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Stereoselective synthesis of the KJ ring system of yessotoxin by Pd (II)-catalyzed cyclization

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ABSTRACT

Yessotoxin was isolated from the digestive glands of the scallop, *Patinopecten yessoensis*, and would be of use as a promising therapeutic tool. We attained the stereoselective construction of KJ ring system of yessotoxin by the intramolecular cyclization of the trisubstituted allylic alcohol using Pd(II) catalyst.

Natural marine products have a number of intriguing structures, which involve the trans-fused ladder pyran ring system.[1] Among them, the synthesis of natural polyether yessotoxin is untrodden area (Fig. 1). Yessotoxin was isolated from the digestive glands of the scallop *Patinopecten yessoensis*, which shows diarrhetic shellfish poisoning. This compound has some biological activities involving the cytotoxicity and modulation of the cytosolic calcium level in human lymphocytes. Recent article reported that it can trigger stress responses like ribotoxic stress. Thus, many synthetic chemists have been challenging its total synthesis for many years.[2]

In 2009, we reported a stereoselective construction of 2,3-trans-tetrahydropyran by intramolecular cyclization of the allylic alcohol in the presence of Pd(II) catalyst as a part of our synthetic studies directed toward yessotoxin.[3] Stereoselective construction of methyl-substituted ring junctions in the trans-fused pyran ring system has been the next challenge in yessotoxin synthesis. In 2006, Yamamoto and Kadota's group showed the synthesis of IJK[2p] and Murata and Oishi's group reported the synthesis of KJ ring of Yessotoxin by epoxide opening.[2q] Mori's group appealed the stereoselective construction of the methyl-substituted ring junction by hydroalkoxylation.[8] Recently we developed the Pd (II)-catalyzed intramolecular cyclization of trisubstituted allylic alcohol. Here, we describe the application of this reaction to the stereoselective construction of the KJ ring system of yessotoxin.

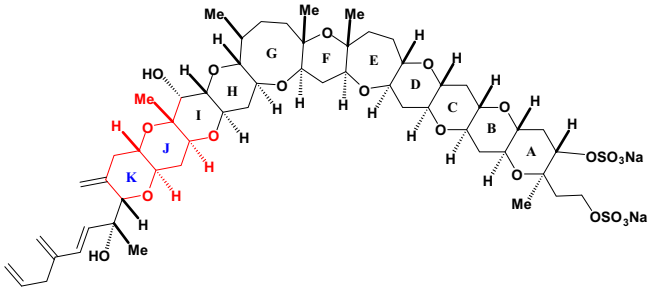
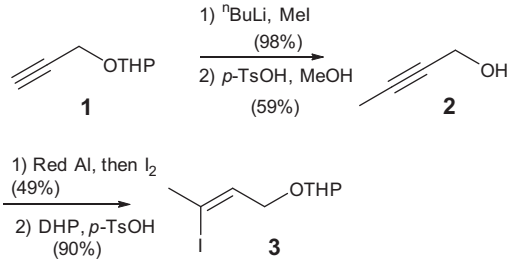


Figure 1. Yessotoxin.



Scheme 1. Preparation of **3**.

