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# Iterative synthesis of the ABCDEF-ring system of yessotoxin and adriatoxin

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**Abstract**—A stereocontrolled linear synthesis of the ABCDEF-ring system of yessotoxin and adriatoxin, diarrhetic shellfish toxins, is described. Iterative application of a tetrahydropyran synthesis by reaction of the alkylation of a sulfonyl-stabilized oxiranyl anion followed by 6-*endo* cyclization of a 4,5-epoxy alcohol led to the synthesis of the *trans*-fused hexacyclic ether system, and the seven-membered E ring was constructed by ring expansion reaction. 

Polycyclic ether marine toxins produced by marine dinoflagellates consist of bioactive agents, the skeletons of which incorporate regular oxygenated heterocycles.[1] A few of them are known as causative toxins of diarrhetic shellfish poisoning. Yessotoxin (**1**) was isolated as a diarrhetic toxin from the digestive glands of scallops, *Patinopecten yessoensis*, infested by toxic dinoflagellates in Japan.[2] More recently, adriatoxin (**2**), a new analog of yessotoxin, was also isolated from the digestive glands of toxic mussels, *Mytilus galloprovincialis*, in Italy.[3] These two molecules contain the same ring system from ring A to ring J, and yessotoxin has an extra K-ring with a side chain containing three olefinic bonds. Both toxins are an interesting synthetic target from the viewpoints of their unique structural frameworks and biological activity, and an initial synthetic approach has been documented by us.[4] The recent synthesis of the ABCDEF-ring system of the toxins by Nakata's group[5] prompted us to publish our own results that utilize the alkylation of a sulfonyl-stabilized oxiranyl anion and 6-*endo* cyclization in the key steps. Our method allows for a linear, iterative synthesis of the ABCDEF-ring system **3** of yessotoxin.

Retrosynthetic analysis based on the oxiranyl anion strategy led to disconnection of the ABCDEF-ring fragment **3** into seven building blocks (Scheme 1). As the building blocks for construction of the B, C, D, and E rings are the same epoxy sulfone, fragment **3** can be constructed from only four building blocks **5**–**8**.

Synthesis of the A ring started from the coupling reaction of the oxiranyl anion generated from epoxy sulfone **5**[6] and triflate **6** prepared from 1,3-*O*-di-*t*-butylsilylene-D-erythritol (**9**)[7] (Scheme 2). A mixture of **5** and **6** in THF–HMPA at −100°C was treated with *n*-BuLi to give epoxy sulfone **10** in 85% yield. Treatment of **10** with $TsOH \cdot H_2O$ in $CHCl_3$ at 0°C led to detriethylsilylation and the subsequent stereospecific 6-*endo* cyclization of the 4,5-epoxy alcohol afforded ketone **11** in 89% yield.

The reaction temperature was critical for the 6-*endo* cyclization of **10**; reaction at 25°C induced a 1,2-shift of the sulfonyl group rather than 6-*endo* cyclization to give α-sulfonyl ketone **14** in 52% yield. Stereoselective reduction with $NaBH_4$ followed by *O*-benzylation and deprotection of the silylene group gave the A ring diol **12**. The diol was transformed into triflate **13** by regioselective *O*-triflation followed by triethylsilylation in one pot.

Construction of rings B, C, and D on the A ring was accomplished sequentially in a five-step iterative manner (Scheme 3). Reaction of triflate **13** and oxiranyllithium of **7**[8] by an in situ quenching method afforded epoxy sulfone **15** (step 1). The 6-*endo* cyclization of **15** was achieved by heating at 55°C with $TsOH \cdot H_2O$ in $CHCl_3$ to give bicyclic ketone **16** (step 2). Reduction with $NaBH_4$ (step 3), desilylation with $n$-$Bu_4NF$ (step 4), and *O*-triflation and -silylation in one pot (step 5)

