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Michael Radical Additions
Two Short Efficient Syntheses of (+)-Conocephalenol from (*R*)-Pulegone

Janine Cossy[a], Samir Bouzbouz[a,b] and Abdelhak Hakiki[b]

a) Laboratoire de Chimie Organique associé au CNRS, ESPCI, 10 rue Vauquelin

75231 - Paris Cedex 05 - France

b) Université Mohammed V, Faculté des Sciences, Rabat - Morocco

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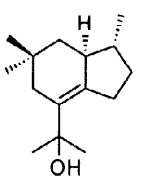
Abstract: Two short and efficient syntheses of (+)-conocephalenol are described from (*R*)-pulegone. The key steps are radical additions of tertiary radicals to enones and an intramolecular aldol cyclization under acidic conditions.

Liverworts are rich sources of terpenoids with unusual frameworks. Such metabolites often exhibit interesting biological properties.[1] *Conocephalum conicum* is a common thalloid liverwort which occurs abundantly. Recently conocephalenol, which is a brasilane sesquiterpene alcohol was isolated from European liverwort *Conocephalum conicum*.[2] This unusual carbon skeleton has previously been found in brasilenol,[3] a marine natural product, but it was the first example of isolation of a compound of this class from a liverwort. The structure and the absolute configuration of conocephalenol were established by Conolly and al.[2]



(+)-Conocephalenol

Previous reported syntheses of (+)-conocephalenol have included a synthesis from (1*R**,7a*S**)-1-methyl-7,7a-dihydroindan-5(6*H*)-one in 20 steps.[4] Another one in which (+)-conocephalenol was obtained by resolution of an alcohol intermediate prepared from a racemic trimethylhydrindenone has been achieved in 14 steps.[5,13]

(*R*)-Pulegone is a well-known precursor in the chiral pool and has been used for a number of chemical transformations.[6] Herein, we give a full account of a practical and convergent route to (+)-conocephalenol from (*R*)-pulegone,[7,8] in addition to an alternative route, both of which involve Michael radical additions of tertiary carbon-centered radicals to α,β-unsaturated ketones. It was anticipated that the construction of the bicyclic system of (+)-conocephalenol could be achieved by an intramolecular aldol condensation of diketone **2**. This compound will be obtained by the addition of a nucleophilic radical derived from 5-bromo-5-methylhexan-2-one to enone **1** in an intermolecular Michael fashion.[9] This

Fax: 33 1 40 79 46 60; e-mail: janine.cossy@espci.fr

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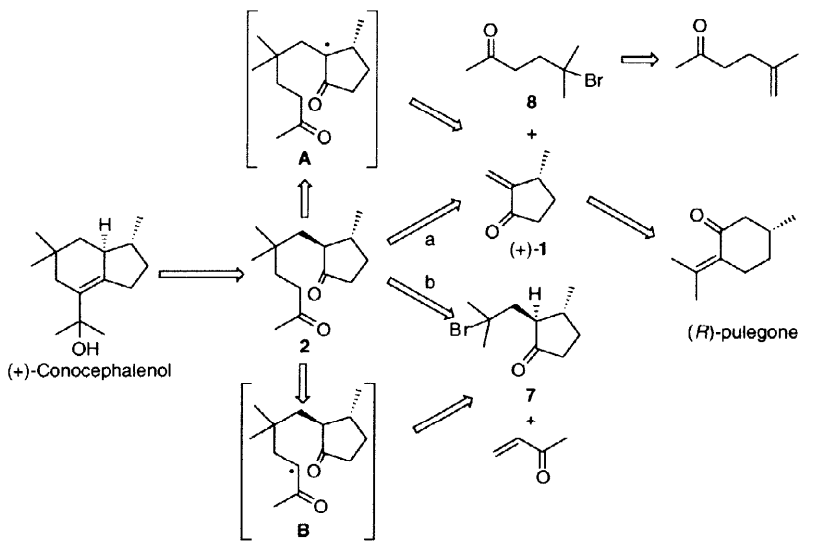
addition will result in the formation of a new radical **A**, which can abstract an hydrogen from Bu_3SnH to produce the thermodynamically more stable *trans* disubstituted cyclopentanone **2**. The alternative route is the addition of a nucleophilic radical, derived from the *trans* disubstituted cyclopentanone **7**, to methyl vinyl ketone which is expected to produce radical intermediate **B** and therefore cyclopentanone **2**. Enone (+)-**1** and cyclopentanone **7** could both be synthesized from (*R*)-pulegone. The retrosynthetic plan is shown in Scheme I.

