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Synthesis of Tonghaosu Analogues†

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Several new analogues of natural antifeedant tonghaosu were synthesized via *m*-CPBA (*m*-chloroperoxybenzoic acid) oxidation of corresponding 3-(*α*-furyl)propanols, Luche reduction of the resulting enone, epoxidation, acid-mediated spiroketalization, and radical mediated dehydration.

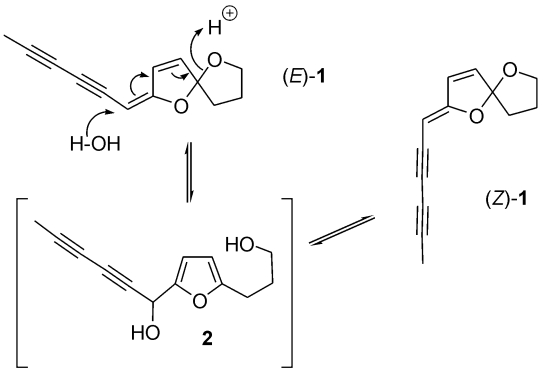
Keywords spiroketal, rearrangement, antifeedant, natural product, epoxide

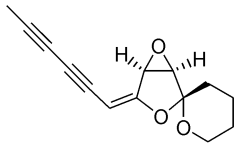
Introduction

It has been known for a long time that tonghao (*Chrysanthemum segetum* L.), a fragrant and delicious vegetable growing in south-eastern parts of China during spring and autumn, is never attacked by insect pests as frequently occurring to many other vegetables found in the same areas.[1] In search of the possible cause for this "mysterious" phenomenon we studied the constitutions of the extracts of tonghao in the late 1980's, which led to isolation of tonghaosu (**1**), a spiroketal compound that later proved to possess significant insect antifeedant activities.[2,3]

During the structural characterization of **1** it was found that the (*E*)- and (*Z*)-isomers could interchange into each other via a furan intermediate **2** (Scheme 1).[2] Using this interesting reaction as a key step we have synthesized an array of tonghaosu analogues,[4] some of which have shown insect antifeedant activities comparable to that of tonghaosu in preliminary tests. The investigations along this line have also led to discovery of a novel intramolecular Friedal-Crafts alkylation with ketal/hemiketal as the alkylating agent.[5]

Scheme 1





(–)-AL-2

From our previous studies we have noticed that the exocyclic C-C double bond in the tonghaosu structure is much more reactive than the endocyclic one. Such a feature makes it very difficult[6] to directly elaborate tonghaosu and/or its analogues into related epoxides such as (—)-AL-2,[7] another natural spiroketal with significant antifeedant and antitumoral activities. It seems that to introduce an epoxy functionality to the endocyclic double bond in the tonghaosu core, some indirect approaches must be developed.

Results and discussion

The present investigation emerged with construction of the key furan intermediates **4a**—**4e** using the previously established route[4a-f] with furfural **3** as the starting material (Scheme 2) via a four-step sequence: (1) a Perkin reaction leading to acid **4**, (2) saturation of the resultant C-C double bond by catalytic hydrogenation, (3) $LiAlH_4$ reduction of the carboxylic acid functionality into the corresponding alcohol, and (4) lithiation of the furan ring followed by treatment with a proper aromatic aldehyde. Then the synthesis took a different direction. Instead of direct treatment with an acid (leading to **8a**) as in the previous investigation, the furan ring

