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Enantiospecific total syntheses of(–)-valeranone

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Two convenient methodologies havebeendescribed for the **enantiospecific** synthesis of (–)-**valeranone** 1. The hydrindanone 12, obtained from the readilyandabundantly available monoterpene (*R*)-carvone,has been converted into theketoaldehyde **16**via the alkene **15b**. In anotherdirectionthe lactone **18**, obtainedfrom the hydrindanone **12**, has beenelaboratedinto the ketoaldehyde **16**employing two methodologies.Intramolecularaldol condensation followedbyhydrogenation transformed the ketoaldehyde **16**into (–)-**valeranone** **1**.

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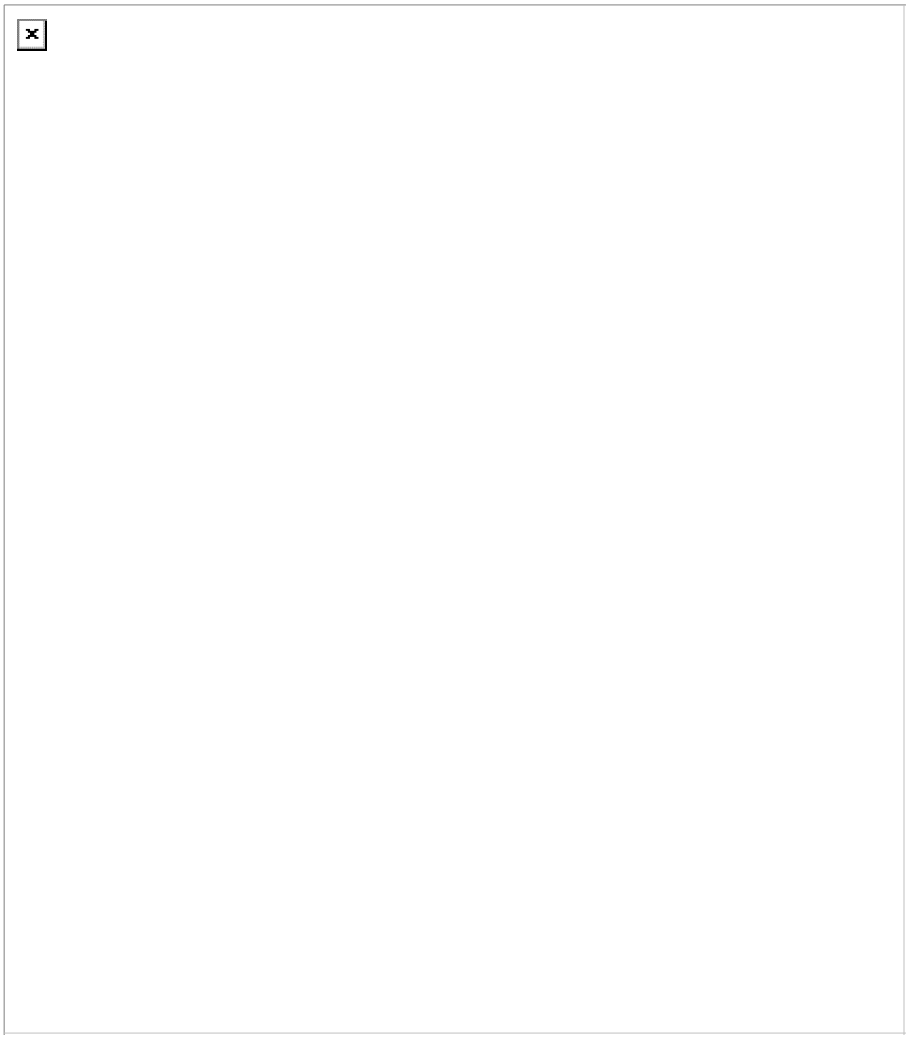
Thesesquiterpene (–)-**valeranone** **1** was the firstmember of a small group of natural products, valeranes, containing a rearrangedeudesmane **2** carbon framework withmethyl substituents at both the ring junctions of the *cis*-decalin system valerane **3**. (–)-**Valeranone** **1** was firstisolated by Stoll and co-workers [1] in 1957 from European valerian, Valeriana officinalis L. and widely distributedin the members of the valerianaceous family. The elucidation of the structureof (–)-**valeranone** **1** has beenthe subject of protracted controversy and has presented a problem insesquiterpene chemistry. Ultimately, Hikino and coworkers [2]established correct stereostructure as well as absolute configuration of (-)-**valeranone** **1**, which was confirmed later by **enantiospecific**synthesis[3] of the optical antipode of **valeranone** (+)-**1**. Inaddition 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 atomswith methyl substituents in a *cis*-decalinframework , and three chiral centres made the valerane group of sesquiterpenesattractive synthetic targets. As a consequence, several approaches to**valeranone** **1** and to the parenthydrocarbon valerane **3**, both inracemic as well as in optically active form, have been reported in theliterature [5]. We have reported an **enantiospecific** synthesis of(+)-valerane **3** starting from (*R*)-carvone **8** via thetricyclic ketone **9**[6]. ~~(Ref. 6)~~ Incontinuation , we have investigated [7] the synthesis of (–)-**valeranone** **1** starting from the C-14 tricyclic ketone **9**.

