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Enantiospecific Synthesis of (+)-(*1S,2R,6S*)-1,2-Dimethylbicyclo[4.3.0]nonan-8-one and (–)-7-Epibakkenolide-A[1]

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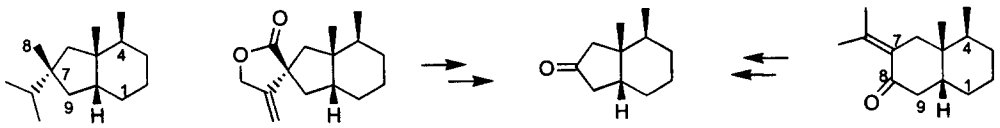
Abstract: Synthesis of the chiral bicyclic ketone mentioned in the title starting from R-carvone, and its elaboration to 7-epibakkenolide-A is described. Conjugate addition of dimethyl copperlithium to R-carvone followed by alkylation of the intermediate enolate generated the allylated compound **6**, which was transformed into the diketone **12** via a sequence of reactions comprising regiospecific Wacker oxidation, ozonation-Criegee rearrangement as key reactions. Intramolecular aldol condensation followed by catalytic hydrogenation converted the diketone **12** into the bicyclic ketone (+)-**3**, the optical antipode of the compound derived from the sesquiterpenes bakkenolide-A and fukinone. A 5-*exo*-dig radical cyclisation based strategy transformed the bicyclic ketone **3** into chiral 7-epibakkenolide-A.

Bakkanes (**1**) are an interesting class of tricyclic sesquiterpenes, believed to be biogenetically derived from eremophilanes, containing an interesting α-spiro-β-methylene-γ-butyrolactone moiety fused to a bicyclo[4.3.0]-nonane carbon framework, and shown to possess biologicial properties, such as cytotoxic activity, anti-feedant properties, etc.[2,3] The simplest member of the class, bakkenolide-A (**2**) was isolated[4] by Kitahara and coworkers from the buds of *Petasites japonicus* subsp. *Gigantius* Maxim., native to the northern parts of Japan along with a few other higher oxygenated analogues, and named after the local name (*Bakke*) of the species, as bakkenolides. Interestingly, at the same time Hayashi *et al.* also reported[4] the isolation of the same set of compounds and named them as fukinanes, after the Japanese name (*Fuki*) of the plant. The structures of bakkenolides were established based on the spectral studies and chemical degradation of bakkenolide-A to (*1R,2S,6R*)-1,2-dimethyl-bicyclo[4.3.0]nonan-8-one [(–)-**3**], which was found to be identical to that obtained by degradation of the eremophilane fukinone (**4**), thus establishing the absolute configuration of bakkanes. It was confirmed by the enan-



Bakkane (**1**) Bakkenolide-A (**2**) (-)-**3** Fukinone (**4**)

