Chinese Journal of Chemistry, **2004**, *22*, 92—99 **Article**

Study on Tonghaosu and Its Analogs: Isolation, Structure Identification and Synthesis of Antifeedant B-ring-homo-tonghaosu

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The methanolic extract from a Chinese endemic *Chrysanthemum* plant, *Dendranthema indicum* var. *aromaticum*, was found to show high antifeeding activity against *Pieris brassicae* L., and by bioassay-guided separation, the active component, B-ring-homo-tonghaosu, 2-(2',4'-hexadiynylidene)-1,6-dioxaspiro-[4,5]-dec-3-ene (**2**) was isolated. Its structure was elucidated by comparing its spectroscopic data with those of **2** reported in the literatures. Furthermore new convenient total synthesis methods of B-ring-homo-tonghaosu were also developed to confirm its structure and make its further application in crop protection available. In addition, extensive comparison of spectroscopic data showed that the structure of compound **21** reported in literature should be revised to **2**.

Keywords spiroketal, B-ring-homo-tonghaosu, *Dendranthema indicum* var. *aromaticum*, *Pieris brassicae*, antifeedant

Introduction

Tonghaosu named for 2-(2',4'-hexadiynylidene)-1,6-dioxaspiro[4,4]-non-3-ene (**1**) is an antifeedant component of vegetable tonghao (*Chrysanthemum sgetum* L. or *C. coronarium* L.) and some other plants of tribe *Anthemideae* of the Compositae.[1,2] B-ring-homo-tonghaosu, 2-(2',4'-hexadiynylidene)-1,6-dioxaspiro-[4,5]-dec-3-ene (**2**), was not found in tonghao, but it has been isolated from many other species of this tribe *Anthemideae*. The investigated genera of *Anthemideae* containing B-ring-homo-tonghaosu has been reviewed,[3] including *Anthemis*, *Artemisia*, *Athanasia*, *Brocchia*, *Chrysanthemum*, *Dendranthema*, *Gonospermum*, *Heteranthemis*, *Leucanthemella*, *Matricaria*, *Pentzia*, *Santolina*, and *Tanacetum*.

In the course of screening novel naturally occurring insecticides from Shennongjia Natural Reserve, Hubei Province, China, the methanolic extract from the whole plant of shennong xiangju was found to exhibit significant insecticidal activity against *Plutella xylostella* L. and *Spodoptera litura* Fabricius. Shennong xiangju distributed in a limited area of Shennongjia Natural Reserve was recognized as a novel variation of genus

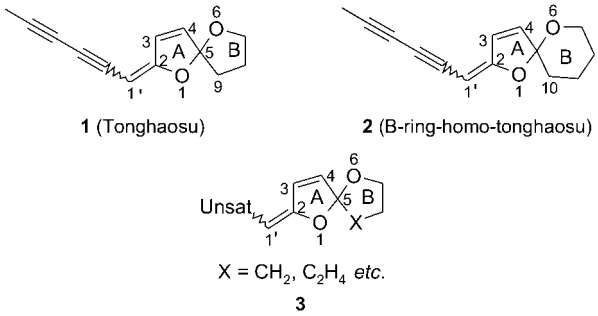

Figure 1 Structures of Tonghaosu and its analogs.

Dendranthema (Compositae), *i.e. D. indicum* (L.) Des Monl. (*Chrysanthemum indicum* L.) var. *aromaticum* Liu *et* Zhang.[4] It possesses rich pleasing fragrance as an important character different from *D. indicum*. It is also a local traditional medicine with obvious anti-inflammatory and antipyretic function, and the chemical constituents of its flowers have been investigated.[5] Thus the observation of insecticidal activity of mathanolic extracts prompted a systematic isolation by bioassay-guided fractionation, and two compounds showing antifeedant activity were isolated and confirmed as B-ring-homo-tonghaosu (**2**). Herein we report the isola-

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tion, determination and total synthesis of **2** as well as its antifeeding activity against *Pieris bassicae* L.

Results and discussion

Isolation and structure elucidation

From 2.6 kg of air-dried whole plant of shennong xiangju, 341 mg of *Z*-B-ring-homo-tonghaosu (**2*Z***) and 152 mg of *E*-isomer (**2*E***) were isolated. All the physical data were identical with those reported in the literature[6,7] and those of synthetic sample (*vide infra*). Their ^{1}H NMR and ^{13}C NMR data are shown in Tables 1 and 2. In Table 1, it is worthy to be mentioned that the assignment of chemical shifts of 3-H and 4-H for **2*Z*** is different from that originally reported in literatures and exchanged with each other according to our NMR experiments, where the NOSEY spectrum shows the correlation signal between 4.61 (1'-H) and 6.18 (3-H), and the HMQC spectrum shows the correlation peak between 6.18 (3-H) and 126.6 (3-C). Thus the chemical shift of 3-H (6.65) of **2*E*** isomer is in much lower field than that of its 4-H (6.23) and also than that of 3-H (6.18) of **2*Z*** isomer, which, in contrast, is just a little higher than that of its 4-H (6.21). This difference may be ascribed to the reason that the 3-H in **2*E*** isomer is probably subjected to the deshielding effect of neighboring diacetylene moiety, but not in the case of 3-H in **2*Z*** isomer.

