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UDC 547.91.057 : 581.192

Synthesis of Bakkenolide A

Bakkenolide A is a spirolactone isolated from flower stems of *Petasites japonicus* Max. subsp. *giganteus* Kitam.[1] A study of its chemical and spectral properties indicated the structure and absolute stereochemistry depicted as **1**. The lactone is a member of sesquiterpenes, perhaps derived from eremophilane-type group.[2] Kitahara, *et al.* suggested its biogenesis as epoxidation and subsequent Favorskii rearrangement of fukinone[3] (**2**) and further oxidation to give the lactone.[4]

We describe here a biomimetic synthesis of bakkenolide A (**1**). Treatment of pulegone β-epoxide[5] (**3**) with NaOH in aqueous EtOH by Cavill's procedure[6] afforded the rearranged product (**4**) in 39% yield which was protected as the methyl ester (**5**) and subjected to dehydration with $SOCl_2$ in pyridine to give the unsaturated methyl ester (**6**), $[\alpha]_D$ +5.0° (c=0.97, MeOH); IR ν_{max}^{film} cm^{-1}: 1730, 1640, 890; NMR (in CCl_4) δ: 4.82 (2H, multiplet). Oxidation of (**6**) with SeO_2 in aqueous AcOH[7] afforded the lactone (**7**) in 38% yield, $[\alpha]_D$ $-20.3°$ (c=0.54, MeOH), IR ν_{max}^{film} cm^{-1}: 1780, 1670, 900.

These results were applied to the synthesis of **1** from fukinone (**2**) isolated form *Cacalia hastata* L. subsp. *orientalis* Kitam.[8] Epoxidation of **2** with 30% H_2O_2 in an alkali condition gave two epoxides separated by column chromatography over silica gel, named epoxide A (**8** or **9**), mp 64.0—66.0°,[9] $[\alpha]_D$ +24° (c=0.50, MeOH), IR ν_{max}^{Nujol} cm^{-1}: 1720; NMR (in CCl_4) δ: 0.98 (3H, doublet, J=6 Hz), 1.13 (6H, singlet), 1.32 (3H, singlet), in 30.6% yield and epoxide B (**9** or **8**), mp 83.0—83.5°, $[\alpha]_D$ +21° (c=0.51, MeOH), IR ν_{max}^{Nujol} cm^{-1}: 1730; NMR (in CCl_4) δ: 0.90 (3H, doublet, J=6 Hz), 0.96 (3H, singlet), 1.12 (3H, singlet), 1.35 (3H, singlet) in 38.4% yield. The former showed a positive Cotton effect while the latter showed a negative Cotton effect on optical rotatory dispersion measurement.[10] Both epoxides gave the same reaction mixture detected by thin-layer chromatography and gas-liquid chromatography when treated with NaOH in aqueous EtOH. Therefore, the epoxide mixture without separation was refluxed under the same condition. Extraction of the acidic fraction from the reaction mixture and isolation as methylester over silica gel column gave (**10**), (**11**), and (**12**) in 42, 42, and 16% yield of the acidic products, respectively. Dehydration of **10** with $SOCl_2$ in pyridine gave the unsaturated ester[11] (**13**), $[\alpha]_D$ +17° (c=0.56, MeOH), IR ν_{max}^{film} cm^{-1}: 1735, 1650, 900; NMR (in CCl_4) δ: 3.60 (3H, singlet), 4.75 (1H, multiplet), 4.84 (1H, multipet), in 89% yield, which was oxidized with SeO_2 in aqueous AcOH to give **1** in 33% yield, and the

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2) V. Herout, "Aspects of Terpenoid Chemistry and Biochemistry," ed. by T.W. Goodwin, Academic Press, Inc., London and New York, 1971 Chapt. 3; J.S. Roberts, "Chemistry of Terpenes and Terpenoids," ed. by A.A. Newman, Academic Press, Inc., London and New York, 1972, Chapter 3.

