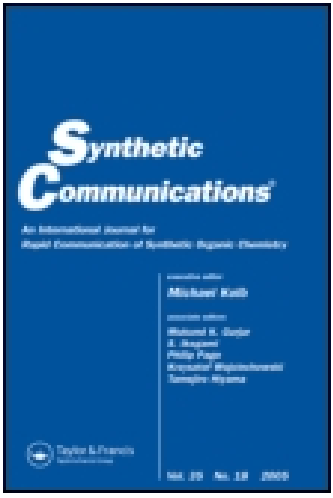

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An Efficient and Stereoselective Synthesis of (+)-α-Cyperone

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AN EFFICIENT AND STEREOSELECTIVE SYNTHESIS OF (+)-α-CYPERONE

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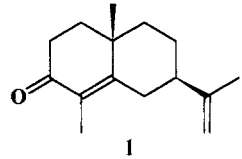
Abstract : An efficient and stereoselective three step synthesis of (+)-α-cyperone **1** is described. The key step involves an stereoselective Michael addition of chiral imine to (R)-dihydrocarvone.

(+)- α-Cyperone **1** has proven to be a useful building block for the synthesis of homochiral sesquiterpenes, like (+)-carissone,[1] α-eudesmol,[2] γ-eudesmol,[3] α-selineno,[4] β-rotunol[5] and (-)-phytuberin.[6]

Recently it was shown that α-cyperone has an *in vitro* activity against *Plasmodium falciparum* strain K1, a multidrug resistent malaria parasite.[7]



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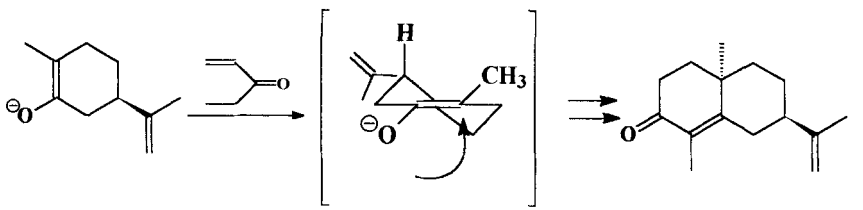
Despite its rather wide use, there are only a few synthetic methods yielding α-cyperone **1**[8]. Its **cis** relationship between the angular methyl and isopropenyl group has been a stereochemical problem in the synthesis involving the Robinson annulation. The original Howe and McQuillin synthesis[9] of **1** proceeded with less than 5% yield, the main product being an octalone with a **trans** relationship between the ring substituent (Scheme I).

