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Convergent, Stereoselective Synthesis of the GHIJ Fragment of Brevetoxin A

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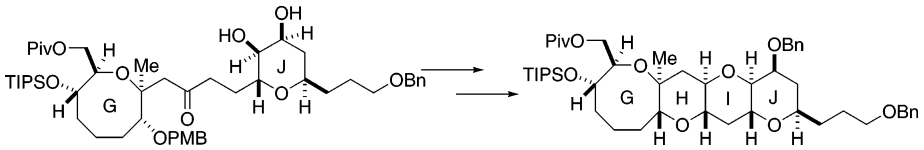
ABSTRACT



A stereoselective synthesis of the GHIJ fragment of brevetoxin A utilizing a convergent assembly strategy is described. Glycolate alkylation, ring-closing metathesis, and Hosomi–Sakurai reactions were central operations in the construction of the G ring and J ring subunits, which were united through a Horner–Wadsworth–Emmons coupling. Subsequent dehydrative cyclization produced an endocyclic enol ether that was further elaborated to the tetracyclic GHIJ fragment of brevetoxin A.

Among the wealth of structurally unique metabolites produced by marine organisms, the ladder ether toxins stand as a prominent illustration of the remarkable complexity of molecules produced by Nature.[1] The challenging architecture of the ladder toxins has inspired a variety of approaches to their synthesis,[2] and several noteworthy total syntheses have been reported.[3] Brevetoxin A (Figure 1),[4] a neurotoxin

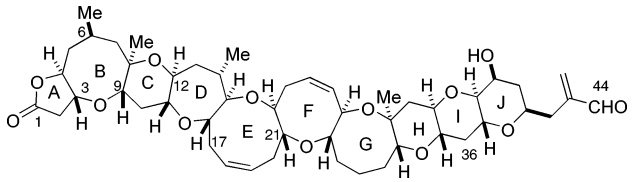


Figure 1. Brevetoxin A.

produced by the red tide dinoflagellates, is one of the more daunting members of the ladder toxins from a synthetic perspective. Brevetoxin A contains 22 tetrahedral stereogenic centers, as well as 10 rings including at least one of five, six, seven, eight, and nine members. The landmark synthesis of brevetoxin A reported in 1998 by the Nicolaou laboratory stands as the only total synthesis to date.[3]

Strategic advances from our laboratory in methods for the construction of medium ring ethers, in particular, the ring-

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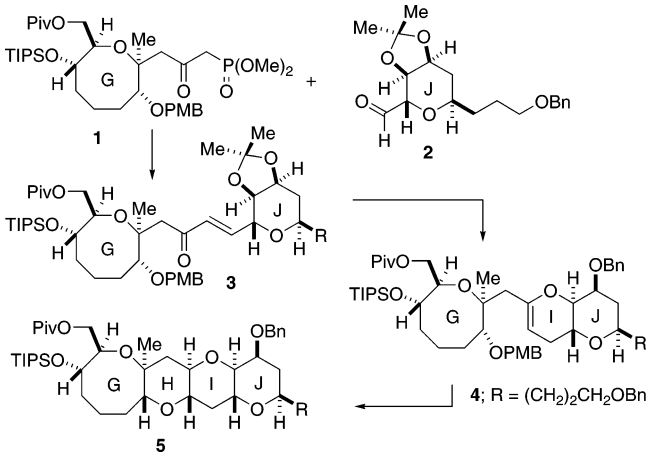
Scheme 1. Convergent Assembly Strategy



closing metathesis of diene intermediates assembled through chiral auxiliary mediated aldol and alkylation reactions, have been realized concomitantly with our syntheses of Laurencia metabolites.[5] Further probing the utility of these methods in solving complex synthetic problems, we have initiated a program toward the total synthesis of brevetoxin A.[6] To this end, we recently described a successful approach to the BCDE fragment of brevetoxin A that combined our synthetic methods for medium ring ether synthesis with a convergent assembly strategy.[6b] We report here the extension of our convergent assembly strategy to the synthesis of the GHIJ fragment of brevetoxin A.

