AN ALTERNATE SYNTHESIS OF FUROVENTALENE USING AN EXTENSION OF HAGIWARA'S CONSTRUCTION OF THE 3-METHYLFURAN MOIETY[+]

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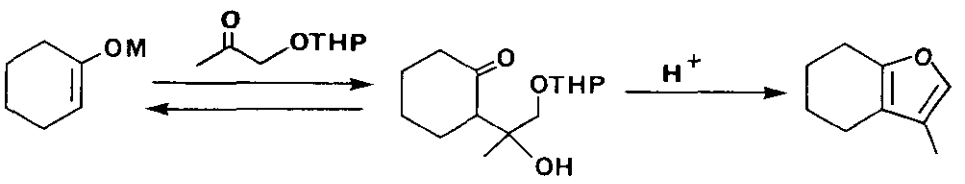
Abstract - A new total synthesis of furoventalene 5 is reported. Key steps in the sequence are the Birch reduction-homoprenylation in situ of aromatic carboxylic acids precursors, construction of the 3-methylfuran moiety by Hagiwara's method and decarboxylative aromatization of an appropriate intermediate.

The 3-methylfuran moiety is somewhat common in natural products of terpenoid origin (e.g. furoventalene 5), but its synthesis usually involves multistep sequences. In 1980 Hagiwara[1] reported a simple solution to thie problem with a method involving an aldol condensation of a ketone enolate with the tetrahydropyranyl (THP) ether of acetol and acid treatment of the resulting adduct :



This method has been successfully used by this author in the synthesis of several natural products[1], including furoventalene itself[2].

In this paper we wish to report a new total synthesis of furoventalene 5, using a modified version of Hagiwara's method in which the 3-methylfuran moiety is incorporated to a preformed cyclohexane ring[3].

The Birch reduction of 3,5-dimethoxybenzoic acid (2.2 equivalents of Na in dry

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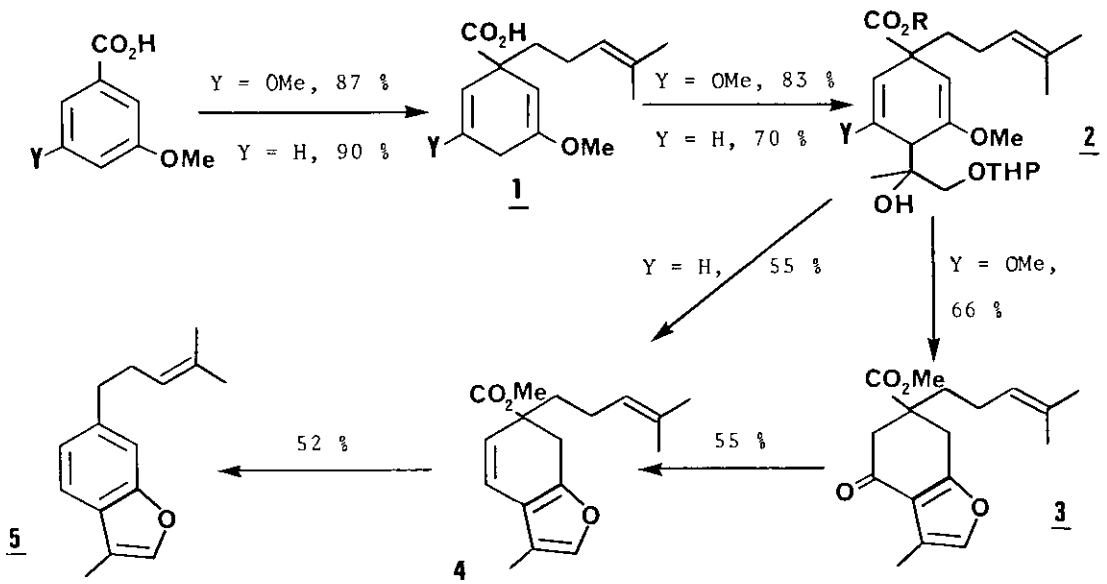
[+]Dedicated to Professor Gilbert Stork on occasion of his 65th birthday.

liquid NH_3) and monoalkylation in situ[4] of the resulting dianion with 4-methyl-3-pentenyl iodide 6[5] gave the acid 1a in 87 % yield. Metalation of this acid with 2.2 equivalents of n-butyllithium (THF, -78°C, 30 min) produced a new dianion which was now alkylated with the THP ether of acetol to afford the adduct 2a (R = H) in 83% yield. This diastereoisomeric mixture[6] was quantitatively esterified with CH_2N_2 (Et_2O) and converted into the fused 3-methylfuran 3 by treatment with a catalytic amount of p-toluenesulfonic acid (TsOH) in wet acetone (reflux, 30 min, 66 % yield) (oil; ir (film) ν 1740, 1680, 1620, 1570 cm^{-1}; ^{1}H-nmr (CCl_4) δ 7.15 (broad s, furan proton), 5.15 (broad t, J = 7 Hz, vinyl proton), 3.67 (s, CO_2CH_3), 3.40 and 2.75 (AB system, J = 18 Hz, furylic CH_2)[7], 2.85 and 2.35 (AB system, J = 15 Hz, $CH_2C{=}O$)[7], 2.15 (d, J = 1.5 Hz, furylic CH_3) and 1.70 and 1.60 (2 broad s, $(CH_3)_2C{=}CH$)).

