Chemistry of Tonghaosu Analogs: Novel Acid-Catalyzed Nucleophilic Addition to the Dienyl Acetal System

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The acid-catalyzed nucleophilic addition reaction of spiroketal enol ether-containing tonghaosu analogs **2** was explored. Soft nucleophiles, such as mercaptans, alcohols and heteroaromatic compounds, gave rise exclusively to 1,6-adducts, while harder nucleophiles, such as Grignard reagents, afforded mixtures of 1,2- and 1,6-adducts. The reaction with cysteine and glutathione, which might be related to the mode of action of insect antifeeding, also took place smoothly. Friedel–Crafts dimerization reactions of **10** and **11** gave the dimers **12** and **13** respectively. By comparison of ^{1}H NMR spectroscopic data, we also suggest that the structure of compound **9** reported in the literature for a natural product is revised to that of compound **13**.

Introduction

Tonghaosu, 2-(2,4-hexadiynylidene)-1,6-dioxaspiro[4,4]-non-3-ene (**1**, Figure 1), is an antifeedant component of the vegetable tonghao (*Chrysanthemum sgetum* L. or *C. Coronarium* L.), and is also found in other plants of the family *Athemdeae*.[1,2] Tonghaosu contains a unique spiroketal enol ether moiety, and was first synthesized in the early 1960s by the Bohlmann group in quite low overall yield.[3] Recently, a general and concise synthetic methodology for tonghaosu and its spiroketal enol ether-containing analogs was developed in our laboratory,[4–6] and now dozens of tonghaosu analogs with various unsaturated groups, including olefins, acetylenes, aromatic rings or aromatic heterocycles, can be easily prepared on a multigram scale. The structures of tonghaosu analogs look very simple, and yet very interesting. Their common structural core, the enol ether spiroketal moiety, can be seen as a special case of the dienyl acetal system. Although the nucleophilic substitution reaction of acetals derived from aldehydes or α,β-unsaturated aldehydes has been well studied and has become a powerful method for C–C bond formation,[7,8] to the best of our knowledge, there is no related report for the dienyl acetal. Herein, we would like to describe the acid-mediated reactions of tonghaosu analogs with a diverse array of nucleophiles.

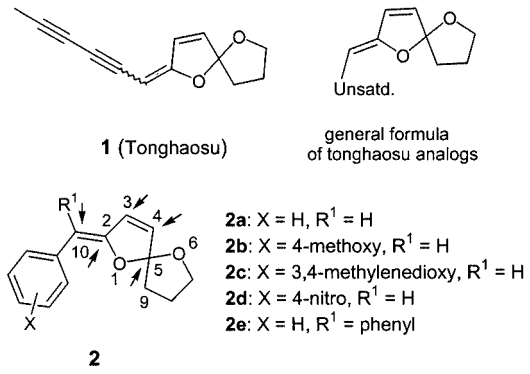

Figure 1. Tonghaosu and analogs

It has been shown that nucleophiles react with α,β-unsaturated acetals to afford 1,2-adducts or 1,4-adducts depending on the nature of the nucleophiles and the reaction conditions.[9] In our dienyl acetal system, the situation seemed to be more complicated. In order to gain a better understanding of the chemical properties of this special dienyl acetal system in tonghaosu analogs, we calculated the net charges of the five carbon atoms indicated and two oxygen atoms of compound **2a**, using a semi-empirical method (AM1), the results of which are listed in Table 1. Clearly, C-5 is the most positive carbon atom, and O-6 has a higher electron density than O-1. Therefore, we anticipated that a Brønsted or Lewis acid would interact preferentially with

Table 1. The net charges of spiroketal enol ether segment of compound **2a**

O-1	C-2	C-3	C-4
−0.224451	0.049685	−0.127253	−0.172121
C-5	O-6	C-10	
0.202139	−0.257257	−0.149155	

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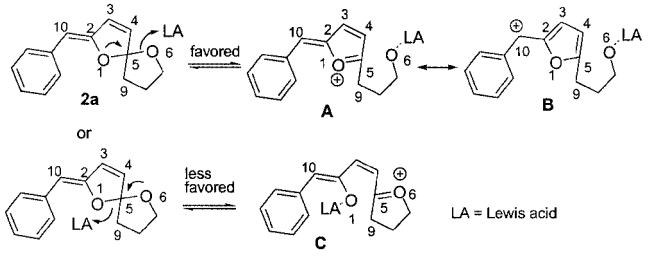


Figure 2. Interaction of a tonghaosu analog with a Lewis acid

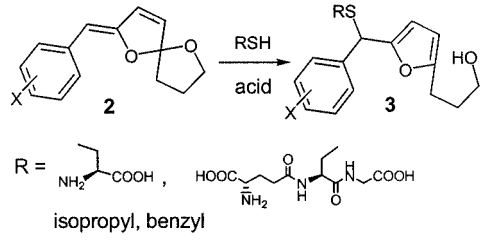
atom O-6 to furnish an intermediate such as **A** or **B** (Figure 2). In turn, C-5 and C-10 would be probable electrophilic centers, due to the driving force of forming an aromatic furan ring or retaining a conjugated system, whereas an attack at C-3 may thus be seen to be less likely. The following sections describe our exploration of the regioselectivity of the C−O cleavage and regioselective addition of nucleophiles, ranging from heteroatom nucleophiles to Grignard reagents and electron-rich aromatic compounds, to this dienyl acetal system.

Results and Discussion

1. Reaction with Mercaptans

Our initial efforts were directed towards the use of mercaptans as nucleophiles. Given that the mercapto group exists widely in biological systems in the form of cysteine, peptides and proteins, the reactions of tonghaosu analogs with mercaptans are interesting not only from a chemical point of view, but also as a plausible mechanism of biological action of these compounds. In view of the importance of Fe^{II} in biological systems, the mild Lewis acid $FeSO_4$ was employed as the catalyst. Thus, cysteine reacted with **2b** at C-10 to give **3a** as a 1:1 mixture of diastereomers in good yield (85%), and no product resulting from attack at C-5 was observed. Similarly, glutathione, 2-propanethiol and benzylthiol all served well as nucleophiles to give the corresponding sulfides **3** (Table 2). A Brønsted acid, as well as other Lewis acids such as Zn^{2+} and Mg^{2+}, also promoted this reaction. For instance, magnesium ion, the central metal ion of chlorophyll, in the form of magnesium chloride, catalyzed the reaction of **2b** and cysteine to give the adduct **3a** in moderate yield (45%).

