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Enantiospecific total syntheses of (−)-valeranone

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Two convenient methodologies have been described for the enantiospecific synthesis of (−)-valeranone 1. The hydrindanone 12, obtained from the readily and abundantly available monoterpe (R)-carvone, has been converted into the ketoaldehyde 16 via the alkene 15b. In another direction the lactone 18, obtained from the hydrindanone 12, has been elaborated into the ketoaldehyde 16 employing two methodologies. Intramolecular aldol condensation followed by hydrogenation transformed the ketoaldehyde 16 into (−)-valeranone 1.

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The sesquiterpene (−)-valeranone 1 was the first member of a small group of natural products, valeranes, containing a rearranged decaman 2 carbon framework with methyl substituents at both the ring junctions of the cis-decalin system valerane 3. (−)-Valeranone 1 was first isolated by Stoll and co-workers 1 in 1957 from European valerian, Valeriana officinalis L. and widely distributed in the members of the valerianaceous family. The elucidation of the structure of (−)-valeranone 1 has been the subject of protracted controversy and has presented a problem in sesquiterpene chemistry. Ultimately, Hikino and coworkers 2 established correct stereochemistry as well as absolute configuration of (−)-valeranone 1, which was confirmed later by enantiospecific synthesis 3 of the optical antipode of valeranone (+)-1. In addition to valeranone 1, subsequently a few other members of the valeranefamily were isolated, viz, cryptofauronol 4, fauronyl acetate 5, kanokonol 6, kanokonol acetate 7 from Japanese valerians. 4

The presence of a rearranged sesquiterpenecarbon framework incorporating two vicinal ring junction quaternary carbon atoms with methyl substituents in a cis-decalin framework, and three chiral centres made the valerane group of sesquiterpenes attractive synthetic targets. As a consequence, several approaches to valeranone 1 and to the parenhydrocarbon valerane 3, both intracemic as well as in optically active form, have been reported in the literature. 5 We have reported an enantiospecific synthesis of (+)-valerane 3 starting from (R)-carvone 8 via thetricyclic ketone 96. (Ref. 6) In continuation, we have investigated 7 the synthesis of (−)-valeranone 1 starting from the C-14 tricyclic ketone 9.

To begin with, a methodology analogous to that used 6 for (+)-valerane 3 was explored via thering expansion
of hydrindanone to decalone. The synthetic sequence is depicted in Scheme 1. To avoid subsequent regiochemical problems, the fifteenth carbon atom required for valeranone was introduced prior to the cleavage of the cyclopropane ring. Thus, regioselective methylation of the tricyclic ketone 9 with LDA and methyl iodide at low temperature furnished the alkylated ketone 10 in 91% yield with a high degree
of stereoselectivity. The stereochemistry of the secondary methyl group in the ketone 10 was assigned as \textit{exo} on the basis of the preferential alkylation of the intermediate enolate from the less hindered \textit{exo} face. Regiospecific reductive cleavage of the tricyclic ketone 10 using lithium in liquid ammonia reduction conditions furnished the hydridanone 11 in 76% yield whose structure rests secured from its spectral data. Hydrogenation of the olefinic moiety in the enone 11 using 10%-Pd/C as the catalyst in methanol at one atmosphere pressure of hydrogen (balloon) furnished the saturated ketone 12 in 99% yield. Sodium borohydride reduction of the hydridanone 12 furnished a 2:1 epimeric mixture of the alcohol 13 in 96% yield. Treatment of the alcohol 13 with triphenylphosphine, imidazole and iodine in benzene generated the iodide 14 in 76% yield, which on de-hydroiodination using 1.8 diazabicyclo[5.4.0]undec-7-ene (DBU) at 160 °C in a Carius tube for 30 min, furnished a 1:3 regiochemical mixture of the olefins 15a and 15b in 89% yield, which was found to be inseparable using conventional methods. Ozonation of the mixture of olefins 15 and reductive work-up of the ozonide with triphenylphosphine followed by purification on a silica gel column furnished the keto-aldehyde 16 in 53% yield. Intramolecular aldol condensation of the keto-aldehyde 16 in THF using 1M aqueous potassium hydroxide in methanol furnished, exclusively, the cyclohexenone 17 (valerenone) in 76% yield. The $^1$H NMR spectrum exhibited resonances, a ddd at 8.81 and a dd at 5.96 due to $\beta$ and a protons, respectively, of an
a,β-unsaturated ketone, a broad doublet at δ 2.85 and a dd at δ 1.79 due to axial (orthogonal to enone moiety) and equatorial protons of the allylic CH₂, respectively, a singlet at δ 1.12 and a doublet at 0.89 (Jₘₙ = 0.5 Hz) due to the two tertiary methyl groups and two doublets at δ 0.87 and 0.84 due to the isopropyl group, establishing the structure of the enone 17. Further confirmation of the structure of the enone 17 came from its 1³C NMR spectrum which exhibited resonances at δ 205.4 due to carbonyl carbon, at δ 146.7 and 127.7 due to the β and α carbons of the enone, respectively, at δ 49.5 and 37.7 due to the two ring junction quaternary carbon atoms, at δ 36.9 (2C), 34.8, 34.7, 32.9, 25.1, 24.8, 19.9, 19.8 and 16.1 ppm due to the rest of the carbons. Finally, hydrogenation of the enone 17 in methanol using 10%-Pd/C as the catalyst at one atmosphere pressure of hydrogen (balloon) furnished the saturated ketone, (D) valeranone 1 {[a]D}²⁵ = -54.3, (c 0.7, CHCl₃), lit. ²⁵{[α]D}²⁶ = -51.9 (c 0.3, CHCl₃) in 80% yield, whose spectral data was found to be identical to that reported for natural valeranone.

