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Convergent Synthesis of the ABCDEF-Ring System of Yessotoxin and Adriatoxin

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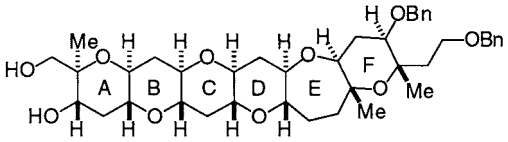
ABSTRACT

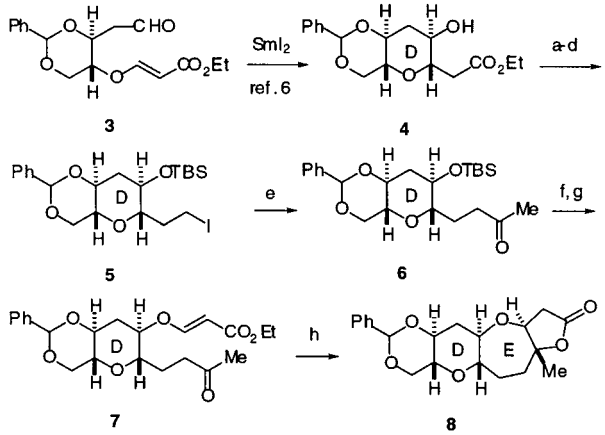


The convergent synthesis of the ABCDEF-ring system of yessotoxin and adriatoxin was accomplished. This efficient convergent strategy was performed on the basis of the coupling of the acetylide of the A-ring and the triflate of the DEF-ring, oxidation of the alkyne to diketone, intramolecular diacetalization, and stereoselective reduction of the diacetal with Et_3SiH–TMSOTf.

Yessotoxin (YTX; **1**), isolated from the digestive glands of DSP (Diarrethic Shellfish Poisoning)-infested scallops, *Patinopecten yessoensis*, is a disulfated polycyclic ether toxin (Figure 1). The relative and absolute configurations have been elucidated by Yasumoto et al.[1] Adriatoxin (ATX; **2**), a new analogue of YTX, was isolated from the digestive glands of DSP-infested mussels, *Mytilus galloprovincialis*, and the structure was determined by Fattorusso et al.[2] As they show potent mouse lethality, contamination of bivalves by these compounds poses a problem worldwide to human health as well as to the shellfish industry. The structure of these compounds features trans-fused polycyclic ether ring systems, in which six-, seven-, and eight-membered ethers are involved. The synthetically challenging structure combined with potent biological activity has attracted the attention of synthetic organic chemists.[3]

We have already reported an efficient strategy for convergent synthesis of trans-fused polycyclic ethers.[4,5] The

Scheme 1[a]



[a] Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (b) DIBAH, CH_2Cl_2, 0 °C (85%, two steps); (c) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C; (d) NaI, acetone, 60 °C (66%, two steps); (e) $Et_2NCHMeCN$, LDA, THF−HMPA, −78 °C, then SiO_2−H_2O (100%); (f) TBAF, THF rt; (g) ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2, rt (90%, two steps); (h) SmI_2, MeOH, THF, rt (84%).

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(1) (a) Murata, M.; Kumagai, M.; Lee, J. S.; Yasumoto, T. *Tetrahedron Lett.* **1987**, *28*, 5869. (b) Satake, M.; Terasawa, K.; Kadowaki, Y.; Yasumoto, T. *Tetrahedron Lett.* **1996**, *37*, 5955. (c) Morohashi, A.; Satake, M.; Oshima, Y.; Yasumoto, T. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 1761.
(2) Ciminiello, P.; Fattorusso, E.; Forino, M.; Magno, S.; Poletti, R.; Viviani, R. *Tetrahedron Lett.* **1998**, *39*, 8897.
(3) The convergent synthesis of the BCDE-ring of **1** was reported: Mori, Y.; Hayashi, H. *Tetrahedron* **2002**, *58*, 1789.