Table 2. Reaction of tonghaosu analogs with mercaptans

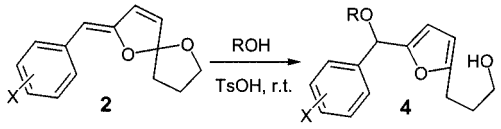


Entry	Tonghaosu analog	Mercaptan	Product	Yield (%)
1	**2b**	Cysteine	**3a**	85
2	**2b**	Glutathione	**3b**	50
3	**2a**	Propane-2-thiol	**3c**	64
4	**2a**	Benzylthiol	**3d**	77
5	**2c**	Propane-2-thiol	**3e**	82
6	**2c**	Benzylthiol	**3f**	80

2. Reaction with Alcohols

In the presence of catalytic amounts of acids, alcohols also reacted with tonghaosu analogs at C-10 to give furan derivatives **4**. The yields ranged from 67 to 91% (Table 3). However, in contrast to the generality of the mercaptans' addition reaction, the range of alcohols was restricted to methanol and ethanol. Furthermore, ethanol reacted with substantially lower yields than methanol (Entry 2 vs. 3 and Entry 5 vs. 6), and higher homologs were not effective at all. It should be pointed out that an excess of the alcohol was necessary for the reaction to take place. In practice, the alcohol was used as the solvent and the reaction proceeded to completion.

Table 3. Reaction of tonghaosu analogs with alcohols

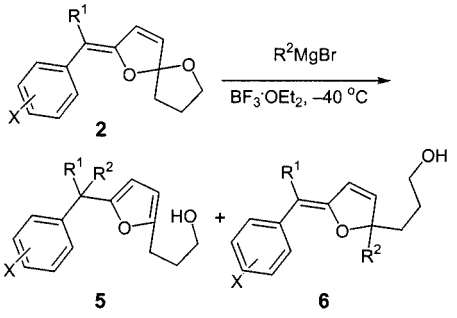


Entry	Tonghaosu analog	ROH	Product	Yield (%)
1	**2a**	MeOH	**4a**	91
2	**2c**	MeOH	**4b**	88
3	**2c**	EtOH	**4c**	67
4	**2d**	MeOH	**4d**	76
5	**2b**	MeOH	**4e**	82
6	**2b**	EtOH	**4f**	70

3. Alkylation and Reduction

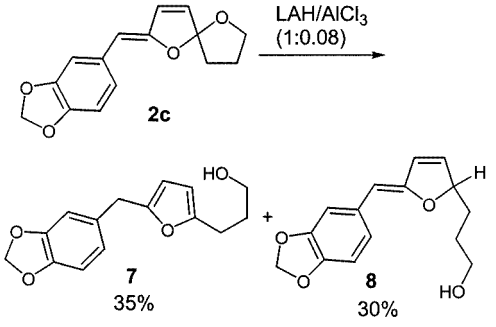
Grignard reagents, the readily available and synthetically useful nucleophiles, were also examined. Here, both the 1,6-adduct **5** (resulting from attack at C-10 of **2**) and the 1,2-adduct **6** (from attack at C-5) could be obtained, depending on the substrate and the nucleophile. The results are summarized in Table 4. When substrate **2** had no substituent at C-10 (R^1 = H), ethylmagnesium bromide gave a mixture of **5** and **6** in ratio of ca. 1.3:1 (Entries 1, 3 and 4), while phenylmagnesium bromide afforded the 1,6-adduct **5** as the only product (Entry 2). This observed regioselectivity was similar to that found in reaction of α,β-unsaturated acetals with Grignard reagents.[10] However, when there was a substituent (R^1 = Ph) at C-10 of **2**, both ethylmagnesium bromide and phenylmagnesium bromide would attack only C5 to give the 1,2-adduct **6** as the exclusive product. Compound **6** contains a 5-ylidene-2,2-dialkyl-2,5-dihydrofuran unit, which otherwise would not be easily accessible. It should be noted that $BF_3{\cdot}OEt_2$ was necessary for the reaction to take place.

Table 4. Reaction of tonghaosu analogs with Grignard reagents



Entry	Tonghaosu analog	R^2MgBr	Product (%) 5	6
1	**2a**	EtMgBr	**5a** (38)	**6a** (27)
2	**2a**	PhMgBr	**5b** (67)	**6b** (0)
3	**2b**	EtMgBr	**5c** (36)	**6c** (30)
4	**2c**	EtMgBr	**5d** (39)	**6d** (31)
5	**2e**	EtMgBr	**5e** (0)	**6e** (67)
6	**2e**	PhMgBr	**5f** (0)	**6f** (61)

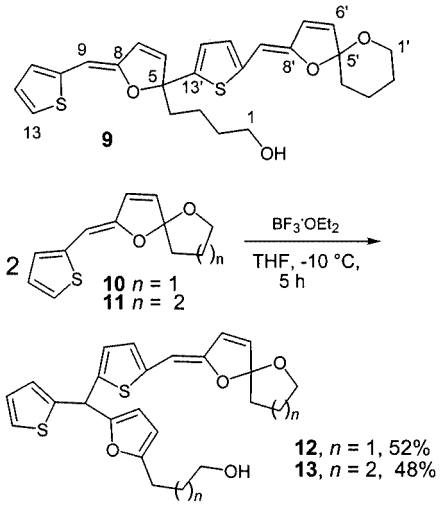
The reduction of ketals is a useful approach for the stereoselective synthesis of cyclic ethers, and diisobutylaluminum hydride or a combination of a Lewis acid and a reducing agent is often employed for this purpose.[11] In the presence of catalytic amounts of $AlCl_3$, compound **2c** was reduced with lithium aluminum hydride ($LiAlH_4$) to yield a 1:1 mixture of furan **7** and dihydrofuran **8** (Scheme 1).



Scheme 1. Reduction of **2c** with $LiAlH_4/AlCl_3$ as reducing agent

4. Friedel–Crafts Reaction

Our previous reports demonstrated that the ketals derived from partially hydrogenated tonghaosu analogs and hemiketals could serve as electrophiles in intramolecular Friedel–Crafts reactions, to produce benzene-fused oxabicyclic ring systems.[12,13] We noticed an interesting compound **9** (Scheme 2) which, together with thiophene-containing tonghaosu analog **11**, was isolated by Hofer et al. from *Artemisia ludoviciana*.[14] It was reasonable to believe that compound **9** might be derived from compound **11** via an intermolecular Friedel–Crafts reaction, and because compound **9** was not fully characterized due to its instability in [D]chloroform, we tried to synthesize this compound and identify its structure.



Scheme 2. Friedel–Crafts dimerization reactions of **10** and **11**

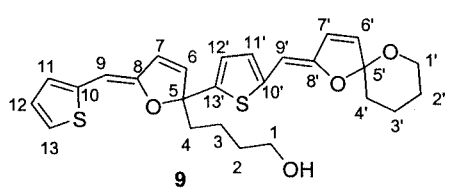
On treatment with $BF_3{\cdot}Et_2O$ in THF at −10 °C, the readily available **11**[4] afforded a product whose ^1H NMR spectrum was coincident with that of compound **9** (Table 5), and it also partially decomposed in $CDCl_3$ during the measurement of a ^{13}C NMR spectrum, as observed by Hofer. However, with [D_6]acetone as the solvent, a clear and beautiful ^{13}C NMR spectrum was obtained. H-H COSY and DEPT experiments were also performed. The ^{13}C NMR and DEPT spectra indicated that there were twenty-six carbon atoms, among which, seven were quaternary carbon atoms whose lowest chemical shift was δ = 114.1 ppm. However, the quaternary carbon C-5 of compound **9** should have a much lower chemical shift than δ = 114.1 ppm. There was also a CH carbon with chemical shift at δ = 42.4 ppm, which could not be assigned to any carbon of compound **9**. In contrast, structure **13** (Scheme 2) agreed very well with all the spectroscopic data. For example, the methine signal at δ = 42.4 ppm could be assigned to C-9 of compound **13** (see Table 5 for the numbering of compound **13**). Thus, we concluded that the compound we had was **13**; it is possible that the originally proposed structure **9** for the natural product should be also revised to structure **13**, and our work may also give some hints about the biosynthesis of this natural product.