To overcome the regiochemical problems, an alternative methodology based on the Baeyer-Villiger oxidation, for the hydrindanone to decalone ring enlargement, was investigated. The hydrindanone 12 was first converted into the lactone 18 via a regioselective Baeyer-Villiger oxidation. Thus, treatment of the hydrindanone 12 with m-chloroperbenzoic acid (MCPBA) and trifluoroacetic acid in methylene chloride for 5 hr resulted in the formation of the δ-lactone 18 in 84% yield in a highly regioselective manner. Presence of the carbonyl absorption band at 1735 cm⁻¹ due to the lactone moiety in the IR spectrum and an upfield shift of the carbonyl carbon resonance to δ 173.5 ppm in the 15 lines ¹³C NMR spectrum clearly established the structure of the lactone 18. Presence of a quartet at δ 4.15 due to OC HCH₃ and an AB quartet at 2.65 and 2.04 due to CH₂=C=O established the regioselectivity of the reaction. Reduction of the δ-lactone 18 with lithium aluminium hydride (LAH) in ether furnished the diol 19 in 98% yield. It was anticipated that the regiospecific conversion of the primary alcohol into a leaving group and oxidation of the secondary alcohol followed by intramolecular alkylation of the resultant ketone 20 would generate valeranone 1. However, treatment of the diol 19 with one equivalent of methanesulfonyl chloride in pyridine and methylene chloride in 84% yield, whose structure was established from its spectral data. In another effort, conversion of the diol 19 into the ketoaldehyde 16, the penultimate precursor of valeranone 1, via controlled oxidation was also unsuccessful, and formed only the lactone 18 (Scheme II).

Subsequently, a strategy based on the regioselective protection of the primary alcohol in the diol 19 was envisaged. Thus, treatment of the diol 19 with tert-butylimethylsilyl chloride and imidazole in methylene chloride furnished the TBDMS ether 22 in 65% yield. Oxidation of the secondary alcohol in the hydroxy ether 22 with pyridinium chlorochromate (PCC) and sodium acetate in methylene chloride generated the keto ether 23 in 82% yield. Tetrabutylammonium fluoride (TBAF) mediated cleavage of the TBDMS ether transformed the keto ether 23 into the hydroxy ketone 24 in 70% yield, which existed in the form of hemiketal 25. Oxidation of the hemi-ketal 25 with PCC and sodium acetate in methylene chloride furnished the keto aldehyde 16 in 72% yield. An alternative strategy was also conceived for the synthesis of the ketoaldehyde 16 via protection of the aldehyde as a terminal olefin. Thus, controlled reduction of the lactone 18 with one equivalent of diisobutylaluminum hydride (DIBAH) in toluene at -78 °C furnished the lactol 26 in 87% yield. Reaction of the lactol 26 with an excess of methylenetriphenylphosphoro-rane in THF generated the hydroxyolefin 27 in 57% yield. Oxidation of the alcohol 27 with PCC and sodium acetate in methylene chloride furnished the keto olefin 28 in 80% yield, whose structure was established from the spectral data. Ozonolysis of the keto olefin 28 in a 1:5 methanol and methylene chloride medium followed by reductive work-up of the ozonide with triphenylphosphine furnished the keto-aldehyde 16 in 71% yield, which was found to be identical with the sample obtained earlier.

In conclusion, enantiospecific syntheses to the natural enantiomer of valeranone have been developed starting from readily available (R)-carvone via the hydrindanone 12. For the ring enlargement of hydrindanone to decalone two paths were employed. In the first path, oxidative cleavage of cyclopentene 15b generated the ketoaldehyde 16, the penultimate precursor of valeranone. In the second path, the hydrindanone 12 was first converted into the lactone 18 via Baeyer-Villiger oxidation. The lactone 18 was then transformed into the...
ketoaldehyde 16 employing two different methodologies.

**Experimental Section**

Melting points were recorded using aTempo melting point apparatus in capillary tubes and are uncorrected. In the NMR spectra, the chemical shifts...
(δ ppm) and the coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for 1H) or the central line (77.1 ppm) of CDCl3 (for 13C). In the 13CNMR spectra the nature of the carbons (C, CH, CH2 and CH3) was obtained either by off-resonance decoupled spectra or DEPT 135 experiment, and are given in parentheses. In the mass spectra, relative intensities of the ions are given in parentheses. Optical rotations were measured using a JascoDIP-370 digital polarimeter; [α]D values are given in the units of 10^-1 deg.cm^2.g^-1. Hydrogenation reactions were carried out using a balloon filled with hydrogen. All small-scale dry reactions were carried out using standard syringe-septum technique. Low temperature reactions were conducted in a bath made of alcohol and liquid nitrogen. Dry THF was obtained by distillation over sodium benzophenoneketyl. Dry ether was obtained by distillation over sodium and stored oversodium wire. Methylene chloride was distilled over P2O5. Dry methanol was prepared by distillation over magnesium and stored overmolecular sieves. Liquid ammonia was obtained in cylinders from Mysore Ammonia Ltd. and distilled over sodamide prior to use. All commercial reagents were used as such without further purification.