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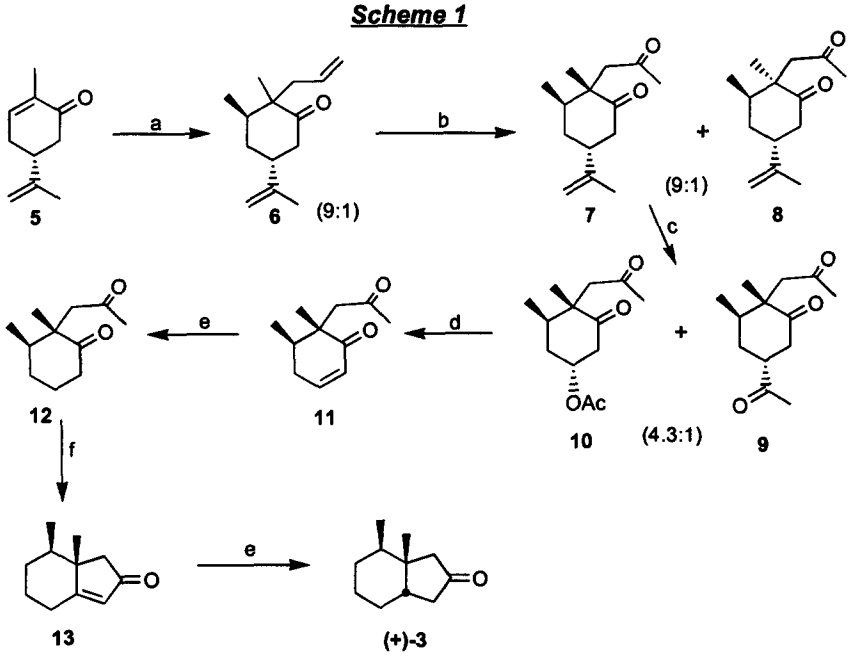
tiospecific synthesis of bakkenolide-A by Greene and coworkers.[6d] On the basis of their biogenetic relationship, the carbon framework of bakkane was numbered following that of eremophilane. Later Sorm *et al.* reported[5] the isolation of homogynolides-A and -B, the angelyl and tiglyl derivatives of 2- and 3-hydroxybakkenolide-A, respectively, from *Homogyne alpina*, possessing the antifeedant activity. The novel structure comprising of a α-spiro-β-methylene-γ-butyrolactone moiety coupled with the biological properties made the bakkanes interesting synthetic targets.[6-9] In continuation of our interest in the synthesis of bakkanes, herein we report an enantiospecific synthesis of the bicyclic ketone (+)-**3** mentioned in the title, the optical antipode of the compound derived from bakkenolide-A and fukinone, and its further elaboration to (–)-7-epibakkenolide-A.

The synthetic sequence starting from R-carvone (**5**) is depicted in Scheme 1. First, the two stereogenic vicinal centres containing the two *cis* oriented methyl groups were created employing a 1,4-conjugate addition-alkylation sequence. Thus, addition of lithium dimethylcopper to R-carvone (**5**)[7b] followed by alkylation of the resulting enolate with allyl bromide in the presence of HMPT furnished a 9:1 epimeric mixture of the allylated compound **6**. The stereochemistry of the secondary methyl group in compound **6** was assigned on the basis of the preferred addition of the nucleophile *trans* to the isopropenyl group. In a similar manner, the stereochemistry at the quaternary carbon atom in the major isomer of **6** was assigned as S, since the substituents at both the C-3 and C-5 carbon atoms direct the incoming electrophile *trans* to the secondary methyl group in the intermediate enolate. The regiospecificity of Wacker reaction[10] in the oxidation of monosubstituted olefins was exploited for the differentiation of the two olefinic moieties in the compound **6** and conversion of the allyl group into an acetonyl

Scheme 1

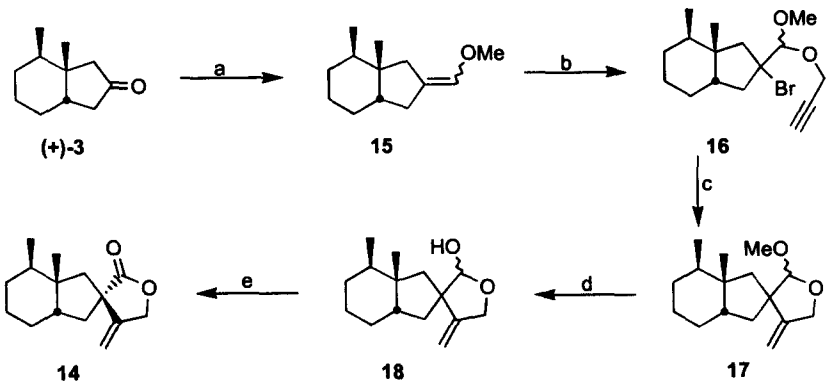


***Reagents and conditions**: (a) i. MeLi, CuI, ether, 30 min. 0 °C, ii. Allyl bromide, HMPT, 0 °C to RT, 24 h; (b) $PdCl_2$, CuCl, O_2, DMF, H_2O, RT, 24 h; (c) i. O_3/O_2, MeOH, CH_2Cl_2, -90 °C, ii. p-NO_2-C_6H_4COCl, Py, CH_2Cl_2, reflux, 20 h; (d) DBU, CH_2Cl_2, RT, 1 h; (e) 10%Pd/C, H_2, EtOAc, RT, 3 h; (f) 10% aq. KOH, MeOH, sealed tube, 120 °C, 4 h.*

