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Regiospecific Syntheses of dl-Phyllostine and dl-Epoxydon (Phyllosinol)

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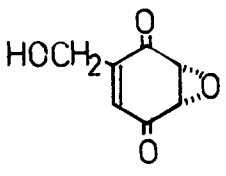
Previously we reported a synthesis of dl-phyllostine[1] 1 and conversion of epoxydon[2] 2 (phyllosinol[3]) to other minor constituents isolated from culture broth of phyllosticta sp[4]. In this communication we would like to describe regiospecific syntheses of dl-phyllostine 1 and dl-epoxydon 2 (phyllosinol), both of which are physiollogically active compounds among highly oxygenated cyclohexane derivatives occurred naturally[5].



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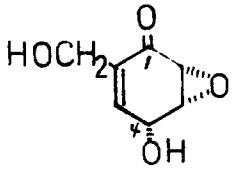
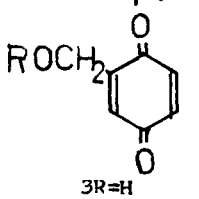


2

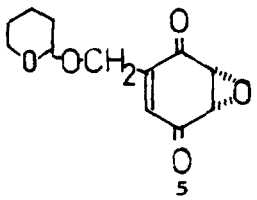
2-Hydroxymethyl-1,4-benzoquinone 3 prepared from gentisyl alcohol[6] was treated with dihydropyrane and p-toluenesulfonic acid in anhydrous ether to give quantitatively pyranylated compound 4 , m.p. 69.4 ~71.1 °C[7], $C_{12}H_{14}O_4$, ir ν_{max}^{KBr} 3050, 1650, 800, 815 cm^{-1}; nmr τ 8.35 (6H, br.s., $-CH_2-$), 6.70 6.20 (2H, m., $R-CH_2\underline{CH_2}O-$), 5.83, 5.45 (2H, d.d., J=16, J=2 Hz, AB part of ABX system $-CH_2-O-$), 5.35 (1H, s., ) 3.33 (3H, br.s., ). Epoxidation[8] of the pyranylated benzoquinone 4 with sodium perborate solution adjusted at pH 8.5 with acetic acid in ethanol-water afforded regiospecifically an epoxide 5 , m.p. 106.9 ~111.8 °C,

$C_{12}H_{14}O_5$, M^+ m/e 238, ir ν_{max}^{KBr} 1685, 810, 790 cm ; nmr τ^{CCl_4} 8.35 (6H, br.s., $-CH_2-$), 6.40 (2H, m., $-CH_2O-$), 6.20 (2H, s., ) 5.60 (2H, s., ), 5.35 (1H, s., ), 3.30 (1H, s., ), in 40% yield, though direct epoxidation of 3 under the same conditions described above yielded a mixture consisting of equal amount of phyllostine and an isomeric epoxide[1b] 6.



3R=H

4R=



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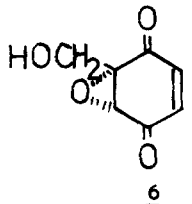
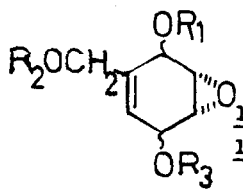


