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A SYNTHETIC METHOD FOR NOVEL 1,2,3-TRISUBSTITUTED CYCLOPENTANE DERIVATIVES, 1-HYDROXYMETHYL-3-METHOXY-2-OXABICYCLO[2.2.1]HEPTANE-7-CARBOXYLIC LACTONES

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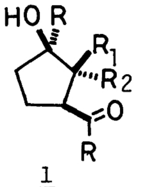
The reaction of furfuryl alcohols with maleic anhydride leads to tricyclic lactone-carboxylic acids through the sequence of esterification and intramolecular Diels-Alder reaction. Anodic oxidative decarboxylation of the hydrogenated products in MeOH affords 1,2,3-trisubstituted cyclopentane derivatives, viz. 1-hydroxymethyl-3-methoxy-2-oxabicyclo[2.2.1]heptane-7-syn-carboxylic lactones, potential intermediates for synthesis of iridoids.

Recently we reported the stereospecific syntheses of c-acyl-c- and t-2-methoxycarbonyl-r-1-cyclopentanols 1 from the acid-catalyzed hydrolysis of methyl 3-methoxy-2-oxabicyclo[2.2.1]heptane-7-carboxylates 2 which were obtained by anodic oxidative decarboxylation of the mono esters of 1,4-dialkyl-7-oxabicyclo[2.2.1]heptane-exo- and endo-cis-2,3-dicarboxylic acids 3[1)] and the application of the products 1 and 2 for the synthesis of a variety of iridoid monoterpenes.[2)]



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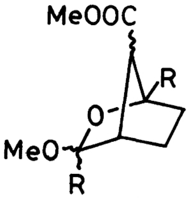

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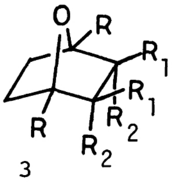

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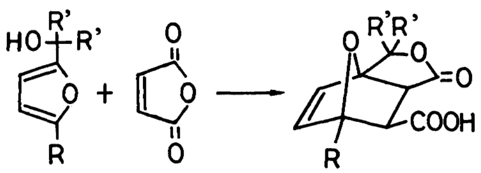
R_1 = COOH, R_2 = H
or R_1 = H, R_2 = COOH

Unfortunately furan derivatives in this investigation is limited to symmetrically disubstituted one because the methanolysis, a step to obtain the starting material, of the Diels-Alder adducts between furans and maleic anhydride (MA) lacks regioselectivity. In order to remove this restriction and to incorporate an additional oxygen function as substituent of the cyclopentanes with the goal of synthesizing a wide variety of iridoids in higher oxidation states, a novel type of 7-oxabicyclo[2.2.1]heptane-2-carboxylic acid derivatives is highly desired. This expectation has now been realized by the intramolecular [4 + 2] cycloaddition reaction[3)] of the esters formed between furfuryl alcohols 4 and MA to give tricyclic lactone-carboxylic acids 5.



4 MA 5

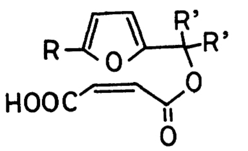


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Table 1. Preparation of Adducts 5 and Their Hydrogenation Products 7

	R	R'	Mp of 5 (°C)	Yield of 5 (%)	Mp of 7 (°C)
a	H	H	82	98	191
b	Me	H	88	98	156
c	H	Me	135	22	200

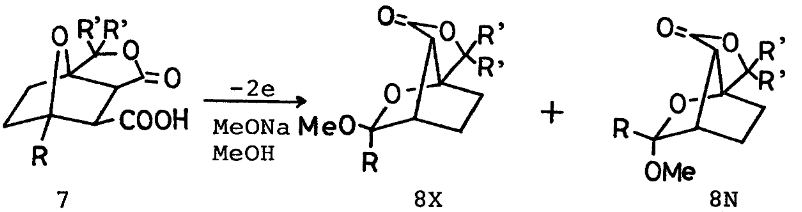
The reaction of equimolar amount of 4a-c and MA in diethyl ether or PhH for three days at room temperature gave tricyclic acids 5a-c[4)] isolable as crystals by simple filtration. The results are listed in Table 1.

