SYNTHESIS OF SALVILENONE

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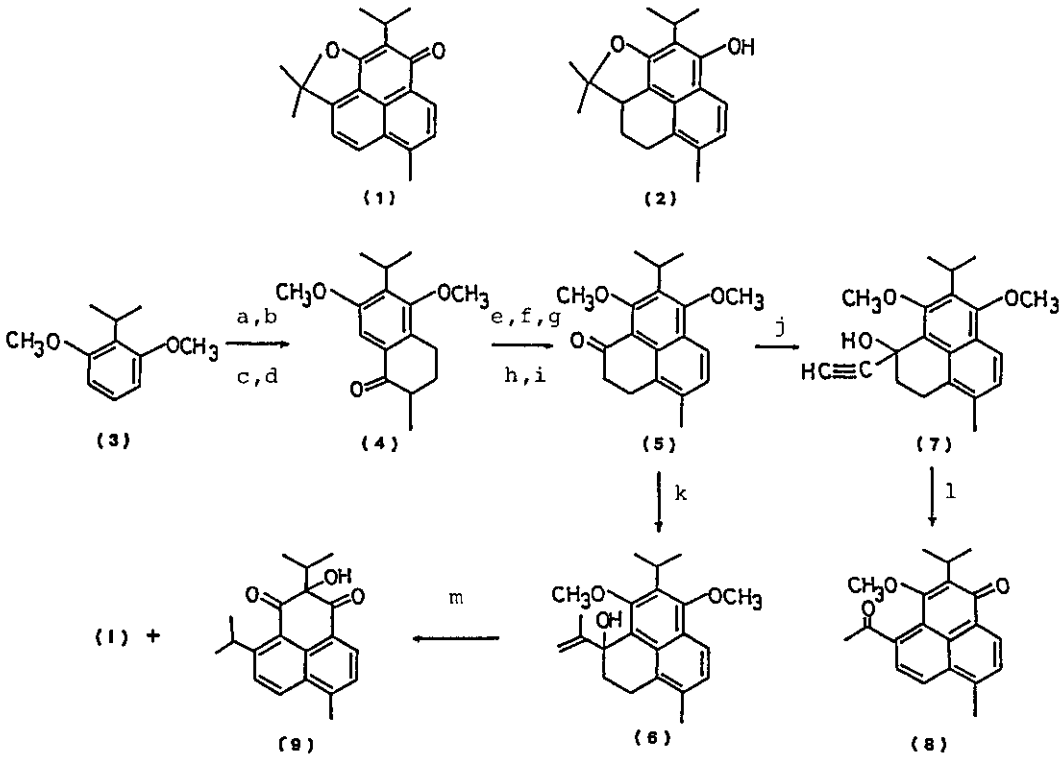
Abstract-----Acid treatment of a tetrahydrophenalenone derivative (6), which have been derived from resorcinol dimethyl ether by 12 steps reactions, afforded salvilenone (1) and hydroxydiketone (9).

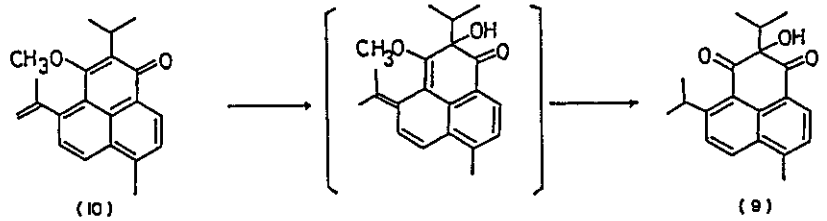
Salvilenone is a diterpene contained in trace amounts in the roots of Salvia miltiorrhiza Bunge, which is a clinically important Chinese medicine used for the treatment of heart disease[1], viral hepatitis[2], and tuberculosis[3], and its structure has been determined as the unique phenalenone (1).[4] The low availability of this compound and scarce distribution of phenalenone derivatives in the nature[5] prompted us to investigate its synthesis.

