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Synthesis of the ABC and IJ ring fragments of yessotoxin

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Abstract—Synthesis of a 6/6/6 tricyclic ether system (**3**) corresponding to the ABC ring fragment of yessotoxin (**1**) has been achieved via coupling of a triflate and a 2-lithiofuran followed by intramolecular hetero-Michael addition. The IJ ring fragment (**4**) of **1** was readily synthesized via successive Sharpless epoxidation and 6-*endo* cyclization of the resulting vinyl epoxide.

Yessotoxin (**1**)[1] is a marine polyether toxin produced by the dinoflagellate *Protoceratium species* (Fig. 1).[2,3] Recently, glycoside analogs of **1**, protoceratins (**2**), which show potent cytotoxicity against human tumor cell lines, have been isolated from this organism.[4] Because of their biological activity, coupled with their fascinating arched molecular structure, **1** and its analogs have attracted the attention of synthetic chemists.[5,6] During the course of our synthetic studies of **1**, we developed an efficient method for convergent synthesis of polycyclic ethers via α-cyano ethers.[7] The methodology was successfully applied to the convergent synthesis of the CDEF[8] and FGHI[9] ring systems via two-ring construction of the central DE and GH rings, respectively. Herein, we describe a stereocontrolled synthesis of the ABC (**3**) and IJ (**4**) ring fragments (Fig. 1), which are pivotal intermediates in the total synthesis of **1**.

Although iterative syntheses of the ABC ring fragments of **1** have already been reported,[5d,g] we developed a novel strategy for synthesizing the 6/6/6 tricyclic system via two-ring construction starting with a triflate **6**[10] prepared from **5**,[11] as shown in Scheme 1. Treatment of **6** with the 2-lithiofuran derivative **9**, which is readily prepared from **7**,[12] resulted in the formation of coupling product **10** in moderate yield (45% for two steps), in contrast to the corresponding coupling reactions with alkynyllithiums (67–94%)[13] or oxiranyllithiums (90–98%),[5d–f,14] but comparable to the reaction with alkenyllithiums (15–55%).[15] Removal of the EE group

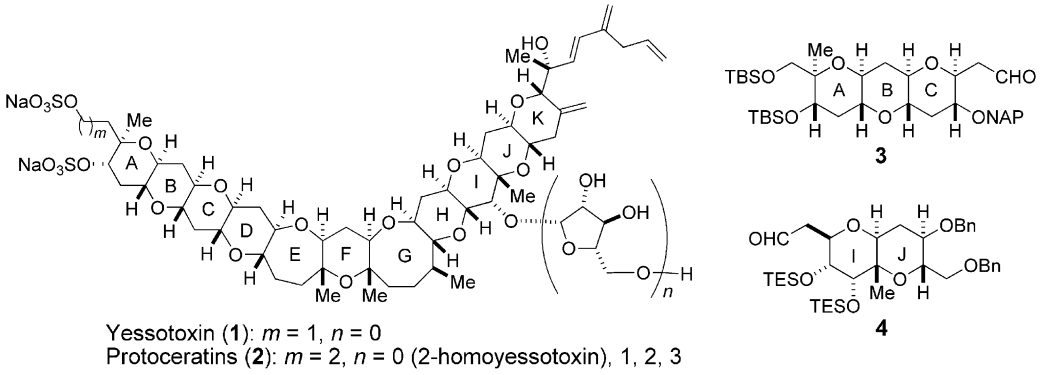

Figure 1. Structures of yessotoxin (**1**), protoceratins (**2**), and the ABC (**3**) and IJ (**4**) ring fragments of yessotoxin.