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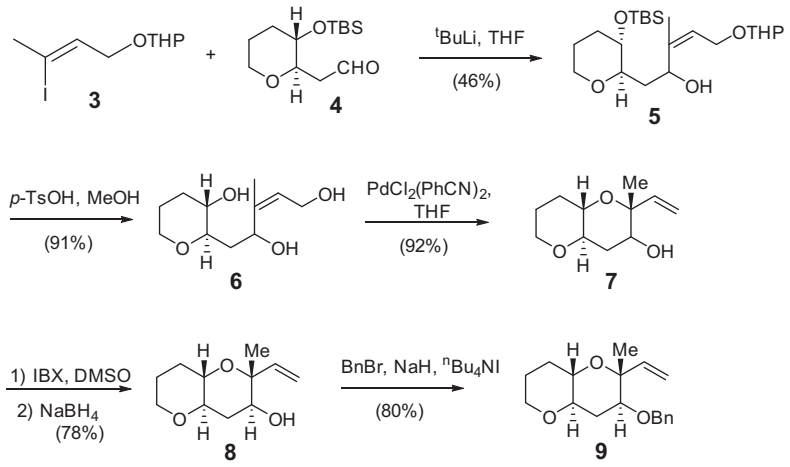
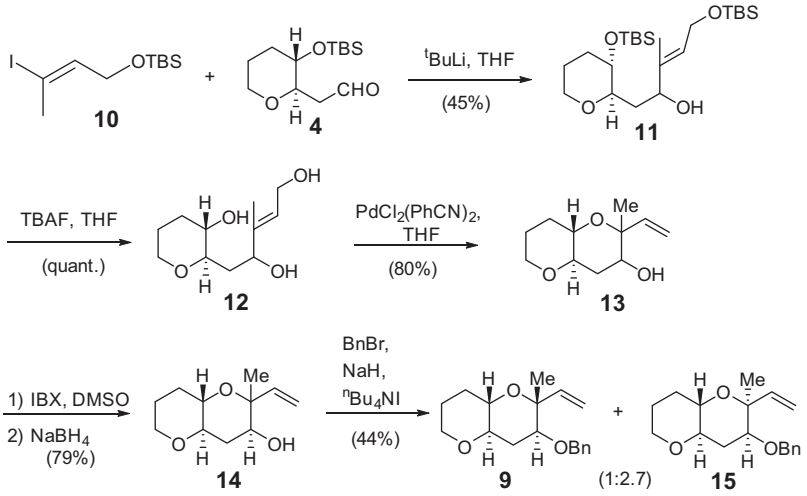


Scheme 2. Pd(II)-catalyzed cyclization of **6**.



Scheme 3. Pd(II)-catalyzed cyclization of **12**.

At first, we tried the preparation of *Z*-vinyl iodide **3**[4] (Scheme 1). The protected propargyl derivative **1** was alkylated with MeI and ^{n}BuLi as a base in 98% yield. The deprotection of the alkylated product with an acid gave 2-butyn-2-ol **2** in 59% yield. Hydroalumination of **2** with Red-Al and iodine transmetalation afforded the alcohol in 49% yield. The THP-protection of resulting alcohol gave *Z*-vinyl iodide **3** in 90% yield.

The aldehyde **4**,[5] which was prepared from tri-*O*-acetyl-D-glucal by the reported method,[3e] was coupled with vinyl lithium derivative after lithiation of *Z*-vinyl iodide **3** to give the adduct **5** in 46% yield (Scheme 2). The adduct **5** was treated with *p*-TsOH in MeOH to afford the *Z*-precursor **6** in 91% yield. The *Z*-precursor **6** was cyclized by 10 mol %-$PdCl_2(PhCN)_2$ catalyst in THF at 0 °C to give the cyclized alcohol in 92% yield.[6] The IBX oxidation of the cyclized compound **7** following reduction with $NaBH_4$ gave the alcohol **8** (i.e. the desired KJ ring system of yessotoxin) in 78% yield as a single isomer.[7] The stereochemistry of the benzyl derivative **9** of this alcohol **8** was determined by NMR analysis and comparison with literature data.[8]

On the contrary, *E*-precursor **12**, which was prepared similarly the aldehyde **4** and *E*-vinyl iodide **10**[9], was treated with $PdCl_2(PhCN)_2$ as a catalyst in THF at 0 °C to give the mixture **13** in 80% yield (Scheme 3). Oxidation of **13**, reduction in the same manner and benzylation as above afforded a mixture of benzyl

