Synthesis of the ABCDEF and FGHI ring system of yessotoxin and adriatoxin

Yuan Zhang and Jon D Rainier

Yessotoxin and adriatoxin are members of the poly cyclic ether family of marine natural products. Outlined in this article is our synthetic approach to two subunits of these targets. Central to our strategy is a coupling sequence that employs an olefinic-ester cyclization reaction. As outlined, this sequence was used in two coupling sequences. First, it was used to merge the A, B, and E, F-bicyclic precursors and in the process generate the C- and D-rings. Second, it was used to couple the F- and I-rings while building the eight-membered G-ring and subsequently the H-ring pyran.

**INTRODUCTION**

Yessotoxin (1, YTX), a disulfated poly cyclic ether natural product was first reported in 1987 by Murate, Yasumoto and co-workers from the digestive gland of the scallop Patinopecten yessoensis (Figure 1). It was subsequently discovered that YTX is produced by the dinoflagellates Protocentrum reticulatum, Lingulodinium polyedrum and Gonyaulax spinifera. YTX is acutely toxic to mice when administered intraperitoneally (LD50 = 286 μg kg⁻¹) but not orally (up to 54 mg kg⁻¹). The bioactivity of YTX ranges from modulating cytosolic calcium homeostasis, inducing lysosomal damage, Adria toxin (2, ATX), a trisulfated glycosyl ether induces apoptosis through the activation of caspases, to inducing lysosomal damage. Adriatoxin (2, ATX), a trisulfated analogue of YTX, was first isolated in 1998 from the digestive gland of the mussel Mytilus galloprovincialis collected in the Adriatic Sea. Structurally, YTX and ATX share the same A-J ring system, with YTX bearing an additional pyran (K-ring in YTX) and a hydrophilic side chain. Both compounds have attracted considerable interest from the organic synthesis community because of their challenging structures and intriguing properties. We have previously reported the syntheses of the AB, EF and HI ring systems of ATX. Our approach to the total synthesis of marine poly cyclic ether natural products has largely focused on a convergent strategy that is centered around an olefinic-ester cyclization reaction that pairs cyclic ether subunits and leads to the generation of two additional rings. Herein, we describe our convergent synthesis of the ABCDEF and FGHI ring systems of YTX and ATX (3 and 4).

**MATERIALS AND METHODS**

NMR spectra were recorded on Varian Inova-400 MHz, Varian Inova-500 MHz or Varian VXR-500 MHz spectrometers. Chemical shifts were reported in δ, p.p.m., relative to benzene (7.16), chloroform (7.27) or dichloromethane (5.32) as internal standards. Coupling constants, J, were reported in Hertz (Hz) and refer to apparent peak multiplicities and not true coupling constants. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Utah at Salt Lake City on a Finnigan MAT 95 mass spectrometer. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Optical rotations were obtained on a Perkin–Elmer Model 343 polarimeter (Na D line) using a microcell with 1 dm path length. Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin, Armarego and Perrin: Oxford, 1966).

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In honor of Professor Amos B. Smith, III and his 50 years of dedication to the Organic Chemistry community
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Figure 1 Structures of yessotoxin, adriatxin, the A-F and G-H ring systems.

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J = 10.2, 9.3, 3.4 \text{ Hz, (1H)}, 3.35 (\text{dd, } J = 12.5, 3.5 \text{ Hz, (1H)}), 3.26 (\text{dd, } J = 8.8, 8.8, 2.9 \text{ Hz, (1H)}), 2.94 (\text{dd, } J = 10.2, 9.8, 4.9 \text{ Hz, (1H)}), 2.75-2.69 (n, (1H)), 2.35 (\text{dd, } J = 7.3, 7.3 \text{ Hz, (1H)}), 2.31 (\text{dd, } J = 11.7, 4.4, 4.4 \text{ Hz, (1H)}), 2.19 (\text{dd, } J = 11.2, 4.4, 4.4 \text{ Hz, (1H)}), 1.88 (\text{dd, } J = 11.2, 11.2, 11.2 \text{ Hz, (1H)}), 1.43 (s, (3H)), 0.93 (s, (9H)), 0.01 (s, (3H)), – 0.01 (s, (3H)); \text{IR (neat) } 3259, 2954, 2861, 1714, 1463, 1377, 1256, 1093 \text{ cm}^{-1}; \text{ESI/MS (m/z) calcd for C}_{25}\text{H}_{37}\text{O}_{7}\text{Si} 477.3 (M+Na^+) , found 477.4.
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2-((2R,4aR,5aS,7R,8S,9aR,10aS)-7-((tert-butyldimethylsilyl)oxy)-4a-methyl-2-phenyloctahydro-4H-pyrano[2',3':5,6]pyrano[3,2-d][1,3]dioxin-8-yl)acetic acid (2-((2R,4aR,5aS,7R,8S,9aR,11aS)-7-((tert-butyldimethylsilyl)oxy)-8,9a-dimethyl-2-phenyloctahydro-4H-pyrano[2',3':5,6][1,3]dioxino[5,4-b][pyrano[2,3-f][oxepin-8-yl]ethan-1-ol (9). To a solution of 8 (28 mg, 0.075 mmol) in THF (5 ml) at RT was added KH (30 mg, 30% dispersion in mineral oil, 0.23 mmol). After being allowed to stir for 10 min, DMPU (4.5 μl, 0.038 mmol), PMBBr (54 μl, 0.38 mmol) and a catalytic amount of TBAI were added to the reaction mixture. After stirring overnight, the reaction mixture was quenched with sat. NH₄Cl (aq., 5 ml). The aqueous phase was extracted with CH₂Cl₂ (3×5 ml) and the combined organic extracts were dried (Na₂SO₄) and concentrated. Flash chromatography (gradient of 10:1 hexanes:ethyl acetate) gave a colorless oil, which was used in the next step without further purification.

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\text{O}_3 \text{ was bubbled through a solution of 6 (30 mg, 0.065 mmol) in CH}_2\text{Cl}_2 (20 \text{ ml}) at } – 78 \text{ °C until the reaction mixture was a light blue color. Excess } \text{O}_3 \text{ was purged from the reaction mixture by bubbling } \text{N}_2 \text{ through it until the light blue color completely faded away. Triphenylphosphine (51 mg, 0.19 mmol) was then added and the reaction mixture was allowed to slowly warm to room temperature (RT). After 12 h, the solution was concentrated under reduced pressure. Flash chromatography (50:1 to 5:1 hexane:hexyl acetate) provided the corresponding aldehyde (28 mg, 92%) as a colorless oil.}
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To a solution of aldehyde obtained above (28 mg, 0.061 mmol) in THF (3 ml) was successively added BuOHN (3 ml), H₂O (3 ml), 2-Me-2-butenen (0.6 ml), NaH₂PO₄ (36 mg, 0.30 mmol) and NaClO₂ (27 mg, 0.30 mmol). The resulting mixture was stirred at RT for 2 h after which the reaction was quenched with H₂O (3 ml). The reaction mixture was extracted with ethyl acetate (3×5 ml) and the organic extracts were combined, dried (Na₂SO₄) and concentrated. Flash chromatography (gradient of 1:1 hexane:hexyl acetate) provided aldehyde (19 mg, 67%) as a colorless oil.

