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TOTAL SYNTHESIS OF DL-CROTEPOXIDE[1)]

Kengo Oda, Akitami Ichihara*, and Sadao Sakamura

Department of Agricultural Chemistry, Faculty of Agriculture

Hokkaido University, Sapporo, Japan

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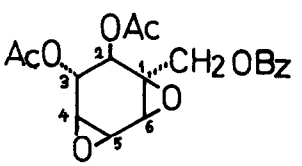
Crotepoxide[2,3)] 1, which was isolated from the fruits of Croton macrostachys and from the leaves and stem of Piper futokadzura and showed significant inhibitory activity against Lewis lung carcinoma in mice, is one of naturally occurring highly oxygenated cyclohexane derivatives[4)]. In this communication, we wish to describe the first total synthesis of dl-crotepoxide via stereoselective manner.



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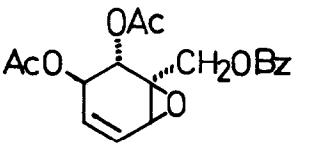
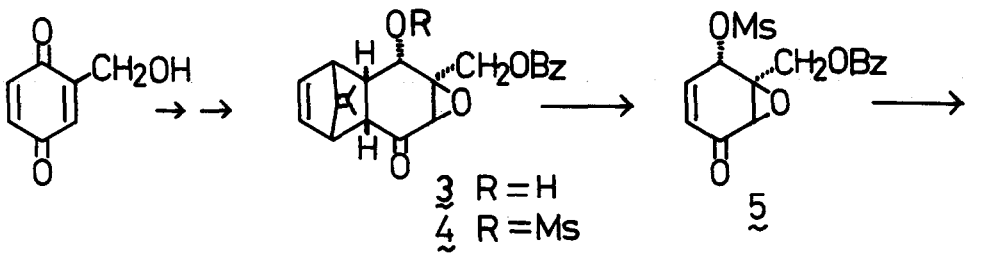


2

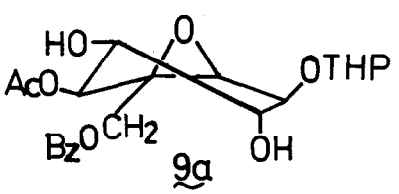
Bz = COC_6H_5

Treatment of 3, synthesized from 2-hydroxymethyl-1,4-benzoquinone via three steps according to the same procedure used for the synthesis of dl-senepoxyde[5)]; with MsCl-pyridine gave a mesylate 4, mp 143°, $C_{23}H_{24}O_7S$; ν_{max}^{KBr} 1720, 1350, 1180 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 1.53 (3H, s, $=C^{CH_3}$), 1.55 (3H, s, $=C^{CH_3}$), 3.10 (3H, s, $-OSO_2CH_3$), 3.20 (2H, m, -CH-), 3.43 (1H, s, ), 3.62 (2H, m, $=C^{H}$), 4.36, 4.88 (2H, ABq, J=13 Hz, $-CH_2O-$), 5.86 (1H, d, J=5 Hz, -CHOMs), 6.38 (2H, m, ), in 91% yield. Retro Diels-Alder reaction[6)] of 4 at 120° in

xylene under atmosphere of nitrogen gave an epoxycyclohexenone 5, ν_{max}^{neat} 1720, 1710, 1680, 1360, 1180 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 3.10 (3H, s, $-OSO_2CH_3$), 3.64 (1H, d d, J =1.5 Hz, J=1.5 Hz, ), 4.36, 5.13 (2H, ABq, J=12 Hz, $-CH_2O-$), 5.86 (1H, m, -CHOMs), 6.24 (1H, m,), 6.84 (1H, d d, J=11 Hz, J=5 Hz, ), in 72% yield. Reduction of the epoxycyclohexenone 5 with $Zn(BH_4)_2$ in anhydrous THF-benzene gave an allyl alcohol 6 stereoselectively.



