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Enantioselective Synthesis of both (+)- and (-)-Derivatives of Bicyclo[4.3.0]nonan-8-one and -3,8-diones from R-carvone[1]

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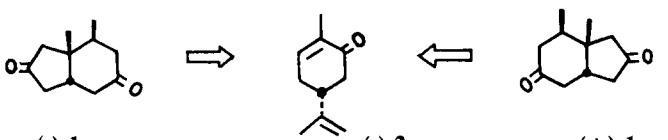
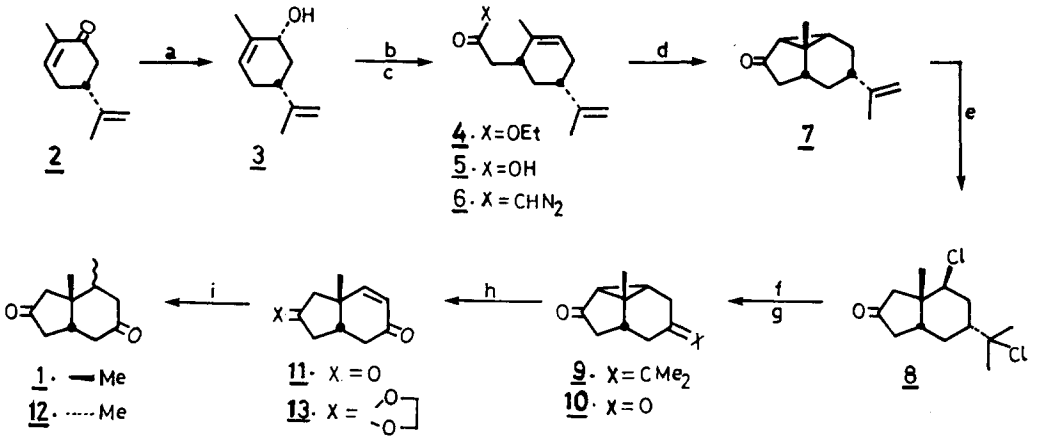
Abstract: Enantioselective synthesis of both the enantiomeric forms of the hydrindane derivatives mentioned in the title, potential chiral precursors in terpenoid synthesis, starting from R-carvone employing two different cyclopentannulation methodologies is described.

Highly functionalised hydrindane systems, in particular with a substituent at one of the ring junction carbons, or as part structures are present in many biologically important natural products, *e.g.* picrotoxinin, bakkanes, zizzanes etc.[2] Our interest in the synthesis of sesquiterpene natural products containing hydrindane framework[3] led us to investigate new approaches for the construction of hydrindanes in optically active form. The readily available monoterpene carvone is an excellent chiral starting material in the synthesis of natural compounds.[4] In the synthesis of several sesquiterpenes, de Groot and coworkers[5] have exploited the use of S-carvone for the construction of several functionalised decalin systems via the Robinson annulation protocol. Starting from R-carvone, herein we describe the synthesis of derivatives of both the enantiomeric series of functionalised hydrindanes mentioned in the title, *e.g.* **1** a precursor to homogynolide-A,[6] employing two different cyclopentannulation methodologies.



(-)-**1** (-)-**2** (+)-**1**

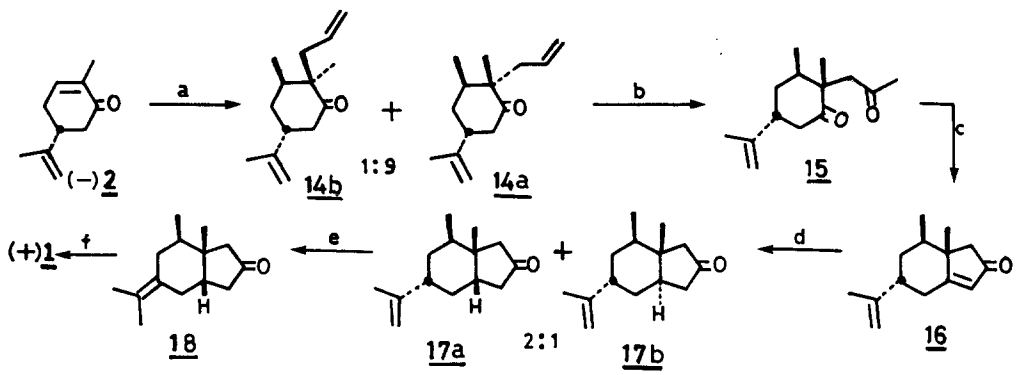
In the first route the stereospecific Johnson orthoester Claisen rearrangement and an intramolecular diazo ketone cyclopropanation reaction are employed as key steps (scheme 1). Thus reduction of R-carvone (**2**) with lithium aluminium hydride at low temperature furnished the syn-alcohol **3**.[7] The orthoester Claisen rearrangement of the allyl alcohol **3** using triethyl orthoacetate in the presence of a catalytic amount of mercuric acetate followed by base catalysed hydrolysis of the resultant ester **4** furnished the acid **5**.[8] Treatment of the acid chloride derived from the acid **5** and oxalyl chloride, with an excess of ethereal diazomethane furnished diazo ketone **6**. Anhydrous copper sulfate catalysed decomposition of the diazo ketone **6** using a tungsten lamp in refluxing cyclohexane furnished the cyclopropyl compound **7**[8] *via* the regiospecific insertion of the resultant keto-carbenoid into the ring olefin. Next the attention was focussed on the degradation of the isopropenyl side chain. Since the direct Craigee rearrangement[9] on the ozonide found to be inefficient, **7** is converted into isopropylidene compound **9**. Thus treatment of the cyclopropyl