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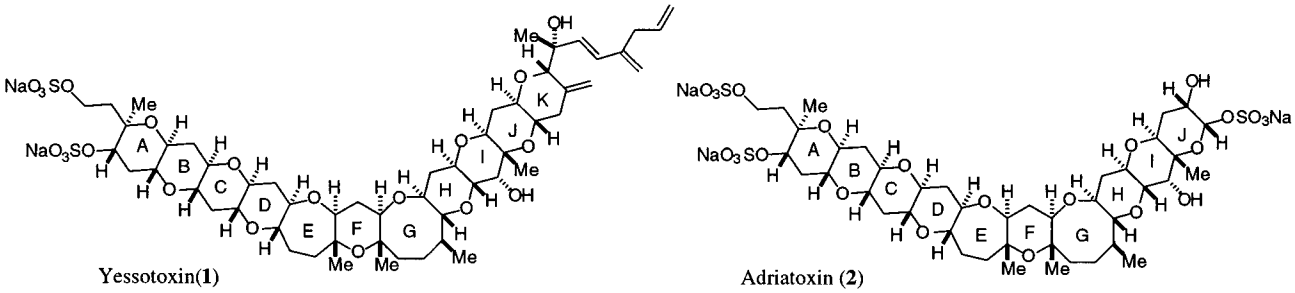
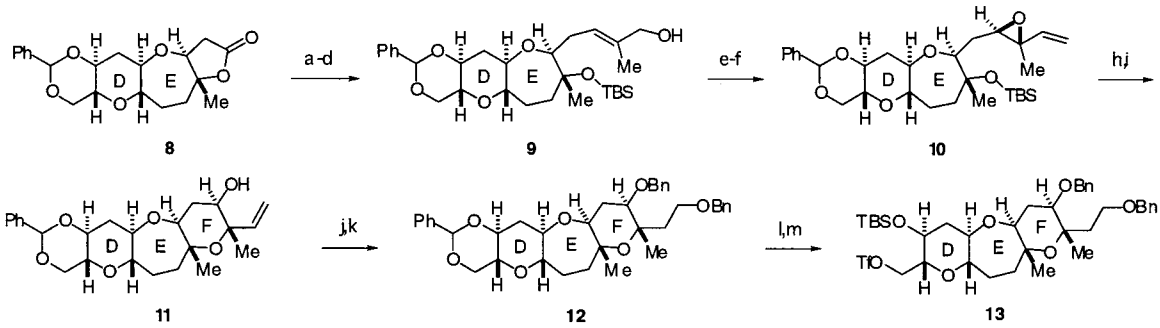


Figure 1. Structures of yessotoxin (**1**) and adriatoxin (**2**).

Scheme 2[a]

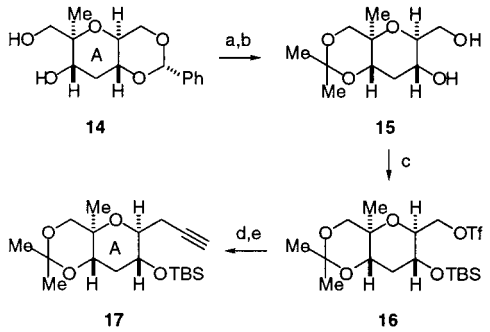


[a] Reagents and conditions: (a) DIBAH, toluene, −78 °C (100%); (b) $Ph_3P{=}CH(Me)CO_2Et$, toluene, 100 °C (100%); (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (100%); (d) DIBAH, toluene, −78 °C (89%); (e) (−)-DET, Ti(Oi-Pr)$_4$, TBHP, 4 Å MS, CH_2Cl_2, −35 °C (96%); (f) SO_3·pyridine, Et_3N, DMSO, CH_2Cl_2, rt; (g) $Ph_3P^+CH_3Br^-$, NaHMDS, THF, 0 °C (96%, 2 steps); (h) TBAF, THF, rt (74%); (i) PPTS, CH_2Cl_2, 0 °C (68%); (j) 9-BBN, THF, 0 °C; then 30% H_2O_2,, 3 N NaOH, 0 °C (82%); (k) BnBr, NaH, Bu_4NI, THF, 0 °C (87%); (l) CSA, MeOH, rt (85%); (m) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C, then TBSOTf, −78 °C (100%).

strategy involves only four steps: (1) the acelylide-triflate coupling of two cyclic ethers, (2) oxidation of the alkyne to the α-diketone, (3) intramolecular diacetalization, and (4) stereoselective Lewis acid-catalyzed silane reduction. As an application of this strategy toward the total synthesis of marine polycyclic ethers, we now report the convergent synthesis of the ABCDEF-ring system of YTX (**1**) and ATX (**2**).