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4) Y. Kitahara, N. Abe, T. Kato, and K. Shirahata, *Nippon Kagaku Zasshi*, **30**, 221 (1969).

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6) G.W.K. Cavill and C.D. Hall, *Tetrahedron*, **23**, 1119 (1967).

7) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, *J. Am. Chem. Soc.*, **78**, 1422 (1956).

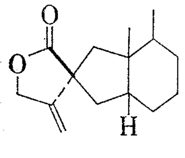
8) K. Hayashi, H. Nakamura, and H. Mitsuhashi, *Phytochemistry*, **12**, in press.

9) Melting points were taken on a Kofler hot stage and are uncorrected. Satisfactory elemental analytical data were obtained for all the compounds.

10) However, we could not depict so far the stereochemistry of each epoxide. The experiments to clarify this point are in progress.

11) During the progress of this work, a similar synthesis of **13** was described by Naya, *et al.* (K. Naya, M. Hayashi, I. Takagi, S. Nakamura, and M. Kobayashi, *Bull. Chem. Soc. Japan*, **45**, 3673 (1972)).

α,β-unsaturated aldehyde (**14**), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1700, 1630; NMR δ: 3.51 (3H, singlet), 5.90 (1H, multiplet), 6.21 (1H, multiplet), 9.42 (1H, singlet); UV λ_{max}^{EtOH} nm(ε): 219 (6970), 333 (660), in 57% yield. Reduction of the aldehyde with $NaBH_4$ yielded **1** in 47% yield. The synthesized **1**, mp 79.0—80.5°, $[\alpha]_D$ +18° (c=0.56, MeOH), showed the following spectroscopic data: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1780, 1675, 905; NMR (in $CDCl_3$) δ: 0.84 (3H, doublet, J=6 Hz), 0.96 (3H, singlet), 4.75 (2H, multiplet), 5.02 (1H, multiplet), 5.09 (1H, multiplet); Mass Spectrum m/e: 234 (M^+), 124, 123, 111, 109 (base peak). These data completely agreed with those of natural bakkenolide A[8] and no depression of mp occurred by mixed fusion.



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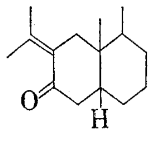

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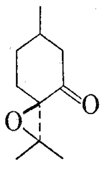

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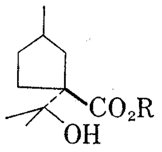
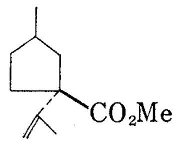


4 : R=H
5 : R=Me



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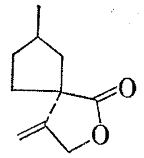

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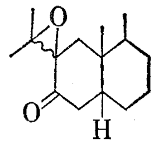

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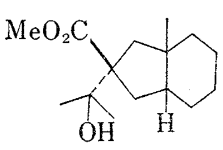

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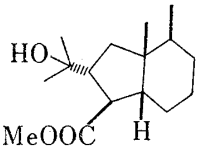

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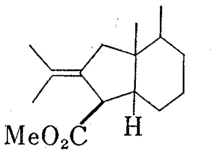

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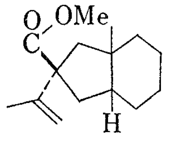

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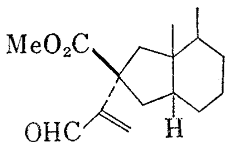

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Absorption Route of ^{131}I-Labeled Lysozyme in Rats

It has recently been suggested that a small amount of enzyme proteins are absorbed from the mammalian small intestine.[1] However, the route in intestinal absorption of enzyme proteins has not yet been clarified. This paper deals with investigations on the intestinal absorption of ^{131}I-labeled hen egg white lysozyme (abbreviated as ^{131}I-EWL) and on the role in the absorption of lymphatics in comparison with the portal vein in rats.

^{131}I–EWL was prepared by the modified method of Hansen, *et al.*[2] The specific radioactivity of ^{131}I–EWL was 97—123 μCi/mg. The radiochemical purity checked by electro-

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