Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 6545–6548

Stereocontrolled synthesis of the IJK ring segment of yessotoxin

Isao Kadota,[a,*] Takashi Abe,[b] Yuki Sato,[b] Chizuko Kabuto[a] and Yoshinori Yamamoto[b]

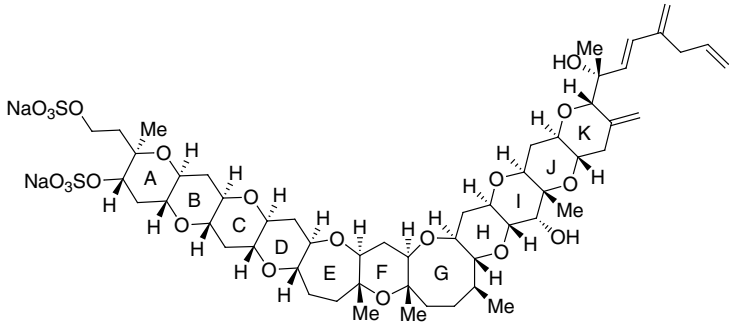
[a]*Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan*
[b]*Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan*

Received 2 June 2006; revised 28 June 2006; accepted 7 July 2006
Available online 31 July 2006

Abstract—A stereocontrolled synthesis of the IJK ring segment of yessotoxin is described. Cyclization of **11** mediated by SmI_2 gave the IJ ring system **12** as the sole product. Construction of the K ring moiety was performed by the acid catalyzed cyclization of epoxy alcohol **20** to afford the IJK ring segment in a highly stereocontrolled manner.

Yessotoxin **1** is a disulfated polycyclic ether isolated from the digestive glands of scallops, *Patinopecten yessoensis*.[1] Due to its novel structural features and biological activities, yessotoxin has attracted the attention of synthetic chemists.[2] During the course of our synthetic study of **1**, we have already reported the synthesis of the A-F and F-I ring segments.[2e,g] Herein, we describe the stereocontrolled synthesis of the IJK ring segment.

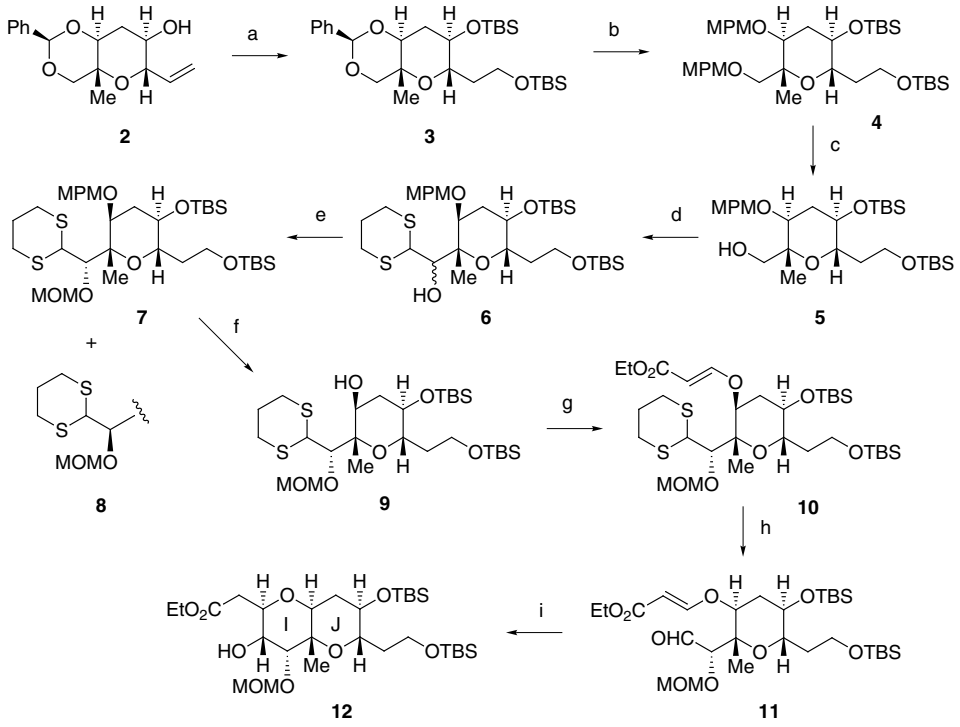
Scheme 1 describes the synthesis of the IJ ring system. Alcohol **2**,[3] prepared from 2-deoxy-D-ribose by a known procedure,[4] was converted to bis-silyl ether **3** via protection with TBSCl/imidazole, hydroboration with thexylborane followed by oxidative work-up, and TBS protection in 86% overall yield. Hydrogenolysis of the benzylidene acetal of **3** followed by protection with MPMCl/KH afforded bis-MPM ether **4** in 84% overall yield. Selective cleavage of the primary MPM ether was carried out with TMSI/HMDS to give primary alcohol **5** in 92% yield.[2e] Swern oxidation of **5** followed by treatment with 2-lithio-1,3-dithiane provided **6** as an inseparable mixture of diastereoisomers in 89% overall yield. Protection of **6** with MOMCl/^{i}Pr$_2$NEt gave a 10:1 mixture of the desired **7** and its stereoisomer **8** in 89% combined yield. These isomers, **7** and **8**, were easily separated by column chromatography at this stage. Deprotection of the