To begin with, a methodology analogousto that used [6] for (+)-valerane **3** was explored via thering expansion

of hydrindanone to decalone. The synthetic sequence is depictedin **Scheme I**. To avoid subsequentregiochemical problems, the fifteenth carbon atom required for **valeranone** wasintroduced prior to the cleavage of the cyclopropane ring. Thus, regioselectivemethylation of the tricyclic ketone **9** with LDA and methyl iodide at lowtemperature furnished the alkylated ketone **10** in 91% yield with a highdegree



Scheme I

ofstereoselectivity. The stereochemistry of the secondary methyl group in the ketone **10** was assigned as *exo* on the basis of the preferential alkylation of the intermediate enolate fromthe less hindered *exo* face. Regiospecific reductive cleavage [8] of the tricyclic ketone **10** using lithium in liquid ammonia reductionconditions furnished the hydrindanone **11** in 76% yield whose structurerests secured from its spectral data. Hydrogenation of the olefinic moiety inthe enone **11** using 10%-Pd/C as the catalyst in methanol at oneatmosphere pressure of hydrogen (balloon) furnished the saturated ketone **12** in 99% yield. Sodium borohydride reduction of the hydrindanone **12** furnisheda 2:1 epimeric mixture of the alcohol **13** in 96% yield. Treatment of thealcohol **13** with triphenylphosphine , imidazole and iodine [9] inbenzene generated the iodide **14** in 76% yield, which on de-hydroiodinationusing 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 mixtureof the olefins **15a** and **15b** in 89% yield, which was found to be inseparableusing conventional methods. Ozonation of the mixture of olefins **15** andreductive work-up of the ozonide with triphenylphosphine followed by purificationon a silica gel column furnished the keto-aldehyde **16** in 53% yield. Intramolecularaldol condensation of the keto-aldehyde **16** in THF using 1M aqueous potassium hydroxide inmethanol furnished, exclusively, the cyclohexenone **17** (valerenone) in76% yield. The ^{1}H NMR spectrum exhibited resonances , a ddd at δ6.81 and a dd at 5.96 due to β and a protons, respectively, of an

a,β-unsaturated ketone, a broad doublet atδ 2.85 and a dd at δ 1.79 dueto axial (orthogonal to enone moiety) and equatorial protons of the allylic CH_2,respectively, a singlet at δ 1.12 anda doublet at 0.89 (J_w = 0.5 Hz) due to the two tertiary methyl groups and two doubletsat δ 0.87 and 0.84 due to the isopropylgroup, establishing the structure of the enone **17**. Further confirmationof the structure of the enone **17** came from its ^{13}C NMRspectrum which exhibited resonances at d 205.4 due to carbonyl carbon, at d 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 ringjunction 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 ofthe carbons. Finally, hydrogenation of the enone **17** in methanol using10%-Pd/C as the catalyst at one atmosphere pressure of hydrogen (balloon) furnishedthe saturated ketone, (□)□**valeranone** **1** {[a]$_D^{25}$ –54.3, (c 0.7, $CHCl_3$), lit.,[5b][α]$_D^{26}$ –51.9 (c 0.3, $CHCl_3$)} in 80%yield, whose spectral data was found to be identical to that reported fornatural **valeranone**.

To overcome the regiochemical problems,an alternative methodology based on the Baeyer-Villiger oxidation, for thehydrindanone to decalone ring enlargement, was investigated. The hydrindanone **12**was first converted into the lactone **18** *via* a regioselectiveBaeyer-Villiger oxidation.[10] Thus, treatment of the hydrindanone **12**with *m*-chloroperbenzoic acid (MCPBA)and triflouroacetic acid in methylene chloride for 5 hr resulted in the formationof the δ-lactone **18** in 84% yield in a highly regioselective manner.Presence of the carbonyl absorption band at 1735 cm□1 due tothe lactone moiety in the IR spectrum and an upfield shift of the carbonylcarbon resonance to δ 173.5 ppm in the 15 lines ^{13}C NMR spectrumclearly established the structure of the lactone **18**. Presence of a quartetat δ 4.15 due to OC *H*CH_3 and an AB quartet at 2.65 and2.04 due to $CH_2C{=}O$ 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 theregiospecific conversion of the primary alcohol into a leaving group andoxidation of the secondary alcohol followed by intramolecular alkylation of theresultant ketone **20** would generate **valeranone** **1**. However,treatment of the diol **19** with one equivalent of methanesulfonyl chloridein pyridine and methylene chloride, instead of the expected hydroxy mesylate,furnished only the cyclic ether **21** in 84% yield, whose structure wasestablished 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**).