SCHEME 1: (a) $LiAlH_4$, Et_2O, -50°C, 2 h, 98%; (b) $CH_3C(OEt)_3$, $Hg(OAc)_2$, 150°C, sealed tube, 6 days, 90%; (c) 15% aq. NaOH-MeOH, reflux, 6 h, 95%; (d) i. $(COCl)_2$, C_6H_6, rt, 2 h; ii. CH_2N_2, Et_2O, rt, 2 h; iii. An.$CuSO_4$, C_6H_{12}, W-lamp, reflux, 5 h, 55%; (e) HCl-Et_2O, rt, 14 h; 65%; (f) DBU, C_6H_6, 160°C, 0.5 h, 80%; (g) i. O_3/O_2, 1:5 MeOH-CH_2Cl_2, -78°C; ii. Me_2S, -78°C→rt, 6 h; (h) CH_2Cl_2, pTSA, 2 h, 89% from 9; (h) Me_2CuLi, Et_2O, 0°C→rt, 3 h, 70%.

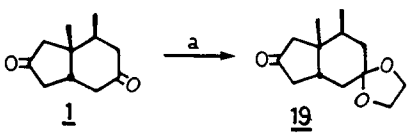
ketone 7 with an excess of freshly prepared hydrogen chloride in ether generated the dichloride 8 via the addition of HCl to both the olefinic as well as cyclopropane moieties. Double dehydrochlorination of the dichloride 8 with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene furnished the isopropylidene compound 9. Ozonolysis of the isopropylidene moiety transformed the compound 9 into the dione 10, which on acid catalysed opening of the cyclopropane ring generated the functionalised hydrindene, endione 11.[8] Finally addition of dimethyl copperlithium to the endione 11 furnished a 3:2 mixture of the epimeric diones 1 and 12.[10,11] In order to improve the selectivity, the endione 11 was converted into its monoketal 13 anticipating the preferential attack of the dimethyl copperlithium from the exo face of the molecule. However reaction of the ketoketal 13 with dimethyl copperlithium followed by hydrolysis of the ketal moiety generated only a 2:1 mixture of the diones 1 and 12.

For the generation of the enantiomeric series, a Wacker mediated cyclopentannulation was adopted. Thus, addition of dimethyl copperlithium to R-carvone followed by quenching of the enolate with allyl bromide furnished a 9:1 mixture of the allylated compounds 14a[8] and 14b, which was separated by silica gel column chromatography. Regiospecific oxidation of the terminal olefin of the allyl moiety employing Wacker conditions [$PdCl_2$, CuCl, DMF, H_2O, O_2][12] transformed the dienone 14a into the 1,4-diketone 15,[8] which on intramolecular aldol condensation generated the enone 16.[8] Interestingly, in contrast to the expectation of generation of only cis isomer,[13] regiospecific reduction of the dienone 16 employing lithium-liquid ammonia reduction conditions furnished a 2:1 mixture of the cis and trans isomers 17a[8] and 17b, which was separted by using silver nitrate impregnated silica gel column. The isopropenyl side chain in 17a was degraded similar to that described in scheme 1. Thus addition of freshly generated HBr in ether followed by dehydrobromination of the resultant tertiary bromide furnished the isopropylidene compound 18. Finally ozonolysis of the compound 18 furnished the (+)-form of the dione 1.[8]