yessotoxin (**1**)

Keywords: Yessotoxin; Polycyclic ethers; Cyclization.
* Corresponding author. Tel.: +81 22 795 6755; fax: +81 22 795 6784; e-mail: ikadota@mail.tains.tohoku.ac.jp

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2006.07.027



Scheme 1. Reagents and conditions: (a) (i) TBSCl, imidazole, DMF, rt, 98%; (ii) thexylborane, THF, 0 °C, then 3 N NaOH, 30% H_2O_2, 89%; (iii) TBSCl, imidazole, DMF, 0 °C, 99%; (b) (i) H_2, $Pd(OH)_2$-C, rt, quant; (ii) MPMCl, KH, THF, 0 °C to rt, 84%; (c) TMSI, HMDS, CH_2Cl_2, 0 °C, then K_2CO_3, MeOH, rt, 92%; (d) (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, −78 °C to rt; (ii) 1,3-dithiane, *n*-BuLi, THF, −78 °C, 89% (2 steps); (e) MOMCl, $^iPr_2NEt$, CH_2Cl_2, reflux; 89% (**7**:**8** = 10:1); (f) DDQ, saturated $NaHCO_3$, CH_2Cl_2, rt; (g) ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2, rt, 86% (2 steps); (h) MeI, saturated $NaHCO_3$, CH_2Cl_2, reflux, 82%; (i) SmI_2, MeOH, THF, −78 °C, 79%.

MPM ether **7** with DDQ followed by treatment with ethyl propiolate/NMM gave acrylate **10** in 86% overall yield. Hydrolysis of the dithio acetal **10** was carried out with MeI to give aldehyde **11** in 82% yield. The cyclization precursor **11** was then subjected to the Nakata protocol. Thus, treatment of **11** with SmI_2 in the presence of MeOH furnished **12** as a single stereoisomer in 79% yield.[5,6]

The stereochemistry of **12** was confirmed by ^1H NMR analysis of the acetate derivative **13**, prepared from **12** with Ac_2O/pyridine, as shown in Figure 1.[7] Coupling constants, $J_{Ha–Hb} = 10.5$ Hz and $J_{Hb–Hc} = 2.4$ Hz observed clearly indicated the ax–ax and ax–eq relationship of these protons, respectively.

