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SYNTHESIS OF THE JK RING FRAGMENTS OF YESSOTOXIN AND 42,43,44,45,46,47,55-HEPTANOR-41-OXOYESSOTOXIN

Koji Watanabe, Hiroaki Minato, Michio Murata, and Tohru Oishi*

Department of Chemistry, Graduate School of Science, Osaka University, Toyonaka, Osaka 560-0043, Japan
E-mail: oishi@ch.wani.osaka-u.ac.jp

Abstract – The JK ring fragment (**7**) of 42,43,44,45,46,47,55-heptanor-41-oxoyessotoxin was synthesized via enyne metathesis and 6-*exo* cyclization of a hydroxy epoxide. Conversion of **7** into the JK ring fragment (**6**) of yessotoxin was achieved in a single step by treatment with an alkenyllithium.

Yessotoxin (YTX, **1**) [1] is a disulfated polyether toxin produced by the dinoflagellate *Protoceratium* and by *Lingulodinium* species (Figure 1).[2] Although YTX was first isolated in association with diarrhetic shellfish poisoning (DSP), it has been removed from the category of DSP toxins due to a lack of diarrhoegenicity.[3] A number of YTX congeners, for instance 42,43,44,45,46,47,55-heptanor-41-oxoyessotoxin (**2**) and **3-5** (Figure 1),[4] have been identified, whose structural diversity is focused on the K ring and side chains. YTX has recently been shown to exhibit intriguing biological activities, e.g., (i) cytotoxicity against human tumor cell lines,[5] (ii) activation of caspases via mitochondrial signal transduction pathways,[6] and (iii) activation of phosphodiesterases.[7] Meanwhile, structure-activity relationship studies using YTX congeners have been hampered by their scarce availability from natural sources. During the course of our synthetic studies of YTX and its congeners,[8] we developed an efficient method for convergent synthesis of the CDEF and FGHI ring systems via α-cyano ethers.[9] Herein, we describe a synthesis of the JK ring fragments of YTX and **2**.[10]

As shown in Scheme 1, the JK ring fragment (**6**) of YTX could be retrosynthetically disconnected into the JK ring fragment (**7**) of **2** and alkenylstannane (**8**). The methylketone (**7**) would be derived from allylic alcohol (**9**) via Sharpless asymmetric epoxidation and 6-*exo* cyclization of a hydroxy epoxide, and

§ Dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday.

