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Convenient Syntheses of Tonghaosu and Two Thiophene Substituted Spiroketal Enol Ether Natural Products

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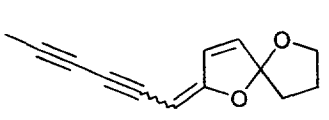
Abstract A convenient synthetic method of spiroketal enol ether by dehydration-spiroketalization reaction from furan intermediate and its application for the syntheses of three natural products, tonghaosu (**1**) and **2**, **3**, was reported.

The spiroketal unit has been found in a number of natural compounds isolated from many sources such as plants, insects, marine organisms, and microorganisms. Great efforts have been made to their structure elucidation and synthesis.[1] Among them a series of natural products with unique spiroketal enol ether structure have been explored by Bohlmann and his colleagues in 1960s and early 1970s.[2] These natural products, for example, compounds **1–3**, usually contain a spiroketal unit of [4, 4]- or [4, 5]-type with an enediyne side chain or an ene-thiophene group. Among them compound **1** named tonghaosu by us was also isolated from vegetable *tonghao* (*Chrysanthemum segetum* L.),[3] and has shown antifeedent activity.[4] Since 1970s only some research work on their isolation[4-7] but not on their syntheses[8] have been reported in the literature.



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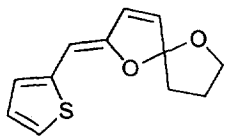

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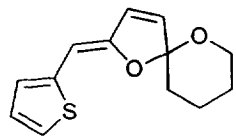
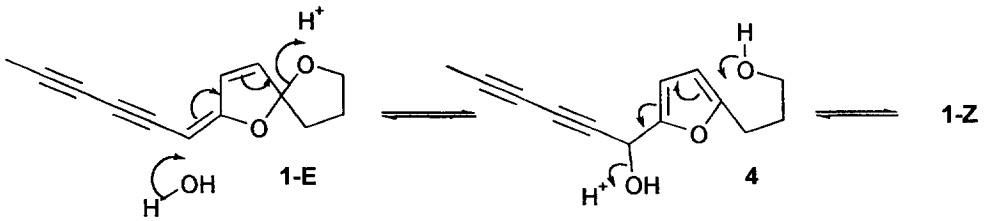
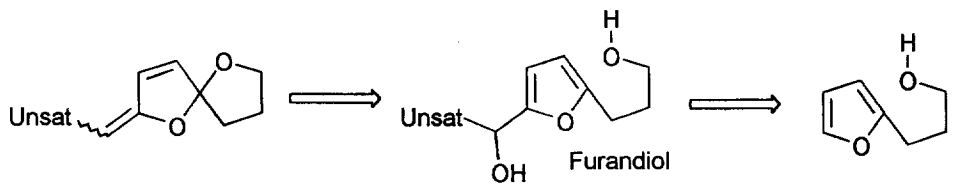


3

Herewith we would like to report their syntheses as the example of a convenient and general method to synthesize this kind of spiroketal enol ether compounds. The key step was based on the observation during the isolation of tonghaosu (**1**) that an equilibrium between the Z and E isomers via furandiol compound **4** occurred in the presence of acid and trace amount of water, or even in aged deuterated chloroform in an NMR tube or during silica gel chromatography. Therefore, furandiol compounds such as **4** would be the key intermediates for these target molecules as shown in the retrosynthesis. Thus, starting from furaldehyde (**5**) we prepared the known compounds 3-(2'-furyl)-propan-1-ol (**6a**) and 4-(2'-furyl)-butan-1-ol (**6b**) according to the procedure described in literature.[9] Treatment of **6** with butyl lithium and 2-thiophenecarboxaldehyde gave the furandiol **7a** and **7b** in 77% and 71% yield. Several acidic conditions have been tested for the last dehydration-spiroketalization step, and it was found that the reaction of 7 in toluene in the presence of 1 equivalent of $CuSO_4 \cdot 5H_2O$[10] afforded smoothly the desired thiophene attached spiroketal enol ethers **2** and **3** in almost quantitative yield. In these cases, only the Z-isomers were obtained and their stereochemistry was unambiguously established by 2-D NMR. All the physical data[11] were in accordance with their structures and those reported in literature.[5,6]