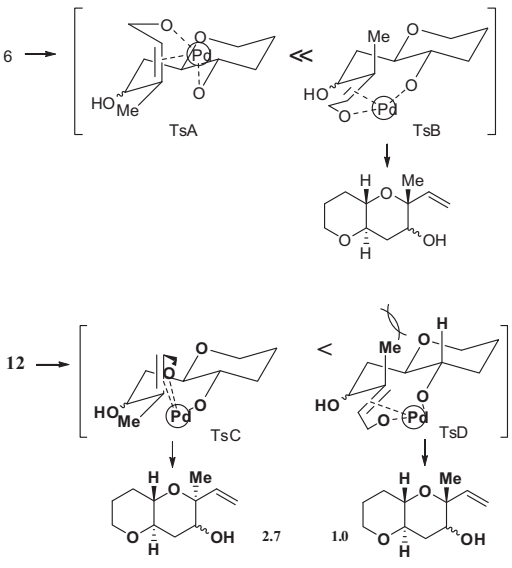


Figure 2. Plausible transition structures.

derivatives. NMR studies of the isolated product showed that it was a mixture of stereoisomers in the ratio of (**9**:**15** = 1:2.7).

The different products obtained suggest it involved no cationic cyclization, but it must have been a kinetic pathway. If any, the reaction of Pd(II)-catalyzed cyclization would involve 6-membered cyclic transition structure (Fig. 2).[3,10,11] It seems to be two transition structures in every case. In *Z*-precursor **6**, TsA suffers marked steric repulsion between the Pd-complex and the junction hydrogen atom, but TsB would lead to the desired product **7**. In *E*-precursor **12**, the moderate steric repulsion between the methyl moiety and junction hydrogen atom in TsD would mean that the major product is formed through TsC.

In summary, we examined the diastereoselectivity in Pd(II)-catalyzed cyclization of trisubstituted allylic alcohol. The *Z*-allylic alcohol afforded the desired trans-fused pyran system and we successfully obtained the KJ ring system **8** of yessotoxin. Our synthetic studies of yessotoxin are ongoing.

Acknowledgment

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6. Pd(II)-catalyzed cyclization to (2*R*,4a*R*,8a*S*)-3-hydroxy-2-methyl-2-vinyl-1,5-dioxadecalin **7**: $PdCl_2(PhCN)_2$ (5.7 mg, 0.015 mmol) was added to a solution of (*Z*)-5-[(2*R*,3*S*)-3-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-yl]-3-methyl-3-pentene-1,4-diol (10.5 mg, 0.048 mmol) in THF (0.48 mL) at 0 °C. After stirring for 3 h at 0 °C, the reaction mixture was diluted with *n*-hexane and filtered through pad of silica gel. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/AcOEt = 3:1) to afford (2*R*,4a*R*,8a*S*)-3-hydroxy-2-methyl-2-vinyl-1,5-dioxadecalin (8.8 mg, 92%) as a colorless oil
7. The selected data of **8**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.93(dd, *J* = 17.4, 11.0 Hz, 1H), 5.33(dd, *J* = 17.6, 1.1 Hz, 1H), 5.22(d, *J* = 10.5Hz, 1H), 3.93–3.90(m, 1H), 3.58(dd, *J* = 12.0, 4.4 Hz, 1H), 3.39(td, *J* = 11.6, 3.4 Hz, 1H), 3.33–3.29(m, 1H), 3.00(ddd, *J* = 10.8, 9.2, 4.4 Hz, 1H), 2.18(dt, *J* = 11.5, 4.4 Hz, 1H), 2.00–1.98(m, 1H,), 1.79–1.22(m, 9H): ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.9, 114.8, 77.7, 77.68, 71.4, 70.5, 68.0, 33.9, 29.66, 25.7, 13.8: IR (neat) 3449, 2925, 2853, 1654, 1261, 1094 cm^{-1}: MS(EI) *m*/*z* 197 (M^+−H).
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11. The relationship between stereochemistry on the chiral secondary allyl alcohol and the diastereoselectivity of Pd(II)-catalyzed cyclization have extensively studied. See Ref. 10f–m