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Enantiospecific Synthesis of (+)-Dihydroerythrodiene, (+)-Dihydrospirojatamol and (+)-Dihydroepispirojatamol[1]

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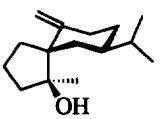
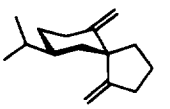
Abstract: Starting from the monoterpene R-carvone, enantiospecific total synthesis of the spirosesquiterpenes (+)-dihydroerythrodiene, (+)-dihydrospirojatamol and (+)-dihydroepispirojatamol is described.

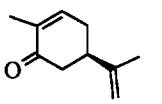
The spirosesquiterpenes spirojatamol **1**, isolated[2] from the root extracts of the Indian medicinal plant *Nardostachys jatamansi* (terrestrial), and erythrodiene **2**, isolated[3] from the Caribbean gorgonian octocoral *Erythropodium caribaeorum* (marine), share the common spiro[4.5]decane carbon framework. It is worth noting that the erythrodiene **2** of marine origin belonged to the antipodal series of the spirojatamol **1** of the terrestrial origin. Synthesis of chiral spiro[4.5]decanes is of growing interest in terpene synthesis.[4] Recently, Forsyth and Huang reported[5] the total synthesis of the natural erythrodiene (-**2**) and the optical antipode (-**1**) of spirojatamol, confirming the absolute stereochemistry of the two compounds, whereas Fukumoto *et al.* reported[6] the synthesis of racemic **1** and **2**. Herein we report the enantiospecific total synthesis of the dihydro derivatives of the natural spirojatamol and epispirojatamol, and antipodal erythrodiene, starting from the readily available monoterpene R-carvone (**3**) *via* dihydrocarvone **4**.



(+)-Spirojatamol (**1**)

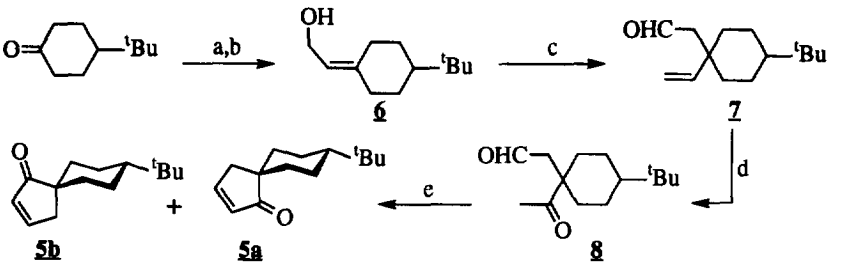


(–)-Erythrodiene (**2**)

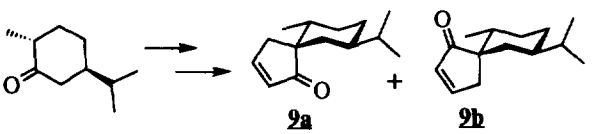


(–)-Carvone (**3**)

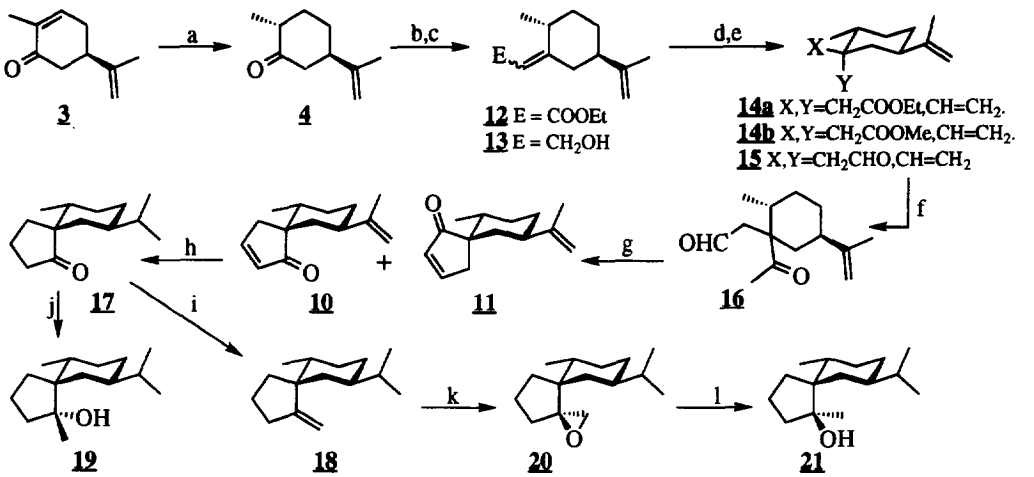
For the construction of the spiro system a Claisen rearrangement based methodology was opted. First as a model study 4-t-butylcyclohexanone was converted into a chromatographically separable 3:1 epimeric mixture of spiroenones **5a**[7] and **5b**, Scheme 1. Thus, one pot Claisen rearrangement of the allyl alcohol **6**,[8] obtained from 4-*tert*-butylcyclohexanone in two steps (Horner-Wadsworth-Emmons reaction and LAH reduction), using ethyl vinyl ether and mercuric acetate generated a ≈5:1 epimeric mixture of the enal **7**. Based on the preferred chair conformation in the transition state of the Claisen rearrangement and steric reasoning, the CH_2CHO group was placed *trans* (equatorial) to *tert*-butyl moiety in the major isomer of **7**. Oxidation of the enal **7** (≈80% conversion) using Wacker conditions generated a 3:1 epimeric mixture of the keto-aldehyde **8**, which on intramolecular aldol condensation and chromatographic purification furnished the spiroenones **5a** and **5b**. However application of the same methodology with tetrahydrocarvone resulted in an inseparable mixture of spiroenones **9a,b**, hence dihydrocarvone **4** was opted as the starting material for the synthesis of the spirocompounds **10** and **11**. The synthetic sequence starting from