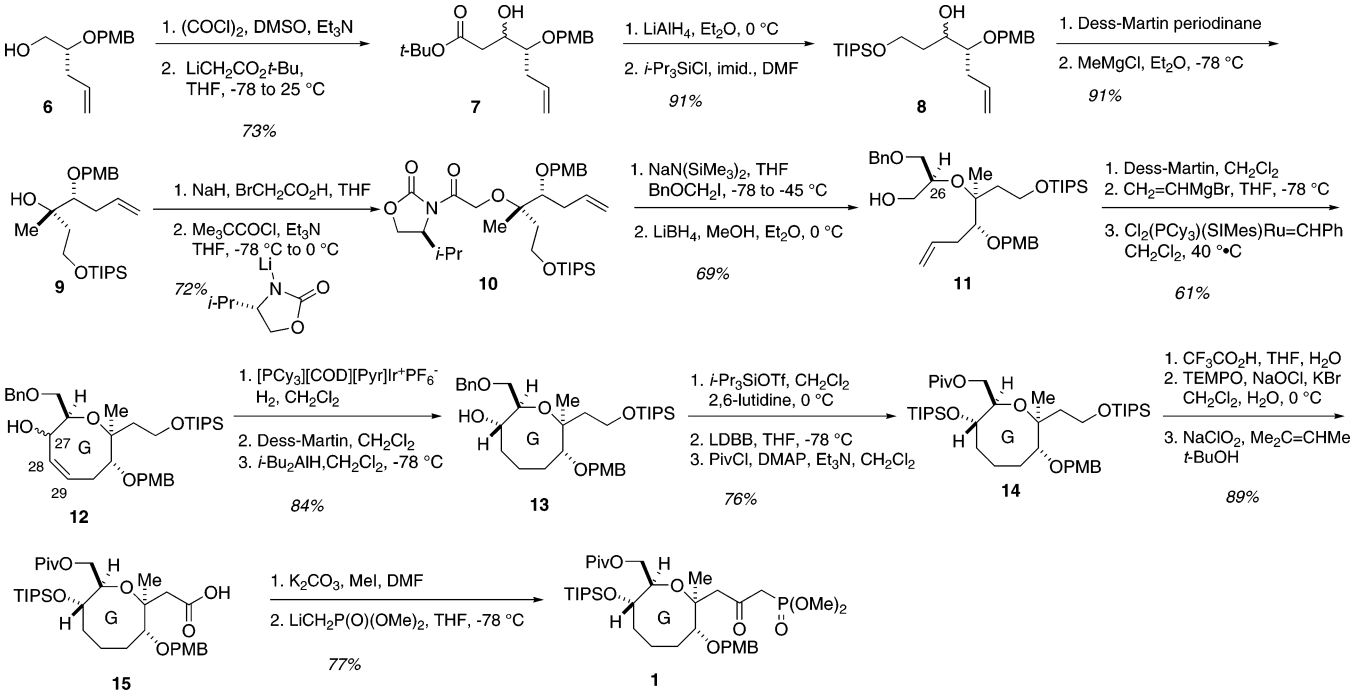
Analogous to our synthesis of the BCDE fragment, we envisioned the assembly of an advanced G ring ketophosphonate **1** and a J ring aldehyde **2** through a Horner−Wadsworth−Emmons (HWE) reaction, which would produce an enone intermediate **3** (Scheme 1). Subsequent 1,4-reduction followed by an *endo*-selective dehydrative cyclization would lead to an enol ether **4**, which could then be oxidized and further advanced to the desired tetracyclic fragment **5**.

As shown in Scheme 2, the synthesis of the requisite G ring β-keto phosphonate began with the oxidation of known alcohol **6**[7] under Swern conditions.[8] Addition of the resulting aldehyde to the lithium enolate of *tert*-butyl acetate provided efficient access to alcohol **7** (inconsequential mixture of diastereomers). Reduction of the ester to the primary alcohol with $LiAlH_4$ and selective protection of the resultant primary alcohols as the triisopropylsilyl ether produced alcohols **8**. The diastereomeric mixture was then converged to a single ketone by oxidation under Dess−Martin conditions.[9] Chelation-controlled addition of methylmagnesium chloride afforded tertiary alcohol **9** as a single isomer in excellent yield.