SCHEME 2: (a) i. Me_2CuLi, Et_2O, 0°C, 0.5 h; ii. HMPA, CH_2=CH-CH_2Br, 0°C→rt, 24 h, 89%; (b) $PdCl_2$, CuCl, H_2O, O_2, DMF, 70%; (c) 10% aq.KOH-MeOH, 95%; (d) i. Li, liq.NH_3, ^{t}BuOH, THF, 1 h; ii. PCC-silica gel, CH_2Cl_2, rt, 1 h, 76%; (e) i. HBr, Et_2O, 0→5°C, 5 h; ii. DBU, C_6H_6, sealed tube, 150°C, 1 h, 97%; (f) i. O_3/O_2, MeOH-CH_2Cl_2, -70°C, 20 min; ii. PPh_3, -70°C→rt, 4 h, 94%.

In conclusion, we have developed synthesis to various functionalised hydrindanone derivatives of both the chiral series starting from R-carvone enroute to the synthesis of (+)- and (-)-forms of bicyclo-[4.3.0]nona-3,8-diones. The generation of both the enantiomers of **1** as well as the ready and regiospecific conversion of the dione **1** into its monoprotected derivative **19** points to the synthetic potential of the diones **1** in the chiral synthesis.



(a) $(CH_2OH)_2$, C_6H_6, pTSA.

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8. All the compounds exhibited spectral data consistent with their structures. Selected IR, ^{1}H and ^{13}C