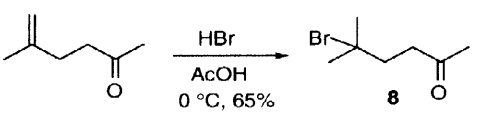
Scheme I: Retrosynthetic analysis of (+)-conocephalenol



a) Synthesis of (+)-conocephalenol from 5-methylhex-5-en-2-one and (R)-3-methyl-2-methylenecyclopentanone (path a).

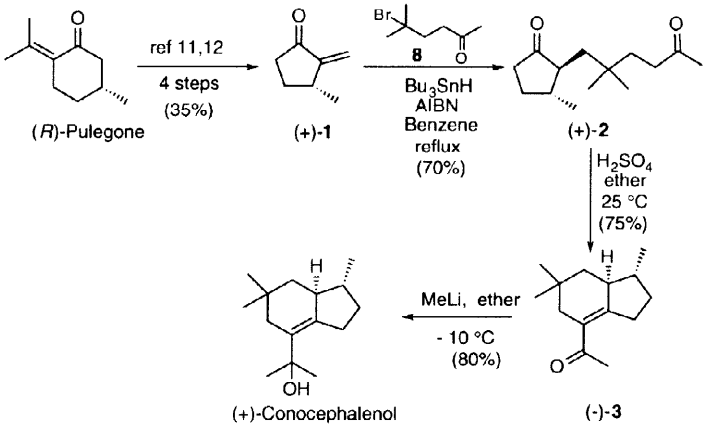
The synthesis of 5-bromo-5-methylhexan-2-one **8** precursor of the nucleophilic radical, was achieved from the commercially available 5-methylhex-5-en-2-one. Thus, the addition of HBr to a solution of 5-methylhex-5-en-2-one in acetic acid at 0 °C afforded the corresponding 5-bromo-5-methylhexan-2-one **8** in 65% yield.[10] (Scheme II)

Scheme II: Preparation of 5-bromo-5-methylhexan-2-one **8**



The synthesis of enone (+)-**1**, (*R*)-3-methyl-2-methylenecyclopentanone, was achieved in 5 steps from (*R*)-pulegone.[11,12] As anticipated, refluxing a 0.1 M benzene solution of bromide **8** with one equivalent of tri-*n*-butyltin hydride and 1.5 equivalents of enone (+)-**1** in the presence of a catalytic amount of AIBN for 1 h afforded diketone (+)-**2** as a single isomer (70% yield). A solution of diketone(+)-**2** in ether was then treated with H_2SO_4 at 25 °C. After 1 h, the bicyclic enone (-)-**3** was isolated in 75% yield. This enone was methylated (MeLi, ether, -10 °C) to give (+)-conocephalenol (yield 80%), spectral data of which were identical in all aspects to those published previously.[5,13]

Scheme III: Synthesis of (+)-conocephalenol from (+)-**1** and **8**

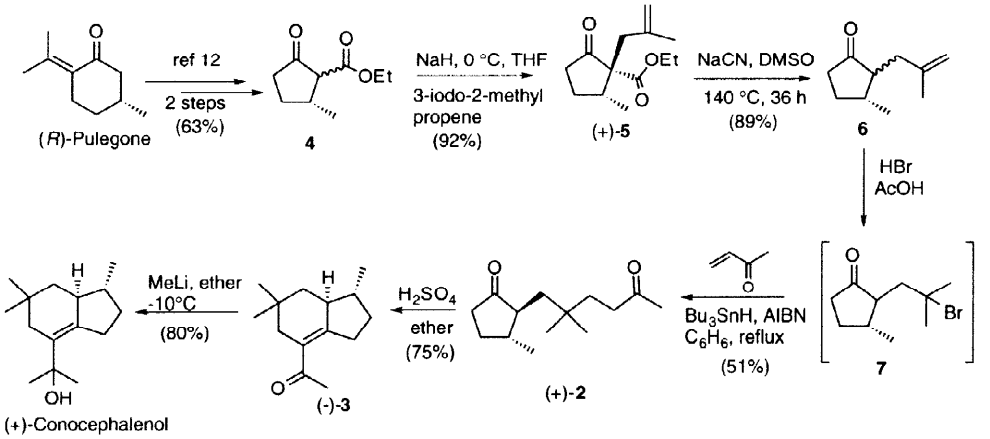


Thus, the synthesis of (+)-conocephalenol was achieved in 8 steps from (*R*)-pulegone with an overall yield of 14.7%.