group, suitable for cyclopentannulation. Consequently, oxidation of a 9:1 epimeric mixture of the compound **6** using typical Wacker conditions ($PdCl_2$, CuCl, O_2, H_2O, DMF) followed by purification on a silica gel column furnished the diketones **7** and **8**. For the degradation of the isopropenyl moiety in **7**, a Criegee rearrangement based protocol[11] was envisaged. Thus, ozonation of the diketone **7** in methanol methylene chloride medium followed by treatment of the resulting methoxyhydroperoxide with 4-nitrobenzoyl chloride and pyridine furnished a 1:4.3 mixture of the triketone **9** and the acetoxy dione **10**, which was separated by silica gel column chromatography. Elimination of the acetoxy group using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) followed by hydrogenation of the resulting enone **11** using 10% palladium over carbon as the catalyst furnished the diketone **12**, which exhibited spectral data identical[6a] to that of the racemic compound. Base catalysed intramolecular aldol condensation followed by catalytic hydrogenation of the resulting enone **13** transformed the diketone **12** into the bicyclic ketone (+)-**3**, $[\alpha]_D^{25}$ +117.3 (c 1.62, $CHCl_3$), the optical antipode[4a] of that derived from bakkenolide-A and fukinone.

After successfully synthesising the chiral bicyclic ketone (+)-**3**, attention was turned towards the synthesis of 7-epibakkenolide (**14**) employing a 5-*exo*-dig radical cyclisation based strategy.[12] The sequence is depicted in Scheme 2. Reaction of the bicyclic ketone **3** with methoxymethylenetriphenylphosphorane in THF furnished a ≈1:1 mixture of E,Z isomers of the enol ether **15**. The bromoacetalisation reaction[13] with N-bromosuccinimide (NBS) and propargyl alcohol in methylene chloride at low temperature transformed the enol ether **15** into a diastereomeric mixture of the bromoacetal **16**. The 5-*exo*-dig radical cyclisation of the bromoacetal **16** using an *in situ* generated catalytic tri-n-butyltin hydride ($^nBu_3SnCl$ and $NaCNBH_3$)[14] in the presence of a catalytic amount of AIBN in refluxing *tert*-butanol furnished a diastereomeric mixture of the sprio acetal **17**. Hydrolysis of the acetal moiety in **17** using 3N aqueous HCl followed by oxidation of the resulting lactol **18** with pyridinium chlorochromate (PCC) furnished 7-epibakkenolide-A (**14**), $[\alpha]_D^{26}$ –24.7 (c 1.8, $CHCl_3$). Quite surprisingly, in the 270 MHz ^1H NMR spectrum in $CDCl_3$, the epibakkenolide-A (**14**) obtained in this study exhibited diagnostic signals due to olefinic, CH_2-O, *sec*- and *tert*-methyl groups identical to those of bakkenolide-A which led to a confusion.[6c] However a close comparison of the rest of the spectrum as well as that recorded in C_6D_6 revealed the difference and established the structure of epibakkenolide-A (**14**).

Scheme 2



***Reagents and conditions**: (a) $CH_3OCH_2PPh_3^+$ Cl, K^+ $^tAmO^-$, THF, RT, 8 h; (b) NBS, HC≡C-CH_2OH, CH_2Cl_2, -40 °C, 45 min; (c) $^nBu_3SnCl$, $NaCNBH_3$, AIBN, ^tBuOH, reflux, 2 h; (d) 3 N HCl, THF, 24 h, RT; (e) PCC, SiO_2, CH_2Cl_2, 4 h.*

In conclusion, we have achieved the synthesis of chiral 1,2-dimethyl-*cis*-bicyclo[4.3.0]nonan-8-one, the optical antipode of the compound derived from the sesquiterpenes bakkenolide-A and fukinone, starting from R-carvone. The ready availability of S-carvone makes the present strategy suitable for the preparation of the natural enantiomer as well. Further, the bicyclic ketone **3** was elaborated into chiral 7-epibakkenolide-A.

