Molecular Diversity of Tonghaosu: Synthesis of Lactam-Containing Tonghaosu Analogs

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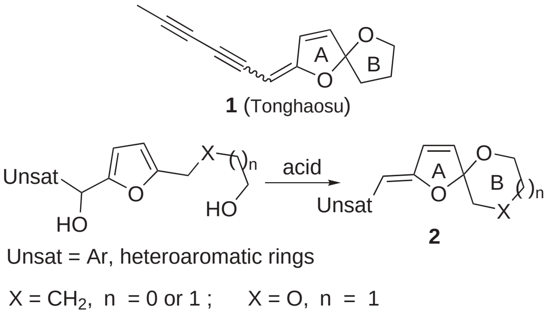
Abstract: A new type of tonghaosu analogs containing spiroketal and lactam functionality was synthesized from methyl 2-furoate and amino alcohols. The stereoselective control of spiroketal chirality was also explored.

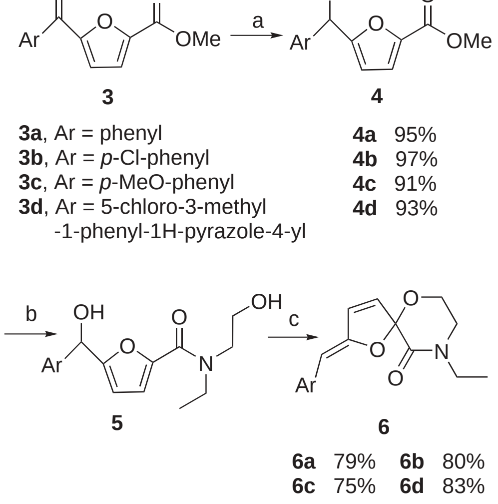
Key words: tonghaosu analogs, antifeedant, lactam, spiroketalization, diastereoselective

Tonghaosu, 2-(2,4-hexadiynylidene)-1,6-dioxaspiro-[4.4]-non-3-ene (**1**) is an antifeedant component of a vegetable called tonghao (*Chrysanthemum sgetum* L. or *C. Coronarium* L.) in China and was also found in other plants of the tribe *Athemdeae*.[1,2] The first synthesis of tonghaosu was reported in early 1960s by Bohlmann and co-workers, however, in quite low overall yield.[3] Recently, we developed a general and concise synthetic methodology for tonghaosu and its spiroketal enol ether characterized analogs, which employed acid-catalyzed dehydration-spiroketalization as the key step (Scheme 1).[4,5] Up to now a diversity of tonghaosu analogs **2** with varied unsaturated groups and B-rings have been prepared and most of them showed antifeeding activity comparable to that of tonghaosu. Herein, we would like to report our further efforts towards the synthesis of both racemic and enantiopure lactam-containing tonghaosu analogs.



Scheme 1

In view of the important roles that amide-containing compounds play in agrochemicals, we anticipated that introduction of an amide functionality into tonghaosu analog might give rise to better biological activity. The synthesis of lactam-containing tonghaosu analogs is outlined in Scheme 2. Keto esters **3**, readily prepared by Friedel–Crafts reaction of methyl 2-furoate with corresponding acyl chlorides,[6] were reduced selectively with $NaBH_4$ to form furanyl alcohols **4** in good yields. Compounds **4** reacted with 2-ethylaminoethanol in refluxing methanol to give amides **5**, which were treated with camphorsulfonic acid (CSA) to afford smoothly lactam-containing tonghaosu analogs **6**. Similarly, compound **10** was prepared starting from acyl chloride **7** and 2-ethylaminophenol (**8**) (Scheme 3). Unlike other kinds of tonghaosu analogs, amide containing tonghaosu analogs were found to be more stable and could be kept at room temperature for long time, which would facilitate further research.



Scheme 2 Synthesis of lactams **6**. *Reagents and conditions*: (a) $NaBH_4$, MeOH; (b) 2-ethylaminoethanol, Et_3N, MeOH, reflux; (c) CSA, CH_2Cl_2, r.t.

Our previous findings demonstrated that compounds resulting from selective reduction of endo-cyclic double bond of tonghaosu analogs were more effective insect antifeedant.[7] With these new compounds in hand, we also carried out the reduction reaction. Compounds **6** and **10** were treated with $NaBH_4/NiCl_2$[8] in methanol with DME as a co-solvent to give **11** and **12** respectively. The reactions were complete in several minutes giving the products in high yields (Scheme 4).