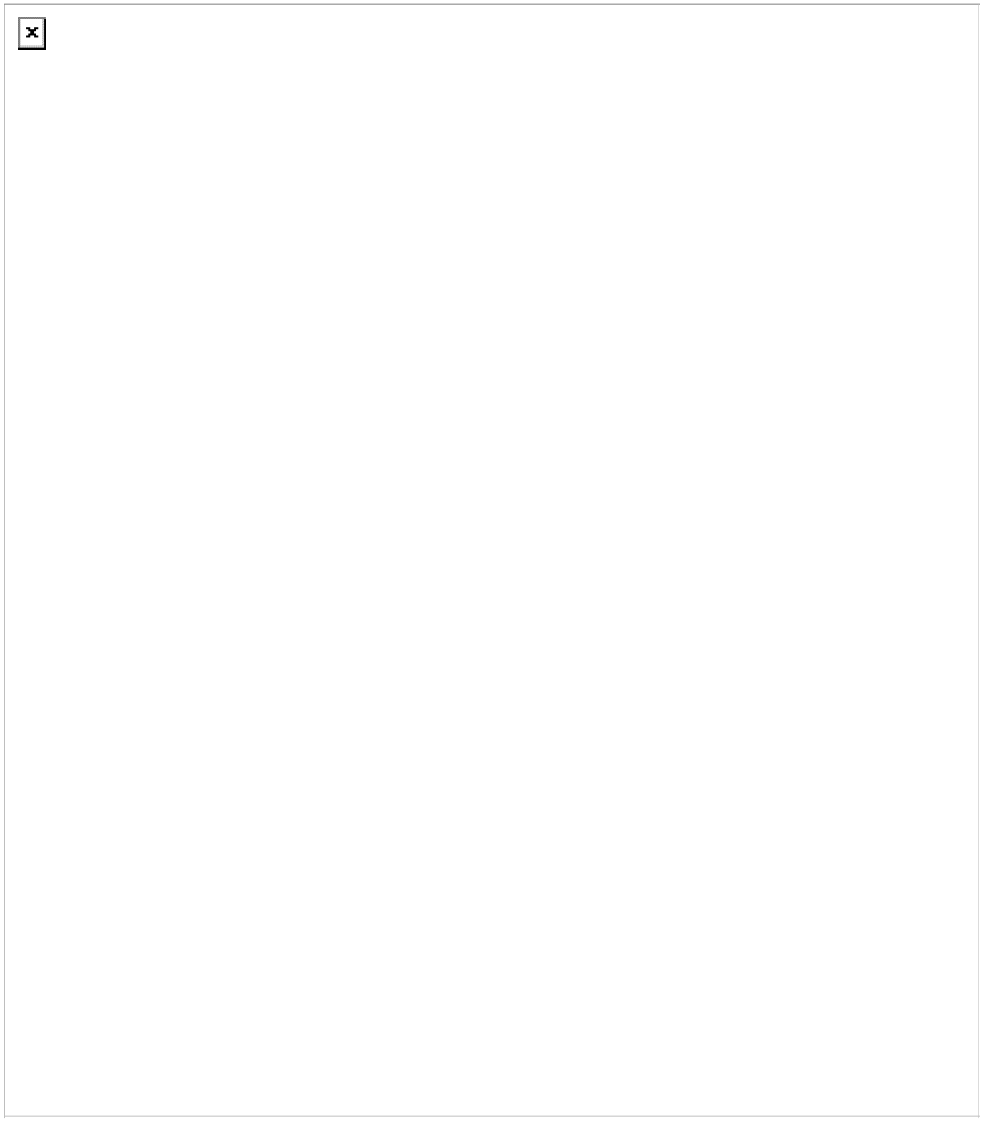
Subsequently, a strategy based on theregioselective protection of the primary alcohol in the diol **19** was envisaged.Thus, treatment of the diol **19** with *tert*-butyldimethyl-silylchloride and imidazole in methylene chloride furnished the TBDMS ether **22**in 65% yield. Oxidation of the secondary alcohol in the hydroxy ether **22**with pyridinium chlorochromate (PCC) and sodium acetate in methylene chloridegenerated the keto ether **23** in 82% yield. Tetrabutylammo-nium 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 ofhemiketal **25**. Oxidation of the hemi-ketal **25** with PCC and sodiumacetate in methylene chloride furnished the keto aldehyde **16** in 72%yield. An alternative strategy was also conceived for the synthesis of theketo-aldehyde **16** via protection of the aldehyde as a terminal olefin.Thus, controlled reduction of the lactone **18** with one equivalent ofdiisobutylaluminum hydride (DIBAH) in toluene at –78 ºCfurnished the lactol **26** in 87% yield. Reaction of the lactol **26**with an excess of methylenetriphenylphospho-rane in THF generated the hydroxyolefin **27** in 57% yield. Oxidation of the alcohol **27** with PCC andsodium acetate in methylene chloride furnished the keto olefin **28** in 80%yield, whose structure was established from the spectral data. Ozonolysis ofthe ketoolefin **28** in a 1:5 methanol and methylene chloride mediumfollowed by reductive work-up of the ozonide with triphenylphosphine furnishedthe keto-aldehyde **16** in 71% yield, which was found to be identical withthe sample obtained earlier.

In conclusion, **enantiospecific syntheses**to the natural enantiomer of **valeranone** have been developed starting from thereadily available (*R*)-carvone via thehydrindanone **12**. For the ring enlargementof hydrindanone to decalone two paths were employed. In the first path, oxidativecleavage of cyclopentene **15b**generated the ketoaldehyde **16**, thepenultimate 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 transformedinto the

ketoaldehyde **16** employingtwo different methodologies.

Experimental Section

Melting points were recorded using aTempo melting point apparatus in capillary tubes and are uncorrected. In theNMR spectra, the chemical shifts



Scheme II

(δ ppm)and the coupling constants (Hz) are reported in the standard fashion withreference to either internal tetramethylsilane (for ^{1}H) or thecentral line (77.1 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}CNMR spectra the nature of the carbons (C, CH, CH_2 and CH_3)was obtained either by off-resonance decoupled spectra or DEPT 135 experiment,and are given in parentheses. In the mass spectra, relative intensities of theions are given in parentheses. Optical rotations were measured using a JascoDIP-370 digital polarimeter; $[\alpha]_D$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- septumtechnique . Low temperature reactions were conducted in a bath made of alcoholand 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 P_2O_5.Dry methanol was prepared by distillation over magnesium and stored overmolecular sieves. Liquid ammonia was obtained in cylinders from Mysore AmmoniaLtd . and distilled over sodamide prior to use. All commercial reagents wereused as such without further purification.

(1*R*,2*R*,4*R*,6*S*,7*S*,9*S*)-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 ofdiisopropylamine (1.1 mL, 7.84 mmoles) in dry THF (2 mL), under

nitrogen, wasslowly added a solution of *n*-BuLi inhexane (1.6 *M*, 4.9 mL, 7.84 mmoles). The resulting colourless mixturewas 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 mmoles)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, 7.84mmoles), and allowed to warm up to room temperature. The resulting mixture wasstirred at room temperature for 4 hr, quenched with 0.5 *N* aq. HCl and extracted with ether (3 ´10 mL). The combined ether extract was washed with brine and dried(Na_2SO_4). Evaporation of the solvent and carefulpurification of the product on a silica gel column using ethyl acetate-hexane(1:40) as eluent provided the methylated ketone **10** (470 mg, 55%); [a] +29.0 (c 2, $CHCl_3$); IR (neat): 3080, 1715, 1645, 1375,1085, 885 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$):δ 4.68 (2 H, m, C=CH_2), 1.69 (3 H, s, olefinic CH_3),2.75-1.40 (8 H, m), 1.20 (3 H, s) and 1.04 (3 H, s) [2 ´*tert*-CH_3], 0.95 (3 H, d, *J*= 7.4 Hz, *sec*-CH_3); ^{13}C NMR(67.5 MHz, $CDCl_3$): δ 215.2 (C=O), 150.1 (*C*=CH_2),109.8 (C=*C*H_2), 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*-CH_3); 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 elutionof the column with ethyl acetate-hexane (1:20) furnished unreacted starting material**9** (315 mg, 39%).

