# ENANIOSELELECTIVE SYNTHESIS OF THE G-RING OF BREVETOXIN A

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Abstract – An enantioselective synthesis of the eight-membered G-ring of brevetoxin A is described. The synthesis exploits a ring-closing metathesis reaction to construct the eight-membered ether ring. The stereochemistry of the α and α' centers of the ether linkage were established through a Sharpless kinetic resolution and an asymmetric glycolate alkylation reaction.

Ladder ether toxins such as the brevetoxins A[1] and B,[2] the ciguatoxins,[3] and the gambieric acids[4] which are produced by algal blooms of marine dinoflagellates[5] can have devastating effects on marine life. The most potent toxin produced by *Gymnodynium breve* Davis is brevetoxin A (**1**). It is reportedly lethal to zebra fish at 3 parts per billion. Brevetoxin binds to site 5 on the voltage sensitive sodium channel (VSSC).[6] An eight or nine membered cyclic ether in the center of the brevetoxin and ciguatoxin structures has been proposed to result in slow conformational changes in the molecule, and function as a hinge mechanism, altering the gating mechanism of the ion channel when the toxin is bound to site 5.[7] The brevetoxin A structure was determined by *X*-Ray crystallography[1] and its only total synthesis was recently reported by Nicolaou.[8] Our previous work on the Laurencia metabolites laurencin,[9] prelaureatin and laurallene,[10] isolaurallene,[11,12] rogioloxepane A,[13] and obtusenyne,[14] have led to strategic advances in methods for the construction of medium ring ethers. Recently, we initiated a program toward the total synthesis of brevetoxin A, which exploits many of these strategic developments. A plan for the construction of brevetoxin A is shown in Scheme 1. The syntheses of the B, E, G, and J ring fragments would first need to be accomplished. The B and E rings would then be assembled to form the ABCDE fragment, and similarly the G and J rings would be joined to form the GHIJ subunit. Assembly of the two key fragments would then be accomplished through formation of the F ring. The synthesis of the G-ring fragment of brevetoxin A is the subject of this report.
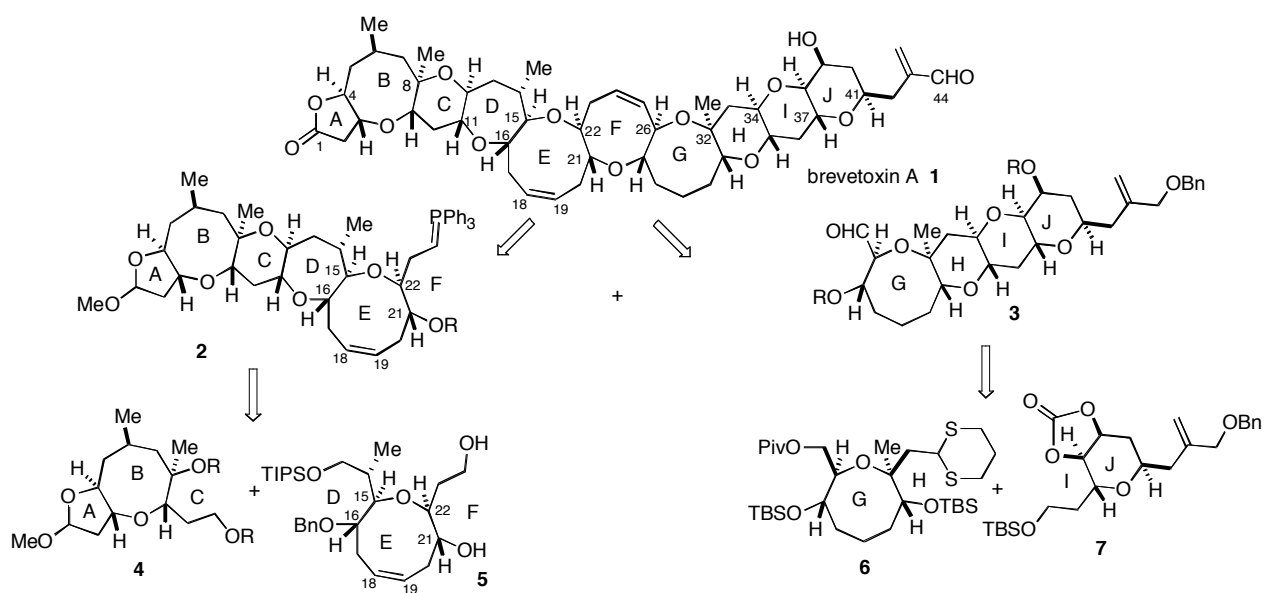
**Scheme 1:** Retrosynthesis for the assembly of brevetoxin A.