***Scheme 1**: (a) $(EtO)_2P(O)CH_2COOEt$, NaH, THF, rt, 8h; (b) $LiAlH_4$, Et_2O, -70°C, 3h; (c) $CH_2=CH\text{-}OEt$, $Hg(OAc)_2$, sealed tube, 180°C, 36h; (d) $PdCl_2$, CuCl, O_2, DMF, H_2O, room temperature, 24h; (e) 1M KOH in CH_3OH, room temperature, THF, 8h.*



(*R*)-carvone (-**3**) is depicted in Scheme 2. The sodium methoxide catalysed equilibration of a ≈3:1 epimeric mixture of dihydrocarvone, obtained by reduction of carvone with zinc,[9] furnished the requisite starting material, *trans* dihydrocarvone **4**. Horner-Wadsworth-Emmons reaction of **4** with triethyl phosphonoacetate and NaH followed by LAH reduction of the resultant conjugated ester **12** furnished the allyl alcohol **13**. Since the product of the normal Claisen rearrangement was found to further rearrange under the reaction conditions, an orthoester variant[10] was employed. Thermal activation of the allyl alcohol **13** with triethyl orthoacetate and a catalytic amount of propionic acid furnished an inseparable ≈3.5:1 diastereomeric mixture of the diene-ester **14a**, which was used as such and separated after the construction of the spirosystem. Analogous to **7**, in the major isomer of **14a** axial orientation was assigned for the vinyl moiety. Reduction of the ester **14a** with LAH and oxidation of the resultant alcohol with pyridinium chlorochromate (PCC) furnished the dieneal **15**. A Wacker methodology was opted for the regiospecific oxidation of the monosubstituted olefin moiety in the diene **15**. Thus, oxidation of the diene-aldehyde **15** using Wacker conditions ($PdCl_2/CuCl/DMF/H_2O/O_2$) furnished regiospecifically the keto-aldehyde **16** which on intramolecular aldol condensation followed by separation of the isomers by column chromatography on silica gel furnished the spiroenones **10** and **11**. The major product **10** was further elaborated. Catalytic hydrogenation of both the olefinic groups in the dienone **10** furnished the spiroketone **17**. Wittig methylenation of the ketone **17** furnished dihydroerythrodiene **18**, whereas reaction of the ketone **17** with methyllithium and anhydrous cerium chloride furnished dihydro-epispirojatamol **19** in a highly stereoselective manner. For the generation of dihydrospirojatamol **21**, the olefinic moiety of the dihydroerythrodiene **18** was epoxidised with magnesium monoperphthalate (MMPA) to furnish the epoxide **20** in a highly stereoselective manner. Finally, reduction of the epoxide **20** with LAH furnished the dihydrospirojatamol **21**. It is worth pointing that the secondary methyl group is playing a key role in the stereoselective formation of the epoxide **20** and the alcohol **19**. This is in contrast with the generation of ≈1:1 epimeric mixtures of the epoxide and alcohols on similar systems with either a ketone or a olefin



Scheme 2: ***Reagents and conditions:*** *(a) i. KOH, Zn, EtOH-H_2O, reflux, 7h; ii. $NaOCH_3$, CH_3OH rt, 36h; 75%; (b) $(EtO)_2P(O)CH_2COOEt$, NaH, THF, rt, 16h, 95%; (c) $LiAlH_4$, Et_2O, -70°C, 2h, 92%; (d) $MeC(OEt)_3$, EtCOOH, sealed tube, 170°C, 48h, 88%; (e) i. $LiAlH_4$, Et_2O, 2h, 90%; ii. PCC, CH_2Cl_2, 2h, 89%; (f) $PdCl_2$, CuCl, DMF, H_2O, O_2, 16h, 74%; (g) 5%aq.KOH, Et_2O, THF, 16h, 78%; silica gel column chromatography; (h) H_2, 10%Pd/C, MeOH, 4h, 98%; (i) $Ph_3P^+CH_3\ I^-$, $K^+\ ^-O$tamy, C_6H_6, rt, 12h, 80%; (j) an. $CeCl_3$, MeLi, THF, 12h, 83% (k) MMPA, EtOH, rt, 24h, 76%; (l) $LiAlH_4$, Et_2O, -40°C→rt, 1h, 70%.*

moiety in the place of the secondary methyl group, in the synthesis of spirojatamol (1) reported by Forsyth[5] and Fukumoto[6] and coworkers.