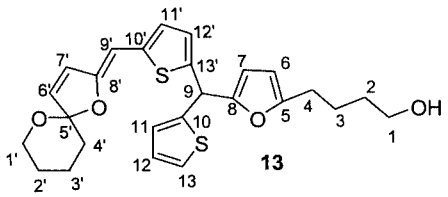
Similarly, in the presence of $BF_3{\cdot}Et_2O$, compound **10** produced dimer **12** in 52% yield. In theory, trimerization or higher oligomerization may take place for substrates **10** and **11**, and this may explain the moderate yields of the dimers in these cases. Although other tonghaosu analogs did not undergo effective dimerization under similar conditions, they proved to be good alkylating agents for Friedel–Crafts reactions of electron-rich aromatic compounds, and C-10 was the only effective electrophilic center. An example is shown in Scheme 3; **2c** reacted with indole to give the 1,6-adduct **14** in 85% yield.

Conclusion

In conclusion, we have explored the chemistry of tonghaosu analogs as electrophiles. Soft nucleophiles, such

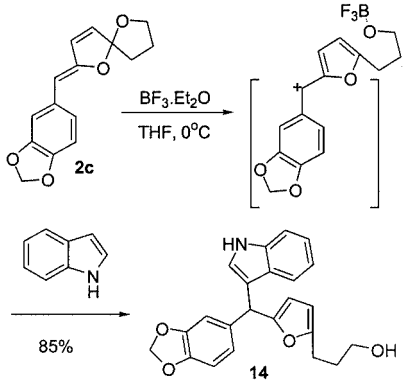
Table 5. ^{1}H NMR spectroscopic data of natural product **9** (the structure proposed in ref.[14]) and synthetic compound **13**





No.	^{1}H NMR spectroscopic data, **9** (250 MHz, $CDCl_3$) Moiety 1 [a]	Moiety 2 [b]	**13** (300 MHz, $CDCl_3$) Moiety 1 [a]	Moiety 2 [b]
1	4.15 (ddd, ax, J = 12, 12, 4 Hz), 3.85 (dm, eq)	3.64 (t, J = 6.5 Hz)	4.16, (m, ax), 3.84 (br. d, J = 11.3 Hz, eq)	3.61 (t, J = 6.3 Hz)
2[c]	2.05 (m, 1 H), 1.80 (m, 1 H)	1.60−1.70 (m)	2.08 (m, 1 H), 1.57−1.82 (m, 1 H)	1.57−1.82 (m)
3[c]	1.80 (m)	1.60−1.70 (m)	1.57−1.82 (m)	1.57−1.82 (m)
4[c]	1.70 (m)	2.64 (t, J = 7.5 Hz)	1.57−1.82 (m)	2.62 (t, J = 7.4 Hz)
6	6.08 (d, J = 6 Hz)	5.94 (d, J = 3.5 Hz)	6.08 (d, J = 5.2 Hz)	5.94 (d, J = 2.8 Hz)
7	6.31 (d, J = 6 Hz)	6.05 (d, J = 3.5 Hz)	6.30 (d, J = 5.8 Hz)	6.07 (br. s)
9	5.82 (s)	5.71 (s)	5.83 (s)	5.71 (s)
11	6.92 (m)	6.92 (m)	6.95 (m)	6.95 (m)
12	6.77 (d, J = 3.5 Hz)	6.92 (m)	6.78 (d, J = 3.3 Hz)	6.95 (m)
13	−	7.21 (d, J = 5 Hz)	−	7.21 (d, J = 3.9 Hz)

[a] Spiroketal-containing segment. [b] Open chain-containing segment. [c] Not exactly assigned.



Scheme 3. Friedel−Crafts reaction of **2c** with indole

as mecaptans, alcohols, thiophene or indole reacted with tonghaosu analogs to afford the 1,6-adducts as the only product, while harder nucleophiles, such as Grignard reagents and lithium aluminum hydride, would lead to a mixture (ca. 1:1) of 1,2- and 1,6-adducts, which suggests it could be possible to improve the regioselectivity of the 1,2-addition by tuning the nature of the nucleophile and the reaction conditions. In addition, the reaction with mercaptans might shed some light on the insect-antifeeding mechanism of tonghaosu and its analogs. Our work has also demonstrated the synthesis of structurally diverse tonghaosu analogs, which will no doubt benefit the search for new lead-compounds for medicine and agrochemicals. The bioassay of these new derivatives is in progress.

Experimental Section

General Remarks: IR spectra were recorded with Perkin−Elmer 983 or Shimadzu IR-440 spectrometers. ^{1}H and ^{13}C NMR spectra were recorded with an AMX-300, DPX-300, Gemini-2000 or INOVA-600 spectrometer with TMS as the internal standard. Mass spectra were taken with a Mariner (PE, for ESI), HP5973N or HP5989A instrument. HRMS (EI or ESI) spectra were obtained with a Kratos CONCEPT 1H or Bruker APEXIII 7.0 TESLA mass spectrometer. Optical rotations were measured with a Perkin−Elmer 241 MC polarimeter. Elemental analyses were carried out at the Microanalytic Laboratory of Shanghai Institute of Organic Chemistry. Flash column chromatography was performed on silica gel H (10−40 μm) with a petroleum ether/ethyl acetate or ethyl acetate/ethanol system as eluent.

Reaction of 2b with L-Cysteine: $NaHCO_3$ (0.26 mmol), compound **2b** (35 mg, 0.14 mmol) and $FeSO_4$ (cat.) were added to a solution of L-cysteine hydrochloride (45 mg, 0.26 mmol) in acetonitrile/water (50 mL, 1:1, v/v). The pH of the resultant mixture was 6.5−7.5. The mixture was stirred at room temperature under nitrogen for 5 h, then the solvents were removed under reduced pressure (rotary evaporator). The residue was further dried by lyophilization, and purified by chromatography to give **3a** (37 mg, 85%) as a white solid. $[\alpha]_D^{20}$ = −23.2 (c = 0.4, CH_3CN/H_2O, 1:1). IR (KBr): $\tilde{\nu}$ = 3419 cm^{-1}, 1577, 1512, 1415, 1251. ^{1}H NMR (600 MHz, CD_3COCD_3): δ = 2.05 (q, J = 6.6 Hz, 2 H), 2.88 (dd, J = 14.4, 6.6 Hz, 2 H), 3.12 (dd, J = 14.4, 8.5 Hz, 1/2 H), 3.19 (dd, J = 14.4, 8.5 Hz, 1/2 H), 3.28 (m, 1/2 H), 3.30 (m, 1/2 H), 3.81 (td, J = 6.6, 2.4 Hz, 2 H), 3.93 (dd, J = 8.6, 4.0 Hz, 1/2 H), 4.005 (m, 1/2H), 4.01 (s, 3 H), 5.55 (s , 1/2H), 5.56 (s , 1/2H), 6.27 (s, 1 H), 6.49 (d, J = 2.4 Hz, 1/2H), 6.51 (d, J = 2.4 Hz, 1/2H), 7.15 (d, J = 8.4 Hz, 2 H), 7.675 (d, J = 8.4 Hz, 1 H), 7.69 (d, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 24.3, 30.62, 32.97, 46.09,