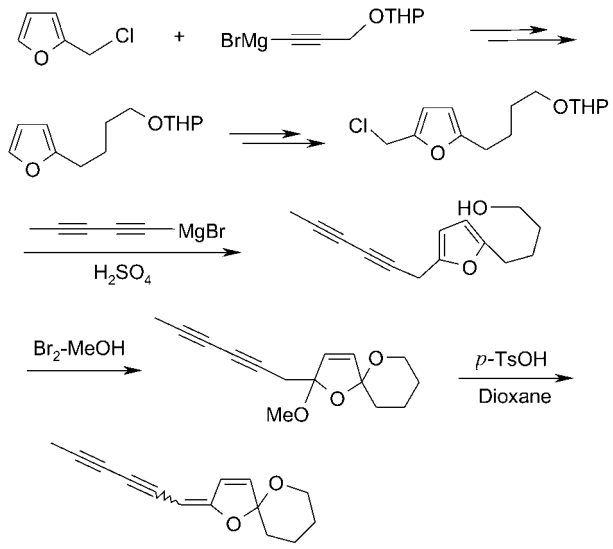
Synthesis

In order to confirm the identification of B-ring-homo-tonghaosu and supply more material for further bioassay, we set out to synthesize these two compounds. B-ring-homo-tonghaosu (**2**) has been synthesized through two methods by Bohlmann's group in 1960's. One route[8] started from 2-chloromethyl furan using bromination-methoxylation of furan as the key step with only about 5% overall yield (Scheme 1), and the other route[9] used photo-cyclization as the key step with somewhat better overall yield.

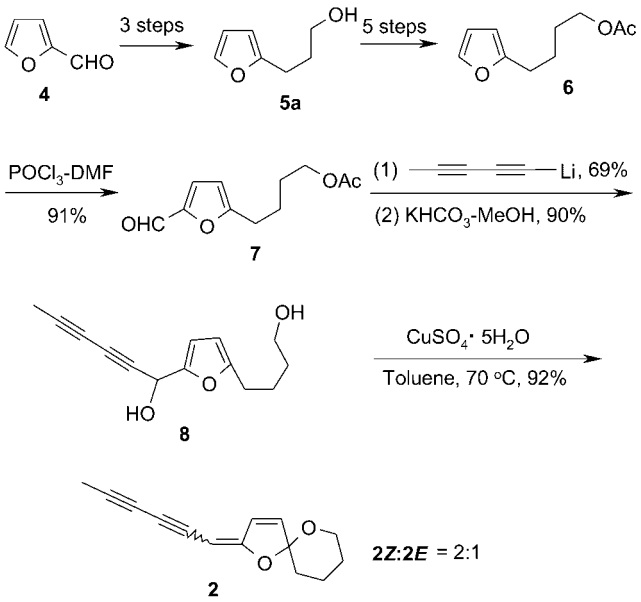
Since then no successful synthesis had been reported, until a concise general synthetic strategy for synthesizing tonghaosu (**1**) and their spiroketal dienol-ether characterized analogs **3** was developed in our laboratory.[10] B-ring-homo-tonghaosu (**2**) was also synthesized using the same strategy, however with 4 steps more than that of synthesis of **1** (Scheme 2).[10b]

With developing more efficient and practical method in mind three alternate routes for the synthesis of key intermediate **7** were explored. The first route was started from furan and used Friedel-Crafts reaction with succinic anhydride to introduce the four carbon chain. The second one took γ-butyrolactone as the 4-carbon building block (Scheme 3). The last preparation of **7** was from furfural and γ-butyrolactone (Scheme 4). And the first route turned out to be the most practical one and could be scaled up easily. As to the pentadiyne moiety of **2**, dibromide **20** instead of pentadiyne was