b) Synthesis of (+)-conocephalenol from methyl vinyl ketone and bromoketone 7 (path b)

One inconvenience in the previous synthesis was the use of 1.5 equivalents of the highly valuable and unstable enone (+)-**1** obtained in 4 steps from (*R*)-pulegone. To avoid the waste of this valuable compound, methyl vinyl ketone was used as the radical acceptor and bromoketone **7** as the precursor of the radical. Hence, (*R*)-pulegone was transformed to the highly reactive bromoketone **7** in 5 steps via β-ketoester **4**.[12] The sodium enolate of **4** was formed regioselectively (NaH, THF, 0 °C) and quenched with 3-iodo-2-methylpropene to give the monoalkylated product (+)-**5** in 92% yield, after 1 h at rt. After decarboxylation of (+)-**5** (NaCN, DMSO, 140 °C, 36 h),[14,15] the unsaturated ketone **6** was obtained as a 9:1 mixture of *trans/cis* stereoisomers (yield 89%). The unsaturated ketone **6** was treated with HBr/AcOH to furnish the unstable bromide **7** which was used directly in a Michael radical reaction. When bromoketone **7** (1 equiv) was treated with Bu_3SnH/AIBN in the presence of methyl vinyl ketone (3 equiv), diketone (+)-**2** was obtained in 51% yield. The ^1H NMR spectrum of the crude reaction mixture shows the presence of only one isomer suggesting that the more stable *trans* isomer of **7** is formed under acidic condition (HBr, AcOH) due to an enolisation of the ketone. Diketone (+)-**2** was then transformed, as previously, to (+)-conocephalenol.

Scheme IV: Synthesis of (+)-conocephalenol from bromoketone **7** and methyl vinyl ketone



By using methyl vinyl ketone as a radical acceptor, (+)-conocephalenol was synthetized from (*R*)-pulegone with an overall yield of 15.8%.

The synthesis of (+)-conocephalenol was achieved with similar overall yields from (*R*)-pulegone by using either bromoketone **7** as the precursor of a nucleophile radical, or by using the methylenic ketone (+)-**1** as the radical acceptor.

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EXPERIMENTAL PART

General methods:

All experiments were run under an Ar atmosphere. ^{1}H NMR and ^{13}C NMR spectra were obtained with a Bruker AC 300 instrument at 300 MHz and 75 MHz respectively, in $CDCl_3$ (Me_4Si as internal standard). IR spectra were recorded on a Perkin-Elmer Infracord 137 spectrometer. Mass spectra were run on a Hewlett-Packard (EI mode at 70 eV) and HRMS on a MS 50 TC Kratos (EI mode at 70 eV). Optical rotations were measured at the sodium line with a Perkin-Elmer Model 241 spectropolarimeter Flash chromatography was performed on Merck silica gel 0.043-0.063 mm with petroleum ether and ether. Dimethylsulfoxide, benzene and amines were distilled from CaH_2.

(2R,3S)-2-(2,2-Dimethyl-5-oxohexyl)-3-methylcyclopentan-1-one(+)-2

To a solution of bromoketone **8** (0.105 g, 0.540 mmol), enone (+)-**1** (0.089 g, 0.81 mmol) and AIBN (0.009 g, 0.0540 mmol) in refluxing benzene (5.5 mL) was added Bu_3SnH (0.147 mL, 0.540 mmol) over a period of 10 min. After 1 h reflux, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (PE/ether: 60/40) yielding 0.085 g of diketone **2** (70%).
$[\alpha]^{22}_D$ = + 24.3 (*c* 5, $CHCl_3$). IR: 1740, 1710 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.82 (s, 6H), 0.97-2.67 (m, 12H), 1.09 (d, *J* = 6.2 Hz, 3H), 2.12 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 19.2 (d), 25.8 (q), 26.7 (q), 27.7 (d), 29.4 (q), 32.4 (s), 35.3 (t), 37.0 (t), 38.8 (t), 39.3 (d), 39.4 (t), 52.9 (d), 209.5 (s), 220.8 (s). MS *m/z* 224 ($M^{\ddagger}$, 3), 209 (8), 195 (32), 168 (39), 153 (56), 111 (100). HRMS *m/z* calcd for $C_{14}H_{25}O_2$ $(M+1)^+$ 225.18546. Found 225.18549.