46.47, 54.08, 55.47, 61.02, 106.25, 106.32, 109.56, 109.62, 114.40, 130.00, 130.03, 131.49, 131.60, 151.37, 151.53, 156.52, 159.19, 171.78 ppm. ESI MS: *m/z* = 366 [M + 1], 388 [M + Na], 732 [2(M +1)]. HRMS calcd. for $C_{18}H_{23}NO_5SNa$ [M + Na]: 388.1189; found 388.1180.

Reaction of 2b with L-Glutathione: Compound **2b** (35 mg, 0.143 mmol), $FeSO_4$ (a 5 mol % solution) and $NaHCO_3$ were added to a solution of L-glutathione (100 mg, 0.326 mmol) in in acetonitrile/water (50 mL, 1:1, v/v). The pH of the resultant mixture was 6.5−7.5. The mixture was stirred at room temperature under nitrogen for 12 h. Then the acetonitrile was removed under reduced pressure (rotary evaporator). The residue was lyophilized, and then purified by chromatography to afford **3b** as a solid (26.4 mg, 50%). $[\alpha]_D^{20} = -7.8$ (*c* = 0.4, CH_3CN/H_2O, 1:1) IR (KBr): $\tilde{\nu}$ = 3424 cm^{-1}, 1580, 1510, 1412, 1250. ^1H NMR (600 MHz, CD_3COCD_3): δ = 2.05 (q, *J* = 6.6 Hz, 2 H), 2.39 (m, 2 H), 2.77 (m, 2 H), 2.87 (t, *J* = 6.6 Hz, 2 H), 2.99 (dd, *J* = 14.4, 9.0 Hz, 1/2H), 3.03 (dd, *J* = 14.4, 9.0 Hz, 1/2H), 3.145 (dd, *J* = 14.4, 5.4 Hz, 1/2H), 3.188 (dd, *J* = 14.4, 5.4 Hz, 1/2H), 3.82 (t, *J* = 6.6 Hz, 2 H), 4.02 (s, 3 H), 4.05 (m, 1 H), 4.14 (m, 2 H), 4.65−4.94 (m, 1 H), 5.473 (s, 1/2H), 5.477 (s ,1/2H), 6.27 (s, 1 H), 6.467 (d, *J* = 3.0 Hz, 1/2H), 6.485 (d, *J* = 3.0 Hz, 1/2H), 7.155 (d, *J* = 3.0 Hz, 1 H), 7.17 (d, *J* = 3.0 Hz, 1 H), 7.64 (d, *J* = 9.0 Hz, 1 H), 7.655 (d, *J* = 9.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, CD_3COCD_3): δ = 24.36, 26.87, 30.30, 30.66, 32.14, 33.55, 33.64, 46.34, 46.63, 53.29, 53.58, 55.48, 61.10, 106.21, 109.20, 109.34, 114.38, 129.90, 131.69, 151.74, 151.80, 156.40, 159.11, 172.25, 174.82 ppm. ESI MS: *m/z* = 552 [M + 1], 1104 [2(M +1)], 1656 [3(M +1)]. HRMS calcd. for $C_{25}H_{34}N_3O_9S$ (MH): 552.2010; found 552.1987.

Typical Procedure for Reaction with Thiols 3c: *p*TsOH (8 mg, 5%mol) or $ZnCl_2$ (10 mg) was added to a mixture of 2-benzylidene-1,6-dioxaspiro[4,4]none-3-ene (**2a**) (0.214 g, 1 mmol) and 2-propanethiol (76 mg) in dry THF (20 mL). The reaction mixture was stirred at room temperature for 4 h until the starting material was consumed (monitoring by TLC). The reaction was quenched by adding saturated aqueous $NaHCO_3$ until pH = 8. The mixture was extracted with diethyl ether, and the combined organic layers were washed with brine and dried with Na_2SO_4. Removal of the solvents yielded a crude product, which was purified by chromatography to afford furan derivative **3c** as an oil (64%). IR (film): $\tilde{\nu}$ = 3415 cm^{-1}, 2926, 1600, 1415, 1053, 787, 698. ^1H NMR (300 MHz, CD_3COCD_3): δ = 7.50−7.25 (m, 5 H), 6.15 (d, *J* = 3.0 Hz, 1 H), 5.97 (d, *J* = 3.0 Hz, 1 H), 5.24 (s, 1 H), 3.56 (t, *J* = 6.3 Hz, 2 H), 2.73 (m, 1 H), 2.66 (t, 2 H, *J* = 7.7 Hz), 1.80 (m, 2 H), 1.21 (d, *J* = 6.7 Hz, 6 H) ppm. ESI MS: 313 [M + Na], 314 (M + Na + 1). HRMS calcd. for $C_{17}H_{22}O_2SNa$: 313.1238; found 313.1232.

Compounds **3d**−**f** were prepared according to the typical procedure for the synthesis **3c**.

3d: 77% yield; oil. IR (film): $\tilde{\nu}$ = 3404 cm^{-1}, 3028, 2927, 1602, 1492, 1452, 1014, 967, 797, 699. ^1H NMR (300 MHz CD_3COCD_3): δ = 7.46−7.23 (m, 10 H), 6.20 (d, *J* = 3.1 Hz, 1 H), 6.01 (d, *J* = 3.1 Hz, 1 H), 5.04 (s, 1 H), 3.68 (dd, *J* = 13.2, *J* = 19.0 Hz, 2 H), 3.58 (t, *J* = 6.3 Hz, 2 H), 2.67 (t, *J* = 7.6 Hz, 2 H), 1.83 (m, 2 H) ppm. ESI MS: *m/z* = 361 [M + Na], 362 [M + Na + 1]. HRMS calcd. for $C_{21}H_{22}O_2SNa$: 361.1238; found 361.1232.

3e: 82% yield; oil. IR (film): $\tilde{\nu}$ = 3393 cm^{-1}, 2950, 1609, 1503, 1489, 1245, 1040, 927, 786. ^1H NMR (300 MHz, CD_3COCD_3): δ = 7.03 (d, *J* = 2.8 Hz, 1 H), 6.97 (dd, *J* = 8.2, 1.8 Hz, 1 H), 6.80 (d, *J* = 7.9 Hz, 1 H), 6.19 (d, *J* = 3.2 Hz, 1 H), 6.00 (d, *J* = 3.5 Hz, 1 H), 5.99 (s, 2 H), 5.23 (s, 1 H), 3.61 (t, *J* = 7.0 Hz, 2 H), 2.73 (m, 1 H), 2.69 (t, *J* = 7.0 Hz, 2 H), 1.84 (m, 2 H), 1.22 (d, *J* = 7.1 Hz, 6 H) ppm. ESI MS: *m/z* = 358 [M + Na + 1], 359. HRMS calcd. for $C_{18}H_{22}O_4SNa$: 357.1136; found 357.1130.

