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THE PHOTOCHEMICAL TOTAL SYNTHESIS OF (±)-3-OXO-α-CADINOL AND (±)-α-CADINOL[1]

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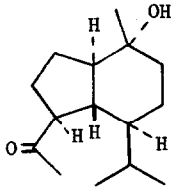
In a recently reported total synthesis of the sesquiterpene (±)-oplopanone (1) we utilized photochemical rearrangement of the 6/5-fused 4-methoxy dienone 2a to prepare the 5/6-fused acetoxy enone 3a which was readily transformed into the natural product.[2] We now wish to report the total synthesis of the cadinane derivatives (±)-3-oxo-α-cadinol (4a)[3] and (±)-α-cadinol (4b)[4] by a sequence which utilizes photochemical rearrangement of the bicyclic dienone 2b in glacial acetic acid to produce the acetoxy enone 3b followed by expansion of the A ring.



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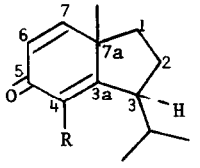
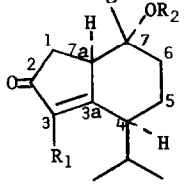
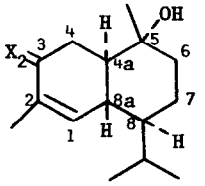


2a. R=OCH_3
b. R=H



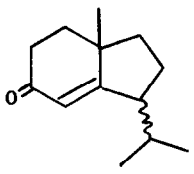
3a. R_1=OCH_3, R_2=Ac
b. R_1=H, R_2=Ac
c. R_1= R_2=H



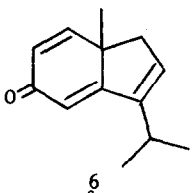
4a. X_2=O
b. X_2=H_2

The bicyclic enone 5a which has a cis relationship of the angular methyl group and the isopropyl group was synthesized in a highly stereoselective manner for use as a precursor to the dienone 2b. A ca. 60:40 mixture of 5a[5] [bp 94°(0.10mm); uv max (95% EtOH) 241 nm (ε 13,400); ir (CCl_4) 1667 (α,β-unsatd. C=O) and 1632 cm^{-1} (conjd. C=C); nmr (CCl_4) δ0.90 and 1.01 (pair of d's, J = 6.5 Hz, 6 H, 3β-CH_3CHCH_3), 1.17 (s, 3 H, 7a-CH_3), and 5.67 ppm (d, J = 2 Hz, 1 H, 4-H)] and the corresponding trans isomer 5b[5] [ir (CCl_4) 1670 (α,β-unsatd. C=O) and 1634 cm^{-1} (conjd. C=C); nmr (CCl_4); δ0.75 and 1.01 (pair of d's, J = 6.5 Hz, 6 H, 3α-CH_3CHCH_3), 1.18 (s, 3 H, 7a-CH_3), and 5.60 ppm (d, J = 2 Hz, 1 H, 4-H)] was obtained in 77% yield by Michael addition of 2-methyl-5-isopropylcyclopentanone[2,6] to methyl vinyl ketone (0.2 equiv KOH-C_2H_5OH, ether, 0°, 4 h) followed by aldol cyclization of the diketone intermediate (10% KOH-C_2H_5OH, reflux, 2 h). Separation of 5a and 5b was difficult because of the extreme ease of epimerization of these compounds, but partial separation could be affected by low pressure chromatography on a pre-packed silica gel column. Pure samples of 5a and 5b were finally obtained by preparative GLC.[7] Appropriate equilibration studies revealed that the aldol cyclization conditions yielded the thermodynamic mixture of isomers. Levisalles and coworkers[8] have reported the degradation of (-)-carotol into the cis enone 5a (actually, the enantiomer of opposite absolute configuration to that shown in 5a) and further conversion of this compound into the corresponding trans isomer by acid treatment. They suggested that the trans

