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SIMPLE SYNTHESES OF DL-PHYLLOSTINE, DL-EPOXYDON AND DL-EPIEPOXYDON

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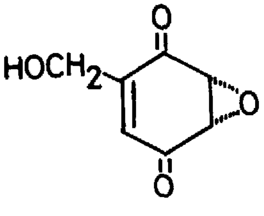
In the series of research works aimed at the synthesis of highly oxygenated cyclohexane derivatives$^{1)}$, we reported the synthesis of dl-phyllostine (1) and an antitumor compound, dl-epoxydon$^{2)}$ (2). However, the previous synthesis was started from rather expensive gentisic acid and involved non-stereoselective multi-step reactions.



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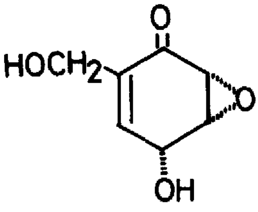

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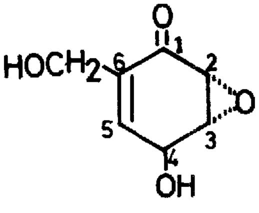

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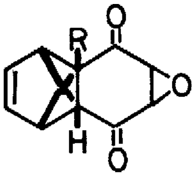
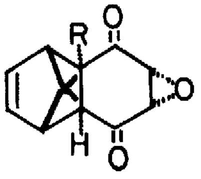
In this communication we would like to describe simple, effective syntheses of titled compounds starting from easily available p-benzoquinone. Dl-Epiepoxydon (3) has been prepared for the first time.

The starting materials, 4a and 4b, for the synthesis of dl-phyllostine (1) were easily prepared by epoxidation of Diels-Alder adduct of p-benzoquinone and dimethylfulvene according to known procedure.$^{3)}$ Treatment of 4a with formalin in the presence of diazabicycloundecene in THF under ice-cooling gave a compound

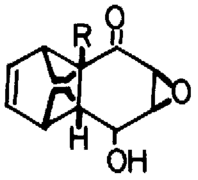
5a, m.p. 122~123°, $C_{15}H_{16}O_4$, ν^{KBr}_{max} 3450, 1710 cm^{-1}; $\delta^{CDCl_3}_{TMS}$ 1.60 (6H, s, $=\!\!/^{CH_3}$), 2.74 (1H, d, J=4Hz, $-\overset{|}{C}H-\underset{O}{\underset{\|}{C}}-$), 3.60, 4.10 (2H, ABq, J=11Hz, CH_2-O), 3.55 (2H, s, $^{H}\overset{O}{\triangle}^{H}$), 3.75 (2H, m, $=\!\!\diagup\!\!\diagdown^{H}$), 6.15 (2H, m, $=\!\!/^{H}$) in 65% yield. Retro-Diels-Alder reaction of 5a at 140° for 30 min in a sealed tube afforded dl-phyllostine (1) whose spectroscopic data are identical with those of authentic specimens in all respects. The similar treatment of 4b afforded also dl-phyllostine through

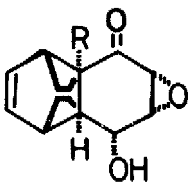

4a R=H
5a R=CH_2OH


4b R=H
5b R=CH_2OH

compound, 5b, m.p. 130~131°, $C_{15}H_{16}O_4$, ν^{KBr}_{max} 3490, 3400, 1705 cm^{-1}; $\delta^{CDCl_3}_{TMS}$ 1.48 (6H, s, $=\!\!/^{CH_3}$), 1.70 (1H, s -OH), 2.10 (1H, s $-\overset{|}{C}H-\underset{O}{\underset{\|}{C}}-$), 3.45 and 4.25 (2H, ABq, J=11Hz, $-CH_2$-O-), 3.75 (2H, s, $^{H}\overset{O}{\triangle}^{H}$), 4.05 (2H, m, $=\!\!\diagup\!\!\diagdown^{H}$), 6.40 (2H, m, $=\!\!/^{H}$) in 73% yield and the conditions and yield of the retro-Diels-Alder reaction are described in Table 1.

The synthesis of dl-epoxydon (2) and dl-epiepoxydon (3) were accomplished starting from known compounds[3)], 6a~6b, which have been obtained by reduction of 4a and 4b. Each of these compounds, 6a~6d, was treated with formalin by the


6a R=H
7a R=CH_2OH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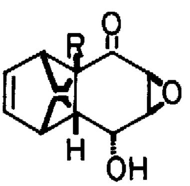
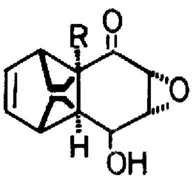
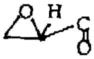
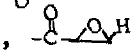
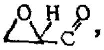
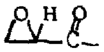
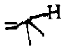
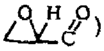
7b R=CH_2OH