3f: 80% yield; oil. IR (film): $\tilde{\nu}$ = 3370 cm^{-1}, 2891, 1603, 1502, 1489, 1246, 1040, 928, 785. ^1H NMR (300 MHz, CD_3COCD_3): δ = 7.34−7.22 (m, 5 H), 6.99 (s, 1 H), 6.88 (dd, *J* = 8.1, 1.8 Hz, 2 H), 6.20 (d, *J* = 3.1 Hz, 1 H), 6.02 (d, *J* = 3.1 Hz, 1 H), 5.98 (s, 2 H), 5.0 (s, 1 H), 3.72 (m, 2 H), 3.59 (t, *J* = 3.6 Hz, 2 H) 2.68 (t, *J* = 7.2 Hz, 2 H), 1.83 (m, 2 H) ppm. ESI MS: 405 [M + Na], 406 [M + Na + 1]. HRMS calcd. for $C_{22}H_{22}O_4SNa$: 405.1136; found 405.1130.

Typical Procedure for Reaction with Alcohols: 2-Benzylidene-1,6-dioxaspiro[4,4]none-3-ene (**2a**) (0.214 g, 1 mmol) was dissolved in 20 mL of absolute methanol, then *p*TsOH (8 mg, 5%mol) or $ZnCl_2$ (10 mg, 8%mol) was added. The reaction mixture was stirred at room temperature for 8 h until the starting material disappeared (checked by TLC), then quenched by adding saturated aqueous $NaHCO_3$ until pH = 8. The mixture was extracted with diethyl ether. The combined organic layers were washed with brine and dried with Na_2SO_4. Removal of the solvent yielded a crude product, which was purified by chromatography to afford the furan derivative **4a** in 91% yield. IR (film): $\tilde{\nu}$ = 3402 cm^{-1}, 2938, 2824, 1558, 1453, 1189, 1087, 947, 788, 701. ^1H NMR (300 MHz, CD_3COCD_3): δ = 7.37 (m, 5 H), 5.97 (d, *J* = 3.1 Hz, 1 H), 5.92 (d, *J* = 3.1 Hz, 1 H), 5.22 (s, 1 H), 3.61 (t, *J* = 6.4 Hz, 2 H), 3.37 (s, 3 H), 2.69 (t, *J* = 7.5 Hz, 2 H), 1.87 (m, 2 H) ppm. EI MS: *m/z* (%) = 246 (8) [M^+] 215 (100), 197 (53), 77 (15), 183 (14), 141 (14), 170 (13), 169 (12), 115 (11). $C_{15}H_{18}O_3$ (246.3): calcd. C 73.15, H 7.37; found C 72.91, H 7.44.

Compounds **4b**−**4f** were prepared according to the typical procedure described above for the synthesis **4a**.

4b: 88% yield; oil. IR (film): $\tilde{\nu}$ = 3403 cm^{-1}, 2937, 1504, 1490, 1444, 1245, 1040, 937, 786. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.94 (d, *J* = 1.5 Hz, 1 H), 6.86 (dd, *J* = 8.0, 1.6 Hz, 1 H), 6.78 (d, *J* = 7.9 Hz, 1 H), 5.99 (d, *J* = 3.2 Hz, 1 H), 5.95 (s, 2 H), 5.92 (d, *J* = 3.0 Hz, 1 H), 5.12 (s, 1 H), 3.64 (t, *J* = 4.4 Hz, 2 H), 3.34 (s, 3 H), 2.69 (t, *J* = 7.6 Hz, 2 H), 1.95 (s, 1 H), 1.89 (m, 2 H) ppm. MS: *m/z* (%) = 290 (40) [M^+], 259 (100), 241 (42), 260 (28), 214 (16), 120 (9), 149 (9), 242 (8). $C_{16}H_{18}O_5$ (290.3): calcd. C 66.19, H 6.25; found C 66.07, H 6.76.

4c: 67% yield; oil. IR (film): $\tilde{\nu}$ = 3404 cm^{-1}, 2975, 2880, 1504, 1490, 1444, 1245, 1040, 929, 784. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.94 (d, *J* = 1.4 Hz, 1 H), 6.84(dd, *J* = 1.4, *J* = 7.8 Hz, 1 H), 6.75 (d, *J* = 8.0 Hz, 1 H), 5.97 (d, *J* = 3.5 Hz, 1 H), 5.92 (s, 2 H), 5.89 (d, *J* = 3.2 Hz, 1 H), 5.22 (s, 1 H), 3.61 (t, *J* = 6.3 Hz, 2 H), 3.49 (m, 2 H), 2.67 (t, *J* = 7.3 Hz, 2 H), 2.27 (s, 1 H), 1.84 (m, 2 H), 1.22 (t, *J* = 7.1 Hz, 3 H) ppm. MS: *m/z* (%) = 304 (13) [M^+], 259 (100), 227 (45), 241 (34), 228 (19), 115 (17), 230 (14), 135 (14), 77 (14). $C_{17}H_{20}O_5$ (304.3): calcd. C 67.09, H 6.63; found C 66.98, H 6.81.

4d: 76% yield; oil. IR (film): $\tilde{\nu}$ = 3392 cm^{-1}, 2937, 1522, 1349, 1191, 1086, 1015, 949, 788, 737. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.8 Hz, 2 H), 7.59 (d, *J* = 8.5 Hz, 2 H), 6.09 (d, *J* = 3.0 Hz, 1 H), 5.96 (d, *J* = 3.0 Hz, 1 H), 5.31 (s, 1 H), 3.64 (t, *J* = 6.3 Hz, 2 H), 3.40 (s, 3 H), 2.69 (t, *J* = 7.5 Hz, 2 H), 1.84 (m, 2 H) ppm. MS: *m/z* (%) = 291 (21) [M^+], 242 (100), 260 (86), 228 (56), 259 (54), 196 (39), 291 (20), 169 (17), 243 (17). $C_{15}H_{17}NO_5$ (291.3): calcd. C 61.86, H 5.84, N 4.81; found C 61.70, H 6.08, N 4.46.

4e: 82% yield. IR (film): $\tilde{\nu}$ = 3415 cm^{-1}, 2937, 1612, 1513, 1249, 1174, 1081, 1035, 948, 790. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33

(dd, J = 8.8, 1.9 Hz, 2 H), 6.89 (dd, J = 6.8, 2.1 Hz, 2 H), 5.94 (d, J = 2.9 Hz, 1 H) 5.91 (d, J = 2.9 Hz, 1 H) 5.58 (s, 1 H), 3.80 (s, 3 H), 3.64 (t, J = 6.4 Hz, 2 H), 3.33 (s, 3 H), 2.70 (t, J = 7.9 Hz, 2 H), 1.89 (m, 2 H) ppm. MS: m/z (%) = 276 (11) [M^+], 245 (100), 43 (62), 83 (58), 85 (47), 41 (37), 57 (26), 55 (25). $C_{16}H_{20}O_4$ (276.3): calcd. C 69.54, H 7.30; found C 69.83, H 6.90.