(1*S*,3*R*,6*R*,9*S*)-3-Isopropenyl-1,6,9-trimethyl-bi-cy- clo-[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 Dewar condenser was added,freshly cut lithium (63 mg, 9.1 mmoles) followed by a solution of the tricyclicketone **10** (495 mg, 2.27 mmoles) in anhydrous THF (2 mL). The resultingblue coloured solution was stirred for 15 min at -33 °C and then the reaction was quenched with solid NH_4Cl.After evaporation of ammonia, the residue was taken in water (3 mL) andextracted with CH_2Cl_2 (3´7 mL). The combined CH_2Cl_2 extract was washedwith brine and dried (Na_2SO_4). Evaporation of the solventand 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%) ascolourless oil; [a] –29.5 (c 2, $CHCl_3$); IR (neat): 3080, 1735, 1640, 1385,1375, 885 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$):δ 4.70 (2 H, m, C=CH_2), 2.70 and 1.83 (2 H, 2 ´d, *J* = 17.9 Hz, H□7), 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 CH_3),1.80-1.20 (6 H, m), 1.13 (3 H, d, *J* = 7.9 Hz, *sec*-CH_3),1.03 (3 H, s) and 0.97 (3 H, s) [2×*tert*-CH_3]; ^{13}C NMR (67.5 MHz, $CDCl_3$):δ 222.1 (C, C=O), 149.6 (C, *C*=CH_2), 108.7 (CH_2,C=*C*H_2), 54.7 (CH, C□9),51.3 (C), 48.6 (CH_2, C□7), 44.2 (CH_2, C□5),42.8 (C), 40.3 (CH, C □3), 33.3 (CH_2, C□2), 26.7 (CH_2,C□4), 26.5 (CH_3), 21.1 (CH_3), 17.0 (CH_3),14.1 (CH_3, *sec*-CH_3); 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 $C_{15}H_{24}O$:220.1828. Found: 220.1818.

(1*S*,3*R*,6*R*,9*S*)-3-Isopropyl-1,6,9-trimethylbicy-clo- -[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 mixturewas stirred in an atmosphere of hydrogen, created by evacuative replacement ofair using a balloon filled with hydrogen, for 12 hr and then the catalyst wasfiltered off. Evaporation of the solvent and purification of the product over asilica gel column using ethyl acetate-hexane (1:40) as eluent furnished thebicyclic ketone **12** (220 mg, 99%) as colourless oil; [a] –25.5 (c 2, $CHCl_3$); IR (neat): 1735, 1455, 1385, 1190 cm^{-1};^1H NMR (270 MHz, $CDCl_3$):δ 2.72 and 1.77 (2 H, 2 ×d, *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*-CH_3), 1.01 (3 H, s) and0.93 (3 H, s) [2 ×*tert*-CH_3],0.86 (6 H, d, *J* = 6.7 Hz, C*H*$_3$□CH□C*H*$_3$);^{13}C NMR (22.5 MHz, $CDCl_3$):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 $C_{15}H_{26}O$:222.1984. Found: 222.1984.

(1*S*,3*R*,6*R*,9*S*)-3-Isopropyl-1,6,9-trimethylbi-cy- clo-[4.3.0]nonan-8-ols 13. To an ice cold, magne-tically stirred solution of the ketone **12**(125 mg, 0.56 mmole) in dry methanol (2 mL) was added sodium borohydride

(12mg, 0.32 mmole). The reaction mixture was stirred at the same temperature for15 min. The solvent was evaporated under reduced pressure and 0.5 mL of 0.5 N aq. HCl was added to consume the excessreagent. 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 (Na_2SO_4).Evaporation of the solvent and purification of the product on a silica gelcolumn using CH_2Cl_2 as solvent furnished the alcohol **13**(120 mg, 96%) as oil; [a]$_D$ +16.5 (c 2, $CHCl_3$); IR (neat): 3350, 1455, 1385, 1015, 795cm $^{-1}$; ^{1}H NMR (200 MHz, $CDCl_3$):δ 4.10-3.80 and 4.50-4.10 (1 H, m, C *H*OH), 2.42-2.15 (1 H,m), 2.10-1.70 (2 H, m, CH_2), 1.60-0.90 (8 H, m), 1.00-0.80 (15 H, m,5 ×CH_3); 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 $C_{15}H_{28}O$:224.2140. Found: 224.2156.

(1*R*,3*R*,6*R*)-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 mmoles) and iodine (162 mg, 0.64mmole), sequentially. The stirring was continued at room temperature for 2 hr.The supernatant layer was separated and the residue was further washed withether. The combined organic phase was evaporated and the product was rapidlyfiltered through a neutral alumina column using ethyl acetate-hexane (1:40) aseluent to furnish the iodide **14** (118 mg, 76%) as oil; IR (neat): 1450, 1375, 1180, 1120 cm $^{-1}$;^{1}H NMR (200 MHz, $CDCl_3$):δ 4.86-4.70 (1 H, m), 2.80-0.95 (11 H, m), 1.00-0.80 (15 H, m, 5 ´CH_3).