isomer was thermodynamically more stable than the cis. However, evidence that 5a is in fact the more stable isomer was obtained by oxidation (2.2 equiv DDQ, dioxane, reflux, 3.5 h) of the thermodynamic mixture of enones to the trienone 6[5] [44% yield; mp 55.9-56.9°; uv max (95% EtOH) 225 nm (ε 8,400), 248 (7,200), and 308 (9,600); ir (CCl_4) 1652 (α,β-unsatd. C=O), 1626 and 1594 cm^{-1} (conjd. C=C); nmr (CCl_4) δ 1.13 and 1.20 (pair of d's, J = 6.5 Hz, 6 H, 3-CH_3CHCH_3), 1.35 (s, 3 H, 7a-CH_3), 6.00 (d, J = 1.5 Hz, 1 H, 4-H), 6.03 (d of d, J = 1.5 and 10 Hz, 1 H, 6-H), 6.17 (m, 1 H, 2-H), and 7.10 ppm (d, J = 10 Hz, 1 H, 7-H)] followed by selective reduction (5% Pd (C), cyclohexene, C_2H_5OH, reflux, 2.5 h) of the γ,δ-double bond and the disubstituted double bond in the A ring by transfer hydrogenation.[9] The latter reaction yielded essentially quantitatively a mixture containing >95% 5a and a trace of 5b. It was expected that addition of hydrogen to the γ,δ-double bond in 6 would occur largely from the side of the molecule opposite the angular methyl group to give the cis isomer 5a - the major product in the equilibrium mixture. The subsequent work supported this premise.



5a. β-i-Pr
b. α-i-Pr



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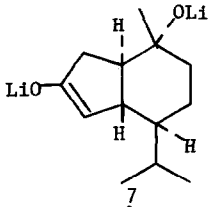

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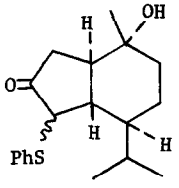
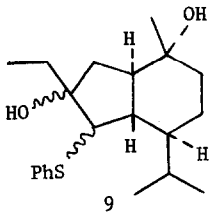


8a. β-SPh
b. α-SPh

Enone 5a was converted into dienone 2b[5] [bp 74°(0.05 mm); uv max (95% EtOH) 240 nm (ε 13,800); ir (CCl_4) 1663 (α,β-unsatd. C=O), 1635 and 1607 cm^{-1} (conjd. C=C); nmr (CCl_4) δ 0.98 and 1.05 (pair of d's, J = 6.5 Hz, 6 H, 3β-CH_3CHCH_3), 1.23 (s, 3 H, 7a-CH_3), 5.97 (d, J = 1.5 Hz, 1 H, 4-H), 6.02 (d of d, J = 1.5 and 10 Hz, 1 H, 6-H), and 6.98 ppm (d, J = 10 Hz, 1 H, 7-H)] in 75% yield by kinetic deprotonation (1.1 equiv LDA, THF, -70°) to form the homoannular lithium dienolate,[10] trapping of the enolate with phenylselenenyl bromide[11a] (1.1 equiv PhSeBr, THF, -70°), and oxidation - elimination of the selenoxide[11a,b] (2 equiv H_2O_2, H_2O, CH_2Cl_2, 25°, 15 min).

Irradiation of a 1% solution of 2b in glacial acetic acid (450- watt Hanovia high pressure Hg lamp, quartz probe, 30 min) yielded the acetoxy enone 3b[5] [40% yield; mp 100.2-101.2°; uv max (95% EtOH) 231 nm (ε 15,700); ir (CCl_4) 1738 (OAc), 1716 (α,β-unsatd. C=O), and 1684 cm^{-1} (conjd. C=C); nmr (CCl_4) δ0.95 and 1.03 (pair of d's, J = 6.5 Hz, 6 H, 4β-CH_3CHCH_3), 1.20 (s, 3 H, 7-CH_3), 1.92 (s, 3 H, 7-OAc), 2.22 (d, J = 4.5 Hz, 2 H, 1-CH_2), 3.27 (t, J = 4.5 Hz, 1 H, 7a-H), and 5.82 ppm (br s, 1 H, 3-H)] which had the proper stereochemistry at three of the four chiral centers present in the target cadinane derivatives.[12] It was expected that the enolate alkoxide 7 could be generated regiospecifically by lithium-ammonia reduction[13] of enone 3b and trapped with a thiophenylating agent[14] to produce the 3-phenylthio ketones 8. Then, by application of the recently reported alkylative-oxidative ring expansion procedure of Trost and Hiori,[15] 8 should be convertible into (±)-3-oxo-α-cadinol. However, attempted lithium-ammonia reduction of 3b was found to be accompanied by extensive reductive cleavage of the tertiary acetoxy group. Therefore, prior to reduction 3b was converted into the hydroxy enone 3c[5,16] [95% yield; mp 110.5-111.5°; uv max (95% EtOH) 235 nm (ε 13,500); ir (CCl_4) 3600 and 3400 (OH), 1714 (α,β-unsatd. C=O), and 1682 cm^{-1} (conjd. C=C); nmr ($CDCl_3$) δ0.93 and 1.03 (pair of d's, J = 6.5 Hz, 6 H, 4β-CH_3CHCH_3), 0.98 (s, 3 H, 7-CH_3),

