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Improved Synthesis of the ABCDE Fragment of Brevetoxin A

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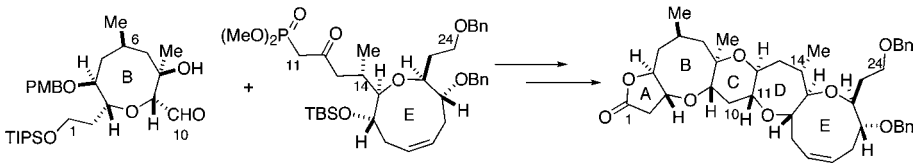
ABSTRACT



A second-generation synthesis of the BCDE fragment of brevetoxin A is described. Novel reactions were developed that extend the utility of the asymmetric glycolate alkylation reaction and improve scale-up to provide gram quantities of the B and E subunits. Significant improvements to the convergent assembly of the tetracycle were also realized. In addition, formation of the A ring lactone was accomplished to complete the ABCDE pentacycle.

Brevetoxin A (Figure 1), a ladder ether toxin which is a metabolite of the notorious *Karenia brevis*, possesses a

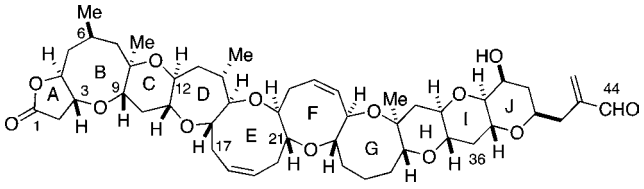


Figure 1. Brevetoxin A.

topographically daunting structure containing 10 rings and 22 stereogenic centers.[1,2] In previous communications, we disclosed successful approaches to the BCDE[3] and GHIJ[4] fragments of brevetoxin A. These reports highlighted the development of a highly efficient coupling strategy[5] centered around a Horner−Wadsworth−Emmons union of two complex ring units followed by a cyclodehydration of a keto-alcohol to form an intermediate cyclic enol ether. The original synthesis of the BCDE fragment focused on the application of our *anti*-glycolate aldol reaction[6] to establish four stereogenic centers. Although this approach proved useful, it ultimately provided the BCDE fragment **1** (Figure 2)

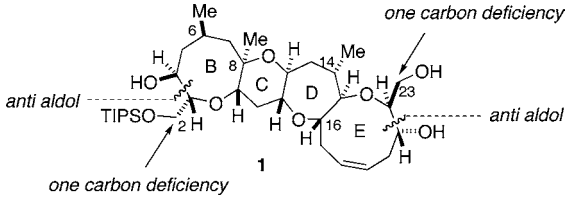


Figure 2. Previous synthesis of the BCDE fragment.

truncated by two carbons (C1 and C24). Consequently, a revised route to the BCDE fragment was envisioned that would obviate a late-stage homologation yet apply the insight gained from our previous synthesis. We report herein an

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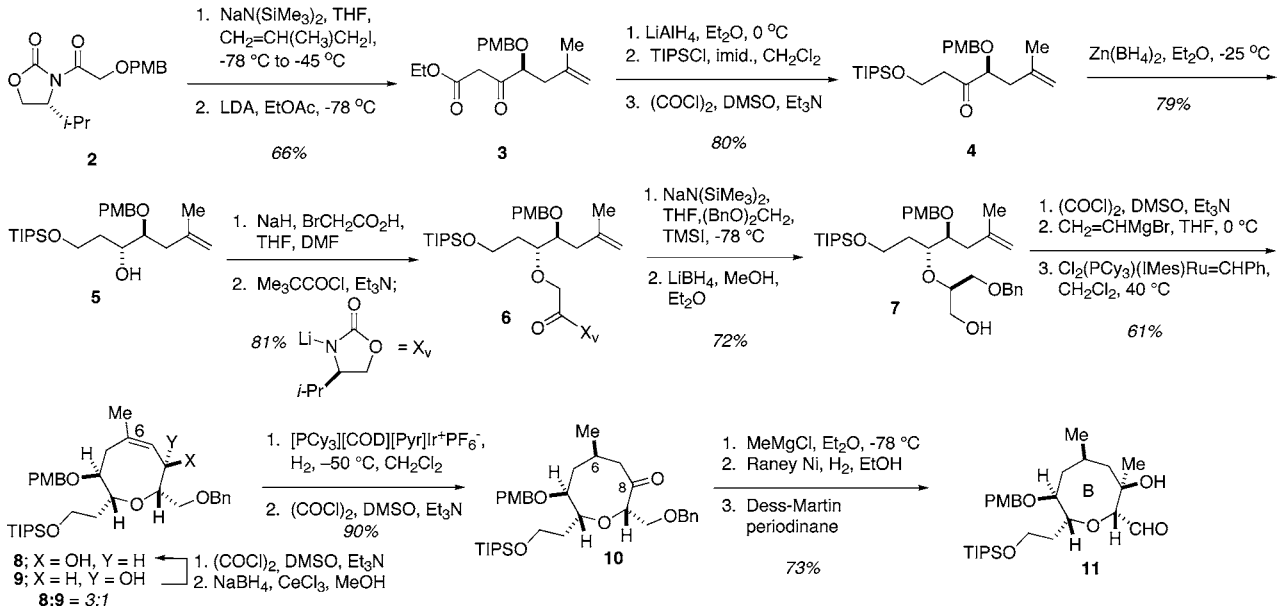
Scheme 1