(1R,2R,4R,6S,7S,9S)-4-Isopropenyl-1,6,7-trime-thyl-tricyclo[4.3.0.0^2,9]nonan-8-one10. To a cold (−78°C) magnetically stirred solution of diisopropylamine (1.1 mL, 7.84 mmoles) in dry THF (2 mL), under
nitrogen, was slowly added a solution of n-BuLi in hexane (1.6 M, 4.9 mL, 7.84 mmole). The resulting colourless mixture was stirred at -78°C for 15 min, and at -20°C for 30 min. The reaction mixture was re-cooled to -78°C, a solution of the tricyclic ketone 9 (800 mg, 3.92 mmole) in dry THF (5 mL) and HMPT (0.7 mL) was added slowly and stirred for 30 min at -70°C and for 10 min at room temperature. The reaction mixture was re-cooled to -78°C and the enolate was then treated with methyl iodide (0.5 mL, 7.84 mmole), and allowed to warm up to room temperature. The resulting mixture was stirred at room temperature for 4 hr, quenched with 0.5 N aq. HCl and extracted with ether (3 x 10 mL). The combined ether extract was washed with brine and dried (Na₂SO₄). Evaporation of the solvent and careful purification of the product on a silica gel column using ethyl acetate-hexane (1:40) as eluent provided the methylated ketone 10 (470 mg, 55%); [α]D 29.0 (c 2, CHCl₃); IR (neat): 3080, 1715, 1645, 1375, 1085, 885 cm⁻¹; 1H NMR (200 MHz, CDCl₃): δ 4.68 (2 H, m, C=CH₂), 1.69 (3 H, s, olefinic CH₃), 2.75-1.40 (8 H, m), 1.20 (3 H, s) and 1.04 (3 H, s) [2 tert-CH₃], 0.95 (3 H, d, J = 7.4 Hz, sec-CH₃); 13C NMR (67.5 MHz, CDCl₃): δ 215.2 (C=O), 150.1 (C=CH₂), 109.8 (C=CH₂), 54.1, 41.5 (2 C), 39.6, 38.2, 33.8 29.9, 23.6, 23.2, 21.2, 19.1, 10.7 (sec-CH₃); Mass: m/z 218 (M⁺, 5%), 175 (25), 149 (20), 147 (30), 135 (28), 133 (35), 121 (93), 120 (40), 119 (50), 109 (40), 108 (55), 107 (100), 105 (55).

Further elution of the column with ethyl acetate-hexane (1:20) furnished unreacted starting material 9 (315 mg, 39%).

(1S,3R,6R,9S)-3-Isopropenyl-1,6,9-trimethyl-bicyclo-[4.3.0]nonan-8-one 11. To a magnetically stirred, freshly distilled (over sodamide) ammonia (80 mL) in a three-necked flask equipped with a magnetic condenser was added, freshly cut lithium (63 mg, 9.1 mmole) followed by a solution of the tricyclic ketone 10 (495 mg, 2.27 mmole) in anhydrous THF (2 mL). The resulting blue solution was stirred for 15 min at -33°C and then the reaction was quenched with solid NH₄Cl. After evaporation of ammonia, the residue was taken in water (3 mL) and extracted with CH₂Cl₂ (3 x 7 mL). The combined CH₂Cl₂ extract was washed with brine and dried (Na₂SO₄). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:40) as eluent furnished the bicyclic ketone 11 (380 mg, 76%) as colourless oil; [α]D 29.5 (c 2, CHCl₃); IR (neat): 3080, 1735, 1640, 1385, 1375, 885 cm⁻¹; 1H NMR (200 MHz, CDCl₃): δ 4.70 (2 H, m, C=CH₂), 2.70 and 1.83 (2 H, 2 ×d, J = 17.9 Hz, H-8), 2.20-1.90 (1 H, m, H-3), 2.00 (1 H, q, J = 7.9 Hz, H-9), 1.73 (3 H, s, olefinic CH₃), 1.80-1.20 (6 H, m), 1.13 (3 H, d, J = 7.9 Hz, sec-CH₃), 1.03 (3 H, s) and 0.97 (3 H, s) [2 × tert-CH₃]; 13C NMR (67.5 MHz, CDCl₃): δ 222.1 (C, C=O), 149.6 (C, C=CH₂), 108.7 (CH₂=CH₂), 54.7 (CH, C-9), 51.3 (C), 48.6 (CH₂, C-7), 44.2 (CH₂, C-5), 42.8 (C), 40.3 (CH, C-3), 33.3 (CH₂, C-2), 26.7 (CH₂=CH₂), 26.5 (CH₃), 21.1 (CH₃), 17.0 (CH₃), 14.1 (CH₃, sec-CH₃); Mass: m/z 220 (M⁺, 8%), 149 (28), 137 (25), 135 (20), 124 (100), 123 (40), 121 (35), 109 (30), 107 (63), 95 (50); HRMS (m/z): Calcd for C₁₃H₂₂O₂: 220.1828. Found: 220.1818.

(1S,3R,6R,9S)-3-Isopropyl-1,6,9-trimethylbicyclo-[4.3.0]nonan-8-one 12. To a magnetically stirred solution of the ketone 11 (220 mg, 1.0 mmole) in dry methanol (3 mL) was added 10% Pd/C (15 mg). The reaction mixture was stirred in an atmosphere of hydrogen, created by evacuative replacement of air using a balloon filled with hydrogen, for 12 hr and then the catalyst was filtered off. Evaporation of the solvent and purification of the product over a silica gel column using ethyl acetate-hexane (1:40) as eluent furnished the bicyclic ketone 12 (220 mg, 99%) as colourless oil; [α]D 25.5 (c 2, CHCl₃); IR (neat): 1735, 1455, 1385, 1190 cm⁻¹; 1H NMR (270 MHz, CDCl₃): δ 2.72 and 1.77 (2 H, 2 × J = 18.0 Hz, H-7), 1.90 (1 H, q, J = 7.8 Hz, H-9), 1.70-1.00 (8 H, m), 1.14 (3 H, d, J = 8.0 Hz, sec-CH₃), 0.91 (3 H, s) and 0.93 (3 H, s) [2 × tert-CH₃], 0.86 (6 H, d, J = 6.7 Hz, CH₃×CH×CH₃); 13C NMR (22.5 MHz, CDCl₃): δ 217.9 (C=O), 55.3, 51.3, 48.4, 43.9, 42.6, 39.4, 33.4, 32.4, 27.0, 24.9, 19.9, 19.6, 16.9, 14.5; Mass: m/z 222 (M⁺, 20%), 151 (100), 109 (30), 95 (97); HRMS (m/z): Calcd for C₁₅H₂₆O₂: 222.1894. Found: 222.1894.

