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SYNTHESIS OF HYDROXYCADALENE AND HYDROXYCALAMENENE VIA 13-HYDROXYXANTHORRHIZOL, A POSSIBLE PRECURSOR OF PARVIFOLIN

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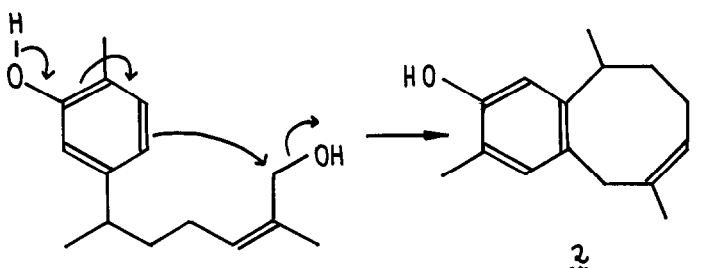
Summary: Starting with an acetophenone derivative three sesquiterpenes, xanthorrhizol, hydroxycadalene and hydroxycalamenene were synthesized. The biomimetic formation of parvifolin could not be achieved.

The unusual sesquiterpene, parvifolin (2), has been isolated from a Mexican Coreopsis species [1]. Inspection of the carbon skeleton led to the proposal that the so far not isolated 13-hydroxyxanthorrhizol (1) could be the precursor (the Scheme). In order to examine this pathway we have synthesized this compound and also three natural occurring sesquiterpenes, xanthorrhizol (6) [2], 2-hydroxycadalene (10) [3] and 2-hydroxycalamenene (12) [4]. Starting with 3-methoxy-4-methyl acetophenone (3) reaction with homoprenyl bromide followed by reduction of the benzylic hydroxy group using triethyl silane/boron-trifluoride etherate [5] the methyl ether 4 was obtained in good yield. Several other methods of reduction were unsatisfactory. Heating of 4 with methyl magnesiumiodide in xylene gave in good yield xanthorrhizol (6) [^{1}H NMR, $CDCl_3$: δ 6.63 d (H-2, J = 2 Hz), 7.04 d (H-5, J = 8), 6.70 dd (H-6, J = 8, 2), 2.63 tq (H-7, J = 7, 7.5), 1.60 m (H-8), 1.90 dt (H-9, J = 7, 7.5), 5.11 br t (H-10, J = 7), 1.70 br s (H-12), 1.55 br s (H-13), 1.22 d (H-14, J = 7), 2.23 br s (H-15)]. Ozonolysis of 4 gave the aldehyde 5 which following the method of Corey et al [6] afforded the desired Z-configurated methyl ether 7. After formation of the corresponding chloride using the method of Corey et al [7] all attemps to hydrolyze the methyl ether were unsuccessful. However, reaction with $ZnCl_2$

in methylene chloride afforded in high yield 2-methoxycadalene (9). Reaction with boron tribromide [8] gave the corresponding phenol 10 which was identical with the natural product [3]. [^{1}H NMR (C_6H_6): δ 6.95 s (H-1), 7.93 s (H-4), 7.21 d (H-6, J = 8 Hz), 7.25 d (H-7, J = 8), 3.61 qq (H-9, J = 7, 7), 1.36 d (H-10, 11, J = 7), 2.52 s (H-12), 2.45 s (H-13), 4.82 br s (OH)]. In order to get the desired free phenol 8 we therefore have protected the phenol 6 with an acetal group. By using the same reactions the 13-hydroxyxanthorrhizol (1) was obtained. After formation of the chloride 8 reaction with potassium tert.-butoxide afforded 11 and no trace of 2. However, the proposed biogenetic formation of parvifolin (2) via the phenol 1 still can not be excluded. Hydrogenation of 11 afforded 2-hydroxycalamenene (12), identical with the natural compound [^{1}H NMR ($CDCl_3$): δ 6.65 s (H-1), 6.94 s (H-4), 2.63 dt (H-5, J = 7, 6.5 Hz), 1.80 and 1.93 m (H-6), 1.30 and 1.55 m (H-7), 2.71 tq (H-8, 6.5, 7), 2.19 m (H-9), 0.99 and 0.70 d (H-10, 11, J ~ 7), 1.24 d (H-12, J = 7), 2.20 br s (H-13), 4.44 br s (OH)]. Together with 12 the 8-epimeric phenol was obtained (ca. 30 %) which was not separated from 12 by GC. [^{1}H NMR ($CDCl_3$): δ 6.56 s (H-1), 6.94 s (H-4), 2.53 dt (H-5), 1.80 and 1.93 m (H-6), 1.55 and 1.30 m (H-7), 2.80 tq (H-8), 2.19 m (H-9), 1.02 and 0.76 d (H-10, 11), 1.23 d (H-12), 2.20 br s (H-13), 4.44 br s (OH)]. The phenol 12 has been synthesized previously [9]. The Z-configuration of 1 followed from the shift of H-13 (δ 9.94) in the corresponding aldehyde.