Scheme 1



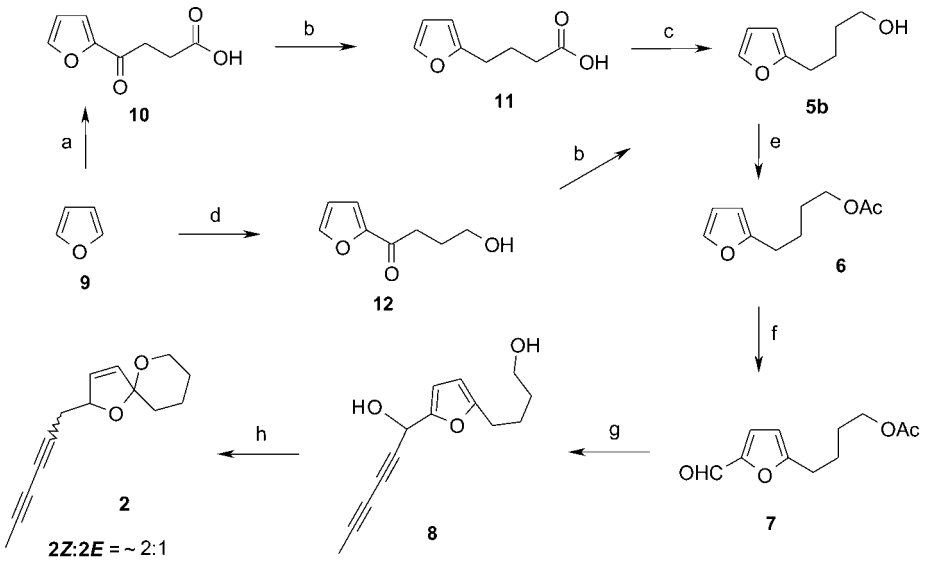
Scheme 2



used to introduce the diacetylene chain. Dibromide **20** was prepared from propargyl alcohol as shown in Scheme 5. Thus according to the known procedures coupling reaction of **7** and **20** followed by acid-catalyzed spiroketalization afforded **2** as a *Z*, *E* mixture, which could be separated by chromatography. And the physical data of synthetic **2*Z*** and **2*E*** are completely in agreement with those of naturally occurring **2*Z*** and **2*E***, respectively.

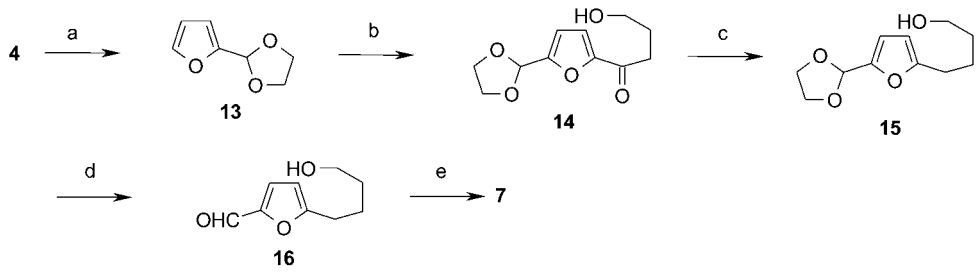
During the isolation and synthesis of B-ring-homo-tonghaosu (**2**) an interesting compound **21** reported in literature[11] attracted our attention (Figure 2). Compound **21** was isolated from the aerial parts of *Artemisia feddei* Levl. *et* Vant., and was assigned as shown according to its spectra, mainly NMR. We have tried to synthesize this structure using several methods, but failed to do that. We also noticed that the structure of **21** possessed a

Scheme 3



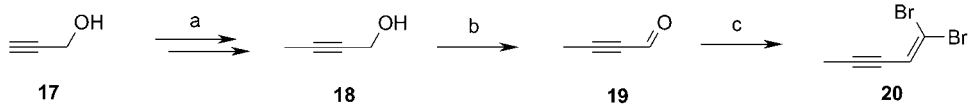
Reagents and conditions: (a) succinic anhydride, $AlCl_3$; (b) NaOH, $H_2NNH_2 \cdot H_2O$, 180 °C, 6—8 h; (c) $LiAlH_4$, 88%; (d) TMEDA, *n*-BuLi, γ-butyrolactone, −78 °C—r.t., 51%; (e) Ac_2O, pyridine, DMAP, 94%; (f) DMF, $POCl_3$, 95%; (g) i) **20**, TMEDA, *n*-BuLi, −78 °C—r.t.; ii) K_2CO_3; (h) $CuSO_4 \cdot 5H_2O$, 110 °C, 6 h.

Scheme 4



Reagents and conditions: (a) ethylene glycol, *p*-TsOH • H_2O, benzene, reflux, 2 h, 53%; (b) TMEDA, *n*-BuLi, γ-butyrolactone, −78 °C—r.t., 52%; (c) NaOH, $H_2NNH_2 \cdot H_2O$,180 °C, 6—8 h; (d) HCl, acetone, reflux for 1 h; (e) Ac_2O, pyridine, DMAP, 89%.

Scheme 5



Reagents and conditions: (a) Method A: i) PPTS, DHP, 95%; ii) *n*-BuLi, CH_3I, 94%; iii) *p*-TsOH • H_2O, 93%; Method B: $LiNH_2$, CH_3I, −40 °C—r.t., 68%; (b) PCC; (c) CBr_4, PPh_3, Zn dust, 0 °C—r.t.

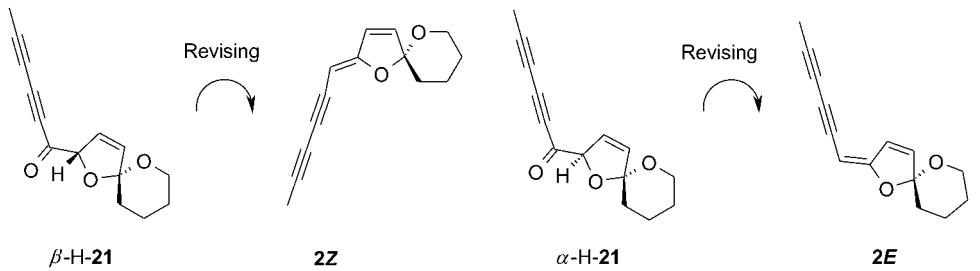


Figure 2 Structure revision of **21.**

very reactive hydrogen adjacent to the carbonyl group, so the ketone form might be not a stable one if this compound indeed existed, and theoretically structure of **2** should have similar NMR spectra to those of **21**. We thus measured the NMR spectra of our sample **2** in deuterated chloroform as in the literature[11] instead of deuterated benzene, which we usually used as the NMR solvent to avoid the acidic hydrolysis of tonghaosu sample, and it was not so surprising to find that its ^{1}H NMR and ^{13}C NMR data were totally coincident with those reported in the literature[11] for compound **21** (Tables 1 and 2). Therefore we are convinced that com-