(1S,3R,6R,9S)-3-Isopropyl-1,6,9-trimethylbicyclo-[4.3.0]nonan-8-ols 13. To an ice cold, magnetically stirred solution of the ketone 12 (125 mg, 0.56 mmole) in dry methanol (2 mL) was added sodium borohydride...
The reaction mixture was stirred at the same temperature for 15 min. The solvent was evaporated under reduced pressure and 0.5 mL of 0.5 N aq. HCl was added to consume the excess reagent. The residue was taken in water (5 mL) and extracted with ether (3 × 5 mL). The ether extract was washed with water and brine, and dried (Na₂SO₄). Evaporation of the solvent and purification of the product on a silica gel column using CH₂Cl₂ as solvent furnished the alcohol 13 (120 mg, 96%) as oil; [α]D +16.5 (c 2, CHCl₃); IR (neat): 3350, 1455, 1385, 1015, 795 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 4.10-3.80 and 4.50-4.10 (1 H, m, C H-OH), 2.42-2.15 (1 H, m, 5 × CH₃); Mass: m/z 224 (M⁺, 1%), 206 (25), 191 (30), 166 (30), 163 (50), 152 (30), 151 (55), 123 (80), 121 (40), 111 (50), 109 (96), 107 (42), 95 (100); HRMS (m/z): Calcd for C₁₅H₂₃O:224.2140. Found: 224.2156.

(1R,3R,6R)-4-Isopropyl-1,6,7-trimethylbicyclo-[4.3.0]nonenes 15a and 15b. To a magnetically stirred solution of the alcohol 13 (104 mg, 0.46 mmole) in benzene (3 mL) at room temperature were added triphenylphosphine (175 mg, 0.67 mmole), imidazole (92 mg, 1.35 mmole) and iodine (162 mg, 0.64 mmole), sequentially. The stirring was continued at room temperature for 2 hr. The supernatant layer was separated and the residue was further washed with ether. The combined organic phase was evaporated and the product was rapidly chromatographed on a silica gel column using hexane as eluent to furnish a 1:3 mixture of the alkenes 15a and 15b (50 mg, 89%) as oil; [α]D −17.5 (c 2, CHCl₃); IR (neat): 1455, 1380, 1370, 1015, 780 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 4.86-4.70 (1 H, m), 2.80-0.95 (11 H, m), 1.00-0.80 (15 H, 5 × CH₃).

A solution of the iodide 14 (90 mg, 0.27 mmole) and DBU (0.05 mL, 0.34 mmole) in dry DMF (0.5 mL) was placed in a Carius tube and heated to 160 °C for 30 min. The reaction mixture was cooled, 0.5 mL of 0.5 N aq. HCl was added and then extracted with ether (3 × 5 mL). The combined ether extract was washed with water, saturated aq. NaHCO₃ and brine, and dried (Na₂SO₄). The solvent was evaporated and the product was rapidly chromatographed on as silica gel column using hexane as eluent to furnish a 1:3 mixture of the alkenes 15a and 15b (50 mg, 89%) as oil; [α]D −17.5 (c 2, CHCl₃); IR (neat): 1455, 1380, 1370, 1015, 780 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 5.16 (1 H, s, olefinic H), 2.60-1.80 (2 H, m, allylic), 1.62 (3 H, s, olefinic CH₃), 1.80-1.00 (8 H, m), 0.89 (3 H, s) and 0.85 (3 H, s) [2 × tert-CH₃], 0.84 (3 H, d, J = 6.7 Hz) and 0.81 (3 H, d, J = 7.3 Hz) [CH₃-CH-CH₃]; ¹³C NMR (100 MHz, CDCl₃, for a 1:3 mixture of the alkenes 15a & 15b): δ 148.8, 121.5, 120.1, 53.5, 44.7, 41.3, 41.0, 38.3, 37.2, 36.7, 34.2, 32.6, 26.8, 26.3, 23.5, 22.9, 21.0, 19.9, 19.6, 17.2, 13.1; Mass: m/z 206 (M⁺, 20%), 191 (52), 122 (40), 121 (100), 109 (80); HRMS (m/z): Calcd for C₁₅H₂₆O: 206.2034. Found: 206.2045.

(1R,2S,6R,9R)-9-Isopropyl-1,2,6-trimethyl-3-oxa-bicyclo[4.4.0]decan-4-one 18. To a magnetically stirred solution of the ketone 12 (220 mg, 0.99 mmole) and m-CPBA (55%, 943 mg, washed with pH 7.5 phosphate buffer, 3 mmoles) in CH₂Cl₂ (15 mL), protected from light, was added trifluoroacetic acid (0.08 mL, 1 mmole) and stirred at room temperature for 5 hr. The reaction mixture was then diluted with CH₂Cl₂ (5 mL), washed sequentially with 10% aq. sodium sulfite solution, saturated aq. NaHCO₃ and brine, and dried (Na₂SO₄). Evaporation of the solvent and purification of the product on a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the lactone 18 (198 mg, 84%) as oil; [α]D −19.5 (c 2, CHCl₃); IR (neat): 1735, 1460, 1380, 1255, 1206, 1065, 970 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 4.15 (1 H, q, J = 6.7 Hz, H-2), 2.65 and 2.04 (2 H, 2 × d, J = 16.0 Hz, H-4), 1.70-1.10 (8 H, m), 1.34 (3 H, d, J = 6.7 Hz, sec-CH₃), 1.03 (3 H, s) and 0.99 (3 H, s) [2 × tert-CH₃], 0.86 (6 H, d, J = 6.4 Hz, CH₃-CHH-CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 173.5 (OC=O), 84.1 (C-2), 42.7, 41.4, 39.1, 38.4, 37.0, 36.2, 32.8, 26.5, 23.9, 19.9, 19.5, 16.91, 16.86; Mass: m/z 238 (M⁺, 0.5%), 152 (90), 109 (100). HRMS (m/z): Calcd for C₁₅H₂₆O₂: 238.1933. Found: 238.1962; Calcd for C₁₁H₂₀ (M⁺-C₄H₆O₂): 152.1565. Found: 152.1568.