improved, scalable route to the BCDE fragment of brevetoxin A and formation of the ABCDE lactone.

To address the issue of incorporating the required C1 and C24 carbons, an asymmetric glycolate alkylation[7] strategy was employed rather than the *anti*-glycolate aldol approach. To this end, the sodium enolate of glycolate **2** (Scheme 1) was alkylated with methallyl iodide to provide a single diastereomer in 78% yield. An unprecedented Claisen condensation of the *N*-acyloxazolidinone with the lithium enolate of ethyl acetate provided β-keto ester **3** directly in high yield. The inductive effect of the ether oxygen likely allows for direct displacement of the oxazolidinone chiral auxiliary by the lithiated nucleophile by increasing the electrophilicity of the adjacent carbonyl. Following reduction of both carbonyl functionalities with $LiAlH_4$, the primary alcohol of the resultant diol was selectively protected as the triisopropylsilyl ether. Oxidation of the secondary alcohol under Swern conditions[8] provided the ketone **4**. A chelation-controlled reduction using zinc borohydride[9] provided the alcohol **5** in 79% yield (>15:1 dr).

Because alcohol **5** was homologous to an intermediate in our first-generation synthesis, a similar strategy was utilized for the completion of the B ring subunit. The alcohol **5** was alkylated with sodium bromoacetate, and the mixed anhydride of the resultant glycolic acid was treated with (*R*)-lithio-4-isopropyl-2-oxazolidinone to provide imide **6** in 90% yield. Exploiting the asymmetric glycolate alkylation strategy[7] once again, the sodium enolate of imide **6** was alkylated, this time with benzyl iodomethyl ether (prepared in situ), to provide a single detectable diastereomer in good yield. Reductive removal of the chiral auxiliary provided alcohol **7**, which was oxidized under Swern conditions.[8] The resultant aldehyde was treated with vinylmagnesium bromide to yield a 3:1 inseparable mixture of diastereomers favoring the desired configuration. Treatment of the mixture of dienes with the Grubbs second-generation catalyst[10] provided oxocenes **8** and **9**. The diastereomers were easily separable at this point, and the minor isomer **9** was inverted to the desired alcohol **8** by sequential Swern oxidation[8] and Luche reduction.[11]

Treatment of oxocene **8** with Crabtree's catalyst[12] under an atmosphere of hydrogen at low temperature provided a single detectable diastereomer of the oxacane in excellent yield. The secondary alcohol was oxidized under Swern conditions,[8] and the resultant ketone **10** was treated with methylmagnesium chloride to provide the tertiary alcohol in 88% yield. Selective cleavage of the benzyl ether was achieved via hydrogenation in the presence of Raney nickel.[13] Finally, Dess−Martin oxidation[14] of the resultant primary alcohol provided aldehyde **11**. This approach has allowed preparation of multigram quantities of the B ring subunit **11** in a single run through the sequence.

The revised E ring synthesis followed the initial stages of the previous approach[3] to generate the advanced glycolyl imide **12** (Scheme 2). To install the requisite two-carbon unit at C22, a novel alkylation using bromoacetonitrile was employed to give the alkylated adduct in good yield and