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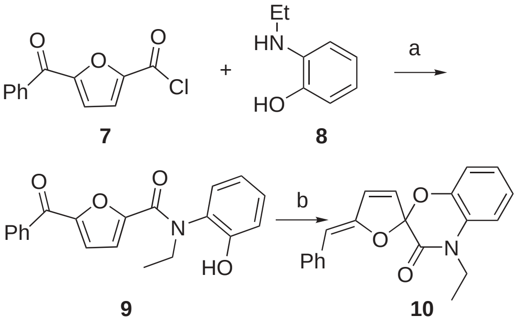
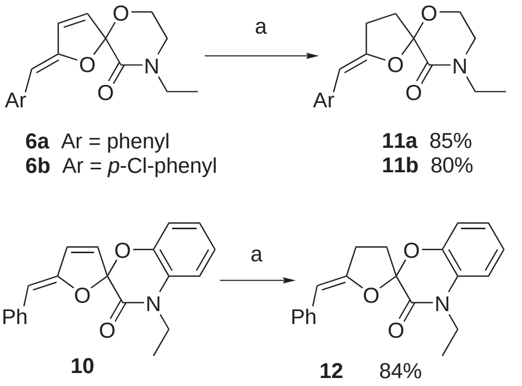


Scheme 3 Synthesis of lactam **10**. *Reagents and conditions*: (a) Et$_3$N, CH$_2$Cl$_2$, 89%; (b) i. NaBH$_4$, MeOH; ii. CSA, CH$_2$Cl$_2$, r.t., 5 h, 84%

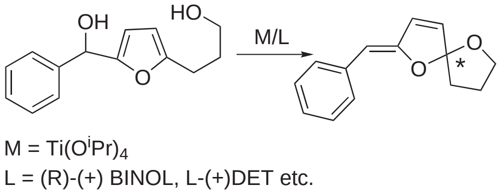


Scheme 4 Selective reduction of **6** and **10**. *Reagents and conditions*: a) NaBH$_4$/NiCl$_2$, DME/MeOH, 0 °C to r.t.

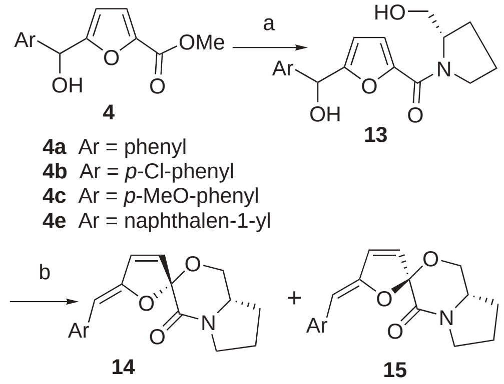
Tonghaosu analogs so far obtained are all recemic compounds. In order to better understand the structure-activity relationships of tonghaosu analogs and to find more effective green agrochemicals, efforts towards the synthesis of enantiopure tonghaosu analogs are urgently needed. Although a variety of methods are available for synthesis of spiroketal containing compounds, no method can be relied on for construction of the stereochemistry of spiroketal carbon.[9]

As mentioned above, acid-catalyzed dehydration spiroketalization was the key step in the synthesis of tonghaosu analogs, and both Brønsted and Lewis acids, such as CuSO$_4$·5H$_2$O, and ZnCl$_2$, were effective promoters. We envisioned that enantioselective spiroketalization might be effected in the presence of a chiral Lewis acid. Our initial investigation was to use titanium(IV) as the Lewis acid and screen a series of chiral ligands. Unfortunately, the preliminary results were unsatisfactory and the best ee value was only up to 20% (Scheme 5), presumably due to the reversibility of spiroketalization under acid conditions, thus eroding the established chirality.

We then turned our attention to substrate-controlled method to construct spiroketal center. Instead of an achiral amino alcohol, for example, 2-ethylaminoethanol, a chiral one was used to prepare spiroketalization precursor. (*S*)-Prolinol reacted with furan ester **4** to afford furan amide **13**, which was treated with CuSO$_4$ for 24 hours in refluxing toluene (Condition A) to give a mixture of **14** and **15** in moderate selectivity (Scheme 6). However, under a milder condition with camphorsulfonic acid as the promoter in dichloromethane at room temperature (Condition B), the spiroketalization was effected in a highly diastereoselective manner with **14** as the predominant product. Results from two cyclization methods are shown in Table 1. The absolute configuration of **14a** was determined unambiguously by X-ray structure (Figure 1). The stereochemistry of **14b**, **14c** and **14e** was assigned as shown in Scheme 5 in analogy with **14a**.



Scheme 5 Chiral Lewis acid catalyzed spiroketalization



Scheme 6 Synthesis of optical tonghaosu analogs **14** and **15**. *Reagents and Conditions*: (a) (*S*)-prolinol, Et$_3$N, MeOH, reflux; (b) Condition A: CuSO$_4$·5H$_2$O, toluene, reflux, 24 h; Condition B: CSA, CH$_2$Cl$_2$, r.t., 24 h

In summary, a series of lactam-containing tonghaosu analogs were prepared in a concise and effective way. Prolinol-derived furan amides afforded lactams **14** and **15** in high diastereoselectivity with **14** as the major product.