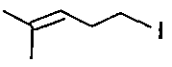
The dihydrobenzofuran derivative 4 was then obtained in 55 % overall yield from 3, by first reducing the keto group ($NaBH_4$ in isopropanol) and dehydration of the resulting alcohol with p-toluenesulfonyl chloride in pyridine at reflux (1 h) (oil; ir (film) ν 3020, 1730, 1580 cm^{-1}; ^{1}H-nmr (CCl_4) δ 7.00 (broad s, furan proton), 6.15 and 5.60 (2 d, J = 9 Hz, ring vinyl protons), 5.00 (broad t, J = 6 Hz, side chain vinyl proton), 3.65 (s, CO_2CH_3), 3.25 and 2.70 (AB system, J = 18 Hz, furylic CH_2)[7], 1.95 (d, J = 1.5 Hz, furylic CH_3) and 1.65 and 1.55 (2 broad s, $(CH_3)_2C{=}CH$)).



a serie : Y = OMe; b serie : Y = H

A second shorter route to 4, patterned along the same lines of the first one (see scheme), started from 3-methoxybenzoic acid which underwent the Birch reduction-monoalkylation in situ reaction with the iodide 6 to afford the acid 1b in 90 % yield. Metalation of this acid with 2.2 equivalents of n-butyllithium for 2.5 h (THF, -78°C) and alkylation with the THP ether of acetol proceeded in somewhat lower, but still acceptable yield (70 %), to give the adduct 2b (R = H). Reasonably, the presence of only one OCH_3 group in 1b as compared to 1a explains the observed lower yield in this reaction. The methyl ester 2b (R = CH_3) (CH_2N_2, Et_2O) was then converted into 4 (55 % yield) by treatment with a catalytic amount of H_2SO_4 in 3 : 1 THF-H_2O (24 h at room temperature, 6 h reflux)[8].

The synthesis of furoventalene 5 was completed by saponification of 4 (Na_2CO_3 in aqueous MeOH, reflux, 6 h) and oxidative decarboxylation of the resulting acid ($Pb(OAc)_4$, C_6H_6, reflux, 1.5 h). The furoventalene thus obtained (52 % overall yield after SiO_2 gel column chromatography, hexane as eluent) was spectroscopically identical with spectra kindly provided by Professors A. Yoshikoshi and D. E. Bergstrom (oil; ir (film) ν 1625, 1580, 860, 810 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 7.47 - 7.00 (complex signals, 3 aromatic protons and the furan proton), 5.20 (broad t, J = 6 Hz, vinyl proton), 2.75 (t, J = 6 Hz, benzylic CH_2), 2.20 (d, J = 1.5 Hz, furylic CH_3) and 1.70 and 1.55 (2 broad s, $(CH_3)_2C{=}CH$)).



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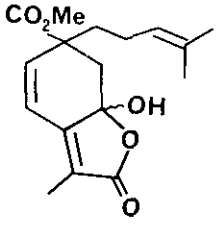

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The synthesis of furoventalene here described, in addition to its shortness and simplicity, also exemplifies an alternative way of approaching the Hagiwara's adduct precursors of the furan ring. This simple modification is devoided of the reversibility of the aldol condensation previously used by Hagiwara and coworkers and should extend further the utility of this method.

ACKNOWLEDGEMENTS

We thank Professor A. Yoshikoshi, Tohoku University, Sendai, Japan and Professor D. E. Bergstrom, University of North Dakota, Grand Forks, U.S.A. for spectra of fu-

roventalene. We also thank Miss A. Acosta, Miss G. Chávez, Miss S. Mendoza, and Mrs. M. Gutiérrez for spectral determinations.

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2. H. Hagiwara and H. Uda, J. Chem. Soc. Perkin Trans. I, 1984, 91. An identical synthesis of furoventalene was also reported from our laboratories: L. A. Maldonado and G. Guevara, Rev. Soc. Quím. Méx., 1984, 28, 347.
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6. Metalation-alkylation of 1-alkyl-3,5-dimethoxy-1,4-dihydrobenzoic acids with a variety of alkylating agents is stereoselective and gives consistently a single isomer (unpublished results from our laboratories). The diastereoisomeric mixture obtained in this case is undoubtedly due to isomers in the C-4 side chain.
7. Assignements were made by comparison of the appropriate signals in the ^{1}H-nmr spectra of compounds 3 and 4.
8. The reflux is necessary to complete the reaction; at room temperature only removal of the THP group was observed. On the other hand, with a catalytic amount of TsOH in 3 : 1 acetone-water (8 h, reflux), compound 7 was obtained in ≃ 50 % yield.

Received, 30th May, 1986