Synthesis of the lactone **8**, corresponding to the DE- ring of **1** and **2**, is shown in Scheme 1. The synthesis started with cyclic ether **4**,[6] corresponding to the D-ring, which was stereoselectively synthesized by our developed SmI_2-induced cyclization[7] of **3**, prepared from 2-deoxy-D-ribose. After protection of the secondary alcohol of **4** with TBSOTf and reduction of the ester, the resultant alcohol was transformed into the iodide **5** in 56% yield (four steps). Treatment of **5** with the lithium anion of diethylaminopropionitrile[8] followed by hydrolysis with wet silica gel effectively afforded ketone **6** in quantitative yield. After removal of the TBS group in

Scheme 3[a]



[a] Reagents and conditions: (a) $Me_2C(OMe)_2$, CSA, DMF, rt (94%); (b) H_2, $Pd(OH)_2$, EtOAc, rt (99%); (c) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C, then TBSOTf, −78 °C; (d) (trimethylsilyl)acetylene, *n*-BuLi, THF, −78 °C (99%, two steps); (e) K_2CO_3, MeOH, rt (83%).

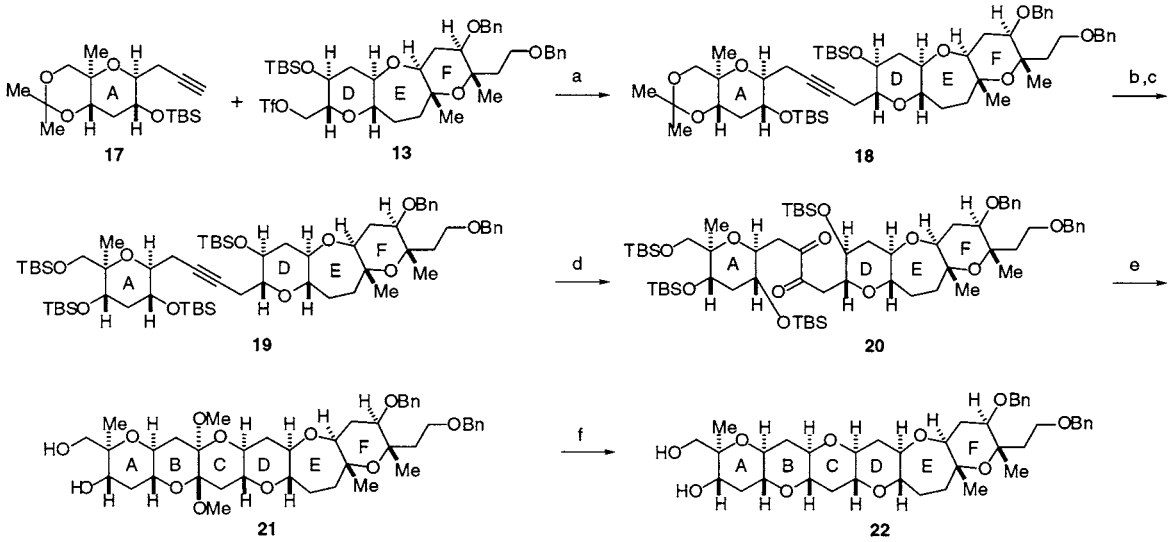
(4) Matsuo, G.; Hinou, H.; Koshino, H.; Suenaga, T.; Nakata, T. *Tetrahedron Lett.* **2000**, *41*, 903.

(5) The same strategy was reported independently by the groups of Murai and Mori at almost the same time: (a) Fujiwara, K.; Morishita, H.; Saka, K.; Murai, A. *Tetrahedron Lett.* **2000**, *41*, 507. (b) Mori, Y.; Mitsuoka, S.; Furukawa, H. *Tetrahedron Lett.* **2000**, *41*, 4161.

(6) The synthesis of **4** will be described in detail elsewhere. See Supporting Information for the synthetic scheme of **4**.

(7) (a) Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 2811. (b) Hori, N.; Matsukura, H.; Nakata, T. *Org. Lett.* **1999**, *1*, 1099. (c) Matsuo, G.; Hori, N.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 8859. (d) Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron* **2002**, *58*, 1853.

Scheme 4[a]



[a] Reagents and conditions: (a) *t*-BuLi, THF, HMPA, −78 °C (100%); (b) CSA, MeOH, rt; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (100%, two steps); (d) RuO_2, $NaIO_4$, MeCN−CCl_4−H_2O, rt (83%); (e) $CH(OMe)_3$, CSA, MeOH, 80 °C (67%); (f) TMSOTf, Et_3SiH, CH_2Cl_2, 0 °C (57%).

6, the hetero-Michael reaction with ethyl propiolate gave ketone **7** in 90% yield. Treatment of **7** with SmI_2 in THF in the presence of MeOH effected the reductive cyclization, accompanied by formation of γ-lactone, to give the desired trans-fused 6,7-membered ether **8**, corresponding to the DE-ring, in 84% yield with complete stereoselection.