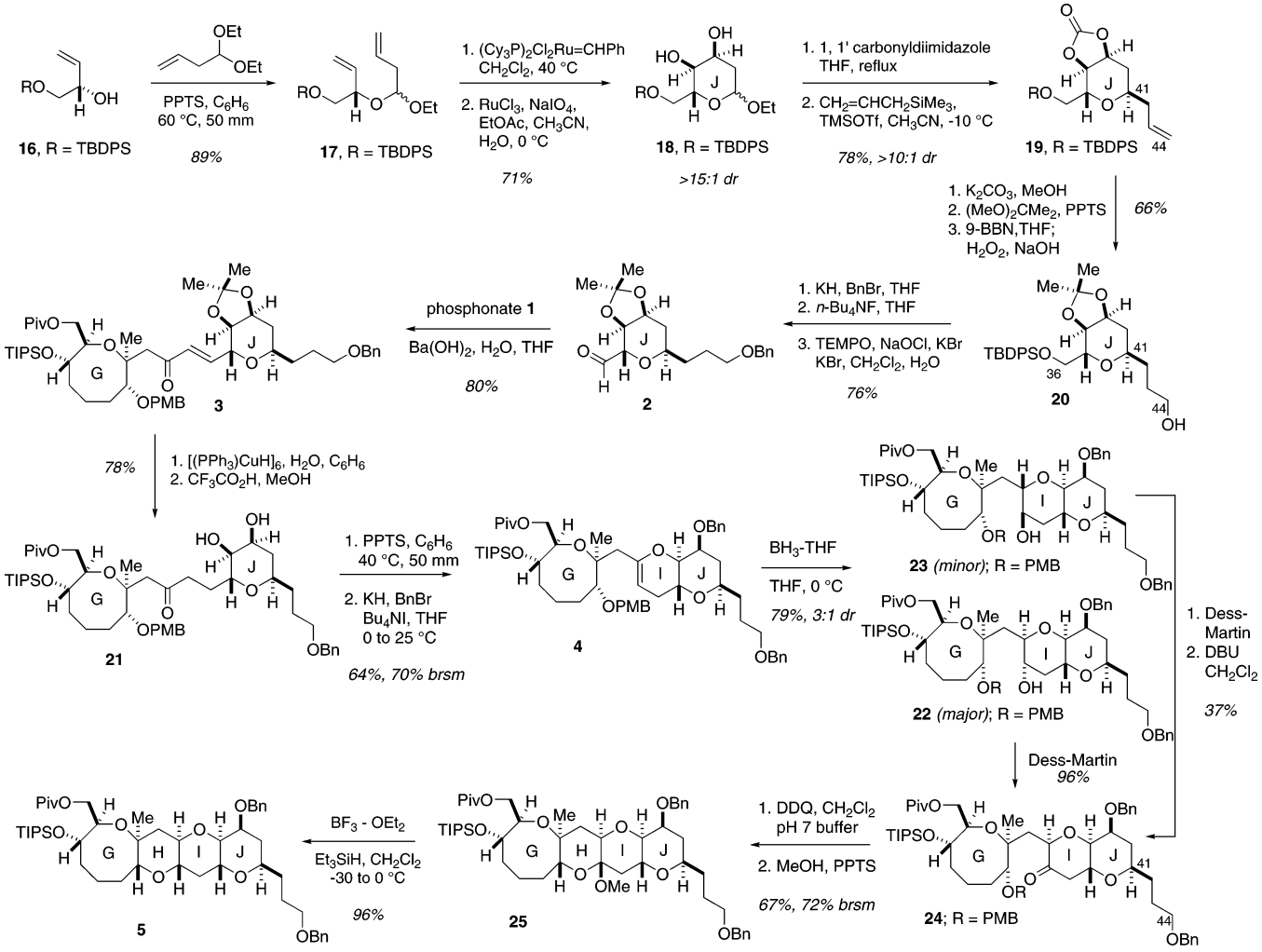
To establish the C26 stereocenter, tertiary alcohol **9** was alkylated with sodium bromoacetate, whereupon the glycolic acid was converted to the mixed anhydride with pivaloyl chloride and treated with (*S*)-lithio-4-isopropyl-2-oxazolidinone to produce imide **10** in good overall yield. Alkylation[7] of the sodium enolate of imide **10** with benzyl iodomethyl ether (prepared in situ) followed immediately by reductive removal of the chiral auxiliary with $LiBH_4$ afforded alcohol **11** in 69% yield (>98:2 dr).

Dess−Martin oxidation of alcohol **11** produced the corresponding aldehyde, which when exposed to vinylmagnesium bromide delivered the diene as a mixture of C27 epimers, setting the stage for closure of the oxocene. Ring-

Scheme 2. Synthesis of the G Ring of Brevetoxin A



Scheme 3. Synthesis of the J Ring and Completion of the GHIJ Fragment



closing metathesis was then accomplished smoothly using the Grubbs catalyst[10] [$Cl_2(Cy_3P)(sIMes)Ru{=}CHPh$], providing oxocene **12** in 61% overall yield for three steps. Exposure of oxocene **12** to Crabtree's catalyst[11] selectively hydrogenated the C28−C29 double bond without cleavage of the benzyl ether. Although the mixture of epimers at C27 was inconsequential for the overall synthetic plan, the diastereomers were converged to a single isomer for convenience. To this end, oxidation of the alcohols to the ketone with Dess−Martin periodinane, followed by reduction with *i*-Bu_2-AlH, yielded alcohol **13** as a single isomer, presumably due to the facial bias of the oxocane ring.

