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# An Improved Synthesis of Homochiral Octalones from (-)-Carvone

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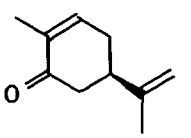
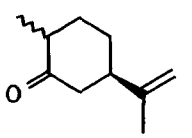
*Abstract: A novel diastereoselective route to octalones* **3** *and* **4** *has been developed. The key step involves an asymmetric Michael addition of the corresponding chiral imine, derived from R-(+)-dihydrocarvone, to methyl vinyl ketone.*

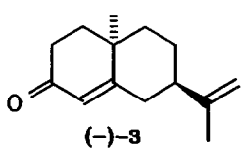
The octalones (-)-**3** and (+)-**4** are useful building blocks for the preparation of homochiral terpenes[1] and steroids. The compounds were previously synthesized as a mixture (**3**/**4** = 2.5/1) by conventional Robinson annulation of **2**[2a,b], easily obtained by reduction of (-)-carvone (**1**)[3].



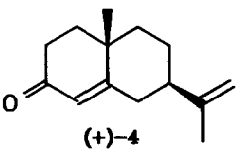
(-)-**1**



**2**



(-)-**3**



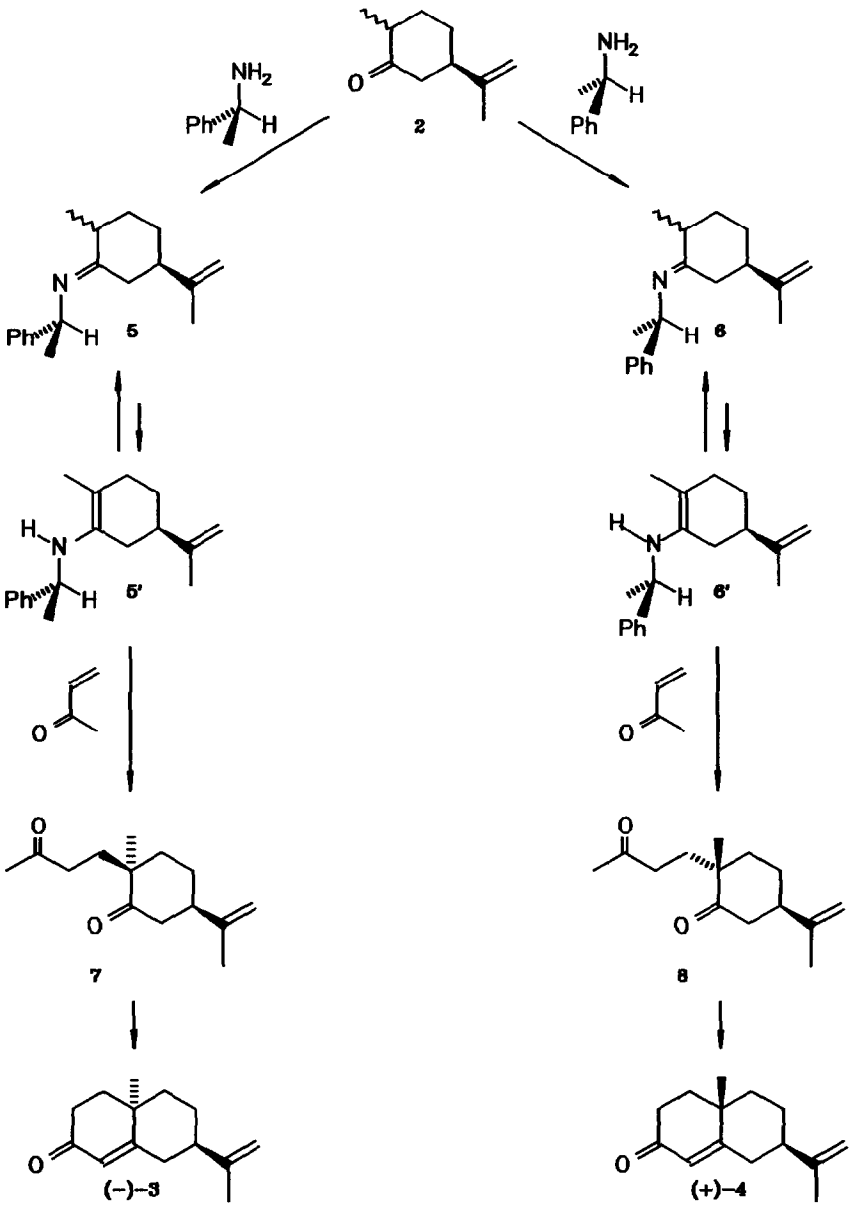
(+)-**4**