Table 1 Spiroketalization of **13** Under Two Different Conditions[a]

Substrate	Condition A		Condition B	
	Ratio of **14:15**	Yield (%)	Ratio of **14:15**	Yield (%)
13a	2.5:1	74	8.4:1	82
13b	2.3:1	70	–	–
13c	–	–	8.8:1	85
13e	3.5:1	84	8.1:1	87

[a] Condition A: CuSO$_4$·5H$_2$O, toluene, reflux, 24 h; Condition B: CSA, CH$_2$Cl$_2$, r.t., 24 h.

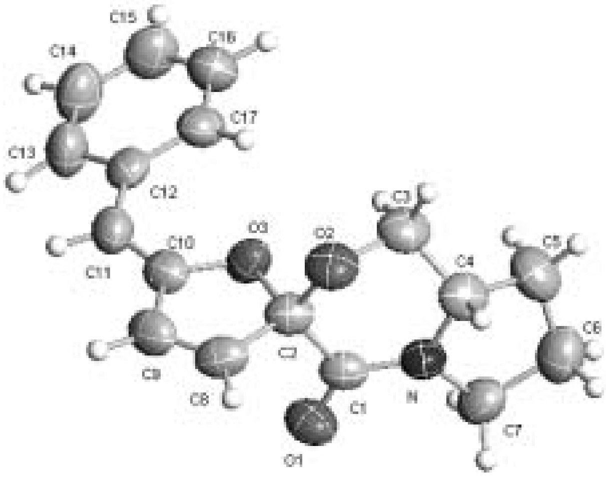


Figure 1 X-ray crystal structure of **14a**

This new type of tonghaosu analogs was more stable than other tonghaosu products including natural ones, and showed obvious antifeedant activity in preliminary biological tests. Compound **14e** also showed good pesticidal activity.

IR spectra were recorded on Perkin-Elmer 983 or Shimadzu IR-440 spectrometer. ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ on an AMX-300, DPX-300 or DRX-400 spectrometer with TMS as the internal standard. Mass spectra were taken on a Mariner (PE, for ESI), HP5973N or HP5989A instrument. HRMS (EI) spectra were obtained on a Kratos CONCEPT 1H mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter at 20°C. 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 petroleum ether (bp 60–90°C)–EtOAc or EtOAc–EtOH system as eluent.

Furanols 4; General Procedure

To a solution of **3** (10 mmol) in absolute MeOH (20 mL) at 0 °C was added $NaBH_4$ (0.19 g, 5 mmol) in portions. The reaction mixture was stirred overnight, and then distilled H_2O (10 mL) was added. The organic solvent was removed under reduced pressure. The residue was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). Removal of solvents and purification by chromatography afforded **4**.

4a

Oil; yield: 2.20 g (95%).

IR (film): 3441, 3032, 2954, 1718, 1142, 1020, 762, 701 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.41 (5 H, m), 7.06 (1 H, d, *J* = 3.9 Hz), 6.20 (1 H, d, *J* = 3.9 Hz), 5.81 (1 H, s), 3.81 (3 H, s).

MS: *m/z* = 232 (M$^+$, 32.1), 173 (100.0), 127 (51.0), 123 (17.9), 117 (27.5), 115 (22.2), 105 (18.4).

Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23, H, 5.21. Found: C, 67.01, H, 5.14.

4b

Oil; yield: 2.59 g (97%).

IR (film): 3419, 1695, 1593, 1536, 1492, 1440, 1410, 1321, 1211, 1140, 983, 771, 760 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (4 H, m), 7.06 (1 H, d, *J* = 3.9 Hz), 6.20 (1 H, d, *J* = 3.9 Hz), 5.81 (1 H, s), 3.81 (3 H, s).

MS: *m/z* = 266 (M$^+$, 32.6), 249 (19.5), 235 (8.9), 231 (21.3), 208 (12.7), 207 (100.0).

HRMS: *m/z* calcd for $C_{13}H_{11}ClO_4$: 266.0346; found: 266.0319.

4c

Oil; yield: 2.37 g (91%).

IR (film): 3419, 2957, 1840, 1733, 1612, 1514, 1439, 1307, 1251, 1141, 1041, 1033, 763 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (2 H, dd, *J* = 7.7, 1.8 Hz), 7.13 (1 H, d, *J* = 3.5 Hz), 7.58 (2 H, dd, *J* = 6.8, 2.0 Hz), 6.18 (1 H, dd, *J* = 3.2, 0.5 Hz), 5.81 (1 H, s), 3.87 (3 H, s), 3.83 (3 H, s).

MS: *m/z* = 262 (M$^+$, 23.6), 245 (27.9), 148 (55.7), 131 (41.6), 99 (26.3), 58 (100.0).

Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.12, H, 5.38. Found: C, 64.33, H, 5.16.

4d

Colorless solid; yield: 3.35 g (93%); mp 92–93 °C.

IR (film): 3358, 2937, 1720, 1595, 1553, 1502, 1304, 1211, 1139, 1015, 761 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (5 H, m), 7.11 (1 H, d, *J* = 3.7 Hz), 6.35 (1 H, dd, *J* = 3.5, 0.9 Hz), 5.85 (1 H, s), 3.84 (3 H, s), 2.22 (3 H, s).

MS: *m/z* = 346 (M$^+$, 35.0), 286 (50.5), 153 (100.0).

HRMS: *m/z* calcd for $C_{18}H_{19}ClN_2O_4$: 346.0720; found: 346.0738.

4e

Syrup; yield: 2.48 g (88%).

IR (KBr): 3347, 2944, 1723, 1587, 1206, 843 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (1 H, d, *J* = 6.6 Hz), 7.85 (2 H, dd, *J* = 9.0, 2.1 Hz), 7.68 (1 H, d, *J* = 7.0 Hz), 7.44 (3 H, m), 7.08 (1 H, d, *J* = 3.6 Hz), 6.21 (1 H, d, *J* = 3.3 Hz), 5.81 (1 H, s), 3.84 (3 H, s).

MS: *m/z* 346 (M$^+$, 74.3), 329 (21.7), 245 (63.1.5), 171 (100.0).

Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.33, H, 5.00. Found: C, 72.47, H, 5.24.

Lactams 6; General Procedure

To a solution of furan ester **4** (10 mmol) in anhyd MeOH (20 mL) under N_2 were added 2-ethylaminoethanol (0.89 g, 10 mmol) and Et_3N (10 mL). The mixture was refluxed for 24 h, cooled to r.t., and concentrated under reduced pressure. The residue obtained was dissolved in CH_2Cl_2 (20 mL), and to the solution was added a catalytic amount of CSA (20 mg, 0.86 mmol). The resulting mixture was stirred at r.t. for 24 h, and then quenched with sat. aq $NaHCO_3$ solution. The separated aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were washed with brine and dried (Na_2SO_4). After removal of the solvent, the residue was chromatographed to afford lactam **6**.

6a

White solid; yield: 2.14 g (79%); mp 165–166 °C.

IR (KBr): 3084, 2978, 2889, 1649, 1493, 1448, 1355, 939, 828, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63–7.13 (5 H, m), 6.53 (1 H, d, *J* = 5.7 Hz), 6.09 (1 H, d, *J* = 6.0 Hz), 5.55 (1 H, s), 4.51 (1 H, td, *J* = 11.7, 3.3 Hz), 4.02 (1 H, ddd, *J* = 11.7, 4.5, 0.9 Hz), 3.78 (1 H, td, *J* = 12.0, 4.5 Hz), 3.59 (1 H, m), 3.47 (1 H, m), 3.28 (1 H, dd, *J* = 3.0, 0.9 Hz), 1.23 (3 H, td, *J* = 6.9, 3.0 Hz).

MS: *m*/*z* = 271 (M^+, 47.0), 227 (26.0), 215 (26.0), 172 (100.0), 144 (31.5), 116 (32.5), 115 (49.1).

Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.33; H, 6.25; N, 5.00.

6b

White solid; yield: 2.44 g (80%); mp 116–117 °C.

IR (KBr): 3088, 2933, 2881, 1652, 1489, 1347, 1197, 937, 846, 718, 512 cm^{-1}.

^1H NMR (300M Hz, $CDCl_3$): δ = 7.53 (2 H, dd, *J* = 6.2, 2.1 Hz), 7.24 (2 H, dd, *J* = 3.9, 1.9 Hz), 6.53 (1 H, d, *J* = 5.7 Hz), 6.11 (1 H, d, *J* = 5.6 Hz), 5.50 (1 H, s), 4.46 (1 H, td, *J* = 11.9, 3.6 Hz), 4.01 (1 H, ddd, *J* = 11.9, 4.2, 1.6 Hz), 3.76 (1 H, td, *J* = 11.9, 4.5 Hz), 3.59 (1 H, m), 3.44 (1 H, m), 3.29 (1 H, ddd, *J* = 12.7, 3.5, 1.5 Hz), 1.21 (3 H, t, *J* = 7.2 Hz).

MS: *m*/*z* = 305 (32.8, M^+), 206 (100.0), 115 (63.7), 233 (39.1), 208 (33.8).

HRMS: *m*/*z* calcd for $C_{16}H_{16}ClNO_3$: 305.0819; found: 305.0841.

6c

White solid; yield: 2.26 g (75%); mp 122–123 °C.