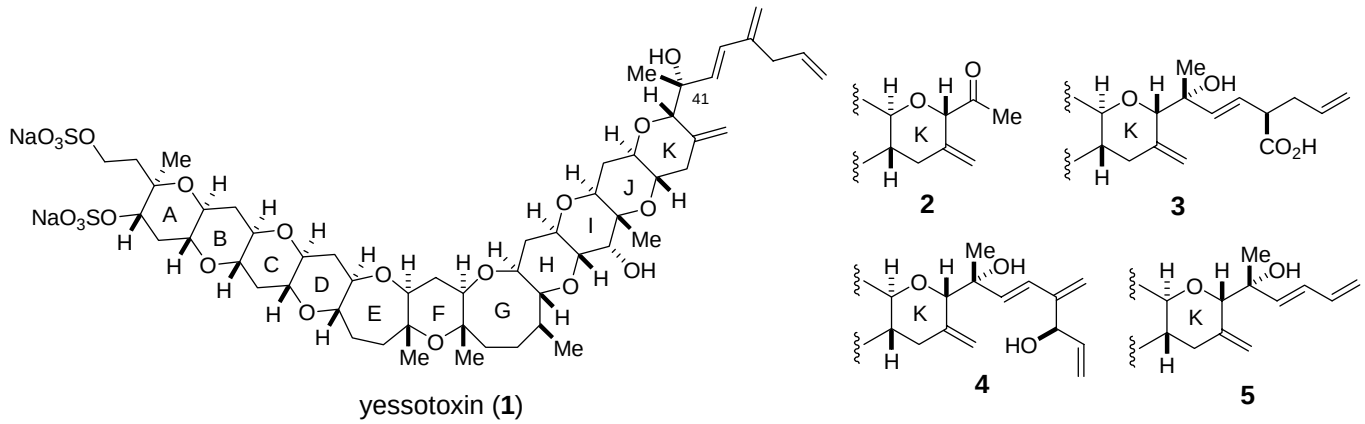
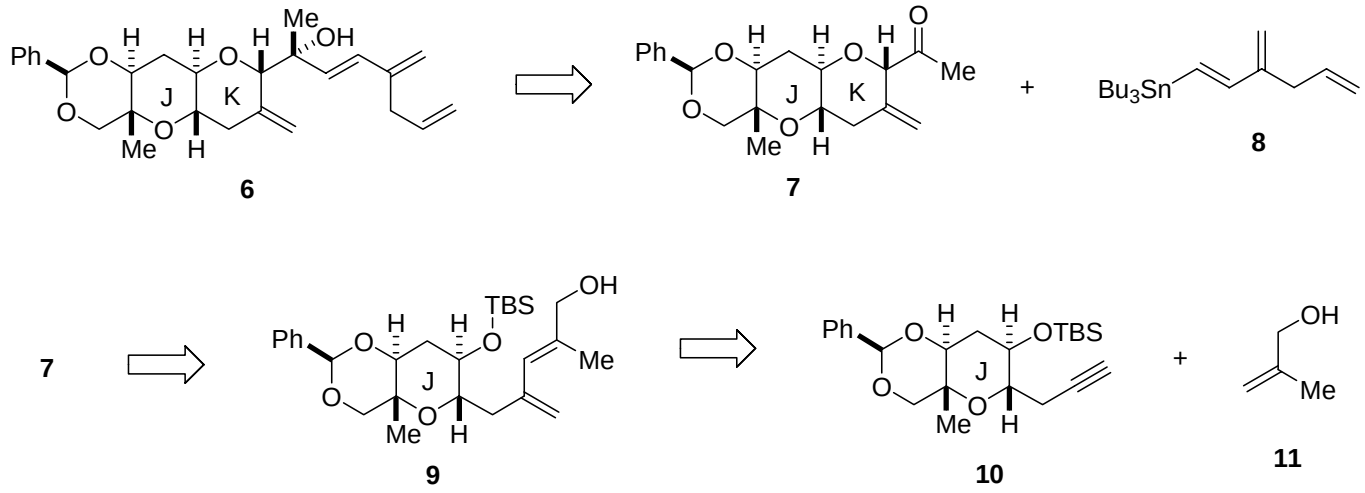


Figure 1. Structures of yessotoxin (**1**) and its congeners (**2**-**5**).

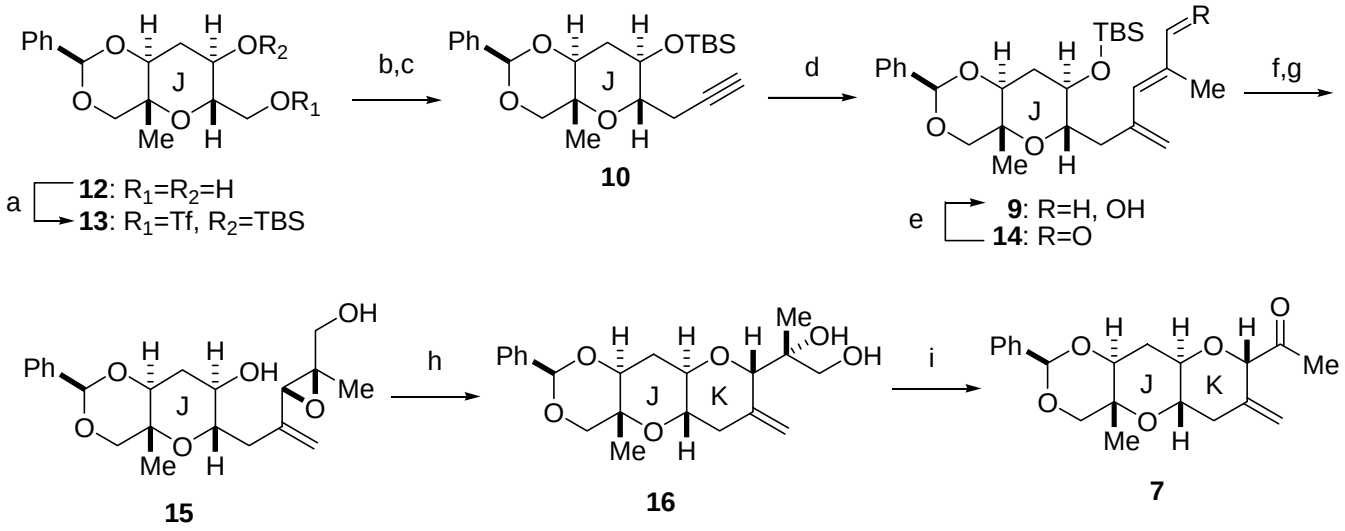
incidentally, construction of the K ring system based on a similar method has recently been reported by Kadota *et al*.[10] For expeditious construction of the conjugated diene system of **9**, we envisaged enyne metathesis[11] of alkyne (**10**) and 2-methyl-2-propen-1-ol (**11**).