(1R,2R,4R)-1,2-Dimethyl-2-(1-hydroxyethyl)-4-isopropylcyclohexane ethanol 19. To a magnetically stirred solution of the lactone 18 (198 mg, 0.8 mmole) in dry ether (5 mL) was added LiAlH₄ (40 mg,
1.07mMoles) at room temperature and stirred for 30 min. The reaction was carefully quenched with 0.5 N aq. HCl and extracted with ether (3×5 mL). The combined ether extract was washed with aq. NaHCO₃ and brine, and dried (Na₂SO₄). Evaporation of the solvent and purification of the product on a silica gel column with ethyl acetate-hexane (1:1) as eluent furnished the diol 19 (190 mg, 98%), which was recrystallised from CH₂Cl₂-hexane; m.p. 52 °C, [α]D +12.5 (c 2, CHCl₃); IR (neat): 3350, 1465, 1375, 1100, 1055, 1020, 935, 755 cm⁻¹; ¹H NMR (270MHz, CDCl₃): δ 3.89 (1H, q, J = 6.4 Hz, HO-CH₂CH₃), 3.75 and 3.71 (2H, t of AB q, J = 9.8 and 6.4 Hz, CH₂), 2.05-0.90 (12H, m), 1.12 (3H, d, J = 6.4 Hz, sec-CH₃), 1.06 (3H, s) and 0.91 (3H, s) [2×tert-CH₃], 0.86 (3H, d, J = 6.5 Hz) and 0.84 (3H, d, J = 6.7 Hz) [CH₃] ; Mass: m/z 225 (M - OH), 197 (35), 179 (20), 153 (50), 152 (45), 123 (75), 109 (95), 97 (60), 95 (62). HRMS (m/z): Calcd for C₁₃H₂₅O(M - CH₂CH₂OH): 197.1905. Found: 197.1902.

(1R,2S,6R,9R)-9-Isopropyl-1,2,6-trimethyl-3-oxa-bicyclo[4.4.0]decane 21. To an ice-cold, magnetically stirred solution of the diol 19 (23 mg, 0.095 mmole) in CH₂Cl₂ (2 mL) was added methanesulfonyl chloride (0.01 mL, 0.13 mmole) and pyridine (0.01 mL, 0.13mmole) and stirred for 1 hr at 0 °C. To the reaction mixture was then added 0.5 Naq. HCl and extracted with CH₂Cl₂ (3×3 mL). The combined CH₂Cl₂ extract was washed with aq. NaHCO₃ and brine, and dried (Na₂SO₄). Evaporation of the solvent and purification of the product on a silica gel column using hexane as eluent furnished the ether 21 (18 mg, 84%) as oil: [α]D +25(c 1, CHCl₃); IR (neat): 1460, 1370, 1105 cm⁻¹; ¹H NMR (270 MHz, CDCl₃): δ 3.87 (1H, d of t, J = 12.0 and 2.6 Hz) and 3.63 (1H, ddd, J = 12.0, 5.5 and 1.8 Hz) [H-4], 3.39 (1H, q, J = 7.2 Hz, H-2), 2.21 (1H, d of t, J = 13.3 and 5.6 Hz) and 1.96 (1H, t, J = 13.3 Hz) [H-5], 1.80-1.00 (8H, m), 1.34 (3H, d, J = 7.2 Hz, sec-CH₃), 1.06 (3H, s) and 0.85 (3H, s) [2×tert-CH₃], 0.87 (6H, d, J = 6.9 Hz, CH₃CH₂CH₂CH₃).

(1S)-1-[(1R,2R,5R)-2-(2-tert-Butyldimethylsilyloxy-ethyl)-5-isopropyl-1,2-dimethylcyclohexyl]-ethanol 22. To a magnetically stirred solution of the diol 19 (185 mg, 0.76 mmole) in dry CH₂Cl₂ we added imidazole (100 mg, 1.46 mmoles) and TBDMSCl (132 mg, 0.88 mmole), and stirred for 1 hr at 0 °C. The reaction mixture was then diluted with CH₂Cl₂, washed with brine and dried (Na₂SO₄). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane as eluent furnished the silyl ether 22 (190 mg, 65%) as colourless oil; IR (neat): 3400, 2980, 1460, 1370, 1240, 1080, 830, 770 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 3.86 (1H, q, J = 6.5 Hz, CHOCH₃), 3.75-3.60 (2H, m, C H₂-OCH₃), 1.90-1.55 (2H, m), 1.50-1.00 (9H, m), 1.09 (3H, d, J = 6.5 Hz), 1.03 (3H, s) and 0.88 (3H, s) [2×tert-CH₃], 0.90 [9H, s, C(CH₃)₂], 0.85 (3H, d, J = 6.5 Hz) and 0.83 (3H, d, J = 6.9 Hz) [CH₃]; ¹³C NMR (75 MHz, CDCl₃+CCL₄): δ 74.2 (CH, CHOCH₃), 60.3 (CH₂, CH₂-OCH₃), 42.7 (C), 38.8 (CH), 37.4 (C), 36.9 (CH₂), 35.5 (CH₂), 34.8 (CH₂), 32.9 (CH), 26.0 [3C, CH₃, C(CH₃)₃], 25.1 (CH₂), 24.9 (CH₃), 20.1 (CH₃), 19.4 (CH₃), 19.3 (CH₃), 18.5 (Si-CMe₃), 13.7 (CH₃), –5.2 (2C, CH₃).