In connection with our efforts towards the enantioselective synthesis of eudesmane sesquiterpenes, a simple and efficient access to homochiral octalones **3** and **4** was required. In this communication we describe an improved method to obtain these compounds via deracemizing alkylation of chiral imines[4] **5** and **6**, easily prepared from **2** by reaction with S-(-) and R-(+)-phenylethylamine, respectively[5] (Scheme 1).

The imines **5** and **6** react via their corresponding enamine tautomers **5'** and **6'**, with methyl vinyl ketone. After hydrolysis, the Michael adducts **7**[6] and **8** were obtained in >95% and 58%

diastereomeric excess, respectively. Compound **7** was directly transformed into the homochiral octalone (-)-**3**[7]. However, compound **8** (a mixture of **8**/**7** = 79/21) required careful cyclization

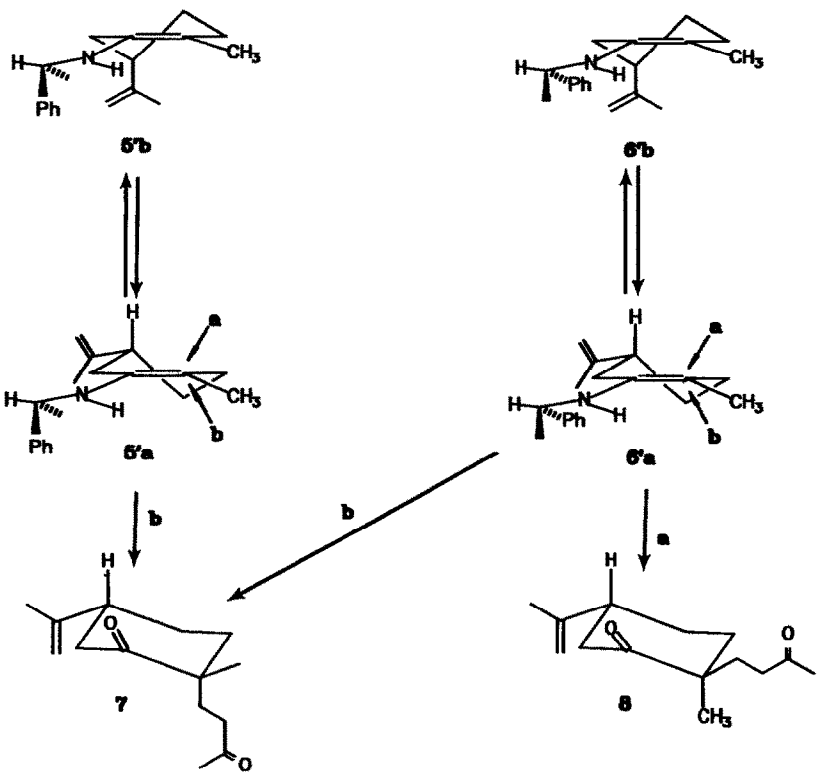
**SCHEME 1**



and selective dehydration (KOH/EtOH, 0°C, 1h) leading to (+)-**4** and the β-hydroxyketone derived from cyclization of **7** (precursor of (-)-**3**). These compounds were easily separated by flash chromatography, furnishing the desired homochiral octalone (+)-**4**[8].

