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Stereospecific Construction of Stereogenic Vicinal Quaternary Carbon Atoms. Enantiospecific Synthesis of (+)-Valerane[1]

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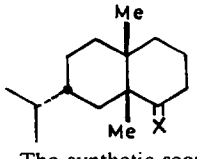
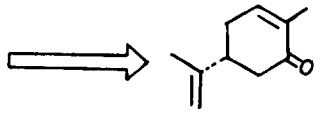
Abstract: Stereo- and enantiospecific synthesis of (+)-valerane starting from R-carvone utilising orthoester Claisen rearrangement and intramolecular diazo ketone cyclopropanation reactions for the construction of the two vicinal quaternary carbon atoms is described.

The presence of quaternary carbon atoms is very frequently encountered in terpene natural products.[2] Even though several methods were developed for the creation of quaternary centers, presence of two or more quaternary carbon atoms in a contiguous manner often creates synthetic challenge. Valeranes[3] are a small group of irregular sesquiterpenes, containing a unique *cis*-decalin carbon skeleton with two methyl substituents at both the ring junction positions. Stereospecific introduction of two methyl groups at the two ring junctions *cis* to each other and *trans* with respect to the isopropyl group makes the valeranes interesting synthetic targets.[3] Herein we report a stereo- and enantiospecific total synthesis of (+)-valerane (**2**) starting from R-carvone, which in addition generated several chiral synthons useful in synthesis of natural products.