Experimental Section

IR spectra were recorded on Perkin-Elmer 781 spectrophotometer. ^1H (90 and 200 MHz) and ^{13}C NMR (22.5 and 50 MHz) spectra were recorded on Jeol FX-90Q and Brucker ACF-200 spectrometers. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal tetramethylsilane (for ^1H) or the central line (77.2 ppm) of $CDCl_3$ (for ^{13}C). In ^{13}C NMR spectra off-resonance multiplicities, when recorded, are given in parentheses. High and low resolution mass spectra were carried out on a Jeol JMS-DX 303 GC-MS instrument using a direct inlet mode. Elemental analyses were carried out using a Carlo-Erba 1106 CHN analyser. Optical rotations were measured using a Jasco DIP-303 polarimeter. All small scale dry reactions were carried out using standard syringe-septum technique. Acme's silica gel (100-200 mesh) was used for column chromatography.

(1-Vinyl-4-tert-butylcyclohexyl)acetaldehyde (7): A solution of the allyl alcohol[8] **6** (850 mg, 4.67 mmol), catalytic amount of mercuric acetate and ethyl vinyl ether (1.91 g, 26.4 mmol) in a carius tube was heated to 180°C for 36 h under nitrogen atmosphere. The reaction was then diluted with ether, washed with $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished a 5:1 epimeric mixture of the enal 7 (356 mg, 55% yield). IR (neat): ν_{max} 3070, 2710, 1720, 1640, 1360, 1230 910 cm^{-1}. ^1H NMR

(90 MHz, $CDCl_3$, Peaks due to the major isomer): δ 9.76 (1 H, t, J=3.2 Hz, H-C=O), 5.8 (1 H, dd, J=18 and 11.6 Hz, C*H*=CH_2), 5.24 (1 H, d, J=11.6 Hz) and 5.09 (1 H, d, J=18 Hz) (CH=C*H*$_2$), 2.24 (2 H, d, J=3.2 Hz, C*H*$_2$CHO), 1.0-2.1 (9 H, m), 0.81 (9 H, s, 3 x CH_3).

(1-Acetyl-4-tert-butylcyclohexyl)acetaldehyde (8): A suspension of palladium chloride (26 mg, 0.15 mmol) and cuprous chloride (200 mg, 2 mmol) in DMF (2.9 ml) and water (0.87 ml) was magnetically stirred in an oxygen atmosphere, created via evacuative displacement of air using an oxygen balloon, for 1 h at room temperature. Then a solution of the enal **7** (600 mg, 2.88 mmol) in 0.5 ml of DMF was added and the reaction mixture was stirred for 24 h at room temperature in the oxygen atmosphere. Aqueous HCl was added to the reaction mixture and it was extracted with ether. The ether layer was washed with saturated aqueous soium bicarbonate 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 (1:10) as eluent, furnished a 3:1 epimeric mixture of the keto-aldehyde **8** (356 mg, 80% conversion, 68%), which was recrystallised from CH_2Cl_2 and hexane. m.p. 76-78 °C. IR (nujol): ν_{max} 1715, 1700, 1380, 1365 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$, Peaks due to the major isomer): δ 9.68 (1 H, t, J=3.2 Hz, H-C=O), 2.47 (2 H, d, J=3.2 Hz, C*H*$_2$CHO), 2.21 (3 H, s, $COCH_3$), 1.0-2.3 (9 H, m), 0.81 (9 H, s, 3 x CH_3). ^{13}C NMR (22.5 MHz, $CDCl_3$, mixture of 3:1 isomers) δ 210.4 & 212.1 (s, *C*OCH_3), 199.7 & 200.1 (d, H-C=O), 53.0 & 44.8 (t, *C*H_2CHO), 49.8 & 49.1 (s), 46.9 (d), 33.7 & 31.7 (2 C, t), 26.8 (q, 3 x Me), 25.1 & 24.6 (q), 23.5 & 21.6 (2 C, t). Anal. Calcd. for $C_{14}H_{24}O_2$, C, 74.95; H, 10.78; Found C, 74.75; H, 11.04%.

