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Convergent synthesis of the A–F ring segment of yessotoxin and adriatoxin

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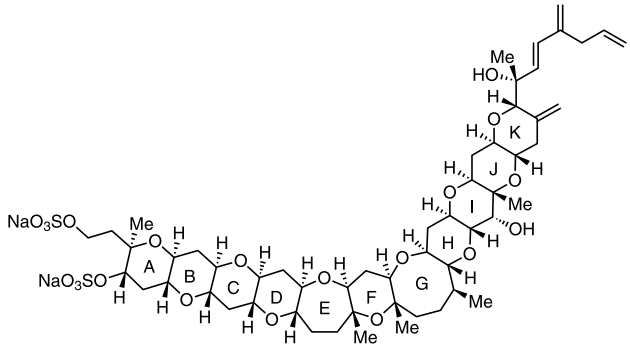
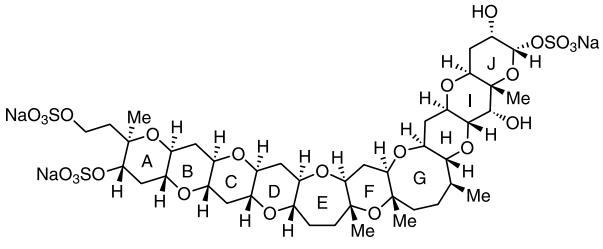
Abstract—A convergent synthesis of the A–F ring segment of yessotoxin and adriatoxin was achieved via the intramolecular allylation of an α-chloroacetoxy ether and subsequent ring-closing metathesis.

Yessotoxin (**1**), a disulfated polycyclic ether, was isolated from the digestive glands of scallops, *Patinopecten yessoensis*, as one of the causative toxins of DSP (Diarrethic Shellfish Poisoning).[1] Recently, a trisulfated derivative, adriatoxin (**2**) was found from the DSP-infested mussels, *Mytilus galloprovincialis*.[2] Due to their novel structural futures and biological activities, both compounds have attracted the attention of synthetic chemists.[3] 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.[4] As part of our total synthetic studies of **1** and **2**, we wish to report the convergent synthesis of the common A–F ring segment based on our methodology.

Scheme 1 shows the synthesis of the ABC ring segment. Reduction of the known ester **3**[3b] with $LiAlH_4$ followed by selective TBS protection of the resulting primary alcohol gave **4** in 74% yield. Treatment of **4** with ethyl propiolate and 4-methylmorpholine followed by desilylation with TBAF afforded the acrylate **5** in 88% yield. Oxidation of the alcohol **5** with SO_3·py/DMSO/Et_3N gave **6** in 88% yield. The aldehyde **6** was then subjected to the Nakata cyclization. Thus, treatment of **6** with SmI_2 in the presence of MeOH afforded **7** as the sole product in 92% yield.[5] Reduction of the ester of **7** with $LiAlH_4$ followed by TIPS protection of the resulting diol gave the bis-silyl ether **8**, which was treated with H_2/$Pd(OH)_2$-C to give the diol **9** in 79% yield. Selective tosylation of the primary alcohol of **9** gave **10** in 86%



Yessotoxin (**1**)



Adriatoxin (**2**)