The retrosynthetic plan for the preparation of the G-ring is illustrated in Scheme 2. It was anticipated that the eight-membered ether ring of the G-ring (**6**) could be constructed by a ring-closing metathesis followed by hydrogenation. The inherent acyclic conformational constraints in the precursor diene (**8**) were expected to facilitate closure of the oxocene as we had previously observed.[11,12,14] The C26 (brevetoxin numbering) stereocenter of diene (**9**) would be established by exploiting the asymmetric glycolate alkylation reaction[15] of oxazolidinone (**10**) with iodomethyl benzyl ether. The oxazolidinone (**10**) would be derived from the alcohol (**11**) in which the C31-32 stereocenters would be incorporated by opening of epoxide (**12**), the result of a Sharpless kinetic resolution of 2-methyl-1,5-hexadien-3-ol (**13**).[16]
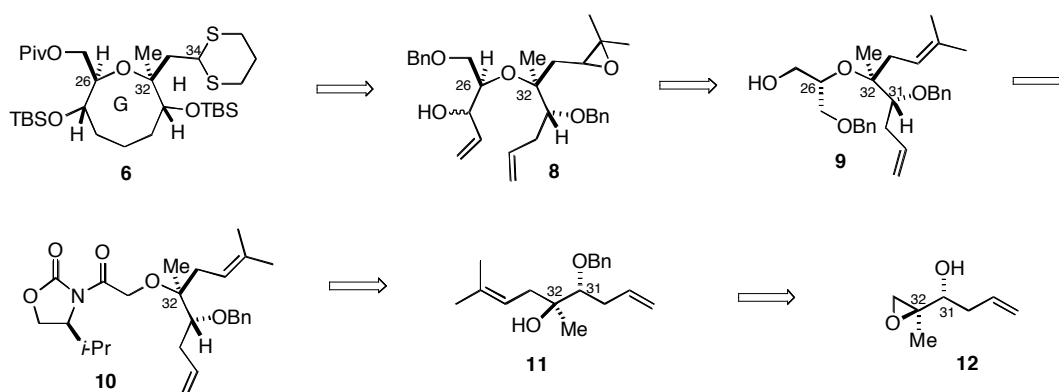
Scheme 2: Strategy for the assembly of the brevetoxin G ring.

The construction of the G ring fragment (**6**) began with the preparation of the epoxide (**12**). Exposure of diene (**13**) to the standard conditions for a Sharpless kinetic resolution [(–)-dicyclohexyl tartrate, Ti(O-i-Pr)$_4$, t-BuOOH, 4Å mol. sieves, CH$_2$Cl$_2$] provided the epoxide (**12**) in 98% e.e. at 43% conversion.