IR (film): 3092, 2941, 1650, 1510, 1254, 1199, 1179, 1008, 985, 939, 846 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.56 (2 H, dd, *J* = 6.8, 2.2 Hz), 6.85 (2 H, dd, *J* = 6.9, 2.0 Hz), 6.51 (1 H, d, *J* = 5.3 Hz), 6.03 (1 H, dd, *J* = 5.5, 0.6 Hz), 5.50 (1 H, s), 4.49 (1 H, td, *J* = 12.0, 3.5 Hz), 4.00 (1 H, ddd, *J* = 12.1, 4.6, 1.4 Hz), 3.80 (3 H, s), 3.76 (1 H, dd, *J* = 8.0, 4.5 Hz), 3.60 (1 H, m), 3.44 (1 H, m) 3.28 (1 H, ddd, *J* = 12.4, 3.0, 1.4 Hz), 1.19 (3 H, t, *J* = 7.6 Hz).

MS: *m*/*z* = 301 (77.2, M^+), 245 (33.5), 230 (41.1), 229 (31.6), 202 (100.0), 153 (84.7), 131 (30.5).

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.85; H, 6.39, N, 4.60.

6d

Syrup; yield: 3.34 g (83%).

IR (KBr): 2984, 1659, 1502, 1378, 1213, 1008, 942, 769 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.31 (5 H, m), 6.55 (1 H, d, *J* = 5.8 Hz), 6.07 (1 H, d, *J* = 5.8 Hz), 5.31 (1 H, s), 4.39 (1 H, td, *J* = 12.1, 3.3 Hz), 3.95 (1 H, dd, *J* = 11.7, 4.1Hz), 3.69 (1 H, td, *J* = 12.3, 4.6 Hz), 3.46 (2 H, m), 3.21 (1 H, dd, *J* = 12.8, 2.3 Hz), 2.37 (3 H, s), 1.16 (3 H, t, *J* = 7.0 Hz).

MS: *m*/*z* = 385 (M^+, 55.0), 286 (50.5), 153(100.0).

HRMS: *m*/*z* calcd for $C_{21}H_{24}ClN_3O_3$: 401.1506; found: 401.1539.

Amide 9

To a solution of 2-ethylaminophenol (0.69 g, 5 mmol) in anhyd THF (20 mL) under N_2 was added the acid chloride **7** (1.17 g, 5 mmol) slowly at 0 °C. The mixture was stirred for 2 h at the same temperature, then for additional 3 h at r.t. Distilled H_2O (10 mL) was added to quench the reaction. The separated aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine and dried (Na_2SO_4). After removal of the solvents, the residue was chromatographed to afford **9**; syrup; yield: 1.49 g (89%).

IR (KBr): 3213, 2983, 1648, 1628, 1591, 1538, 1419, 1278 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.15 (1 H, s), 7.88 (2 H, d, *J* = 6.9 Hz), 7.55 (1 H, t, *J* = 7.5 Hz), 7.43 (2 H, t, *J* = 7.5 Hz), 7.24–7.18 (1 H, m), 7.04–6.98 (2 H, m), 6.94 (1 H, d, *J* = 3.3 Hz), 6.84 (1 H, t, *J* = 7.2 Hz), 5.99 (1 H, d, *J* = 3.0 Hz), 4.15–4.08 (1 H, m), 3.56–3.49 (1 H, m), 1.33–1.15 (3 H, m).

MS: *m*/*z* = 335 (M^+, 15.0), 230 (73.0), 202 (28.7), 199 (55.8), 136 (80.5).

HRMS: *m*/*z* calcd for $C_{20}H_{17}NO_4$: 335.1158. found: 335.1121.

Lactam 10

To a solution of **9** (3.36 g, 5 mmol) in MeOH (20 mL) was added $NaBH_4$ (0.39 g, 5 mmol) in portions at 0 °C. The resulting mixture was stirred for 4 h at r.t. and distilled H_2O (10 mL) was added to quench the reaction. The solvent was removed under reduced pressure. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine and dried (Na_2SO_4). The solvents were evaporated and the obtained residue was dissolved in CH_2Cl_2 (20 mL). To this solution was added a catalytic amount of CSA (20 mg, 0.86 mmol) and the resulting mixture was stirred at r.t. for 24 h, and then quenched with sat. aq $NaHCO_3$ solution. The aqueous phase was separated and extracted with CH_2Cl_2, and the combined organic layers were washed with brine and dried (Na_2SO_4). After removal of the solvent, the residue was chromatographed to afford **10**; amorphous solid; yield: 2.68 g (84%).

IR (KBr): 3105, 1684, 1501, 1413, 1360, 1244, 1099, 989, 924 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.07 (9 H, m), 6.65 (1 H, d, *J* = 5.7 Hz), 6.37 (1 H, d, *J* = 5.7 Hz), 5.60 (1 H, s), 4.10 (2 H, m), 1.33 (3 H, t, *J* = 7.2 Hz).