Keywords: yessotoxin; adriatoxin; polycyclic ethers; convergent synthesis.
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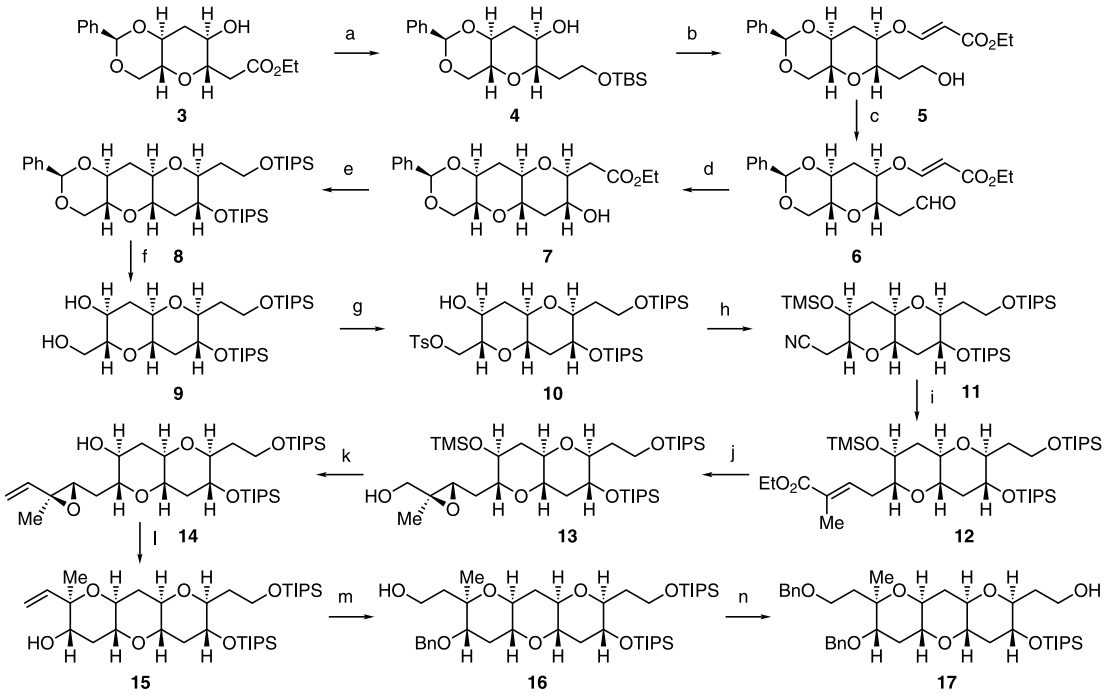
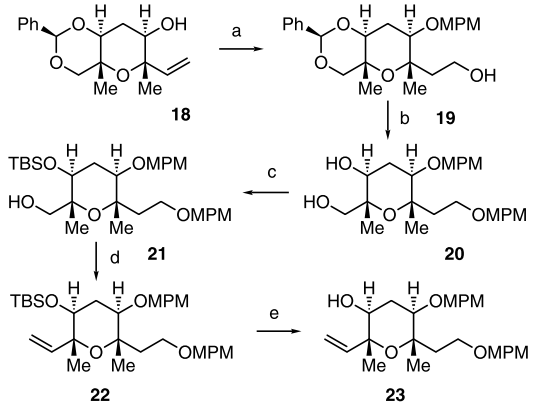


