ORGANIC LETTERS

1999
Vol. 1, No. 3
399−401

# The First Synthesis of Tonkinecin, an Annonaceous Acetogenin with a C-5 Carbinol Center

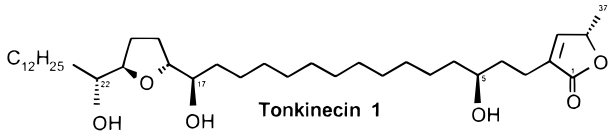
**Tai-Shan Hu, Qian Yu, Qi Lin, Yu-Lin Wu,* and Yikang Wu**

*State Key Laboratory of Bio-organic & Natural Products Chemistry and Shanghai-Hong Kong Joint Laboratory in Chemical Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China*

*ylwu@pub.sioc.ac.cn*

**Received April 28, 1999**

## ABSTRACT




**Reported herein is the first synthetic approach to tonkinecin (1) which uses a palladium-catalyzed cross-coupling reaction between the tetrahydrofuran unit (4) and the butenolide (3) as the key step for constructing the backbone of 1. The stereogenic centers at C-5, C-21, C-22, and C-36 were derived from D-xylose, D-glucose, and L-lactate, respectively, whereas those at C-17, and C-18 were generated using Sharpless asymmetric dihydroxylation.**

Tonkinecin **1** is a monotetrahydrofuran acetogenin with a hydroxyl group at C-5 recently isolated from roots of *Uvaria tonkinesis* by Yu and co-workers. This compound has demonstrated potent cytotoxity against the Bel 7402 (heptoma), BGC (gastrocarcinoma), HCT-8 (colon adenocarinoma), and HL-60 (leukemia) human tumor cell lines.[1] Because among the several hundreds of known acetogenins only a few[2] have a hydroxyl at C-5 and (to the best of our

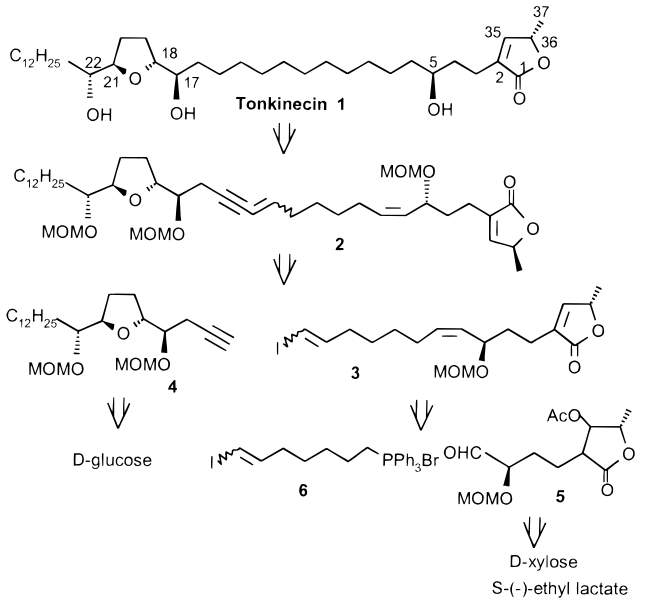
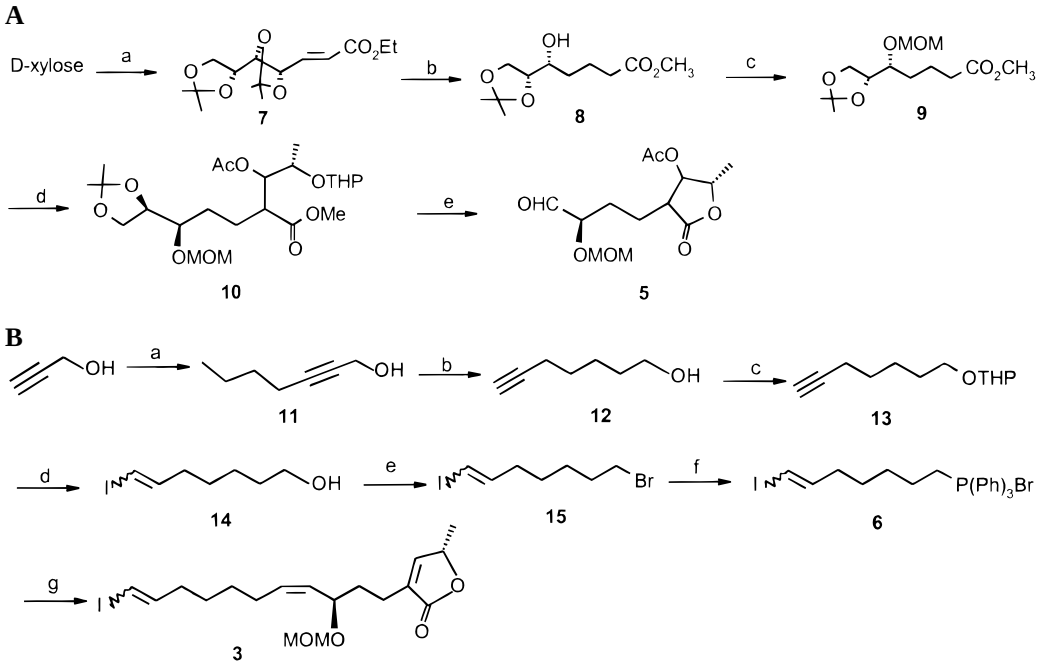



