COMMUNICATION

Acid catalysed rearrangement of a spiroketal enol ether. An easy synthesis of chrycorin

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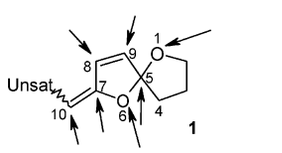
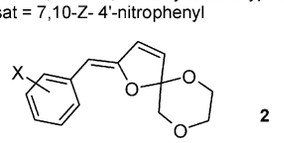
Tonghaosu, 2-[(*Z*)-hexa-2,4-diynylidene]-1,6-dioxaspiro-[4,4]non-3-ene (1a), and its spiroketal enol ether analogues (1b–d and 2) were efficiently converted into interesting cyclopentenone derived oxabicyclic compounds. By applying this reaction protocol the natural product chrycorin was easily synthesized in its racemic form. A reaction mechanism for this is proposed.

Tonghaosu, 2-[(*Z*)-hexa-2,4-diynylidene]-1,6-dioxaspiro[4,4]-non-3-ene (**1a**) is an antifeedant component of the vegetable tonghao (*Chrysanthemum segetum* L. or *Chrysanthemum coronarium* L.) and other plants of the tribe *Athemideae*.[1,2] Tonghaosu was first synthesized in the early 1960's by Bohlmann and co-workers in low overall yields.[3] Recently a concise general synthetic strategy for synthesizing tonghaosu and its spiroketal enol ether analogues **1b–d** and **2** was developed in our laboratory.[4–6] This strategy enables the facile preparation of more than a dozen tonghaosu analogues on multigram scales, and thus provides a solid foundation for further studies on the bioactivity and chemical reactivity of this type of compound.

Inspection of the spiroketal enol ether segment of the tonghaosu analogues reveals that there are five carbon and two oxygen reaction centers, each with different reactivities as shown with arrows in Fig. 1. Therefore, it is reasonable to anticipate that a number of reactions could take place thus providing potential access to a variety of derivatives. We describe herein an acid-catalysed rearrangement of these tonghaosu analogues and the first synthesis of chrycorin.



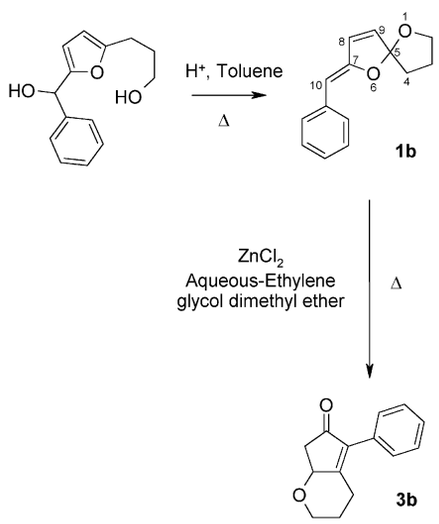
1a (**Tonghaosu**), Unsat =H_3C—≡—≡—
1b Unsat = 7,10-Z- phenyl
1c Unsat = 7,10-Z- 3',4'-methylenedioxyphenyl
1d Unsat = 7,10-Z- 4'-nitrophenyl



2a X = H
2b X = 3',4'-methylenedioxy
2c X = 4'-nitro

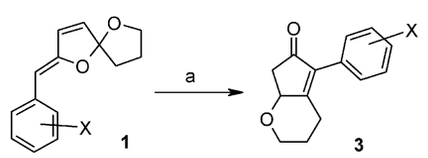
Fig. 1

Our syntheses of tonghaosu analogues were based on either a Brønsted or a Lewis acid catalysed dehydration–spiroketalization reaction of the corresponding furandiol in an aprotic aromatic solvent such as toluene (Scheme 1).[4] However, if a tonghaosu analogue, such as compound **1b**, was heated under reflux with a catalytic amount of *p*-TsOH, or more preferably $ZnCl_2$, in aqueous ethylene glycol dimethyl ether a new compound of the same molecular weight was formed in 83% yield. Spectroscopic data (IR, NMR, MS) show the existence of a molecule containing a ketone carbonyl group but no olefinic protons, clearly suggesting a cyclopentenone derivative **3b**.

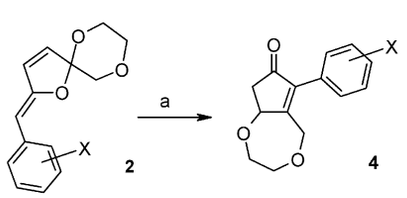


Scheme 1

Under the same reaction conditions other tonghaosu analogues[7] gave similar cyclopentenone derivatives in 70–90% yields as shown in Scheme 2, with those substrates carrying an



3b X= H Yield: 83%
3c X = *m*,*p*-methylenedioxy Yield: 88%
3d X = *p*-nitro Yield 80%



4b X= H Yield: 74%
4c X = *m*,*p*-methylenedioxy Yield: 77%
4d X = *p*-nitro Yield: 72%

Scheme 2 *Reagents and conditions*: a) $ZnCl_2$, aqueous ethylene glycol dimethyl ether, Δ.

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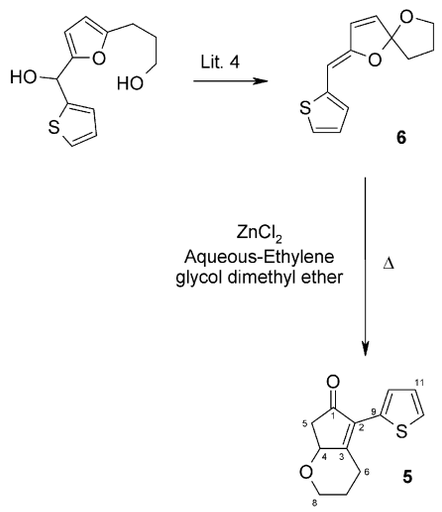
electron-donating group on the benzene ring giving slightly higher yields.