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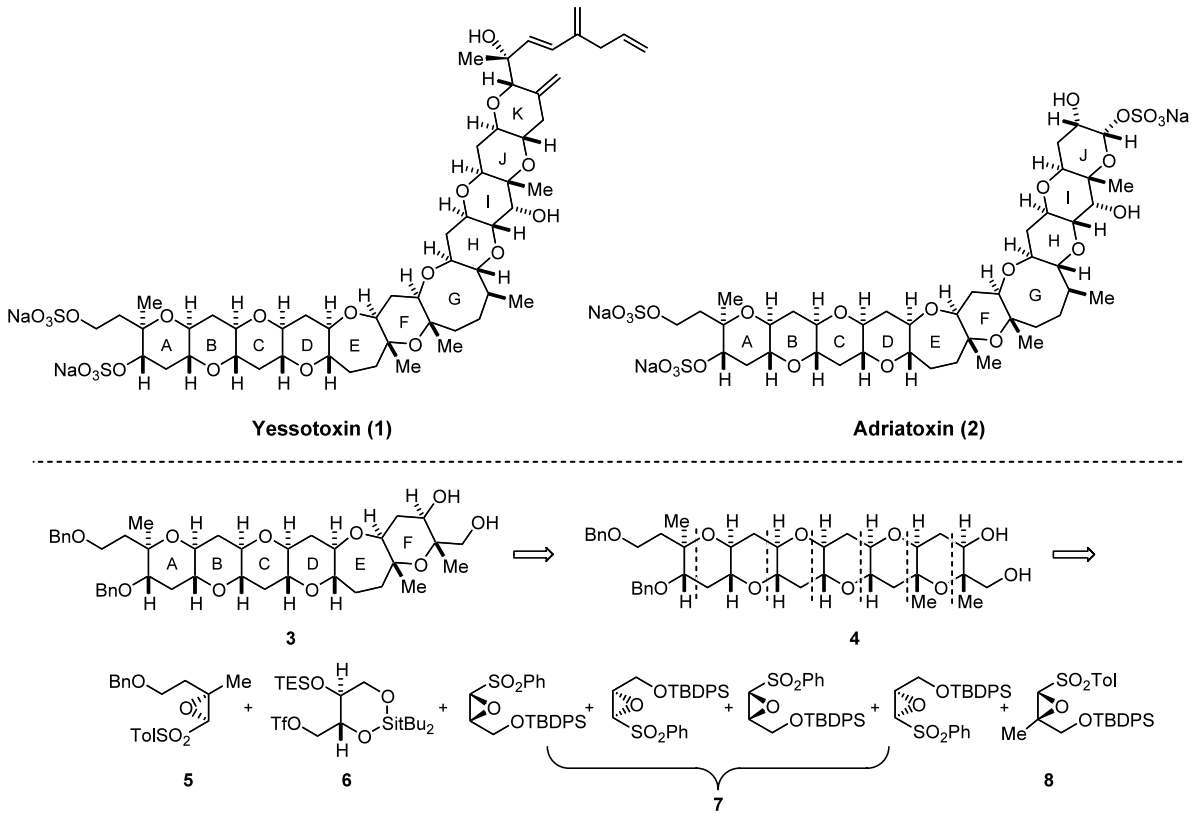
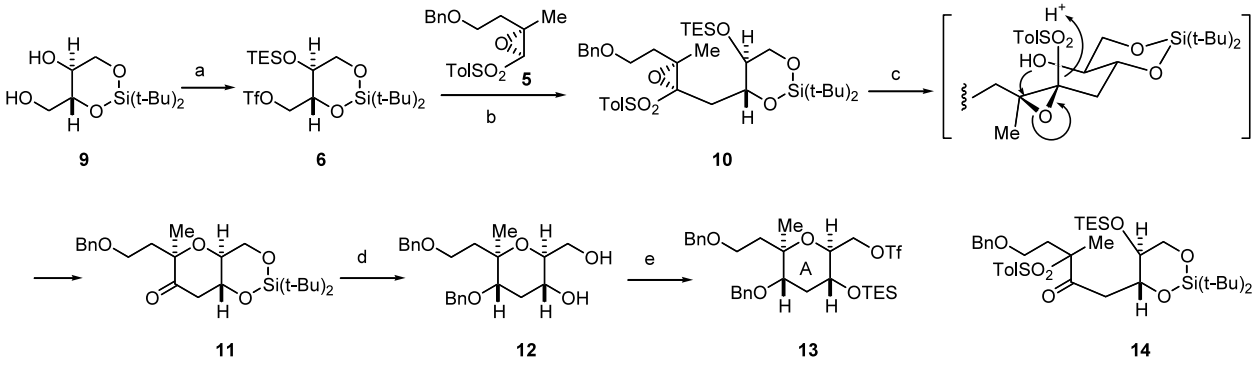