A solution ofthe iodide **14** (90 mg, 0.27 mmole) and DBU (0.05 mL, 0.34 mmole) in dryDMF (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 extractedwith ether (3×5 mL). The combined ether extract waswashed with water, saturated aq. $NaHCO_3$ and brine, and dried (Na_2SO_4).The solvent was evaporated and the product was rapidly chromatographed on asilica gel column using hexane as eluent to furnish a 1:3 mixture of thealkenes **15a** and **15b**(50 mg, 89%) as oil; [a]$_D$ –17.5 (c 2, $CHCl_3$); IR (neat): 1455, 1380, 1370, 1015, 780cm $^{-1}$; ^{1}H NMR (200 MHz, $CDCl_3$,peaks due to the major isomer): δ 5.16 (1 H, s, olefinic H), 2.60-1.80 (2H, m, allylic), 1.62 (3 H, s, olefinic CH_3), 1.80-1.00 (8 H, m),0.89 (3 H, s) and 0.85 (3 H, s) [2 ×*tert*-CH_3], 0.84 (3 H, d, J = 6.7 Hz) and 0.81 (3 H, d,J = 7.3 Hz) [C*H*$_3$CHC*H*$_3$]; ^{13}C NMR (100 MHz, $CDCl_3$, for a 1:3 mixture of theolefins **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 $C_{15}H_{26}$: 206.2034.Found: 206.2045.

(1*R*,2*S*,6*R*,9*R*)-9-Isopropyl-1,2,6-trimethyl-3-oxa- bicyclo[4.4.0]decan-4-one18. To a magneti-cally stirred solution of theketone **12** (220 mg, 0.99 mmole) and *m*-CPBA(55%, 943 mg, washed with *p*H 7.5 phosphatebuffer , 3 mmoles) in CH_2Cl_2 (15 mL), protected fromlight, was added triflouroacetic acid (0.08 mL, 1 mmole) and stirred at roomtemperature for 5 hr. The reaction mixture was then diluted with CH_2Cl_2(5 mL), washed sequentially with 10% aq. sodium sulfite solution, saturated aq.$NaHCO_3$ and brine, and dried (Na_2SO_4). Evaporationof the solvent and purification of the product on a silica gel column usingethyl acetate-hexane (1:10) as eluent furnished the lactone **18** (198 mg,84%) as oil; [a]$_D$ –19.5 (c 2, $CHCl_3$); IR (neat): 1735, 1460, 1380, 1255,1220, 1065, 970 cm $^{-1}$; ^{1}H NMR (200MHz, $CDCl_3$): δ 4.15 (1 H, q, J = 6.7 Hz, H2),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*-CH_3),1.03 (3 H, s) and 0.99 (3 H, s) [2 ×*tert*-CH_3], 0.86 (6 H, d, J = 6.4 Hz, C*H*$_3$CHC*H*$_3$);^{13}C NMR (100 MHz, $CDCl_3$):δ 173.5 (OC=O), 84.1 (C2), 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 $C_{15}H_{26}O_2$:238.1933. Found: 238.1962; Calcd for $C_{11}H_{20}$ (M^+-$C_4H_6O_2$):152.1565. Found: 152.1568.

(1*R*,2*R*,4*R*)-1,2-Dimethyl-2-(1-hydroxyethyl)-4-iso-- propylcyclohexaneethanol 19. To a magne-tically stirred solution of the lactone **18** (190mg, 0.8 mmole) in dry ether (5 mL) was added $LiAlH_4$ (40 mg,

1.07mmoles) at room temperature and stirred for 30 min. The reaction was carefullyquenched with 0.5 *N* aq. HCl andextracted with ether (3×5 mL).The combined ether extract was washed with aq. $NaHCO_3$ and brine, anddried (Na_2SO_4). Evaporation of the solvent and purificationof the product on a silica gel column with ethyl acetate-hexane (1:1) as eluentfurnished the diol **19** (190 mg, 98%), which was recrystallised from CH_2Cl_2-hexane; m.p. 52°C, [a] +12.5 (c 2, $CHCl_3$); IR (neat): 3350, 1465, 1375, 1100,1055, 1020, 935, 755 cm^{-1}; ^1H NMR (270MHz, $CDCl_3$): δ 3.89 (1 H, q, *J* = 6.4 Hz, HO-C*H*CH_3),3.75 and 3.71 (2 H, t of AB q, *J* = 9.8 and 6.4 Hz, CH_2CH_2-OH),2.05-0.90 (12 H, m), 1.12 (3 H, d, *J* = 6.4 Hz, *sec*-CH_3),1.06 (3 H, s) and 0.91 (3 H, s) [2×*tert*-CH_3], 0.86 (3 H, d, *J* = 6.5 Hz) and 0.84 (3 H, d,*J* = 6.7 Hz) [CH_3-CH-CH_3];Mass: m/z 225 [(M - OH), 10%],197 (35), 179 (20), 153 (50), 152 (45), 123 (75), 109 (95), 97 (60), 95 (62). HRMS (m/z): Calcd for $C_{13}H_{25}O$(M -CH_2CH_2OH): 197.1905. Found: 197.1902.