Tetrahydrophenalenone derivative (2) of salvilenone was chosen as a key intermediate for the synthesis because it had been found in the course of the structural determination that the tetrahydroderivative (2) was smoothly autooxidized to salvilenone. A dihydrophenalenone derivative (5) was synthesized from resorcinol dimethyl ether by eleven steps-process as shown in Scheme I, and it was converted into an ethynyl derivative (7) by reaction with lithium acetylide. Treatment of this ethynyl carbinol with mercuric sulfate and sulfuric acid at 55 °C by Rupe's reaction conditions resulted in the formation of acetylphenalenone (8)[6] with concomitant demethylation in these mild conditions. This reaction confirmed the remarkably facile formation of phenalenone from a tetrahydrophenalenone. Because selective conversion of the acetyl group of (8) to isopropenyl group was unsuccessful, isopropenyl lithium was allowed to react with dihydrophenalenone (5)



a) Succinic anhydride, $AlCl_3$, $PhNO_2$ b) H_2/Pd-C(10%), $HClO_4$, AcOH c) PPA, CH_2Cl_2 d) MMC, then CH_3I, DMF e) $CH_2=CHCH_2CH_2MgBr$, ether f) TsOH, PhH g) DDQ, PhH h) $KMnO_4$, KIO_4, Na_2CO_3, H_2O, dioxane i) $POCl_3$, $SnCl_4$, PhH j) $LiC{\equiv}CNH_2CH_2CH_2NH_2$, THF k) n-BuLi, 2-bromopropene, THF l) $HgSO_4$, H_2SO_4, CH_3OH/H_2O m) 47%HBr, AcOH

Scheme 1



Scheme 2

to obtain the key intermediate (6).[6] Treatment of the tetrahydrophenalenone (6) with hydrobromic acid in boiling acetic acid afforded salvilenone (1) (66%), identical with authentic sample by spectroscopic and tlc analyses, accompanied with the formation of a byproduct hydroxydiketone (9) (20%) (m/z 310(M^+, $C_{20}H_{22}O_3$), 292(M^+-H_2O), 267(M^+-C_3H_7); ^{1}H-nmr δ 0.95(3H,d,J=6 Hz), 0.97(3H,d,6), 1.35(3H,d,7), 1.47(3H,d,7), 2.34(1H,sept,6), 2.80(3H,s), 4.10(1H,sept,7), 7.53 and 8.35(2H, ABq, 8), 7.79 and 8.27(2H, ABq, 9), 9.67(1H,br.s) ppm; ^{13}C-nmr δ 16.6(q), 17.0(q), 20.2(q), 23.3(q), 24.7(q), 29.3(d), 36.1(d), 101.6(s), 126.0(d), 126.7(s), 126.8(s), 127.2(d), 129.0(d), 129.7(d), 130.3(s), 131.8(s), 142.9(s), 152.8(s), 193.2(s), 197.7(s) ppm). Two of three oxygen atoms of the byproduct were considered to comprise two carbonyl groups from ^{13}C-nmr signals at 193.2 and 197.7, and remaining one was hydroxyl group from ^{1}H-nmr signal at 9.67 ppm and ir absorption at 3460 cm.$^{-1}$ The presence of an asymmetric carbon atom was infered from the nonequivalence of the methyl groups in two isopropyl groups in nmr spectra. ^{1}H-nmr spectrum showed also the presence of two sets of AB-quartet systems at aromatic regions. From these spectral properties structure (9) was assigned for the byproduct.

On treating with hydriodic acid tetrahydrophenalenone (6) afforded the hydroxydiketone (9) as the sole product, while heating of (6) with iodine in carbon tetrachloride afforded a methoxyphenalenone (10).[6] The hydroxydiketone (9) is considered to be produced from methoxyphenalenone (10); protonation by hydriodic acid (a soft acid) may take place preferably at isopropenyl terminal of (10) rather than at the carbonyl oxygen, and subsequent hydrolysis of methoxyl group affords hydroxydiketone (9).

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6 ^{1}H-nmr of (6): δ 1.39(3H,d,J=7.3Hz), 1.49(3H,d,7.3),1.98(3H,s), 2.40(3H,s), 2.6-3.3(4H,m), 3.42(1H,sept, 7.3), 3.77(3H,s), 3.94(3H,s), 4.9(2H,br s), 7.20(1H,d, 8.7), 7.76(1H,d, 8.7).

^{1}H-nmr of (8): δ 1.44(6H,d,J=7Hz), 2.52(3H,s), 2.81(3H,s), 3.34(1H,sept,7), 3.65(3H,s), 7.33(1H,d,8.5), 7.58(1H,d,7.7), 8.19(1H,d,8.5), 8.48(1H,d,7.7).

^{1}H-nmr of (10): δ 1.42(6H,d, J=7Hz), 2.12(3H,s), 2.81(3H,s), 3.44(1H,sept. 7), 3.70(3H,s), 5.10(2H,br s), 7.27(1H,d, 9), 7.63(1H,d, 8), 8.12(1H,d, 9), 8.48(1H,d, 8).

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