Having established this general synthetic method, we aimed to produce the first synthesis of chrycorin (**5**). This compound was isolated from *Chrysanthemum coronarium* by Tada and Chiba in 1984[8] and was shown to possess medium inhibitory activity toward the root growth of lettuce seedlings. By treating the tonghaosu thiophene derivative **6**, a natural product synthesized[4] in our laboratory earlier, with $ZnCl_2$ under the same reaction conditions as described above we obtained the desired compound **5** in 88% yield (Scheme 3). All the



Scheme 3

spectroscopic data[9] were in accordance with the data reported by Tada and Chiba.[8]

The molecular rearrangement of 2-furylcarbinols† to cyclopentenones is a well known reaction and has been used for the syntheses of prostanoids *etc*.[10] The rearrangement reported here is an adaptation of this common rearrangement of 2-furylcarbinols. It should be noted that the rearrangements of the systems demonstrated here were realized under significantly milder conditions and within shorter reaction times compared with those of the 2-furylcarbinols. The dienyl enol ether structure present in the tonghaosu derivatives may also be an intermediate in the rearrangement of other 2-furylcarbinols to 5-substituted 4-hydroxycyclopent-2-en-1-ones. In 1976 Piancatelli and co-workers suggested that the reaction mechanism could be a thermal electrocyclic reaction of a 4π electron system through a dienyl enol intermediate.[11] Therefore a simple and similar mechanism is suggested for our rearrangement (Fig. 2).

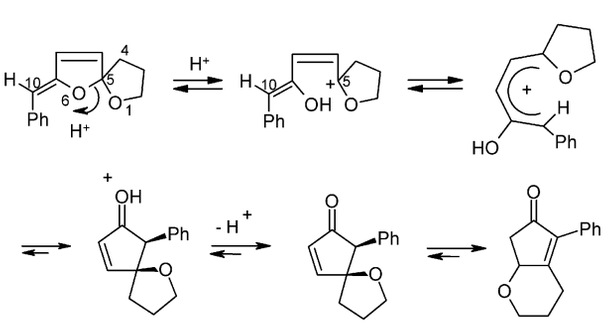


Fig. 2 A possible mechanism for the rearrangement.

In conclusion, a facile reaction without any special conditions has been developed for the synthesis of some structurally interesting molecules and creates potential access to a variety of tonghaosu derivatives. This protocol has also been successfully applied to the synthesis of the otherwise not easily accessible natural product chrycorin.

Acknowledgements

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† The IUPAC name for carbinol is methanol.

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7 Typical procedure for converting spiroketal enol ether to cyclopentenone: To a 100 mL round-bottomed flask were added tonghaosu analogue **1b** (426 mg, 20 mmol), $ZnCl_2$ (30 mg), water (20 mL) and ethylene glycol dimethyl ether (20 mL). The reaction mixture was heated under reflux for about 2 h until the starting material disappeared on TLC. The reaction mixture was then extracted with ether. The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent yielded a crude product, which was purified by column chromatography to afford the cyclopentenone compound **3b** (353 mg, 83% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (m, 5H), 4.51 (dd, J = 6.6, 2.6 Hz, 1H), 4.07 (ddd, J = 11.9, 5.0, 3.0 Hz, 1H), 3.75 (m, 1H), 3.04 (ddd, J = 14.6, 4.4, 3.3 Hz, 1H), 2.85 (dd, J = 18.3, 6.5 Hz, 1H), 2.52 (dt, J = 14.4, 9.5 Hz, 1H), 2.47 (dd, J = 18.3, 2.4 Hz, 1H), 1.83 (m, 2H); MS *m*/*z* (relative intensity) 214 (M^+, 15%), 186 (100), 185 (75), 116 (51), 115 (54), 144 (49), 129 (32), 128 (42), 102 (25); IR (film): ν 2955, 2848, 1716, 1630, 1496, 1326, 1090, 699 cm^{-1}. Elemental anal. calcd for $C_{14}H_{14}O_2$: C, 78.50; H, 6.54. Found: C, 78.32; H, 6.40%.

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9 Synthetic compound **5**, racemic chrycorin: mp 70–71 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50 (d, J = 3 Hz, 1H), 7.40 (d, J = 5 Hz, 1H), 7.12 (dd, J = 5, 3 Hz, 1H), 4.51 (br d, J = 6.0 Hz, 1H), 4.11 (br d, J = 11 Hz, 1H), 3.79 (m, 1H), 3.46 (br d, J = 15.0 Hz, 1H), 2.87 (dd, J = 6.0, 18.6 Hz, 1H), 2.61 (dt, J = 15.0, 10 Hz, 1H), 2.48 (dd, J = 18.6, 2.7 Hz, 1H), 1.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.3, 166.4, 131.1, 130.9, 127.7, 126.8, 126.4, 75.3, 69.1, 41.6, 26.6, 26; MS *m*/*z* (relative intensity) 220 (M^+, 77), 192 (100), 191 (64), 178 (32), 150 (36), 135 (36); IR (KBr) ν 3103, 2958, 2849, 1710, 1630, 1429 cm^{-1}.

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