8-tert-Butylspiro[4,5]dec-2-en-1-one (5): To a solution of the keto aldehyde **8** (52 mg, 0.232 mmol) in THF (3 ml) was added 1 N methanolic KOH solution (0.232 ml, 0.232 mmol). The reaction mixture was stirred for 8 h and the solvent was removed under reduced pressure. The reaction mixture was then taken in ether (10 ml) and washed with brine and dried (Na_2SO_4). Evaporation of the solvent and careful purification of the residue on a silica gel column using ethyl acetate-hexane (1:49 to 1:20) as eluent furnished first the minor isomer **5b** (8 mg, 16.7%) contaminated with trace amount of major isomer and further elution furnished the major isomer **5a** (23 mg, 48%) which was recrystallised from hexanes. For the major isomer **5a**:[7] m.p. 70-72°C. IR (nujol): ν_{max} 1710, 1600, 1365, 1230, 810 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.42 (1 H, t of d, J=5.8, 2.7 Hz, C*H*=CH-CO), 5.87 (1 H, t of d, J=5.8, 2.4 Hz, CH=C*H*-CO), 2.37 (2 H, t, J=2.5 Hz, allylic CH_2), 1.0-1.8 (9 H, m), 0.82 (9 H, s, 3 x CH_3). ^{13}C NMR (50 MHz, $CHCl_3$): δ 213.9 (C=O), 160.1 (*C*H=CH-C=O), 132.4 (CH=*C*H-C=O), 47.5, 46.8, 44.7, 35.2 (2 C), 32.4, 27.6 (3 C, 3 x CH_3), 22.2 (2 C). Anal. Calcd. for $C_{14}H_{22}O$, C, 81.5; H, 10.75; Found C, 81.85; H, 10.96%. For the minor isomer **5b**: IR (neat): ν_{max} 1690, 1585, 1270, 1260, 1200, 805 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.58 (1 H, t of d, J=5.8 and 2.7 Hz, C*H*=CHC=O), 6.09 (1 H, t of d, J=5.8 and 2 Hz, CH=C*H*C=O), 2.47 (2 H, t, J=*ca* 2.3 Hz), 1.0-2.0 (9 H, m), 0.79 (9 H, s).

Equilibration of dihydrocarvone (4): To a magnetically stirred solution of NaOMe in MeOH (prepared from 400 mg of sodium and 6 ml of methanol) was added, dropwise, a solution of 3:1 epimeric mixture of dihydrocarvone[6] (1 g, 6.6 mmol) in MeOH (1.4 ml) and stirred for 36 h at room temperature. Methanol was evaporated under reduced pressure, the residue was taken in ether and washed successively with water and brine, and dried (Na_2SO_4). Evaporation of the solvent furnished *trans*-dihydrocarvone **4** (980 mg, 98%).

Ethyl [(2R,5R)-5-Isopropenyl-2-methylcyclohexylidene)acetate (12): A suspension of sodium hydride (60% in oil, 766 mg, 20 mmol) in hexanes under N_2 atmosphere was magnetically stirred for 10 min and the solvent was syringed out. The oil free sodium hydride was suspended in dry THF (15 ml) and cooled in an ice bath. Triethyl phosphonoacetate (4.4 ml, 22.35 mmol) in dry THF (3 ml) was added dropwise and the reaction mixture was stirred for 0.5 h at room temperature. The reacton mixture was cooled to 0°C and a solution of dihydrocarvone **4** (2 g, 13.15 mmol) in dry THF (2 ml) was added dropwise and stirred

for 16 h at room temperature. The reaction was quenched by careful addition of saturated aqueous ammonium chloride solution and diluted with ether (25 ml). The ether layer was separated and the aqueous layer was extracted with ether (20 ml). The combined ether extract was washed with brine and dried (Na_2SO_4). Solvent was evaporated and the residue was purified on a silica gel column using hexanes as eluent to furnish the unsaturated ester **12** (2.8 g, 95%) as an oil. $[\alpha]_D^{26}$: 15.2 (c 2.1, $CHCl_3$). IR (neat): ν_{max} 3070, 1710, 1640, 895 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 5.53 (1 H, s, C=CH), 4.69 (2 H, s, $C=CH_2$), 4.11 (2 H, q, J=7.7 Hz, O-CH_2CH_3), 1.5-2.2 (8 H, m), 1.71 (3 H, s, CH_3-C=), 1.24 (3 H, t, J=7.7 Hz, O-CH_2CH_3), 1.02 (3 H, d, J=6.4, *sec*-CH_3). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 166 (s, O-C=O), 164.9 (s, CH=CH-CO), 148.3 (s, $C=CH_2$), 110.4 (d, C=CH), 108.4 (t, $C=CH_2$), 58.7 (t, O-CH_2CH_3), 46.6 (d), 39.1 (d), 36.5 (t), 35.0 (t), 31.0 (t), 20.4 (q, O-CH_2CH_3), 17.3 (q, *sec*-CH_3), 13.9 (q, CH_3-C=). Mass: m/z 222 (M^+, 95%), 193 (62), 179 (100), 177 (85), 176 (80), 149 (80), 107 (75). HRMS: Calcd. for $C_{14}H_{22}O_2$ ***M*** 222.1620. Found, m/z 222.1610.

