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SYNTHESIS OF (–)-ACETYLSATUREJOL AND (+)-ISOACETYLSATUREJOL

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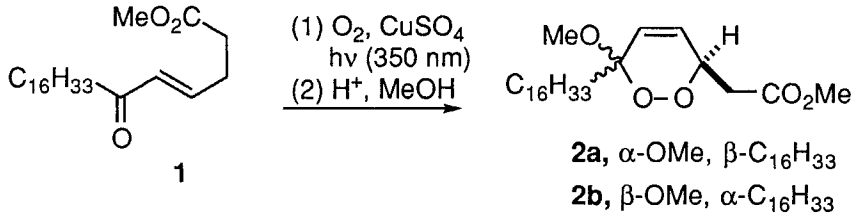
Abstract: (-)-Acetylsaturejol (**11**) and (+)-isoacetylsaturejol (**12a**) have been prepared from (-)-*cis*-4-acetoxypulegone (**10**) by photosensitized singlet oxygen and non-singlet oxygen addition, respectively.

We recently reported the first syntheses of chondrillin (**2a**) and plakorin (**2b**) using the novel, non-singlet oxygen photooxygenation of conjugated enone **1** with a sunlamp in the presence of copper sulfate or rose bengal lactone.[1]



1

2a, α-OMe, β-$C_{16}H_{33}$

2b, β-OMe, α-$C_{16}H_{33}$

This photooxygenation procedure is general for any enone that can undergo photoenolization by transfer of a γ-hydrogen to the carbonyl oxygen. For instance, bubbling oxygen through a sunlamp-irradiated solution of pulegone (**3**) in 9:1 CH_2Cl_2/MeOH containing either $CuSO_4$ or rose bengal lactone afforded mixtures

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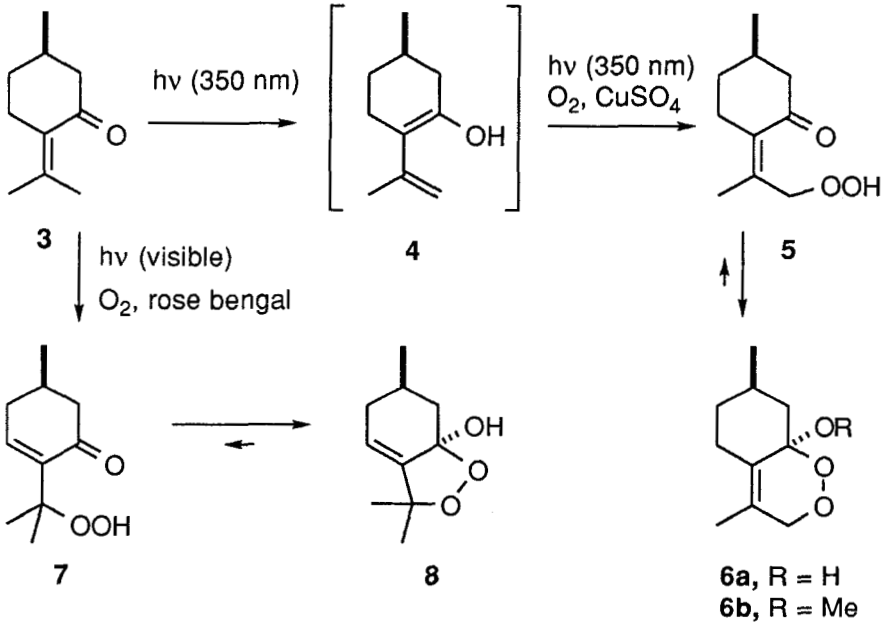
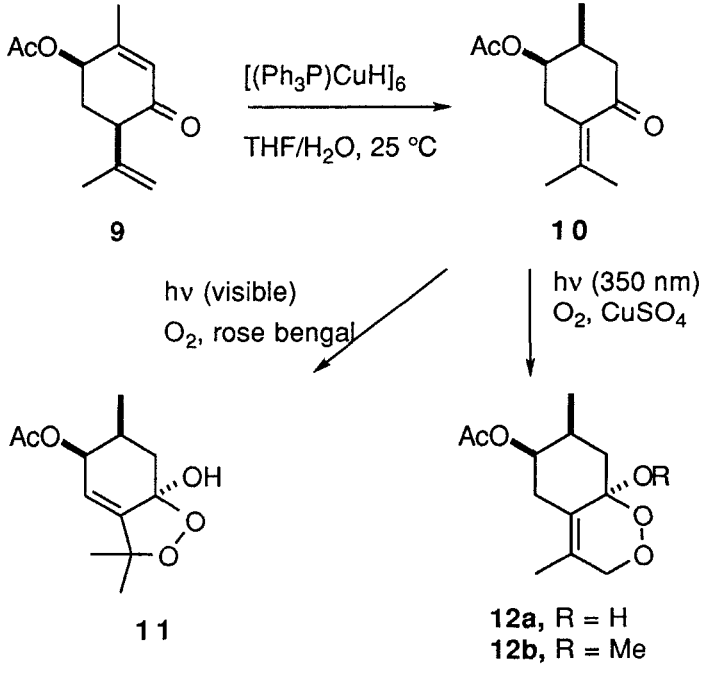
of peroxy hemiketal **6a** and peroxy ketal **6b** in >80% yield. The first step in this sequence appears to be reversible photoenolization, which does not require oxygen or the photosensitizer, to give **4**. In the presence of the photosensitizer and oxygen, enol **4** reacts further to give hydroperoxide **5**. The details of this step are not understood, but singlet oxygen is not involved. Hydroperoxy enone **5** spontaneously cyclizes to give peroxy hemiketal **6a**, which reacts further to form peroxy ketal **6b** when $CuSO_4$ is used as the sensitizer. By contrast, Ensley and coworkers demonstrated that pulegone (**3**) reacts very rapidly with singlet oxygen to give the ene adduct **7**, which spontaneously cyclizes to peroxy hemiketal **8**.[2]