4f: 70% yield; oil. IR (film): $\tilde{\nu}$ = 3397 cm^{-1}, 2971, 2882, 1517, 1482, 1443, 1245, 1040, 931, 789. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33 (dd, J = 6.3, 1.5 Hz, 2 H), 6.88 (dd, J = 6.7, 2.1 Hz, 2 H), 5.93 (d, J = 3.3 Hz, 1 H), 5.89 (d, J = 2.9 Hz, 1 H), 5.27 (s, 1 H), 3.78 (s, 3 H), 3.60 (t, J = 6.6 Hz, 2 H), 3.50 (m, 2 H), 2.67 (t, J = 7.4 Hz, 2 H), 2.36 (s, 1 H), 1.83 (m, 2 H), 1.22 (t, J = 7.1 Hz, 2 H) ppm. MS: m/z (%) = 290 (5) [M^+], 245 (100), 213 (24), 227 (22), 246 (18), 214 (9), 216 (8), 135 (7), 185 (7). $C_{17}H_{22}O_4$ (290.4): calcd. C 70.32, H 7.64; found C 70.17, H 7.58.

Typical Procedure for Reaction with Grignard Reagents: C_2H_5MgBr (2 mL, 1 M) in diethyl ether was added to a stirred solution of tonghaosu analog **2a** (428 mg, 2 mmol) in 15 mL of dry THF at −78 °C. Then, $BF_3{\cdot}Et_2O$ (50 μL) was added and the reaction mixture was stirred at the same temperature for 8 h. After this time, the reaction was quenched with 3 mL of saturated aqueous $NaHCO_3$ solution and extracted with diethyl ether (10 mL × 3). The combined organic layers were washed with brine and dried with Na_2SO_4. Removal of the solvents yielded a crude product, which was purified by chromatography to afford **5a** (179 mg, 37%) and **6a** (128 mg, 26%).

5a: IR (film): $\tilde{\nu}$ = 3340 cm^{-1}, 2962, 2934, 2875, 1603, 1562. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.26 (m, 5 H), 5.29 (d, J = 4.9 Hz, 2 H), 3.76 (t, J = 7.5 Hz, 1 H), 3.64 (m, 2 H), 2.66 (t, J = 7.2 Hz, 2 H), 2.12 (m, 1 H), 1.86 (m, 3 H), 1.42 (s, 1 H), 0.89 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.0, 154.12, 142.94, 128.56, 128.29, 128.14, 127.85 126.33, 105.70, 105.32, 62.07, 47.16, 31.06, 27.90, 24.37, 12.34 ppm. MS: m/z (%) = 244 (19) [M^+], 216 (18), 215 (100), 213 (10), 197 (46), 141 (10), 115 (9). $C_{16}H_{20}O_2$ (244.3): calcd. C 78.69, H 8.20; found C 78.66, H 8.01.

6a: IR (film): $\tilde{\nu}$ = 3369 cm^{-1}, 2968, 2939, 2879, 1647, 1596. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.61 (m, 2 H), 7.27 (m, 2 H), 7.10 (m, 1 H), 6.21 (d, J = 5.8 Hz, 1 H), 6.09 (d, J = 5.8 Hz, 1 H), 5.26 (s, 1 H), 3.60 (t, J = 6.5 Hz, 2 H), 1.86−1.72 (m, 4 H), 1.59 (m, 2 H), 0.88 (t, J = 7.5 Hz, 3 H) ppm. MS: m/z (%) = 244 (18) [M^+], 185 (100), 111 (61), 153 (53), 85 (46). $C_{16}H_{20}O_2$ (244.3): calcd. C 78.69, H 8.20; found C 78.67, H 8.24.

5b−5d, **6c−6f** were prepared according to the typical procedure described above for the synthesis of **5a** and **6a**.

5b: IR (film): $\tilde{\nu}$ = 3343 cm^{-1}, 3028, 2928, 1601, 1560, 1495. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36−7.19 (m, 10 H), 5.96 (d, J = 3.0 Hz, 1 H) 5.80 (d, J = 3.1 Hz, 1 H), 5.43 (s, 1 H), 3.68 (t, J = 6.3 Hz, 2 H), 2.72 (t, J = 7.4 Hz, 2 H), 1.89 (m, 2 H) ppm. MS: m/z (%) = 292 (100.0) [M^+], 233 (66), 215 (67), 205 (58), 197 (45), 105 (68). $C_{16}H_{20}O_2$ (244.3): calcd. C 82.19, H 6.85; found C 82.18, H 6.96.

5c: IR (film): $\tilde{\nu}$ = 3353 cm^{-1}, 2960, 2875, 1611, 1512. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.13 (d, J = 7.6 Hz, 2 H), 6.83 (d, J = 7.0 Hz, 2 H), 5.90 (s, 2 H), 3.78 (s, 3 H), 3.71 (t, J = 6.3 Hz, 1 H), 3.64 (t, J = 6.3 Hz, 2 H), 2.66 (t, J = 7.5 Hz, 2 H), 2.05 (m, 1 H), 1.83 (m, 3 H), 0.88 (t, J = 7.4 Hz, 3 H) ppm. MS: m/z (%) = 274 (7) [M^+], 246 (15), 245 (100.0), 241 (21), 227 (26), 200 (9), 185 (9). HRMS calcd. for $C_{17}H_{22}O_3$: 274.1569; found 274.1591

6c: IR (film): $\tilde{\nu}$ = 3353 cm^{-1}, 2960, 2875, 1611, 1512. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.55 (d, J = 8.8 Hz, 2 H), 6.85 (d, J = 8.7 Hz, 2 H), 6.18 (d, J = 5.7 Hz, 1 H), 6.03 (d, J = 5.5 Hz, 1 H), 5.22 (s, 1 H), 3.79 (s, 1 H), 3.63 (t, J = 6.2 Hz, 2 H), 1.79 (m, 2 H), 1.58 (m, 2 H), 1.25 (m, 2 H), 0.86 (t, J = 7.4 Hz, 3 H) ppm. MS: m/z (%) = 274 (9) [M^+], 246 (12), 245 (100.0), 227 (26), 185 (10), 121 (11). HRMS calcd. for $C_{17}H_{22}O_3$: 274.1569; found 274.1577

5d: IR (film): $\tilde{\nu}$ = 3352 cm^{-1}, 2962, 2934, 2876, 1610, 1561, 1504, 1489. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.74−6.55 (m, 3 H), 5.91 (d, J = 3.1 Hz, 1 H), 5.89 (s, 2 H), 5.87 (d, J = 3.1 Hz, 1 H), 3.67 (t, J = 7.8 Hz, 1 H), 3.62 (t, J = 6.4 Hz, 2 H), 2.64 (t, J = 7.4 Hz, 2 H), 2.03 (m, 1 H), 1.84 (m, 3 H), 0.87 (t, J = 7.3 Hz, 3 H) ppm. MS: m/z (%) = 288 (11.1) [M^+], 260 (12.9), 259 (100), 241(34.4), 214 (7.0), 155 (4.2), 128 (6.3), 115 (4.6). $C_{17}H_{20}O_4$ (288.3): calcd. C 70.81, H 6.99; found C 70.84, H 7.15.

