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Convergent synthesis of the FGHI ring segment of yessotoxin

Isao Kadota,[a,*] Hirokazu Ueno,[b] Yuki Sato[b] and Yoshinori Yamamoto[b]

[a]*Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan*
[b]*Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan*

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Abstract—A convergent synthesis of the FGHI ring segment of yessotoxin was achieved via the intramolecular allylation of an α-chloroacetoxy ether and subsequent ring-closing metathesis.

Yessotoxin **1** is a disulfated polycyclic ether isolated from the digestive glands of the scallops, *Patinopecten yessoensis*.[1] Due to its novel structural features and biological activities, yessotoxin has attracted the attention of synthetic chemists.[2] Recently, we developed an efficient method for the convergent synthesis of polycyclic ethers via the intramolecular allylation of an α-acetoxy ether and subsequent ring-closing metathesis.[3] The methodology was successfully applied to the stereoselective synthesis of the A–F ring segment of **1**.[4] We now wish to report the further application of this technology to the synthesis of the FGHI ring system of **1**.[5]

Scheme 1 shows the synthesis of the F ring fragment. The olefin **2**, synthesized by the reported procedure,[6] was converted to alcohol **3** in 87% overall yield via MPM protection followed by hydroboration–oxidation. Protection of **3** with TBDPSCl and selective removal of the MPM group afforded **4** in 96% overall yield.

The I ring moiety **6** was prepared from diol **5**[7] by several steps including acetalization with anisaldehyde, DIBAL-H reduction, Swern oxidation of the resulting primary alcohol, Wittig reaction, hydroboration–oxidation, TEMPO oxidation, and $NaClO_2$ oxidation of the resulting aldehyde (Scheme 2). Esterification of carboxylic acid **6** with alcohol **4** was carried out under the Yamaguchi conditions[8] to provide ester **7**. A series of reactions including deprotection of the MPM ether of **7** with DDQ, acid catalyzed acetal formation with **8**, and cleavage of the resulting methyl acetal with TMSI/HMDS furnished the allylic stannane **9** in 78% overall yield.[9] Modified Rychnovsky acetylation of **9** via DIBAL-H reduction followed by treatment with $(CH_2ClCO)_2O$/DMAP/pyridine gave α-chloroacetoxy ether **10** in 94% yield.[10,11] Intramolecular allylation of **10** with $MgBr_2{\cdot}OEt_2$ in CH_3CN gave a 78:22 mixture of the desired product **11** and its stereoisomer **12** in 99% combined yield.

The next task was the construction of the G ring having a methyl group. Wacker oxidation of **11** provided methyl ketone **13** in 81% yield (Scheme 3). Desilylation of **13** with TBAF, oxidation of the resulting alcohol, and Wittig olefination gave diene **14** in 90% overall yield. Ring-closing metathesis of **14** was carried out using the second generation Grubbs catalyst **15** to give **16** in 88% yield.[12] Hydrogenation of **16** under standard conditions afforded **17** as the sole product in 52% yield. However, the stereochemistry of the methyl group of the G ring was opposite to that required. We attempted other conditions such as the use of $Pd(OH)_2$ and Crabtree's catalyst[13] in order to obtain the desired stereochemistry of the Me group, but all the approaches resulted in failure: the undesired stereochemistry was always obtained.[14]

Finally, we found that the following method gave the desired stereochemistry (Scheme 4). Treatment of **13** with KHMDS/$PhNTf_2$[15] gave the corresponding enol triflate, which was then subjected to palladium-catalyzed reaction with CO/MeOH to provide ester **18** in 74% overall yield.[16,17] DIBAL-H reduction of **18** followed by MPM protection gave **19** in 94% overall yield.