To a solution of the aldehyde obtained above in MeOH (5 ml) at 0 °C was added NaBH₄ (8.5 mg, 0.23 mmol). The reaction mixture was stirred for 2 h, after which the reaction was quenched with acetone (3 ml). The mixture was concentrated and the residue was purified using flash chromatography (4:1 hexane:ethyl acetate) to give 9 as a colorless oil (28 mg, 74% over three steps). Rf 0.50 (2:1 hexane:ethyl acetate); [α]$_D^{20}$ = -52.2° ($c = 0.39$ THF);
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\text{H NMR (500 MHz, CD}_2\text{Cl}_2) \delta 7.51-7.47 (m, (2H)), 7.41-7.37 (m, (3H)), 5.58 (s, (1H)), 3.92 (d, $J = 10.2$ Hz, (1H)), 3.69-3.60 (m, (3H)), 3.55 (dd, $J = 10.7, 9.3, 4.9$ Hz, (1H)), 3.48 (dd, $J = 11.2, 9.3, 3.9$ Hz, (1H)), 3.22 (dd, $J = 11.2, 9.8, 4.4$ Hz, (1H)), 2.89 (dd, $J = 15.6, 2.9$ Hz, (1H)), 2.42 (dd, $J = 16.6, 9.3$ Hz, (1H)), 2.27 (dd, $J = 11.7, 4.4, 4.4$ Hz, (1H)), 2.00 (dd, $J = 11.2, 4.4, 4.4$ Hz, (1H)), 1.78 (dd, $J = 11.7, 11.7$ Hz, (1H)), 1.53 (dd, $J = 11.7, 11.7, 11.7$ Hz, (1H)), 1.52 (s, (3H)), 0.92 (s, (9H)), 0.14 (s, (3H)), 0.13 (s, (3H)); \text{ESI/MS (m/z) calcd for C}_{29}\text{H}_{38}\text{O}_{7}\text{Na} 521.2 (M+Na^+) , found 521.3.}
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The residue from above was dissolved in MeOH (15 ml) and the mixture was cooled to 0 °C. CSA (15 mg, 0.065 mmol) was added and the reaction mixture was allowed to slowly warm to RT. The reaction was quenched with sat. NaHCO3 (aq., 10 ml) after 5 h. The aqueous phase was extracted with ethyl acetate (3 × 10 ml) and the combined organic extracts were dried (Na2SO4) and concentrated. The residue formed above was dissolved in MeOH (15 ml) and the mixture was cooled to 0 °C. CSA (15 mg, 0.065 mmol) was added and the reaction mixture was allowed to slowly warm to RT. The reaction was quenched with sat. NaHCO3 (aq., 10 ml) after 5 h. The aqueous phase was extracted with ethyl acetate (3 × 10 ml) and the combined organic extracts were dried (Na2SO4) and concentrated. Flash chromatography (4:1 hexanes/ethyl acetate) gave 12 as a colorless oil (85.7 mg, 0.169 mmol) and the reaction mixture was stirred for 2 h before it was passed through a Celite plug with ethyl acetate. The filtrate was concentrated and flash chromatography (4:1 hexanes/ethyl acetate) gave 13 as a colorless oil (78.8 mg, 92%). Rf 0.55 (2:1 hexanes/ethyl acetate); [α]20D = −14.9° (c = 0.43, THF); 1H NMR (500 MHz, CDCl3) δ 7.38–7.28 (m, 5H), 7.26 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.3 Hz, 2H), 5.89 (ddd, J = 17.1, 10.3, 6.8, 6.8 Hz, 1H), 5.14–5.07 (m, 2H), 4.58 (d, J = 11.2 Hz, 1H), 4.47 (s, 2H), 4.37 (d, J = 11.2 Hz, 1H), 3.89 (br d, J = 5.9 Hz, 1H), 3.85 (s, 3H), 3.65 (t, J = 11.2 Hz, 1H), 3.57 (s, 3H), 2.74 (m, 1H) and 2.57 (m, 1H). 13C NMR (125 MHz, CDCl3) δ 159.4, 139.2, 131.1, 129.4, 128.5, 127.8, 127.5, 113.9, 85.7, 79.6, 73.9, 76.5, 75.5, 73.0, 71.0, 70.8, 66.7, 64.5, 55.4, 41.7, 39.4, 35.9, 28.8, 26.7, 22.3, 20.1; IR (neat) 3423, 2929, 2613, 1515, 1454, 1374, 1248, 1087 cm−1; ESI/MS (m/z) calc'd for C20H15NaO2N3Na+ 353.3 (M+Na+) found 333.3.

(2S,3R,4aS,6R,7S,9aR)-2-((2R,4aR,5aS,7R,8S,9aR,10aS)-10a-((2-(benzyloxy)ethyl)-3-((4-methoxyfluoromethyl)oxy)-2,9a-dimethyl-3H-pyrano[3,2-b]oxepin-7-yl)-2,3-dimethyl-6-((4aR,5aS,7R,8S,9aR,11aS)-8-(2-(benzyloxy)ethyl)-7-hydroxy-4-methyl-2-phenylcyclohexa-2,3-diene-1(3H)-yl)acetate (14). To a solution of acid 7 (36.0 mg, 0.0753 mmol) in THF (8 ml) were added triethylamine (45.9 μl, 0.330 mmol) and 2,4,6-trichlorobenzoyl chloride (35.3 μl, 0.223 mmol). The reaction mixture was heated to 40 °C and stirred for 2 h before being concentrated. A solution of alcohol 13 (36.8 mg, 0.0722 mmol) in toluene (10 ml) was transferred via cannula to the resulting residue. DMAP (42.3 mg, 0.347 mmol) was then added and the reaction mixture was heated at 40 °C for 2 h after which the reaction was quenched with sat. NaHCO3 (aq., 10 ml). The aqueous phase was extracted with CH2Cl2 (3 × 10 ml) and the organic extract was dried (Na2SO4) and concentrated. Flash chromatography (4:1 hexanes/ethyl acetate) provided ester 14 (67.8 mg, 97%) as a colorless oil. Rf 0.25 (5:1 hexanes/ethyl acetate); [α]20D = −14.8° (c = 0.30, THF); 1H NMR (500 MHz, CDCl3) δ 7.46–7.43 (m, 2H), 7.38–7.34 (m, 7H), 7.32–7.27 (m, 1H), 7.22 (d, J = 8.3 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 5.88 (dd, J = 17.1, 10.3, 6.8, 6.8 Hz, 1H), 5.52 (s, 1H), 5.13 (dd, J = 18.1, 1.0 Hz, 1H), 5.09 (d, J = 10.7 Hz, 1H), 4.99 (d, J = 6.3 Hz, 1H), 4.57 (d, J = 10.7 Hz, 1H), 4.49 (d, J = 11.7 Hz, 1H), 4.45 (d, J = 11.7 Hz, 1H), 3.93 (d, J = 10.3 Hz, 1H), 3.97 (s, 3H), 3.75 (dd, J = 6.2, 6.2 Hz, 1H), 3.72–3.58 (m, 5H), 3.55 (dd, J = 9.8, 9.8, 4.4 Hz, 1H), 3.48 (partially observed dd, J = 10.8, 9.3, 9.3 Hz, 1H), 3.44 (partially observed dd, J = 10.8, 9.3, 9.3 Hz, 1H), 3.39 (partially observed dd, J = 10.8, 9.3, 9.3 Hz, 1H), 3.19 (dd, J = 10.7, 9.3, 4.4 Hz, 1H), 2.87 (dd, J = 14.9, 2.7 Hz, 1H), 2.39 (dd, J = 14.9, 9.5 Hz, 1H), 2.13–2.23 (m, 3H), 2.16 (dd, J = 11.2, 3.9 Hz, 1H), 2.12 (dd, J = 11.2, 3.9 Hz, 1H), 1.97–1.64 (m, 4H), 1.59–1.48 (m, 1H), 1.50 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 0.92 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 170.8, 159.4, 139.3, 138.0, 134.8, 131.1, 129.3, 128.5, 128.4, 128.7, 127.6, 126.7, 117.2, 113.8, 103.1, 82.6, 80.5, 80.1, 79.9, 78.9, 78.2, 77.1, 76.3, 76.2, 75.4, 73.0, 71.0, 70.4, 70.0, 69.4, 66.8, 55.4, 42.0, 39.6, 39.2, 38.3, 36.6, 30.7, 28.9, 25.8, 23.6, 22.0, 19.8, 18.0, 15.1, 14.1, –4.8; IR (neat) 3293, 2589, 1735, 1613, 1514, 1456, 1378, 1250, 1092 cm−1; ESI/MS (m/z) calc'd for C23H24O3N4Na+ 503.4 (M+Na+) found 493.5.
Activated Zn dust (330 mg, 5.08 mmol) and PbCl₂ (74.0 mg, 0.266 mmol) were then added. The resulting mixture went through a series of color changes from brown to green to purple and finally to blue-green over the course of 3–5 min.