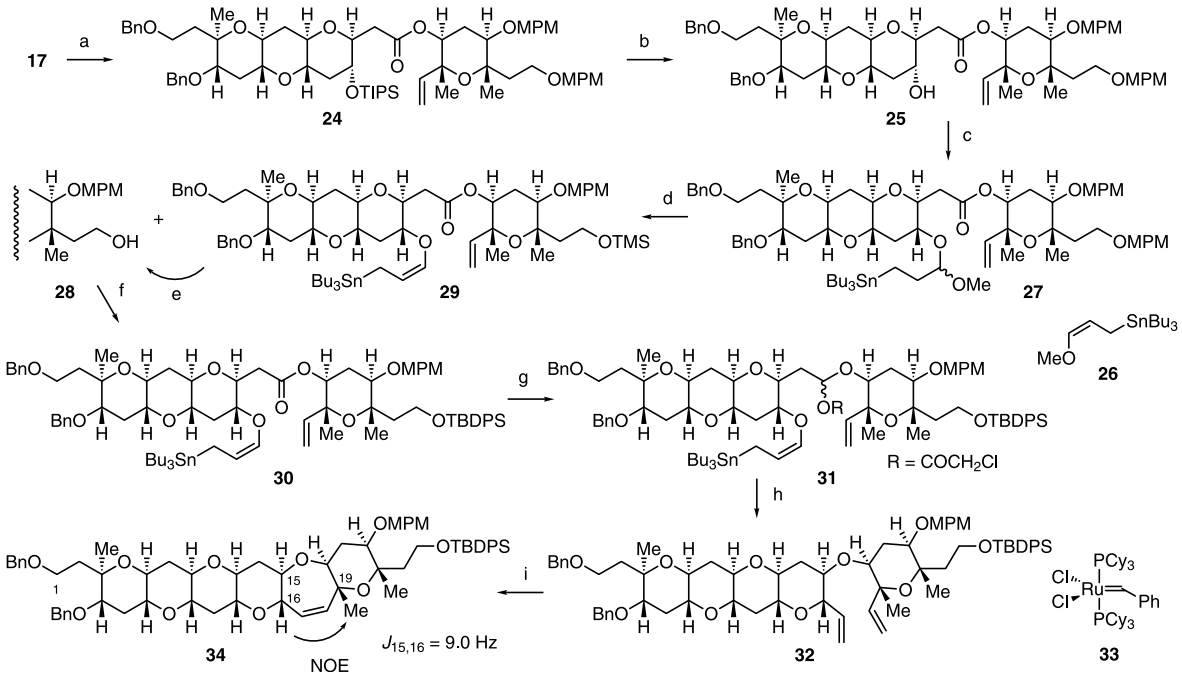
Scheme 1. *Reagents and conditions*: (a) (i) $LiAlH_4$, ether, 0°C; (ii) TBSCl, imidazole, DMF, 0°C, 74% (two steps); (b) (i) ethyl propiolate, 4-methylmorpholine, CH_2Cl_2, rt; (ii) TBAF, THF, rt, 88% (two steps); (c) SO_3·py, DMSO, Et_3N, CH_2Cl_2, 0°C, 88%; (d) SmI_2, MeOH, THF, 0°C, 92%; (e) (i) $LiAlH_4$, ether, 0°C; (ii) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0°C to rt; (f) H_2, $Pd(OH)_2$-C, EtOAc, rt, 79% (three steps); (g) TsCl, pyridine, CH_2Cl_2, rt, 86%; (h) (i) NaCN, DMSO, 50°C; (ii) TMS-imidazole, CH_2Cl_2, reflux, 72% (two steps); (i) (i) DIBAL-H, CH_2Cl_2, −78°C; (ii) $Ph_3P{=}C(Me)CO_2Et$, CH_2Cl_2, reflux, 72% (two steps); (j) (i) DIBAL-H, CH_2Cl_2, −78°C, 95%; (ii) *t*-BuOOH, $Ti(O^iPr)_4$, (+)-DET, 4 Å MS, CH_2Cl_2, −20°C, 90%; (k) (i) SO_3·py, DMSO, Et_3N, CH_2Cl_2, 0°C; (ii) $Ph_3P^+CH_3Br^-$, NaHMDS, THF, 0°C, 93% (two steps); (iii) TBAF, THF, rt, 92%; (l) PPTS, CH_2Cl_2, rt, 90%; (m) (i) BnBr, KH, THF, reflux; (ii) $(c\text{-Hex})_2BH$, THF, 0°C, then 30% H_2O_2, 3N NaOH, 0°C; (n) (i) BnBr, KH, THF, reflux; (ii) CSA, CH_2Cl_2–MeOH, 0°C to rt, 77% (four steps).

