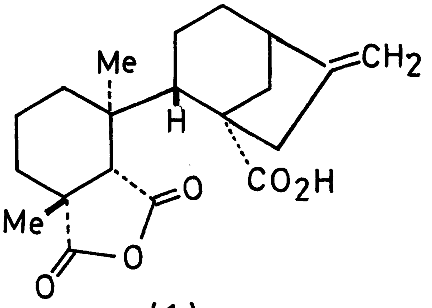
CHEMISTRY LETTERS, pp. 887-890, 1976. Published by the Chemical Society of Japan

# SYNTHETIC APPROACH TO FUJENOIC ACID III.
# SYNTHESIS OF DEMETHYLFUJENOIC ACID DERIVATIVE

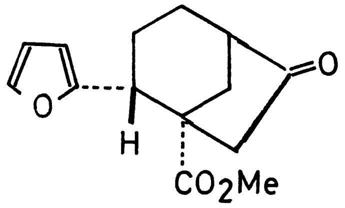
Tadahiro KATO*, Takeshi SUZUKI, Noboru OTOTANI,
and the late Yoshio KITAHARA
Department of Chemistry, Faculty of Science,
Tohoku University, Sendai 980

Demethylfujenoic acid derivative (14) has been synthesized from the key intermediate (2) by the application of Diels-Alder and subsequent reactions as shown in the scheme.

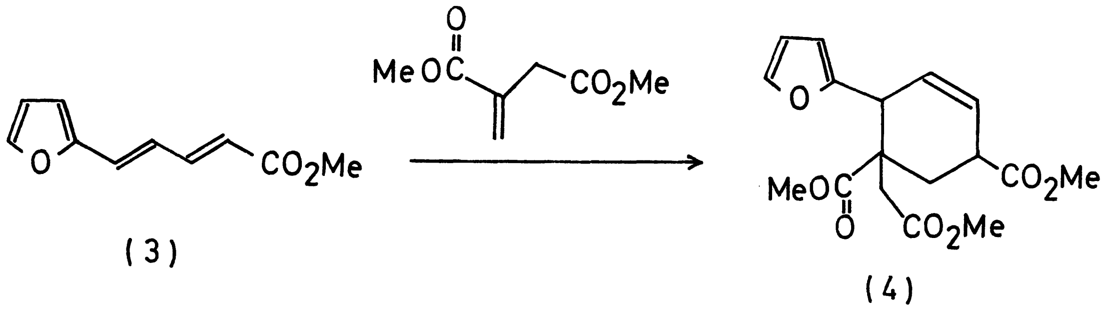
Directed toward the total synthesis of fujenoic acid (1)[1], a typical B-secokauranolide, 1α-carbomethoxy-2α-(2-furyl)-6-oxo-bicyclo[3,2,1]octane (2) has been synthesized from methyl furfurydenecrotonate (3) by the Diels-Alder reaction with methyl itaconate followed by sequential reactions of catalytic hydrogenation, Dieckmann condensation and then decarbomethoxylation. The details of the synthesis will be described elsewhere[2].



(1)



(2)



(3)

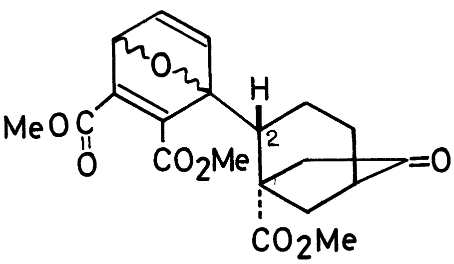
(4)

This paper deals with the synthesis of demethylfujenoic acid derivative (14) from the key intermediate (2). 2 was inert to maleic anhydride under Diels-Alder reaction conditions although its model compound, methylfuran, afforded the corresponding adduct in moderate yield[3]. When methyl acetylenedicarboxylate reacted with the compound (2), however, the Diels-Alder reaction proceeded smoothly giving two kinds of adducts, (5a, oil) and (5b, mp 131 - 132°)[4], in 60 and 21% yields, respectively. Since both adducts are convertible in 80% yield to the same phenolic ketone (6), mp 137 - 138°, when treated with $BF_3$-etherate, each of these adducts is a stereoisomer concerning the ether oxygen and $C_2$-proton of bicyclo[3,2,1]octane system. Although exact stereostructure of these adducts could not be determined, the phenolic ketone (6) was gained in 56% yield from the intermediate (2) without isolation of the adducts, (5a) and (5b).

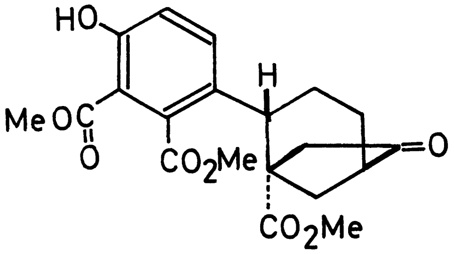
The phenol ring of compound (6) and its derivatives (7), mp 162 - 163°, and (8) is strictly resistant to the Birch or catalytic reduction under various conditions[5], under which model compound, 2,3-bismethoxycarbonyl-4-methylphenol, was reduced easily. Consequently, another route was explored in order to get enolic compound (13).

Catalytic reduction of the Diels-Alder adduct, (5a), afforded the corresponding keto ether (9a), mp 142 - 143°, in high yield. The anti-configuration of ether oxygen with respect to the newly formed secondary carbomethoxy groups was decided by NMR spectrum, in which Ha appeared at 4.60 ppm as a triplet with 4.5 Hz while two multiplet signals at 3.06 (ddd, 12, 4.5, and 1.5 Hz) and 3.27 (dd, 12 and 1.5 Hz) ppm were assigned to Hb and Hc, respectively. Observations of W type long range coupling (1.5 Hz) of Hb and Hc and the triplet nature of Ha demonstrate the stereostructure of 9a as shown in the scheme. Similarly, the isomeric adduct, (5b), afforded the corresponding keto ether (9b), mp 101 - 102°.