2-[(2R,5R)-5-Isopropenyl-2-methylcyclohexylidene]ethanol (13): To a cold (-78°C), magnetically stirred soluion of the unsaturated ester **12** (2 g, 9 mmols) in dry ether (25 ml) was added lithium aluminium hydride (170 mg, 4.5 mmol) in one portion. The reaction mixture was stirred at -78°C for 2 h and allowed to warm upto -20°C over a period of 30 min. Ethyl acetate (1 ml) was carefully introduced to consume the excess reagent and the reaction was quenched with ice-cold water (5 ml). The solution was filtered through a sintered funnel and the residue thoroughly washed with ether (3 x 10 ml). The ether layer was separated, washed with brine and dried (Na_2SO_4). The solvent was evaporated and the residue was purified on a silica gel column using ethyl acetate-hexane (1:10) as eluent to furnish the allyl alcohol **13** (1.5 g, 92%) as an oil. $[\alpha]_D^{29}$: -28.3 (c 3.2, $CHCl_3$). IR (neat): ν_{max} 3350, 3080, 1645, 1025, 895 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, peaks due to the major isomer): δ 5.34 (1 H, t, J=6.9 Hz, C=C*H*), 4.71 (2 H, s, $C=CH_2$), 4.2 (2 H, d, J=6.9 Hz, CH_2-OH), 2.70 (1 H, t of d, J=12.5 and 2.4 Hz), 1.1-2.45 (7 H, m), 1.74 (3 H, s, =C-CH_3), 1.05 (3 H, d, J=6.4 Hz, *sec*-CH_3). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 149.5 (s, C=CH), 145.9 (s, $C=CH_2$), 118.2 (d, C=CH), 108.5 (t, $C=CH_2$), 58.2 (t, OCH_2), 46.6 (d), 37.6 (t), 36.5 (t), 34.5 (d), 31.8 (t), 20.6 (q, *sec*-CH_3), 17.95 (q, =CCH_3). Mass: m/z 180 (M^+, 47%), 162 (56), 149 (50), 119 (65), 107 (70), 93 (100). HRMS: Calcd. for $C_{12}H_{20}O$ ***M*** 180.1514. Found, m/z 180.1516.

Methyl [(2R,5R)-5-Isopropenyl-2-methyl-1-vinylcyclohexyl]acetate (14b): A solution of the allyl alcohol **13** (1 g, 5.55 mmol), triethyl orthoacetate (5 ml, 27.76 mmol) and a catalytic amount of propionic acid were taken in a Carius tube under nitrogen atmosphere and heated to 160-170 °C for 48 h. The reaction mixture was cooled, diluted with ether (20 ml), washed with 0.5 N HCl followed by saturated aqueous $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel coumn using ethyl acetate-hexane (1:20) as eluent furnished an epimeric mixture of the ester **14a** (1.14 g, 88%) as a colourless oil. The ethyl ester **14a** (200 mg) thus obtained was refluxed with 10% aqueous potassium hydroxide (2 ml) and MeOH (2 ml) for 6 h. The reaction mixture was washed with dichloromethane, acidified with 3 N HCl and extracted with dichloromethane. Evaporation of the solvent furnished the acid (150 mg, 0.67 mmol). The acid thus obtained was esterified with an excess of ethereal diazomethane and purified on a silica gel column using ethyl acetate-hexane (1:20) as eluent to furnish an epimeric mixture of the methyl ester **14b** (148 mg, 93%) as a colourless oil. $[\alpha]_D^{25}$: 24.3 (c 2.0, $CHCl_3$). IR (neat): ν_{max} 3080, 1735, 1640, 1205, 885 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$, peaks due to the major isomer): δ 5.97 (1 H, dd, J=16.9 and 11.6 Hz, C*H*=CH_2), 5.16 (1 H, d, J=11.6 Hz) and 5.02 (1 H, d, J=16.9 Hz) (CH=CH_2), 4.59 (2 H, s, C=CH_2), 3.59 (3 H, s, O-CH_3), 2.38 (2 H, s, CH_2C=O), 1.67 (3 H, s, CH_3C=C), 1.2-2.5 (8 H, m), 0.86 (3 H, d, J=6.3 Hz, *sec*-CH_3). ^{13}C NMR (22.5 MHz, $CDCl_3$, peaks due to the major isomer): δ 172.6 (s, O-C=O), 149.8 (s, $C=CH_2$), 139.4 (d, CH=CH_2), 114.8 (t,

$CHCH_2$), 108.4 (t, C=CH_2), 50.9 (q, O-CH_3), 43.8, 42.7, 40.6, 40.1, 38.5, 31.7 (t), 31.3 (t), 20.7 (q, *sec*-CH_3), 15.8 (q, C=CCH_3). Mass: m/z 236 (20%, M^+), 221 (15), 163 (30), 162 (100), 147 (28). HRMS: Calcd. for $C_{15}H_{24}O_2$ *M* 236.1776. Found, m/z 236.1781.