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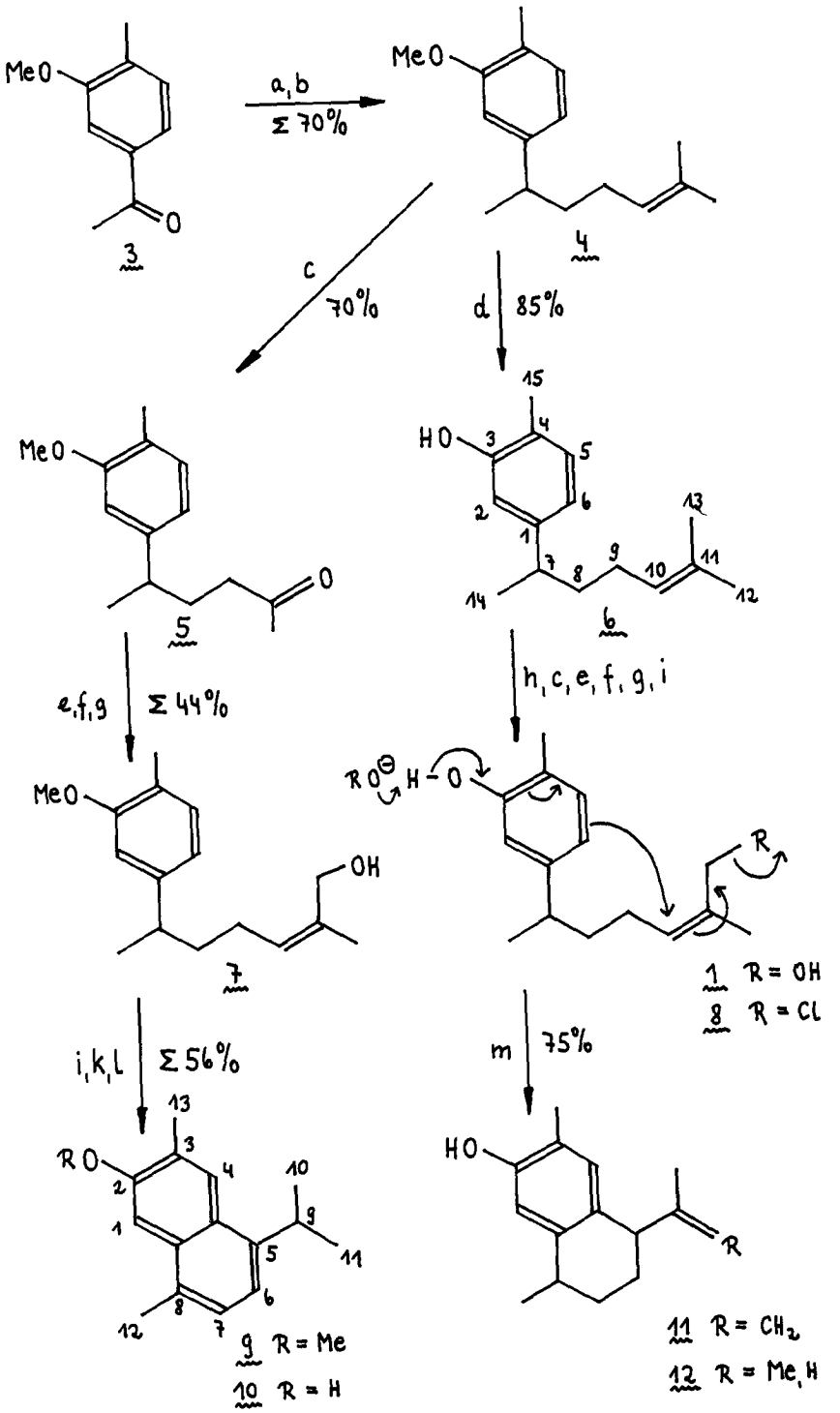
MeO
a, b
Σ 70%
3
4
c
70%
d 85%
5
6
e, f, g Σ 44%
h, c, e, f, g, i
7
1 R = OH
8 R = Cl
i, k, l Σ 56%
m 75%
9 R = Me
10 R = H
11 R = CH2
12 R = Me, H

a) $Me_2C=CHCH_2CH_2MgBr$, then NH_4Cl; b) $Et_3SiH/BF_3.Et_2O$; c) O_3/Me_2S, -70^{o}; d) MeMgI/xylene/Δ ; e) $Ph_3P=CHMe$/ -78^{o}; f) BuLi; g) CH_2O; h) ClCH(Me)OEt/ $EtN(CHMe_2)_2$; i) NCS/Me_2S/ 0^{o}; k) $ZnCl_2/CH_2Cl_2$/ 24 h; l) BBr_3/ -78^{o}; m) $^{-}OCMe_3$/ $HOCMe_3$.

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