Construction of the K ring moiety is illustrated in Scheme 2. Reduction of the ester **12** with $LiAlH_4$ gave the corresponding diol, which was converted to bis-benzyl ether **14** in 97% overall yield. Selective removal of the primary TBS group with CSA, iodination of the resulting primary alcohol, and treatment with NaCN afforded **15** in 87% yield. Reduction of the nitrile **15** with DIBAL-H gave aldehyde **16** in 81% yield. Treatment of **16** with Eschenmoser's salt afforded α-vinyl aldehyde **17**,[8] which was then subjected to Wittig reaction to provide **18** in 93% overall yield. Reduction of the dienyl ester **18** with DIBAL-H afforded **19** in 96% yield. Regio- and stereoselective epoxidation of the diene **19** was performed under Sharpless conditions to give **20** as a single stereoisomer in quantitative yield. Removal of the TBS protection with TBAF afforded diol **21** in quantitative yield. Regio- and stereoselective *exo*-cyclization of the epoxy alcohol **21** was carried out with CSA to furnish the IJK ring segment **22** as a single stereoisomer in 84% yield.[9] The stereochemistry of **22** was unambiguously determined by X-ray crystallographic analysis of a crystalline derivative **23**, Figure 2, prepared by esterification with *p*-Br-BzCl/pyridine followed by removal of the MOM protection with CSA in 77% overall yield.[10]

In conclusion, we have achieved the synthesis of the IJK ring segment of yessotoxin **1** via SmI_2 mediated cyclization and acid catalyzed cyclization as key ring-closure processes in highly stereocontrolled manner. Further studies towards the total synthesis of **1** are now in progress in our laboratories.

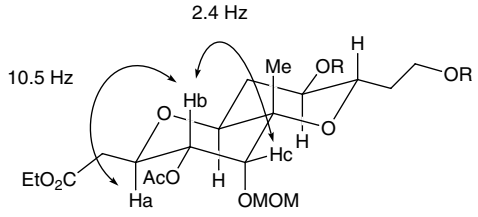
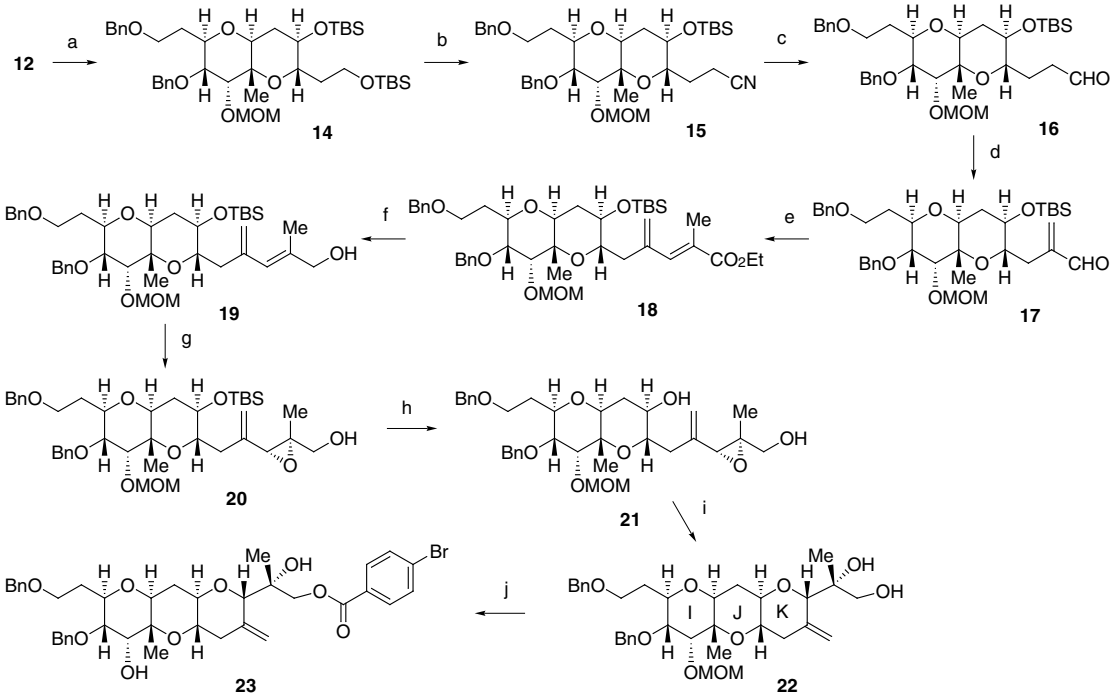


Figure 1. ^1H NMR analysis of **13**.