These results can be rationalized as shown in Scheme 2. The conformational analysis of **5'** and **6'** was performed with a molecular mechanics force field (MMX) and conformers **5'a** and **6'a** were indicated as the more stable in each case. The conformational preference around the N-C bonds are in accord with the model proposed by d'Angelo et al. to explain the stereoselectivity of Michael additions involving chiral imines[9]. Although the preferential conformations in the ground state and in the transition state are not necessarily the same, we can assume that the Michael addition occurs in the conformers **5'a** and **6'a**. In the reaction of **5'a**, axial attack (b) on the opposite face from the phenyl group, which is eletronically and sterically favoured, explains the high selectivity in the alkylation step, leading to **7** as the sole diastereomer observed by $^{13}C$ NMR and HPLC. However, a mismatched situation is observed for the reaction of **6'a**. The main product, compound **8**, is formed by an equatorial attack on the opposite side of the phenyl group, which is sterically favoured but eletronically disfavoured. The minor product, **7**, comes from a

SCHEME 2



sterically disfavoured, but eletronically favoured axial attack on the same side as the phenyl group. These results show that control of the stereochemical outcome of the alkylation of chiral imines depends mainly on steric factors, but the eletronic factor cannot be ignored.

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**References and Notes:**

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3) Fairlie, J.C.; Hodgson, G.L.; Money, J.; *J. Chem. Soc. Perkin I* **1973**, 2109.

4) For a review, see: D'Angelo, J.; Desmaele, D.;Dumas, F.; Guingant, A.; *Tetrahedron: Asymmetry* **1992**, *3*, 459.

5) Compound **5** was prepared in 89% yield from R-(+)-dihydrocarvone **2** and S-(-)-phenylethylamine, by azeotropic removal of water in refluxing benzene, in the presence of a catalytic amount of p-TSA. Compound **6** was prepared in 89% yield following the same procedure, by reaction with R-(+)-phenylethylamine.

6) Diketone **7** was prepared in 91% yield from compound **5** and methyl vinyl ketone in THF, r.t., 3 days, followed by treatment with 10% aqueous AcOH. Diketone **8** was obtained as described above, from compound **6**, in 91% yield.

7) Cyclization of **7**, leading to octalone (-)-**3**, in 79% yield, was performed in EtONa/EtOH, 45°C, 1h.
**3**: $^1$H NMR (200MHz, $CDCl_3$): $\delta$ (ppm) 5.74 (s, 1H); 4.80 (br s, 1H); 4.69 (br s, 1H); 2.22-2.63 (m, 5H); 1.70-1.94 (m, 4H); 1.65 (s, 3H); 0.96-1.43 (m, 2H); 1.21 (s, 3H) .
$^{13}$C NMR (50MHz, $CDCl_3$): $\delta$ (ppm) 22.26, 22.35, 23.37, 33.90, 35.31, 35.63, 37.72, 40.18, 112.04, 125.39, 146.42, 170.01, 198.74.
$[\alpha]^{20}$ = -85 (c = 0.05, ethanol)

8) **4**: $^1$H NMR (200MHz, $CDCl_3$): $\delta$ (ppm) 5.76 (s, 1H), 4.77(br s, 2H) 2.26-2.54 (m, 4H); 2.09-2.15 (m, 1H); 1.74 -1.93 (m, 4H); 1.77(s, 3H); 1.26 (s, 3H); 1.26-1.70 (m, 2H).
$^{13}$C NMR (50MHz, $CDCl_3$): $\delta$ (ppm) 20.52, 22.00, 26.96, 33.85, 35.41, 37.66, 41.11, 46.02, 109.19, 124.41, 148.38, 169.71, 199.44.
$[\alpha]^{20}$ = +48.9 (c = 0.08, ethanol)

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