Experimental Section

Melting points are recorded using a Tempo melting point apparatus in capillary tubes and are uncorrected. IR spectra as thin films were recorded on a Perkin-Elmer 781 spectrophotometer. ^{1}H (60, 90, 200 and 270 MHz) and ^{13}C NMR (22.5 and 50 MHz) spectra were recorded on Varian T-60, Jeol FX-90Q, Brucker ACF-200 and WH-270 spectrometers. The chemical shifts (δ ppm) and the coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.1 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra off-resonance multiplicities, when recorded are given in parentheses. Low and High resolution mass measurements were carried out using a Jeol JMS-DX 303 GC-MS instrument using a direct inlet mode. Relative intensities of the ions are given in parentheses. Optical rotations were measured using a Jasco DIP-370 digital polarimeter and $[\alpha]_D$ values are given in the units of 10^{-1} deg cm^2 g^{-1}. Ozonolysis experiments were carried out using a Penwalt Wallace and Tierman ozonator. Hydrogenation reactions at one atmosphere pressure were carried out using a balloon. Acme's silica gel (100-200 mesh) was used for column chromatography. All small scale dry reactions were carried out using standard syringe-septum technique. Anhydrous solvents were obtained by standard procedures. AIBN was recrystallised from methanol and stored in dark. All the commercial reagents, obtained from Fluka or Merck, were used without further purification.

(2S,3R,5R)-(+)-2-Allyl-5-isopropenyl-2,3-dimethylcyclohexanone (6a): To a cold (-10 °C), magnetically stirred solution of lithium dimethylcopper [prepared from cuprous iodide (1.9 g, 10 mmol) and methyllithium in ether (20 mmol, 26 ml of a 0.765 M solution in ether)] was added a solution of R-carvone (**5**, 1.0 g, 6.66 mmol) in dry ether (15 ml) over a period of 15 min. The reaction mixture was stirred for 30 min at RT, and a mixture of allyl bromide (8.0 g, 5.6 ml, 66.1 mmol) and HMPT (1.43 g, 1.4 ml, 8 mmol) was added over 5 min. The reaction mixture was stirred for 24 h at RT, quenched with 25% aq. ammonia solution and extracted with ether (3 x 15 ml). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column, using ethyl acetate-hexane (1:48) as eluent, furnished a 9:1 epimeric mixture of the allylated compounds **6** (1.22 g, 89%) as pale yellow oil. Partial purification on a long silica gel column furnished a small amount of pure major product **6a**. $[\alpha]_D^{24}$ +37.0 (c 1.2, $CHCl_3$). IR (neat): ν_{max} 3080, 1705 (C=O), 1640 (C=C), 910, 890 (C=CH_2) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.63 (1 H, t of dd, J=17.5, 9.5 and 7.3 Hz, H-2'), 5.08 (1 H, d, J_{trans}=17.5 Hz) and 5.07 (1 H, d, J_{cis}=9.5 Hz) [H-3'], 4.79 (1 H, s) and 4.72 (1 H, s) [C=CH_2], 2.70-2.30 (5 H, m), 2.20-1.90 (2 H, m), 1.70-1.60 (1 H, m), 1.75 (3 H, s, olefinic CH_3), 1.00 (3 H, s, *tert*-CH_3), 0.91 (3 H, d, J=7.2 Hz, *sec*-CH_3). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 213.4 (s, C=O), 146.8 (s, *C*=CH_2), 133.2 (d, *CH*=CH_2), 117.0 (t, CH=*CH*$_2$), 109.7 (t, C=*C*H_2), 51.1 (s, C-2), 42.2, 41.3, 39.9, 36.0 (d), 32.2 (t), 20.4 (q), 18.3 (q) and 15.3 (q) [3 x CH_3]. Mass: m/z 206 (M^+, 10%), 191 (20, M - Me), 163 (30, M - allyl), 123 (25), 109 (40), 95 (95), 41 (100). HRMS: m/z for $C_{14}H_{22}O$, Calcd.: 206.1671. Found: 206.1679.

