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TOTAL SYNTHESIS OF (±)-LAURENE AND EPILAURENE BY RADICAL CYCLISATION REACTION

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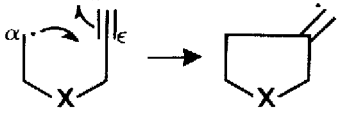
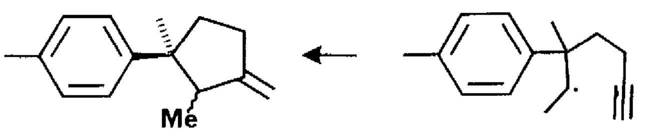
Abstract: Total synthesis of (±)-laurene and epilaurene, via the radical cyclisation of the xanthate (11) derived from the acetylenic alcohol (10), is described.

Cyclisation of the ϵ-acetylenic radicals is a mild and very useful method for the construction of cyclopentanoids with an exo methylene group.[1] We have efficiently employed this methodology in the synthesis of variety of furanoids.[2] We have now extended this strategy to carbocyclic sesquiterpenes with an exo methylene moiety, laurene (1) and epilaurene (2) via the radical 3, which is the subject of this communication.

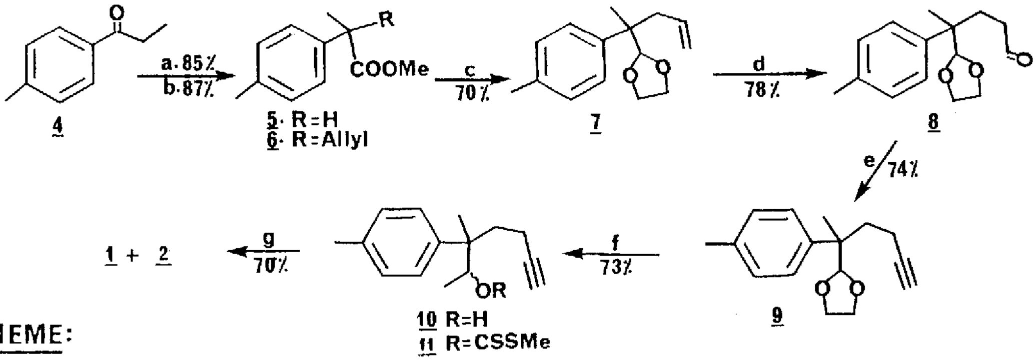




1. —Me
2. ''''''Me

3

Laurene (1) was first isolated by Irie et al. from Laurentia glandulifera, later from several Laurentia species and more recently from the marine red algae Laurentia elata.[3,4] Our approach to laurenes (1 and 2) starts from the readily available p-methyl propiophenone (4) via the 2-tolyl propionate (5). The synthetic sequence is depicted in the Scheme. The propionate 5, obtained in 85% yield from the ketone 4 in one step according to the procedure of Yamauchi et al.,[5] was allylated cleanly (LDA, THF, allyl bromide) to yield the ester 6. The acetal 7 was obtained from the ester 6 in a straight forward manner, reduction to primary alcohol (LAH), oxidation to aldehyde (PCC) and protection with ethylene glycol. Next target in the synthesis is the conversion of the allyl side chain to butynyl chain (7→9). Towards this end, acetal 7 was hydroborated (BH_3-THF; NaOH-H_2O_2) and oxidised (PCC) to yield the aldehyde 8. The conversion of the aldehyde 8 into the acetylene 9 was most conveniently accomplished[6] in 75% yield through dibromomethylene Wittig (CBr_4-PPh_3) followed by reaction with BuLi.[7] The acetylenic acetal 9 was elaborated into the alcohol 10, the key intermediate, via hydrolysis of the acetal group (aq.HCl-THF) followed by Grignard reaction (MeMgI-Et_2O).[7] The alcohol 10 was then transformed into the radical precursor, xanthate 11 (NaH-THF-CS_2-MeI) and finally the radical cycli-



SCHEME:

a) I_2, $HC(OMe)_3$, RT, 24 hr; b) LDA, THF, -78^oC, 1 hr; allyl bromide, -78^oC to RT; c) i. THF, LAH, Et_2O, 14 hr at RT, reflux 1 hr; ii. PCC, NaOAc, CH_2Cl_2, 5 hr; iii. $(CH_2OH)_2$, PTSA, C_6H_6, 14 hr; d) i. BH_3.THF, 0^oC to RT, 1.5 hr; 3N NaOH, 30% H_2O_2, 2 hr; ii. PCC, NaOAc, CH_2Cl_2, 2 hr; e) i. PPh_3 (4 eq), CBr_4 (2 eq), 0^oC, 1.5 hr; ii. n-BuLi, THF, -78^oC to RT, 2 hr; f) i. 2N HCl, THF, RT, 12 hr; ii. MeMgI, Et_2O, 3 hr; g) i. NaH, THF, Imidazole (cat.), 60^oC, 3 hr; CS_2, 50^oC, 15 min; MeI, 50^oC, 0.5 hr; ii. n-Bu_3SnH, AIBN (cat.), C_6H_6 (0.02M).

sation of the crude xanthate 11 under standard condtions[1] (0.02M n-Bu_3SnH-Benzene-AIBN) cleanly furnished a ~1:1 mixture (by NMR) of laurene (1) and epilaurene (2), whose spectral data is identical to that reported in the literature.[3,4]

In summary, we have described here a total synthesis of laurene and epilaurene starting from p-methyl propiophenone in an overall yield of ~15% using radical cyclisation as the key reaction. Currently, we are extending this methodology to cuparenes and these details will be discussed in a full paper.

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7. Spectral data for 9: IR(neat): 3300,2140,1100 cm^{-1}; ^1H NMR(270MHz,$CDCl_3$): δ 7.25(2H,d,J=8Hz),7.12(2H,d,J=8Hz),4.85(1H,s),3.79(4H,brs),2.31(3H,s), 2.3-1.6(5H,m),1.33(3H,s); ^{13}C NMR(22.5MHz,$CDCl_3$):δ139.1(s),135.8(s),128.9 (2C,d),127.2(2C,d),109.5(d),84.9(s),68(d),65.3(2C,t),44.8(s),35.6(t),20.9 (q),18.2(q),13.4(t). For 10(3:1 mixture of diastereoisomers): IR(neat): 3450,3400,2140 cm^{-1}; ^1H NMR(270MHz,$CDCl_3$):δ 7.15(4H,m),3.83&3.74(1H,q,J=6Hz),2.32(3H,s),2.19-1.8(6H,m),1.28&1.27(3H,s),0.95&1.12(3H,d,J=6.4Hz).

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