Table 1 ^{1}H NMR data for compound **2** ($CDCl_3$, TMS)

Position	**2*Z***		**2*E***	
	Natural (400 MHz)	Synthetic (300 MHz)	Natural (400 MHz)	Synthetic (300 MHz)
3	6.18 (d, *J*=5.9 Hz)	6.18 (d, *J*=5.7 Hz)	6.64 (d, *J*=6.0 Hz)	6.66 (dd, *J*=0.9, 6.0 Hz)
4	6.21 (d, *J*=5.8 Hz)	6.21 (d, *J*=5.7 Hz)	6.23 (dd, *J*=1.5, 5.8 Hz)	6.23 (dd, *J*=1.8, 5.7 Hz)
7ax	4.11 (td, *J*=2.1, 11.5 Hz)	4.12 (td, *J*=3.3, 11.4 Hz)	3.96 (td, *J*=2.8, 11.5 Hz)	3.98 (td, *J*=3.6, 11.1 Hz)
7eq	3.82—3.86 (m)	3.81—3.87 (m)	3.81—3.84 (m)	3.81—3.88 (m)
8, 9, 10	1.64—1.84 (m)	1.62—1.85 (m)	1.63—1.92 (m)	1.63—1.93 (m)
1'	4.61 (s)	4.61 (d, *J*=0.6 Hz)	4.95 (s)	4.97 (m)
6'	2.01 (s)	2.01 (d, *J*=0.9 Hz)	2.00 (s)	2.00 (d, *J*=1.2 Hz)

Continued

Position	Ref. 6 **2*Z*** (500 MHz)	Ref. 7 **2*E*** (200 MHz)	Ref. 11 (400 MHz)	
			2*Z* (α-H-**21**)	**2*E*** (β-H-**21**)
3	6.20 (d, *J*=5.7 Hz)	6.63 (d, *J*=5.7 Hz)	6.21 (d, *J*=5.8 Hz)	6.55 (d, *J*=5.8 Hz)
4	6.17 (dd, *J*=0.5, 5.7 Hz)	6.22 (dd, *J*=1.8, 5.7 Hz)	6.18 (brd, *J*=5.8 Hz)	6.22 (brd, *J*=5.8 Hz)
7ax	4.11 (ddd, *J*=3.1, 11.7, 11.7 Hz)	3.80—4.00 (m)	4.10 (ddd, *J*=3.5, 11.2, 12 Hz)	3.97 (ddd, *J*=3.5, 11.2, 12 Hz)
7eq	3.83 (ddd, *J*=2.0, 2.3, 11.7 Hz)		3.82 (ddd, *J*=2.1, 2.4, 12 Hz)	3.83 (ddd, *J*=2.1, 2.4, 12 Hz)
8, 9, 10	1.6—2.1 (m)	1.50—2.10 (m)	1.6—2.1 (m)	1.6—2.1 (m)
1'	4.61 (brs)	4.94 (brs)	4.61 (brs)	4.95 (brs)
6'	2.01 (d, *J*=1.1 Hz)	1.97(d, *J*=1.0 Hz)	2.05 (s)	1.98 (s)

Table 2 ^{13}C NMR data for compound **2** ($CDCl_3$, TMS)

Position	**2*Z***		**2*E***		Ref. 7 DEPT (50 MHz)		Ref. 11 (100 MHz)	
	Natural (100 MHz)	Synthetic(75 MHz)	Natural (100 MHz)	Synthetic (75 MHz)		**2*E***	**2*Z***	**2*E***
2	167.99	167.95	169.80	169.74	C	169.83	167.8	169.8
3	126.60	126.58	125.01	125.02	CH	125.00	126.3	125.1
4	137.93	137.89	138.48	138.37	CH	138.54	137.8	138.4
5	112.88	112.78	112.76	112.67	C	112.78	112.7	112.7
7	64.22	64.17	64.24	64.22	CH_2	64.25	63.9	64.2
8	24.46	24.34	24.40	24.31	CH_2	24.44	24.2	24.4
9	19.16	19.04	19.24	19.15	CH_2	19.28	18.9	19.2
10	32.57	32.43	32.49	32.40	CH_2	32.51	32.3	32.5
1'	78.75	78.60	79.72	79.69	CH	79.73	78.3	79.8
2'	70.85	70.72	71.61	71.54	C	71.60	70.6	71.6
3'	78.75	78.55	76.28	76.12	C	76.32	78.8	76.2
4'	65.29	65.11	65.07	64.92	C	65.11	65.1	65.1
5'	80.36	80.46	79.54	79.55	C	79.54	80.2	79.5
6'	4.70	4.74	4.56	4.61	CH_3	4.59	4.3	4.6

pound **21** should be B-ring-homo-tonghaosu and the so-called α-H-isomer was **2*Z*** and *β*-H-isomer was **2*E***. As to their peaks of *m/z* 230 in EIMS reported in the literature[11] they might come from their hydrolysis product **8** or other impurities.

