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INTRAMOLECULAR DIELS-ALDER REACTIONS OF VINYLFURAN DERIVATIVES
A NOVEL APPROACH TO BENZOFURANS

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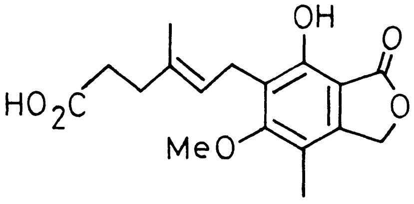
A successful intramolecular Diels-Alder reaction of vinylfuran derivatives was reported. The adducts were proved to be a useful precursor of substituted benzofurans.

Recently considerable efforts have been directed toward the application of intramolecular Diels-Alder reactions to natural product syntheses.$^{1)}$ We report herewith the feasibility of this approach to the preparation of benzofurans like **3**, which could be a key intermediate for the synthesis of mycophenolic acid **1**,$^{2)}$ secofuranoeremophilane (**2**),$^{3)}$ and its related compounds.



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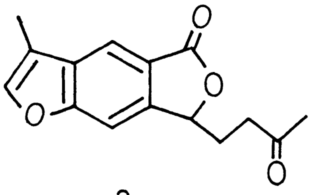

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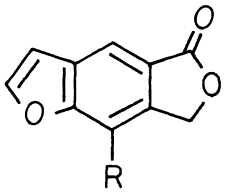


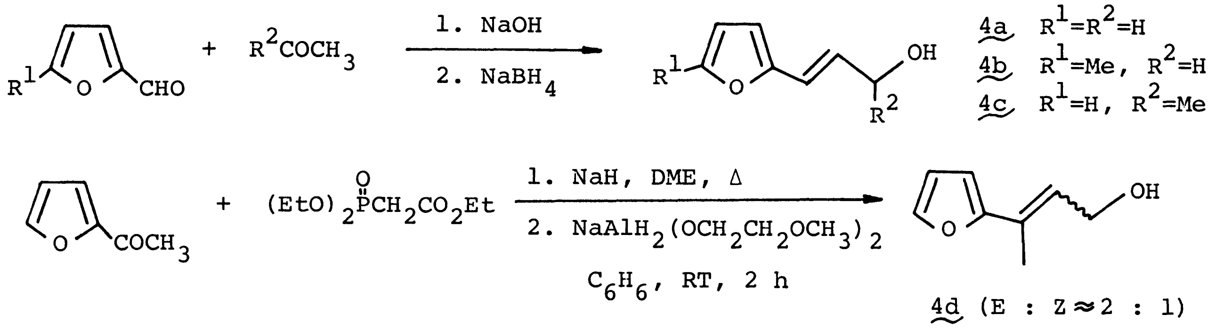
3 (R=H or Me)

In the Diels-Alder reactions of vinylfurans, it is known that the conjugated system involving the exocyclic double bond is more reactive than the furan ring system itself.$^{4)}$ A convenient route to the synthesis of **3** would be the Diels-Alder reaction of vinylfurans with unsaturated carboxylic acid derivatives followed by dehydrogenation. After numerous trials, we found the monomethyl fumaryl esters **5** to be most satisfactory for effecting the intramolecular Diels-

Alder reactions in our strategy.[5)]

As shown in Scheme 1, the starting alcohols 4 which contain a vinylfuran moiety were readily prepared by usual methods starting from furfural, 5-methylfurfural, and acetylfuran in high yields.

Scheme 1.



The desired esters 5 were prepared from 4 by treatment with monomethyl fumarylchloride in CH_2Cl_2 using pyridine as a base and were used for the next reaction without further purification.[6)]

Scheme 2.

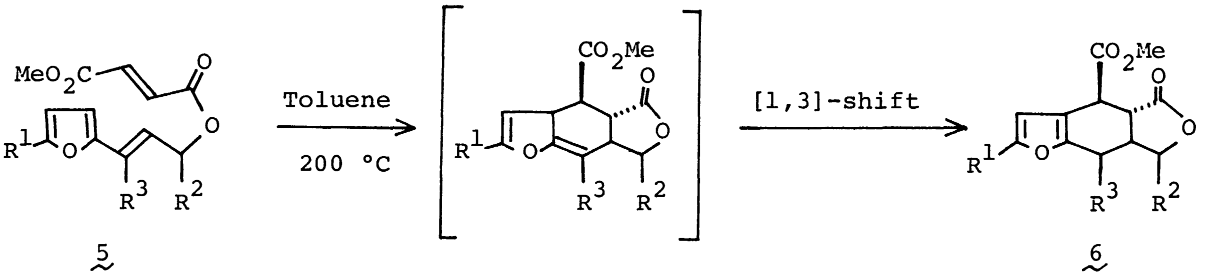
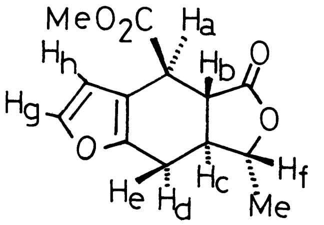


Table 1.