6



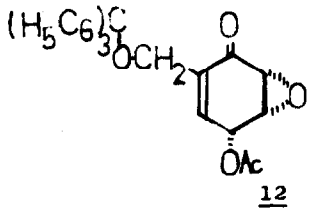
7 R_1, R_3=H, R_2=

8 R_1, R_3=Ac, R_2=

9 R_1, R_3=Ac, R_2=H

10 R_1, R_2=H R_3=Ac

11 R_1=H, R_2=$-C(C_6H_5)_3$ R_3=Ac



12

Removal of pyranyl group of the epoxide 5 with p-toluenesulfonic acid in ethanol heating at 40~50 °C for 2 hr produced dl-phyllostine 1 , m.p. 48.0 - 48.5 C $C_7H_4O_4$, which was perfectly identical with natural phyllostine in all respects. The synthesis of dl-epoxydon was completed as follows[9]. The pyranylated phyllostine 5 was treated with sodium borohydride in tetrahydrofuran-methanol to give a stereoisomeric mixture of the diols 7 in 63% yield[10]: ir ν_{max}^{film} 3400 cm^{-1}, no carbonyl absorption; nmr τ^{CDCl_3} 4.50 (1H, d., ). The mixture of diols 7 was acetylated with acetic anhydride in pyridine to yield quantitatively diacetates 8 , ir ν_{max}^{film} 1740 cm^{-1}; nmr τ^{ccl_4} 8.00 (6H, s., CH_3CO), 4.50 (3H, m., and 2-CHOAc). Treatment of the diacetates 8 with p-toluenesulfonic acid in methanol gave hydroxy diacetates 9 , ir ν_{max}^{film} 3400 cm^{-1}; nmr τ^{ccl_4, c_6d_6} 8.18 (6H, s., $2CH_3CO$), 6.75 (2H, s., ), 6.25, 6.10 (2H, ABq., J=15 Hz $-CH_2-O$), 4.35-4.43 (3H, m.,  and 2-CHOAc), in 70% yield. It was expected that of the

two acetoxyl groups in the diacetates 9 , the one at C-1 could be selectively hydrolyzed by neighboring group participation of the hydroxyl group at C-7[11]. In fact, hydrolysis of 9 with potassium bicarbonate (0.8 eq) in tetrahydrofuran-methanol-water (5 : 3 : 2) at room temperature afforded regiospecifically hydrolyzed products 10 , nmr τ^{CDCl} 7.93 (3H, CH_3CO), 4.10 4.85 (2H, m., $\rightleftharpoons^{H}$ and -CH-OAc). The evidence that the hydrolysis occurred selectively at C-1 position was obtained by the fact that in later stage, compound 12 exibited a signal at τ 3.52 ascribable to a β-proton of α,β-unsaturated ketone in the nmr spectrum. Reaction of 10 with tritylchloride in pyridine at room temperature yielded trityl derivatives 11 , ir ν_{max}^{film} 1600, 1480; τ^{CDCl_3} 7.96 (3H, s., CH_3CO), 6.44 ~ 6.66 (2H, m $\overset{H}{\underset{}{\diagup O \diagdown}}\overset{H}{\underset{}{}}$), 6.32 (2H, ABq., J=15 Hz $-CH_2-O$), 2.50 3.10 (15 H, m., ArH) in 60% yield. Oxidation of 11 with manganese dioxide in benzene at room temparature and subsequent purification by column chromatography using silicic acid gave a α,β-conjugated ketone 12 ,a more stable isomer which might be resulted from equilibrium at C-4, m.p. 124.6~125.5, $C_{18}H_{24}O_5$; ir ν_{max}^{KBr} 1738, 1685 cm^{-1}; nmr τ^{ccl_4} 7.80 (3H, s., CH_3CO) 6.75 (1H, d., J=4 Hz, $\diagup O \diagdown$) 6.32, 6.09 (2H, t. of ABq., J=16Hz, $-CH_2-O$), 6.28 (1H, m., $\diagup O \diagdown^{H}$), 4.35 (1H, m., -CHOAc) 3.52 (1H, m., $\rightleftharpoons^{H}$), 2.50 3.10 (15H, m., ArH) in 88% yield. Treatment of the tritylacetylepoxydon 12 with p-toluenesulfonic acid in methanol afforded dl-epoxydon, m.p. 60.1~61.7 , $C_7H_8O_4$, which was identical with the natural specimen in ir and nmr spectra and behaviors on TLC.

References and Footnotes

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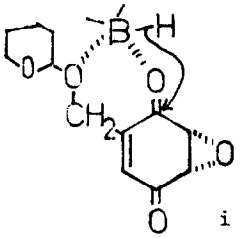
6) A. Brack, Helv. Chim. Acta., 30 , 1 (1947).

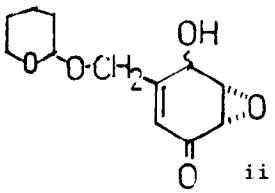
7) Satisfactory micro analytical results were obtained for all crystalline compounds.

8) A. Rashid and G. Read, J. Chem. Soc., (C), 1323 (1967).

9) An attempt obtaining epoxydon by direct reduction of 5 with one equivalent amount of sodium borohydride was failed because of selective formation of ii which might be resulted from an intermediate i.



i



ii

10) The stereoisomers in compounds 7 ~ 11 were not separated, since the asymmetric center at C-1 is eliminated in compound 12.

11) Further examples for application of neighboring hydroxyl group participation, see A. Ichihara, H. Shirahama, and T. Matsumoto, Tetrahedron Letters , 3965 (1969). T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, and F. Sakan. Tetrahedron Letters, 1171 (1970).