(1S,7aR)-4-Acetyl-1,6,6-trimethyl-2,3,5,6,7,7a-hexahydro-1H-indene(-)-3

To a solution of diketone (+)-**2** (0.06 g, 0.27 mmol) in ether (2 mL), was added concentrated H_2SO_4 (0.10 mL). After 1 h at 25 °C, water (1 mL) was added and the reaction mixture was extracted with ether (3 x 3 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (PE/ether: 75/25) yielding 0.042 g of enone (-)-**3** (75%). $[\alpha]^{22}_D$ = - 4.6 (*c* 1.17, EtOH) [litt: $[\alpha]^{22}_D$ = - 6.0 (*c* 1.68, EtOH)][5,13]. IR: 1700, 1670 cm^{-1}. ^{1}H NMR (C_6D_6) δ: 0.80 (s, 3H), 0.95 (d, *J* = 6.0 Hz, 3H), 0.98 (s, 3H), 0.90-1.80 (m, 6H), 2.01 (s, 3H), 2.05 (m, 2H), 2.50-2.90 (m, 2H). ^{13}C NMR (C_6D_6) δ: 18.4 (q), 26.8 (q), 29.9 (q), 30.4 (s), 32.6 (t), 32.7 (q), 34.0 (t), 40.0 (t), 40.9 (d), 41.5 (t), 49.3 (d), 128.7 (s), 157.1 (s), 198.9 (s). MS *m/z* 206 ($M^{\ddagger}$, 71), 191 (100), 177 (4), 163 (50), 135 (34), 107 (49).

(1S,7aR)-2-(1,6,6-Trimethyl-2,3,5,6,7,7a-hexahydro-1H-inden-4-yl)propan-2-ol (+)-conocephalenol

To a solution of bicyclic enone (-)-**3** (0.03 g, 0.145 mmol) in ether (1.5 mL) at -10 °C, was added a solution of MeLi 1.6 M (0.154 mL, 0.247 mmol). After 1 h, an aqueous saturated solution of NH_4Cl (1 mL) was added, and the reaction mixture was extracted with ether (3 x 2 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (PE/ether: 70/30) yielding 0.026 g of (+)-conocephalenol (80%).
$[\alpha]^{22}_D$ = + 5.5 (*c* 2, EtOH) [litt: $[\alpha]^{22}_D$ = + 5.85 (*c* 0.94, EtOH)][5, 13]. IR: 3400 cm^{-1}. ^1H NMR (C_6D_6) δ: 0.90 (s, 3H), 1.00 (s, 3H), 1.02 (d, *J* = 6.2 Hz, 3H), 1.26 (s, 6H), 0.80-1.70 (m, 7H), 1.80 (m, 2H), 2.50-2.70 (m, 2H). ^{13}C NMR (C_6D_6) δ: 18.6 (q), 27.0 (q), 29.8 (q), 30.0 (t), 30.5 (q), 33.0 (s), 33.1 (q), 34.6 (t), 41.0 (t), 41.2 (d), 41.9 (t), 48.8 (d), 74.4 (s), 133.1 (s), 136.4 (s). MS *m/z* 222 (M^+, 5), 207 (81), 204 (82), 175 (15), 164 (31), 149 (98), 59 (100).

5-Bromo-5-methylhexan-2-one 8

To a solution of HBr in acetic acid 30% (6 mL) at 0 °C, was added a solution of 5-methylhex-5-en-2-one (0.25 g, 2.23 mmol) in acetic acid (3 mL). After 30 min at rt, the reaction mixture was neutralized by a saturated aqueous solution of $NaHCO_3$ and extracted with ether (3 x 50 mL). The organic phase was washed with water, brine and then dried over $MgSO_4$. The solvent was removed in *vacuo* and the residue purified by flash column chromatography (PE/ether: 60/40) yielding 0.28 g of **8** (65%).
^1H NMR ($CDCl_3$) δ: 1.66 (s, 6H), 1.86 (m, 2H), 2.08 (s, 3H), 2.67 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 29.6 (q), 33.7 (2q), 39.9 (t), 40.5 (t), 66.5 (s), 207.0 (s).

