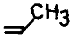
Tetrahedron Letters No. 48, pp 4235 - 4238, 1974. Pergamon Press. Printed in Great Britain.

STEREOSELECTIVE SYNTHESIS OF DL-SENEPOXYDE[1)]

Akitami Ichihara*, Kengo Oda, Makio Kobayashi and Sadao Sakamura
Department of Agricultural Chemistry, Faculty of Agriculture
Hokkaido University, Sapporo, Japan

(Received in Japan 2 August 1974; received in UK for publication 21 October 1974)

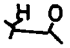
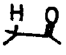
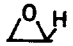
Senepoxyde[2)] (9) which was isolated from medicinal plant, Uvaria Catcarpa in France, is known as one of naturally occurring highly oxygenated cyclohexane derivatives[3)]. In this communication, we would like to describe the total synthesis of dl-senepoxyde in stereoselective manner.

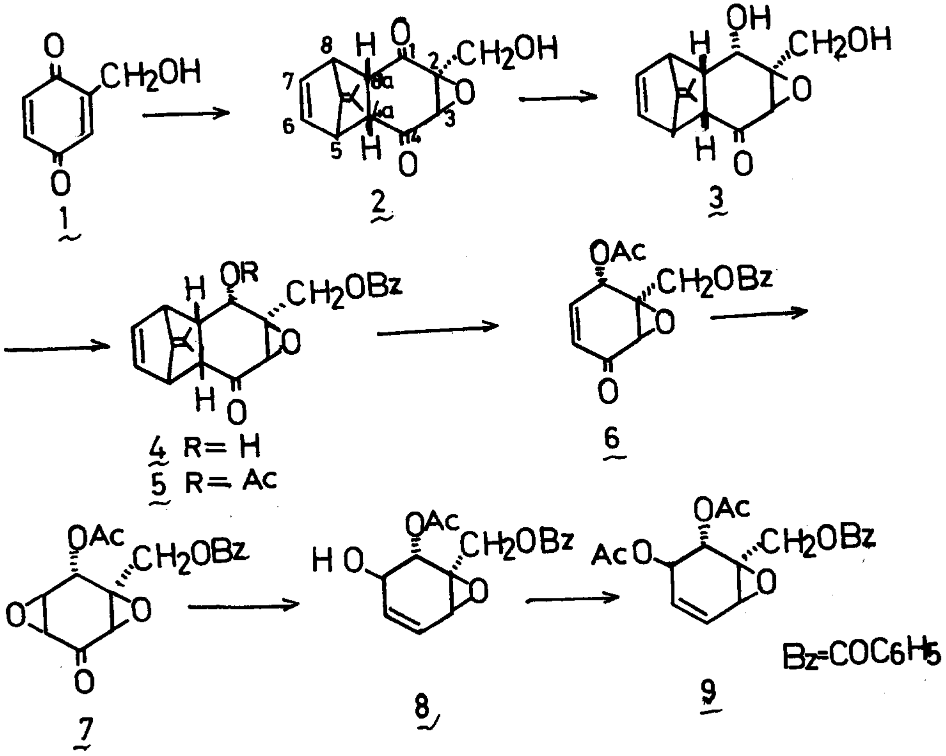
Diels-Alder reaction of 2-hydroxymethyl-1,4-benzoquinone 1 with dimethylfulvene and subsequent epoxidation of the adduct gave 2, m.p. 101 ~ 102°, $C_{15}H_{16}O_4$, ν^{KBr}_{max} 1710 cm^{-1} ; $\delta^{CDCl_3}_{TMS}$ 1.53 (6H, s, 

), 3.42 (2H, m, -CHCO-), 3.56 (1H, s, 

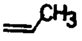
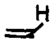
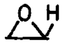
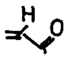
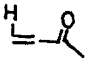
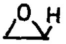
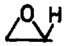
), 3.72 (2H, m, 

), 3.85, 4.00 (2H, ABq, J_{AB} = 14 Hz -CH_2-O), 6.19 (2H, m, 

). The fulvene part of the compound 2 plays an important role not only to produce the regio- and stereoselectivity but also to stabilize the intermediates in the course of the synthesis and could be easily removed in later stage. The stereochemistry of compound 2 was determined by the fact that two protons attached to ring juncture C-4a and C-8a in endo compound 2 appeared at δ 3.42, lower field compared with the signal at δ 2.80 which is shielded by double bond in exo compound[4,5)] and epoxidation should be preferably occurred from exo side to give a sole product 2. Regioselective reduction of 2 with 1.1 equivalent of sodium borohydride utilizing neighboring hydroxyl group effect gave a diol 3, in 73.5% yield, m.p. 149.5~150°, $C_{15}H_{18}O_4$, ν_{max}^{KBr} 3500, 3300, 1705 cm^{-1} ; $\delta_{TMS}^{acetone-d_6}$ 1.48 (6H, s, ) 2.74 (1H, A part of ABXY, J_{AB} = 12 Hz, J_{AX} = 3Hz, J_{AY} = 5 Hz ), 3.00 (1H, B part of ABX', J_{AB} = 12 Hz, J_{BX} = 3 Hz ), 3.16 (1H, s, ), 3.39 (2H, m, ), 3.54, 3.98 (2H, ABq, J_{AB} = 13 Hz, -CH$_2$-O-), 4.64 (1H, d, J = 5 Hz, -CH-O-), 6.05 (1H, m, ), 6.23 (1H, m, ). The regio- and stereoselective reduction was confirmed by the fact that α-proton to hydroxyl group appeared at δ 4.64 (d, J = 5 Hz) and in the later stage compound 6 showed a signal at δ 3.57 due to α-proton to epoxide, coupled (1.5 Hz) with α-proton to acetoxyl group through W-configuration.