Scheme 2. Reagents and conditions: (a) (i) $LiAlH_4$, ether, 0 °C; (ii) BnBr, NaH, THF, reflux, 97% (2 steps); (b) (i) CSA, MeOH, 0 °C, 90%; (ii) I_2, PPh_3, imidazole, benzene–ether, quant; (iii) NaCN, DMF, 50 °C, 97%; (c) DIBAL-H, CH_2Cl_2, −78 °C, 81%; (d) $Me_2N^+{=}CH_2I^-$, Et_3N, CH_2Cl_2, rt; (e) $Ph_3P{=}C(Me)CO_2Et$, CH_2Cl_2, rt, 93% (2 steps); (f) DIBAL-H, CH_2Cl_2, −78 °C, 96%; (g) (−)-DET, $Ti(O^iPr)_4$, TBHP, 4 Å MS, CH_2Cl_2, −20 °C, quant; (h) TBAF, THF, rt, quant; (i) CSA, CH_2Cl_2, 0 °C, 84%; (j) (i) *p*-Br-BzCl, pyridine, CH_2Cl_2, 77%; (ii) CSA, MeOH, rt, quant.

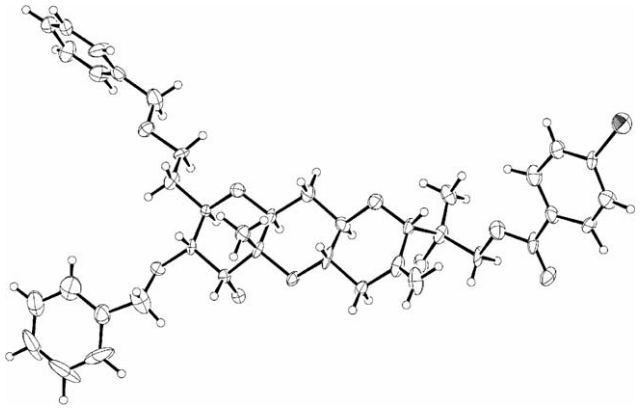


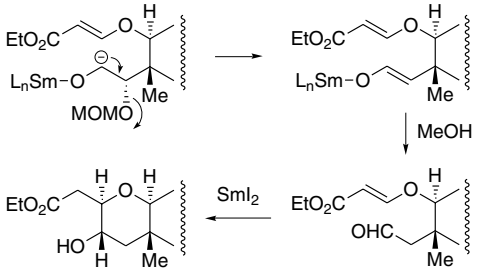
Figure 2. ORTEP drawing of **23**.

Acknowledgements

This work was financially supported by the Novartis Foundation for the Promotion of Science, the Kurata Memorial Hitachi Science and Technology Foundation, the Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and notes

1. (a) Murata, M.; Kumagai, M.; Lee, J. S.; Yasumoto, T. *Tetrahedron Lett.* **1987**, *28*, 5869–5872; (b) Satake, M.; Terasawa, K.; Kadowaki, Y.; Yasumoto, T. *Tetrahedron Lett.* **1996**, *37*, 5955–5958.
2. For synthetic studies of **1**, see: (a) Mori, Y.; Hayashi, H. *Tetrahedron* **2002**, *58*, 1789–1797; (b) Suzuki, K.; Nakata, T. *Org. Lett.* **2002**, *4*, 3943–3946; (c) Mori, Y.; Takase, T.; Noyori, R. *Tetrahedron Lett.* **2003**, *44*, 2319–2322; (d) Oishi, T.; Watanabe, K.; Murata, M. *Tetrahedron Lett.* **2003**, *44*, 7315–7319; (e) Kadota, I.; Ueno, H.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 8935–8938; (f) Watanabe, K.; Suzuki, M.; Murata, M.; Oishi, T. *Tetrahedron Lett.* **2005**, *46*, 3991–3995; (g) Kadota, I.; Ueno, H.; Sato, Y.; Yamamoto, Y. *Tetrahedron Lett.* **2006**, *47*, 89–92; (h) Oishi, T.; Suzuki, M.; Watanabe, K.; Murata, M. *Tetrahedron Lett.* **2006**, *47*, 3975–3978.
3. Kadota, I.; Kadowaki, C.; Park, C.-H.; Takamura, H.; Sato, K.; Chan, P. W. H.; Thorand, S.; Yamamoto, Y. *Tetrahedron* **2002**, *58*, 1799–1816.
4. Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron* **1990**, *46*, 4517–4552.
5. (a) Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 2811–2814; (b) Hori, N.; Matsukura, H.; Nakata, T. *Org. Lett.* **1999**, *1*, 1099–1101; (c) Matsuo, G.; Hori, N.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 8859–8862.
6. The SmI_2 mediated reaction of **11** at 0 °C gave a cyclized product which had no MOMO group on the I ring. Elimination of the MOMO group from the ketyl intermediate would be faster than the cyclization at higher temperature.