(1*R*,2*S*,6*R*,9*R*)-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 CH_2Cl_2 (2 mL) was addedmethanesulfonyl chloride (0.01 mL, 0.13 mmole) and pyridine (0.01 mL, 0.13mmole) and stirred for 1 hr at 0 °C. To thereaction mixture was then added 0.5 *N*aq. HCl and extracted with CH_2Cl_2 (3´3 mL). The combined CH_2Cl_2 extract was washedwith aq. $NaHCO_3$ and brine, and dried (Na_2SO_4).Evaporation of the solvent and purification of the product on a silica gel columnusing hexane as eluent furnished the ether **21** (18 mg, 84%) as oil; [a] +35 (c 1, $CHCl_3$); IR (neat): 1460, 1370, 1105 cm^{-1};^1H NMR (270 MHz, $CDCl_3$):δ 3.87 (1 H, d of t, *J* = 12.0 and 2.6 Hz) and 3.63 (1 H, ddd, *J*= 12.0, 5.5 and 1.8 Hz) [H-4], 3.39 (1 H, q, *J* = 7.2 Hz, H-2),2.21 (1 H, d of t, *J* = 13.3 and 5.6 Hz) and 1.96 (1 H, t, *J* =13.3 Hz) [H-5], 1.80-1.00 (8 H, m), 1.34 (3 H, d, *J* = 7.2 Hz, *sec*-CH_3),1.06 (3 H, s) and 0.85 (3 H, s) [2 ×*tert*-CH_3], 0.87 (6 H, d, *J* = 6.9 Hz, CH_3-CH-CH_3).

(1S)-1-[(1*R*,2*R*,5*R*)-2-(2-*tert*-Butyldimethyl-silyl-oxyethyl)-5-isopropyl-1,2-dimethylcyclohex-yl]ethanol 22. To a magneticallystirred solution of the diol **19** (185 mg, 0.76 mmole) in dry CH_2Cl_2were 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 dilutedwith CH_2Cl_2, washed with brine and dried (Na_2SO_4).Evaporation of the solvent and purification of the residue on a silica gelcolumn 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,$CDCl_3$): δ 3.86 (1H, q, *J* = 6.5 Hz, C*H*OH), 3.75-3.60 (2 H, m, CH_2-OSi),1.90-1.55 (2 H, m), 1.50-1.00 (9 H, m), 1.09 (3 H, d, *J* = 6.5 Hz), 1.03(3 H, s) and 0.88 (3 H, s) [2 ×*tert*-CH_3], 0.90 [9 H, s, C(CH_3)$_3$],0.85 (3 H, d, *J* = 6.5 Hz) and 0.83 (3 H, d, *J* = 6.9 Hz) [CH_3-CH-CH_3],0.06 [6 H, s, Si(CH_3)$_2$]; ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): d 72.4 (CH, *C*HOH), 60.3 (CH_2, *C*H_2-OSi),42.7 (C), 38.8 (CH), 37.4 (C), 36.9 (CH_2), 35.5 (CH_2),34.8 (CH_2), 32.9 (CH), 26.0 [3 C, CH_3, C(*C*H_3)$_3$],25.1 (CH_2), 24.9 (CH_3), 20.1 (CH_3), 19.4 (CH_3),19.3 (CH_3), 18.5 (Si-*C*Me_3), 13.7 (CH_3),–5.2 (2 C, CH_3).

1-[(1*R*,2*R*,5*R*)-2-(2-(*tert*-Butyldimethylsilyloxy-ethyl)-5-isopropyl-1,2-dimethylcyclo-hexyl]-1-ethan-one 23. To a magneticallystirred suspension of PCC (350 mg, 1.6 mmoles) and sodium acetate (350 mg, 4.27mmoles) in CH_2Cl_2 was added a solution of the alcohol **22**(190 mg, 0.53 mmole) in CH_2Cl_2 in one portion. Thereaction mixture was stirred at room temperature for 30 min, filtered throughsilica gel column, and eluted the column with more CH_2Cl_2.Evaporation of the solvent furnished the keto ether **23** (156 mg, 82%) as oil; [a] +6.7 (c 0.6, $CHCl_3$); IR (neat): 2950, 2860, 1700, 1460,1380, 1320, 1250, 1090, 1000, 830, 780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): d 3.70-3.50 (2 H, m, CH_2OSi), 2.15 (3 H, s, $COCH_3$), 2.05-1.90 (2 H, m),1.55-1.00 (8 H, m), 1.16 (3 H, s) and 1.00 (3 H, s) [2 ´*tert*-CH_3], 0.90 (3 H, d, *J*= 6.9 Hz) and 0.89 (3 H, d, *J* = 6.3 Hz) [CH_3-CH-CH_3],0.88 [9 H, s, C(CH_3)$_3$] and 0.03 [6 H, s, Si(CH_3)$_2$];^{13}C NMR (75 MHz, $CDCl_3$): d 214.0 (C, C=O), 59.8 (CH_2, CH_2-OSi), 54.0 (C,C-1'), 38.8 (CH, C-5'), 37.3 (C, C-2'), 36.8 (CH_2), 35.4 (CH_2),33.0 (CH), 32.8 (CH_2), 29.4 (CH_3), 26.1 [3 C, CH_3,C(*C*H_3)$_3$], 25.1 (CH_2), 23.0 (CH_3),20.2 (CH_3), 19.8 (CH_3), 19.0

(CH_3), 18.4 (C,Si-*C*Me_3), 5.1 [2 C, CH_3, Si$(CH_3)_2$];Mass: 339 (M-CH_3,2%), 313 (5), 279 (5), 257 (2), 239 (5), 205 (5), 149 (70), 69 (90), 57 (100).