Treatment of the diol 3 with benzoyl chloride afforded a benzoate 4, m.p. 150.5°, $C_{22}H_{22}O_5$, which was further acetylated with acetic anhydride-pyridine to an acetate 5, m.p. 152°, $C_{24}H_{24}O_6$, m/e 408 (M$^+$); ν_{max}^{KBr} 1730, 1715, 1600 cm^{-1};

$\delta^{CDCl_3}_{TMS}$ 1.47 (6H, s, ), 2.00 (3H, s, $OCOCH_3$), 2.97 (1H, A part of ABXY, J_{AB} = 11 Hz, J_{AX} = 3 Hz, J_{AY} = 5 Hz, ), 3.15 (1H, B part of ABX', J_{AB} = 11, J_{BX} = 3.5 Hz ), 4.06, 4.73 (2H, ABq, J_{AB} = 12 Hz, $-CH_2-O-$), 5.89 (1H, dd, J = 5 Hz, J = 3 Hz, ), 5.99 (1H, d, J = 5 Hz, -CHOAc), 6.34 (1H, dd, J = 5 Hz, J = 3 Hz, ), 7.50 (3H, m, ArH), 8.04 (2H, dd, J = 9 Hz, J = 2 Hz, ArH). Retro Diels-Alder reaction[5] of the acetate **5** in diglyme by heating at 160°C for 1hr under atmosphere of nitrogen gave an epoxycyclohexenone **6**, m/e 302 (M^+), ν^{neat}_{max} 1750, 1720, 1690, 1600 cm^{-1}; $\delta^{CDCl_3}_{TMS}$ 2.05 (3H, s, $-OCOCH_3$), 3.57 (1H, dd, J = 1.5, J = 1.5 Hz, ), 4.25, 5.00 (2H, ABq, J = 12 Hz, $-CH_2-O-$), 5.98 (1H, m, -CHOAc), 6.11 (1H, m, ), 6.67 (1H, dd, J = 10 Hz, J = 5 Hz, ) in 78% yield. Epoxidation and subsequent acetylation yielded a diepoxide **7**, ν^{neat}_{max} 1745, 1730, 1600 cm^{-1}; $\delta^{CDCl_3}_{TMS}$ 2.10 (3H, s, $-OCOCH_3$), 3.47 (2H, m, ), 3.59 (1H, dd, J = 4 Hz, J = 2 Hz, ), 4.00, 4.79 (2H, ABq, J_{AB} = 13 Hz, $-CH_2-O$), 6.00 (1H, s, -CH-OAc), 7.50 (3H, m, ArH), 8.05 (2H, dd, J = 8 Hz, J = 2 Hz, ArH). In the NMR spectrum of the diepoxide **7**, the fact that a signal at δ 6.00 due to α-proton to acetoxyl group has rather small half width (J = 3 Hz) indicates that the hydrogen occupies trans position with a dihedral angle of nearly 90° to the vicinal hydrogen and the stereochemistry must be as shown. Finally reductive cleavage of an epoxy ring in the diepoxide with hydrazine hydrate (ca. 2 equivalent, in benzene-isopropyl alcohol-THF) proceeded regioselectively to give **8** which was directly acetylated with acetic anhydride-pyridine to afford dl-senepoxyde m.p. 97 ~ 98°, $C_{18}H_{18}O_7$. The synthetic senepoxyde is identical with natural specimen in IR, NMR, MS spectra, and behavior on TLC.

Acknowledgment. We wish to thank Mme J. Polonsky, Institut de chemie des substances Naturelles, CNRS, Gif-sur-Yvette, France, for providing valuable

sample of natural senepoxyde.

References and footnotes

1) This paper constitutes part VI of "Synthetic studies of highly oxygenated cyclohexane derivatives". For part V, see reference$^{5)}$.

2) R. Hollands, D. Becher, A. Gaudemer, and J. Polonsky, *Teterahedron*, **24** , 1633 (1968).

3) Other members of this class are, epoxydon : A. Closse, R. Mauli, and H. P. Sigg., *Helv. Chim. Acta*, **49**, 204 (1966). S. Sakamura, H. Niki, Y. Obata, R. Sakai, and T. Matsumoto, *Agr. Biol. Chem.*, **33**, 198 (1969), crotepoxide: S. M. Kupchan, R. J. Hemingway, and R. M. Smith, *J. Org. Chem.*, **34**, 3898 (1969), S. Takahashi, *Phytochemistry*, **8**, 321 (1969), terreic acid : J. C. Sheehan, W. B. Lawson, and R. J. Gaul, *J. Am. Chem. Soc.*, **80**, 5536 (1958), terremutin: M. W. Miller, *Tetrahedron*, **24**, 4839 (1968).

4) D. F. O'Brien and J. W. Gates, Jr. *J. Org. Chem.*, **30**, 2593 (1965).

5) A. Ichihara, M. Kobayashi, K. Oda, and S. Sakamura, submitted for publication.