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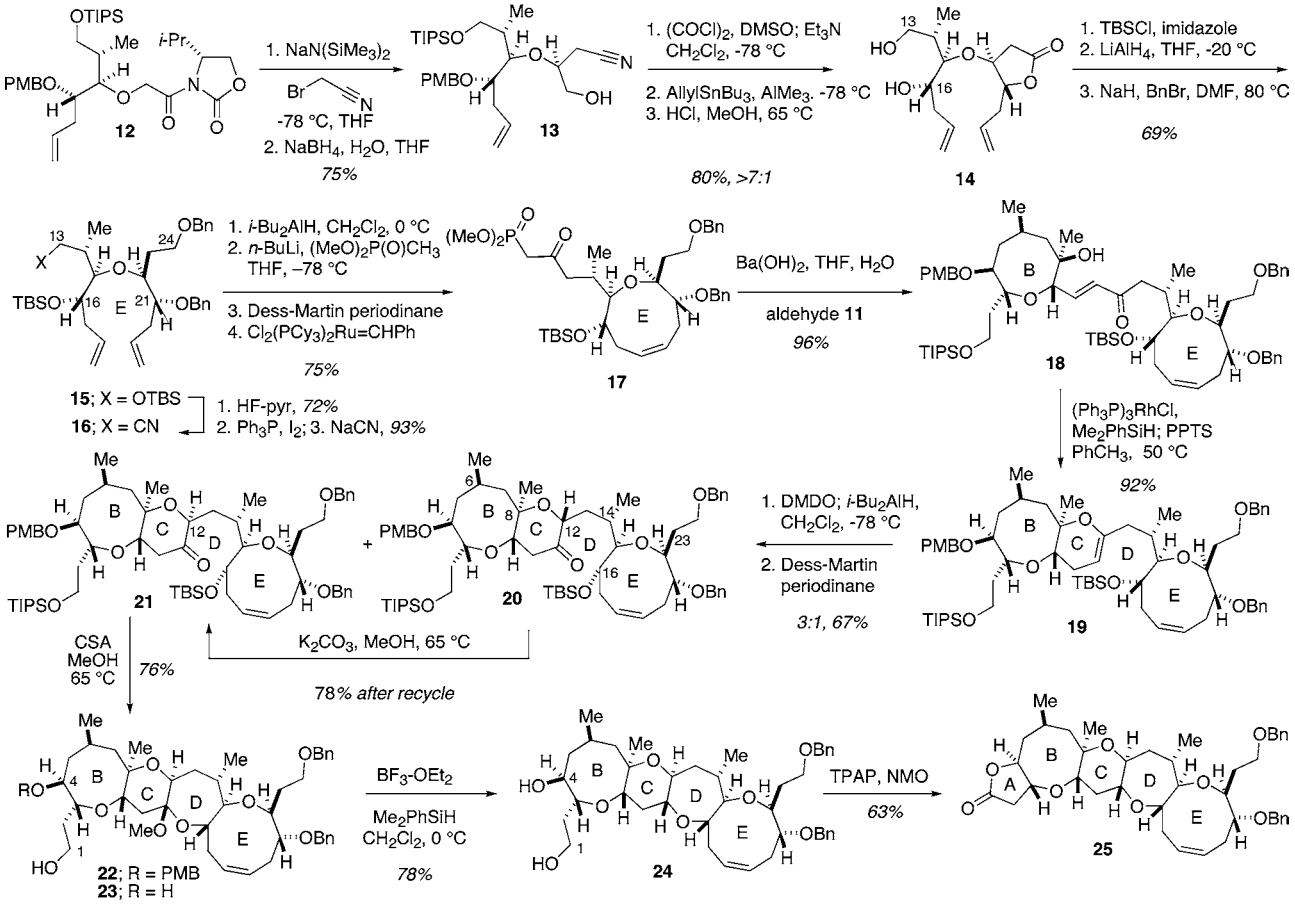
Scheme 2



excellent diastereoselectivity (>98:2 dr). Reductive removal of the auxiliary provided the primary alcohol **13**. Oxidation of the alcohol under Swern conditions[8] followed by Felkin−Anh-controlled allylation using allyltributylstannane and trimethylaluminum[15] delivered the product with the highest levels of diastereoselection (>7:1 dr). Treatment of the mixture of diastereomers with HCl in methanol at 65 °C resulted in hydrolysis of the nitrile, cleavage of the TIPS and PMB ethers, and lactonization leading to lactone **14**. Separation of the two diastereomers was readily achieved at this stage.

It was anticipated that protecting group choice would be critical to a successful coupling strategy and material throughput. Thus, protection of the C13, C16 diol as the bis-TBS ether was followed by subsequent reduction of the lactone using $LiAlH_4$ to give the C21, C24 diol in excellent yield. Orthogonal protection of the C21, C24 diol as the bisbenzyl ether led to the fully protected E ring fragment **15**. Treatment with HF−pyridine selectively removed the C13 silyl ether to give 72% of the desired primary alcohol along with 16% of the C13, C16 diol, which could be easily recycled.