(1S,5S)-Ethyl 5-methyl-1-(2-methylallyl)-2-oxocyclopentane-1-carboxylate (+)-5

A solution of ketoester **4** (0.60 g, 3.53 mmol) in THF (8 mL) was added dropwise to a suspension of NaH (0.14 g, 3.53 mmol) in THF (10 mL) at 0 °C over a period of 10 min. After 20 min at rt, the solution was cooled to 0 °C, and 3-iodo-2-methylpropene (0.642 g, 3.53 mmol) in THF (5 mL) was added to the reaction mixture. After 1 h, the reaction mixture was extracted with ether (3 x 20 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (PE/ether: 60/40) yielding 0.727 g of ketoester (+)- **5** (92%).
$[\alpha]^{22}_D$ = + 126 (*c* 4.4, $CHCl_3$). IR: 1750, 1725 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.96 (d, *J* = 6.1 Hz, 3H), 1.20 (t, *J* = 7.0 Hz, 3H), 1.50 (s, 3H), 1.65-2.70 (m, 7H), 3.86-4.16 (m, 2H), 4.66 (s, 1H), 4.76 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 14.0 (q), 15.1 (q), 24.0 (q), 27.7 (t), 37.4 (d), 37.8 (t), 38.6 (t), 60.8 (t), 62.7 (s), 115.9 (d), 141.1 (s), 170.2 (s), 216.4 (s). MS *m/z* 224 (M^+, 0.5), 196 (7), 179 (11), 168 (22), 123 (100), 109 (22), 95 (41). HRMS *m/z* calcd for $C_{13}H_{21}O_3$ $(M+1)^+$ 225.14906. Found 225.14946.

(3S)-3-methyl-2-(methylallyl)cyclopentan-1-one 6

To a solution of ketoester (+)-**5** (0.50 g, 2.23 mmol) in DMSO (2 mL) was added NaCN (0.11 g, 2.23 mmol). After 36 h at 140 °C, water (2 mL) was added and the reaction mixture was extracted with ether (3 x 5 mL). The organic phase was washed with brine (5 mL), dried over $MgSO_4$, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (PE/ether: 70/30) yielding 0.30 g of ketone **6** (89 %). The ratio *trans/cis* (90/10) was determined by ^1H NMR spectrum.
IR: 1735, 1740 cm^{-1}. ^1H NMR ($CDCl_3$) Major isomer δ: 1.15 (d, *J* = 6.5 Hz, 3H); Minor isomer δ: 0.85 (d, *J* = 6.5 Hz, 3H); For both isomers δ: 1.40-2.50 (m, 8H), 1.70 (s, 3H), 4.80 (m, 2H). ^{13}C NMR Major isomer δ: 19.6 (q), 22.1 (q), 29.4 (t), 36.9 (t), 37.2 (d), 37.4 (t), 54.2 (d), 112.2 (t), 143.2 (s),

220.6 (s); Minor isomer δ: 14.2 (q), 22.2 (q), 27.7 (t), 32.4 (d), 32.5 (t), 34.3 (t), 52.0 (d), 110.8 (t), 143.3 (s), 219.6 (s). MS *m/z* 152 (M^{+}, 1), 137 (13), 110 (100), 90 (63), 81 (63), 67 (39), 56 (14). HRMS *m/z* calcd for $C_{10}H_{17}O$ $(M+1)^{+}$ 153.12011. Found 153.12041.

(2R,3S)-2-(2bromo-2-methylpropyl)-3-methylcyclopentanone 7

To a solution of HBr in acetic acid 30% (4 mL) was added a solution of ketone **6** (0.18 g, 1.18 mmol) in acetic acid (1.5 mL). After 15 min at rt, water and ice were added. The reaction mixture was extracted with ether (3 x 50 mL) washed with brine and then dried over $MgSO_4$. After removal of the solvent *in vacuo*, the residue was directly used in the following reaction.

Preparation of (+)-2 from 7 and methyl vinyl ketone

To a solution of methyl vinyl ketone (0.29 mL, 3.55 mmol), AIBN (0.019 g, 0.118 mmol) and compound **7** in refluxing benzene (12 mL), was added Bu_3SnH (0.32 mL, 1.18 mmol). After 1 h, the solvent was evaporated and the residue was purified by flash column chromatography (PE/ether: 60/40) yielding 0.135 g of diketone (+)-**2** (51% from **6**).

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