Peroxy hemiketals acetylsaturejol (**11**) and isoacetylsaturejol (**12a**), which differ from **8** and **6a**, respectively, only by the addition of an acetoxy group, were isolated from the leaves of *Satureja gilliesii*.[3] These natural products should be readily available from *cis*-4-acetoxypulegone (**10**) by singlet and non-singlet photooxygenation, respectively.

cis-4-Acetoxypulegone (**10**) was not known, so the first challenge was the efficient preparation of this compound. *t*-Butyl chromate oxidation of *cis*-carvyl acetate[4] by the literature procedure[5] afforded 40% (based on recovered starting material) of enone **9**, which contained some of the conjugated isomer. Conjugate reduction of this mixture by Stryker's procedure[6] with $[(Ph_3P)CuH]_6$ in wet THF at 25 °C provided 74% of *cis*-4-acetoxypulegone (**10**), whose stereochemistry was established by the 2.5 Hz coupling constant between the methine hydrogens. The desired cis stereochemistry was anticipated since a similar reduction of 4-acetoxy-3-methyl-2-cyclohexenone gave 94% of *cis*-4-acetoxy-3-methylcyclohexanone.[6b] The isopropenyl double bond isomerizes into conjugation under the basic reaction conditions. The tetrasubstituted double bond of **10** is apparently too hindered to react with $[(Ph_3P)CuH]_6$.



Singlet oxygen photooxygenation of **10** with a visible wavelength flood lamp and rose bengal as the sensitizer afforded 75% of (-)-acetylsaturejol (**11**) whose spectral data are identical to those reported.[7] Non-singlet oxygen photooxygenation of **10** with a sunlamp using $CuSO_4$ as a sensitizer in CH_2Cl_2/MeOH provided a 2:3 mixture of **12a** and **12b**. Hydrolysis of the mixture in acidic aqueous DME yielded 52% of (+)-isoacetylsaturejol (**12a**) whose spectral data are identical to those reported.[7] Although the absolute configuration of synthetic **11** and **12a** is known since they are derived from (-)-carvone, the absolute configuration of the natural products remains unknown since rotations were not recorded and samples are no longer available.[7]

Acetylsaturejol (**11**) and isoacetylsaturejol (**12a**) have been prepared by two-step sequences using photooxygenation procedures that may be related to the biosynthesis of these novel natural products.

Experimental Section

(-)-*cis*-4-Acetoxypulegone (10). A solution of 280 mg of H_2O in 15 mL of THF was deoxygenated by bubbling N_2 through the solution for 10 min. A 10 mL portion of this solution was added to 500 mg (0.26 mmol, 2.9 equiv) of $[(Ph_3P)CuH]_6$ under N_2. Enone **9** (110 mg, 0.53 mmol) was taken up in the remaining 5 mL of wet THF and added to the copper hydride. The solution was stirred at rt for 24 h under N_2, opened to the air, stirred for 1 h, filtered through celite, diluted with H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (10:1 hexane/EtOAc) gave 82 mg (74%) of **10**: $[\alpha]_D$ –37.8° (c

= 0.29, $CHCl_3$); IR (neat) 2963, 1738, 1681, 1372, 1243, 1033 cm^{-1}; ^1H NMR 5.13 (ddd, 1, J = 4.4, 4.1, 2.5), 2.88 (br dd, 1, J = 16.6, 4.4), 2.58 (br d, 1, J = 16.6), 2.45 (dd, 1, J = 16.5, 6.6), 2.38 (dd, 1, J = 16.5, 9.3), 2.25 (dddq, 1, J = 9.3, 6.6, 2.5, 6.7), 2.07 (s, 3), 2.05 (br s, 3), 1.77 (br s, 3), 1.00 (d, 3, J = 6.7); ^{13}C NMR 201.8, 170.8, 146.4, 127.1, 72.0, 45.0, 33.4, 33.3, 23.3, 22.5, 21.1, 16.8.