6d: IR (film): $\tilde{\nu}$ = 3399 cm^{-1}, 2968, 2881, 1647, 1503, 1484. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, J = 1.3 Hz, 1 H), 6.94 (dd, J = 8.1, 1.7 Hz, 1 H), 6.75 (d, J = 8.0 Hz, 1 H), 6.17 (d, J = 5.6 Hz, 1 H), 6.04 (d, J = 5.5 Hz, 1 H), 5.90 (s, 2 H), 5.20 (s, 1 H), 3.81−3.60 (m, 3 H), 1.93−1.73 (m, 4 H), 1.64−1.50 (m, 2 H), 1.04 (t, J = 7.5 Hz, 3 H) ppm. MS: m/z (%) = 288 (58) [M^+], 259 (75), 241 (25), 229 (100), 162 (25), 135 (19), 111 (22), 84 (23). $C_{17}H_{20}O_4$ (288.3): calcd. C 70.81, H 6.99; found C 70.55, H 7.03.

6e: IR (film): $\tilde{\nu}$ = 3343 cm^{-1}, 2937, 1617, 1493, 1444, 981, 771, 697. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.52−7.14 (m, 10 H), 6.18 (d, J = 5.9 Hz, 1 H), 6.09 (d, J = 5.9 Hz, 1 H), 3.64 (m, 2 H), 2.18−1.60 (m, 6 H), 0.94 (t, J = 7.4 Hz, 3 H) ppm. MS: m/z (%) = 320 (26) [M^+], 319 (31), 291 (76), 273 (25), 262 (13), 261 (100), 165 (15). HRMS calcd. for $C_{22}H_{24}O_2$: 320.1776; found 320.1733.

6f: IR (film): $\tilde{\nu}$ = 3375 cm^{-1}, 3056, 2952, 1621, 1597, 1492, 1212, 968, 768, 756, 698. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.63−7.29 (m, 15 H), 6.45 (d, J = 5.8 Hz, 1 H), 6.19 (d, J = 5.9 Hz, 1 H), 3.68 (t, J = 6.4 Hz, 2 H), 2.26−2.15 (m, 2 H), 1.74−1.65 (m, 2 H) ppm. MS: m/z (%) = 368 (9) [M^+], 310 (15), 309 (100), 268 (9), 202 (7), 203 (6), 165(7). $C_{26}H_{24}O_2$ (368.5): calcd. C 84.78, H 6.52; found C 84.87, H 6.50.

Compound 7 and 8: $LiAlH_4$ (38 mg 1 mmol) and $AlCl_3$ (10 mg, 0.075 mmol) were added to a stirred solution of tonghaosu analog **2c** (258 mg, 1 mmol) in 10 mL of anhydrous THF at 0 °C. The reaction mixture was stirred at the same temperature for 5 h, then quenched with 3 mL of saturated $NaHCO_3$ solution and extracted with diethyl ether (10 mL × 3). The combined organic extracts were washed with brine and dried with Na_2SO_4. Removal of the solvents yielded a crude product, which was purified by chromatography to afford **7** (90.3 mg, 35%) and **8** (77.4 mg, 30%).

7: IR (film): $\tilde{\nu}$ = 3298 cm^{-1}, 3188, 2940, 2922, 1859, 1490, 1249,935, 820. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.75−6.66 (m, 3 H), 5.93 (s, 2 H), 5.90 (d, J = 3.0 Hz, 1 H), 5.86 (d, J = 3.0 Hz, 1 H), 3.83 (s, 2 H), 3.67 (m, 2 H), 2.68 (t, J = 4.5 Hz, 2 H), 1.93 (m, 2 H) ppm. MS: m/z (%) = 260 (100) [M^+], 135 (47), 215 (46), 201 (44), 149 (28), 157 (26), 115 (21), 261 (17). $C_{15}H_{16}O_4$ (260.3): calcd. C 69.22, H 6.20; found C 69.31, H 6.25.

8: IR (film): $\tilde{\nu}$ = 3365 cm^{-1}, 2973, 2878, 1649, 1503, 1255, 1240, 1153, 935, 820. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31 (d, J = 1.5 Hz, 1 H), 6.95 (dd, J = 6.8, 1.8 Hz, 1 H), 6.74 (d, J = 6.8 Hz, 1 H), 6.21 (d, J = 6.0 Hz, 2 H), 5.91 (s, 2 H), 5.35 (t, J = 4.8 Hz, 1 H), 5.27 (s, 1 H), 3.68 (t, J = 6.0 Hz, 2 H), 1.89−1.90 (m, 4 H) ppm. MS: m/z (%) = 260 (11) [M^+], 219 (20), 201 (29), 101 (19). HRMS calcd. for $C_{15}H_{16}O_4$ 260.1049, found: 260.1040.

Dimer 12: $BF_3{\cdot}Et_2O$ (50 μL) was added to a stirred solution of tonghaosu analog **10** (660 mg, 3 mmol) in 20 mL of dry THF at −20 °C. The reaction mixture was stirred at −20−0 °C for 8 h until the starting material disappeared according to TLC. Then 3 mL of saturated aqueous $NaHCO_3$ solution was added, and the mixture was extracted with diethyl ether (10 mL × 3). The combined organic extracts were washed with brine and dried with Na_2SO_4. After removal of the solvents, the residue was purified by chromatography to afford **12** (343 mg, 52%). IR (film): $\tilde{\nu}$ = 3431 cm^{-1}, 2948, 2890, 1648, 1560, 1436. ^1H NMR (300 MHz, CD_3COCD_3): δ = 7.19 (dd, *J* = 4.8, 1.1 Hz, 1 H), 6.94−6.89 (m, 3 H), 6.74 (t, *J* = 3.1 Hz, 1 H), 6.31 (d, *J* = 5.4 Hz, 1 H), 6.03 (m, 2 H), 5.94 (d, *J* = 2.7 Hz, 1 H), 5.78 (s, 1 H), 5.65 (s, 1 H), 4.22 (d, *J* = 4.0 Hz, 1 H), 3.99 (m, 1 H), 3.63 (t, *J* = 4.5 Hz, 2 H), 2.69 (t, *J* = 7.3 Hz, 2 H), 2.23−1.82 (m, 6 H) ppm. MS: *m/z* (%) = 441 (74), 440 (76) [M^+], 221 (68), 205 (47). HRMS calcd. for $C_{24}H_{24}O_4S_2$: 440.1116; found 440.1101.