Investigation of the ^1H NMR spectra of the reaction mixtures at the early reaction stage showed existence of the intermediary esters 6a-c.[5] This fact implies that the ester formation between 4 and MA occurrs before [4 + 2] cycloaddition.[6]

Atmospheric hydrogenation of 5a-c in MeOH over Pd-C or Pd black gave saturated tricyclic acids 7a-c in nearly quantitative yields.

Electrolyses of 7a-c in MeOH in the presence of NaOMe in an undivided cell using graphite electrodes gave in good yields mixtures of 1-hydroxymethyl-3-methoxy-2-oxabicyclo[2.2.1]heptane-7-syn-carboxylic lactones 8Xa-c and 8Na-c[7] in the ratios as shown in Table 2.[8] When R = Me (b series), the product having 3-exo-methoxy group (8Xb) was overwhelmingly produced. Similar stereospecificity has been observed in our earlier work.[1]

Thus the sequence of intramolecular cycloaddition reaction, hydrogenation, followed by anodic oxidative decarboxylation constitutes a synthetic method for novel 1,2,3-trisubstituted cyclopentane derivatives 8. Since 8 can be regarded as the potential intermediates for the synthesis of iridoid monoterpenes especially in higher oxidation states, the hydrolysis as well as other transformations of 8a-c are actively investigated in this laboratory.[9]



7 8X 8N

Table 2. Electrolyses of 7

	R	R'	Yield of 8 (%)	8X : 8N
a	H	H	96	2.3 : 1
b	Me	H	98	>13 : 1
c	H	Me	87	3.8 : 1

References and Notes

1) (a) T. Akiyama, T. Fujii, H. Ishiwari, T. Imagawa, and M. Kawanisi, Tetrahedron Lett., 2165 (1978); (b) T. Imagawa, S. Sugita, T. Akiyama, and M. Kawanisi, Tetrahedron Lett., 22, in press.

2) (a) T. Imagawa, N. Murai, T. Akiyama, and M. Kawanisi, Tetrahedron Lett., 1691 (1979); (b) T. Imagawa, T. Sonobe, H. Ishiwari, T. Akiyama, and M. Kawanisi, J. Org. Chem., 45, 2005 (1980).

3) Intramolecular Diels-Alder reactions of the esters containing furan nucleus were reported; K. A. Parker and M. R. Adamchuk, Tetrahedron Lett., 1689 (1978).

4) The carbinyl methylene protons of 4a,b, 6a,b, and 7a,b in the ^1H NMR spectra clearly showed AB quartets, signifying the methylenes to be included in a rigid cyclic structure.

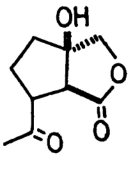
5) If the amount of the solvent was exceedingly minimized, 6b was crystallized out along with 5b and the conversion of 6b into 5b seemed not to take place in solid state.

6) Steric hindrance seems to affect sensitively the cycloaddition; In the reaction of MA and 2,5-furandimethanol mono acetate, only the ester 6d (R = CH_2OAc; R' = H) was obtained in about 70% yield and more forced conditions (heating at 50 or 80°C) did not lead to the intramolecular cycloaddition reaction.

7) Only 8Xc (mp 122-123°C) and 8Nc (mp 84.5-86.5°C) were obtained as crystals.

8) For the method of the determination of the stereochemistry of the methoxy group, see ref. 1(b).

9) Acid-catalyzed hydrolysis of the products 8a-c experienced considerable difficulty since the products of hydrolysis have a trans-3-oxa-2-oxobicyclo[3.3.0]octane frame work such as 9 with considerable strain. On hydrolysis by $HClO_4$ in aq THF at room temperature, 8b gave 9 in 54% yield after preparative TLC separation and the same treatment of 8c resulted in the recovery of the greater part of the starting material with slight formation of 1-(1-hydroxy-1-methylethyl)-2-oxabicyclo[2.2.1]heptane-7,3-carbolactone.



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