MS: *m*/*z* = 319 (M^+, 55.3), 291 (48.1), 274 (10.5), 263 (100.0), 234 (18.8), 128 (100.0).

HRMS: *m*/*z* calcd for $C_{20}H_{17}NO_3$: 319.1208. found: 319.1234.

$NaBH_4$/$NiCl_2$ Reduction of 6a,b and 10; 9-Ethyl-2-[(*Z*)-phenylmethylidene]-1,6-dioxa-9-azaspiro[4.5]decan-10-one (11a); Typical procedure

To a solution of compound **6a** (1 mmol) in DME (5 mL) and anhyd MeOH was added $NaBH_4$ (190 mg, 5 mmol) at 0 °C, and then $NiCl_2$ (20 mg) in portions. The mixture was stirred at r.t. for 1 h until the material disappeared according to TLC. Sat. aq $NaHCO_3$ was then added until pH 8, the mixture was extracted with Et_2O and the combined organic layers were washed with brine and dried (Na_2SO_4). Removal of solvents yielded the crude product, which was purified by chromatography to afford **11a**; syrup; yield: 116 mg (85%).

IR (film): 2959, 2934, 1675, 1653, 1490, 1449, 1355, 1187, 1040, 987, 921 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.53 (2 H, m), 7.23 (2 H, m), 7.08 (1 H, m), 5.31 (1 H, s), 4.33 (1 H, td, *J* = 8.0, 3.3 Hz), 3.87 (1 H, dd, *J* = 12, 4.2 Hz), 3.76–3.54 (2 H,m), 3.47–3.38 (1 H, m), 3.21 (1 H, dd, *J* = 12.0, 3.3 Hz), 2.91 (2 H, m), 2.72 (1 H, m), 1.99 (1 H, m), 1.20 (3 H, m).

MS: *m*/*z* = 273 (M^+, 71.4), 182 (72.3), 155 (100.0), 154 (35.9), 128 (22.9), 126 (29.5).

Anal. Calcd for $C_{16}H_{19}O_3N$: C, 70.33; H, 6.96; N, 5.13. Found: C, 70.06; H, 6.53; N, 4.89.

11b

This compound was prepared from **6b** according to the procedure similar to **11a**; white solid; yield: 122 mg (80%); mp 84–86 °C.

IR (film): 2978, 2937, 1668, 1490, 1357, 1303, 1203, 1089, 988, 843 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.42 (2 H, d, *J* = 8.4 Hz), 7.21 (2 H, d, *J* = 8.4 Hz), 5.26 (1 H, s), 4.29 (1 H, td, *J* = 12.0, 3.3 Hz), 3.88 (1 H, dd, *J* = 12.0, 4.5 Hz,), 3.70 (1 H, td, *J* = 11.7, 4.5 Hz,), 3.83 (1 H, m), 3.43 (1 H, m), 3.20 (1 H, dd, *J* = 12.8, 3.3 Hz), 2.91 (2 H, m), 2.70 (1 H, m), 2.04–1.95 (1 H, m), 1.21 (3 H, t, *J* = 7.5 Hz).

MS: *m*/*z* = 307 (M^+, 30.6), 182 (100.0), 155 (94.4), 152 (62.5), 126 (42.8).

HRMS: *m*/*z* calcd for $C_{17}H_{18}ClNO_3$: 307.0975; found: 307.0961.

12
This compound was prepared from **10** according to the procedure similar to **11a**; syrup; yield: 130 mg (81%).

IR (KBr): 2975, 1686, 1503, 1417, 1316, 1271, 958, 918 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.25–6.97 (9 H, m), 5.32 (1 H, s), 4.12–4.03 (2 H, m), 3.12–2.94 (3 H, m), 2.32–2.28 (1 H, m), 1.34–1.25 (3 H, m).

MS: *m*/*z* = 322 (M^+ + 1, 22.6), 321 (M^+, 100.0), 276 (11.9), 232 (11.2), 230 (16.0), 203 (98.0), 202 (31.4).

Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.35. Found: C, 74.66; H, 5.81; N, 4.55.

Optical Tonghaosu Analogs 14 and 15; General Procedure
Method A: To a solution of furan ester **4** (10 mmol) in anhyd MeOH (20 mL) under N_2 was added (*S*)-prolinol (1.01 g, 10 mmol) and Et_3N (10 mL). The mixture was refluxed for 24 h, cooled to r.t., and concentrated under reduced pressure. The obtained residue was treated with $CuSO_4{\cdot}5H_2O$ (2.5 g, 10 mmol) in refluxing toluene (20 mL) until the material disappeared according to TLC. After removal of the solvent, the residue was chromatographed to afford **14** and **15**.

