Pergamon

Tetrahedron Letters, Vol. 38, No. 51, pp. 8853-8854, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10391-4

A Very Short and Efficient Synthesis of (+)-Conocephalenol

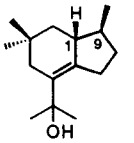
Janine Cossy *[a], Samir BouzBouz [a,b] and Abdelhak Hakiki [b]

[a] Laboratoire de Chimie Organique, Associé au CNRS, ESPCI, 10 rue Vauquelin
75231 - Paris Cedex 05 - France

[b] Université Mohammed V, Faculté de Sciences, Rabat, Maroc

Abstract: The synthesis of (+)-conocephalenol, a brasilane sesquiterpenoid alcohol, was achieved in seven steps from *(R)*-pulegone with an overall yield of 15%. The key steps were a radical addition of a tertiary radical to the electrophilic radicophile, *(R)*-3-methyl-2-methylenecyclopentanone, and an aldol cyclization under acidic conditions. © 1997 Elsevier Science Ltd.

Liverworts are rich sources of terpenoids with unusual frameworks.[1] 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 the European liverwort *Conocephalum conicum*.[2] This unusual carbon skeleton has previously been reported from brasilenol,[3] a marine natural product, but it was the first example of the isolation of a compound of this class from a liverwort. The structure and the absolute stereochemistry of conocephalenol were established by Connolly and al.[2]



Conocephalenol

The first synthesis of conocephalenol was achieved from the (1*R**, 7a*S**)-1-methyl-7,7a-dihydroindan-5(6*H*)-one in 20 steps,[4] and (+)-conocephalenol was obtained by resolution of an alcohol intermediate obtained from a racemic trimethylhydrindenone in 14 steps.[5]

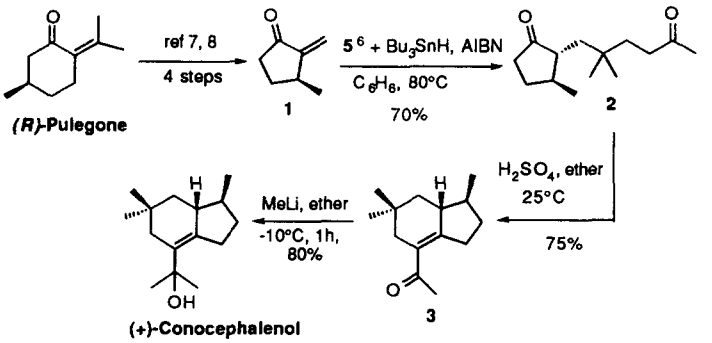
Here, we report a short synthesis of (+)-conocephalenol starting from (*R*)-pulegone and 5-bromo-5-methylhexan-2-one **5**[6] and employing the addition of a tertiary radical to 5-methylenehexan-2-one **4**. The synthesis of the electrophilic radicophile **1**, the (*R*)-3-methyl-2-methylenecyclopentanone, was achieved in 4 steps from (*R*)-pulegone[7,8] (overall yield = 35%).

When a 0.1 molar benzene solution of the bromide **5** was heated at refluxed for 1 h with 1 equivalent of tri-*n*-butyltin hydride, 1.5 equivalent of the enone **1** and a catalytic amount of AIBN, the diketone **2** was obtained as a single isomer in 70% yield. The structure of **2** was deduced from its spectral data.[9] A solution of diketone **2** in ether was then treated with H_2SO_4 at 25 °C. After 2 h the bicyclic enone **3** was isolated in 75% yield.[10] This enone was methylated (MeLi) to give (+)-conocephalenol [yield = 80%, $[\alpha]_D$ = +5.5 (*c* = 2, EtOH)], identical in all respects with the published spectral data.[11]

The synthesis of (+)-conocephalenol was thus achieved in seven steps from (*R*)-pulegone with an overall yield of 15%.