**Figure 1.**

(1) Chen, Y.; Yu, D.-Q. *J. Nat. Prod.* **1996**, *59*, 507.
(2) Hisham, A.; Pieters, L. A. C.; Claeys, M.; Esmans, E.; Dommisse, R.; Vlietink, A. J. *Phytochemistry* **1991**, *30*, 545. (b) Hisham, A.; Pieters, L. A. C.; Claeys, M.; Esmans, E.; Dommisse, R.; Vlietink, A. J. *Phytochemistry* **1991**, *30*, 2373. (c) Raynaud, S.; Fourneau, C.; Hocquemiller, R.; Sevenet, T.; Hadio, H. A.; Cave, A. *Phytochemistry* **1997**, *46*, 321.
(3) Yao, Z.-J.; Wu, Y.-L. *Tetrahedron Lett.* **1994**, *35*, 157.
(4) Yadav, J. S.; Barma, D. K. *Tetrahedron* **1996**, *52*, 4457.
(5) (a) Kang, S. K.; Kim, S. G.; Park, D. C.; Lee, J. S.; Yoo, W. J.; Pak, C. S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 9. (b) Wu, W.-L.; Li, J.; Wu, Y.-L. *Chin. J. Chem.* **1994**, *12*, 562.
(6) Wu, W.-L.; Wu, Y.-L. *J. Org. Chem.* **1993**, *58*, 3586.
(7) Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988; p 245.
(8) Yu, Q.; Wu, Y.-K.; Ding, H.; Wu, Y.-L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1183.
(9) Hoye, T. R.; Hanson, P. R.; Kovelesky, A. C.; Ocain, T. D.; Zhuang, Z. P. *J. Am. Chem. Soc.* **1991**, *113*, 9369.
(10) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1997**, *62*, 5989.

10.1021/ol990062y CCC: $18.00 
**Published on Web 06/25/1999**

**Scheme 1**[a,b]




[a] Reagents and conditions for part A: (a) (i) $Ph_3P{=}CHCO_2Et$, benzoic acid (cat.), THF, reflux; (ii) acetone, concentrated $H_2SO_4$ (cat.), $CuSO_4$, room temperature, 52%; (b) Mg, $CH_3OH$, reflux, 61%; (c) MOMCl, *i*-$Pr_2NEt$, $CH_2Cl_2$, 0 °C → room temperature, 98%; (d) (i) LDA, THF−HMPA (6:1,v/v), −78 °C; then (*S*)-*O*-tetrahydropyranyl lactal, 71%; (ii) $Ac_2O$, Py, room temperature, 90%; (e) $H_5IO_6$, $Et_2O$, room temperature, 84%. [b] Reagents and conditions fot part B: (a) $LiNH_2$, $NH_3$ (liquid), *n*-$C_4H_9Br$, 72%; (b) KAPA, 1,3-diaminopropane, 73%; (c) DHP, PPTS (cat.), $CH_2Cl_2$, room temperature, 95%; (d) (i) $Bu_3SnH$, AIBN (cat.), 130 °C; $I_2$, $Et_2O$; (ii) PTSA (cat.), $CH_3OH$, room temperature, 94%; (e) $PPh_3$, $CBr_4$, $CH_2Cl_2$, 0 °C → room temperature, 90%; (f) $PPh_3$, $CH_3CN$, reflux, quantitative; (g) LiHMDS, THF−HMPA (6:1, v/v), −78 °C, then **5**, 31%.

knowledge) no synthesis has been done on these compounds, development of synthetic routes to such compounds is warranted. Herein, we describe the first total synthesis of one of them, tonkinecin (**1**).

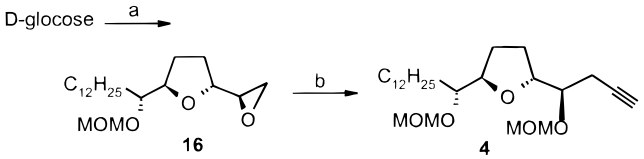
Our retrosynthesis of **1** is illustrated in Figure 1. Thus the key precursor **2** would be synthesized by the Pd(0)-catalyzed cross-coupling reaction of tetrahydrofuran unit **4** with vinyl iodide **3**. The chiral center C-5(*S*) of **1** was derived from D-xylose, C-17(*R*) and C-18(*R*) from D-glucose, and C-36-(*S*) from (*S*)-ethyl lactate, respectively, while the desired stereochemistries at C-21(*R*) and C-22(*R*) were established by Sharpless asymmetric dihydroxylation.