Method B: To a solution of furan ester **4** (10 mmol) in anhyd MeOH (20 mL) under N_2 was added prolinol (1.01 g, 10mmol) and Et_3N (10 mL). The mixture was refluxed for 24 h, cooled to r.t., and concentrated under reduced pressure. The obtained residue was dissolved in CH_2Cl_2 (20 mL), and to the solution was added a catalytic amount of CSA (20 mg, 0.86 mmol). The resulting mixture was stirred at r.t. for 24 h, and then quenched with sat. aq $NaHCO_3$ solution. The separated aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were washed with brine and dried (Na_2SO_4). After removal of the solvent, the residue was chromatographed to afford **14** and **15**.

14a
White solid; Method A: yield: 1.60 g (50%); Method B: 2.71 g (73%); mp 204–206 °C; $[\alpha]_D$ +99.6 (*c* = 1.0, $CHCl_3$).

IR (KBr): 3092, 3019, 2960, 2882, 1668, 1595, 1489, 1349, 1137, 1096, 938, 812, 692 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.58 (2 H, d, *J* = 7.5 Hz), 7.31 (2 H, m), 7.17 (1 H, d, *J* = 7.4 Hz), 6.49 (1 H, d, *J* = 5.8 Hz), 6.24 (1 H, d, *J* = 5.6 Hz), 5.53 (1 H, s), 4.36–4.23 (2 H, m), 3.70–3.58 (3 H, m), 2.29–2.22 (1 H, m), 2.07–1.94 (2 H, m), 1.64–1.43 (1 H, m).

MS: *m*/*z* = 283 (58.6, M^+), 239 (100.0), 227 (38.6), 172 (77.6), 144 (51.5), 116 (46.6), 115 (57.6).

HRMS: *m*/*z* calcd for $C_{17}H_{17}NO_{3:}$ 283.1208; found: 283.1196.

15a
White solid; Method A: 0.60 g (25%); Method B: 0.29 g (9%); mp 162–163 °C; $[\alpha]_D$ –275.3 (*c* = 1.0, $CHCl_3$).

IR (KBr): 3082, 2977, 2889, 1663, 1489, 1458, 1348, 1335, 1241, 994, 947, 815, 691 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.61 (2 H, d, *J* = 7.9 Hz), 7.29 (2 H, m), 7.15 (1 H,, *J* = 7.8 Hz), 6.56 (1 H, d, *J* = 5.9 Hz), 6.06 (1 H, d, *J* = 5.8 Hz), 5.55 (1 H, s), 4.15 (1 H, dt, *J* = 11.3, 1.9 Hz), 3.99 (1 H, m), 3.86 (1 H, m), 3.71 (1 H, m), 3.83 (1 H, m), 2.06 (2 H, m), 1.87 (1 H, m), 1.52 (1 H, m).

MS: *m*/*z* = 283 (3.6, M^+), 239 (44.4), 172 (54.0), 144 (50.0), 116 (68.1), 115 (100.0).

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.85; H, 6.09; N, 4.90.

14b
White solid; Method A: 1.54 g; (49%); mp 204–206 °C; $[\alpha]_D$ +169.0 (*c* = 1.0, $CHCl_3$).

IR (KBr): 2982, 2888, 1671, 1582, 1488, 1456, 1253, 1083, 933, 851, 738 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.52 (2 H, dt, *J* = 2.4, 9.1Hz), 7.23 (2 H, dt, *J* = 6.8, 2.0 Hz,), 6.53 (1 H, d, *J* = 5.6 Hz), 6.09 (1 H, d, *J* = 5.6 Hz), 5.49 (1 H, s), 4.17 (1 H, dd, *J* = 10.5, 3.0 Hz), 3.97 (1 H, t, *J* = 10.4 Hz), 3.89 (1 H, m), 3.75 (1 H, m), 3.51 (1 H, td, *J* = 10.5, 1.8 Hz), 2.12 (2 H, m), 1.89 (1 H, m), 1.57 (1 H, m).

MS: *m*/*z* = 317 (27.1, M^+), 273 (75.2), 261 (34.0), 206 (100.0), 208 (34.2), 115 (73.2).

HRMS: *m*/*z* calcd for $C_{17}H_{16}ClNO_3$: 317.0819; found: 317.0835.

15b
White solid; Method A: 0.67 g (21%); mp 162–163 °C; $[\alpha]_{D-}$ 232.0 (*c* = 1.0, $CHCl_3$).

IR (KBr): 2983, 2875, 1671, 1488, 1327, 1253, 1084, 925, 850, 737, 62 5 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.49 (2 H, dd, *J* = 9.3, 3.3 Hz), 7.28 (2 H, dd, *J* = 9.3, 3.3 Hz), 6.47 (1 H, d, *J* = 5.4 Hz), 6.26 (1 H, d, *J* = 5.7 Hz), 5.48 (1 H, s), 4.33 (1 H, dd, *J* = 9.9, 4.5 Hz), 4.22 (1 H, m), 3.62 (3 H, m), 2.27 (1 H, m), 2.04 (2 H, m), 1.60 (1 H, m).