7. Compound **13**: ^{1}H NMR (400 MHz, C_6D_6) δ 5.05 (dd, $J = 10.5$, 2.4 Hz, 1H), 4.89 (d, $J = 6.6$ Hz, 1H), 4.70 (d, $J = 6.6$;Hz, 1H), 4.57 (m, 1H), 4.14 (d, $J = 2.4$ Hz, 1H), 3.98–3.90 (m, 3H), 3.76–3.73 (m, 2H), 3.61–3.56 (m, 1H), 3.30–3.25 (m, 4H), 2.55 (dd, $J = 15.6$, 3.6 Hz, 1H), 2.46 (dd, $J = 15.6$, 8.0 Hz, 1H), 2.23–2.10 (m, 2H), 1.71 (s, 3H), 1.69–1.48 (m, 2H), 1.16 (s, 3H), 0.98 (s, 9H), 0.93 (t, $J = 7.3$ Hz, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), −0.03 (s, 3H), −0.09 (s, 3H).
8. (a) Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 330–331; (b) Takano, S.; Inomata, K.; Samizu, K.; Tomita, S.; Yanase, M.; Suzuki, M.; Iwabuchi, Y.; Sugihara, T.; Ogasawara, K. *Chem. Lett.* **1989**, 1283–1284.
9. Compound **22**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.33 (m, 10H), 5.08 (s, 1H), 4.89 (s, 1H), 4.83 (d, $J = 6.4$ Hz, 1H), 4.69 (d, $J = 7.6$ Hz, 1H), 4.68 (d, $J = 6.4$ Hz, 1H), 4.52 (d, $J = 12.0$ Hz, 1H), 4.46 (d, $J = 12.0$ Hz, 1H), 4.45 (d, $J = 7.6$ Hz, 1H), 3.95 (d, $J = 2.8$ Hz, 1H), 3.91 (s, 1H), 3.83–3.74 (m, 3H), 3.63–3.57 (m, 3H), 3.39–3.32 (m, 3H), 3.35 (s, 3H), 2.53–2.51 (m, 2H), 2.19 (dddd, $J = 14.4$, 7.6, 7.2, 2.8 Hz, 1H), 2.09–2.02 (m, 2H), 1.70–1.41 (m, 3H), 1.28 (s, 3H), 1.07 (s, 3H).
10. Crystal data for **23**: $4(C_{39}H_{45}O_9Br)\cdot(CH_3CO_2C_2H_5)$; $M_W = 3024.8$, monoclinic, space group $P2_1$ (#4); $a = 13.427(3)$, $b = 46.89(1)$, $c = 13.452(3)$ Å, $b = 92.953(1)°$, $V = 8459(3)$ Å^3; $Z = 2$, $D_c = 1.188$ g/cm^3, $F(000) = 3168$, μ(Mo-Kα) = 1.024 cm^{-1}, Rigaku/MSC CCD diffractometer, $T = 173$ K, 95,659 reflections measured, 34,323 unique ($R_{int} = 0.059$), final $R1 = 0.155$ and wR (all data) = 0.423. The relatively high R values are due to the fact that four independent molecules are included in the asymmetric unit as well as the crystals being of poor quality. Each four independent molecule adopts a different conformation of the terminal benzyl groups. Complete crystallographic data, as a CIF file, have been deposited with Cambridge Crystallographic Data Centre (CCDC No. 612577). Copies can be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk).