (300 MHz) δ 6.29 (br s, 1 H, -OH), 5.77 (br d, *J* = 1 Hz, 1 H, -C=CHC=O), 4.96 (dd, *J* = 13, 4 Hz, 1 H, -CHOAc), 2.85 (dd, *J* = 4, 1 Hz, 1 H, $-CH_{\alpha}C=O$), 2.12 (s, 3 H, -OAc), 2.11 (d, *J* = 1.5 Hz, 3 H, $CH_3C=CHC=O$), 1.89-2.01 (complex, 3 H), 1.51-1.62 (complex, 5 H), 1.32 (s, 3 H, C-12 CH_3), 1.30 (s, 3 H, C-5 CH_3), 1.11 (d, *J* = 7 Hz, 3 H, C-8 CH_3), 0.97 (s, 3 H, C-9 CH_3); hrms M$^+$ 334.2143 (calcd. for $C_{20}H_{30}O_4$: 334.2144).

Further elution gave a 1.5:1 mixture of *cis*-clerodanes **5** and **14** (1.7 mg, 40% yield) as a colorless oil: ir (CCl_4 solution) 3600 (OH), 1741 (C=O, ester) and 1670 cm^{-1} (C=O, enone); hrms M$^+$ 362.2452 (calcd. for $C_{22}H_{34}O_4$: 362.2457), [M-H_2O]$^+$ 344.2352 (calcd. for $C_{22}H_{32}O_3$: 344.2351), [M-HOAc]$^+$ 302.2240 (calcd. for $C_{20}H_{30}O_2$: 302.2245), [M-H_2O-HOAc]$^+$ 284.2134 (calcd. for $C_{20}H_{28}O$ 284.2140). The ^{1}H nmr spectrum (300 MHz) displayed a major set of signals identical to those observed for pure isomer **5** (see below) and a minor set of signals for isomer **14**: δ 5.95 (br s, 1 H, -C=CHC=O), 5.87 (dd, *J* = 17.5, 11 Hz, 1 H, C-14 H), 5.21 (dd, *J* = 17.5, 1 Hz, 1 H, C-15 H_t), 5.08 (dd, *J* = 11, 1 Hz, 1 H, C-15 H_c), 5.07 (br s, 1 H,

-CHOAc), 2.71 (dd, J = 17, 10.5 Hz, 1 H, -CH$_\beta$HC=O), 2.42 (m, 1 H, -CH$_\alpha$HC=O), 1.95 (br s, 3 H, -OAc), 1.93 (br s, 3 H, C-4 CH_3), 1.36 (s, 3 H, C-5 CH_3), 1.29 (s, 3 H, C-13 CH_3), 0.95 (br s, 6 H, C-8 CH_3 and C-9 CH_3).

(1S*, 2R*, 3'R*, 4R*, 5R*, 6S*, 10S*)- and (1S*, 2R*, 3'S*, 4R*, 5R*, 6S*, 10S*)-5-(3'-hydroxy-3'-vinylbutyl)-1,4,5,10-tetramethylbicyclo[4.4.0]dec-8-en-2-ol (16)

To a solution of compound **12** (12 mg, 0.043 mmol) in THF (5 mL) at 0°C under an argon atmosphere, was added vinylmagnesium bromide (216 µL, 1 M in THF, 0.216 mmol). The resulting mixture was allowed to warm up and stirred at room temperature for 2 h. The mixture was diluted with ether (6 mL). Water (3 mL) and saturated aqueous NH_4Cl (2 mL) were then added. The aqueous layer was extracted with ether (2 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residual oil was purified by flash chromatography on silica gel with 10% ethyl acetate in hexane to give a 1:1 mixture of diastereomeric diols **16** (12.2 mg, 93% yield) as a colorless oil: ir (CH_2Cl_2 cast) 3425 (OH, broad) cm^{-1}; ^{1}H nmr (300 MHz) δ 5.84 (dd, J = 17.5, 10.5 Hz, 1 H, -CH=CH_2), 5.82 (dd, J =17.5, 10.5 Hz, 1 H, -CH=CH_2), 5.80 (m, 1 H, -CH=CH-), 5.78 (m, 1 H, -CH=CH-), 5.54 (dm, J = 10 Hz, 2 H, 2 x -CH=CH-), 5.18 (d, J = 17.5 Hz, 2 H, 2 x -CH=CHH), 5.03 (d, J = 10.5 Hz, 2 H, 2 x -CH=CHH), 3.68 (br s, 2 H, 2 x -CHOH), 1.27 (s, 3 H, -CH_3), 1.26 (s, 3 H, -CH_3), 1.12 (d, J = 7 Hz, 3 H, -CH_3), 1.10 (s, 3 H, -CH_3), 1.09 (d, J = 7.5 Hz, 3 H, -CH_3), 1.08 (s, 3 H, -CH_3), 0.93 (s, 3 H, -CH_3), 0.92 (s, 3 H, -CH_3), 0.83 (d, J = 7 Hz, 3 H, -CH_3), 0.82 (d, J = 7 Hz, 3 H, -CH_3); hrms $[M-H_2O]^+$ 288.2453 (calcd. for $C_{20}H_{32}O$: 288.2451); cims $[M+NH_4]^+$ 324.2, $[M-H_2O+NH_4]^+$ 306.4.

(±)-6β-Acetoxy-2-oxokolavenool (5)

A solution of diols **16** (12 mg, 0.04 mmol), acetic anhydride (0.015 mL, 0.16 mmol), pyridine (0.016 mL, 0.2 mmol), a catalytic amount of 4-dimethylaminopyridine, and 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (3 mg) in dry carbon tetrachloride (20 mL) was saturated with oxygen for 10 min and then irradiated with two 200 W tungsten lamps for 62 h. During this period of time, a gentle stream of oxygen was bubbled through the reaction mixture. After irradiation was stopped, oxygen was kept bubbling for another 10 h. The reaction mixture was then diluted with carbon tetrachloride (15 mL) and washed sequentially with saturated aqueous sodium bicarbonate (2 x 5 mL), 1 M hydrochloric acid (2 x 5 mL), saturated aqueous copper sulfate (1 x 5 mL) and saturated aqueous sodium chloride. After being dried over $MgSO_4$, the organic solution was filtered and concentrated. The resulting residue was subjected to flash chromatography on silica gel using 5-20% ethyl acetate in *n*-hexane as eluent to afford a 1:1 mixture of *cis*-clerodane **5** and its epimer **14** (9.4 mg, 66% yield). This mixture was further purified by HPLC using a LiChrospher DIOL column (Merck, LiChroCART 250-4, LiChrospher 100 DIOL (5 µm), 4 mm x 250 mm) under following conditions: eluent: ethyl acetate/*n*-hexane (20/80; v/v); flow rate: 1 mL/min; detection: UV (254 nm). The desired *cis*-clerodane **5** (1.1 mg), which showed a retention time of 28.72 min, was obtained as a colorless oil: ir (CCl_4 solution) 3600 (OH), 1741 (C=O, ester) and 1670 cm^{-1}(C=O, enone); ^{1}H nmr (300 MHz): δ 5.94 (br s, 1 H, -C=CHC=O), 5.88 (dd, J = 17.5, 11 Hz, 1 H, C-14 H), 5.21 (dd, J = 17.5, 1 Hz, 1 H, C-15 H_t), 5.07 (dd, J = 11, 1 Hz, 1 H, C-15 H_c), 5.06 (br s, 1 H, -CHOAc), 2.69 (dd, J = 17, 10.5 Hz, 1 H, -CH$_\beta$HC=O), 2.40 (m, 1 H, -CH$_\alpha$HC=O), 2.15 (m, 1H), 1.95 (br s, 3 H, CH_3COO-), 1.93 (br s, 3 H, C-4 CH_3), 1.41-1.85 (complex, 8 H), 1.32 (s, 3 H, C-5 CH_3), 1.29 (s, 3 H, C-13 CH_3), 0.95 (br s, 6 H, C-8 CH_3 and C-9 CH_3); hrms M^+

362.2452 (calcd. for $C_{22}H_{34}O_4$: 362.2457). Compound **14**, which showed a retention time of 30.27 min, was not obtained in pure form.

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References and Notes

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