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Synthesis of Salviolone, a Cytotoxic Benzotropolonoid Bisnorditerpene from Salvia miltiorrhiza

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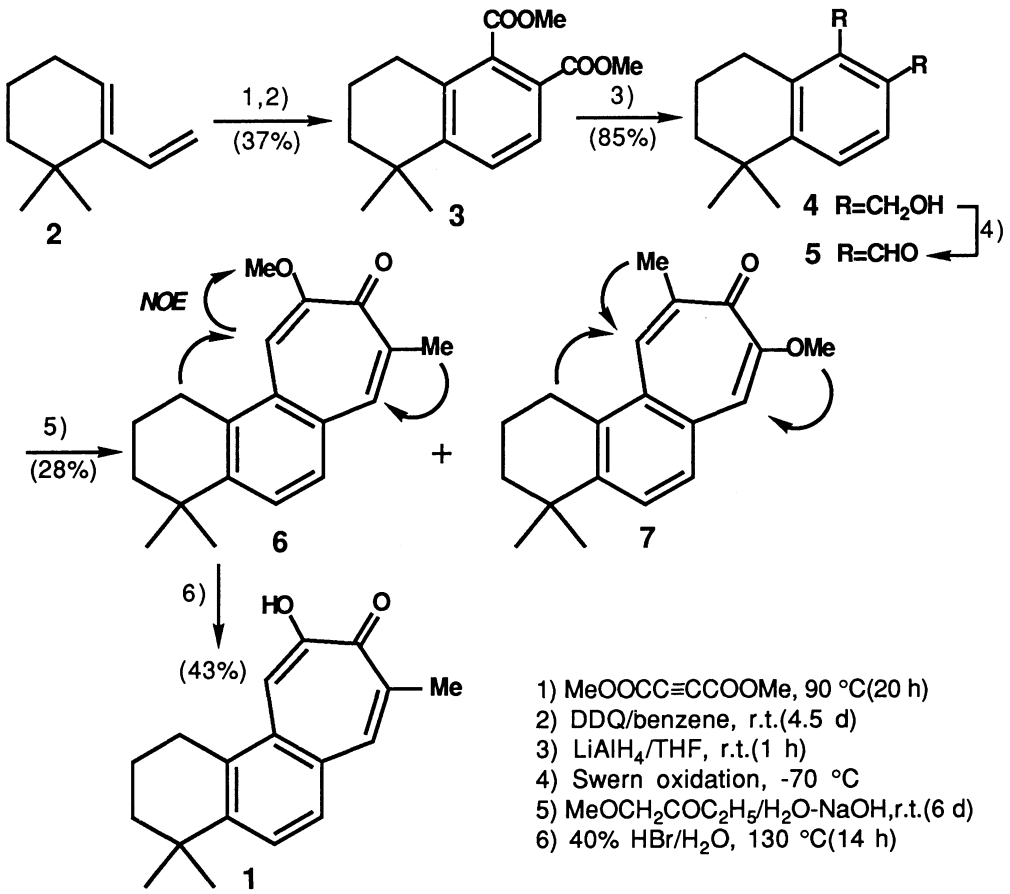
The structure of salviolone was unequivocally confirmed by synthesis in six steps starting from 3,3-dimethyl-2-vinylcyclohexene and methyl acetylenedicarboxylate.

Salviolone (**1**), isolated from a Chinese drug 'Dan-shen' (the dried root of Salvia miltiorrhiza), is the first natural norditerpene having a benzotropolonoid chromophore and has shown to exhibit a cytotoxic activity against Vero cells.[1] As the structure has been characterized by only spectroscopic methods, we present here its unequivocal confirmation by chemical synthesis.



Scheme 1.

Diels-Alder reaction between 3,3-dimethyl-2-vinylcyclohexene (**2**)[2] and methyl acetylenedicarboxylate proceeded smoothly by heating the mixture to give an adduct, which without isolation was treated with DDQ in benzene at room temperature to afford a phthalic ester **3**.[3] The ester **3** was reduced to a diol **4**, which was then subjected to the Swern oxidation at -70 °C to give a dialdehyde **5**. As the dialdehyde was unstable, the crude **5** isolated by filtration of the reaction mixture through a short anhydrous magnesium sulfate layer was used immediately in a following step.

The suspension of the dialdehyde **5** and 1-methoxy-2-butanone[4] in an aqueous 0.05 M NaOH[5,6] was stirred for 6 days to afford a mixture of salviolone methyl ether **6** and its regioisomer **7** (**6**:**7**=2:1) in 28% yield from the diol **4**. Both products were separated by preparative TLC (silica-gel, hexane-ethyl acetate) and were characterized by the ^{1}H NMR spectra and NOE experiments. The reactions in aqueous alcoholic media[5,7] did not proceed at all.

The major isomer **6** was heated in 40% aqueous HBr solution to give salviolone **1**. The spectroscopic properties (^{1}H- and ^{13}C-NMR, IR, and UV spectra) of the synthetic and natural salviolones were identical in all respects.

References

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3) All new compounds except **5** gave satisfactory elemental analyses.

3: bath temp: 180-190 °C/0.3 mmHg; (CCl_4)=7.71(d,1H,J=8.6 Hz), 7.34(d,1H,J=8.6 Hz), 3.81(s,6H), 2.8-2.6(m,2H), 2.5-1.7(m,4H),1.32(s,6H).

4: mp: 83.5-85 °C; ($CDCl_3$)=7.30(d,1H,J=8 Hz), 7.10(d,1H,J=8 Hz), 4.82(s,2H), 4.78 (s,2H), 3.0-2.8(m,2H), 2.0-1.5(m,4H), 1.28(s,6H).

5: oil; (C_6D_6)=10.4(s,1H), 10.0(s,1H), 7.4(d,1H,J=10 Hz), 7.2(d,1H,J=10 Hz), 2.7 -2.4(m,2H), 1.7-1.2(m,4H), 1.1(s,6H).

6: mp: 177-178 °C; ($CDCl_3$)=7.71(s,1H), 7.50(d,1H,J=8.5 Hz), 7.47(d,1H,J=8.5 Hz), 7.34(s,1H), 3.93(s,3H), 3.04(t,2H,J=6.4 Hz), 2.37(s,3H), 1.94(m,2H), 1.71(m, 2H), 1.34(s,6H).

7: oil; ($CDCl_3$)=8.14(s,1H), 7.54(d,1H,J=8.5 Hz), 7.48(d,1H,J=8.5 Hz), 7.01(s,1H), 3.93(s,3H), 3.07(t,2H,J=6.4 Hz), 2.43(s,3H), 1.92(m,2H), 1.69(m,2H), 1.33(s, 6H).

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