3 R=H
4 R=Ms
5
6
7 R=H
8 R=THP
1
9 $R_1=R_2=H, R_3=THP$
10 $R_1=Ac, R_2=H, R_3=THP$
11 $R_1=H, R_2=Ac, R_3=THP$
12 $R_1=Ac, R_2=Ms, R_3=H$



9a

The stereochemistry at C-5 in the alcohol 6 was confirmed by the fact that α-proton to epoxy group showed a relatively small coupling (J=2 Hz) with the vicinal proton in the nmr spectrum. This stereoselectivity was probably caused by the steric and/or electonic effect expected on the basis of the more stable "O-axial" conformation[7] of the epoxy group. Acetolysis[8] of 6 with AcOK in acetone-acetic acid at 60° gave an acetate 7,[9] mp 98°, $C_{16}H_{16}O_6$,

ν_{max}^{KBr} 3500, 1735 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 2.15 (3H, s, $-OCOCH_3$), 3.72 (1H, d d, J=2 Hz, J=2 Hz, ), 4.50 (1H, m, -CHO-), 4.40, 4.63 (2H, ABq, J=12 Hz, $-CH_2O-$), 5.53, 5.72 (2H, m of ABq, J=10 Hz, ), 5.83 (1H, m, -CHOAc), in 54% yield from 5. Protection of the hydroxyl group of 7 with dihydropyran and p-toluenesulfonic acid in anhydrous THF gave a tetrahydropyranyl ether 8 in a quantitative yield. Hydroxylation of 8 with osmium tetroxide gave a glycol 9 stereoselectively since osmium tetroxide attacks preferentially from the less hindered side of the double bond of 8, and the stereochemixtry was confirmed by the fact that α-proton to C-2 acetyl group in the diacetate 10 showed the coupling constant, 6 Hz, which is compatible trans diaxial protons.

Acetylation of 9 with acetic anhydride-pyridine (1.2 eq.) in anhydrous ether at 5° gave a chromatographically inseparable mixture of diacetates 10 and 11 in a ratio of 3 : 1 as determined by nmr signals due to C-2 acetate methyl at δ 2.15 and 2.12 respectively. The regioselective acetylation of the glycol 9 was expected from the favorable conformation 9a, in which the hydroxyl group at C-3 occupies easily acylable equatorial position. The mixture was used for further reaction since it is expected that in the final stage the derivative of undesired product 11 would be removed from synthetic crotepoxide. Mesylation of 10 with MsCl-pyridine, followed by removal of tetrahydropyranyl group with p-toluenesulfonic acid in ethanol gave alcohol 12, ν_{max}^{neat} 3500, 1750, 1730 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 2.05 (3H, s, $-OCOCH_3$), 2.18 (3H, s, $-OCOCH_3$), 3.03 (3H, s, $-OSO_2CH_3$), 3.71 (1H, d, J=3.5 Hz, ), 4.27 (1H, d d, J=5 Hz, J=3.5 Hz, -CHO-), 4.37, 4.55 (2H, ABq, J=13 Hz, $-CH_2O-$), 4.94 (1H, d d, J=5 Hz, J=2 Hz, -CHOMs), 5.15 (1H, d d, J=5.5 Hz, J=2 Hz, -CHOAc), 5.66 (1H, d, J=5.5 Hz, -CHOAc). Treatment of 12 with basic alumina[10] gave dl-crotepoxide 1, identical with

natural crotepoxide by tlc and nmr, ir, mass spectral comparison.

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References and footnotes

1) This paper constitutes part VII of "Synthetic studies of highly oxygenated cyclohexane derivatives." For part VI, see reference 5).

2) S. M. Kupchan, R. J. Hemingway, and R. M. Smith, J. Org. Chem., 34, 3898 (1969). P. Coggan, A. T. McPhail and G. A. Sim, J. Chem. Soc., (B), 534 (1969).

3) S. Takahashi, Phytochemistry, 8, 321 (1969).

4) Other members of this class are cited in reference 5).

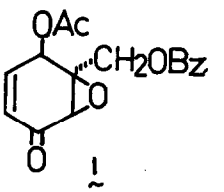
5) A. Ichihara, K. Oda, M. Kobayashi, and S. Sakamura, Tetrahedron Lett., 4235 (1974).

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

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

8) Acetolysis of 4 was unsuccessful owing to steric hindrance probably caused by the isobutenyl group in 4.

9) Inversion at C-2 in the reaction was clearly demonstrated by the fact that, in the oxidation product (i) of 7, long range coupling of α-proton to epoxy group with the proton at C-2 through W-configuration was no longer observed.



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10) S. Takahashi, Chem. Pharm. Bull., 18, 199 (1970).