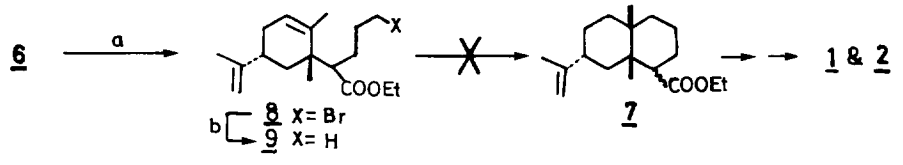


1 R=O (valeranone)
2 R=H_2 (valerane)

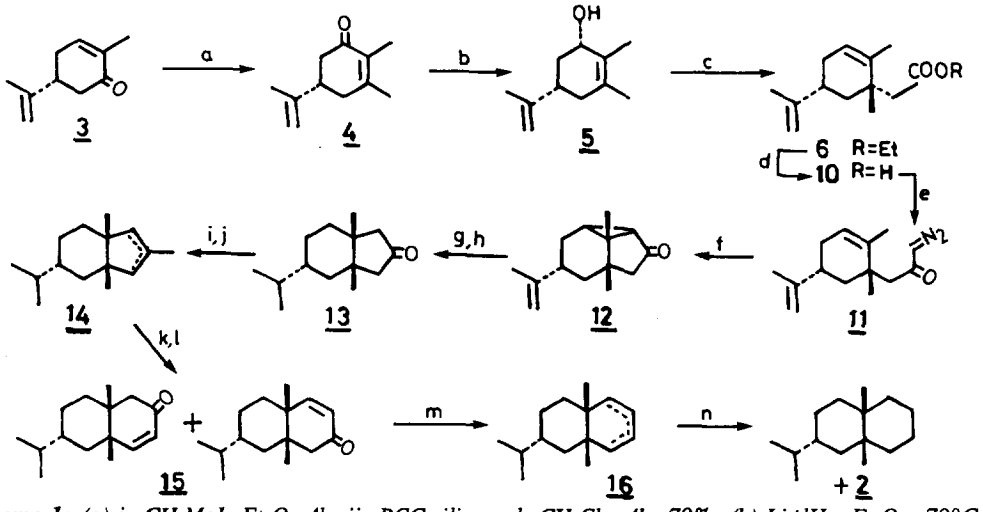


R-(-)-carvone
3

The synthetic sequence is given in schemes 1 and 2. To begin with the R-carvone (**3**) was converted into 6-methylcarvone (**4**) via an alkylative 1,3-enone transposition methodology.[4] For the creation of the first quaternary carbon atom, a stereospecific orthoester Claisen rearrangement was employed. Thus lithium aluminium hydride reduction of the enone **4** furnished the syn alcohol **5** in a highly stereoselective manner.[5] Treatment of the allyl alcohol **5** with triethyl orthoacetate in the presence of a catalytic amount of propionic acid generated the ester **6**, $[\alpha]_D^{24}$ -26.2° (c 2.3, $CHCl_3$), stereospecifically creating the first quaternary carbon atom with methyl group *trans* to the isopropenyl group. For the creation of the second quaternary carbon atom, first a 6-*exo-trig* radical cyclisation reaction based methodology was attempted, anticipating that the decalin ester **7** can serve as precursor to both valerane and valeranone. The radical precursor bromoester **8** was obtained by alkylation of the ester **6** with LDA and 1,3-dibromopropane. In contrast to our expectation, the radical derived from the bromoester **8** failed to cyclise, and furnished only the reduced product **9**. The failure of the radical cyclisation reaction forced us to alter the methodology, and for the stereospecific creation of the second quaternary carbon atom an intramolecular diazo ketone cyclopropanation reaction was opted. Thus base catalysed hydrolysis of the ester **6** furnished the acid **10**, mp. 58°C, $[\alpha]_D^{26}$ -30° (c 2, $CHCl_3$). Treatment of the acid chloride derived from the acid **10** with an excess of ethereal diazomethane furnished the diazo ketone **11**. Anhydrous copper sulfate catalysed decomposition of the diazo



Scheme 2: (a) LDA, THF, $Br(CH_2)_3Br$; 80%; (b) $^nBu_3SnH$, C_6H_6, AIBN, reflux, 2h, 87%.



Scheme 1: (a) i. CH_3MgI, Et_2O, 4h; ii. PCC-silica gel, CH_2Cl_2, 4h; 70%; (b) $LiAlH_4$, Et_2O, -70°C, 2h, 95%; (c) $CH_3C(OEt)_3$, EtCOOH, 160°C, 5 days, 80%; (d) 10% aq.NaOH, MeOH, reflux, 6h, 75%; (e) i. $(COCl)_2$, C_6H_6, rt, 1h; ii. CH_2N_2, Et_2O, rt, 1.5h; 71%; (f) $CuSO_4$, c-C_6H_{12}, W-lamp, reflux, 4h, 57%; (g) Li, liq. NH_3, 0.5h, 76%; (h) H_2, 10%Pd/C, MeOH, 1 atm, 6h, 98%; (i) CH_3MgI, Et_2O, 10h, 85%; (j) p-TSA, C_6H_6, reflux, 5h, 98%; (k) i. O_3/O_2, CH_2Cl_2-MeOH (5:1), -70°C; ii. PPh_3, -70°C→rt, 4h; (l) 1M KOH in MeOH, THF, rt, 12h; 60% from 14; (m) $BF_3.OEt_2$, $NaCNBH_3$, THF, reflux, 10 min, 89%; (n) H_2, 10%Pd/C, MeOH, 1 atm, 12h, 80%.

ketone **11** in refluxing cyclohexane (tungsten lamp) furnished regio- and stereospecifically the cyclopropyl ketone **12**, $[\alpha]_D^{24}$ 27.5° (c 2.0, $CHCl_3$), via the insertion of the ketocarbenoid in ring olefin. Regiospecific cleavage of the cyclopropane ring[6] using lithium in liquid ammonia reduction conditions followed by the catalytic hydrogenation of the olefin moiety transformed enone **12** into the hydrindanone **13**, $[\alpha]_D^{23}$ -29.5° (c 2.0, $CHCl_3$). Further transformation of the hydrindanone **13** into valerane was achieved via ring enlargement. Thus Grignard reaction of the hydrindanone **13** with methylmagnesium iodide followed by dehydration of the resultant tertiary alcohol with p-toluenesulfonic acid (p-TSA) furnished a mixture of olefins **14**. Ozonolysis of the olefinic mixture **14** followed by intramolecular aldol condensation of the resultant keto-aldehydes furnished a ≈1:1.1 mixture of the enones **15**. Deoxygenation reaction of the enone mixture **15** with sodium cyanoborohydride in the presence of boron trifluoride etherate[7] generated a mixture of olefins **16**. Finally catalytic hydrogenation of the olefinic mixture **16** furnished valerane (**2**), $[\alpha]_D^{26}$ 88.0° (c 0.5, $CHCl_3$), which exhibited 400 MHz ^1H NMR spectrum [$CDCl_3$, δ 0.86 (s), 0.84 (s), 0.86 (d, J=6.54 Hz)] and ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ 39.53, 37.31, 37.28, 37.02, 35.51, 34.87, 33.16, 33.12, 25.07, 24.78, 23.66, 22.52, 21.89, 20.1, 19.83 ppm) matching with those reported[3c] in the literature. The extension of this methodology for the synthesis of chiral valeranone and other related compounds is in progress and will be described in a full paper.

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