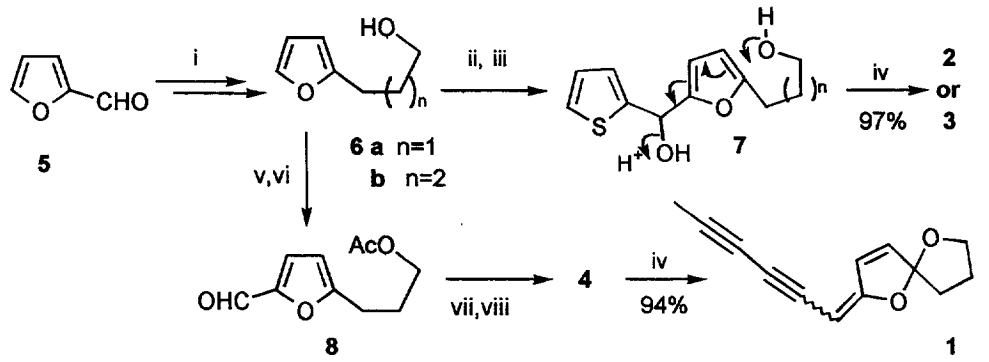
Equilibrium between Z- and E-isomer



Retrosynthesis

For the synthesis of tonghaosu (**1**), due to the problem in availability and handling of 2,4-hexandiynaldehyde, compound **6a** was firstly converted to 5-(3'-acetoxypropanyl)-furaldehyde (**8**) by acetylation and Vilsmaier-Haack formylation. Treatment of **8** with pentadiynyl lithium and hydrolysis of the acetyl protecting group gave the desired furandiol **4** in excellent yield. Dehydration-spiroketalization of **4**

according to the same procedure ($CuSO_4$•$5H_2O$-Toluene, 60°C) yielded a 1:1 Z/E mixture of tonghaosu (1)[12] in ca. 90% yield.



Scheme 1 *Reagents and conditions:* i, reference 9; ii, BuLi, THF, TMEDA, O°C--r.t.; iii, 2-Thiophene-carboxaldehyde, -78°C--r.t.; iv, $CuSO_4$•$5H_2O$, Toluene, 60°C. v, Ac_2O, Py, DMAP, 94%. vi, $POCl_3$, DMF, 92%. vii, 1,3-Pentandiyne, BuLi, THF, 75%. viii, $KHCO_3$, MeOH-H_2O, 92%.

In conclusion, three natural products incorporating the spiroketal enol ether unit have been synthesized by using a very convenient method. This methodology may also be applied to the syntheses of other spiroketal enol ethers which are a kind of potentially bioactive compounds or useful synthetic intermediates, and will be reported in due time.

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11. Compound **2** : M.p. 59-60°C; ν_{max} (KBr, cm^{-1}): 2978, 2900, 1651, 1590, 1490; δ_H (600MHz, $CDCl_3$) 7.17 (1H, d, *J*=5.1Hz), 7.05 (1H, d, *J*=3.3Hz), 6.96 (1H, dd, *J*=3.3Hz, 5.1Hz), 6.34 (1H, d, *J*=5.6Hz), 6.11 (1H, d, *J*= 5.6 Hz), 5.74 (1H, s), 4.27 (1H, m), 4.03 (1H, dd, *J*=7.6Hz, 15.3Hz), 2.37 (1H, m), 2.22 (1H, m), 2.09 (2H, m); *m/z* (relative intensity): 220 (M+, 100), 203 (2.9), 189 (36), 178 (20), 150 (11), 136 (30); Anal.Calc. for $C_{12}H_{12}O_2S$: C, 65.43; H, 5.49; S, 14.56; Found: C, 65.77; H, 5.43; S, 14.33. Compound **3**: Oil; ν_{max} (film, cm^{-1}): 3098, 2945, 2877, 1649, 1582, 1468, 1244; δ_H (600MHz, C_6D_6): 7.27 (1H, d, *J*=3.4Hz), 7.22 (1H, d, *J*=5.1Hz), 7.05 (1H, dd, *J*=3.4Hz, 5.1Hz), 6.08 (1H, d, *J*=5.6Hz), 6.02 (1H, d, *J*=5.6 Hz), 5.82 (1H, s), 4.47 (1H, m), 3.91 (1H, m), 2.35 (1H, m), 1.89~1.66 (5H, m); *m/z* (relative intensity): 234 (M^+, 100), 217 (4), 189 (13), 176 (27), 150 (15), 123 (19); Anal. Calc. for $C_{13}H_{14}O_2S$: C, 66.64; H, 6.02; S, 13.68; Found: C, 66.64; H, 6.26; S, 13.66.

12. Compound **1** (tonghaosu) (the ratio of Z/E was about 1:1): Oil; ν_{max} (film, cm^{-1}): 3035, 2985, 2139, 1630, 1581, 1438, 1348; δ_H (600MHz, C_6D_6): **1-E** : 6.53 (1H, d, *J* = 5.6Hz), 5.69 (1H, dd, *J* = 1.6Hz, 5.6Hz), 5.11 (1H, s), 3.88 (1H, m), 3.58 (1H, dd, *J* = 7.4Hz 15.0Hz), 1.85 ~1.73 (2H, m), 1.52 ~ 1.39 (5H, m): **1-Z:** 5.68 (1H, d, *J* = 5.6Hz),5.64 (1H, d, *J* = 5.6Hz), 4.50 (1H, s), 3.88 (1H, m), 3.58 (1H, dd, *J* = 7.4Hz, 15.0Hz), 1.85 ~ 1.73 (2H, m), 1.52 ~1.39 (5H, m): m/z (relative intensity): 200 (M^+, 100), 199 (25), 185 (19), 170 (20), 157 (26), 128 (25), 115 (38); Anal. calcd. for $C_{13}H_{12}O_2$: C, 77.98: H, 6.04: Found: C, 77.93; H, 6.39.

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