[(2R,5R)-5-Isopropenyl-2-methyl-1-vinylcyclohexyl]acetaldehyde (15): Reduction of the ene-ester **14a** (1 g, 4.23 mmol) in dry ether (5 ml) with lithium aluminium hydride (80 mg, 2.12 mmol) for 2 h as described for the allyl alcohol and purification of the product on a silica gel column using ethyl acetate-hexane (1:15) furnished an alcohol (795 mg, 90%) as an oil. $[\alpha]_D^{25}$: 5.3 (c 2.4, $CHCl_3$). IR (neat): ν_{max} 3350, 3080, 1645, 915, 890 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$, peaks due to the major isomer): δ 5.92 (1 H, dd, J=16.7 and 11.0 Hz, C*H*=CH_2), 5.18 (1 H, d, J=11.0) and 5.01 (1 H, d, J=16.7 Hz) (HC=CH_2), 4.70 (2 H, s, C=CH_2), 3.66 (2 H, m, CH_2OH), 1.70 (3 H, s, =CCH_3), 1.2-2.2 (8 H, m), 0.89 (3 H, d, J=5.6 Hz, sec-CH_3). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 149.8 (*C*=CH_2), 139.7 (*C*H=CH_2), 114.7 (CH=CH_2), 108.2 (C=CH_2), 58.1, 41.9, 40.2, 39.6, 39.5, 31.7, 31.3, 20.7, 15.5. Mass: m/z 208 (M^+, 5%), 163 (40), 121 (58), 107 (100). HRMS: Calcd. for $C_{14}H_{24}O$, *M* 208.1827. Found, m/z 208.1824. To a magnetically stirred solution of the dienol (1 g, 4.8 mmol), obtained above, in dichloromethane (3 ml) was added a mixture of PCC (1.55 g, 7.2 mmol) and silica gel (1.55 g) in one portion. The reaction mixture was stirred at room temperature for 1 h and filtered through a silical gel coulmn and the column was further eluted with dichloromethane. The solvent was evaporated to furnish the ene-aldehyde **15** (884 mg, 89%). $[\alpha]_D^{28}$: 43.7 (c 3.3, $CHCl_3$). IR (neat): ν_{max} 3080, 2750, 1725, 1645, 920, 890 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$, peaks due to the major isomer): δ 9.85 (1 H, t, J=2.5 Hz, C*H*O), 6.07 (1 H, dd, J=17 and 10.8 Hz, C*H*=CH_2), 5.3 (1 H, dd, J=10.8 and 1.3 Hz) and 5.06 (1 H, dd, J=17.0 and 1.3 Hz) (CH=CH_2), 4.66 (2 H, s, C=CH_2), 2.6 and 2.2 (2 H, d of ABq, J=14.5 and 2.5 Hz, CH_2CHO), 1.69 (3 H, s, CH_3-C=), 1.2-2.5 (8 H, m), 0.87 (3 H, d, J=6.2 Hz). ^{13}C NMR (22.5 MHz, $CDCl_3$, peaks due to the major isomer): δ 203.1 (d, C=O), 149.4 (s, *C*=CH_2), 138.57 (*C*H=C), 115.8 (C=CH_2), 108.5 (CH=CH_2), 52.33 (*C*H_2CHO), 41.7 (s), 41.1, 40.1, 39.7, 31.0 (t), 31.0 (t), 20.6 (q, *sec*-CH_3), 15.6 (q, =CCH_3). Mass: m/z 206 (M^+, 2%), 162 (100), 121 (55), 107 (75), 93 (85). HRMS: Calcd. for $C_{14}H_{22}O$ *M* 206.1671. Found, m/z 206.1670.

[(2R,5R)-1-Acetyl-5-Isopropenyl-2-methylcyclohexyl]acetaldehyde (16): A suspension of $PdCl_2$ (178 mg, 1 mmol) and CuCl (1.43 g, 14.4 mmol) in H_2O (1.5 ml) and DMF (6 ml) under oxygen atmosphere was stirred magnetically till oxygen absorption ceased. To this suspension was added a solution of the ene-aldehyde **15** (1 g, 4.85 mmol) in DMF (2 ml) and stirred for 24 h under oxygen atmosphere at room temperature. To the reaction mixture, dil HCl was added and extracted with ether. The ether extract was washed with water and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column with ethyl acetate-hexane (1:7) as eluent furnished the keto-aldehyde **16** (794 mg, 74%) as an oil. $[\alpha]_D^{29}$: -18.6 (c 3.1, $CHCl_3$). IR (neat): ν_{max} 3080, 2730, 1720, 1690, 1650, 890 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, peaks due to the major isomer): δ 9.8 (1 H, t, J=1.8 Hz, C*H*O), 4.7 (2 H, brs, =CH_2), 1.0-3.0 (8 H, m), 2.22 (3 H, s, COCH_3), 2.15 (2 H, s, CH_2CHO), 1.71 (3 H, s, =CCH_3), 0.74 (3 H, d, J=6.8 Hz, *sec*-CH_3). ^{13}C NMR (22.5 MHz, $CDCl_3$, for the mixture of isomers): δ 211.3 and 209.6 (C=O), 200.1 and 201.7 (CHO), 148.5 and 148.9 (*C*=CH_2), 108.6 (C=CH_2), 55.9, 52.9, 52.3, 40.8, 39.9, 39.7, 38.3, 36.8, 36.0, 31.2, 30.7, 29.9, 27.8, 24.2, 20.5, 16.7, 16.4. Mass: m/z 222 (M^+, 2%), 178 (M-CH_3CHO, 65), 135 (50). HRMS: Calcd. for $C_{14}H_{22}O_2$ *M* 222.1620. Found, m/z 222.1634.