Keywords: Yessotoxin; Ladder-shaped polyether; Alkylative coupling; 2-Lithiofuran; Intramolecular hetero-Michael addition; Reductive etherification.
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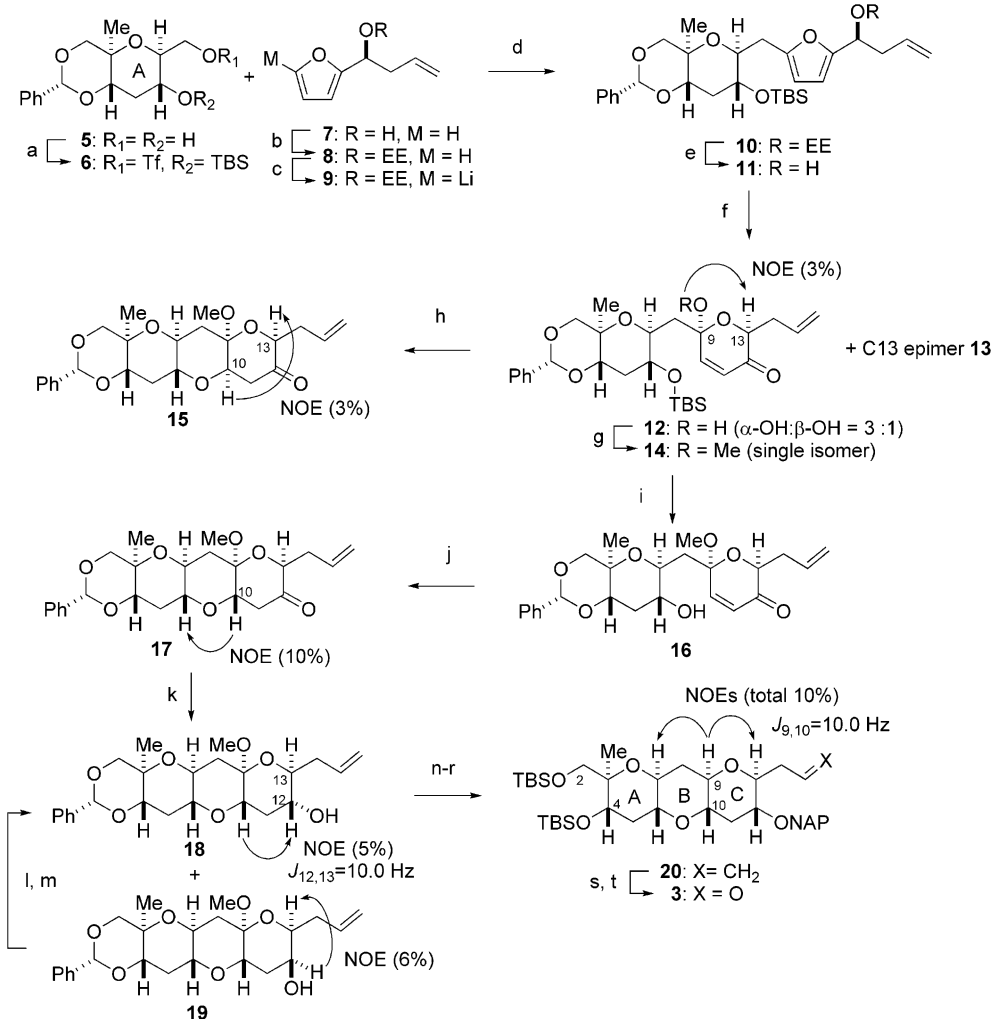
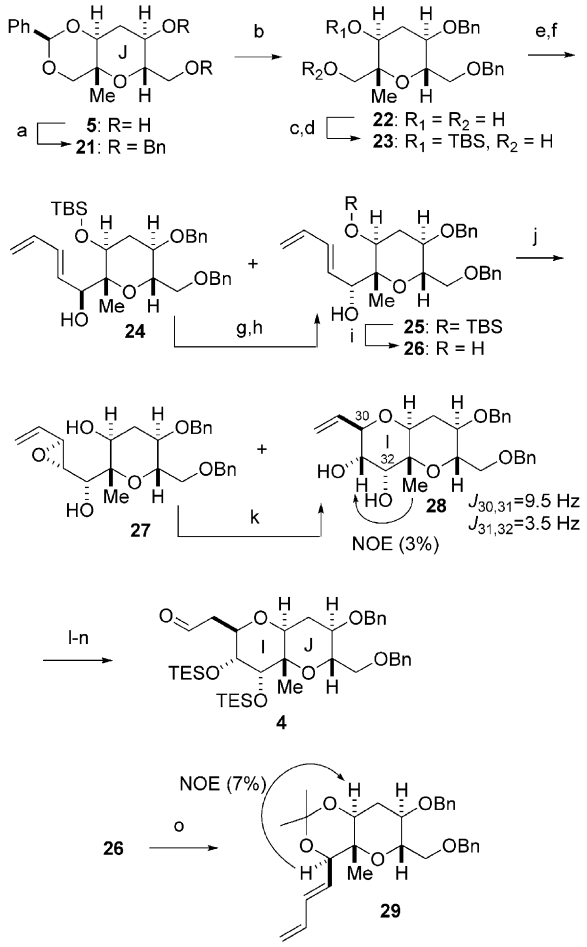