We next investigated the construction of the F-ring from the lactone **8** (Scheme 2). DIBAH reduction of **8** followed by the Wittig reaction with $Ph_3P{=}CH(Me)CO_2Et$ gave α,β-unsaturated ester (100%), which was converted into allyl alcohol **9** in 89% yield by successive treatments with TBSOTf and DIBAH. The Sharpless asymmetric epoxidation[9] of **9** using (−)-DET stereoselectively gave the β-epoxide (96%), which was subjected to oxidation with SO_3·pyridine and Wittig reaction with $Ph_3P{=}CH_2$ to afford vinylepoxide **10** in 96% yield. After removal of the TBS group of **10** with TBAF, treatment of the resultant alcohol with PPTS[10] in CH_2Cl_2 effected 6-endo-cyclization[11] to stereoselectively give 6,7,6-membered ether **11**, corresponding to the DEF-ring. Then, conversion of **11** to triflate **13**, the coupling partner of the A-ring acetylide, was carried out. Hydroboration of the double bond in **11** gave a diol (82%), which was protected by treatment with BnBr to give dibenzyl ether **12** in 87% yield. Deprotection of the benzylidene in **12** with CSA in MeOH and selective triflation and silylation in one pot[12] gave the desired triflate **13** in 85% yield.

Synthesis of acetylene **17** as the other coupling partner, corresponding to the A-ring, started with diol **14**,[13] which was prepared from 2-deoxy-L-ribose (Scheme 3). Protection of the diol in **14** as an acetonide followed by removal of the benzylidene group afforded diol **15** in 93% yield. After triflation and silylation in one pot,[12] reaction of the resultant product **16** with lithium (trimethylsilyl)acetylide followed by removal of the TMS group afforded **17** in 82% yield from **15**.

After having established suitable coupling conditions in a model study,[14] we turned to the coupling of **13** and **17** toward the convergent synthesis of the ABCDEF-ring system (Scheme 4). Upon treatment of **17** with *t*-BuLi in THF−HMPA followed by addition of **13**, coupling reaction proceeded smoothly to give acetylene **18** in quantitative yield. Deprotection of the acetonide **18** and subsequent protection of the resultant diol with TBSOTf quantitatively gave tetra-TBS ether **19**. Oxidation of alkyne **19** with RuO_2−$NaIO_4$[15] gave diketone **20** (83%), which was treated with CSA in $CH(OMe)_3$−MeOH to effect simultaneous TBS deprotection and methylacetalization to give hexacyclic diacetal **21** in 67% yield. Reduction of **21** with Et_3SiH−TMSOTf at 0 °C smoothly proceeded to give the desired trans-fused 6,6,6,6,7,6-membered hexacyclic ether **22**, corresponding to the ABCDEF-ring of YTX (**1**) and ATX (**2**), in 57% yield. The

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(9) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5976.
(10) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.
(11) (a) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K.; Somers, P. K. *J. Chem. Soc., Chem. Commun.* **1985**, 1359. (b) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330. (c) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5335.
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(13) (a) Sakamoto, Y.; Matsuo, G.; Matsukura, H.; Hori, N.; Nakata, T. *Org. Lett.* **2001**, *3*, 2749. (b) Matsuo, G.; Matsukura, H.; Hori, N.; Nakata, T.; *Tetrahedron Lett.* **2000**, *41*, 7673.
(14) In a model study, we found that acetonide **17** was a more suitable coupling partner than the corresponding benzylidene and di-*tert*-butyl silylene derivatives and that use of *t*-BuLi gave the best result in generating acetylide. See Supporting Information for the model study.
(15) (a) Carling, R. W.; Holmes, A. B. *Tetrahedron Lett.* **1986**, *27*, 6133. (b) Zibuck, R.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 237.

structure of hexacyclic ether **22** was confirmed by ^{1}H and ^{13}C NMR, PFG-NOESY, and PFG-HMBC analysis.[16]

In summary, we have accomplished a convergent synthesis of the ABCDEF-ring system of YTX (**1**) and ATX (**2**). Progress toward the completion of the total synthesis of **1** and **2** is under way in this laboratory.

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Supporting Information Available: Synthetic scheme for compound **4**, a model study for the coupling reaction, and characterization data for compounds **8**, **11**, **17**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) See Supporting Information for stereochemical confirmation of **22** by extensive NMR analysis.