MS: *m*/*z* = 317 (16.3, M^+), 273 (47.8), 261 (22.7).

HRMS: *m*/*z* calcd for $C_{17}H_{16}ClNO_3$: 317.0819; found: 317.0829.

14c
Syrup; Method B: 239 mg (76%); $[\alpha]_D$ +116.0 (*c* = 1.0, $CHCl_3$).

IR (KBr): 2942, 2876, 1671, 1450, 1300, 1250, 1179, 928, 852, 737 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.52 (2 H, d, *J* = 8.8 Hz), 6.85 (2 H, d, *J* = 8.8 Hz), 6.48 (1 H, d, *J* = 5.6 Hz), 6.19 (1 H, d, *J* = 5.7 Hz), 5.49 (1 H, s), 4.31 (2 H,m), 3.81 (3 H, s), 3.63 (3 H, m), 2.27 (1 H, m), 2.02 (2 H, m), 1.60 (1 H, m).

MS: *m*/*z* = 313 (M^+, 100.0), 269 (46.6), 257 (34.8), 242 (25.0): 202 (96.4), 174 (32.9), 165 (73.7), 131 (26.2).

Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.88; H, 6.25; N, 4.42.

15c
Syrup; Method B: 27.2 mg (9%); $[\alpha]_D$ –208.6 (*c* = 1.0, $CHCl_3$).

IR (KBr): 2942, 2876,1671, 1606, 1584, 1509, 1450, 1300, 1250, 1179, 928, 852, 817, 737 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.55 (2 H, d, *J* = 8.7 Hz), 6.84 (2 H, dd, *J* = 7.5, 2.1 Hz), 6.45 (1 H, dd, *J* = 5.7, 1.5 Hz), 6.01 (1 H, dd, *J* = 6.0, 0.9 Hz), 5.50 (1 H, s), 4.16 (1 H, dd, *J* = 11.1, 3.9 Hz), 4.00 (1 H, t, *J* = 11.8 Hz), 3.86 (1 H, m), 3.79 (3 H, s), 3.75 (1 H, m), 3.51 (1 H, t, *J* = 11.4 Hz), 2.07 (2 H, m), 1.89 (1 H, m), 1.55 (1 H, m).

MS: *m*/*z* = 313 (M^+, 100.0), 269 (45.8), 257 (35.3), 202 (85.9), 174 (29.8), 165 (51.6), 131 (25.6).

Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.77; H, 5.98; N, 4.36.

14e
Syrup; Method A: 217.6 mg (65%); Method B: 257.9 mg (77%); $[\alpha]_D$ +145.3 (*c* = 1.0, $CHCl_3$).

IR (KBr): 2961, 2881, 1666, 1456, 1269, 1235, 1035, 930, 777 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (1 H, m), 7.84 (1 H, d, J = 6.9 Hz), 7.72 (1 H, d, J = 8. 3 Hz), 7.53–7.42 (4 H, m), 6.66 (1 H, d, J = 5. 5 Hz), 6.33 (1 H, d, J = 5.7 Hz), 6.24 (1 H, s), 4.34 (1 H, dd, J = 4.3, 9.8 Hz), 4.21 (1 H, m), 3.70–3.60 (3 H, m), 2.25–2.19 (1 H, m), 2.06–1.95 (2 H, m), 1.62–1.55 (1 H, m).

MS: m/z = 334 (M^+ + 1, 97.8), 333 (M^+, 31.0), 288 (12.3), 276 (15.1), 260 (7.0), 205 (13.9), 194 (24.8), 165 (100.0).

Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.84, H, 5.91; N, 4.33.

15e

Amorphous solid; Method A: 62.2 mg (19%); Method B: 31.8 mg (10%); $[\alpha]_D$ –192.7 (c = 1.0, $CHCl_3$).

IR (KBr): 2925, 2887, 1663, 1456, 1335, 1197, 994, 779 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (1 H, m), 7.82 (1 H, m), 7.74 (1 H, m), 7.49 (4 H, m), 6.80 (1 H, d, J = 5.7 Hz), 6.26 (1 H, s), 6.13 (1 H, d, J = 5.7 Hz), 4.03 (1 H, m), 3.91 (1 H, m), 3.75 (2 H, m), 3.54 (1 H, m), 2.27–2.20 (1 H, m), 2.05–1.94 (2 H, m), 1.63–1.53 (1 H, m).

MS: m/z = 334 (M^+ + 1, 14.0), 333 (M^+, 58.4), 289 (10.5), 277 (18.1), 222 (48.6), 194 (23.8), 165 (100.0).

Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 76.04, H, 5.81; N, 4.17.

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