SCHEME I

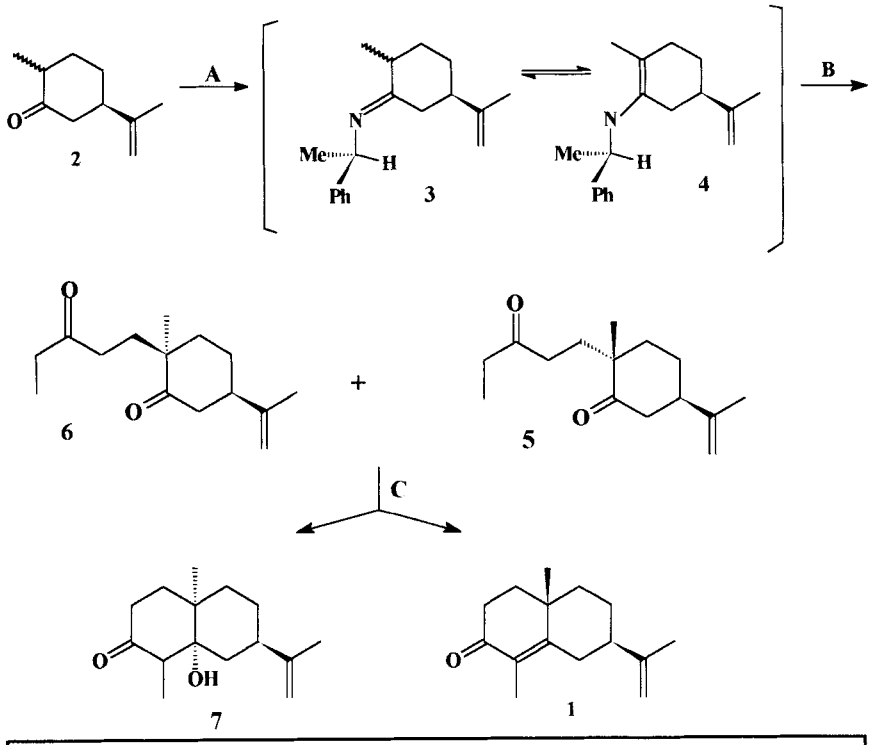


Piers and Cheng[8b] synthesised **1** in eight steps from (-) - Santonin with 20% overall yield. The major improvement was obtained by Caine and Gupton[8a] in a stereoselective three step synthesis of **1** from (-)-2-Carone. More recently, (+)-α-Cyperone **1** was prepared via the Diels-Alder reaction of (+)-Carvone and a silyloxy diene by A. de Groot et al[8e] (7 steps, 40% yield), and from oxycarvone via chiral catalysis[8f].

We here wish to describe an improved three steps synthesis of **1**, over the conventional Robinson annulation, featuring an stereoselective Michael addition as the key step.[10,11]

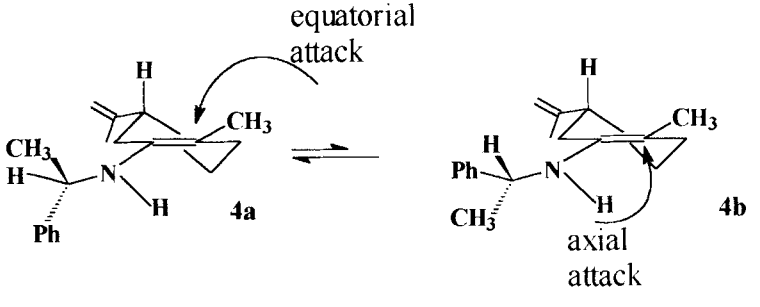
This metodology involves the addition of the chiral imine derivative **3**, prepared from (R)-(+)-1-phenylethylamine and (R)-dihydrocarvone (**2**), to ethyl vinyl ketone, leading to diketones **5** and **6** (a mixture of **5/6** = 80/20). Actually, the reactive nucleophilic species in this process is the secondary enamine **4**, present in the equilibrium with imine **3**. Finally, carefull cyclization of the diastereomeric mixture of **5** and **6**, and selective dehydration of the corresponding keto alcohols, lead to an easily separable mixture of **1** (in 46% overall yield from dihydrocarvone) and β–hydroxy ketone **7** (scheme II).

SCHEME II



A) (R)-(+)-1-phenylethylamine, cat TsOH,benzene,91%
B) EVK, THF, rt, 3days,and then 10% aqueous AcOH, 88%
C) KOH, Et_2O, 0°C, 1h, 76%

This result could be rationalized assuming that the Michael addition occurs as depicted below :



In **4a** the eletronically favoured axial attack is blocked by the bulky phenyl ring, with the main product **5** being formed from the disfavoured equatorial approach. The minor product **6** arise from an axial attack on the sterically disfavoured conformer **4b**, in which the phenyl group lies in the plane of the enamine.

EXPERIMENTAL SECTION

^1H and ^{13}C NMR spectra were determined in $CDCl_3$ solution with a Varian VXR-200 instrument. Chemical shifts (δ) are reported in ppm downfield from internal tetramethyl silane. ^1H NMR data are reported in the following order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet) and number of protons. Infrared spectra were determined with a Matteson Galaxy series FT-300 spectrophotometer. Silica gel 60 F_{254} plates were used for TLC; 230-400 mesh silica gel were used for chromatography. All chemicals and solvents were of analytical grade and were used without further purification. THF was distilled from sodium/benzophenone under nitrogen immediately before use.The reactions were carried out under argon where necessary. Organic extracts were dried over $MgSO_4$. Gas chromatography analyses were carried out with a Hewlett-Packard 5890 chromatograph 50M HP1 capillary column. Specific rotations were mesured at 25^0C on a Polamat polarimeter (Carl Zeiss) at 546 nm (Hg lamp) and corrected to 589 nm (sodium line), at the Universidade de Campinas, SP, Brazil.