2.42 (d, J = 4.5 Hz, 2 H, 1-CH_2), 2.92 (t, J = 4.5 Hz, 1 H, 7a-H), and 5.93 ppm (br s, 1 H, 3-H)] by reduction (2 equiv LAH, ether, reflux, 1.5 h) of both the saturated carbonyl group and the ester function followed by Jones oxidation of the secondary allylic alcohol. Enone 3c was then subjected to lithium-ammonia reduction (2.5 g.at. Li, NH_3-THF, -33°, 1.25 h); the excess lithium was destroyed with sodium benzoate, and the ammonia was allowed to evaporate at atmospheric pressure and finally removed completely under vacuum (<1 mm, 50°). The solid enolate alkoxide 7 was then dissolved in anhydrous THF and the solution was cooled to -70° and treated first with 1.1 equiv of LDA[17] in THF-hexane followed by diphenyldisulfide (3.5 equiv, -70° ⟶ 25°, 2.5 h). Workup gave a 1:3 mixture of the 3-phenylthio ketones 8a[5] [19% yield; mp 138.5-139.0°; uv max (95% EtOH) 212 nm (ε 8,700 as a shoulder), 250 (5,000), and 306 (380); ir (CCl_4) 3600 and 3420 (OH), 1748 (C=O), and 1581 cm^{-1} (aromatic C=C); nmr ($CDCl_3$) δ 0.90 and 0.93 (pair of d's, J = 7 Hz, 6 H, 4β-CH_3CHCH_3), 1.10 (s, 3 H, 7-CH_3), 3.17 (br d, J = 8 Hz, 1 H, 3α-H), and 7.20-7.63 ppm (m, 5 H, β-SPh)] and 8b[5] [57% yield; mp 111.5-112.5°; uv max (95% EtOH) 219 nm (ε 8,000), 242 (4,200 as a shoulder), and 312 (910); ir (CCl_4) 3600 and 3420 (OH), 1739 (C=O), and 1584 cm^{-1} (aromatic C=C); nmr ($CDCl_3$) δ0.82 and 0.92 (pair of d's, J = 7 Hz, 6 H, 4β-CH_3CHCH_3), 1.15 (s, 3 H, 7-CH_3), 3.58 (d, J = 4 Hz, 1 H, 3β-H), and 7.20-7.63 ppm (m, 5 H, α-SPh)] which were isolated by chromatography on florisil. These isomers were independently converted into the same equilibrium mixture (35% 8a: 65% 8b) upon mild base treatment. Examination of the configurations of possible β carbanionic intermediates in the lithium-ammonia reduction[14] suggested that the trans-fused enolate should be obtained. This stereochemistry as well as the regiospecificity of the sulfenylation reaction was confirmed by a single crystal X-ray structure on the minor isomer 8a.[18]



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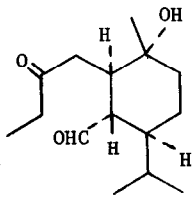

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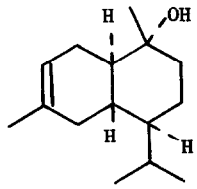