1-[(1R,2R,5R)-2-(2-tert-Butyldimethylsilyloxy-ethyl)-5-isopropyl-1,2-dimethylcyclohexyl]-1-ethaneone 23. To a magnetically stirred suspension of PCC (350 mg, 1.6 mmoles) and sodium acetate (350 mg, 4.27mmoles) in CH₂Cl₂ was added a solution of the alcohol 22 (190 mg, 0.53 mmole) in CH₂Cl₂ in one portion. The reaction mixture was stirred at room temperature for 30 min, filtered through silica gel column, and eluted the column with more CH₂Cl₂. Evaporation of the solvent furnished the keto ether 23 (156 mg, 82%) as oil: [α]D +6.7 (c 0.6, CHCl₃); IR (neat): 2950, 2860, 1700, 1460, 1380, 1320, 1250, 1090, 1000, 830, 780 cm⁻¹; ¹H NMR (300 MHz, CDCl₃); δ 3.70-3.50 (2H, m, CH₂-OH), 2.15 (3H, s, COCH₃), 2.05-1.90 (2H, m), 1.55-1.00 (8H, m), 1.16 (3H, s) and 1.00 (3H, s) [2×tert-CH₃], 0.90 (3H, d, J = 6.9 Hz) and 0.89 (3H, d, J = 6.3 Hz) [CH₃]; ¹³C NMR (75 MHz, CDCl₃): δ 214.0 (C, C=O), 59.8 (CH₂, CH₂-OH), 54.0 (C, C=O), 38.8 (CH, C=O), 37.3 (C, C=O), 36.8 (CH₂), 35.4 (CH₂), 33.0 (CH), 32.8 (CH₂), 29.4 (CH₃), 26.1 [3C, CH₃, C(CH₃)₃], 25.1 (CH₂), 23.0 (CH₂), 20.2 (CH₃), 19.8 (CH₃), 19.0
(CH₃), 18.4 (C,Si-CMe₃), 5.1 [2 C, CH₃, Si(CH₃)₂]; Mass: 339 (M-CH₂₂%, 313 (5), 279 (5), 257 (2), 239 (5), 205 (5), 149 (70), 69 (90), 57 (100).

(1R,6R,9R)-9-Isopropyl-1,2,6-trimethyl-3-oxa-bicyclo[4.4.0]decan-2-ol 25. To a magnetically stirred solution of the ketoether 23 (140 mg, 0.39 mmole) in THF was added TBAF (420 mg, 1.6 mmoles). The reaction mixture was stirred at room temperature for 4 hr. It was then washed with ether and dried(Na₂SO₄). Evaporation of the solvent and purification of the product on a silica gel column using ethyl acetate-hexane(1:10) as eluent furnished the hemiketal 25 (90 mg, 70%) as colourless oil; IR (neat): 3350, 1460,1360, 1220, 1090, 1050, 1010 cm⁻¹; ¹H NMR (300 MHz, CDCl₃+CCl₄): d 4.15 (1 H, ddd, J = 13.5 and 5.1 Hz) and 3.54 (1 H, d, J = 11.4 and 5.1 Hz, H-4), 2.28 (1 H, d of t, J = 13.5 and 5.1 Hz), 1.70-1.00 (9 H, m), 1.16 (3 H, s), 1.04 (3 H, s) and 0.91 (3 H, s)[3 ²t-CH₃], 0.88 (3 H, d), 0.87 (3 H, d, J = 6.9 Hz) [CH₃-CH₂-CH₃]and 0.69 (1 H, d, J = 13.0 Hz); ¹³C NMR (75 MHz,CDCl₃+CCl₄): d 101.5 (C, C-4), 80.3 (C), 75.4 (C), 56.1 (C), 38.6 (CH₂), 35.6 (CH₂), 33.6 (C), 33.1 (CH), 32.0 (CH₂), 26.4 (CH₃), 25.8 (CH₃), 24.1 (CH₂), 20.3 (CH₃). 

(1R,2R,6R,9R)-9-Isopropyl-1,2,6-trimethyl-3-oxa-bicyclo[4.4.0]decan-4-ol 26. To amagnetically stirred, cold (-78 °C)solution of the lactone 18 (60 mg, 0.27 mmole) in toluene (1 mL) was added DIBAH (0.25 mL, -1.2 M solution in toluene, 0.3 mmole). The reactionmixture was stirred at the same temperature for 1 hr. It was then washed with water (5 mL) and extracted with ether (3 × 5 mL). The combined organic extract was washed with brine and dried(Na₂SO₄). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane(1:1) as eluent furnished the alcohol 26 (50 mg, 87%) as oil: [α]D +28.0 (c 4.0, CHCl₃); IR (neat): 3330, 2950, 2870, 1460,1370, 1060, 1010 cm⁻¹; ¹H NMR (300 MHz,CDCl₃+CCl₄): d 5.22 (1 H, dd, J = 9.0 and 3.9 Hz, H-4), 3.66 (1 H, q, J = 6.9 Hz, H-2), 1.88 (1 H, dd, J = 13.2 and 9 Hz), 1.65-0.70 (10 H, m), 1.28 (3 H, d, J = 6.9 Hz, sec-CH₃), 1.04 (3 H, s) and 0.86 (3 H, s)[2 ²t-CH₃], 0.85 (6 H, d, J = 6.3 Hz, CH₃-CH₂-CH₃); ¹³C NMR (75 MHz, CDCl₃+CCl₄): δ 90.8 (CH, C-2), 87.8 (CH, C-6), 40.0 (CH₂), 39.4 (CH₂), 39.0 (CH), 38.6 (CH₂), 38.4 (C), 34.9 (C), 32.8 (CH), 27.6 (CH₃), 24.8 (CH₂), 20.2 (CH₃), 19.8 (CH₃), 18.0 (CH₃), 16.7 (CH₃); Mass: m/z 240 (M⁺,C₁₅H₂₆O₂, 2%), 207 (10), 152 (60), 109 (100), 95 (15), 82 (20).