Keywords: Yessotoxin; Polycyclic ethers; Convergent synthesis.
* Corresponding author. Tel.: +81 227956755; fax: +81 227956784; e-mail: ikadota@mail.tains.tohoku.ac.jp

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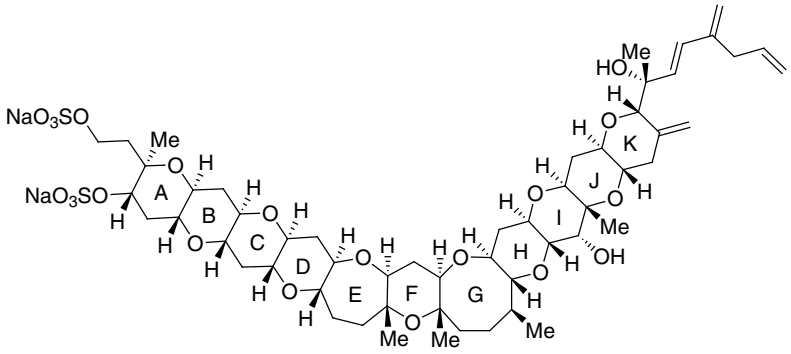
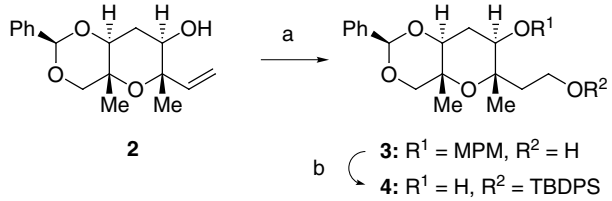


yessotoxin **1**



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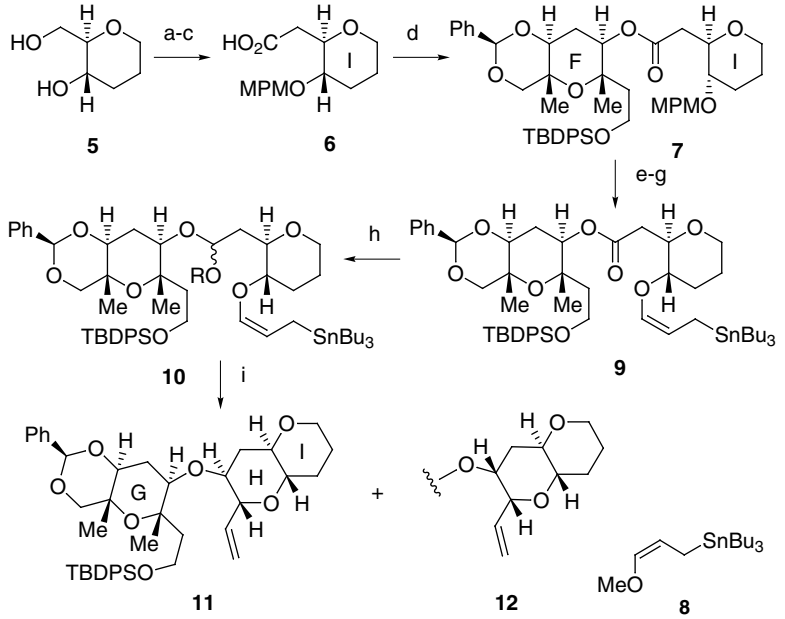
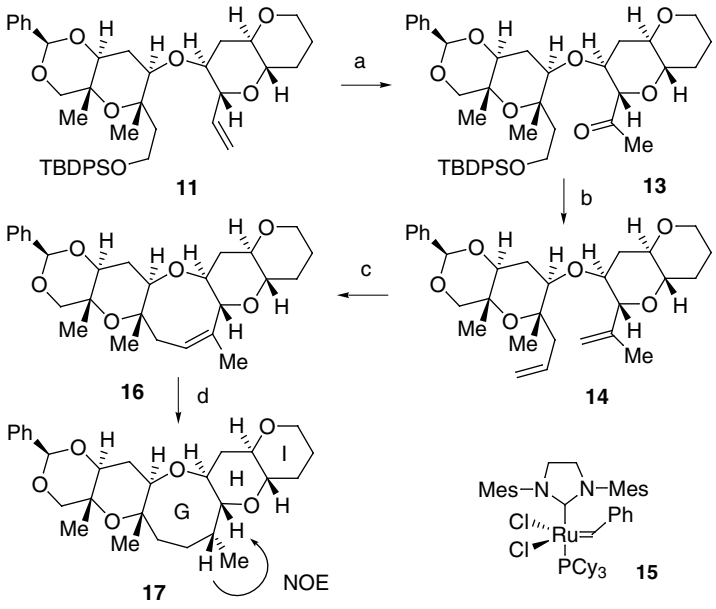
Scheme 1. Reagents and conditions: (a) (i) MPMCl, KH, THF, 0 °C to rt; (ii) (*c*-Hex)$_2$BH, THF, 0 °C, then 30% H_2O_2, 3 N NaOH, 0 °C, 87%; (b) (i) TBDPSCl, imidazole, DMF, rt; (ii) DDQ, $NaHCO_3$, CH_2Cl_2–H_2O (10:1), rt, 96%.