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Addition of ethyllithium (3 equiv C_2H_5Li, ether-THF; 3 equiv HOAc; 4 equiv C_2H_5Li, -70° ⟶ 25°, 4.5 h) to the 3α-phenylthio ketone 8b gave a mixture of isomeric phenylthio alcohols 9. Without purification, this material was oxidized (2 equiv $Pb(OAc)_4$, toluene-HOAc, 0°, 5 h) and hydrolyzed (2 equiv $HgCl_2$, CH_3CN-H_2O, reflux, 4 h) to give a single product having spectral properties consistent with the keto aldehyde structure 10. Aldol cyclization (5% KOH-CH_3OH, reflux, 2 h) of this intermediate gave (±)-3-oxo-α-cadinol (4a)[5,19] [mp 111.5-111.8°; uv max (95% EtOH) 237 nm (ε 9,800); ir (CCl_4) 3400 (OH), 1681 (α,β-unsatd. C=O), and 1649 cm^{-1} (conjd. C=C); nmr ($CDCl_3$) δ 0.83 and 0.98 (pair of d's, J = 7 Hz, 6 H, 8β-CH_3CHCH_3), 1.17 (s, 3 H, 5-CH_3), 1.78 (br s 3 H, 2-CH_3), and 6.83 ppm (br s $W_{1/2}$ = 4 Hz, 1 H, 1-H)] in 52% yield (from 8b) after chromatography on florisil.

Wolff-Kishner reduction[20] (N_2H_4, C_2H_5OH-py, reflux, 15 h, $(CH_3)_3COK$, $C_6H_5CH_3$, reflux, 6 h) of 4a gave a 2:1 mixture of unsaturated alcohols in 94% yield. These compounds were isolated by preparative GLC[7] and the major product (a colorless oil) proved to be (±)-α-cadinol (4b). It showed ir[21,22] and nmr[22] spectal properties essentially identical to those previously reported for (-)-α-cadinol. It also gave a p-nitrobenzoate derivative[5] (mp 164-165°) having identical spectral (ir, nmr, ms) and TLC properties to those of an authentic sample of (-)-α-cadinol-p-nitrobenzoate.[23] The minor isomer from the reduction was assigned structure 11 [mp 91.0-91.9°, ir (CCl_4) 3600 and 3400 (OH),

1655 and 817 (-CH=C<), 1384, 1376, and 1367 (CH_3CHCH_3), and 1123 cm^{-1} (C-O); nmr (CCl_4) δ 0.75 and 0.91 (pair of d's, J = 7 Hz, 6 H, 8β-CH_3CHCH_3), 1.03 (s, 3 H, 5-CH_3), 1.60 (br s, 3 H, 2-CH_3), and 5.38 ppm (br d, J = 5 Hz, 1 H, 3-H] on the basis of its spectral properties.

References and Notes

1. This investigation was supported by Public Health Service Grant No. CA 12193 from the National Cancer Institute.
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5. Correct exact mass data and/or elemental analyses have been obtained for all compounds for which spectral data are reported.
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7. A 10 ft. x 1/4 in. stainless steel column containing 20% Carbowax K-20M on Chromosorb W HMDS was employed.
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12. A conjugated dienone formally derived form elimination of acetic acid from 3b was also isolated in about 20% yield from the photolysis. However, no tricyclic product of the type obtained on photolysis of the model dienone containing no isopropyl substituent was observed. (See D. Caine, J. T. Gupton III, K. Ming, and W. J. Powers III, Chem. Commun., 469 (1973)).
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16. Hydroxy enone 3c could be obtained directly but in very low yield by irradiation of 2b in 45% aqueous acetic acid.
17. See ref. 14 for the role of a second equiv of strong base in sulfenylations at secondary centers.
18. The details of the X-ray crystallographic structure of 8a will be published later in a full paper. We are grateful to Professor J. A. Bertrand, Dr. H. Deutsch, and Dr. D. Van Deever of carrying out this determination.
19. The nmr spectral properties of 4a differ slightly from those reported for the natural product (ref. 3). Since neither a sample of authentic 4a nor its nmr spectrum were available to us, we are unable to explain this discrepancy.
20. M. F. Grundon, H. B. Henbest, and M. D. Scott, J. Chem. Soc., 1855 (1963).
21. We are grateful to Professor V. Herout for a copy of the ir spectrum of (-)-α-cadinol.
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23. We are grateful to Professor R. C. Cambie for supplying us with an authenic sample of (-)-α-cadinol p-nitrobenzoate prepared by the late Professor L. H. Briggs.