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4,5,6,7-TETRAHYDROISOBENZOFURAN-5-ONE AS A VERSATILE BUILDING BLOCK LEADING TO THE BASIC SKELETON OF NATURALLY OCCURRING FUSED FURANS

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Abstract — 4,5,6,7-Tetrahydroisobenzofuran-5-one as a building block has been prepared via the furan ring transfer (FRT) reactions utilizing an allene intramolecular Diels-Alder reaction, which provides a single route to the construction of the tricyclic furans.

Previously we have developed the furan ring transfer (FRT) reaction: a novel ring transfer reaction of furans to fused furans via the intramolecular Diels-Alder reaction of allenyl furfuryl ethers followed by ring opening of the resulting cycloadducts.

As part of our effort to develop the synthetic methods for the fused furans based on the furan ring transfer (FRT) reaction,1) we describe here a new building block approach using 4,5,6,7-tetrahydroisobenzofuran-5-one (**1**), a potential key intermediate leading to the tricyclic furans, which are present in antifungal marine natural products.2-5)

Compound (**1**) was readily prepared from furfuryl alcohol in four steps (Scheme 1). Propargylation of furfuryl alcohol [n-butyllithium (1.1 equiv.), dimethyl sulfoxide-benzene (1:1), 0°C, 1 h, then 1.2 equiv. of propargyl bromide, room temperature, 12 h] gave **2**, which was converted into the alcohol (**3**) by the FRT reaction (2 equiv. of potassium t-butoxide, t-butanol, reflux, 1 h). Selective hydrogenation of **3** (H_2, cat. 5%Pd/C, methanol) and oxidation of **4** according to Swern's protocol6) afforded the corresponding ketone (**1**)7,8) as a colorless oil in 78% overall yield from furfuryl alcohol. It should be noted that purification is not necessary during these steps except at the final stage, and multigram quantities of **1** (≥50 g) can be prepared in this manner.

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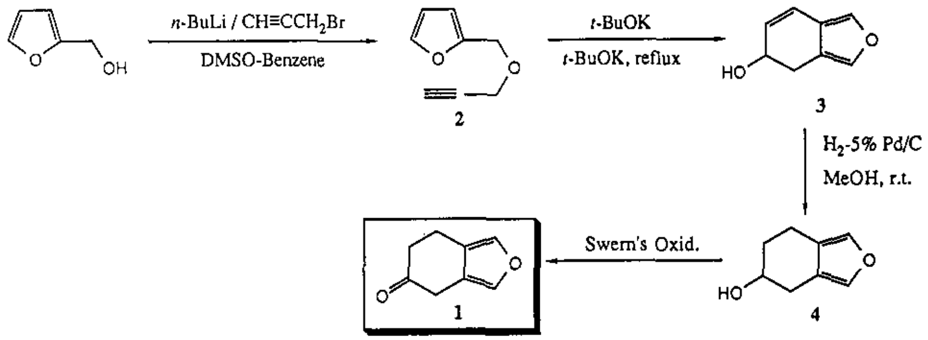
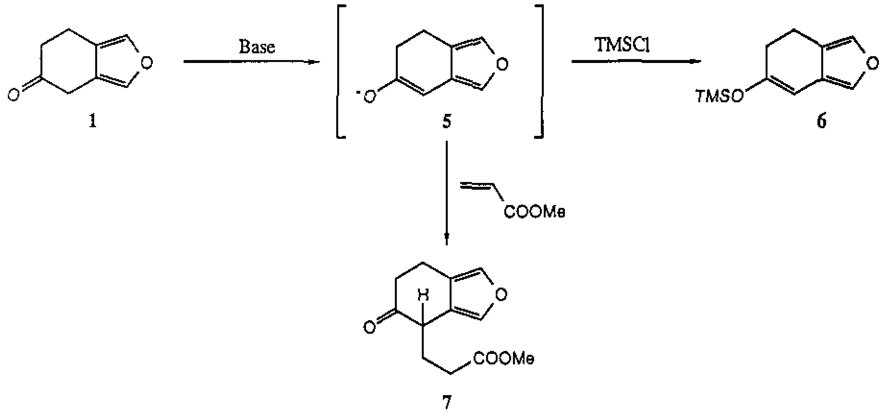
* This paper is dedicated to the memory of late Professor Tetsuji Kametani.

Scheme I



In order to determine the regiochemistry of the enolate anion generated by the base-treatment of **1**, the enolate anion was isolated as the corresponding trimethylsilyl enol ether: treatment of **1** with 1.2 equiv. of lithium hexamethyldisilylamide (LHMDS) in the presence of trimethylsilyl chloride (TMSCl) at -78°C gave **6** in 98% yield.9) The regiochemistry of **6** was apparent from ^{1}H-nmr spectrum [δ 5.65 (1H, s, C_4-H)] and no by-products were detected by capillary GC analysis. Similarly, reaction of **1** with TMSCl using triethylamine in dimethylformamide afforded **6** in 82% yield. These facts indicate the regiospecific formation of the enolate anion under either kinetic or *thermodynamic basic conditions*. Michael addition reaction of **1** with methyl acrylate was examined in the basic conditions: the lithium enolate (**5**), which was generated by the treatment of **1** with LHMDS (1 equiv.) in THF at -78°C, was allowed to react with methyl acrylate (1 equiv.) to give **7**10) in 63% yield.