Scheme 1. Synthesis plan for the JK ring fragments.

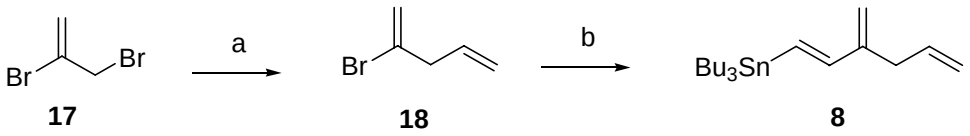
Synthesis of the JK ring fragment began with a one-pot preparation of triflate (**13**) from diol (**12**)[9,12] by Mori's protocol[13] (Scheme 2). Alkylation of **13** with lithium trimethylsilylacetylide, followed by removal of the TMS group afforded alkyne (**10**) in 68% yield for three steps. One of the key steps of the present synthesis, enyne metathesis of **10** and 2-methyl-2-propen-1-ol (**11**) using Grubbs' second generation catalyst,[14] proceeded smoothly to afford *E*-diene (**9**) as the major product (*E* : *Z* = 7 : 1) in 57% yield with concomitant formation of dienal (**14**) (10%) as a byproduct, which was readily converted to **9** by Luche reduction.[15] Portionwise addition of the Grubbs catalyst was important for the selective formation of the *E*-diene. For instance, addition of the Grubbs catalyst (0.5 eq) in one portion reduced the ratio of the *E*-diene (*E* : *Z* = 3 : 1). Sharpless epoxidation of **9**, followed by removal of the TBS group with TBAF

furnished hydroxy epoxide (**15**). Acid catalyzed 6-*exo* cyclization[16] of **15** by treatment with CSA in dichloromethane afforded *vic*-diol (**16**). Oxidative cleavage of the glycol (**16**) with $NaIO_4$ resulted in the formation of the JK ring fragment (**7**) of **2**.