(5S,6R,9R) and (5R,6R,9R) 9-Isopropenyl-6-methylspiro[4,5]dec-2-en-1-ones (10 and 11): To a magnetically stirred solution of the ketoaldehyde (500 mg, 2.25 mmol) in 1:1 ether and THF (6 ml) was added 5% aqueous potassium hydroxide (1 M, 3.5 ml) solution and stirred for 16 h. The reaction mixture was extracted with ether and the ether extract was washed with water, brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column with dichloromethane-

hexane (1:5) as eluent furnished the minor **11** (96 mg, 21%) and the major **10** (263 mg, 57%) products. For the major isomer **10**: $[\alpha]_D^{23}$: 8.5 (c 4.0, $CHCl_3$). IR (neat): ν_{max} 3050, 1700, 1645, 1595, 890 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.64 (1 H, t of d, J=5.8 and 2.6 Hz, C*H*=CHC=O), 6.12 (1 H, t of d, J=5.8 and 1.5 Hz, CH=C*H*C=O), 4.61 (s, C=CH_2), 2.58 and 2.3 (2 H, t of ABq, J=19.5 and *ca.* 2.3 Hz, CH=CHCH_2), 1.0-2.0 (8 H, m), 1.63 (3 H, s, C=CCH_3), 0.56 (3 H, d, J=6.4 Hz, *sec*-CH_3). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 214.8 (C=O), 163.7 (*H*C=CHC=O), 149.4 (*C*=CH_2), 133.5 (CH=*C*HC=O), 109.0 (C=*C*H_2), 51.9 (spiro C), 42.0, 39.9, 36.9, 36.1, 31.7, 31.3, 20.6 (*sec*-CH_3), 15.8 (C=C*C*H_3). Mass: m/z 204 (M^+, 42%), 122 (40), 109 (68), 95 (100). HRMS: Calcd for $C_{14}H_{20}O$ *M* 204.1514. Found, m/z 204.1514. For the minor isomer **11**: $[\alpha]_D^{24}$ -8.8 (c 4.0, $CHCl_3$). IR (neat): ν_{max} 3090, 1690, 1640, 1590, 1170, 880, 810 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.55 (t of d, 1 H, J=5.8 and 2.7 Hz, C*H*=CHC=O), 5.97 (t of d, 1 H, J=5.8 and 1.4 Hz, CH=C*H*C=O), 4.64 (s, 2 H, C=CH_2), 2.68 and 2.57 (2 H, t of ABq, J=19.3 and 2.4 Hz), 1.0-2.2 (8 H, m), 1.67 (3 H, s, C=CCH_3), 0.75 (d, J=6.54 Hz, *sec*-CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 213.6 (C=O), 161.3 (*C*H=CHC=O), 150.3 (*C*=CH_2), 134.2 (CH=*C*HC=O), 108.2 (C=*C*H_2), 49.4 (spiro C), 45.6, 40.9, 38.5 (2 C), 31.6, 29.9, 21.0, 16.3. Mass: m/z 204 (M^+, 65%), 189 (15, M^+-15), 161 (35), 122 (35), 109 (100). HRMS: Calcd for $C_{14}H_{20}O$ *M* 204.1514. Found, m/z 205.1512.

(5S,6R,9R) 9-Isopropyl-6-methylspiro[4,5]decan-1-one (17): To a magnetically stirred solution of the enone **10** (100 mg, 0.49 mmol) in dry methanol (1 ml) was added 10%-Pd/C (5 mg). The reaction mixture was stirred in an atmosphere of hydrogen (balloon) for 4 h, and the catalyst was filtered off. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the saturated ketone **17** (98 mg, 98%) as a colourless oil. $[\alpha]_D^{24}$: 4.75 (c 4.0, $CHCl_3$). IR (neat): ν_{max} 1725, 1160 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.0-2.4 (2 H, m, CH_2C=O), 1.0-2.0 (9 H, m), 0.84 (6 H, d, J=6.7 Hz, CH(CH_3)$_2$), 0.69 (3 H, d, J=6.7 Hz, *sec*-CH_3). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 224.5 (C=O), 53.7, 39.1, 38.9, 37.3, 36.3, 32.5, 31.5, 29.1, 27.7, 19.8, 19.5 (2 C), 17.3. Mass: m/z 208 (M^+, 64%), 165 (30), 147 (65), 111 (100). HRMS: Calcd. for $C_{14}H_{24}O$ *M* 208.1827. Found, m/z 208.1824.