**Scheme 1.**

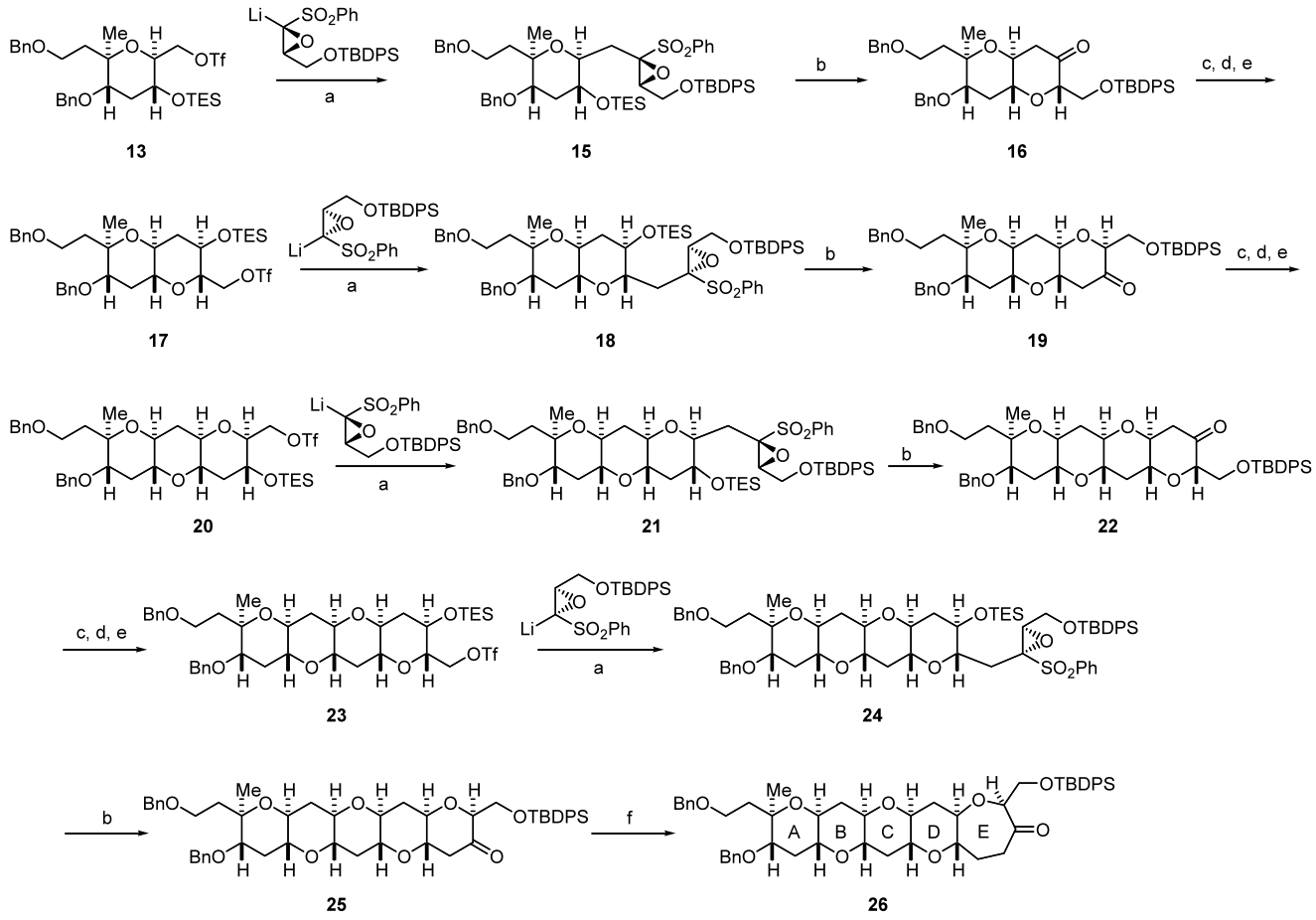



**Scheme 2.** *Reagents and conditions:* (a) $Tf_2O$, 2,6-lutidine, $CH_2Cl_2$, −78°C, 30 min, then TESOTf, 95%; (b) **5**, *n*-BuLi, THF, HMPA, −100°C, 85%; (c) $TsOH{\cdot}H_2O$, $CHCl_3$, 0°C, 89%; (d) (i) $NaBH_4$, MeOH–$CH_2Cl_2$, −78°C, 97%; (ii) KH, BnBr, THF, rt, 96%; (iii) TBAF, THF, 100%; (e) $Tf_2O$, 2,6-lutidine, $CH_2Cl_2$, −78°C, 30 min, then TESOTf, 86%.

yielded the AB-ring triflate **17**. Construction of the C ring on **17** was performed by iteration of the five-step reaction sequence described above, and the tricyclic triflate **20** was obtained in 55% overall yield. Reiterative application of the tetrahydropyran synthesis with **20** led to the tetracyclic triflate **23** in 49% overall yield, which was then converted into pentacyclic ketone **25** by applying the steps 1–3 of the iterative process.

The oxepane (E ring) formation was accomplished simply by using a ring-expansion reaction of a keto tetrahydropyran.[8] Thus, reaction of **25** with trimethylsilyldiazomethane in the presence of $BF_3{\cdot}OEt_2$ in $CH_2Cl_2$ at −78°C gave the seven-membered ketone **26** in 56% yield along with 5% of its isomeric ketone.

In order to construct a tertiary alcohol on the E ring, direct methylation of **26** with MeMgBr, MeLi, and $Me_3Al$ was examined. However, the major product was a compound methylated undesirably from the less-hindered α-side. Then, a methyl group was introduced in a stepwise manner (Scheme 4). Methylenation of the keto