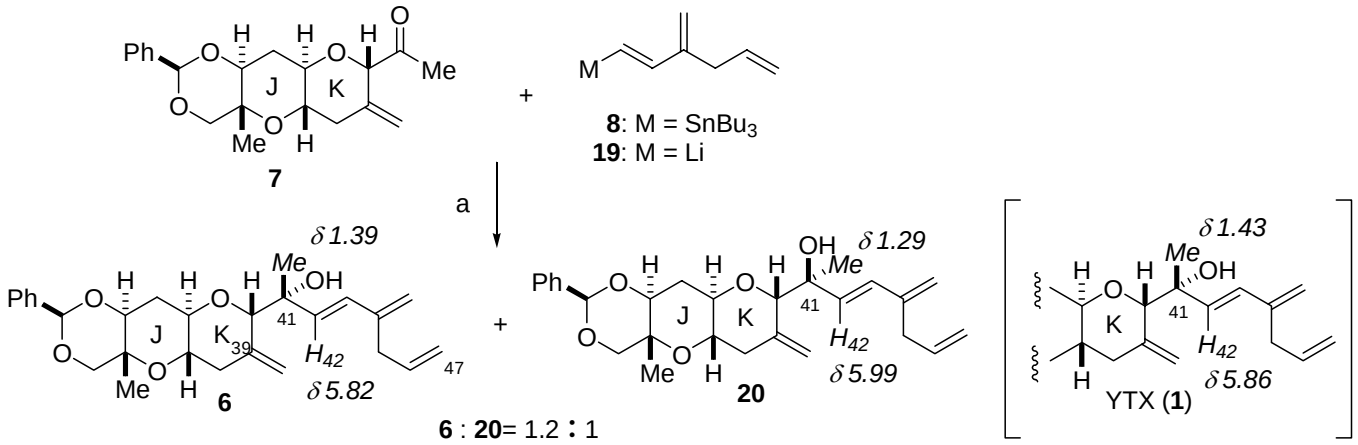


Scheme 2. *Reagents and conditions:* (a) Tf_2O, 2,6-lutidine, CH_2Cl_2, -78 °C to -60 °C, 40 min, then TBSOTf, -78 °C to -55 °C, 3 h; (b) trimethylsilylacetylene, *n*-BuLi, HMPA, THF, -78 °C to -55 °C, 30 min; (c) K_2CO_3, MeOH, rt, 15 h, 68% (3 steps); (d) Grubbs' 2nd generation cat. (0.1 eq + 0.1 eq + 0.05 eq), 2-methyl-2-propen-1-ol (10 eq), toluene, reflux, 3 h, **9**: 57%, **14**: 10%; (e) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, EtOH, 0 °C, 30 min, 50%; (f) D-(-)-DET, Ti(O*i*-Pr)$_4$, TBHP, MS4A, CH_2Cl_2, -20 °C, 1 h; (g) TBAF, THF, rt, 46% (2 steps); (h) CSA, CH_2Cl_2, 0 °C, 3 h; (i) $NaIO_4$, THF, pH 7 buffer, rt, 6 h, 50% (2 steps).

We then turned our attention to the synthesis of the JK ring fragment (**6**) of YTX. The alkenylstannane (**8**) was prepared as shown in Scheme 3. Treatment of 2,3-dibromo-1-propene (**17**) with vinylmagnesium bromide in THF at 60 °C gave 2-bromo-1,4-pentadiene (**18**),[17] which was purified by distillation. Stille coupling of **18** using 2.0 equivalent of *trans*-1,2-bis(tri-*n*-butylstannyl)ethylene with $Pd(PPh_3)_4$ gave the stannane (**8**).[18] Treatment of the methylketone (**7**) with alkenyllithium (**19**) generated from **8** resulted in the formation of desired **6** and its 41-epimer (**20**) (**6**:**20** = 1.2 : 1) in 66% yield, which were separated by silica gel chromatography (Scheme 4).[19] Judging from the ^{1}H NMR spectra,[20] chemical shifts of Me-41 and H-42 of **6** (δ 1.39 and 5.82, respectively) more resembled those of YTX (δ 1.43 and 5.86, respectively) than those of **20** (δ 1.29 and 5.99), and therefore, we assigned the structures as depicted in Scheme 4. Although improvement of the stereoselectivity of the final alkylation step is required, the present method would be a straightforward way for the diverse synthesis of YTX congeners, not only naturally occurring but also 41-epimers useful for structure-activity relationship studies.



Scheme 3. *Reagents and conditions:* (a) vinylmagnesium bromide (2.0 eq), THF, 60 °C, 15 h, 7% (isolated yield, ca. 50% conversion yield); (b) *trans*-1,2-bis(tri-*n*-butylstannyl)ethylene (2.0 eq), $Pd(PPh_3)_4$ (0.15 eq), benzene, reflux, 12 h, 37%.



Scheme 4. *Reagents and conditions:* (a) *n*-BuLi, **8**, THF, -78 °C, 3 min, then **7**, -78 °C to -55 °C, 1 h, 66%.