(2S,3R,5R) and (2R,3R,5R)-5-Isopropenyl-2,3-dimethyl-2-(2-oxopropyl)cyclohexanone (7 and 8): A suspension of palladium chloride (61 mg, 0.34 mmol) and cuprous chloride (500 mg, 5 mmol) in DMF (2.5 ml) and water (0.5

ml, 27.8 mmol) was magnetically stirred in an oxygen atmosphere, created via evacuative displacement of air using an oxygen balloon, for 1 h at RT. A solution of the 9:1 mixture of allylated compound **6** (1.03 g, 5 mmol) in 1 ml of DMF was then added, and the reaction mixture was stirred for 24 hr at RT in the oxygen atmosphere. To the reaction mixture 3 N HCl (5 ml) was added and extracted with ether (3 x 10 ml). The ether extract was washed with saturated aq. $NaHCO_3$ solution followed by brine and dried (Na_2SO_4). Evaporation of the solvent and careful chromatography of the residue on a silica gel column using ethyl acetate-hexane (1:20 to 1:10) as eluent, first furnished the diketone **8** (86 mg, 12.9%). Further elution of the column furnished the diketone **7** (775 mg, 70%) as a white solid, which was recrystallised from hexane. m.p.: 53-54 °C. $[\alpha]_D^{23}$ +6.1 (c 1.14, $CHCl_3$). IR (neat): ν_{max} 1710, 1700, 1650, 1380, 1175, 895 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 4.83 (1 H, s) and 4.75 (1 H, s) [C=CH_2], 2.78 (2 H, br s), 2.56 (2 H, br s), 2.50-2.20 (1 H, m), 2.12 (3 H, s, $COCH_3$), 1.85-1.65 (3 H, m), 1.72 (3 H, s, olefinic CH_3), 1.02 (3 H, s, *tert*-CH_3), 0.88 (3 H, d, J=7.2 Hz, *sec*-CH_3). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 211.8 (s, ring C=O), 205.5 (s, C=O), 146.3 (s, C=CH_2), 109.6 (t, C=CH_2), 49.4 (s, C-2), 49.1 (t, CH_2COCH_3), 41.1 (t, C-6), 39.5 (d, C-5), 34.4 (d, C-3), 31.7 (t, C-4), 30.2 (q, $COCH_3$), 20.0 (q), 17.8 (q) and 14.4 (q) [3 x CH_3]. Mass: m/z 222 (M^+, 5%), 165 (90), 109 (22), 95 (25), 43 (100). Anal. for $C_{14}H_{22}O_2$, Calcd.: C, 75.63%, H 9.97%. Found: C, 75.74%, H 10.19%.