(1S)-1-(1R,2R,5R)-(2-Allyl-5-isopropyl-1,2-dimethyl-cyclohexyl)ethanol 27. To a magnetically stirred suspension of methyltriphenylophosphinum iodide (2.6 g, 6.43 mmoles) in dry THF (2 mL) was added a solution of K⁺AmO⁻ in THF (1 mL, 4.85 mmoles) and the resultant yellow colouredsolution was stirred for 30 min at room temperature. To the methylenetriphenylophos-phoranethus formed, was added a THF (1 mL) solution of the lactol 26 (40 mg,0.16 mmole) and stirred for 1 hr at 40 °C. The reaction was quenched with saturated aq. NH₄Cl solution (2 mL) and extracted with ether (5 mL). The combined ether extract was washed with brine and dried (Na₂SO₄). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane(1:30) as eluent furnished the alcohol 27 (20 mg, 57%) as colourless oil; IR (neat): 3330,3280, 2860, 1630, 1460, 1370, 1100, 1050, 900 cm⁻¹; ¹H NMR (300 MHz,CDCl₃+CCl₄): d 5.79 (1 H, t of dd, J = 15.9, 11.1 and 6.9 Hz), 5.03 (1 H, dd, J = 15.9 Hz), 5.01 (1 H, d, J = 11.1 Hz), 3.83 (1 H, q, J = 6.5 Hz, CHOH), 2.32 (1 H, dd, J = 13.2 and 7.5 Hz), 2.17 (1 H, dd, J = 13.2 and 6.9 Hz), 1.40-0.90 (9 H, m), 1.10 (3 H, d, J = 6.5 Hz), 0.99 (3 H, s) and 0.91 (3 H, s)[2 ²t-CH₃], 0.86 (3 H, d, J = 6.6 Hz) and 0.84 (3 H, d, J = 6.6 Hz)[CH₃-CH₂-CH₃]; ¹³C NMR (75 MHz,CDCl₃+CCl₄): δ 136.2 (CH, CH=CH₂), 116.8 (CH₂, CH=CH₂), 72.8 (CH), 42.6 (C), 39.0 (CH), 38.6 (C), 37.6 (CH₂), 37.2 (CH₂), 34.5 (CH₂), 33.1 (CH), 24.7 (2 C, CH₃ and CH₂), 20.3 (CH₃), 19.6 (CH₃), 19.5 (CH₃) 14.3 (CH₃).

1-[(1R,2R,5R)-2-Allyl-5-isopropyl-1,2-dimethyl-cyclohexyl]ethane 28. To a magnetically stirred suspension of PCC (55 mg, 0.25 mmole) and sodium acetate (55 mg) in CH₂Cl₂(0.5 mL) was added a solution of the alcohol 27 (20 mg, 0.08mmole) in CH₂Cl₂ (0.5 mL). The reaction mixture was stirred at room temperature for 30 min, filtered through a silica gel column, and the column eluted with more CH₂Cl₂.
Evaporation of the solvent furnished the ketone 28 (16 mg, 80%) as oil; [α]D +43.0 (c 1.0, CHCl₃); IR (neat): 3080, 3060, 2910, 2830, 1690, 1635, 1465, 1380, 1365, 1350, 1220, 1200, 990, 900 cm⁻¹. ¹H NMR (300 MHz, CDCl₃+CDCl₄): δ 5.69 (1 H, t of dd, J = 18.0, 10.5 and 7.2 Hz, C H=CH₂), 5.00 (1 H, d, J = 10.5 Hz) and 4.99 (1 H, d, J = 18.0 Hz) [CH=CH₂], 2.46 (1 H, dd, J = 13.5 and 7.5 Hz), 2.16 (3H, s, CH₃CO), 1.91 (1 H, t, J = 13.2 Hz), 1.65 (1 H, dd, J = 13.5 and 7.2 Hz), 1.40-1.30 (7 H, m), 1.20 (3 H, s, tert-CH₃). ¹⁰Bromine 1.08 (1 H, d of t, J = 12.0 and 4.5 Hz), 0.95 (3 H, s, tert-CH₃), 0.90 (3 H, d, J = 6.6 Hz) and 0.89 (3 H, d, J = 6.6 Hz, CH₃-CH-CH₃);¹³C NMR (75 MHz, CDCl₃): δ 213.8 (C, C=O), 134.7 (CH, CH=CH₂), 117.6 (CH₂CH=CH₂), 53.6 (C, C-1), 38.9 (CH₂), 38.8 (CH₃), 38.1 (C, C-6), 35.3 (CH₂), 33.1 (CH), 32.5 (CH₂), 29.5 (CH₃), 24.7 (CH₂), 22.6 (CH₃), 20.3 (CH₃), 19.8 (CH₃), 19.4 (CH₃); Mass: m/z 236 (M⁺, C₁₆H₂₈O₂%). 221 (2), 193 (12), 149 (40), 95 (55), 83 (50), 43 (100).

2-[(1R,2R,4R)-2-Acetyl-4-isopropyl-1,2-dimethyl-cyclohexyl]acetaldheyde 16.  

Procedure I (from the olefins 15). Prepared cooled dry ozone in oxygen gas was passed through a cold (−75°C) suspension of a mixture of the alkenes 15 (50 mg, 0.24mmole) and NaHCO₃ (10 mg) in a mixture of 1:5 methanol and methylene chloride (1.5 mL) till blue colour appears. Excess ozone was flushed off with oxygen and the reaction mixture was kept at room temperature for 30 min. Triphenylphosphine (180 mg, 0.69 mmole) was added to the cold (−30°C) reaction mixture and stirred for 8 hr at room temperature. Evaporation of the solvent under reduced pressure and purification of the residue over a silica gel column using ethyl acetate/hexane(1:20) as eluent furnished the keto aldehyde 16 (30 mg, 53%) as colourless oil.