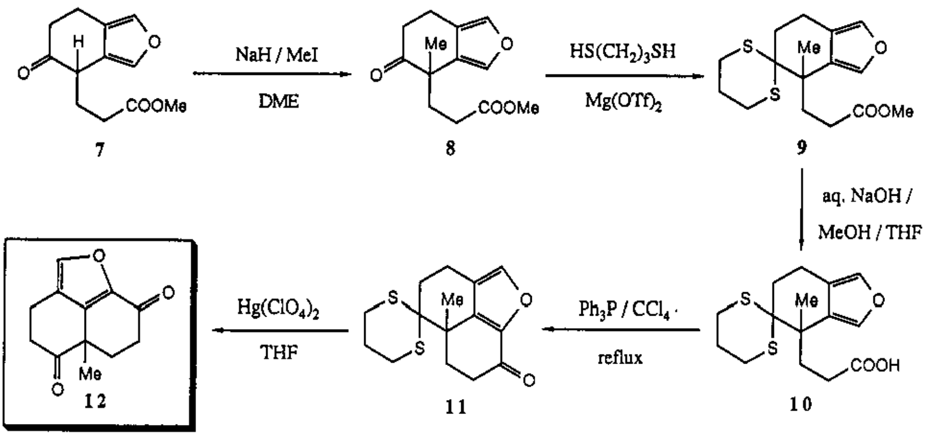
Scheme II



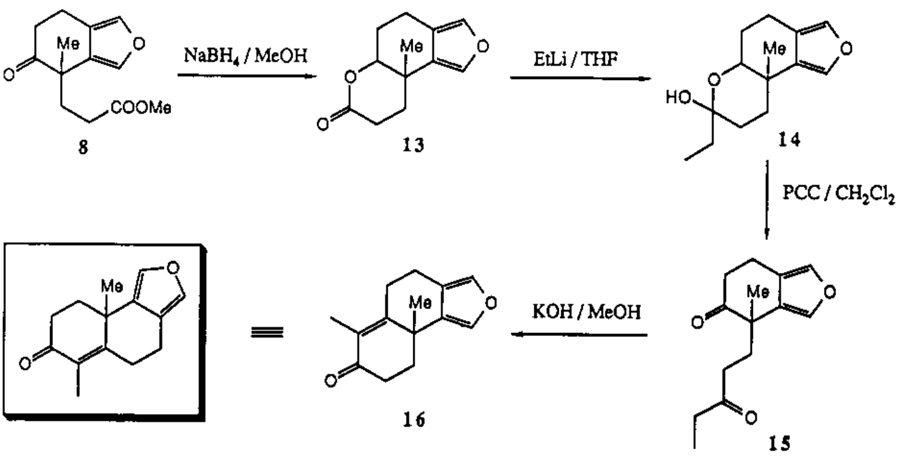
Then, we focused on the synthesis of tricyclic furans **12** and **16** which are basic structural units of natural occurring furans (Schemes III and IV). Treatment of Michael adduct (**7**) with sodium hydride and methyl iodide in dimethoxyethane gave **8** in *70% yield. Protection of carbonyl group* as a dithioketal11) and subsequent hydrolysis of ester group with aqueous sodium hydroxide afforded the carboxylic acid (**10**). The cyclization step was easily achieved by a single step: treatment of **10** with 1.5 equiv. of triphenyl phosphine in refluxing carbon tetrachloride[12) for 30 min gave **11** (86%). Finally, cleavage of dithioketal moiety of **11** afforded the tricyclic furan (**12**) as colorless crystals (mp 140-141°C).[13)

On the other hand, synthesis of **16** has been achieved in following manners. Reduction of **8** with sodium borohydride in methanol and the subsequent acidic work-up afforded the lactone (**13**) in 65% yield. Treatment of **13** with ethyllithium in THF at 0°C gave the hemiacetal (**14**) which was converted to **15** by PCC oxidation. Intramolecular aldol condensation of **15** using potassium hydroxide in methanol gave the tricyclic furan (**16**) in 78% yield.

Scheme III



Scheme IV



In conclusion, we have demonstrated the utility of **1** as an efficient building block for the synthesis of fused furans. A wide variety of fused furans can be easily prepared on the basis of this approach, hence it may be useful not only for synthetic studies but also for pharmaceutical studies. Further synthetic application of **1** are currently underway in our laboratory.

References and Notes

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7. All new compounds gave appropriate spectral data.
8. Compound **1**: ^{1}H-Nmr δ($CDCl_3$) 2.44-2.66(m, 2H), 2.80-3.04(m, 2H), 3.43(d, J=0.5 Hz, 2H), 7.25-7.26(m, 2H); ir (neat) 1710, 890 cm^{-1}; ms m/z 136(M$^+$), 94, 79.
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10. Compound **7**: ^{1}H-Nmr δ($CDCl_3$) 1.92-3.05(m, 8H), 3.43(t, J=5 Hz, 1H), 3.65(s, 3H), 7.28(m, 2H); ir (neat) 1730, 1710, 885 cm^{-1}; ms m/z 222(M$^+$), 190, 148.
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13. Compound **12**: ^{1}H-Nmr δ($CDCl_3$) 1.47(s, 3H), 2.01-2.40(m, 2H),2.46-3.16(m, 6H), 7.46(t, J=1.5 Hz, 1H); ir ($CHCl_3$) 1715, 1675 cm^{-1}; ms m/z 204(M$^+$).
14. Compound **16**: ^{1}H-Nmr δ($CDCl_3$) 1.49(s, 3H), 1.84(bs, 3H), 1.99-2.98(m, 8H), 7.14-7.18(m, 1H),7.24-7.27(m, 1H); ir (neat) 1655, 890 cm^{-1}; ms m/z 216(M$^+$).

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