(–)-(5R,6S)-5,6-Dimethyl-6-(2-oxopropyl)cyclohex-2-enone (11): To a cold (-90 °C) solution of the diketone 7 (1.0 g, 4.5 mmol), methanol (0.23 ml) and $NaHCO_3$ (100 mg) in 20 ml of CH_2Cl_2 was passed a mixture of pre-cooled ozone in oxygen until the solution turns blue in colour. The excess ozone was flushed off with oxygen. To the reaction mixture was added pyridine (1.32 g, 1.35 ml, 16.7 mmol) and freshly distilled p-nitrobenzoyl chloride (2.48 g, 13.4 mmol) and slowly warmed up to room temperature during 1 h. It was then refluxed for 20 h and filtered off the solution. The filtrate was evaporated and diluted with 50 ml of ether and washed with 2 N HCl (15 ml), 10% aq. NaOH (20 ml) and brine, dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:40 to 1:5) furnished the enone **11** (20 mg) and further elution with ethyl acetate-hexane (1:5 to 1:2) furnished the diketo acetate **10** (824 mg) and triketone **9** (200 mg). To a solution of the diketoacetate **10**, obtained above, in 20 ml of CH_2Cl_2 was added DBU (450 mg, 0.45 ml, 3 mmol) and stirred for 1 h. The reaction mixture was diluted with CH_2Cl_2 (10 ml), washed with 3 N HCl (10 ml), aq. $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:10 to 1:5) as eluent furnished the enone **11** (422 mg) (overall yield 54.6% in two steps). 2,4-DNP derivative mp. 193-5 °C. $[\alpha]_D^{26}$ –71.3° (c 2.3, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3030, 2960, 1710 (C=O), 1665 (ring C=O), 1380, 1355, 1275, 1190, 1160, 1100, 810. ^1H NMR (270 MHz, $CDCl_3$): δ 6.95-6.85 (1 H, m, CH=CH-C=O), 6.0 (1 H, dd, J= 10.1 and 1.9 Hz, HC=CH-C=O), 3.12 (1 H, d, J=17.7 Hz, HCH-C=O), 2.80-2.65 (1 H, m), 2.54 (1 H, d, J=17.7 Hz, HCH-C=O), 2.30 (1 H, td, J=19.3 and 5.3 Hz) and 2.15 (1 H, td, J=19.3 and 2.5 Hz) [allylic CH_2], 2.12 (3 H, s, CH_3C=O), 0.96 (3 H, s, *tert*-CH_3), 0.92 (3 H, d, J=6.8 Hz, *sec*-CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 206.4 (C=O), 203 (ring C=O), 147.9 (C=CH-C=O), 128.1 (C=CH-C=O), 47.3 (2 C), 32.6, 31.2, 30.5, 16.3, 14.9. Mass: m/z 180 (M^+, 2%), 165 (5, M-Me), 123 (55), 122 (35), 97 (8), 68 (95), 43 (100). Analysis of 2,4-DNP derivative: Calcd. for $C_{23}H_{24}N_8O_8$, C, 51.11, H, 4.47; N, 20.73; Found: C, 51.02; H, 4.44; N, 20.41%.

(–)-(2S,3R)-2,3-Dimethyl-2-(2-oxopropyl)cyclohexanone (12): To a pre-activated 10%-Pd/C (40 mg) was added the enone **11** (342 mg, 1.9 mmol) in dry ethyl acetate (4 ml). The reaction mixture was magnetically stirred for 3 h at RT in an atmosphere of hydrogen (balloon) and the catalyst was filtered off. Evaporation of the solvent and

purification of the residue on a small silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the diketone **12** (300 mg, 87%) as an oil.[6a] $[\alpha]_D^{24}$ –88.2 (c 2.9, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 2970, 2940, 1700 (C=O), 1465, 1360, 1180, 1150, 1055, 955. ^1H NMR (90 MHz, $CDCl_3$): δ 2.84 (1 H, d, J=19 Hz) and 2.46 (1 H, d, J=19 Hz) [CH_2COCH_3], 2.50-1.50 (7 H, m), 2.11 (3 H, s, CH_3-C=O), 1.00 (3 H, s, *tert*-CH_3), 0.87 (3 H, d, J=6.3 Hz, *sec*-CH_3).

(-)-(1S,2R)-1,2-Dimethylbicylo[4.3.0]nonan-6-en-8-one (13): A solution of the diketone **12** (217 mg, 1.19 mmol) and aq. 10% KOH (0.72 ml, 1.39 mmol) in 1.2 ml of dry methanol was refluxed for 4 h at 120 °C in a sealed tube. The reaction mixture was cooled to RT and diluted with water. It was then extracted with ether (2 x 5 ml). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the enone **13** (179 mg, 91.6%).[6a] $[\alpha]_D^{23}$ –8.2 (c 2.1, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 2960, 2910, 2860, 1705, 1620, 1440, 1420, 1325, 1255, 1225, 1165, 845. ^1H NMR (270 MHz, $CDCl_3$): δ 5.74 (1 H, s, C=C*H*-C=O), 2.62 (1 H, d, J=14.1 Hz), 2.40-1.90 (4 H, m), 1.65-1.30 (4 H, m), 1.08 (3 H, s, *tert*-CH_3), 0.93 (3 H, d, J=4.6 Hz, *sec*-CH_3).