The antifeeding activities of natural and synthetic B-ring-homo-tonghaosu were tested by the conventional leaf disk method against the 3rd-instar larvae of *P. brassicae* L. The results (Table 3) indicated that antifeeding activity of **2*E*** was less active in some degree than that of **2*Z***. And there was no obvious difference between natural and synthetic **2*Z***-isomers or **2*E***-isomers.

Table 3 Antifeeding activity of natural and synthetic B-ring-homo-tonghaosu against *P. brassicae* L.

Compound		Antifeedancy/% at 1000 μg/mL
Natural	**2*Z***	90.58
	2*E*	81.26
Synthetic	**2*Z***	89.93
	2*E*	85.30

In conclusion, the B-ring-homo-tonghaosu, 2-(2′,4′-hexadiynylidene)-1,6-dioxaspiro-[4,5]-dec-3-ene (**2**) was isolated as an antifeeding component from a Chinese endemic *Chrysanthemum* plant, *Dendranthema indicum* var. *aromaticum*, and its new synthesis aimed for scale-up has been explored. It is also suggested that the structure of **21** reported in the literature[11] should be revised to **2**.

Experimental

Melting points were uncorrected. IR spectra were recorded on a Perkin-Elmer 983 or a Shimadzu IR-440 spectrometers. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ or C_6D_6 on an AMX-300, a DPX-300 or a DRX-400 spectrometer with TMS as the internal standard. EIMS and HREIMS spectra were taken on a Mariner, an HP5973N or an HP5989A instrument. Flash column chromatography was performed on silica gel H (10—40 μm) with petroleum ether-ethyl acetate system as eluent.

Extraction and isolation

The air-dried whole plant of *Dendranthema indicum* var. *aromaticum* (2.6 kg, collected from Shennongjia Natural Reserve, Hubei Province, China, in September 1999) was finely ground and extracted three times with methanol under reflux. Evaporation of the solvents from the combined extracts under reduced pressure gave the MeOH extract (290 g). Further fractionation was carried out by monitoring the insecticidal activity on the 3rd-instar larvae of *Pieris brassicae* L. The MeOH extract was partitioned in a petroleum ether-H_2O (V∶V=2∶1) mixture. Removal of the solvent from the organic layer *in vacuo* yielded 50 g of active syrup which was chromatographed over 1000 g silica gel eluting successively with petroleum ether-EtOAc gradients to afford 33 fractions. The active fractions (F-4, F-5, F-6 and F-7) were combined as F-4 (3.1 g) and were separated by silica gel chromatography. The further purification of the active fractions (712 mg) gave the active components, B-ring-homo-tonghaosu **2*Z***-isomer (colorless crystal, 341 mg) and **2*E***-isomer (yellow oil, 152 mg). **2*Z***: m.p. 86—88 ℃; NMR spectral data see Tables 1 and 2; IR ν: 2945, 2924, 2876, 2137, 1635, 1585 cm^{-1}; EIMS *m/z* (%): 214 (M^+, 100), 199 (7.2), 185 (31.7), 171 (19.8), 156 (57.6), 129 (26.3), 115 (35.7), 102 (24.9), 76 (34.1), 55 (31.9). **2*E***: NMR spectral data see Tables 1 and 2; IR ν: 2949, 2882, 2233, 2140, 1630, 1581 cm^{-1}; EIMS *m/z* (%): 214 (M^+, 100), 199 (7.5), 185 (32.1), 171 (20.3), 156 (57.3), 129 (26.9), 115 (36.4), 102 (25.2), 76 (34.7), 55 (30.0).

Bioassay

Antifeeding activity was assayed by the conventional leaf-disk method. The larvae of the cabbage butterfly were collected from suburban vegetable fields of Kunming, Yunnan Povince, China, and reared with cabbage (*Brassica oleracea* L.) seedling in an environmental chamber held at (25±1) ℃ under a photoperiod of 14∶10 (*L*∶*D*) h. Larvae of second generation were reared to third instar for a feeding test. The test compounds were dissolved in acetone at concentration of 1000 μg/mL. Leaf disks (d=1.25 cm) of cabbage were dipped into the prepared solutions for 1 s according to the method of Yee and Toscano,[12] and control disks were dipped into acetone. These treated disks were allowed to stand on a plate to evaporate the acetone. Three disks and two larvae were placed on a wet filter paper disk in 9.0 cm dia. Petri dish, with 5 replicates each concentration. Remaining uneaten leaf areas were measured using an LI-COR 3000 leaf area meter (LI-COR, Lincoln, USA) 48 h after treatment. 10 randomly chosen leaf disks dipped in acetone, and unexposed to larvae were used to determine the leaf areas consumed. The antifeeding percentage was calculated as

$$\text{Antifeedancy}=(\text{CK}-T)/\text{CK}\times 100\%$$

Where CK and T are control disk areas eaten and treated disk areas eaten, respectively.