(1*R*,6*R*,9*R*)-9-Isopropyl-1,2,6-trimethyl-3-oxa-bi-cyclo[4.4.0]decan-2-ol25. To a magnetically stirred solution of the ketoether **23** (140 mg, 0.39 mmole) in THF was added TBAF (420 mg, 1.6mmoles). The reaction mixture was stirred at room temperature for 4 hr. It wasthen extracted with ether and the combined ether extract was washed with brineand dried (Na_2SO_4). Evaporation of the solvent andpurification of the product on a silica gel column using ethyl acetate-hexane(1:10) as eluent furnished the hemiketal **25** (90 mg, 70%) as colourlessoil; IR (neat): 3350, 1460,1360, 1220, 1090, 1050, 1010 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): d 4.15 (1 H, ddd, *J* = 13.5, 11.4 and 2.4 Hz) and 3.54 (1 H,dd, *J* = 11.4 and 5.1 Hz, H-4), 2.28 (1 H, d of t, *J* = 13.5and 5.1 Hz), 1.70-1.00 (9 H, m), 1.16 (3 H, s), 1.04 (3 H, s) and 0.91 (3H, s)[3 ×*tert*-CH_3], 0.88 (3 H, d, *J*= 6.6 Hz) and 0.87 (3 H, d, *J* = 6.9 Hz) [C*H*$_3$-CH-C*H*$_3$]and 0.69 (1 H, d, *J* = 13.0 Hz); ^{13}C NMR (75 MHz,$CDCl_3$+CCl_4): d 101.5 (C, C-2), 57.5 (CH_2, C-4), 42.0 (C), 39.0 (CH, C-9),38.6 (CH_2), 35.6 (CH_2), 33.6 (C), 33.1 (CH), 32.0 (CH_2),26.4 (CH_3), 25.8 (CH_3), 24.1 (CH_2), 20.3 (CH_3),19.6 (CH_3), 17.1 (CH_3).

(1*R*,2*R*,6*R*,9*R*)-9-Isopropyl-1,2,6-trimethyl-3-oxa- bicyclo[4.4.0]decan-4-ol 26. To amagneti-cally stirred, cold (-78 °C)solution of the lactone **18** (60 mg, 0.27 mmole) in toluene (1 mL) wasadded 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 quenched withwater (5 mL) and extracted with ether (3 ´5 mL). The combined organic extract was washed with brine and dried(Na_2SO_4). Evaporation of the solvent and purification ofthe residue on a silica gel column using ethyl acetate-hexane (1:10) as eluentfurnished the lactol **26** (50 mg, 87%) as oil; [α] +28.0 (c 4.0, $CHCl_3$); IR (neat): 3330, 2950, 2870, 1460,1370, 1060, 1010 cm $^{-1}$; ^{1}H NMR (300 MHz,$CDCl_3$ + CCl_4): 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*-CH_3), 1.04 (3 H, s) and0.86 (3 H, s) [2 ×*tert*-CH_3],0.85 (6 H, d, *J* = 6.3 Hz, C*H*$_3$-CH-C*H*$_3$);^{13}C NMR (75 MHz, $CDCl_3$+CCl_4):δ 90.8 (CH, C-4), 78.7 (CH, C-2), 40.0 (CH_2),39.4 (CH_2), 39.0 (CH), 38.6 (CH_2), 38.4 (C), 34.9 (C),32.8 (CH), 26.7 (CH_3), 24.8 (CH_2), 20.2 (CH_3),19.8 (CH_3), 18.0 (CH_3), 16.7 (CH_3); Mass: m/z 240 (M^+,$C_{15}H_{28}O_2$, 2%), 207 (10), 152 (60), 109 (100),95 (15), 82 (20).

(1*S*)-1-[(1*R*,2*R*,5*R*)-(2-Allyl-5-isopropyl-1,2-dime- thyl-cyclohexyl]ethanol 27. To a magneticallystirred suspension of methyltriphenylphosphonium iodide (2.6 g, 6.43 mmoles) indry THF (2 mL) was added a solution of K^+*t*-AmO^- in THF (1 mL, 4.85 mmoles) and the resultant yellow colouredsolution was stirred for 30 min at room temperature. To the methylenetriphenylphos-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 quenchedwith saturated aq. NH_4Cl solution (2 mL) and extracted with ether (5mL). The combined ether extract was washed with brine and dried (Na_2SO_4).Evaporation of the solvent and purification of the residue over a silica gelcolumn using ethyl acetate-hexane (1:30) as eluent furnished the alcohol **27** (20mg 57%) as colourless oil; IR (neat): 3330,2860, 2830, 1630, 1460, 1370, 1100, 1050, 900 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$ + CCl_4): d 5.79 (1 H, t of dd, *J* = 15.9, 11.1 and 6.9 Hz), 5.03 (1 H,d, *J* = 15.9 Hz), 5.01 (1 H, d, *J* = 11.1 Hz), 3.83 (1 H, q, *J*= 6.5 Hz, C*H*OH), 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 ´*tert*-CH_3], 0.86 (3 H, d, *J*= 6.6 Hz) and 0.84 (3 H, d, *J* = 6.6 Hz) [C*H*$_3$-CH-C*H*$_3$]; ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): d 136.2 (CH, *C*H=CH_2), 116.8 (CH_2, CH=*C*H_2),72.8 (CH), 42.6 (C), 39.0 (CH), 38.6 (C), 37.6 (CH_2), 37.2 (CH_2),34.5 (CH_2), 33.1 (CH), 24.7 (2 C, CH_3 and CH_2),20.3 (CH_3), 19.6 (CH_3), 19.5 (CH_3) 14.3 (CH_3).

1-[(1*R*,2*R*,5*R*)-2-Allyl-5-isopropyl-1,2-dimethyl- cyclohexyl)]ethanone 28. To a magneticallystirred suspension of PCC (55 mg, 0.25 mmole) and sodium acetate (55 mg) in CH_2Cl_2(0.5 mL) was added a solution of the alcohol **27** (20 mg, 0.08mmole) in CH_2Cl_2 (0.5 mL). The reaction mixture wasstirred at room temperature for 30 min, filtered through a silica gel column,and the column eluted with more CH_2Cl_2.