To the slurry was transferred a solution of ester 14 (67.8 mg, 0.0699 mmol) and CH₂CHBr₂ (0.200 mL, 2.23 mmol) in CH₂Cl₂ (5 mL) via cannula. The reaction mixture was then heated to reflux for 30 min before it was cooled to 0°C. The reaction was quenched by adding sat. K₂CO₃ (aq., 1.0 mL) for 30 min and filtering the mixture. Concentration and flash chromatography (10:1 hexanes:ethyl acetate) gave 15 as a colorless oil (32.9 mg, 50%). ³⁷R (0.20 (5:1 hexanes:ethyl acetate); [α]pD = −40.3° (c = 0.29, THF); ²H NMR (500 MHz, CD₂Cl₂) δ 7.48–7.45 (m, 2H), 7.40–7.32 (m, 7H), 7.30–7.26 (m, 1H), 7.24 (d, J = 8.3 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 5.56 (s, 1H), 4.56 (d, J = 11.2 Hz, 1H), 4.52 (br d, J = 3.4 Hz, 1H), 4.47 (d, J = 11.7 Hz, 1H), 4.42 (d, J = 11.7 Hz, 1H), 4.37 (d, J = 11.2 Hz, 1H), 3.90 (d, J = 10.2 Hz, 1H), 3.78 (s, 3H), 3.67–3.60 (m, 2H), 3.60–3.52 (m, 2H), 3.50–3.40 (m, 3H), 3.37 (dd, J = 12.2, 3.9 Hz, 1H), 3.31 (dd, J = 9.3, 2.0 Hz, 1H), 3.12 (dd, J = 11.2, 9.3 Hz, 1H), 2.54 (d, J = 15.1 Hz, 1H), 2.28 (br d, J = 16.6 Hz, 1H), 2.22 (d, J = 11.2, 4.4 Hz, 1H), 2.16 (d, J = 11.7, 3.9 Hz, 1H), 2.12 (dd, J = 12.2, 3.9 Hz, 1H), 2.05–1.66 (m, 10H), 1.50 (s, 3H), 1.47 (d, J = 10.7, 10.7 Hz, 1H), 1.24 (s, 3H), 1.19 (s, 9.0H), 0.99 (s, 10H), 0.09 (s, 3H); ¹³C NMR (125 MHz, CD₂Cl₂) δ 159.4, 151.6, 139.3, 138.1, 131.1, 129.4, 128.5, 128.4, 127.6, 127.6, 113.5, 103.3, 94.8, 80.6, 80.0, 79.7, 79.7, 79.1, 78.8, 78.0, 77.0, 76.4, 75.6, 73.8, 69.7, 69.5, 66.5, 55.4, 41.9, 40.0, 39.9, 35.9, 30.7, 29.7, 29.4, 28.8, 25.8, 23.5, 22.3, 15.0, 1.1, 4.8; IR (neat) 2933, 2859, 1651, 1513, 1458, 1377, 1250, 1093 cm⁻¹; ESI/MS (m/z) calc for C₃₈H₆₀O₁₂SiN₃Na 693.5 (M⁺Na⁺), found 693.6.

A solution of 15 (28.6 mg, 0.0304 mmol) in CH₂Cl₂ (5 mL) at 78°C was added a solution of dimethyl dioxirane (0.61 ml of 0.1 M solution in CH₂Cl₂, 0.061 mmol) dropwise. The reaction mixture was warmed to 0°C and then concentrated. The resulting residue was dissolved in CH₂Cl₂ (5 mL) and cooled to −78°C. To this was added a solution of DBU (0.304 ml of 1 M solution in TFH, 0.30 mmol). After stirring for 2 h, the reaction was quenched with sat. NH₄Cl (aq., 3 mL) and allowed to warm to RT. A solution of potassium sodium tartrate solution (aq., 10 mL) was added and the resulting mixture was stirred for 30 min. The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL) and the combined organic phase was dried (Na₂SO₄) and concentrated. Flash chromatography (5:1 hexanes:ethyl acetate) provided major alcohol 16 (17.5 mg, 60%) and minor alcohol (6.1 mg, 21%) both as colorless oil.