Synthesis of B-ring-homo-tonghaosu (2)

3-(2-Furoyl)propanoic acid (10)[13] $AlCl_3$ (13.34 g, 100 mmol) was added to a mixture of succinic anhydride (10 g, 100 mmol) and furan (13.6 g, 200 mmol) in CH_2Cl_2 (200 mL) at 0 ℃. The reaction mixture was stirred at 0—5 ℃ for 1 h, and then was allowed to warm to room temperature and stirred for 4 h. 3 mol/L HCl was added to acidify to pH=2 at 0 ℃, and the layers were partitioned. The aqueous layer was extracted with ethyl acetate thoroughly, and the organic layer was washed with water and saturated brine, dried with Na_2SO_4 and concentrated *in vacuo*. After purification by flash chromatography (ethyl acetate∶petroleum

ether=1∶2, *V*∶*V*) 5.72 g (34%) of grey granular solid was afforded. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.60 (dd, *J*=0.7, 1.7 Hz, 1H), 7.24 (dd, *J*=0.5, 3.3 Hz, 1H), 6.55 (dd, *J*=1.7, 3.4 Hz, 1H), 3.18 (t, *J*=6.7 Hz, 2H), 2.80 (t, *J*=6.7 Hz, 2H).

4-(2'-Furyl)butanoic acid (11)[14] A mixture of 8.4 g (50 mmol) of 3-(2-furoyl)propanoic acid, 12 g of NaOH pellets (300 mmol) and 12.5 g (250 mmol) of hydrazine hydrate in 350 mL of ethylene glycol was heated at 180 ℃ for 6—8 h. The cooled solution was acidified with 4 mol/L HCl to pH=2 and extracted thoroughly with ethyl acetate. The extract was washed with saturated NaCl solution, dried and evaporated. After chromatography of the residue, and elution with ethyl acetate/petroleum ether (1∶2, *V*∶*V*) 5.24 g of pale yellow oil (68% yield) was yielded. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 11.25 (brs, 1H, COOH), 7.30 (dd, *J*=0.9, 1.8 Hz, 1H), 6.27 (dd, *J*=1.8, 3.0 Hz, 1H), 6.01 (qd, *J*=0.9, 3.0 Hz, 1H), 2.68 (t, *J*=7.3 Hz, 2H), 2.38 (t, *J*=7.4 Hz, 2H), 1.92—2.02 (m, 2H).

1-(2-Furyl)-4-hydroxy-1-butanone (12)[15] ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.62 (dd, *J*=0.9, 1.8 Hz, 1H), 7.24 (dd, *J*=0.6, 3.6 Hz, 1H), 6.54 (dd, *J*=2.1, 3.9 Hz, 1H), 3.78 (brs, 1H, OH), 3.70 (t, *J*=6.0 Hz, 2H), 2.96 (t, *J*=7.2 Hz, 2H), 1.92—2.01 (m, 2H).

4-(2'-Furyl)-butan-1-ol (5b) Compound **5b** (51%) was obtained from the reduction of **12** as a colorless oil in a manner similar to the synthesis of **11**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.29 (d, *J*=0.6 Hz, 1H), 6.27 (dd, *J*=1.9, 3.0 Hz, 1H), 5.98 (dd, *J*=1.0, 3.4 Hz, 1H), 3.60 (t, *J*=6.3 Hz, 2H), 2.89 (brs, 1H, OH), 2.64 (t, *J*=7.8 Hz, 2H), 1.54—1.75 (m, 4H).

1-(5-[1,3]Dioxolan-2-yl-furan-2-yl)-4-hydroxy-butan-1-one (14) To a solution of 2-(2-furyl)-1,3-dioxolane (2.8 g, 20 mmol) and TMEDA (4.65 g, 40 mmol) in tetrahydrofuran (20 mL) at −78 ℃ was added 12.5 mL of 1.6 mol/L *n*-butyllithium (20 mmol) and allowed to stir for 1 h at 0 ℃. The solution was then cannulated into another flask containing γ-butyrolactone (3.44 g, 40 mmol) in tetrahydrofuran (20 mL) at −78 ℃. The reaction mixture was stirred for 1 h and allowed to warm to room temperature over 30 min. 20 mL of saturated NH_4Cl solution was added, and the layers were partitioned. The aqueous layer was extracted with ethyl acetate (4×35 mL), and the organic layer was then dried over anhydrous magnesium sulfate and filtered, and the solvent was removed *in vacuo* to afford a brown oil. The product was purified by flash chromatography (ethyl acetate∶petroleum ether=1∶1, *V*∶*V*) to afford 2.33 g of a yellow oil (52% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.17 (d, *J*=3.4 Hz, 1H), 6.57 (d, *J*=3.6 Hz, 1H), 5.96 (s, 1H), 4.36 (t, *J*=7.1 Hz, 2H), 4.10—4.13 (m, 2H), 4.01—4.05 (m, 2H), 3.68 (t, *J*=6.3 Hz, 2H), 2.75 (brs, 1H, OH), 1.91—1.96 (m, 2H); EIMS *m/z* (%): 226 (M^+, 4.3), 208 (82.8), 182 (14.8), 149 (38.7), 123 (42.5), 95 (100), 73 (71.2).