In conclusion, the JK ring fragment (**7**) of 42,43,44,45,46,47,55-heptanor-41-oxoyessotoxin (**2**) was synthesized via enyne metathesis and 6-*exo* cyclization of a hydroxy epoxide. Single step conversion of **7** into the JK ring fragment (**6**) of YTX has been achieved by treatment with the alkenyllithium (**19**) prepared from stannane (**8**). Further studies directed towards the total synthesis of YTX and its congeners are currently in progress in our laboratory.

ACKNOWLEDGEMENTS

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19. Spectral data of **6**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.45 (2H, m, Ph), 7.37-7.34 (3H, m, Ph), 6.30 (1H, d, *J* = 16.0 Hz, H43), 5.88 (1H, dddd, *J* = 17.0, 10.5, 6.5, 6.5 Hz, H46), 5.82 (1H, d, *J* = 16.0 Hz, H42), 5.08 (1H, dddd, *J* = 17.0, 1.5, 1.5, 1.5 Hz, H47), 5.05 (1H, d, *J* = 2.0 Hz, 44=CH_2), 5.04 (1H, dddd, *J* = 10.5, 1.5, 1.5, 1.5 Hz, H47), 5.02 (1H, d, *J* = 2.0 Hz, 44=CH_2), 4.98 (1H, s, 39=CH_2), 4.79 (1H, s, 39=CH_2), 4.18 (1H, ddd, *J* = 11.5, 10.5, 4.5 Hz, H36), 3.88 (1H, s, H40), 3.86 (1H, d, *J* = 10.0 Hz, H32), 3.73 (1H, dd, *J* = 11.5, 4.5 Hz, H34), 3.66 (1H, d, *J* = 10.0 Hz, H32), 3.45 (1H, ddd, *J* = 12.0, 10.5, 4.5 Hz, H37), 2.97 (2H, dd, *J* = 6.5, 1.5 Hz, H45), 2.65 (1H, dd, *J* = 12.0, 12.0 Hz, H38), 2.43 (1H, dd, *J* = 12.0, 4.5 Hz, H38), 2.17 (1H, ddd, *J* = 11.5, 4.5, 4.5 Hz, H35eq), 1.67 (1H, ddd, *J* = 11.5, 11.5, 11.5Hz, H35ax), 1.48 (3H, s, 33-Me), 1.39 (3H, s, 41-Me); ESI-MS 461 ($M+Na^+$).

    Spectral data of **20**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.44 (2H, m, Ph), 7.36-7.34 (3H, m, Ph), 6.41 (1H, d, *J* = 16.0 Hz, H43), 5.99 (1H, d, *J* = 16.0 Hz, H42), 5.92 (1H, ddd, *J* = 17.0, 10.5, 6.5, 6.5 Hz, H46), 5.11 (1H, d, *J* = 2.0 Hz, 44=CH_2), 5.10 (1H, dd, *J* = 17.0, 1.5 Hz, H47), 5.06 (1H, d, *J* = 2.0 Hz, 44=CH_2), 5.04 (1H, dd, *J* = 10.5, 1.5 Hz, H47), 4.98 (1H, s, 39=CH_2), 4.93 (1H, s, 39=CH_2), 4.08 (1H, ddd, *J* = 11.5, 9.5, 4.5 Hz, H36), 3.90 (1H, s, H40), 3.85 (1H, d, *J* = 10.0 Hz, H32), 3.71 (1H, dd, *J* = 11.5, 4.5 Hz, H34), 3.66 (1H, d, *J* = 10.0 Hz, H32), 3.44 (1H, ddd, *J* = 12.5, 9.5, 5.0 Hz, H37), 3.01 (2H, d, *J* = 6.5 Hz, H45), 2.70 (1H, dd, *J* = 12.5, 12.5 Hz, H38), 2.44 (1H, dd, *J* = 12.5, 5.0 Hz, H38), 2.00 (1H, ddd, *J* = 11.5, 4.5, 4.5 Hz, H35eq), 1.60 (1H, ddd, *J* = 11.5, 11.5, 11.5 Hz, H35ax), 1.46 (3H, s, 33-Me), 1.29 (3H, s, 41-Me); ESI-MS 461 ($M+Na^+$).
20. The carbon numbering of compounds in this article corresponds to that of yessotoxin.