To a solution of 16 (17.5 mg, 0.0183 mmol) in CH₂Cl₂ (5 mL) was added activated 4 Å MS (20 mg), NMO (21.4 mg, 0.183 mmol) and TPAP (1 mg, 0.003 mmol). The reaction mixture was stirred at RT for 2 h before being concentrated. Flash chromatography (5:1 hexanes:ethyl acetate) gave ketone 17 as a colorless oil (17.4 mg, 100%). ¹³R (0.55 (5:1 hexanes:ethyl acetate); [α]pD = −27.0° (c = 1.00, THF); ²H NMR (500 MHz, CD₂Cl₂) δ 7.48–7.45 (m, 2H), 7.39–7.24 (m, 7H), 7.23 (d, J = 8.3 Hz, 2H), 6.86 (d, J = 8.3 Hz, 2H), 5.56 (s, 1H), 4.55 (d, J = 11.2 Hz, 1H), 4.50 (d, J = 11.2 Hz, 1H), 4.36 (d, J = 11.7 Hz, 1H), 4.17 (d, J = 11.7 Hz, 1H), 4.08 (dd, J = 7, 3.5 Hz, 3.4 Hz, 1H), 3.92 (d, J = 10.2 Hz, 1H), 3.78–3.70 (m, 2H), 3.66–3.60 (m, 1H), 3.56–3.50 (partially resolved, m, 1H), 3.53 (partially resolved, d, J = 10.2 Hz, 1H), 3.45–3.25 (m, 4H), 3.28 (s, 3H), 3.16 (dd, J = 8.3, 8.3, 4.4 Hz, 1H), 3.08–3.00 (m, 2H), 2.97 (dd, J = 15.6, 6.4 Hz, 1H), 2.76 (dd, J = 15.2, 7.8, 2.4 Hz, 1H), 2.36–2.22 (m, 3H), 2.16–2.00 (m, 2H), 2.00–1.88 (m, 2H), 1.86–1.62 (m, 6H), 1.43 (s, 1H), 1.33 (s, 1H), 1.18 (s, 3H), 0.98 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ¹³C NMR (125 MHz, CD₂Cl₂) δ 7.501, 151.9, 139.4, 138.4, 131.0, 129.2, 128.9, 128.4, 128.4, 127.4, 116.4, 102.8, 81.0, 80.2, 80.1, 79.8, 79.5, 79.4, 78.9, 76.4, 76.4, 75.7, 73.0, 71.0, 69.9, 69.5, 66.5, 54.6, 46.1, 42.2, 40.2, 36.9, 36.7, 33.3, 31.0, 30.1, 29.2, 28.8, 25.8, 24.8, 22.8, 22.6, 18.0, 15.1, −1.1, 4.8; IR (neat) 2931, 2858, 1727, 1513, 1460, 1377, 1290 cm⁻¹; ESI/MS (m/z) calc for C₃₉H₇₂O₁₂SiK 995.5 (M⁺K⁺), found 995.5.
To the solution of the triol obtained above in DMF (10 ml) at −20 °C was added Bu4SiOTf (14.0 μl, 0.0384 mmol). The reaction mixture was stirred at −20 °C for 1 h before pyridine (6.2 ml, 0.077 mmol) was added. The mixture was stirred for another 5 min and the reaction was quenched with sat. NaHCO3 (aq., 10 ml). The aqueous phase was extracted with Et2O (3 × 10 ml) and the combined organic phase was dried (Na2SO4) and concentrated. Flash chromatography (3:1 hexanesethyl acetate) provided a colorless oil, which was taken on to the next transformation without additional purification.

To the solution of the colorless oil obtained above in toluene (10 ml) was added Ph2SH (200 mg, 0.570 mmol). The reaction mixture was heated to reflux and AIBN (0.0046 s solution in toluene, 2.0 ml, 9.2 mmol) was added via syringe pump over 2 h. The mixture was then cooled to RT and solvent was removed under reduced pressure. Flash chromatography (2:1 hexanes:ethyl acetate) provided 3 as a colorless oil (7.3 mg, 51% in 3 steps). Rf 0.20 (2:1 hexanes:ethyl acetate); [α]23D = −7.6° (c = 0.10, THF); 1H NMR (500 MHz, CDCl3) δ 7.39–7.27 (m, 27, m), 4.50 (s, 2H), 4.07 (dd, 1, f = 12.2, 4.4 Hz, 1H), 3.88 (d, f = 10.2 Hz, 1H), 3.75 (d, f = 10.2 Hz, 1H), 3.59 (dd, f = 6.4, 4.4 Hz, 1H), 3.54 (dd, f = 12.2, 3.9 Hz, 1H), 3.40–3.35 (m, 1H), 3.33 (dd, f = 11.7, 3.9 Hz, 1H), 3.26 (ddd, f = 10.8, 9.4, 4.4 Hz, 1H), 3.19 (ddd, f = 12.7, 8.8, 4.4 Hz, 1H), 3.13–2.95 (m, 6H), 2.32–2.24 (m, 2H), 2.18–2.10 (m, 2H), 2.01–1.68 (m, 10H), 1.65 (ddd, f = 11.7, 11.7, 11.7 Hz, 1H), 1.42 (s, 3H), 1.41–1.34 (m, 1H), 1.23 (s, 3H), 1.16 (s, 3H), 1.10 (s, 9H), 1.03 (s, 9H); 13C NMR (125 MHz, CD2Cl2) δ 152.1, 138.4, 129.0, 128.4, 81.9, 81.4, 80.4, 76.8, 77.6, 77.7, 77.4, 76.8, 75.0, 74.9, 74.3, 73.7, 73.2, 69.8, 67.1, 43.8, 40.5, 37.4, 35.9, 35.7, 34.0, 32.3, 29.9, 29.3, 23.0, 23.9, 20.4, 20.1, 15.6; IR (neat) 2985, 2921, 2859, 1673, 1453, 1378, 1312, 1150, 1093 cm−1; ESI/MS (m/z) calcd for C37H40O8Na 693.28 (M+Na+) and found 693.4.

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Summary of COSY spectrum for 26
1. Proton at 5.77 p.p.m. (C-25) shows cross peaks with protons at 5.03 p.p.m. (C-26) and 4.99 p.p.m. (C-24) and 2.30 p.p.m. (C-23).
2. 263
was (0.245 g, 0.578 mmol) in THF (15 ml) at 0 °C was added BH$_3$ (3 × 10 ml). The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated. Flash chromatography (15:1 hexanes:acetone) gave 29 as a colorless oil (42.1 mg, 55% for three steps). R$_f$ 0.60 (5:1 hexanes:acetone); [α]$^29$$_D$ = -24.2° (c = 0.24, THF); 1H NMR (500 MHz, CD$_2$$_3$) δ 7.66 (d, J = 7.3 Hz, 2H), 7.22 (t, J = 7.3 Hz, 2H), 7.20–7.12 (m, 3H), 6.82 (d, J = 8.8 Hz, 2H), 5.83 (ddd, J = 16.6, 9.8, 6.3 Hz, 1H), 5.41 (s, 1H), 5.08 (dd, J = 17.1, 1.5 Hz, 1H), 5.02 (d, J = 10.2 Hz, 1H), 4.46 (d, J = 11.7 Hz, 1H), 4.20 (d, J = 11.7 Hz, 1H), 3.85 (d, J = 9.8 Hz, 1H), 3.40 (d, J = 10.3 Hz, 1H), 3.37 (dd, J = 11.2, 4.9 Hz, 1H), 3.31 (s, 3H), 3.25 (dd, J = 12.2, 3.4 Hz, 1H), 2.24–2.12 (m, 3H), 1.86 (ddd, J = 11.7, 11.7, 11.7 Hz, 1H), 1.81 (ddd, J = 13.2, 11.2, 5.4 Hz, 1H), 1.53 (s, 1H), 1.33 (s, 3H); 13C NMR (125 MHz, CD$_2$$_3$) δ 160.2, 140.0, 139.2, 131.1, 129.9, 128.7, 127.2, 114.5, 110.5, 81.3, 79.5, 77.9, 77.5, 70.7, 69.3, 55.2, 42.1, 28.3, 27.1, 23.5, 19.6; IR (neat) 2943, 2865, 1639, 1513, 1460, 1375, 1248, 1086 cm$^{-1}$; ESI/MS (m/z) calc 473.4 (M+Na$^+$) for [C$_{28}$H$_{36}$O$_5$Na]; found 473.4.

To a solution of the diol obtained above in CH$_2$Cl$_2$ (4.5 ml) was added pH 7 buffer (0.5 ml) and DDQ (36.5 mg, 0.161 mmol). The reaction mixture was stirred at RT for 2 h after 2H$_2$O (5 ml) was added. The aqueous phase was extracted with ethyl acetate (3 × 5 ml). The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated. Flash chromatography (3:1 hexanes:acetone) gave the corresponding triol as a colorless oil (29.3 mg, 86%).