4-(5-[1,3]Dioxolan-2-yl-furan-2-yl)-butan-1-ol (15) Compound **15** (45%) was obtained as a yellow oil in a manner similar to the synthesis of **11**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.34 (d, *J*=3.3 Hz, 1H), 5.96 (dd, *J*=1.2, 2.4 Hz, 1H), 5.85 (s, 1H), 4.11—4.15 (m, 2H), 3.97—4.01 (m, 2H), 3.62 (t, *J*=6.6 Hz, 2H), 2.65 (t, *J*=7.2 Hz, 2H), 1.54—1.77 (m, 4H); EIMS *m/z* (%): 212 (M^+, 38.5), 167 (32.5), 153 (20.1), 139 (60.8), 107 (36.2), 81 (100), 73 (49.7).

5-(4-Hydroxy-butyl)-furan-2-carbaldehyde (16) The acetal **15** (4.24 g, 20 mmol) was dissolved in a mixture of acetone (150 mL) and 6 mol/L HCl (15 mL), and this solution was stirred and heated at reflux for 1 h. The major part of the solvent was removed *in vacuo* and to the residue was added CH_2Cl_2 (150 mL). This organic solution was washed successively with 15% aqueous K_2CO_3 (3×100 mL), H_2O (100 mL), saturated NaCl solution, and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was purified with flash chromatography to afford 1.95 g (58%) of product as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.50 (s, 1H), 7.24 (d, *J*=3.6 Hz, 1H), 6.30 (d, *J*=3.6 Hz, 1H), 3.67 (t, *J*=6.3 Hz, 2H), 2.78 (t, *J*=7.8 Hz, 2H), 1.76—1.84 (m, 2H), 1.62—1.69 (m, 2H); EIMS *m/z* (%): 168 (M^+, 41.9), 150 (5.5), 137 (12.1), 122 (100), 109 (53.0), 97 (46.7), 81 (44.4).

1,1-Dibromo-pent-1-en-3-yne (20)[16,17] In a 250 mL of round-bottomed flask fitted with a reflux condense was suspended 16.15 g (75 mmol) of pyridinium chlorochromate (PCC) in 100 mL of anhydrous CH_2Cl_2. 2-Butyn-1-ol (**18**) (3.5 g, 50 mmol) in CH_2Cl_2 (20 mL) was added in one portion to the magnetically stirred solution. After 2 h 200 mL of dry ether was added and introduced to a 5 cm of silica gel column, which was then eluted with ether. The solvent was removed by distillation to give the crude product that was used directly in the next reaction.

Carbon tetrabromide (33.16 g, 100 mmol) in CH_2Cl_2 (60 mL) was added to a stirred solution of triphenylphosphine (26.2 g, 100 mmol) in CH_2Cl_2 (200 mL) under N_2 at 0 ℃. After 10 min, zinc dust (6.5 g, 100 mmol) was added, and the deep red suspension was stirred for 24 h at room temperature. The crude aldehyde dissolved in CH_2Cl_2 (30 mL) was carefully added at 0 ℃ and the reaction mixture was stirred at room temperature for 2 h and then poured into rapidly swirling ice-cooled pentane (400 mL). The pentane fractions were combined and concentrated *in vacuo*. The crude product was flash chromatographed (pentane) to provide 1,1-dibromide (3.02 g, 27% over two steps). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.51 (q, *J*=2.4 Hz, 1H), 1.97 (d, *J*=2.1 Hz, 3H); IR *v*: 3019, 2958, 2916, 2224, 1573, 565 cm^{-1}; EIMS *m/z* (%), 224 (M^+, 94.5), 143 (100), 117 (27.2), 63 (62.2). HREIMS *m/z* cacld for $C_5H_4Br_2$ 221.8680, found 221.8716.

α-(1,3-Pentadiynyl)-5-(4-hydroxybutyl)-2-furanmethanol (8) To a solution of 1,1-dibromide **20** (2.46 g, 11 mmol) in 20 mL of dry THF and 2.56 g (22 mmol) of TMEDA cooled to −78 ℃ under a nitrogen atmosphere was added dropwise a 1.6 mol/L solution of *n*-butyllithium in hexane (13.75 mL, 22 mmol). The reaction mixture was stirred for 30 min at −78 ℃,

warmed to room temperature, and then added dropwise to another solution of furaldehyde (2.1 g, 10 mmol) in 20 mL of dry THF cooled to −78 ℃ under a nitrogen atmosphere. The resulting mixture was allowed to warm to room temperature and stirred overnight, and was then quenched with saturated NH_4Cl solution (15 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography (petroleum ether∶ethyl acetate=5∶1, *V*∶*V*) to give 1.94 g (71%) of *α*-(1,3-pentadiynyl)-5-(4-acetoxybutyl)-2-furanmethanol as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 6.33 (d, *J*=3.0 Hz, 1H), 5.94 (d, *J*=3.0 Hz, 1H), 5.42 (d, *J*=4.5 Hz, 1H), 4.06 (t, *J*=6.1 Hz, 2H), 2.83 (brs, 1H, OH), 2.71 (t, *J*=7.6 Hz, 2H), 2.04 (s, 3H), 1.94 (s, 3H), 1.66—1.69 (m, 4H).