Protection of the alcohol as its benzyl ether, followed by treatment of the epoxide with 2-methyl-1-propenylmagnesium bromide in the presence of cuprous iodide gave 86% of tertiary alcohol (**11**).
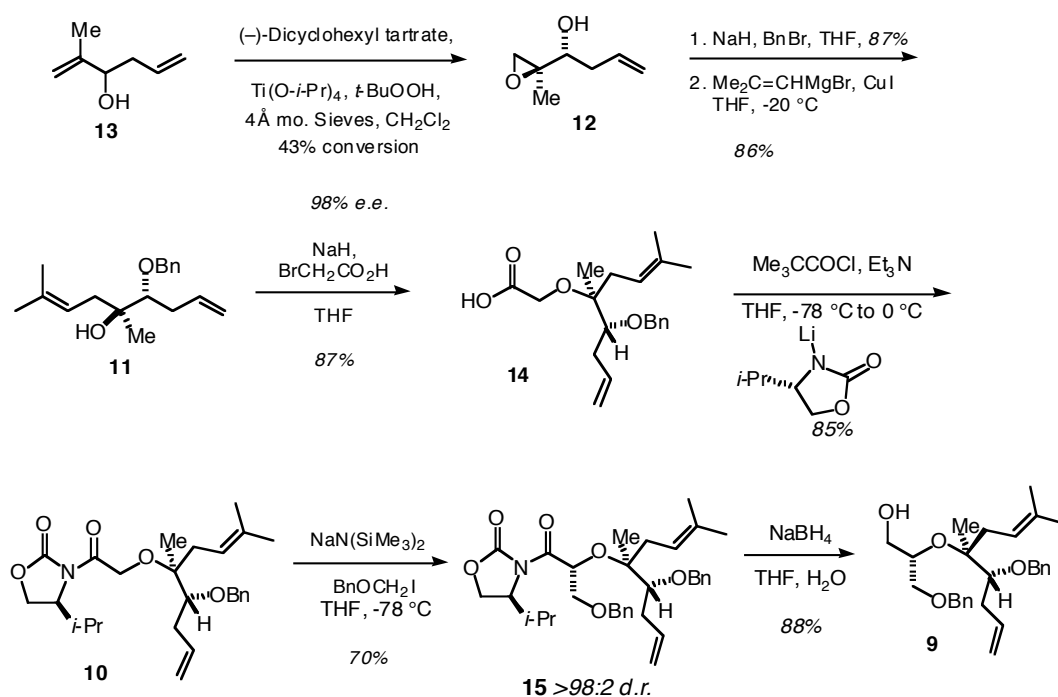

Scheme 3: Synthesis of alcohol (**9**).

Alkylation of the tertiary alcohol with bromoacetic acid and sodium hydride delivered the glycolic acid (**14**) in excellent yield. The glycolic acid (**14**) was acylated *via* the mixed pivalic anhydride to produce the oxazolidinone (**10**). The C26 stereocenter was incorporated by an asymmetric glycolate alkylation[15] of the sodium enolate of glycolyl oxazolidinone (**10**) with iodomethyl benzyl ether at –78 °C. The alkylation proceeds much more rapidly than is typically experienced with allyl iodide. The iodomethyl benzyl ether was prepared immediately prior to use by exposure of dibenzyloxymethane to trimethylsilyl iodide. While the alkylation product (**15**) proved somewhat difficult to purify, the alcohol (**9**) was obtained in 70% overall yield and >98:2 diastereoselectivity after reductive removal of the auxiliary with sodium borohydride.[16]

With the C26, C31 and C32 stereocenters in place, it remained only to refunctionalize the side chains and close the eight membered ring. The final two carbons were added by oxidation of alcohol (**9**) under Dess-Martin[17] conditions followed by addition of vinylmagnesium bromide to afford the allylic alcohol (**16**) in 80% yield as a 1:1 mixture of diastereomers. It was anticipated that the attempted closure of the triene (**16**) to an oxocene by ring-closing metathesis would be problematic because of competing cyclohexene formation.[18] We therefore opted to selectively epoxidize the trisubstituted alkene. Exposure of the triene (**16**) to *m*-CPBA at –78 °C led to a highly regioselective epoxidation of the