To a solution of the triol obtained from the procedure outlined in the previous paragraph in CH$_2$Cl$_2$ (5 ml) was added anisidine dimethylacetal (19.8 µl, 0.116 mmol) and CSA (9.0 mg, 39 µmol). The reaction mixture was stirred at RT overnight before the reaction was quenched with NaHCO$_3$ (aq., 5 ml). The aqueous phase was extracted with ethyl acetate (3 × 5 ml) and the combined organic extracts were dried (Na$_2$SO$_4$) and concentrated. Flash chromatography (2:1 hexanes:acetone) gave the corresponding triol as a colorless oil (18.9 mg, 96%).

To a slurry of methyltriphenylphosphonium bromide (1.03 g, 2.88 mmol) in THF (10 ml) was added BuOK (2.9 ml of 1.0 M solution in THF, 2.9 mmol). After stirring at RT for 30 min, the solution was transferred to a solution of the crude aldehyde from above in THF (10 ml). After 2 h the reaction was quenched with NH$_4$Cl (aq., 10 ml). The aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 10 ml). The organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated. Flash chromatography (10:1 hexanes:acetone) gave 28 as a colorless oil (0.154 g, 61% for 3 steps). R$_f$ 0.60 (5:1 hexanes:acetone); [α]$^29$$_D$ = -54.5° (c = 0.37, THF); 1H NMR (500 MHz, CD$_2$$_3$) δ 7.64 (d, J = 7.3 Hz, 2H), 7.22 (t, J = 7.3 Hz, 2H), 7.18–7.12 (m, 3H), 6.81 (d, J = 8.3 Hz, 2H), 5.85 (ddd, J = 17.1, 10.2, 6.3 Hz, 1H), 5.42 (s, 1H), 5.09 (dd, J = 17.1, 1.5 Hz, 1H), 5.00 (dd, J = 10.2, 1.5 Hz, 1H), 4.44 (d, J = 11.2 Hz, 1H), 4.20 (d, J = 11.7 Hz, 1H), 3.84 (d, J = 9.8 Hz, 1H), 3.39 (d, J = 10.8 Hz, 1H), 3.36 (ddd, J = 11.2, 4.9 Hz, 1H), 3.31 (s, 3H), 3.24 (dd, J = 12.2, 3.4 Hz, 1H), 2.24–2.12 (m, 3H), 1.86 (ddd, J = 11.7, 11.7, 11.7 Hz, 1H), 1.81 (ddd, J = 13.2, 11.2, 5.4 Hz, 1H), 1.53 (s, 1H), 1.33 (s, 3H); 13C NMR (125 MHz, CD$_2$$_3$) δ 160.2, 140.0, 139.2, 131.1, 129.9, 128.7, 127.2, 114.5, 110.5, 81.3, 79.5, 77.9, 77.5, 70.7, 69.3, 55.2, 42.1, 28.3, 27.1, 23.5, 19.6; IR (neat) 2943, 2865, 1639, 1513, 1460, 1375, 1248, 1086 cm$^{-1}$; ESI/MS (m/z) calc 477.2 (M+K$^+$) for [C$_{28}$H$_{36}$O$_5$Na]; found 477.2.

To a slurry of methyltriphenylphosphonium bromide (300 mg, 0.840 mmol) in THF (5 ml) was added BuOK (0.84 ml of 1.0 M solution in THF, 0.84 mmol). After stirring at RT for 30 min, the solution was transferred to a solution of the crude aldehyde from above in THF (5 ml). The reaction mixture was stirred for an additional 2 h before the reaction was quenched with NH$_4$Cl (aq., 10 ml). The aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 10 ml) and the organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated. Flash chromatography (20:1 hexanes:acetone) provided the corresponding ketone (1.85 g, 98%) as a colorless oil.
To a solution of the ketone obtained from the protocol outlined in the previous paragraph (1.80 g, 4.17 mmol) in 80 ml toluene at −90 °C was added MeLi (18 ml of 1.6 M in diethyl ether, 29 mmol) dropwise. After stirring the reaction mixture for 1 h at −90 °C, the reaction was quenched with NH4Cl (aq., 50 ml) and allowed to warm to RT. The aqueous phase was extracted with CH2Cl2 (3 × 20 ml) and the combined organic extracts were dried (Na2SO4) and concentrated. Flash chromatography (2:1 hexanexane acetate) provided the corresponding tertiary alcohol (1.56 g, 84%) as a colorless oil.

To a solution of the tertiary alcohol from above (0.80 g, 0.31 mmol) in a mixture of CH2Cl2 (6 ml) and DMSO (3 ml) were added Et3N (0.21 ml, 1.65 mmol) and SO3•Py (0.24 g, 1.65 mmol). The reaction mixture was stirred for 3 h at RT before the reaction was quenched with H2O (10 ml). The aqueous phase was extracted with CH2Cl2 (3 × 5 ml) and the combined organic extracts were dried (Na2SO4) and concentrated. Flash chromatography (2:1 hexanexane acetate) gave the corresponding diol as a colorless oil (0.57 g, 95%).

To a solution of the diol from above (0.11 g, 0.31 mmol) in a mixture of CH2Cl2 (6 ml) and DMSO (3 ml) were added Et3N (0.21 ml, 1.65 mmol) and SO3•Py and concentrated to give triethylsilane (10:1 hexanes:ethyl acetate) and concentrated to give a colorless oil (1.90 g, 100%).

To a solution of TMS ether (1.90 g, 4.44 mmol) in THF (40 ml) at −78 °C was added L-Selectride (6.7 ml of 1.0 M solution in THF, 6.7 mmol). The reaction mixture was allowed to slowly warm to RT over 2 h before it was quenched with H2O (20 ml). The aqueous phase was extracted with CH2Cl2 (3 × 10 ml). The combined organic extracts were dried (Na2SO4) and concentrated. Flash chromatography (2:1 hexanexane acetate) gave the TMS ether as a colorless oil (1.90 g, 100%).

To a solution of the TMS ether (1.90 g, 4.44 mmol) in THF (40 ml) at −78 °C was added L-Selectride (6.7 ml of 1.0 M solution in THF, 6.7 mmol). The reaction mixture was allowed to slowly warm to RT over 2 h before the reaction was quenched with sat. NH4Cl (aq., 20 ml). The aqueous phase was extracted with CH2Cl2 (3 × 10 ml). The combined organic extracts were dried (Na2SO4) and concentrated. The resulting residue was passed through a plug of silica gel (10:1 hexanexane acetate) and concentrated giving a colorless oil that was used in the subsequent transformation without additional purification.