Procedure II (from the hemiketal 25). To a magnetically stirred suspension of PCC (220 mg, 1.0 mmole) and sodium acetate (220 mg) in CH₂Cl₂ (0.5 mL) was added a solution of the hemiketal 25 (90 mg, 0.09 mmole) in CH₂Cl₂ (0.5 mL) in one portion. The reaction mixture was stirred at room temperature for 30 min, filtered through silica gel column, and the column eluted with more CH₂Cl₂. Evaporation of the solvent furnished the keto aldehyde 16 (65 mg, 72%) as oil.

Procedure III (from the enone 28). Prepared cooled dry ozone in oxygen gas was passed through a cold (−75°C) suspension of the enone 28 (16mg, 0.067 mmole) and NaHCO₃ (10 mg) in a mixture of methanol (1 mL) and methylene chloride (5 mL) till blue colour appears. Excess ozone was flushed off with oxygen for 5 min and the reaction mixture was kept at room temperature for 30 min. Triphenylphosphine (18 mg, 0.07 mmole) was added to the cold (−30°C) reaction mixture and stirred for 8 hr at room temperature. Evaporation of the solvent under reduced pressure and purification of the residue over a silica gel column using ethyl acetate/hexane (1:20 to 1:5) as eluent furnished the keto aldehyde 16 (16 mg, 71%) as colourless oil; IR (neat): 2730, 1715, 1695, 1465, 1380, 1350, 925 cm⁻¹. ¹H NMR (900MHz, CDCl₃): δ 9.77 (1 H, t, J = 3 Hz, CHO), 2.60 and 2.25 (2 H, d of AB q, J = 16 and 3 Hz, C H₂C=O), 2.12 (3 H, s, CH₃C=O), 2.00-1.00 (8 H, m), 1.20 (6 H, s, 2 × tert-CH₃). 0.86 (6 H, d, J = 7.2 Hz, CH₃-CH-CH₃).

(1R,6R,9R)-1,6-Dimethyl-9-isopropylbicyclo-[4.4.0]-dec-3-en-2-one 17. To a solution of the keto-aldehyde 16 (30 mg, 0.13 mmole) in dry THF (0.5 mL) was added 0.15 mL of 1 M KOH in methanol and the reaction mixture stirred at room temperature for 8 hrs. The solvent was removed under reduced pressure. The residue was taken in water (1.5 mL) and extracted with ether (3 × 5 mL). The ether extract was washed with brine and dried (Na₂SO₄). Evaporation of the solvent and purification of the product on a silica gel column using ethyl acetate/hexane (1:20) as solvent furnished the enone 17 (21 mg, 76%) as oil; [α]D +37.0 (c 1, CHCl₃); IR (neat): 1670, 1460, 1385, 810 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 6.81 (1 H, ddd, J = 10.1, 5.9 and 2.3 Hz, H-4), 5.96 (1 H, ddd, J = 10.1 and 3.2 Hz, H-3), 2.85 (1 H, br d, J = 19.4 Hz) and 1.79 (1 H, dd, J = 19.4 and 6.0 Hz) [H-5], 1.70-0.70 (8 H, m), 1.12 (3 H, s) and 0.89 (3 H, d, Jw = 0.5 Hz) [2 × tert-CH₃], 0.87 (3 H, d, J = 6.4 Hz) and 0.84 (3 H, d, J = 6.4 Hz) [CH₃-CH-CH₃]; ¹³C NMR (100 MHz, CDCl₃): δ 205.4 (C=O), 146.7 (C-4), 127.7 (C-3), 49.5, 37.7, 36.9 (2C), 34.8, 34.7, 32.9, 25.1, 24.8, 19.9, 19.8, 16.1. Mass: m/z 220 (M⁺, 15%), 152 (60), 123 (15), 109 (100), 95 (18). HRMS (m/z): Calcd for C₁₅H₂₀O₂: 220.1827. Found: 220.1830.

(1S,6R,9R)-1,6-Dimethyl-9-isopropylbicyclo-[4.4.0]-decan -2-one [(-)[valeranone] 1]. Hydroge-nation of
the enone 17 (20 mg, 0.09 mmole) in drymethanol (0.5 mL) using 10%-Pd/C (5 mg) as the catalyst for 12 hr and purification of the product on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished valeranone (1,16.2 mg, 80%) as a colourless oil; [α]D +54.3 (c 0.7, CHCl3); IR (neat): 1695, 1460, 1380, 1260, 1030, 940, 800 cm−1; 1H NMR (400MHz, CDCl3): δ 2.65 (1 H, d of t, J = 13.7 and 7.9 Hz) and 2.19 (1 H, quintet of d, J = 14.8 and 2.2 Hz) [H ئ3], 2.40 (1H, d of t, J = 13.3 and 5.2 Hz), 1.0-1.92 (11 H, m), 1.05 (3 H, s) and 0.80 (3 H, s) [2 × tert-CH3], 0.87 (3 H, d, J = 6.9 Hz) and 0.85 (3 H, d, J = 6.9 Hz) [CH3 × CH(=CH)3]; 13C NMR (100 MHz, CDCl3): δ 217.5 (C=O), 53.1 (C ئ 3), 38.6 (C ئ 6), 38.5, 37.4, 37.0, 36.2, 32.9, 32.0, 24.9, 24.7, 21.8, 19.9, 19.8, 16.8; Mass: m/z 222 (M+, 53%), 179 (20), 161 (18), 151 (35), 125 (100), 123 (45), 109 (45), 98 (80). HRMS (m/z): Calcd for C13H26O: 222.1984. Found: 222.1978.

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References