Scheme 1. Reagents and conditions: (a) 2,6-lutidine, Tf_2O, THF, −78 to −30 °C, 1 h, then TBSOTf, −78 to −10 °C, 1 h; (b) PPTS, ethyl vinyl ether, CH_2Cl_2, rt, 1 h, 95%; (c) *n*-BuLi, HMPA, THF, −78 °C, 7 min; (d) HMPA, THF, −78 °C, 30 min, 45% (two steps from **5**); (e) PPTS, *t*-BuOH/H_2O (3:1), rt, 13 h, 82%; (f) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, $CHCl_3$/H_2O/pH 4.0 buffer/*t*-BuOH (1:1:2:1), 40 °C, 7 h, **12** 58%, **13** 21%; (g) PPTS, $(MeO)_3CH$, CH_2Cl_2, rt, 8 h, **14** 64%, recovery of **12** 28%; (h) TBAF, THF, rt, 45 min, 44%; (i) 70% HF–pyridine, pyridine, THF, 59 °C, 8 h, **16** 77%, **17** 6%; (j) *p*-TsOH·H_2O, benzaldehyde dimethylacetal, CH_2Cl_2, rt, 3 h, 87%; (k) $NaBH_4$, EtOH, −78 °C to rt, 25 min, **18** 46%, **19** 46%; (l) DMP, pyridine, CH_2Cl_2, rt, 3 h; (m) $NaBH_4$, EtOH, rt, 1 h, **18** 50%, **19** 50% (two steps); (n) NAPBr, NaHMDS, THF/DMF (2:1), rt, 3.5 h; (o) CSA, MeOH/CH_2Cl_2 (1:1), rt, 2.5 h; (p) 2,6-lutidine, TBSOTf, CH_2Cl_2, rt, 99% (three steps); (q) Et_3SiH, BF_3·OEt_2, CH_2Cl_2, −50 to −20 °C, 1 h; (r) 2,6-lutidine, TBSOTf, CH_2Cl_2, 0 °C, 30 min, 84% (two steps); (s) K_2OsO_4, NMO, acetone/H_2O (2:1), rt, 2.5 h; (t) $NaIO_4$, THF/H_2O (1:1), rt, 2 h, 82% (two steps).

of **10** was successfully achieved by treating with PPTS in *t*-BuOH and H_2O (3:1) to afford furyl alcohol **11**. Despite the considerable number of precedents for oxidative ring expansion of furyl alcohols with $VO(acac)_2$ and TBHP,[12,16] the ring expansion of **11** was not an easy task, giving hemiacetal **12** (40%) with concomitant formation of its C13[17] epimer **13** (13%) and byproducts corresponding to *t*-butylperoxy acetals (30%). After considerable experimentation (oxidation with MCPBA,[18] NBS,[19] or singlet oxygen[20]), we found that oxidation with $NaClO_2$ in pH 4.0 buffer and chloroform[21] afforded **12** in better yield (58%). The hemiacetal **12**, in a mixture with its C9 epimer (3:1), was converted to methyl acetal **14** as a single isomer by treatment with PPTS and methyl orthoformate in 64% yield, with recovery of **12** (28%). Under the reaction conditions for removal of the TBS group of **14** with TBAF, intramolecular hetero-Michael addition[22] spontaneously occurred in a stereoselective manner to form the tricyclic system **15**. However, ^1H NMR analysis showed this to be the undesirable cis-isomer. Meanwhile, removal of the TBS group of **14** with HF·Py yielded hydroxyenone **16**. In contrast to the previous results, treatment of **16** with *p*-toluenesulfonic acid in dichloromethane at room temperature afforded the desired compound **17** as a single isomer without formation of spiroketals.[23] The diastereo-switchable hetero-Michael reaction of the enone under basic or acidic conditions is noteworthy from both the synthetic and mechanistic point of view. Attempts to convert the cis-isomer **15** into the trans-isomer **17** failed under acidic (*p*-TsOH) and basic (DBU) conditions.