As shown in Scheme 1, the butenolide unit **3** was furnished by Wittig reaction of the chiral aldehyde **5** and the Wittig reagent **6**. The synthesis of chiral aldehyde **5** began with D-xylose and involved construction of a $\gamma$-lactone moiety utilizing the methodology[3] developed by us. Thus D-xylose was converted to $\alpha,\beta$-unsaturated ester **7** in 52% yield according to a known procedure.[4] Reductive cleavage of this $\alpha,\beta$-unsaturated ester with Mg in methanol[5] provided the $\delta$-hydroxyl ester **8** in 61% yield which was then protected as MOM ether. Condensation of the enolate derived from **9** with (*S*)-*O*-tertrahydropyranyl lactal from (+)-ethyl lactate, followed by acetylation of the resulting $\beta$-hydroxy group, gave compound **10** as a mixture of diastereoisomers. Selective removal of isopropylidene acetal and THP group in **10** and subsequent glycol cleavage by periodic acid in one-pot[6] led to chiral aldehyde **5** in 84% yield.

Phosphonium salt **6** was prepared from prop-2-yn-1-ol and 1-bromobutane via a series of transformations. First, an alkylation of prop-2-yn-1-ol with 1-bromobutane gave acetylenic alcohol **11** in 72% yield. The latter was then subjected to the acetylene zipper reaction[7] with potassium 3-aminopropylamide (KAPA) in 3-aminopropylamine to give the terminal acetylene **12** in 71% yield. After protection as THP ether, compound **13** was treated with tributyltin hydride and iodine. The subsequent cleavage of THP group in **13** afforded alcohol **14** (89% overall yield from **12**). Substitution of the OH with Br using $PPh_3/CBr_2$ gave bromide **15**, which was then converted to the phosphonium salt **6** before being subjected to further coupling with aldehyde **5** and concomitant elimination of acetate ester to afford the desired butenolide unit **3** in 31% yield. The low yield at the Wittig reaction step is believed to be caused by elimination of the vinyl iodide under the basic conditions, and better alternatives are currently under exploration.

The tertrahydrofuran part of **4** was constructed (Scheme 2) from D-glucose via epoxide **16** employing a sequence reported[8] by us earlier. Ring opening of this epoxide with lithiotrimethysilyacetylide in the presence of boron trifloride etherate afforded the alkynol, which after removal of the TMS group at the triple bond terminal and protecting the

**Scheme 2**[a]

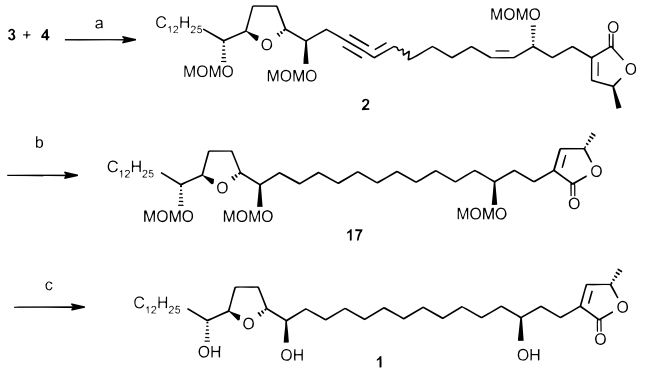



[a] Reagents and conditions: (a) ref 8; (b) i. trimethylsilylacetylene, *n*-BuLi, $BF_3{\cdot}Et_2O$ then **16**, THF; ii. *n*-$Bu_4NF$, THF, 90%; iii. MOMCl, $^iPr_2NEt$, $CH_2Cl_2$, 86%.

OH as MOM ether gave the tetrahydrofuran unit **4**. Unlike in our previous[8] work, where **4** was used directly in the subsequent reaction, this time we isolated this compound and subjected it to full characterization.

The completion of the construction of the entire carbon skeleton was achieved by Pd(0)-catalyzed cross-coupling reaction[9] between the tertrahydrofuran unit **4** and the butenolide unit **3**, which occurred smoothly giving **2** in 93% yield (Scheme 3). Selective hydrogenation with diimide[10]

**Scheme 3**[a]




[a] Reagents and conditions: (a) $(PPh_3)_2PdCl_2$, CuI, $Et_3N$, room temperature, 93%; (b) $TsNHNH_2$, $NaOAc{\cdot}3H_2O$, DME, reflux, 64%; (c) $BF_3{\cdot}Et_2O$, $Me_2S$, 0 °C, 81%.

and removal of the MOM protecting group with boron trifloride etherate in the presence of dimethyl sulfide gave tonkinecin **1**.[11] The physical data of our synthetic sample are identical to those of the natural one.