To a solution of the colorless oil obtained from the above procedure in THF (15 ml) at 0 °C was added BH3•DMS (2.0 M solution in THF, 11 ml, 22 mmol). H2O (1.0 ml), NaOH (25 ml of 3.0 M aq. solution), and H2O2 (30 ml of 30% aq. solution) were added after 2 h. The reaction mixture was warmed to RT and stirred overnight. The aqueous phase was extracted with ethyl acetate (3 × 20 ml). The combined organic extracts were dried (Na2SO4) and concentrated. Flash chromatography gave 34 as a colorless oil (1.17 g, 70% over 2 steps). Rf 0.35 (1:1 hexanexane acetate); [α]25D = −39.3° (c = 0.29, THF); 1H NMR (500 MHz, CDCl3) δ 4.10 (dd, J = 9.5, 4.6 Hz, 1H), 3.78 (dd, J = 9.9, 2.7 Hz, 1H), 3.73 (dd, J = 10.2, 10.2 Hz, 1H), 3.71-3.63 (m, 3H), 3.58-3.53 (m, 2H), 3.34 (dd, J = 10.2, 10.2 Hz, 1H), 3.10 (br s, 1H), 1.36 (br s, 1H), 0.73 (br s, 1H), 1.76 (dd, J = 14.2, 7.1, 7.1 Hz, 1H), 1.71-1.62 (m, 1H), 1.60-1.50 (m, 1H), 1.29-1.21 (m, 1H), 1.08 (s, 9H), 0.98 (s, 9H), 0.95 (s, 9H); 13C NMR (125 MHz, CDCl3) δ 78.9, 75.8, 74.3, 71.8, 70.9, 67.0, 62.5, 30.1, 27.6, 27.4, 24.6, 22.9, 20.4, 18.8; IR (neat) 3414, 2936, 2893, 2862, 1472, 1392, 1157, 1102 cm−1; ESI/MS (m/z) calc. for C31H30O5SiNa 529.3 (M+Na+) found 529.3.

Synthesis of the A-F and F-I yessotoxin rings

Y Zhang and JD Ranier
transferred a solution of alcohol 30 (24.8 mg, 0.085 mmol) in toluene (8 ml) followed by DMAP (0.100 g, 0.820 mmol). The resulting reaction mixture was heated at 40 °C for 2 h and then the reaction was quenched with sat. NaHCO₃ (aq., 10 ml). The aqueous phase was extracted with CH₂Cl₂ (3 × 10 ml), the organic extracts were combined, dried (Na₂SO₄) and concentrated. Flash chromatography (0.1:1 hexanes:ethyl acetate) provided ester 40 (54.7 mg, 84%) as a colorless oil. Rf 0.70 (1 atm hexanes:ethyl acetate); [α]D₂₀ = 26.2° (c = 0.29, THF). ¹H NMR (500 MHz, CD₃OD) δ 7.55 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 7.3 Hz, 2H), 7.35 (d, J = 7.3 Hz, 2H), 7.29 (d, J = 7.8 Hz, 2H), 7.20–7.05 (m, 9H), 6.82 (d, J = 8.3 Hz, 2H), 5.84 (ddd, J = 17.1, 10.3, 6.8 Hz, 1H), 5.32 (s, 1H), 5.22 (dd, J = 11.2, 4.9 Hz, 1H), 5.11 (d, J = 11.2 Hz, 1H), 5.08 (dd, J = 15.6, 1.5 Hz, 1H), 5.02 (dd, J = 10.3, 1.0 Hz, 1H), 4.68 (d, J = 11.2 Hz, 1H), 4.49 (ddd, J = 10.3, 3.4 Hz, 1H), 4.43 (d, J = 11.2 Hz, 1H), 4.38 (d, J = 11.2 Hz, 1H), 4.33 (s, 2H), 4.13 (d, J = 10.0 Hz, 1H), 3.99 (dd, J = 9.6, 2.0 Hz, 1H), 3.88 (d, J = 9.0 Hz, 1H), 3.80 (d, J = 9.8 Hz, 1H), 3.42–3.34 (m, 3H), 3.27 (s, 3H), 3.28–3.24 (partially obscured m, 1H), 2.86 (dd, J = 14.7, 3.4 Hz, 1H), 2.62 (d, J = 14.7, 3.4 Hz, 1H), 2.29 (ddd, J = 11.2, 4.4, 3.9 Hz, 1H), 2.08–1.96 (m, 5H), 1.80–1.55 (m, 6H), 1.49 (s, 3H), 1.30 (s, 3H), 1.22 (s, 3H), 1.00 (t, J = 8.3 Hz, 3H), 0.67 (q, J = 7.8 Hz, 3H), 0.66 (q, J = 8.3 Hz, 3H); ¹C NMR (125 MHz, CD₃OD) δ 170.7, 160.8, 140.2, 140.0, 139.8, 139.5, 131.6, 128.9, 128.8, 128.5, 128.0, 127.9, 127.9, 127.9, 127.8, 127.7, 115.1, 114.1, 103.1, 82.6, 80.5, 78.1, 78.0, 77.0, 76.0, 74.3, 74.0, 73.2, 73.2, 73.0, 70.1, 69.5, 65.9, 51.4, 34.8, 37.9, 30.5, 28.2, 27.8, 26.1, 23.6, 23.0, 19.5, 17.6, 7.6; IR (neat) 2954, 2876, 1741, 1496, 1379, 1249, 1106 cm⁻¹; ESI/MS (m/z) calcd for C₃₅H₅₀O₁₂SiNa 1015.6 (M+Na⁺), found 1015.3.

2-((2R,3R,5S,6S)-4-((benzoxyl)oxy)-6-((3-benzoxyl)propoxy)-5-methyl-3-(triethylsilyloxy)tetrathydro-2H-pyran-2-yl)acetic acid (38). O₂ was bubbled through a solution of 38 (638 mg, 1.01 mmol) in CH₂Cl₂ (60 ml) at −78 °C until the reaction mixture remained light blue in color. The excess O₃ was purged from the reaction mixture by bubbling N₂ through it until the light blue color completely dissipated (ca. 10 min). Triphenylphosphine (1.13 g, 5.08 mmol) was then added and the mixture was allowed to slowly warm to RT. After 12 h, the solution was concentrated under reduced pressure. Flash chromatography (50:1 to 1:1 hexanes:ethyl acetate) provided the aldehyde (600 mg, 94%) as a colorless oil.

To a solution of the aldehyde from the ozonolysis (600. mg, 0.949 mmol) in THF (10 ml) at 0 °C was added dibuOH (10 ml), H₂O (10 ml), 2-Me-2-butenone (2.0 ml), NaH₂PO₄ (570 mg, 0.475 mmol) and NaClO₃ (430 mg, 0.48 mmol). The reaction was quenched after 30 min by adding H₂O (30 ml). The resulting mixture was extracted with ethyl acetate (3 × 15 ml) and the organic extracts were combined, dried (Na₂SO₄) and concentrated. Flash chromatography (1:1 hexanes:ethyl acetate) provided acid 39 (615 mg, 100%) as a colorless oil. Rf 0.50 (2:1 hexanes:ethyl acetate); [α]D₂₀ = −92.4° (c = 0.27, THF); ¹H NMR (500 MHz, CDCl₃) δ 11.7 br s (1H), 7.44 (d, J = 7.8 Hz, 2H), 7.32 (d, J = 7.8 Hz, 2H), 7.29 (d, J = 7.4 Hz, 2H), 7.19–7.08 (m, 9H), 5.09 (d, J = 11.2 Hz, 1H), 4.65 (d, J = 11.2 Hz, 1H), 4.52 (ddd, J = 8.8, 8.8, 3.4 Hz, 1H), 4.41 (d, J = 11.2 Hz, 1H), 4.37 (d, J = 11.2 Hz, 1H), 4.31 (s, 2H), 4.11 (d, J = 10.7 Hz, 1H), 3.82 (d, J = 2.0 Hz, 1H), 3.73 (dd, J = 9.2, 2.0 Hz, 1H), 3.40–3.32 (m, 2H), 2.86 (ddd, J = 15.4, 3.2 Hz, 1H), 2.54 (dcd, J = 15.4, 9.0 Hz, 1H), 2.02–1.92 (m, 2H), 1.72–1.62 (m, 1H), 1.50 (d, J = 9.3, 9.3 Hz, 3H), 1.16 (s, 3H), 0.96 (t, J = 7.8 Hz, 9H), 0.58 (q, J = 7.8 Hz, 6H); ¹C NMR (125 MHz, CDCl₃) δ 178.3, 140.1, 140.0, 139.9, 128.9, 128.8, 128.8, 128.1, 127.9, 127.8, 127.7, 88.2, 78.0, 77.0, 76.0, 73.8, 73.0, 70.8, 63.9, 38.2, 27.4, 25.7, 17.6, 5.7; IR (neat) 3330, 2596, 2877, 1713, 1454, 1241, 1111 cm⁻¹; ESI/MS (m/z) calcd for C₅₀H₈₀O₁₁Si 711.4 (M+Na⁺), found 763.1.