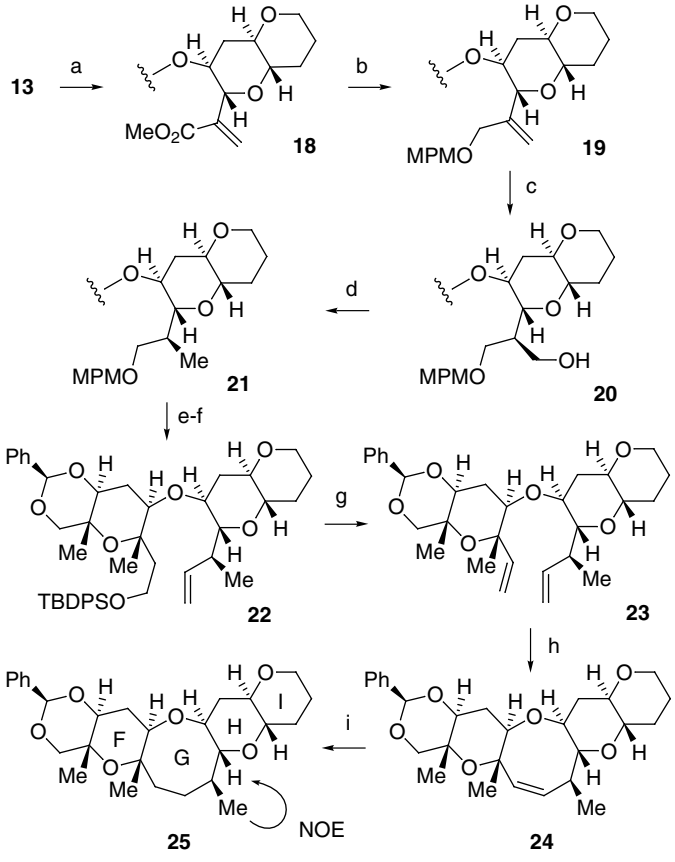
5 **6** **7** **9** **10** **11** **12** **8**

Scheme 2. Reagents and conditions: (a) (i) anisaldehyde, PPTS, benzene, reflux; (ii) DIBAL-H, CH_2Cl_2, rt, 81%; (b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N; (ii) $CH_3PPh_3^+Br^-$, NaHMDS, THF, 0 °C; (iii) 9-BBN, THF, rt, then 3 N NaOH, 30% H_2O_2, 0 °C, 63%; (c) TEMPO, NaClO, KBr, $NaHCO_3$, CH_2Cl_2–H_2O, 0 °C, (ii) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH–THF–H_2O, 0 °C, quant; (d) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, then **4**, DMAP, toluene, rt, 88%; (e) DDQ, $NaHCO_3$, CH_2Cl_2–H_2O, rt, 96%; (f) **8**, CSA, CH_2Cl_2, rt, 93%; (g) HMDS, TMSI, CH_2Cl_2, 0 °C, 87%; (h) DIBAL-H, CH_2Cl_2, −78 °C, then $(CH_2ClCO)_2O$, pyridine, DMAP, −78 °C, 94%; (i) $MgBr_2{\cdot}OEt_2$, CH_3CN, 40 °C, 99% (**11**:**12** = 78:22).