yield. Treatment of the tosylate **10** with NaCN followed by TMS protection of the remaining secondary alcohol gave the nitrile **11** in 72% yield. DIBAL-H reduction of **11** and subsequent Wittig reaction of the resulting aldehyde gave the α,β-unsaturated ester **12** in 72% yield. DIBAL-H reduction of the ester **12** followed by Sharpless oxidation of the resulting allylic alcohol gave the epoxide **13** as a single stereoisomer in 86% yield (two steps). Oxidation of the alcohol **13** with SO_3·py/DMSO/Et_3N, Wittig reaction of the resulting aldehyde, and selective removal of the TMS group with TBAF afforded the epoxy alcohol **14** in 86% yield (three steps). Acid catalyzed cyclization of **14** was performed using PPTS according to the Nicolaou's procedure to furnish the tricyclic compound **15** as the sole product in 90% yield.[6] Benzyl protection of the secondary alcohol **15** with BnBr/KH followed by hydroboration gave the primary alcohol **16**. Benzyl protection of **16** followed by selective removal of the primary TIPS group with CSA afforded the ABC segment **17** in 77% yield.

Preparation of the F ring segment is described in Scheme 2. Transformation of the known alcohol **18**[7] to the corresponding MPM ether followed by hydroboration gave the alcohol **19** in 92% yield. MPM protection of **19** and subsequent removal of the benzylidene acetal with CSA afforded the diol **20** in 82% yield. Protection of **20** with TBSOTf/2,6-lutidine gave the corresponding bis-silyl derivative, which was treated with CSA in MeOH to give the primary alcohol **21** in 75% yield. Swern oxidation of **21** followed by Wittig reaction of the resulting aldehyde afforded the olefin **22**. Desilyla-



Scheme 2. *Reagents and conditions*: (a) (i) MPMCl, KH, THF, reflux; (ii) $(c\text{-Hex})_2BH$, THF, 0°C, then 30% H_2O_2, 3N NaOH, 0°C, 92% (two steps); (b) (i) MPMCl, KH, THF, reflux; (ii) CSA, MeOH, rt, 82% (two steps); (c) (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C to rt; (ii) CSA, MeOH, 75% (two steps); (d) $(COCl)_2$, DMSO, CH_2Cl_2 −78°C, then Et_3N, −78°C to rt; (ii) $Ph_3P^+CH_3Br^-$, NaHMDS, THF, 0°C; (e) TBAF, THF, rt, 76% (three steps).



Scheme 3. *Reagents and conditions*: (a) (i) 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, rt; (iii) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, then **23**, DMAP, toluene, rt, 97% (three steps); (b) TBAF, THF, rt, 86%; (c) **26**, CSA, CH_2Cl_2, 0°C, 90%; (d) TMSI, HMDS, CH_2Cl_2, −15°C, 55% for **28**, 27% for **29**; (e) TBAF, THF, rt, 100%; (f) TBDPSCl, imidazole, DMF, rt, 87%; (g) DIBAL-H, CH_2Cl_2, −78°C, then $(CH_2ClCO)_2O$, pyridine, DMAP, −78°C, 89%; (h) $BF_3{\cdot}OEt_2$, CH_3CN–CH_2Cl_2 (20:1), −45 to 0°C, 65%; (i) **33**, benzene, 70°C, 78%.

tion of **22** with TBAF furnished the F ring segment **23** in 76% yield.