Compd.	Yield of 5(%),	$\nu_{C=O}$ cm^{-1}	Yield of 6(%),	$\nu_{C=O}$ cm^{-1}
a $R^1=R^2=R^3=H$	100	1720	73	1780, 1740, oil
b $R^1=Me$, $R^2=R^3=H$	91	1720	57	1780, 1740, oil
c $R^1=R^3=H$, $R^2=Me$	83	1720	56	1780, 1740, mp 117-119.5 °C
d $R^1=R^2=H$, $R^3=Me$	62	1720	46	1780, 1740, oil

The esters 5 were dissolved in toluene containing a small amount of hydroquinone and the solution was heated at 200 °C for 20 h in a sealed tube under N_2 (Scheme 2). Removal of the solvent, followed by preparative TLC (silica gel, benzene-ethyl acetate; 9 : 1) provided 6 in good yields (Table 1).[7] The structures of 6 were substantiated by their IR and NMR spectra. The stereochemistry of 6 was confirmed by NMDR experiment and the result for 6c is shown in Table 2.

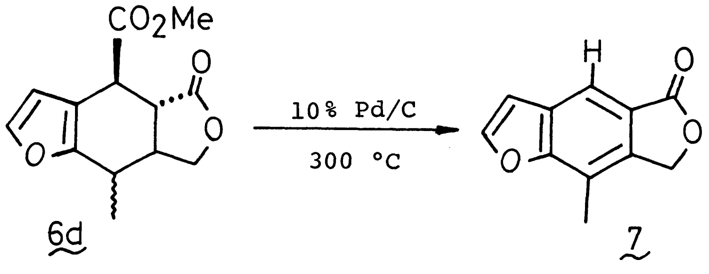
Table 2. ^1H NMR Data of 6c ($CDCl_3$, δ)



Chemical shifts (ppm)				Coupling constants, J (Hz)	
H_a	3.65 (ddd)	H_f	4.40 (dq)	H_a, H_b = 10.8	H_d, H_e = 15.2
H_b	3.13 (dd)	H_g	7.28 (d)	H_b, H_c = 13.6	H_a, H_d = 3.0
H_c	2.18 (dddd)	H_h	6.32 (d)	H_c, H_d = 10.8	H_a, H_e = 1.6
H_d	2.80 (ddd)	Me	1.48 (d)	H_c, H_e = 5.6	H_g, H_h = 2.0
H_e	2.90 (ddd)	CO_2Me	3.82 (s)	H_c, H_f = 9.6	H_f, Me = 6.0

Thus, the intramolecular Diels-Alder reaction of 5 was proved to proceed in the direction as predicted from "endo" rule.[8] The concurrent 1,3-hydrogen shift in the reaction condition is worth to note in connection with the selectivity rule for sigmatropy.[9]

Dehydrogenation of 6d (10% Pd/C, 300 °C, 1 h) gave a desired benzofuran 7[10] accompanying decarbomethoxylation.



The present work provides an efficient entry to substituted benzofuran derivatives. We are continuing to develop these reactions to a natural product synthesis.

References and Notes

1) For a review see, W. Oppolzer, Angew. Chem., **89**, 10 (1977); idem, Synthesis, 793 (1978); G. Brieger and J. N. Bennett, Chem. Rev., **80**, 63 (1980).

2) Synthetic studies of mycophenolic acid have been reported by several groups: A. J. Birch and J. J. Wright, Chem. Commun., **1969**, 788; idem, Aust. J. Chem., **2**, 2645 (1969); L. Canonica, B. Rindone, and C. Scolastico, Tetrahedron Lett., **1971**, 2689; L. Canonica, B. Rindone, E. Santaniello, and C. Scolastico, ibid., **1971**, 2691; idem, Tetrahedron, **28**, 4395 (1972); M. Asaoka, K. Miyake, and H. Takei, Chem. Lett., **1977**, 167; A. P. Kozikowski and R. Schmiesing, Tetrahedron Lett., **1978**, 4241; L. Colombo, C. Gennari, D. Potenza, C. Scolastico, and F. Aragozzini, J. C. S., Chem. Commun., **1979**, 1021.

3) F. Bohlmann, C. Zdero, and M. Grenz, Chem. Ber., **107**, 2730 (1974); F. Bohlmann and G. Fritz, Tetrahedron Lett., **1981**, 95.

4) W. J. Davidson and J. A. Elix, Aust. J. Chem., **26**, 1059 (1973), and references cited therein.

5) The corresponding acrylic esters gave no adducts.

6) These esterifications of **4** were somewhat troublesome, since the alcohols **4** were relatively unstable.

7) Analytical sample was purified by LC (Merck LiChroprep Si 60, eluted with benzene-ethyl acetate; 9 : 1).

8) For the recent discussion on the stereochemistry of intramolecular Diels-Alder reactions, see W. R. Roush, J. Org. Chem., **44**, 4008 (1979); W. R. Roush, A. I. Ko, and H. R. Gillis, ibid., **45**, 4264 (1980); W. R. Roush and H. R. Gillis, ibid., **45**, 4267 (1980).

9) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag Chemie, 1970, pp 120; I. Fleming, "Frontier Orbitals and Organic Chemical Reactions," Wiley, New York, N.Y., 1976, pp 99.

10) Mp 187 °C(sublimed); $\nu_{max}(CHCl_3)$, 1760 cm^{-1}; λ_{max}(EtOH), 228(ε 24000), 250 (6400), and 294(1900) nm; ^1H NMR ($CDCl_3$), δ 2.49(3H, s), 5.31(2H, s), 6.87 (1H, d, J = 2 Hz), 7.72(1H, d, J = 2 Hz), 7.98(1H, s).

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