Evaporation ofthe solvent furnished the keto olefin **28** (16 mg, 80%) as oil; [a]$_D$ +43.0 (c 1.0, $CHCl_3$); IR (neat): 3080, 3060, 2910, 2830,1690, 1635, 1465, 1380, 1365, 1350, 1220, 1200, 990, 900 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$+CCl_4):δ 5.69 (1 H, t of dd, *J* = 18.0, 10.5 and 7.2 Hz, C H=CH_2), 5.00 (1 H, d, *J* =10.5 Hz) and 4.99 (1 H, d, *J* = 18.0 Hz) [CH=CH_2], 2.46 (1 H, dd, *J* = 13.5 and 7.5 Hz), 2.16 (3H, s, CH_3C=O), 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*-CH_3),1.08 (1 H, d of t, *J* = 12.0 and 4.5 Hz), 0.95 (3 H, s, *tert*-CH_3),0.90 (3 H, d, *J* = 6.6 Hz) and 0.89 (3 H, d, *J* = 6.6 Hz, CH_3□CH□CH_3);^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4):δ 213.8 (C, C=O), 134.7 (CH, *C*H=CH_2), 117.6 (CH_2,CH=*C*H_2), 53.6 (C, C-1), 38.9 (CH_2), 38.8 (CH),38.1 (C, C-6), 35.3 (CH_2), 33.1 (CH), 32.5 (CH_2), 29.5(CH_3, *C*H_3C=O), 24.7 (CH_2), 22.6 (CH_3),20.3 (CH_3), 19.8 (CH_3), 19.4 (CH_3); Mass: m/z 236 (M^+, $C_{16}H_{28}O$,2%), 221 (2), 193 (12), 149 (40), 95 (55), 83 (50), 43 (100).

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

ProcedureI (from the olefins 15). Pre□cooled dry ozonein oxygen gas was passed through a cold (□75°C) suspension of a mixture of the alkenes **15** (50 mg, 0.24mmole) and $NaHCO_3$ (10 mg) in a mixture of 1:5 methanol and methylenechloride (1.5 mL) till blue colour appears. Excess ozone was flushed off withoxygen 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 8hr at room temperature. Evaporation of the solvent under reduced pressure andpurification 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 colourlessoil.

ProcedureII (from the hemiketal 25). To a magnetically stirred suspension of PCC (220 mg, 1.0 mmole) andsodium acetate (220 mg) in CH_2Cl_2 (0.5 mL) was added asolution of the hemiketal **25** (90 mg, 0.09 mmole) in CH_2Cl_2(0.5 mL) in one portion. The reaction mixture was stirred at room temperaturefor 30 min, filtered through silica gel column, and the column eluted with moreCH_2Cl_2. Evaporation of the solvent furnished the keto aldehyde **16** (65 mg, 72%) as oil.

ProcedureIII (from the enone 28). Pre□cooled dry ozone in oxygen gas was passed through a cold(□75°C) suspension of the enone **28** (16mg, 0.067 mmole) and $NaHCO_3$ (10 mg) in a mixture of methanol (1 mL)and methylene chloride (5 mL) till blue colour appears. Excess ozone wasflushed off with oxygen for 5 min and the reaction mixture was kept at roomtemperature for 30 min. Triphenylphosphine (18 mg, 0.07 mmole) was added to thecold (–30°C) reaction mixture and stirred for 8 hr at room temperature.Evaporation of the solvent under reduced pressure and purification of theresidue 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}; ^{1}H NMR (90MHz, $CDCl_3$): δ 9.77 (1 H, t, *J* = 3 Hz, CHO), 2.60 and2.25 (2 H, d of AB q, *J* = 16 and 3 Hz, C H_2C=O), 2.12 (3 H, s, CH_3C=O), 2.00-1.00(8 H, m), 1.20 (6 H, s, 2 ×*tert*-CH_3), 0.86 (6 H, d, *J* = 7.2 Hz, CH_3□CH□CH_3).

(1*R*,6*R*,9*R*)-1,6-Dimethyl-9-isopropylbicyclo-[4.4.0]-dec-3-en-2-one17. 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 inmethanol and the reaction mixture stirred at room temperature for 8 hr. Thesolvent was removed under reduced pressure. The residue was taken in water (1.5mL) and extracted with ether (3 ×5 mL).The ether extract was washed with brine and dried (Na_2SO_4).Evaporation of the solvent and purification of the product on a silica gelcolumn using ethyl acetate-hexane (1:20) as solvent furnished the enone **17**(21 mg, 76%) as oil; [a]$_D$+37.0 (c 1, $CHCl_3$); IR (neat): 1670, 1460, 1385, 810 cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$):δ 6.81 (1 H, ddd, *J* = 10.1, 5.9 and 2.3 Hz, H□4), 5.96 (1 H,dd, *J* = 10.1 and 3.2 Hz, H □3), 2.85 (1 H, br d, *J* = 19.4Hz) 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, J_w = 0.5 Hz) [2´*tert*-CH_3], 0.87 (3 H, d, *J*= 6.4 Hz) and 0.84 (3 H, d, *J* = 6.4 Hz) [CH_3□CH□CH_3];^{13}C NMR (100 MHz, $CDCl_3$):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 $C_{15}H_{24}O$:220.1827. Found: 220.1830.

(1*S*,6*R*,9*R*)-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 purificationof the product on a silica gel column using ethyl acetate-hexane (1:20) aseluent furnished **valeranone** (**1**,16.2 mg, 80%) as a colourless oil; [a] –54.3 (c 0.7, $CHCl_3$); IR (neat): 1695, 1460, 1380, 1260,1030, 940, 800 cm $^{-1}$; ^{1}H NMR (400MHz, $CDCl_3$): 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 3], 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) and0.80 (3 H, s) [2 ×*tert*-CH_3],0.87 (3 H, d, J = 6.9 Hz) and 0.85 (3 H, d, J = 6.9 Hz) [C*H*$_3$CHC*H*$_3$];^{13}C NMR (100 MHz, $CDCl_3$):δ 217.5 (C=O), 53.1 (C 1), 38.6 (C 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 $C_{15}H_{26}O$: 222.1984. Found: 222.1978.

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