Fax: 33 1 40 79 44 25. e-mail: janine.cossy@espci.fr

Scheme : Synthesis of (+)-conocephalenol from *(R)*-pulegone



Acknowledgment: One of us, S. B. thanks the CNRS for a grant.

References and Notes

1. Asakawa, Y. *Progress in the Chemistry of Organic Natural Products*, Ed. Herz, W.; Grisebach, H.; Kifby, G. W.; Springer-Verlarg, Wien, **1982**, *42*, 1; in *Bryophites: Their Chemistry and Chemical Taxonomy*, Ed. Zinsmeister, H. D.; Mues, R. Oxford University Press, Oxford, **1990**, 369; in *Bioactive Natural Products: Detection, Isolation, and Structural Determination*, Ed. Colegate, S. M.; Molyneux, R. J., CRS Press, Florida, **1993**, 319.

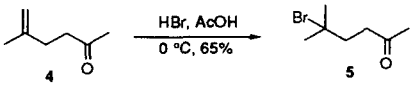
2. Connolly, J. D. in *Studies in Natural Products Chemistry*, Ed. Atta-ur-Rahman, Elsevier, Amsterdam, **1988**, *2*, 273.

3. Stallard, M. O.; Fenical, W. *Tetrahedron* **1978**, *34*, 2077-2081.

4. Tori, M.; Sono, M.; Nakashima, K.; Nakaki, Y.; Asawaka, Y. *J. Chem. Soc., Perkin Trans 1* **1991**, 447-450.

5. Tori, M.; Sono, M.; Nakashima, K.; Nakaki, Y.; Asawaka, Y.; Connolly, J. D.; Harrison, L. J.; Rycroft, D. S.; Singh, J.; Woods, N. *J. Chem. Soc., Perkin Trans 1* **1995**, 593-597.

6. Preparation of 5-bromo-5-methylhexan-2-one:



7. Nangia, A.; Prasuna, G. *Tetrahedron* **1996**, *52*, 3435-3450.

8. Marx, J. N.; Norman, L. R. *J. Org. Chem.* **1975**, *40*, 1602-1606.

9. **Compound 2** : $[\alpha]_D$ = +24.3 (*c* = 5, $CHCl_3$); IR (film): 1740, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) *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 ($CDCl_3$, 75 MHz) *δ*: 19.2 (q), 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 (EI, 70 eV) *m/z* 224 (3), 209 (8), 195 (32), 168 (39), 153 (56), 111 (100).

10. **Compound 3** : $[\alpha]_D$ = +4.2 (*c* = 1.4, $CHCl_3$); IR (film): 1700, 1670 cm^{-1}; ^1H NMR (C_6D_6, 300MHz) *δ*: 0.80 (s, 3H), 0.95 (d, *J* = 6.0 Hz, 3H), 0.98 (s, 3H), 0.9-1.8 (m, 6H), 2.01 (s, 3H), 2.05 (m, 2H), 2.5-2.9 (m, 2H); ^{13}C NMR (C_6D_6, 75 MHz) *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 (EI, 70 eV) *m/z* 206 (71), 191 (100), 177 (4), 163 (50), 135 (34), 107 (49), 91 (21).

11. **(+)-Conocephalenol** : $[\alpha]_D$ = +5.5 (*c* = 2, EtOH); IR (film): 3400, 1680 cm^{-1}; ^1H NMR (C_6D_6, 300MHz) *δ*: 0.9 (s, 3H), 1.0 (s, 3H), 1.02 (d, *J* = 6.2 Hz, 3H), 1.26 (s, 6H), 0.8-1.7 (m, 7H), 1.8 (m, 2H), 2.5-2.7 (m, 2H) ; ^{13}C NMR (C_6D_6, 75 MHz) *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 (EI, 70 eV) *m/z* 222 (5), 207(81), 204 (82), 175(15), 164 (31), 149 (98), 59 (100).

(*Received in France* 23 *June* 1997; *accepted* 13 *October* 1997)