Contrary to our expectations,[5d] the reduction of ketone **17** with $NaBH_4$ gave a mixture of the desired alcohol **19** and its epimer **18** in a 1:1 ratio as a separable mixture (the reaction did not proceed at −78 °C). The undesired **19** was recycled to form **18** via an oxidation and reduction sequence. Protecting group manipulation of **18**, that is, NAP[24] ether formation at C12 and subsequent conversion of the benzylidene acetal to a bis-TBS ether (99%), followed by reduction of the methyl ketal with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$[25] afforded **20** as a single isomer in 84% yield (partial removal of the TBS group occurred under conditions of reductive etherification to give a mixture of alcohols, which were again protected as TBS ethers). Finally, oxidative cleavage of the terminal olefin provided the ABC ring fragment **3**.[26]



Scheme 2. Reagents and conditions: (a) NaHMDS, BnBr, THF, 15 h; (b) *p*-TsOH·H_2O, THF, MeOH, H_2O, 18 h, quant. (two steps); (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 1.5 h; (d) CSA, MeOH, 2 h, 76% (two steps); (e) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 30 min, then Et_3N, −78 °C to rt, 1 h, quant.; (f) (*E*)-1-tri-*n*-butylstanylbutadiene, MeLi, THF, −78 to −10 °C, 3 h, 93%; (g) Dess–Martin periodinane, CH_2Cl_2, 2.5 h; (h) $NaBH_4$, $CeCl_3 7H_2O$, EtOH, −78 to −55 °C, 3 h, 80% (2 steps), **25**:**24** = 5:1; (i) TBAF, THF, 30 min, 88%; (j) (+)-diethyl tartrate, Ti(O-*i*-Pr)$_4$, *t*-BuOOH, MS 4 Å, −20 °C, 1 h; (k) PPTS, CH_2Cl_2, 1 h, 93% (two steps); (l) TESOTf, 2,6-lutidine, CH_2Cl_2, 96%; (m) 9-BBN, THF, 3.5 h, then 30% H_2O_2, aq $NaHCO_3$, 6 h; (n) Dess–Martin periodinane, CH_2Cl_2, 2 h, 79% (two steps); (o) 2-methoxypropene, PPTS, CH_2Cl_2, rt, 30 min, quant.

Having synthesized the ABC ring system (**3**), we turned our attention to the synthesis of the IJ ring fragment (**4**), starting with the tetrahydropyran derivative **5**,[9] which is a common intermediate with the A ring (Scheme 2). Successive protecting group manipulation of the diol **5**—that is, bis-benzyl ether formation (**21**), hydrolysis of the benzylidene acetal (**22**), bis-TBS ether formation and subsequent selective hydrolysis—furnished primary alcohol **23**. Swern oxidation of **23** followed by treatment of the resulting aldehyde with (*E*)-1-lithio-1,3-butadiene generated from the corresponding tributylstannane[27] afforded a mixture of alcohol **24** and its epimer **25** in a 1:2 ratio, which was separated by silica gel chromatography. The stereochemistry of **25** was unambiguously determined by NOE experiments on acetonide **29** derived from **25**. The undesired **24** was converted to **25** via an oxidation and Luche reduction sequence (**25**:**24** = 5:1). Removal of the TBS group of **25** and subsequent Sharpless epoxidation using L-(+)-diethyl tartrate yielded hydroxyl epoxide **27**. Under the reaction conditions described, partial cyclization occurred to give an inseparable mixture of **27** and pyranopyran **28** (1.5:1), which was treated with PPTS to give **28** in 93% yield for two steps. Protection of the diol **28** as a bis-TES ether, followed by hydroboration and Dess–Martin oxidation, afforded the IJ ring fragment **4**.[28]

In conclusion, we have achieved a stereocontrolled synthesis of the ABC and IJ ring fragments of yessotoxin. Further studies directed toward the total synthesis of yessotoxin are currently in progress in our laboratory.