(5S,6R,9R) 9-Isopropyl-6-methyl-1-methylenespiro[4,5]decane (18): To a magnetically stirred suspension of methyltriphenylphosphonium bromide (400 mg, 0.99 mmol) in dry benzene (2 ml) was added 1M solution of K^+ $^-O^tAm$ in ^tAmOH (0.9 ml) and stirred at room temperature for 30 min. To the Wittig reagent was added a solution of the spiro-ketone **17** (100 mg, 0.48 mmol) in dry benzene (0.5 ml). The reaction mixture was stirred at room temperature for 10 h, diluted with ether (4 ml), washed with aqueous 0.5 N HCl (0.5 ml) followed by brine and dried (Na_2SO_4). The solvent was evaporated and the residue was purified on a silical gel column with hexane as eluent to furnish the olefin **18** (78 mg, 80%). $[\alpha]_D^{27}$ 15.0 (c 1.0, $CHCl_3$). IR (neat): ν_{max} 3070, 1650, 1360, 885 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.86 (1 H, s) and 4.59 (1 H, s) (C=CH_2), 2.33 (2 H, m), 1.0-2.0 (13 H, m), 0.87 (6 H, d, J=6.66 Hz, CH(CH_3)$_2$), 0.83 (3 H, d, *sec*-CH_3). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 128.5, 102.7, 49.8, 44.4, 40.6, 40.1, 35.2, 32.8, 32.4, 30.9, 30.0, 24.1, 20.0, 17.0. Mass: m/z 206 (M^+, 5%), 177 (8%), 111 (28%) 97 (40).

(1R,5S,6R,9R) 9-Isopropyl-1,6-dimethylspiro[4,5]decan-1-ol (19): To a cold (-70°C) magnetically stirred suspension of anhydrous cerium chloride (77 mg, 0.31 mmol, obtained from 116 mg of $CeCl_3.7H_2O$) in dry THF was added 1M solution of methyllithium in ether (0.25 ml, 0.25 mmol). After 0.5h the spiro-ketone **17** (50 mg, 0.24 mmol) in dry THF (0.5 ml) was added to the reaction mixture and stirred at room temperature for 12 h. The reaction was quenched with ice-cold saturated solution of NH_4Cl and extracted with ether. The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silical gel column using ethyl acetate-hexane (1:20) as eluent furnished

dihydroepispirojatamol **19** (44.5 mg, 82%) as a colourless oil. $[\alpha]_D^{26}$ 8.4° (c 2.2, $CHCl_3$). IR (neat): ν_{max} 3475 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.2-2.2 (16 H, m), 1.27 (3 H, s, *tert*-CH_3), 1.06 (3 H, d, J=7.02 Hz, *sec*-CH_3), 0.87 (6 H, d, J=6.48 Hz, $CH(CH_3)_2$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 84.4 (C-OH), 50.4 (spiro C), 41.1, 40.4, 38.7, 35.3, 34.6, 32.9, 29.7, 27.4 (2 C), 24.6 (2 C). Mass: m/z 224 (M^+, 7%), 206 (18), 163 (100).

***(1S,5S,6R,9R) 9-Isopropyl-6-methylspiro[4,5]decane-1-spirooxirane (20)*:** To a magnetically stirred solution of magnesium monoperoxyphthalate hexahydrate (119 mg, 0.24 mmol) in absolute ethanol (1 ml) was added a solution of the olefin **18** (50 mg, 0.24 mmol) in ethanol (0.5 ml) and stirred at room temperature for 24 h. Water was added to the reaction mixture and extracted with ether. 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 as eluent furnished the epoxide **20** (41.5 mg, 76%) as a colourless oil. $[\alpha]_D^{23}$ 9.0 (c 2.0, $CHCl_3$). IR (neat): ν_{max} 1380, 950. ^1H NMR (200 MHz, $CDCl_3$): δ 2.77 (2 H, s, O-CH_2), 1.0-2.3 (14 H, m), 0.77 (3 H, J=6.7 Hz, *sec*-CH_3), 0.76 (6 H, d, J=6.7 Hz). Mass: m/z 222 (M^+, 9%) 207 (25), 179 (98), 147 (50), 111 (100). HRMS: Calcd. for $C_{15}H_{26}O$ *M* 222.1984. Found, m/z 222.1976.

***(1S,5S,6R,9R) 9-Isopropyl-1,6-dimethylspiro[4,5]decan-1-ol (21)*:** To a magnetically stirred solution of the epoxide (40 mg, 0.18 mmol) in dry ether (1 ml) at -40°C was added lithium aluminium hydride (4 mg, 0.1 mmol). The reaction mixture was allowed to attain room temperature and stirred for 1 h. Ethyl acetate (0.5 ml) was added and the reaction was quenched with water and the resulting mixture was filtered through a sintered funnel. Evaporation of the solvent and purification of the residue on a silica gel column with ethyl acetate-hexane (1:20) as eluent furnished dihydrospirojatamol **21** (27 mg, 70%) as a colourless oil. $[\alpha]_D^{26}$ 17.5° (c 2.0, $CHCl_3$). IR (neat): ν_{max} 3450, 1455, 1375 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 1.2-2.2 (16 H, m), 1.26 (3 H, s, *tert*-CH_3), 1.03 (3 H, d, J=7 Hz, *sec*-CH_3), 0.88 (3 H, d, J=6.5 Hz) and 0.89 (3 H, d, J=6.54 Hz) [$CH(CH_3)_2$]. Mass: m/z 224 (M^+, 13%), 206 (30), 163 (100). HRMS: Calcd. for $C_{15}H_{28}O$ *M* 224.2140. Found M^+ 224.2145.

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