Dimer **13** was prepared from **11** according to the above procedure: IR (film): $\tilde{\nu}$ = 3402 cm^{-1}, 2944, 2868, 1648, 1439. ^1H NMR (300 MHz, CD_3COCD_3): δ = 7.32 (dd, *J* = 4.0, 2.4 Hz, 1 H), 6.94−6.97 (m, 2 H), 6.92 (d, *J* = 3.7 Hz, 1 H), 6.82 (d, *J* = 3.7 Hz, 1 H), 6.40 (d, *J* = 5.7 Hz, 1 H), 6.15 (d, *J* = 5.7 Hz, 1 H), 6.12 (d, *J* = 3.0 Hz, 1 H), 6.01 (d, *J* = 3.0 Hz, 1 H), 5.95 (s, 1 H), 5.80 (s, 1 H), 4.10 (m, 1 H), 3.76 (br. d, *J* = 9.7 Hz, 1 H), 3.57 (t, *J* = 6.3 Hz, 2 H), 3.49 (br. s, 1 H), 2.63 (t, *J* = 7.2 Hz, 2 H), 2.05 (m, 1 H), 1.53−1.86 (m, 9 H) ppm. ^1H NMR (300 MHz, $CDCl_3$): see Table 5. ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 156.9, 156.4, 154.7, 146.7, 144.9, 140.2, 136.1, 128.0, 127.6, 126.7, 126.5, 125.8, 125.5, 114.1, 108.8, 106.5, 96.1, 64.3, 62.4, 42.2, 33.9, 33.3, 28.7, 25.7, 25.6, 20.2 ppm. MS: *m/z* (%) = 469 (31) [M^+ + 1], 468 (100) [M^+], 235 (39), 470 (15). HRMS calcd. for $C_{26}H_{28}O_4S_2$ 468.1430; found 468.1383.

Compound 14: $BF_3{\cdot}Et_2O$ (20 μL, 0.16 mmol) was added to a stirred mixture of tonghaosu analog **2c** (258 mg, 1 mmol) and indole (117 mg, 1 mmol) in 15 mL of anhydrous THF at 0 °C. The reaction mixture was stirred at same temperature for 2 h, until the starting material disappeared as indicated by TLC. Then 3 mL of saturated aqueous $NaHCO_3$ solution was added and the aqueous layer was separated and extracted with diethyl ether (10 mL × 3). The combined organic extracts were washed with brine and dried with Na_2SO_4. Removal of the solvents yielded a crude product, which was purified by chromatography to afford **14** (318.7 mg, 85%). IR (film): $\tilde{\nu}$ = 3416 cm^{-1}, 2943, 2885, 1726, 1502, 1488, 1245, 926, 744. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.1 (s, 1 H), 7.38 (d, *J* = 7.9 Hz, 1 H), 7.65 (d, *J* = 8.3 Hz, 1 H), 7.20 (d, *J* = 7.2 Hz, 1 H), 7.04 (t, *J* = 7.2 Hz, 1 H), 6.76 (m, 4 H), 5.93 (d, *J* = 3.0 Hz, 1 H), 5.92 (s, 2 H), 5.86 (d, *J* = 2.8 Hz, 1 H), 5.54 (s, 1 H), 3.64 (t, *J* = 6.3 Hz, 2 H), 2.69 (t, *J* = 7.4 Hz, 2 H), 1.86 (m, 2 H), 1.71 (s, 1 H) ppm. MS: *m/z* (%) = 376 (89), 375 (100) [M^+], 288 (73), 258 (47), 254 (36), 230 (32), $C_{23}H_{21}O_4N$: calcd. C 73.58, H 5.64, N 3.73; found C 73.44, H 5.78, N 3.79.

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[1] Partial results have been published in: Z.-H. Wu, J. Wang, J.-C. Li, Y.-Z. X, A.-L. Yu, Z.-R. Feng, J. Shen, Y.-L. Wu, P.-F. Guo, Y.-N. Wang, *Nat. Prod. R & D [China]* **1994**, *6*, 1.

[2] [2a] R. Hegnauer, in: *Chemotaxonomie der Pflanzen*, vol. 3, Birkhauser Verlag, Basel, **1964**, pp. 447. [2b] F. Bohlmann, T. Burkhardt, C. Zdero, *Naturally Occurring Acetylenes*, Academic Press, London, **1973**. [2c] H. Greger, in *The Biology and Chemistry of Compositae*, (Eds.: V. H. Heywood, J. B. Harborne, B. L. Turner), chapter 32, Academic Press, London, **1977**. [2d] F. Bohlmann, in *Chemistry and Biology of Naturally Occurring Acetylenes and Related Compounds*, (Eds.: J. Lam, H. Bretler, T. Anason, L. Hansen,), Elsvier, Amsterdam, **1988**, pp.1. [2e]C. Zdero, F. Bohlmann, *Plant Syst. Evol.* **1990**, *171*, 1.

[3] [3a] F. Bohlmann, H. Jastrow, G. Ertringshausen, D. Kramer, *Chem. Ber.* **1964**, *97*, 801. [3b] F. Bohlmann, G. Florentz, *Chem. Ber.* **1966**, *99*, 990.

[4] [4a] Y. Gao, W.-L. Wu, B. Ye, R. Zhou, Y.-L. Wu, *Tetrahedron Lett.* **1996**, *37*, 893. [4b] Y. Gao, W.-L. Wu, Y.-L. Wu, B. Ye, R. Zhou, *Tetrahedron* **1998**, *54*, 12523.

[5] J.-F. Fan, Y.-F. Zhang, Y. Wu, Y.-L. Wu, *Chinese J. Chem.* **2001**, *19*, 1254.

[6] J.-F. Fan, B.-L. Yin, Y.-F. Zhang, Y.-L. Wu, Y. Wu, *Huaxue Xuebao* **2001**, *59*, 1756.

[7] [7a] I. Mori, K. Ishihara, L. A. Flippin, K. Nozaki, H. Yamamoto, P. A. Bartlett, C. H. Heathcock, *J. Org. Chem.* **1990**, *55*, 6107. [7b] S. E. Denmark, N. G. Almstead, *J. Am. Chem. Soc.* **1991**, *113*, 8089. [7c] S. E. Denmark, N. G. Almstead, *J. Org. Chem.* **1991**, *56*, 6458.

[8] Reviews: [8a] T. Mukaiyama, M. Murakami, *Synthesis* **1987**, 1043. [8b] A. Alexakis, P. Mangeney, *Tetrahedron: Asymmetry* **1990**, *1*, 477.

[9] T.-J. Lu, S.-M. Cheng, L.-J. Sheu, *J. Org. Chem.* **1998**, *63*, 2738 and references cited therein.

[10] T. Mukaiyama, H. Ishikawa, *Chem. Lett.* **1974**, 1077.

[11] S. Bogaczyk, M.-R. Brescia, Y. C. Shimshock, P. DeShong, *J. Org. Chem.* **2001**, *66*, 4352 and references cited therein.

[12] J.-F. Fan, Y.-K. Wu, Y.-L. Wu, *J. Chem. Soc., Perkin Trans. 1* **1999**, 1189.

[13] Y. Wu, Y. Li, Y.-L. Wu, *Helv. Chim. Acta* **2001**, *84*, 163.

[14] O. Hofer, B. Wallnöfer, M. Widhalm, H. Greger, *Liebigs Ann. Chem.* **1988**, 525.

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