[4R]-N-(1-methyl-4-isopropenyl)-2-cyclohexylidene-1-phenyl ethylamine (**3**)

A solution of (R)-dihydrocarvone (10.2 g - 66.9 mmol) in benzene (40 ml) was placed in a 100 ml round-bottom flask equipped with a Dean-Stark trap. (R)-(+)-1-phenylethylamine (9.6 g - 79.8 mmol) was added, followed by catalytic amount of p-toluenesulfonic acid. The reaction mixture was refluxed for 4 h, with azeotropic removal of water. After cooling, the reaction mixture was concentred under reduced pressure and then distilled (10^{-2} mmHg - 135 ^oC) to afford **3** in 91% yield (15.5 g).

IR (film): 3075, 2000, 1700, 1653, 1603, 891, 760 cm^{-1}
^{1}H-NMR ($CDCl_3$): δ 7.80 (m,5H), 4.70 (m,2H), 1.60 (s,3H), 1.40 (d,3H), 1.15 (d,3H).
^{13}C-NMR ($CDCl_3$):δ 17.09, 20.52, 26.43, 31.02, 35.94, 36.73, 42.22, 46.59, 57.99,108.11,125.32,126.04, 128.82, 147.41, 149.89,172.00.

[1S,4R]-1-methyl-1-(3-pentanone)-4-isopropenyl-2-oxocyclo hexane (**5**)
To a solution of **3** (15.5 g - 61 mmol) in dry THF (20 ml) was added dropwise, ethyl vinyl ketone (5.88 g - 70 mmol). The reaction mixture was stirred at room temperature, under argon, for 3 days, and then was added a solution of 10% aqueous acetic acid (25 ml). The solvents were removed under reduced pressure, and 1N HCl (25 ml) was added to the residual oil. The mixture was extracted with ether and organic phases were treated with brine, dried and concentrated in vacuo to afford 12.6 g (88%) of a mixture of diketones **5** and **6** (**5**/**6**= 80/20 determined by capillary GC on a HP1 column (oven parameters-initial temperature: 80^{0}C; final temperature: 230^{0}C; rate:15^{0}C min^{-1}; temperature detection: 230^{0}C; carrier gas: N_2).

(+)- [4aS,7R]-4,4a,5,6,7,8-hexahydro-1,4a-dimethyl-7β(1-methylethenyl)-2(3H)-naphtalenone **(1)**
To a solution of KOH (2.24 g) in dry ethanol (10 ml) and ethyl ether (190 ml) was added dropwise a solution of diketones **5** and **6** in 10 ml of ether. The reaction mixture was stirred at 0^{0}C for 1.5 h, under argon. The reaction mixture was washed with water, brine and the etheral solution was dried over $MgSO_4$. The ether was evaporated, furnishing 9.87 g of crude material.Flash chromatography on silica gel (hexane:ethyl ether, 1:1) gave α-cyperone (**1**) in optically pure form (6.97 g - 32 mmol) and β-hydroxy ketone **7** (2.9 g - 8.13 mmol).

1 $[\alpha]_D$= +107,24^0 (c=2.1, $CHCl_3$), Lit.: $[\alpha]_D$ = + 91.1^0 (c=0.7, $CHCl_3$)[8e] and +87.9^0 (c=1.5, $CHCl_3$)[8f]
IR(film): 3050, 1680, 1640, 890 cm^{-1}.
^{1}H-NMR ($CDCl_3$):δ 4.77 (s,2H), 2.75-2.70 (d,1H), 2.71-

2.39 (m,2H), 2.06-2.01 (d,2H), 1.79-1.70 (m,5H), 1.82 (s,6H), 1.60- 1.41 (m.1H), 1.22 (s,3H).
^{13}C-NMR ($CDCl_3$): δ 10.87, 20.60, 22.44, 26.83, 32.85, 33.74, 35.76, 37.39 41.85 45.84 109.13, 128.70, 149.02, 162.01,198.92.

7 IR (film): 3537, 3069, 1699, 1641, 894 cm^{-1}.
^{1}H-NMR ($CDCl_3$): δ 4.74 (s,2H), 2.85 (m,1H), 2.80-1.21 (m,12H), 1.70 (s,3H), 1.29 (s,3H), 1.08 (d,3H)
^{13}C-NMR ($CDCl_3$): δ 20.82, 20.86, 21.70, 25.74, 31.57, 33.38, 36.66, 37.93, 39.47, 39.70, 51.74, 76.38, 109.06, 148.55, 210.11

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