K_2CO_3 was added to a solution of α-(1,3-pentadiynyl)-5-(4-acetoxybutyl)-2-furanmethanol (1.22 g, 4.45 mmol) in methanol (20 mL) and H_2O (2 mL), and stirred for 6 h. Methanol was evaporated, and the resultant mixture was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography (2∶1 petroleum ether/ethyl acetate +1% triethylamine, *V*∶*V*) to give 904 mg (88%) of *α*-(1,3-pentadiynyl)-5-(4-hydroxybutyl)-2-furanmethanol (**8**) as a brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 6.33 (d, *J*=2.7 Hz, 1H), 5.95 (d, *J*=2.7 Hz, 1H), 5.42 (s, 1H), 3.64 (t, *J*=6.3 Hz, 2H), 2.65 (t, *J*=7.3 Hz, 2H), 1.95 (s, 3H), 1.58—1.75 (m, 4H).

2-(2',4'-Hexadiynylidene)-1,6-dioxaspiro[4,5]dec-3-ene (2) To a solution of fruandiol **8** (1.02 g, 4.4 mmol) in 30 mL of toluene was added 1.65 g of $CuSO_4 \cdot 5H_2O$ (6.6 mmol). The reaction mixture was stirred at 110 °C over 6 h, while the reaction appeared complete by TLC, the copper salt was filtrated. The filtrate was concentrated *in vacuo*, the residue was carefully chromatographed (silica gel, 20∶1 petroleum ether/ethyl acetate+0.5% triethylamine, *V*∶*V*) to give the title compounds (**2*Z***, colorless crystal, 533 mg; **2*E***, pale yellow oil, 287 mg, 87%).

2*Z* m.p. 87—89 °C; ^{1}H NMR and ^{13}C NMR data in $CDCl_3$ see Tables 1 and 2. ^{1}H NMR (C_6D_6, 400 MHz) *δ*: 5.71 (d, *J*=5.5 Hz, 1H), 5.55 (d, *J*=5.6 Hz, 1H), 4.47 (s, 1H), 3.91—3.97 (m, 1H), 3.51—3.55 (m, 1H), 1.40 (d, *J*=1.1 Hz, 3H), 1.04—1.85 (m, 6H); ^{13}C NMR (C_6D_6, 100 MHz) *δ*: 168.69 (C-2), 126.36 (C-3), 138.32 (C-4), 113.20 (C-5), 63.94 (C-7), 24.65 (C-8), 19.31 (C-9), 32.78 (C-10), 79.20 (C-1'), 71.70 (C-2'), 79.95 (C-3'), 66.49 (C-4'), 80.75 (C-5'), 4.12 (C6'); IR *ν*: 3099, 3051, 2966, 2947, 2923, 2877, 2138, 1635, 1585 cm^{-1}; EIMS *m/z* (%): 214 (M^+, 100), 199 (6.9), 185 (32.7), 171 (29.2), 156 (62.4), 129 (29.0), 115 (37.9), 102 (24.7), 76 (31.7), 55 (19.3). Anal. calcd for $C_{14}H_{14}O_2$: C 78.48, H 6.59; found C 78.74, H 6.38.

2*E* ^{1}H NMR and ^{13}C NMR data in $CDCl_3$ see Tables 1 and 2. ^{1}H NMR (C_6D_6, 400 MHz) *δ*: 6.46 (d, *J*=5.7 Hz, 1H), 5.74 (dd, *J*=1.7, 5.8 Hz, 1H), 5.12 (s, 1H), 3.81 (td, *J*=2.5, 12.3 Hz, 1H), 3.53—3.57 (m, 1H), 2.00 (d, *J*=1.2 Hz, 3H), 1.08—1.73 (m, 6H); ^{13}C NMR (C_6D_6, 100 MHz) δ: 170.50 (C-2), 124.86 (C-3), 139.09 (C-4), 113.02 (C-5), 63.96 (C-7), 24.59 (C-8), 19.46 (C-9), 32.65 (C-10), 80.08 (C-1'), 72.33 (C-2'), 77.58 (C-3'), 66.27 (C-4'), 79.75 (C-5'), 4.09 (C-6'); IR *ν*: 2949, 2915, 2882, 2851, 2233, 2140, 1630, 1581 cm^{-1}; EIMS *m/z* (%): 214 (M^+, 100), 199 (6.9), 185 (30.3), 171 (18.7), 156 (51.0), 129 (22.5), 115 (29.0), 102 (18.3), 76 (19.3), 55 (11.6). Anal. calcd for $C_{14}H_{14}O_2$: C 78.48, H 6.59; found C 78.19, H 6.58.

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1 Partial result has been published in: Wu, Z.-H.; Wang, J.; Li, J.-C.; Xu, Y.-Z.; Yu, A.-L.; Feng, Z.-R.; Shen, J.; Wu, Y.-L.; Guo, P.-F.; Wang, Y.-N. *Nat. Prod. Res. Dev.* **1994**, *6*(1), 1 (in Chinese).

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