(-)-Acetylsaturejol (11). Oxygen was bubbled through a solution of 44 mg (0.21 mmol) of **10** and 1 mg of rose bengal in 20 mL of 19:1 CH_2Cl_2/MeOH in a test tube submersed in a water bath cooled by circulating water through a copper coil immersed in the bath. The solution was irradiated with a 150 W incandescent flood lamp placed 5-10 cm from the test tube for 7.5 h. Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (10:1 to 5:1 hexane/EtOAc) gave 38 mg (75%) of pure **11** as a white solid which was recrystallized from hexane/CH_2Cl_2: mp 90-90.5 °C (lit.[3] mp 93-94 °C); $[\alpha]_D$ −331.2° (c = 0.5, $CHCl_3$); IR (KBr) 3458, 2973, 1731, 1372, 1240, 1012 cm^{-1}; ^1H NMR 5.56 (d, 1, J = 4.0), 5.32 (dd, 1, J = 4.5, 4.0), 3.09 (d, 1, J = 1.6, OH), 2.34 (dddq, 1, J = 12.7, 4.5, 3.0, 7.1), 2.07 (s, 3), 1.88 (dd, 1, J = 12.4, 3.0), 1.60 (ddd, 1, J = 12.7, 12.4, 1.6), 1.47 (s, 3), 1.42 (s, 3), 1.06 (d, 3, J = 7.1); ^{13}C NMR 170.8, 154.6, 117.0, 101.9, 82.2, 68.7, 34.4, 29.6, 28.1, 25.2, 20.9, 16.1. The spectral data are identical to those previously reported.[3,7]

(+)-Isoacetylsaturejol (12a). Oxygen was bubbled through a solution of 20 mg (0.09 mmol) of **10** and 1 mg of $CuSO_4$ in 20 mL of 19:1 CH_2Cl_2/MeOH in a test tube cooled as described above. The reaction was irradiated with two 275 W sunlamps placed 5-10 cm from the test tube for 7 h. The solution was diluted

with CH_2Cl_2, washed with H_2O to remove the $CuSO_4$ and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a 2:3 mixture of **12a** and **12b**, which was dissolved in 25 mL of 4:1 DME/H_2O containing 2 drops of conc HCl. The solution was stirred at rt for 24 h, poured into 25 mL of H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried ($MgSO_4$) and concentrated under reduced pressure to give 18.5 mg of crude **12a**. Flash chromatography on silica gel (10:1 to 5:1 hexane/EtOAc) gave 12 mg (52%) of pure **12a** which was recrystallized from hexane/CH_2Cl_2: mp 101-102.5 °C (lit.[3] mp 100-102 °C); $[\alpha]_D$ +64.3° (c = 0.27, $CHCl_3$); IR ($CHCl_3$) 3576, 3020, 1729, 1255, 1210, 1023 cm^{-1}; ^1H NMR 4.98 (ddd, 1, *J* = 3.5, 3.5, 3.2), 4.75 (ddd, 1, *J* = 16.1, 2.7, 1.1), 4.06 (dd, 1, *J* = 16.1, 2.8), 3.16 (d, 1, *J* = 2.1, OH), 2.95 (dd, 1, *J* = 15.3, 3.2), 2.29 (dddd, 1, *J* = 15.3, 3.5, 2.8, 2.7), 2.24, (m, 1), 2.03 (s, 3), 1.71 (dd, 1, *J* = 13.1, 3.7), 1.60 (br s, 3), 1.51 (ddd, 1, *J* = 13.1, 12.9, 2.1), 0.94 (d, 3, *J* = 6.8); ^{13}C NMR 170.9, 127.7, 125.3, 96.9, 73.2, 73.0, 36.1, 31.6, 29.6, 21.0, 17.3, 13.4. The spectral data are identical to those previously reported,[3] except for the ^1H NMR absorption at δ 4.98 which was reported at δ 5.28.[7]

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(7) We thank Dr. Mariano Castillo for copies of the spectral data of **11** and **12a**, for indicating that the ^{1}H NMR absorption reported at δ 5.28 in ref. 3a for isoacetylsaturejol should be corrected to δ 4.95 and for helpful correspondence regarding the absolute stereochemistry of the natural products.

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