Scheme 3 illustrates the coupling of the ABC and F ring segments. TEMPO oxidation of **17** followed by further oxidation of the resulting aldehyde with $NaClO_2$ gave the carboxylic acid, which was subjected to the Yamaguchi esterification[8] with the alcohol **23** to give the ester **24** in 97% yield. Removal of the TIPS group of **24** with TBAF gave the alcohol **25** in 86% yield. Reaction of **25** with the γ-methoxyallylstannane **26** in the presence of catalytic CSA afforded the mixed acetal **27** in 90% yield. Treatment of **27** with TMSI/HMDS promoted the acetal cleavage efficiently, as expected.[9] However, selective cleavage of the primary MPM ether was accomplished due to an excess amount of TMSI/HMDS, to give a mixture of the deprotected primary alcohol **28** and its TMS ether **29** in 55% and 27% yields, respectively.[10] The selective removal of the TMS group of **29** was carried out upon treatment with TBAF, affording **28** in a quantitative yield. Protection of the primary alcohol **28** with TBDPSCl/imidazole gave **30** in 87% yield. Modified Rychnovsky acetylation including the partial reduction of **30** with DIBAL-H followed by trapping of the resulting aluminum hemiacetal with chloroacetic anhydride gave the cyclization precursor **31** in 89% yield.[11,12] Intramolecular allylation of **31** was carried out using $BF_3{\cdot}OEt_2$ to afford **32** as a single stereoisomer in 65% yield. Finally, the diene **32** was subjected to the ring-closing metathesis using the Grubbs catalyst **33**[13] to furnish the A–F ring segment **34** in 78% yield.[14] The stereochemistries at the C-15 and C-16 positions were unambiguously determined by the large coupling constant, $J_{15,16}=9.0$ Hz, and the NOE observed between 16-H and 19-Me.

In conclusion, we have achieved the convergent and stereoselective synthesis of the common A–F ring segment of yessotoxin (**1**) and adriatoxin (**2**) via the intramolecular allylation of an α-chloroacetoxy ether and subsequent ring-closing metathesis. Further studies toward the total syntheses of **1** and **2** are now in progress in our laboratories.

Acknowledgements

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14. NMR data for **34**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66–7.65 (m, 4H), 7.42–7.26 (m, 16H), 7.19 (d, $J=8.5$ Hz, 2H), 6.85 (d, $J=8.5$ Hz, 2H), 5.66 (dd, $J=13.0$, 3.0 Hz, 1H), 5.37 (dd, $J=13.0$, 2.0 Hz, 1H), 4.58 (d, $J=12.0$ Hz, 1H), 4.52 (d, $J=11.5$ Hz, 1H), 4.47 (d, $J=12.0$ Hz, 1H), 4.45 (d, $J=12.0$ Hz, 1H), 4.43 (d, $J=12.0$ Hz, 1H), 4.32 (d, $J=11.5$ Hz, 1H), 3.91 (ddd, $J=9.0$, 2.5, 2.5 Hz, 1H), 3.85 (ddd, $J=9.5$, 8.5, 6.0 Hz, 1H), 3.80 (s, 3H), 3.81–3.76 (m, 1H), 3.61–3.57 (m, 2H), 3.41 (dd, $J=11.5$, 4.5 Hz, 1H), 3.37–3.32 (m, 3H), 3.28 (ddd, $J=11.0$, 9.0, 4.0 Hz, 1H), 3.12–3.02 (m, 4H), 2.91 (ddd, $J=11.5$, 9.0, 4.0 Hz, 1H), 2.34–2.27 (m, 3H), 2.20 (ddd, $J=11.5$, 4.0, 4.0 Hz, 1H), 2.06 (ddd, $J=11.5$, 3.5, 3.5 Hz, 1H), 2.01 (dd, $J=14.0$, 7.5 Hz, 1H), 1.94–1.88 (m, 2H), 1.78 (ddd, $J=14.0$, 8.5, 6.0 Hz, 1H), 1.68 (ddd, $J=12.0$, 12.0, 12.0 Hz, 1H), 1.58–1.35 (m, 4H), 1.29 (s, 3H), 1.22 (s, 3H), 1.14 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 141.7, 138.6, 138.3, 135.6, 134.0, 130.6, 129.5, 128.9, 128.3, 127.6, 127.5, 127.4, 127.0, 113.7, 81.9, 80.1, 79.8, 79.4, 78.2, 78.0, 77.5, 77.3, 77.1, 77.0, 76.9, 76.7, 76.5, 76.3, 76.0, 75.4, 72.9, 71.0, 70.7, 69.0, 65.8, 59.9, 55.2, 44.6, 39.6, 35.5, 35.1, 30.4, 28.9, 26.9, 21.9, 20.3, 19.1, 16.6.