Hydroboration of **19** with $BH_3{\cdot}SMe_2$ followed by oxidative work-up furnished the corresponding alcohol **20** as a single stereoisomer in 76% yield.[18] Iodination of **20** with I_2/PPh_3/imidazole followed by lithiation with *t*-BuLi and protonation with MeOH gave **21** in 86% overall yield.[19] Deprotection of the MPM ether, oxidation of the resulting alcohol, and Wittig reaction afforded **22** in 55% overall yield. Desilylation of **22** with TBAF, treatment of the resulting alcohol with 2-nitrophenyl selenocyanate/PBu_3, and oxidative work-up gave diene **23** in



Scheme 3. Reagents and conditions: (a) $PdCl_2$, CuCl, O_2, DMF–H_2O, 30 °C, 81%; (b) (i) TBAF, THF, rt; (ii) SO_3·py, DMSO, Et_3N, CH_2Cl_2, rt; (iii) $CH_3PPh_3^+Br^-$, NaHMDS, THF, 0 °C; 90%; (c) **15**, CH_2Cl_2, rt, 88%; (d) H_2, 10% Pd–C, EtOAc, rt, 52%.



Scheme 4. Reagents and conditions: (a) (i) $PhNTf_2$, KHMDS, DMPU, THF, −78 °C; (ii) CO, MeOH, $Pd(PPh_3)_4$, DMF, rt, 74%; (b) (i) DIBAL-H, CH_2Cl_2, −78 °C; (ii) MPMCl, KH, THF, rt, 94%; (c) BH_3·SMe_2, THF, 0 °C, then 3 N NaOH, 30% H_2O_2, 0 °C, 76%; (d) (i) I_2, PPh_3, imidazole, benzene, rt; (ii) *t*-BuLi, THF, −78 °C, then MeOH, 86%; (e) DDQ, $NaHCO_3$, CH_2Cl_2–H_2O, rt, 84%; (f) (i) SO_3·py, DMSO, Et_3N, CH_2Cl_2, rt; (ii) $CH_3PPh_3^+Br^-$, NaHMDS, THF, 0 °C, 66%; (g) (i) TBAF, THF, rt; (ii) 2-nitrophenyl selenocyanate, PBu_3, THF, rt, then, 30% H_2O_2, 90%; (h) **15**, toluene, 130 °C, sealed tube, 90% ; (i) 5% Pd–C, EtOAc, 98%.

90% overall yield.[20] Diene **23** was subjected to the ring-closing metathesis using **15** to furnish **24** in 90% yield. Finally, hydrogenation of **24** afforded the FGHI ring segment **25** in 98% yield.[21] The stereochemistry of the methyl group was confirmed by NOE experiments.

In conclusion, we have achieved a convergent and stereoselective synthesis of the FGHI ring segment of yessotoxin **1** via the intramolecular allylation of an α-chloroacetoxy ether and ring-closing metathesis. Further studies toward the total synthesis of **1** are now in progress in our laboratories.

Acknowledgments

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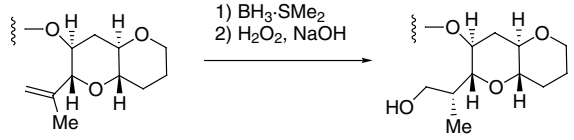
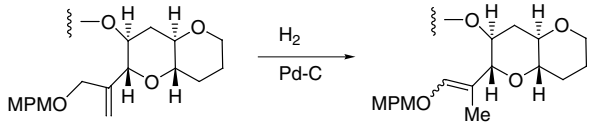
17. Hydroboration–oxidation of the *exo*-olefin prepared from **12** afforded the undesired stereoisomer as shown below.



18. The hydrogenation of **18** under the standard conditions gave the corresponding enol ether via olefin migration.



19. Reduction of iodide with metal hydrides such as $LiAlH_4$ resulted in failure.
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21. A referee pointed out that hydrogenation of the sterically hindered olefin **24** seems to be problematic, or olefin migration may occur under the reaction conditions. So we carried out the hydrogenation of **24** conditions. Although the reaction was relatively slow, neither olefinic migration nor epimerization of the methyl group was observed in this reaction. The desired compound **25** was obtained as the sole product.