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26. Compound **3**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (1H, t, $J = 2.5$ Hz, H15), 7.82–7.79 (3H, m, NAP), 7.70 (1H, s, NAP), 7.49–7.45 (2H, m, NAP), 7.39 (1H, dd, $J = 8.5$, 1.5 Hz, NAP), 4.74 (1H, d, $J = 12.0$ Hz, NAP), 4.58 (1H, d, $J = 12.0$ Hz, NAP), 3.93 (1H, dd, $J = 11.0$, 5.0 Hz, H4), 3.82 (1H, td, $J = 8.5$, 4.5 Hz, H13), 3.52 (1H, d, $J = 11.5$ Hz, H2a), 3.40 (1H, d, $J = 11.5$ Hz, H2b), 3.28 (1H, td, $J = 10.0$, 4.5 Hz, H12), 3.23 (1H, td, $J = 10.0$, 4.5 Hz, H7), 3.15 (1H, td, $J = 10.0$, 4.5 Hz, H9), 2.98 (1H, td, $J = 10.5$, 4.5 Hz, H10), 2.90 (1H, td, $J = 10.5$, 4.0 Hz, H6), 2.81 (1H, ddd, $J = 16.0$, 4.5, 2.5 Hz, H14a), 2.57 (1H, dt, $J = 11.5$, 4.5 Hz, H11eq), 2.51 (1H, ddd, $J = 16.0$, 8.0, 2.5 Hz, H14b), 2.17 (1H, dt, $J = 11.0$, 4.0 Hz, H8eq), 2.02 (1H, dt, $J = 11.5$, 4.5 Hz, H5eq), 1.58 (1H, q, $J = 11.5$ Hz, H5ax), 1.49 (1H, q, $J = 11.0$ Hz, H11ax), 1.33 (1H, q, $J = 11.5$ Hz, H8ax), 0.98 (3H, s, Me), 0.84 (9H, s, TBS), 0.83 (9H, s, TBS), 0.03 (3H, s, TBS), 0.02 (3H, s, TBS), −0.02 (6H, s, TBS); ESI MS 739 ($M + Na^+ + MeOH$).
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28. Compound **4**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (1H, dd, $J = 3.5$, 1.5 Hz, H28), 7.32–7.19 (10H, m, Bn), 4.56 (1H, d, $J = 11.5$ Hz, Bn), 4.53 (1H, d, $J = 12.0$ Hz, Bn), 4.50 (1H, d, $J = 12.0$ Hz, Bn), 4.34 (1H, d, $J = 11.5$ Hz, Bn), 4.19 (1H, td, $J = 10.0$, 3.0 Hz, H30), 3.81 (1H, d, $J = 2.5$ Hz, H32), 3.75 (1H, ddd, $J = 10.0$, 7.0, 2.5 Hz, H37), 3.73 (1H, dd, $J = 12.0$, 4.5 Hz, H34), 3.69 (1H, dd, $J = 10.0$, 2.0 Hz, H38), 3.58 (1H, dd, $J = 10.0$, 2.5 Hz, H31), 3.52 (1H, dd, $J = 10.0$, 7.0 Hz, H38), 3.27 (1H, ddd, $J = 11.5$, 10.0, 4.5 Hz, H36), 2.65 (1H, ddd, $J = 16.0$, 3.0, 1.5 Hz, H29), 2.37 (1H, ddd, $J = 16.0$, 10.0, 3.5 Hz, H29), 2.28 (1H, dt, $J = 11.5$, 4.5 Hz, H35eq), 1.50 (1H, dt, $J = 12.0$, 11.5 Hz, H35ax), 1.13 (3H, s, 33-Me), 0.95 (3H, t, $J = 8.0$ Hz, TES), 0.93 (3H, t, $J = 8.0$ Hz, TES), 0.61 (2H, q, $J = 8.0$ Hz, TES), 0.60 (2H, q, $J = 8.0$ Hz, TES). ESI-MS 707 ($M + Na^+$).