Preparation of the β-keto phosphonate **17** was examined under a variety of conditions. The most reliable and efficient route began with formation of the alkyl iodide followed by displacement with cyanide to give the nitrile **16** in excellent yield. Reduction of the nitrile to the aldehyde using *i*-Bu_2-AlH, followed by the addition of lithiated dimethyl methyl phosphonate, gave an inconsequential mixture of β-hydroxy phosphonates in good yield. Oxidation of the β-hydroxy phosphonates to the β-keto phosphonate was readily accomplished using the Dess−Martin reagent.[14] Finally, closure of the E ring was accomplished upon exposure of the diene to the Grubbs first-generation catalyst[16] to give the completed E ring fragment **17**. The yields of these final steps were highly reproducible and readily amenable to scale-up.

Union of the revised B and E rings proceeded smoothly by exposure of aldehyde **11** and phosphonate **17** to aqueous $Ba(OH)_2$ to give the enone **18** in excellent yield (Scheme 2).[17] Although our original route relied upon the highly air-sensitive Stryker's reagent[18] for the selective reduction of the enone C−C π bond, an alternative protocol was developed with the use of Wilkinson's catalyst in the presence of a silane source.[19] The addition of PPTS directly

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to the reaction mixture following enone consumption allowed for a one-pot, efficient conversion of enone **18** to the desired enol ether **19**. Conversion of enol ether **19** to ketone **21** utilized an in situ epoxidation−reduction protocol,[20] which was adopted as a result of the highly sensitive nature of the epoxy enol ether. This procedure required DMDO solutions that were nearly free of acetone to minimize the amount of *i*-Bu_2AlH required. However, inconsistencies in the reaction were observed, likely the result of varying concentrations of acetone present in the DMDO solution. A simple modification to the original extraction procedure,[21] utilizing CH_2Cl_2−pentane solvent mixtures, gave DMDO solutions that were superior in the aforementioned reaction. In practice, oxidation of the enol ether followed by the addition of *i*-Bu_2-AlH led to a diastereomeric mixture of alcohols in good, reproducible yield. The configuration of the diastereomers that were formed was not ascertained at this stage of the synthesis. However, subsequent oxidation to the ketones using Dess−Martin periodinane revealed the presence of two C12 epimers **20** and **21** in an approximate 3:1 ratio favoring the undesired epimer **20**.

The next challenge in the synthesis required identification of an efficient method for the isomerization of the C12 epimer **20** to the desired diastereomer **21**. The use of several bases, including DBU,[22] NaOMe, LiOMe, and imidazole resulted in either significant decomposition or very slow isomerization. Fortunately, the use of potassium carbonate in methanol at 65 °C, resulted in isomerization at C12 with minimal decomposition. One exposure of ketone **20** to the isomerization conditions led to 66% of the ketone **21** accompanied by 22% of ketone **20**. The mixture was readily separated, and ketone **20** was resubjected to the reaction conditions. The desired isomer **21** was obtained in 78% yield after recycle.

Previous efforts to cyclize the remaining D ring to the mixed methyl ketal were rather inefficient (∼30%) and required a three-step sequence from the protected keto alcohol. However, after considerable experimentation, it was found that simply treating ketone **21** with camphorsulfonic acid in methanol led to a remarkably efficient transformation involving cleavage of the silyl ethers and direct cyclization to the mixed ketals **22** and **23** (inconsequential partial loss of the PMB group was also observed). Reduction of both mixed methyl ketals (R = PMB or H) using BF_3−OEt_2 and Me_2PhSiH led to the formation of the BCDE fragment **24** in good yield and as a single detectable isomer. In an effort to explore the formation of the A ring lactone, the diol **24** was treated with tetrapropylammonium perruthanate (TPAP) and stoichiometric 4-methylmorpholine *N*-oxide (NMO)[23] to give exclusive formation of the ABCDE lactone **25** in 63% yield. Stereochemical confirmation of the ABCDE fragment was obtained using 2D NMR.

In summary, a highly stereoselective synthesis of the ABCDE fragment of brevetoxin A has been completed. This second-generation approach proved far more amenable to scale-up enabling the preparation of significant quantities of the BCDE fragment. To date, more than three grams of aldehyde **11** and five grams of phosphonate **17** have been prepared by the sequence described herein. During the course of these studies, several novel transformations were disclosed, including a direct displacement of an oxazolidinone chiral auxiliary with a lithium enolate and a glycolate alkylation using bromoacetonitrile. Our convergent coupling strategy was again employed for the formation of the C and D rings, this time providing the BCDE fragment more efficiently than previously reported. Efforts toward the completion of the total synthesis of brevetoxin A are ongoing.

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Supporting Information Available: Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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