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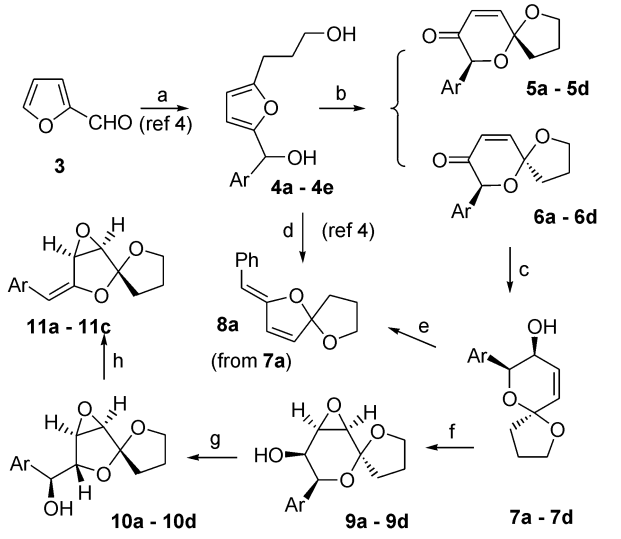
was first oxidized[4g] with *m*-CPBA. Such a strategy worked well for those substrates with the Ar group being phenyl (**4a**), *p*-chlorophenyl (**4b**), *p*-tolyl (**4c**), or *p*-anisyl (**4d**), giving the corresponding spiroketals **5a**—**5d** and **6a**—**6d** in 6%—24% and 20%—44% yields, respectively. However, when the Ar group was *p*-nitrophenyl (**4e**), the reaction simply failed, leading to a range of unidentified side-products.

Scheme 2



a: Ar = Ph; **b**: Ar = 4-Cl-C_6H_4; **c**: Ar = 4-CH_3-Ph;
d: Ar = 4-anisyl; **e**: Ar = 4-NO_2-C_6H_4

Reagents and conditions: (a) i) Malonic acid, pyridine, 90%; ii) H_2 (101.325 kPa), 10% Pd-C, EtOH, 100%; iii) $LiAlH_4$, THF, 100%; iv) *n*-BuLi, TMEDA, Ar-CHO, THF, 72% for **4a**, 77% for **4b**, 65% for **4c**, 71% for **4d**, 40% for **4e**. (b) *m*-CPBA, 10-camphorsulfonic (CSA), CH_2Cl_2; 12% and 44% for **5a** and **6a**; 6% and 20% for **5b** and **6b**; 24% and 36% for **5c** and **6c**; 16% and 26% for **5d** and **6d**, respectively. (c) $NaBH_4$, $CeCl_3$, MeOH, 0 ℃; 89%—99%. (d) H^+, ref. 4. (e) CSA, EtOAc, 36%. (f) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; 57% for **9a** (along with 40% of recovered **7a**), 57% for **9b** (along with 40% of recovered **7b**), 47% for **9c** (along with 52% of recovered **7c**), 52% for **9d** (along with 35% of recovered **7d**). (g) CSA, CH_2Cl_2; 39% for **10a** (along with 59% of recovered **9a**), 9% for **10b** (along with 91% of recovered **9b**), 23% for **10c** (along with 74% of recovered **9c**), 32% for **10d** (along with 35% of recovered **9d**). (h) *o*-NO_2-C_6H_4SeCN, *n*-Bu_3P, Pyridine, H_2O_2, THF; 94% for **11a**, 25% for **11b**, 94% for **11c**.

Further elaborations started with the major isomers **6a**—**6d**. As these enones tended to undergo Bayer-Villiger reaction under the epoxidation conditions, the ketone carbonyl group was first reduced under the Luche[8] conditions ($CeCl_3$/$NaBH_4$/MeOH). The resulting **7a**, which could be readily converted into **8a** on treatment with an acid, was transformed to the corresponding epoxide **9a** with excellent stereocontrol. Subsequent exposure of **9a** to CSA (10-camphorsulfonic acid) in CH_2Cl_2 did not give any anticipated **11a** as expected according to our previous results. Instead, compound **10a** was obtained as the only isolatable product. It seems that with an epoxy rather than a C-C double bond in the five-membered ring elimination of water becomes much more difficult. Indeed, we tried a number of conventional dehydration protocols without success. Acid catalyzed dehydration attempts always resulted in a rather complicated product mixture, presumably because of the presence of an epoxy functionality. Base-mediated elimination of the mesylate, tosylate or triflate of **10a** did not lead to any detectable products. Close inspection of its molecular model reveals that in **10a** the dihedral angel between the leaving group and the adjacent proton is almost 90 degrees, which is too far away from the optimal conformation required by typical E2 reactions. We reasoned that a radical mediated reaction might be a solution to such a problem.