**Scheme 3.** *Reagents and conditions:* (a) **7**, *n*-BuLi, THF, HMPA, −100°C, **15**: 91%, **18**: 89%, **21**: 95%, **24**: 89%; (b) $TsOH{\cdot}H_2O$, $CHCl_3$, 55°C, **16**: 74%, **19**: 74%, **22**: 73%, **25**: 73%; (c) $NaBH_4$, MeOH–$CH_2Cl_2$, −78°C, 95% (1st), 96% (2nd), 93% (3rd); (d) TBAF, THF, rt, 89% (1st), 96% (2nd), 86% (3rd); (e) $Tf_2O$, 2,6-lutidine, $CH_2Cl_2$, −78°C, 30 min, then TESOTf, 92% (1st), 91% (2nd), 84% (3rd); (f) $Me_3SiCHN_2$, $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, −78°C; PPTS, MeOH, rt, 56% (isomeric ketone: 5%).

function with the Tebbe reagent and epoxidation with *m*-CPBA gave a mixture of epoxides (α:β = 4:1), from which α-epoxide **28** was isolated in 56% yield. Reduction with lithium triethylborohydride yielded the desired tertiary alcohol **29** after desilylation with *n*-$Bu_4NF$. Synthesis of the F ring on **29** includes the construction of sterically congested 1,3-diaxial dimethyl groups. Our oxiranyl anion strategy also provides an effective method to construct such methyl-substituted tetrahydropyans.[9] One-pot triflation of the primary alcohol and trimethylsilylation of the tertiary alcohol of **29** gave **30**. Coupling reaction of the triflate **30** with the oxiranyllithium generated from **8**[6] afforded epoxy sulfone **31** in 90% yield. The crucial 6-*endo* cyclization was performed by exposure of **31** to $BF_3{\cdot}OEt_2$ to give the hexacyclic ketone **32** in 72% yield.

The 1,3-diaxial stereochemistry of the two methyl groups in the F ring was established by NOE experiments. Finally, reduction of the ketone with $NaBH_4$ followed by desilylation afforded the target ABCDEF-ring system **3** of yessotoxin and adriatoxin.