trisubstituted alkene. The resultant mixture of diastereomers of diene (**8**) was treated with the Grubbs second generation ruthenium catalyst[19] [5 mol %, 0.003M, CH_2Cl_2, 40 °C, 5 h] affording oxocene (**17**) in excellent yield.
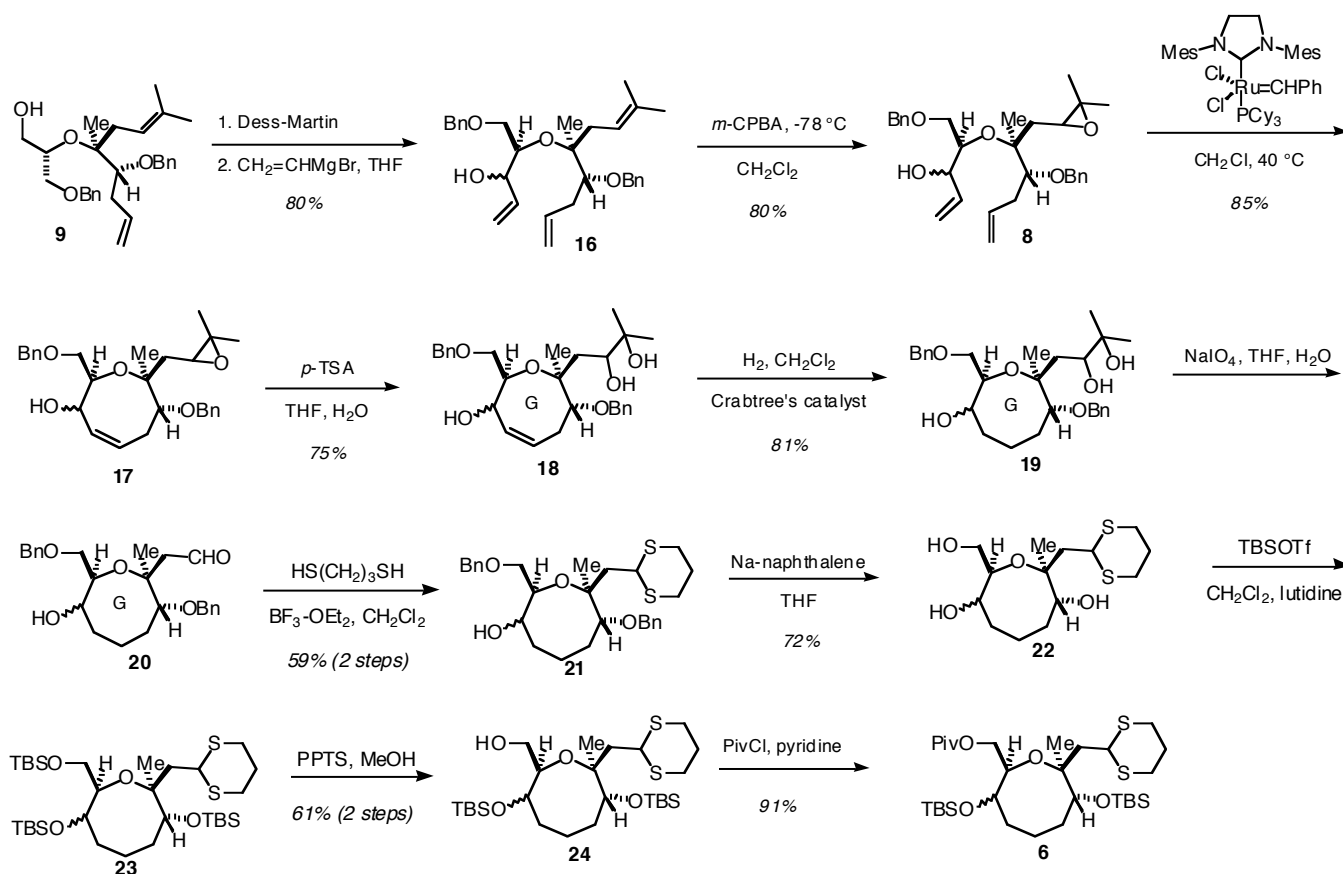
Scheme 4: Synthesis of the brevetoxin G ring.

The final refunctionalization necessitated cleavage of the C34-C35 epoxide. Acid catalyzed opening of the oxirane produced the desired diol (**18**) in 75% yield. While a number of conditions were investigated to reduce the oxocene double bond, the most effective method was the use of Crabtree's catalyst[20] [CH_2Cl_2, H_2] which effectively reduced the alkene without reductive cleavage of the benzyl ethers. With triol (**19**) in hand, the vicinal diol was oxidatively cleaved [$NaIO_4$, THF, H_2O] to provide aldehyde (**20**) which was immediately converted to the dithiane (**21**) under standard conditions. The benzyl ethers were reductively cleaved and the resultant triol (**22**) was smoothly converted to the silyl ether (**23**). Finally, selective removal of the primary TBS ether and acylation of the alcohol with pivaloyl chloride gave the desired G-ring fragment (**6**). The fully elaborated G-ring is well positioned for further elaboration to the GHIJ fragment and ultimately brevetoxin A. Additional details of the elaboration of the G-ring toward brevetoxin A will be reported in due course.

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