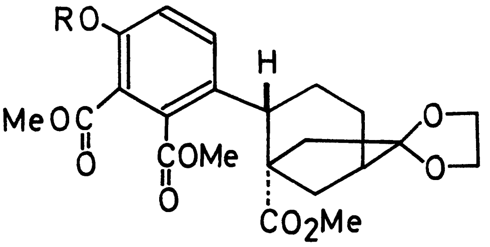
The previous model experiment revealed that ether bond of model compound (9c) was easily cleaved by the action of $BF_3$-etherate in $Ac_2O$ or P-TsOAc. On the other hand, ether linkage of both (9a) and (9b) remained unchanged when the same conditions were applied to these compounds. After several trials under different conditions, the ether linkage of keto ether (9a) was successfully cleaved when 9a in $Ac_2O$ was warmed at 50° C for 5 days in the presence of concentrated $H_2SO_4$. By this procedure keto acetate (10), mp 169 - 170°, was obtained in 56% yield. Hydrolysis of the acetyl group was achieved by the action of methanolic HCl, giving oily keto alcohol (11) in quantitative yield. After ketalization of the keto alcohol, the



(5a,b)

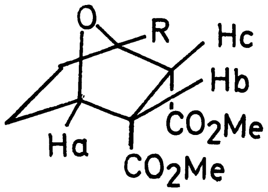


(6)

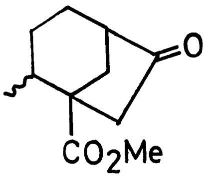


(7) R = H

(8) R = Me or Et

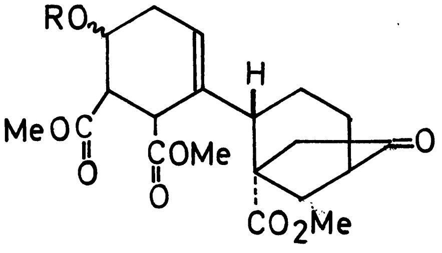


(9a,b) R =



i

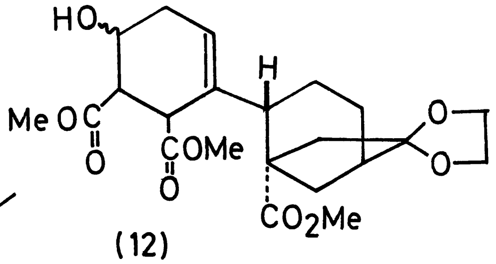
(9c) R = Me



(10) R = Ac, (11) R = H

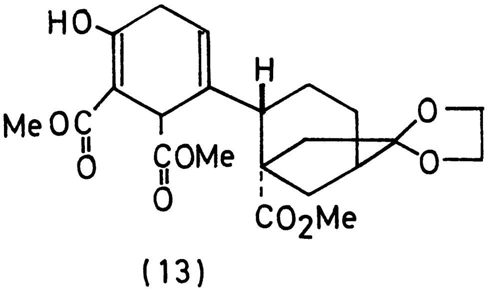
ii(10→11)

iii(11→12)



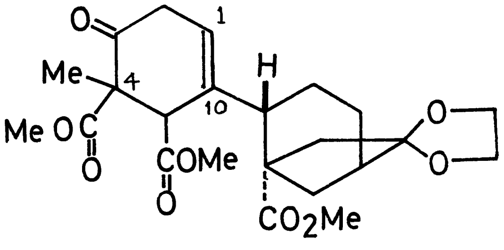
(12)

iv



(13)

v



(14)

i) $Ac_2O/H_2SO_4$ ii) HCl/MeOH iii) $C_2H_4(OH)_2$/p-TsOH iv) $CrO_3\cdot Py$

v) MeI/NaOMe

resulting ketal alcohol (12), oil, was oxidized with $CrO_3$-pyridine complex to give a 1 : 4 mixture of phenolic ketal (7) and enolic ketal (13). Although the mixture showed one spot on $SiO_2$ thin layer chromatography under several solvent systems and hence both could not be separated, the NMR spectrum of the mixture exhibited two singlets at 12.33 ppm due to enolic proton of (13) and 10.80 ppm assigned to phenolic proton of 7 in the ratio of 4 : 1.

Methylation of the mixture with MeI in the presence of NaOMe afforded the corresponding methylation product (14), which was separated by repeated chromatographies. The compound showed the sharp methyl signal at 1.50 ppm, the down field shift of which was explained by deshielding effect of two carbonyl groups located near the methyl group. Although the stereochemistry of the newly introduced methyl group at $C_4$ with respect to $C_2$-H of C/D ring remains unsolved at present, the compound (14) corresponds to demethylfujenoic acid derivative. Further investigation is needed for the determination of its stereochemistry as well as for the introduction of another methyl group at $C_{10}$ position of the derivative.

## References

* To whom correspondence should be addressed.

1. B. E. Cross, R. H. B. Galt, and J. R. Hanson, J. Chem. Soc., 1963, 2937.
2. Part II. Y. Kitahara, T. Kato, T. Suzuki, H. Maeda, and N. Ototani, J. Chem. Soc. (C), submitted.
3. Y. Kitahara, T. Kato, N. Ototani, A. Inoue, and H. Izumi, J. Chem. Soc. (C), 1968, 2508.
4. All the compounds described herein have the satisfactory spectral and analytical data.
5. Part I. Y. Kitahara, T. Kato, T. Suzuki, and N. Ototani, to be submitted elsewhere.

(Received June 21, 1976)