(+)-(1S,2R,6S)-1,2-Dimethylbicylo[4.3.0]nonan-8-one (3): Catalytic hydrogenation of the bicyclic enone **13** (158 mg, 0.963 mmol) in ethyl acetate (3 ml) using 10%Pd-C (20 mg) using the procedure described for the compound **12** furnished the bicyclic ketone **3** (152 mg, 95.1%).[6a] $[\alpha]_D^{25}$ +117.3 (c 1.62, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1735, 1380, 1265, 1200, 1180, 1140, 1120, 1015. ^1H NMR (90 MHz, $CDCl_3$): δ 2.40 (1 H, d, J=18 Hz) and 1.90 (1 H, d, J=18 Hz) [CH_2C=O], 2.22 (2 H, d, J=5 Hz), 1.65-1.15 (8 H, m), 1.04 (3 H, s, *tert*-CH_3), 0.80 (3 H, d, J=6.0 Hz, *sec*-CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 219.2 (C=O), 53.1, 43.1, 41.1, 40.3, 33.6, 30.1, 23.5, 20.5, 19.2, 16.4. Mass: m/z 166 (M^+, 40%), 151 (5), 109 (100), 123 (10), 95 (20).

(-)-(1S,2R,6S,8R)-1,2-Dimethylbicyclo[4.3.0]nonan-8,3'-spiro[4'-methylenedihydrofuran-2'(3'H)-one] (7-Epibakkenolide-A 14): To a magnetically stirred solution of potassium *tert*-amylate (189 mg, 1.51 mmol) in dry THF (1.5 ml) at RT was added methoxymethyltriphenyphosphonium chloride (587 mg, 1.73 mmol) and the resulting red coloured solution was stirred at RT for 15 min. To the methoxymethylenetriphenylphosphorane thus formed, was added the ketone **3** (100 mg, 0.6 mmol) in THF (0.5 ml) and stirred at RT for 8 h. It was then diluted with ether (10 ml), washed with brine and dried (Na_2SO_4). Careful evaporation of the solvent and purification of the residue on a neutral alumina column using ethyl acetate-hexane (1:40 to 1:20) as eluent furnished a E,Z mixture of the enol ether **15** as a colourless oil, which was contaminated with small amount of triphenylphosphine. IR (neat): ν_{max}/cm^{-1} 1685, 1185, 1115. ^1H NMR (60 MHz, $CDCl_3$): δ 5.89 (1 H, br s), 3.55 (3 H, s), 2.60-1.20 (12 H, m), 0.93 and 0.89 (3 H, s, *tert*-CH_3), 0.80 and 0.76 (3 H, d, J=5.7 Hz, *sec*-CH_3). To a cold (-40 °C), magnetically stirred solution of NBS (195 mg, 1.1 mmol) and propargyl alcohol (280 mg, 0.29 ml, 5.0 mmol) in CH_2Cl_2 (4 ml) was added a solution of the enol ether **15** (170 mg), obtained above, in CH_2Cl_2 (2 ml) over a period of 10 min. The reaction mixture was stirred for 45 min at the same temperature, diluted with CH_2Cl_2 (5 ml), washed with 1% aq. NaOH solution (5 ml) followed by brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a neutral alumina column using ethyl acetate-hexane (0:1 to 1:20) as eluent furnished a diastereomeric mixture of the bromoacetal **16** (170 mg, 85.7% overall yield from ketone) as a colourless oil. IR (neat): ν_{max}/cm^{-1} 3280, 2110, 1050. ^1H NMR (90 MHz, $CDCl_3$): δ 4.58 (1 H, s, O-C*H*-O), 4.40 (2 H, d, J=2.8 Hz, O-CH_2C≡CH), 3.61 and 3.62 (3 H, s, O-CH_3), 2.40 (1 H, m, C≡C*H*), 2.20-1.10 (12 H, m), 1.00 (3 H, s, *tert*-CH_3), 0.80 and 0.71 (3 H, d, J=7.0 Hz, *sec*-CH_3). A magnetically stirred solution of the bromoacetal **16** (165 mg, 0.5