**Acknowledgment.** This work was supported by the State Committee of Science and Technology of China, Chinese Academy of Sciences (KJ-951-A1-504-04, KJ-952-S1-503) and the National Science Foundation of China (29472070, 29790126). We are grateful to Professor De-Quan Yu of Institute of Materia Medica, Chinese Academy of Medical Sciences for comparing the spectra of our **1** with those of the natural one.

OL990062Y

(11) Physical and spectroscopic data. For **3** (as a 1:5 mixture of *cis* and *trans* isomers): IR (film) 1747, 1651 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.02 (s, 1H), 6.49 (dt, $J$ = 14.3, 7.1 Hz, 0.83 H, from one proton in the *trans* isomer), 6.17 (m, 0.33 H, from two olefinic protons in the *cis* isomer), 5.99 (d, $J$ = 14.3 Hz, 0.83 H, from one proton in the *trans* isomer), 5.61 (dt, $J$ = 11.0, 7.2 Hz, 1H), 5.23 (m, 1H), 5.01 (dq, $J$ = 1.8, 6.6 Hz, 1H), 4.39 (m, 1H), 3.37 (s, 3H), 2.36 (m, 2H), 2.07 (m, 4H), 1.92−1.65 (m, 2H), 1.41 (d, $J$ = 6.6 Hz, 3H), 1.45−1.31 (m, 4H). For **4**: $[\alpha]_D$ 23.0 (*c* 0.5, $CHCl_3$); EI MS (*m*/*z*) 365 ($M^+$ − MOM); $^1H$ NMR (300 MHz, $CD_3COCD_3$) $\delta$ 4.82 (d, $J$ = 6.7 Hz, 1H), 4.75 (s, 2H), 4.61 (d, $J$ = 6.7 Hz, 1H), 4.12 (m, 1H), 3.97 (m, 1H), 3.60 (m, 1H), 3.44 (m, 1H), 3.35 (s, 3H), 3.32 (s, 3H), 2.43 (m, 3H), 1.98 (m, 2H), 1.70 (m, 2H), 1.30−1.20 (m, 22H), 0.87 (t, $J$ = 6.6 Hz, 3H). For **2**: ESI MS (*m*/*z*) 756 ($M^+$ + Na); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.02 (d, $J$ = 1.4 Hz, 1H), 6.03 (dt, $J$ = 15.8, 7.1 Hz, 1H), 5.60 (dt, $J$ = 10.7, 7.4 Hz, 1H), 5.43 (d, $J$ = 15.8 Hz, 1H), 5.23 (m, 1H), 5.00 (m, 1H), 4.84 (d, $J$ = 6.9 Hz, 1H), 4.77 (s, 2H), 4.67 (d, $J$ = 6.9 Hz, 1H), 4.66 (d, $J$ = 6.6 Hz, 1H), 4.48 (d, $J$ = 6.6 Hz, 1H), 4.40 (m, 1H), 4.13 (m, 1H), 4.00 (m, 1H), 3.47 (m, 1H), 3.41 (s, 3H), 3.39 (s, 3H), 3.36 (s, 3H), 2.65−2.22 (m, 3H), 2.13−1.55 (m, 11H), 1.41 (d, $J$ = 6.9 Hz, 3H), 1.39 (m, 6H), 1.30−1.18 (m, 20H), 0.87 (t, $J$ = 6.7 Hz, 3H). For **1**: $[\alpha]_D$ 21.0 (*c* 0.57, $CHCl_3$) (lit.[1] $[\alpha]_D$ 26.54 (*c* 0.09, $CHCl_3$)); EI MS (*m*/*z*) 609, 391, 373, 339, 321, 155; ESI MS (*m*/*z*) 632 ($M^+$ + Na), 610 (M + 1), 592 (M + 1 − $H_2O$), 556 (M + 1 − $3H_2O$); $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 7.03 (d, $J$ = 1.2 Hz, 1H), 5.01 (dq, $J$ = 1.2, 6.6 Hz, 1H), 3.81 (m, 2H), 3.60 (m, 1H), 3.41 (m, 2H), 2.46 (m, 1H), 2.38 (m, 1H), 1.99 (m, 2H), 1.76−1.60 (m, 4H), 1.54−1.37 (m, 6H), 1.41 (d, $J$ = 6.6 Hz, 3H), 1.33−1.24(m, 38H), 0.88 (t, $J$ = 6.6 Hz, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) $\delta$ 174.10, 149.48, 134.08, 82.64, 77.57, 74.10, 70.93, 37.54, 35.40, 33.55, 31.94, 30.00−29.40 (br), 29.38, 28.80, 25.66, 22.71, 21.52, 19.19, 14.11.