Finally, to complete the β-keto phosphonate G ring fragment, a series of protecting group manipulations were carried out to produce oxacane **14**. Selective removal of the primary triisopropylsilyl protecting group under acidic conditions followed by a two-step oxidation process provided carboxylic acid **15** in high yield. Conversion to the methyl ester and treatment with lithio dimethyl methylphosphonate furnished the desired β-keto phosphonate **1** in 77% yield.[12]

The synthesis of the J ring aldehyde **2** commenced with the conversion of known alcohol **16**[13] to mixed acetal **17** (Scheme 3). Ring-closing metathesis with Grubbs catalyst[14] and oxidation of the resulting glycal with $RuCl_3/NaIO_4$

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(12) Careful addition of lithiated dimethyl methylphosphonate solution at −78 °C to the methyl ester of acid **15** allowed for selective addition into the methyl ester over the pivaloyl ester.

produced diol **18** in 71% yield. Protection of the diol as the carbonate using 1,1′-carbonyldiimidazole preceded a high yielding Hosomi−Sakurai reaction[15] to afford pyran **19**, thus installing C42−C44 and setting the C41 stereocenter (dr > 10:1). The carbonate group was then removed under basic conditions, and the resulting diol was reprotected as the acetonide. Hydroboration of the terminal olefin with 9-BBN gave the primary alcohol **20** exclusively. Protection of the C44 primary alcohol as its benzyl ether and removal of the C36 TBDPS group with *n*-Bu_4NF, followed by TEMPO oxidation, furnished aldehyde **2** in 76% overall yield.

The HWE coupling of β-keto phosphonate **1** and aldehyde **2** with $Ba(OH)_2$[16] proceeded smoothly, generating enone **3** in 80% yield. Subsequent 1,4-reduction of the enone with Stryker's reagent[17] and removal of the acetonide group produced diol **21**, setting the stage for intramolecular cyclization of the I ring. Due to the observed sensitivity of this reaction, a number of acids, solvents, and temperatures were screened; optimized cyclization conditions[18] realized the endocyclic enol ether as the sole observable product, with recovery of a small amount of starting material. Protection of the remaining secondary alcohol as the benzyl ether afforded tricycle **4** in 64% overall yield (70% brsm).

The critical oxidation of the enol ether was accomplished through hydroboration with BH_3·THF,[3f,l,n] which after alkaline peroxide workup gave a 3:1 mixture of desired diastereomer **22** and undesired **23** in 79% combined yield. Alcohol **22** was oxidized to the ketone **24** under Dess−Martin conditions in 96% yield, whereas undesired alcohol diastereomer **23** was converted to ketone **24** in modest yield by oxidation followed by isomerization under basic conditions.

Oxidative removal of the PMB group from ketone **24** with DDQ and treatment of the resulting hemiketal with PPTS in MeOH effected nearly complete conversion to mixed methoxy ketal **25** in 67% yield over two steps (72% brsm). Reduction of the ketal with BF_3·Et_2O and Et_3SiH yielded the GHIJ fragment **5** as a single isomer in 96% yield; ^1H,^{13}C, and 2-D NMR spectral analysis of an acetate derivative provided structural verification.[19]

To summarize, we have completed an efficient synthesis of the GHIJ fragment of brevetoxin A that draws upon our synthetic methods for medium ring ether synthesis. Asymmetric glycolate alkylation, along with the Hosomi−Sakurai reaction, formed key carbon−carbon bonds stereoselectively to generate G and J ring precursors for ring closing metathesis. The G and J subunits were united via a HWE coupling, and subsequent cyclodehydration formed the I ring, paving the way for completion of the tetracyle. Assembly of the BCDE and GHIJ fragments for the completion of brevetoxin A will be reported in due course.

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Note Added after ASAP Publication. There was an incorrect stereochemical assignment in the brevetoxin GHIJ fragment at C27 on the G ring structure shown in the graphical abstract and Schemes 1−3 in the version published ASAP December 6, 2005; the corrected version was published ASAP December 13, 2005.

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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(18) Conditions: PPTS, benzene, 40 °C, aspirator vacuum. See Supporting Information for more detail. See: Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997. Kawamura, K.; Hinou, H.; Matsuo, G.; Nakata, T. *Tetrahedron Lett.* **2003**, *44*, 5259.

(19) See Supporting Information.