mmol), tributyltin chloride (24 mg, 0.02 ml, 0.075 mmol), $NaCNBH_3$ (50 mg, 0.78 mmol) and a catalytic amount of AIBN in *tert*-butanol (4 ml) was refluxed for 2 h. The solvent was evaporated under reduced pressure. The residue was taken in water (3 ml) and extracted with ether (3 x 5 ml). The ether extract was washed with 1% aq. ammonia solution followed by brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (0:1 to 1:20) as eluent furnished an epimeric mixture of the spiro acetal **17** (112 mg, 89.6%) as a colourless oil. IR (neat): ν_{max}/cm^{-1} 3040, 1665, 1100, 1055, 1020, 880. ^1H NMR (90 MHz, $CDCl_3$): δ 4.82 (2 H, br s, C=CH_2), 4.60 (1 H, s, C*H*-OMe), 4.32 (2 H, br s, O-CH_2C=), 3.28 (3 H, s, O-CH_3), 2.30-2.10 (12 H, m), 0.89 & 0.83 (3 H, s, *tert*-CH_3), 0.79 & 0.75 (3 H, 2 d, J=5.1 Hz, *sec*-CH_3). A solution of the spiro acetal **17** (70 mg, 0.28 mmol) in THF (1 ml) and 3 N HCl (2.2 ml) was stirred for 24 h at RT. The reaction mixture was diluted with ether (5 ml), washed with water, saturated aq. $NaHCO_3$ solution and brine, and dried (Na_2SO_4). The solvent was evaporated and the residue filtered through a silica gel column using ethyl acetate-hexane (1:20 to 1:5) as eluent to furnish an epimeric mixture of the keto spirolactol **18** (25 mg, 72.5% based on consumed starting material). To a magnetically stirred solution of the spirolactol **18** (25 mg, 0.106 mmol) in CH_2Cl_2 (1.0 ml) was added a homogeneous mixture of PCC (30 mg, 0.14 mmol) and silica gel (30 mg). The reaction mixture was stirred at RT for 4 h and then filtered through a silica gel column using CH_2Cl_2 as eluent. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:40 to 1:20) as eluent furnished epibakkenolide-A **14** (20 mg, 80.6%). $[\alpha]_D^{26}$ –24.7 (c 1.8, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3080, 1775, 1670, 1235, 1145, 1125, 1025, 890. ^1H NMR (270 MHz, $CDCl_3$): δ 5.07 (1 H, s) and 4.99 (1 H, s) [C=CH_2], 4.75 (2 H, s, O-CH_2), 2.48 (1 H, d, J=13.1 Hz), 2.39 (1 H, d, J=14.1 Hz), 2.10-1.40 (10 H, m), 0.97 (3 H, s, *tert*-CH_3), 0.82 (3 H, d, J=6.6 Hz, *sec*-CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 182.3 (O-C=O), 152.1 (*C*=CH_2), 105.5 (C=*C*H_2), 70.2 (O-*C*H_2), 50.2, 50.1, 47.0, 44.2, 41.6, 33.1, 30.8, 23.7, 21.1, 19.7, 16.6. Mass: m/z 234 (M^+, 40%), 219 (25), 189 (15), 175 (30), 1476 (25), 133 (40), 124 (90), 109 (100), 41 (90). HRMS: m/z Calcd. for $C_{15}H_{22}O_2$, 234.1620; Found, 234.1613.

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