NMR spctral data for select compounds: For the acid **5**: $[\alpha]_D^{24}$: +21.3° (*c* 4.0, $CHCl_3$). IR (neat): ν_{max} 3000 (br), 1707, 1644, 1410, 1284, 885 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 11.6 (1H, bs, COOH), 5.5 (1H, br s, C=CH), 4.64 (2H, s, $C=CH_2$), 2.5-2.8 (2H, m, $CH_2C=O$), 1.0-2.3 (6H, m), 1.67 (3H, s, Me-C=), 1.63 (3H, s, Me-C=). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9 (C=O), 149.6 (*C*=CH_2), 134.3 (*C*=CH), 123.9 (C=*C*H), 108.8 (C=*C*H_2), 41.3, 38.8, 37.1, 35.1, 31.1, 21.0, 20.7. For 1-Methyl-4-isopropenyltricyclo[4.3.0.$0^{2,9}$]nonan-8-one (**7**): $[\alpha]_D^{24}$: -100.5° (*c* 1.9, $CHCl_3$). IR (neat): ν_{max} 3060, 2920, 1720, 1640, 890 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 4.7 (2H, q, J=*ca* 1 Hz, $C=CH_2$), 2.73 (1H, dd, J=19.5 and 12 Hz), 2.5-2.7 (1H, m), 2.3 (1H, m), 1.9-2.2 (2H, m), 1.5-1.8 (3H, m), 1.68 (3H, s, Me-C=), 1.35 (3H, s, *tert*-Me), 1.25 (1H, dd, J=14.2 and 8.8 Hz), 1.04 (1H, d of t, J=14.2 and 6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.3 (C=O), 149.2 (*C*=CH_2), 109.1 (C=*C*H_2), 48.1, 41.1, 39.8, 33.3, 31.4, 29.0, 27.5, 23.5, 20.6, 20.3. For cis-6-methylbicyclo[4.3.0]non-4-en-3,8-dione (**11**): $[\alpha]_D^{25}$: -55° (*c* 2.5, MeOH). IR (neat): ν_{max} 1745, 1675, 1240, 795 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.61 (1H, d, J=10.2 Hz, H-5), 6.0 (1H, d, J=10.2 Hz, H-4), 2.0-2.78 (7H, m), 1.4 (3H, s, *tert*-Me). ^{13}C NMR (50 MHz, $CHCl_3$): δ 214.3 (C-8), 196.8 (C-3), 154.0 (C-5), 128.1 (C-4), 60.4, 51.9, 42.8, 40.8, 37.5, 25.0. For the ketone **14a**: $[\alpha]_D^{24}$: +37° (*c* 1.2, $CHCl_3$). IR (neat): ν_{max} 3078, 1705, 1640, 1450, 890 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.63 (1H, t of dd, J=17.5, 9.5 and 7.3 Hz, C*H*=CH_2), 5.08 (1H, d, J=17.5 Hz) and 5.07 (1H, d, J=9.5 Hz) (CH=CH_2), 4.79 (1H, s) and 4.72 (1H, s) ($C=CH_2$), 2.3-2.7 (5H, m), 1.9-2.2 (2H, m), 1.6-1.7 (1H, m), 1.75 (3H, s, Me-C=), 1.0 (3H,s, *tert*-Me), 0.91 (3H, d, J=7.2 Hz, *sec*-Me). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 215.6 (C=O), 148.2 (*C*=CH_2), 134.3 (H*C*=CH_2), 118.5 (HC=*C*H_2), 110.9 (C=*C*H_2), 52.4, 43.5, 42.7, 41.1, 37.4, 33.4, 21.5, 19.6, 16.6. For the dione **15**. mp. 53-54°C. $[\alpha]_D^{23}$: +6.1° (*c* 1.14, $CHCl_3$). IR (nujol): ν_{max} 3070, 1710, 1700, 1645, 1460, 1380, 895 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 4.83 (1H, s) and 4.75 (1H, s) ($C=CH_2$), 2.78 (2H, bs), 2.56 (2H, bs), 2.2-2.5 (1H, m), 2.12 (3H, s, Me-C=O), 1.65-1.85 (3H, m), 1.72 (3H, s, Me-C=), 1.02 (3H, s, *tert*-Me), 0.88 (3H, d, J=7.2 Hz, *sec*-Me). ^{13}C NMR (50.0 MHz, $CDCl_3$): δ 214.8 (ring C=O), 207.0 (C=O), 147.0 (*C*=CH_2), 110.8 (C=*C*H_2), 56.3, 49.9, 42.0, 40.1, 34.6, 32.4, 31.2, 21.1, 18.8, 15.3. For 1β,2β,4α-1,2-dimethyl-4-isopropenylbicylo[4.3.0]non-6-en-8-one (**16**): $[\alpha]_D^{25}$: +44.2° (*c* 1.0, $CHCl_3$). IR (neat): ν_{max} 3090, 1700, 1618, 1440, 888, 840 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.8 (1H, s, H-7), 4.73 (1H, s) and 4.84 (1H, s) ($C=CH_2$), 2.5-3.1 (3H, m), 2.2 (2H, s, H-9), 1.5-1.8 (3H, m), 1.7 (3H, s, Me-C=), 1.12 (3H, s, *tert*-Me), 0.91 (3H, d, J=6.14 Hz, *sec*-Me). ^{13}C NMR (50.0 MHz, $CHCl_3$ + $CDCl_3$): δ 207.6 (C-8), 187.3 (C-6), 146.0 (*C*=CH_2), 127.4 (C-7), 111.7 (C=*C*H_2), 58.0, 50.6, 40.5, 36.4, 31.4, 30.0, 22.5, 18.5, 16.6. For 1β,2β,4α,6β-1,2-dimethyl-4-isopropenylbicyclo-[4.3.0]nonan-8-one (**17a**): $[\alpha]_D^{26}$: -100.4° (*c* 2.5, $CHCl_3$). IR (neat): ν_{max} 3070, 1740, 1640, 1460, 1405, 1380, 1165, 890 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 4.69 (1H, s) and 4.72 (1H, s) ($C=CH_2$), 2.54 (1H, dd, J=18.7, 8.5 Hz, H-7a), 1.95 and 2.52 (2H, ABq, J=18.5 Hz, H-9), 1.5-2.3 (8H, m), 1.72 (3H, s, Me-C=), 1.057 (3H, d, J=7.1 Hz, *sec*-Me), 1.03 (3H, s, *tert*-Me). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 219.2 (s, C=O), 149.4 (s, *C*=CH_2), 108.5 (t, C=*C*H_2), 48.1 (t, C-9), 44.8 (t, C-7), 40.5 (s, C-1), 38.6 (d), 37.1 (d), 34.6 (t), 33.8 (2C, d & t), 25.8 (q), 21.0 (q), 16.0 (q). For 1β,5β,6β-5,6-dimethylbicyclo[4.3.0]nona-3,8-dione (+)-**1**: $[\alpha]_D^{24}$: +88.4° (*c* 1.9, $CHCl_3$). IR (neat): ν_{max} 1740, 1710, 1240 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 1.7-2.9 (10H, m), 1.24 (3H, s, *tert*-Me), 0.95 (3H, d, J=7.1 Hz, *sec*-Me). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 216.4 (C-8), 210.9 (C-3), 52.5, 46.1, 45.6, 42.7, 41.3, 36.3, 19.4, 17.2.

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