In summary, we have completed a linear synthesis of the ABCDEF hexacyclic system of yessotoxin and adriatoxin based on the oxiranyl anion strategy. Reiterative application of the tetrahydropyran synthesis via a five-step sequence of triflation-silylation of a diol, reaction with oxiranyl anion, 6-*endo* cyclization of a 4,5-epoxy alcohol, carbonyl reduction, and *O*-deprotection provided a useful method for the construction of a *trans*-fused polycyclic ethers system containing sterically congested methyl-substituted and 1,3-diaxial dimethyl-substituted tetrahydropyrans. Further efforts directed toward total synthesis of natural products are in progress.

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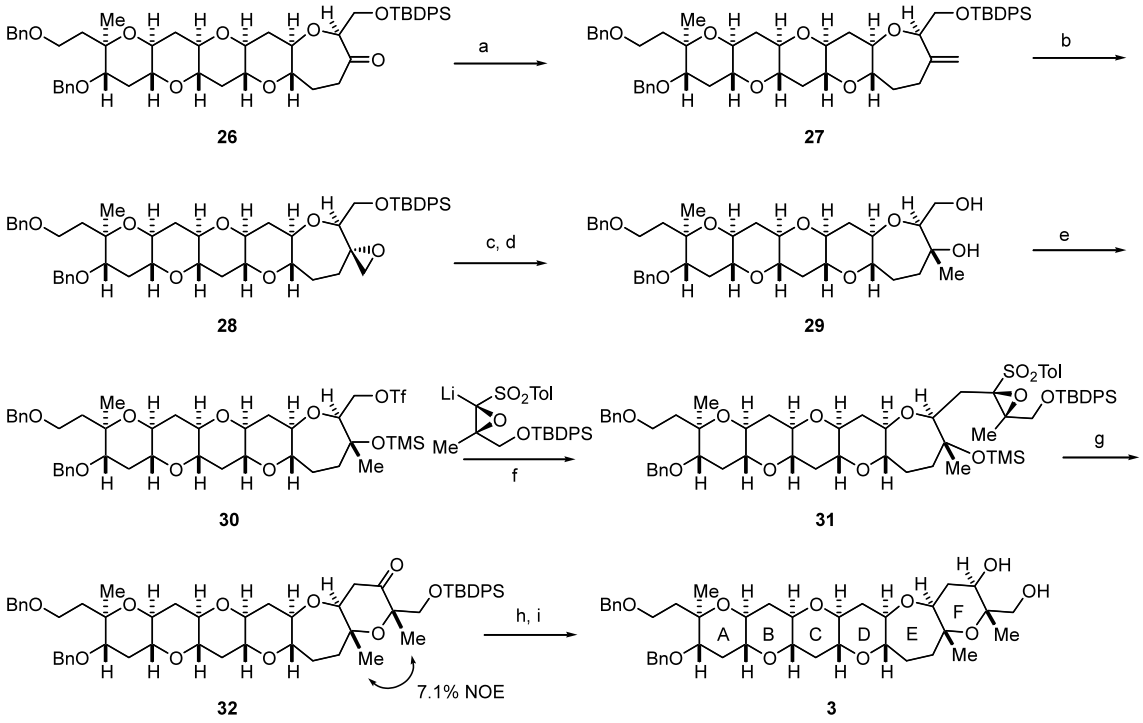


**Scheme 4.** *Reagents and conditions:* (a) Tebbe, THF, rt, 80%; (b) *m*-CPBA, $CH_2Cl_2$, rt, 56% (β-epoxide: 13%); (c) $LiBHEt_3$, THF, 0°C, 92%; (d) TBAF, THF, rt, 89%; (e) $Tf_2O$, 2,6-lutidine, $CH_2Cl_2$, −78°C, 30 min, then TMSOTf, 85%; (f) **8**, *n*-BuLi, THF, HMPA, −100°C, 90%; (g) $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, 0°C, 72%; (h) $NaBH_4$, MeOH–$CH_2Cl_2$, 0°C, 95%; (i) TBAF, THF, rt, 90%.

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