After careful study of the literature we noticed the method[9] (*o*-NO_2-C_6H_4SeCN/*n*-Bu_3P/H_2O_2) developed by Sharpless, which appeared to be suitable to our system. To our delight, under such conditions, the desired **11a** was indeed formed in good to excellent yields. Similar treatments of **6b**—**6c** eventually gave the corresponding **11b**—**11c**.[10] However, compound **10d** failed to undergo the same transformation under the identical conditions.

In conclusion, we have developed a feasible approach to the epoxidation of endocyclic C-C double bond in the tonghaosu core in analogues carrying an aromatic substituent. Extension of this methodology to other analogues with *e.g.* an acetylenic substituent is currently under investigation. Bioactivities of these compounds are being tested and the results will be disclosed in due time.

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10 Data for **11a** (colorless oil): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.35—7.21 (m, 5H), 6.24 (s, 1H), 4.26 (d, J=2.9 Hz, 1H), 4.20—4.13 (m, 1H), 4.05—3.98 (m, 1H), 3.88 (d, J=3.0 Hz, 1H), 2.36—2.02 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.7, 135.2, 128.5, 128.1, 126.4, 112.2, 107.4, 69.6, 59.6, 52.9, 32.1, 24.6; FT-IR (film) v: 3059, 2924, 1677, 1389, 1230, 1137, 1086, 1018, 919, 701 cm^{-1}; EI-MS m/z (%): 230 (M^+, 34), 160 (38), 118 (39), 116 (42), 115 (78), 112 (100), 90 (31), 71 (49); EI-HRMS calcd for $C_{14}H_{14}O_3$ (M^+) 230.0943, found 230.0947. Data for **11b** (colorless oil): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.31—7.24 (m, 4H), 6.17 (s, 1H), 4.19—4.12 (m, 2H), 4.05—3.88 (m, 2H), 2.38—2.00 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.1, 133.7, 132.1, 129.2, 128.7, 112.3, 106.2, 69.7, 59.5, 52.8, 32.1, 24.5; FT-IR (film) v: 3052, 2957, 2918, 2849, 1676, 1491, 1089, 1014, 889, 738 cm^{-1}; EI-MS m/z (%): 264 (M^+, 5), 150 (35), 149 (43), 115 (100), 112 (51), 89 (37), 69 (54), 44 (49), 42 (48); EI-HRMS calcd for $C_{14}H_{13}O_3Cl$ (M^+) 264.0553, found 264.0560. Data for **11c** (colorless oil): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7. 24 (d, J=8.0 Hz, 2H), 7.14 (d, J=7.9 Hz, 2H), 6.21 (s, 1H), 4.25 (d, J=2.7 Hz, 1H), 4.20—4.12 (m, 1H), 4.05—3.97 (m, 1H), 3.87 (d, J=2.5 Hz, 1H), 2.34 (s, 3H), 2.31—2.01 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.1, 136.2, 132.2, 129.2, 128.0, 112.1, 107.4, 69.6, 59.6, 53.0, 32.2, 24.6, 21.1; FT-IR (film) v: 2959, 2922, 1676, 1514, 1086, 1018, 889, 809 cm^{-1}; EI-MS m/z (%): 244 (M^+, 11), 158 (59), 130 (62), 129 (84), 115 (89), 69 (74), 44 (100), 42 (67), 41 (73); EI-HRMS calcd for $C_{15}H_{16}O_3$ (M^+) 244.1099, found 244.1104.

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