(2R,4aR,5S,7R,8aS)-2-((4-methoxyphenyl)-4a,6-dimethyl-6-((pent-4-en-1-y1)hexahydropropyrazino)[2,3-d][1,3]dioxin-7-yl)-2-((2R,3R,5S,6S)-4-((benzoxyl)oxy)-6-((3-benzoxyl)propoxy)-5-methyl-3-(triethylsilyloxy)tetrathydro-2H-pyran-2-yl)acetic acid (40). To a solution of acid 39 (53.4 mg, 82.2 mmol) in THF (8 ml) was added triethyamine (0.100 ml, 0.719 mmol) and 2,4,6-trichlorobenzoyl chloride (77.0 ml, 0.493 mmol). The reaction mixture was heated at 40 °C for 2 h before the solvent was removed in vacuo. To the resulting residue was synthesized by Y Zhang and JD Rainier
M solution in CH₂Cl₂ (0.042 mmol) dropwise. The reaction mixture was warmed to 0 °C and the solvent was removed in vacuo. The residue was dissolved in CH₂Cl₂ (5 ml) and the reaction mixture was cooled to −78 °C and a solution of i-BuLi (0.21 ml of 1.0 M solution in THF, 0.21 mmol) was added. After stirring for 2 h at −78 °C, the reaction was quenched with sat. NH₄Cl (aq, 3 ml) and allowed to warm to RT. A solution of saturated potassium sodium tartrate (10 ml) was added and the mixture was stirred vigorously for 30 min. The aqueous phase was extracted with CH₂Cl₂ (3 × 10 ml) and the combined organic extracts were dried (Na₂SO₄) and concentrated to give alcohol 43.

To a solution of the alcohol obtained from above in CH₂Cl₂ (5 ml) was added activated 4 Å MS (20 mg), NMO (25 mg, 0.213 mmol) and TPAP (1 mg, 0.003 mmol). The reaction mixture was stirred at RT for 2 h being concentrated. Flash chromatography (5:1 hexanes:ethyl acetate) gave ketone 44 as a colorless oil (12.2 mg, 61% two steps). Rf 0.55 (3:1 hexanes:ethyl acetate). [α] 20D = −2.02° (c = 0.18, THF); 1H NMR (500 MHz, CDCl₃) δ 7.58 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 7.3 Hz, 2H), 7.36 (d, J = 7.8 Hz, 2H), 7.30 (d, J = 7.8 Hz, 2H), 7.21–7.06 (m, 9H), 6.83 (d, J = 8.3 Hz, 2H), 5.36 (s, 1H), 5.08 (d, J = 11.2 Hz, 1H), 4.70 (d, J = 11.2 Hz, 1H), 4.50 (dd, J = 9.3, 6.3 Hz, 1H), 4.44 (d, J = 11.2 Hz, 1H), 4.40 (d, J = 11.2 Hz, 1H), 4.32 (s, 2H), 4.12 (ddd, J = 9.8, 6.8, 2.9 Hz, 1H), 4.09 (dd, J = 10.3, 1.3 Hz, 1H), 3.85 (d, J = 2.0 Hz, 1H), 3.81 (d, J = 9.8 Hz, 1H), 3.79 (dd, J = 9.4, 2.4 Hz, 1H), 3.44–3.33 (m, 4H), 3.27 (s, 3H), 3.14 (dd, J = 12.2, 3.0 Hz, 1H), 2.87 (ddd, J = 14.2, 7.8, 4.9 Hz, 1H), 2.31–2.06 (m, 5H), 2.04–1.94 (m, 3H), 1.84–1.70 (m, 2H), 1.64–1.54 (m, 5H), 1.52 (s, 3H), 1.34 (s, 3H), 1.24 (s, 3H), 1.03 (t, J = 7.8 Hz, 9H), 0.69 (q, J = 7.8 Hz, 6H); 13C NMR (100 MHz, CDCl₃) δ 213.9, 160.9, 140.1, 139.9, 131.6, 128.9, 128.8, 128.5, 128.0, 127.9, 127.8, 127.7, 114.1, 103.1, 85.4, 83.3, 82.9, 81.4, 78.0, 77.9, 77.4, 76.0, 73.9, 73.2, 73.2, 71.1, 69.7, 63.9, 55.1, 44.0, 40.2, 35.4, 28.9, 27.8, 26.3, 21.5, 21.1, 20.2, 17.6, 7.6, 5.9; IR ( neat) 2934, 2876, 1704, 1614, 1496, 1378, 1249, 1124, 1077, 973 cm⁻¹; ESI/MS (m/z) calcd for C₂₉H₅₄O₃SiNa 1015.6 (M⁺Na⁺), found 1015.5.

Summary of COSY spectrum for 44

1. Proton at 4.50 p.p.m. (C-28) shows cross peaks with proton at 2.28 p.p.m. (C-29).
2. Proton at 4.12 p.p.m. (C-30) shows cross peaks with proton at 3.79 p.p.m. (C-31).
3. Proton at 4.09 p.p.m. (C-34) shows cross peaks with protons at 1.62 p.p.m. (C-35).
4. Proton at 3.81 p.p.m. (C-18) shows cross peaks with proton at 3.40 p.p.m. (C-18).
5. Proton at 2.06 p.p.m. (C-21) shows cross peaks with proton at 3.36 p.p.m. (C-22) and 3.14 (C-20).

Summary of 1D NOE spectrum for 44

1. Irradiation at 4.50 p.p.m. (C-28) resulted in enhancement at 3.36 p.p.m. (C-29).
2. Irradiation at 3.14 p.p.m. (C-20) resulted in enhancement at 5.36 p.p.m. (C-a), 3.40 p.p.m. (C-18), and 3.36 p.p.m. (C-22).