6c R=H
7c R=CH_2OH

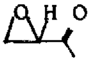

6d R=H
7d R=CH_2OH

same procedure used for the synthesis of 1 and converted to compounds, 7a, m.p. 144~145°, $C_{15}H_{18}O_4$, ν^{KBr}_{max} 3450, 3360, 1700 cm^{-1}; $\delta^{acetone-d_6}_{TMS}$ 1.60 (6H, s, $=\!\!/^{CH_3}$), 1.85 (1H, dd, J=4Hz, 8Hz, $-\overset{|}{C}\underline{H}\overset{|}{C}HOH$), 2.85 (1H, s, COH), 3.20 (1H, d, J=4Hz, ), 3.35 and 4.35 (2H, ABq, J_{AB}=11Hz, CH_2O-), 3.45~3.90 (4H, m, , CHOH, ), 4.60 (1H, d, J=6Hz, OH), 6.22 (2H, m, =/H); 7b, m.p. 171~173°, $C_{15}H_{18}O_4$, ν_{max}^{KBr} 3350, 1700, 1680 cm^{-1}; $\delta_{TMS}^{acetone-d_6}$ 1.25 (1H, d, J=8Hz, -CH-COH), 1.50 (6H, s, =/CH_3), 2.90 (1H, br, s, OH), 3.20 and 4.10 (2H, ABq, J=11Hz, -CH_2O), 3.30~3.40 (2H, m, , -CHOH), 3.55~3.70 (2H, m, , ), 3.80 (1H, m, ), 4.80 (1H, br, s, OH), 6.25 (2H, m, =/H), 7c, m.p. 114~117°C, ν_{max}^{KBr} 3450, 3300, 1700 cm^{-1}; $\delta_{TMS}^{acetone-d_6}$ 1.55 (6H, s, =/CH_3), 3.15 (1H, d, J=4Hz, ), 3.30 and 4.20 (2H, ABq, J=11Hz, CH_2OH), 3.40~3.70 (4H, m, , , -CH-C-OH), 4.60 (1H, m, -CHOH), 6.00, 6.20 (each 1H, m, =/H); and 7d, m.p. 131~132°, $C_{15}H_{18}O_4$ 1/2 H_2O, ν_{max}^{KBr} 3450, 1695 cm^{-1}; $\delta_{TMS}^{acetone-d_6}$ 1.42, 1.46 (each 3H, s, =/CH_3), 3.20 and 4.12 (2H, ABq, J_{AB}=11Hz, -CH_2OH), 3.25 (1H, d, J=4Hz, ), 3.59 (1H, dd, J=4Hz, 3Hz, ), 3.84 (1H, b. q, ), 4.60 (1H, dd, J=6Hz, 3Hz, CHOH), 6.30 (2H, m, =/H). The yields of these compounds, 7a~7d, are in the range of 86% to 92%. Retro-Diels-Alder reactions of 7a and 7b under conditions described in Table 1 afforded dl-epoxydon (2), m.p. 64~65°, whose mixed melting point with authentic sample showed no depression and the spectral data are identical with those of previous sample.

The present synthetic method of epoxydon (2) raised the overall yield (10% from p-benzoquinone) ten times of the previous one[2)] (1% from gentisyl alcohol).

Table 1, Retro-Diels-Alder reactions of the hydroxymethylated compounds[4)]

starting material	solvent	temp (°C)	reaction time (min)	product	yield (%)
5a	THF	140~150	30	1	70
5b	THF	140~150	40	1	62
7a	AcOEt	140~150	30	2	65
7b	AcOEt	160~170	50	2	60
7c	THF	110~120	30	3	76
7d	THF	140~150	30	3	70

The same treatment of 7c and 7d (see Table 1) gave a stereoisomer, dl-epi-epoxydon (3), m.p. 78.5~79°, $C_7H_8O_4$, ν_{max}^{KBr} 3350, 1680 cm^{-1}; $\delta_{TMS}^{acetone-d_6}$ 3.40 (1H, dd, $J_{2,3}$=3.5Hz, $J_{2,4}$=1Hz, ), 3.78 (1H, m, ), 4.20 (2H, s, $-CH_2O-$), 4.65 (1H, broad dd, $J_{4,5}$=5Hz, $J_{2,4}$=1Hz, -C<u>H</u>OH), 6.70 (1H, dd, $J_{4,5}$=5Hz, $J_{3,5}$=2.5Hz, ). The stereochemistry of 3, in which epoxy and hydroxy group occupy trans configuration, was confirmed by the NMR spectrum which exhibits a long range-coupling (J=1Hz) between 2-H and 4-H due to W-arrangement.[5)]

The synthetic method described above made possible synthesis of naturally occurring labile epoxy compounds 1~3 and would be applied for the synthesis of the related compounds physiologically interested.

References and footnotes

1) This paper constitutes part VIII of "Synthetic studies of highly oxygenated cyclohexane derivatives". For part VII, K. Oda, A. Ichihara, and S. Sakamura Tetrahedron Letters, 3187 (1975).

2) a. A. Ichihara, K. Oda, and S. Sakamura, Agr. Biol. Chem., 35, 445 (1971).
   b. A. Ichihara, K. Oda, and S. Sakamura, Tetrahedron Letters, 5105 (1972).
   c. A. Ichihara, K. Oda, and S. Sakamura, Agr. Biol. Chem., 39, 555 (1975).

3) A. Ichihara, M. Kobayashi, K. Oda, and S. Sakamura, Tetrahedron Letters, 4231 (1974).

4) All the reactions were carried out in a sealed tube.

5) G. Read and V. M. Ruiz, J. Chem. Soc., (C) 1945 (1970).