Synthesis of the A-F and F-I yeosotoxin rings

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RESULTS AND DISCUSSION

The synthesis of the AB bicyclic coupling precursor is depicted in Scheme 1. From known tricyclic substrate 5,32 TBS ether formation

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and ozonolysis gave 7 after conversion of the aldehyde into the corresponding carboxylic acid.33

Outlined in Scheme 2 is our synthesis of the EF bicyclic coupling precursor. From tricycle 8,32 PMB ether formation, ozonolysis and reduction of the resulting aldehyde gave primary alcohol 9. Benzyl ether generation and acetal hydrolysis gave diol 10. A single-flask conversion of the 1° alcohol in 10 into the corresponding trilate and the 2° alcohol into the corresponding TBS ether gave 11. Displacement of the trilate in 11 by lithium trimethylsilylacetylide and removal of the TBS group afforded 12.34 Partial hydrogenation provided EF coupling precursor 13.35

With 7 and 13 in hand, esterification using Yamaguchi’s conditions gave 14 (Scheme 3).36 When subjected to our modified Takai–Utimoto reaction conditions, 14 underwent a smooth olefinic ester cyclization to afford D ring cyclic enol ether 15 as the only product in 50% yield.37 On the basis of our inability to isolate by-products, we believe that the modest yield was due to the instability of 15 and not the inefficiency of the reaction. Treatment of 15 with DMDO followed by reduction of the resulting epoxide with TBDsAlH generated secondary alcohol 16 in 60% yield as a 3:1 mixture of diastereomers.38 The stereochemistry at C12 and C13 in 16 was established using 1H NMR and the 3J value between C12 and C13 following the conversion of 16 into the corresponding acetate 17 (TYX and ATX numbering). Oxidation of the mixture of diastereomers to ketone 18 followed by removal of the TBS group afforded hemiketal 19. Treatment of 19 with Zn(OiPr)2 and EtSH gave the corresponding O,S-mixed ketal as a single diastereomer with concomitant removal of the benzylidene and PMB groups. The C2 and C4 hydroxyl groups of triol 20 were selectively converted into cyclic silylene 21. When 21 was subjected to Ph2SnH and AIBN in refluxing toluene, the O,S-mixed ketal was reduced to give 3 containing the A–F ring system of both YTX and ATX.39

Having completed the synthesis of the A–F ring system, we turned our attention to the F–I subunit. Depicted in Scheme 4 is the synthesis of the F-ring coupling precursor 30. From known alcohol 22,40 acetylation followed by olefinic ester cyclization gave cyclic enol ether 24. The C19 angular methyl group helped to direct a stereoselective epoxidation of 24 with mCPBA. In situ epoxide opening with MeOH and alkylation of the resulting alcohol generated 25. The treatment of 25 with PPTS, pyridine, and heat initiated a Claisen rearrangement giving ketone 26 as a single diastereomer.28,41 The stereochemistry of the newly installed angular methyl group was confirmed through the indicated nOe correlations. Reduction of the ketone and PMB ether formation afforded 27. Although the extension of the propenyl side chain in 27 into the pentenyl side chain present in 29 was relatively inefficient, it could be carried out on a reasonable scale. Removal of the benzylidene and PMB groups followed by selective C-18, C-20 PMB acetal formation provide the F-ring coupling precursor 30.42

The I-ring subunit 39 was synthesized according to the route outlined in Scheme 5. From the previously reported alcohol 31,42 tertiary alcohol formation, removal of PMB group and oxidation gave 32. Formation of the TMS ether and reduction gave alcohol 33. Hydroboration and oxidative work-up provided the 1° alcohol while simultaneously removing the TMS group to give 34. Tris-benzyl ether formation and removal of the silylene group generated diol 35. Primary trilate formation and secondary TES ether formation gave 36. The coupling of 36 with lithium acetylide gave 37 after removal of the silyl protecting groups. TES ether formation and partial hydrogeration of the alkyne followed by ozonolysis and oxidation afforded the I-ring coupling precursor 39.
Scheme 3 Reagents and conditions: (a) 2,4,6-Cl₃C₆H₂COCl, Et₃N, THF, 40 °C; 13, DMAP, toluene, 40 °C, 97%; (b) TiCl₄, THF, TMEDA, Zn, PbCl₂, CH₃CHBr₂, CH₂Cl₂, 65 °C, 50%; (c) DMDO, CH₂Cl₂, −78 °C to 0 °C; Bu₂AlH, CH₂Cl₂, −78 °C, 60% (+21% diastereomer); (d) Ac₂O, Et₃N, DMAP, CH₂Cl₂, 81%; (e) NMO, TPAP, 4 Å MS, CH₂Cl₂, 100%; (f) HF•Py, THF, 0 °C to RT, 99%; (g) Zn(OTf)₂, EtSH, CH₂Cl₂, 40 °C; (h) tBu₂Si(OTf)₂, Py, DMF, −20 °C; (i) Ph₃SnH, AIBN, toluene, 110 °C, 51% (three steps).

Scheme 4 Reagents and conditions: (a) Ac₂O, Et₃N, DMAP, CH₂Cl₂, 79%; (b) TiCl₄, THF, TMEDA, Zn, PbCl₂, CH₃CHBr₂, CH₂Cl₂, 65 °C, 92%; (c) mCPBA, MeOH, −78 °C to 0 °C, 80%; (d) NaH, allyl bromide, TBAI, DMF, 0 °C to 65 °C; (e) PPTS, Py, toluene, 110 °C, 72% (two steps); (f) NaBH₄, MeOH, −78 °C to RT, 100%; (g) NaH, PMBBr, TBAI, HMPA, THF, 0 °C to RT, 83%; (h) BH₃•DMS, THF, 0 °C; NaOH, H₂O₂, 0 °C to RT; (i) NMO, TPAP, 4 Å MS, CH₂Cl₂; (j) Ph₃PCH₂Br, tBuOK, THF, 61% (three steps) for 28, 55% (three steps) for 29; (k) CSA, MeOH, 0 °C to RT, 86%; (l) DDQ, CH₂Cl₂-H₂O, 96%; (m) p-MeOC₆H₄CH(OMe)₂, CSA, CH₂Cl₂, 88%.
Yamaguchi esterification using alcohol 30 and acid 39 gave ester 40 (Scheme 6). Olefinic-ester cyclization gave eight-membered G-ring cyclic enol ether 41 in 40% yield. We are unaware of any other reports of eight-membered cyclic enol ether formation using either olefinic-ester cyclization or olefinic enol ether cyclization conditions.

Having access to 41, we next examined the incorporation of the H-ring and the C-26 methyl group (Scheme 7). The oxidation of 41 with DMDO was followed by the in situ reduction of the resulting epoxide with tBu2AlH giving secondary alcohol 43 as a single diastereomer. Oxidation provided ketone 44 whose stereochemistry was determined from the indicated nOe enhancements. The incorporation of the C-26 methyl group was accomplished through alkylation of the enolate from 44 to give 45. Reductive cyclization of the TES-protected hydroxy ketone 45 using TMSOTf and Et3SiH resulted in the generation of the G-ring. This transformation also resulted in the removal of the PMB acetal. Interestingly, when a benzylidene acetal rather than a p-methoxy benzylidene actal was used as the protecting group on the F-ring, it could not be cleanly removed under the reductive cyclization conditions, giving instead a mixture of benzyl protected alcohols. We were able to ascertain the relative stereochemistry of 4 using the indicated nOe enhancements.

In summary, we have achieved the convergent syntheses of both the ABCDEF and FGHI ring system of YTX and ATX using our olefinic ester cyclization strategy. We have also demonstrated that eight-membered cyclic enol ethers can be generated using an olefinic ester.
cyclization reaction. Further studies toward the total syntheses of YTX and ATX are currently in progress in our laboratory.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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