ITERATIVE STRATEGIES FOR POLYCYCLIC ETHER SYNTHESIS

Reported by Steven Tymonko September 23, 2002

INTRODUCTION

Since the isolation and structural elucidation of Brevetoxin B from *Ptychodiscus brevis* in 1981,[1] marine ladder toxins have gained considerable interest among synthetic and medicinal chemists due to their potent toxicity and structural complexity. Ladder toxins have been implicated in the large-scale fish kills of "red tides" in the Gulf of Mexico, as well as ciguatera food poisoning common in tropical climates.[2] These toxins operate by binding voltage-sensitive sodium channels, resulting in uncontrolled sodium influx into cells. Exemplified by brevetoxins, ciguatoxins,[3] gambieric acids,[4] and yessotoxins, marine ladder toxins consist of *trans-syn-trans* fused polycyclic ethers with a central core of seven-, eight-, or nine-membered rings.

Synthetic efforts toward the study of marine ladder toxins have culminated in the total synthesis of brevetoxin A by Nicolaou in 1998 (Figure 1),[5] ciguatoxin CTX3C by Hirama in 2001,[6] and most recently gambierol by Sasaki.[7] These syntheses were accomplished through traditional convergent approaches utilizing numerous methodologies. In recent years, increasing focus has been placed on the development of iterative strategies to construct the polycyclic skeleton of marine ladder toxins. These strategies are designed to take advantage of the repetitive features in the target structures. This strategy typically involves a series of steps culminating in a ring closure that yields an appropriate precursor for repetition of the same steps. In this manner, a single set of reactions can be used to construct a highly complex compound.

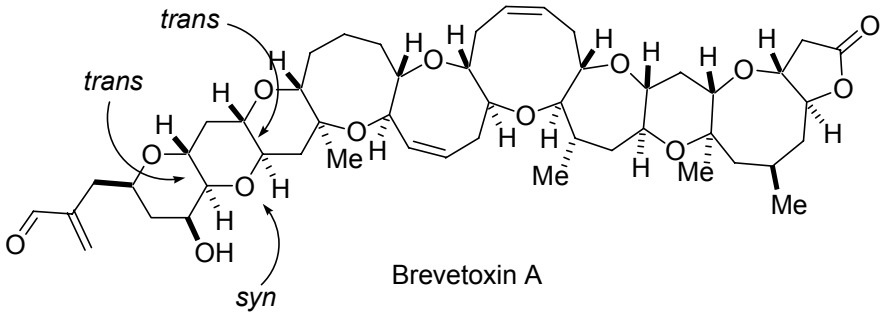


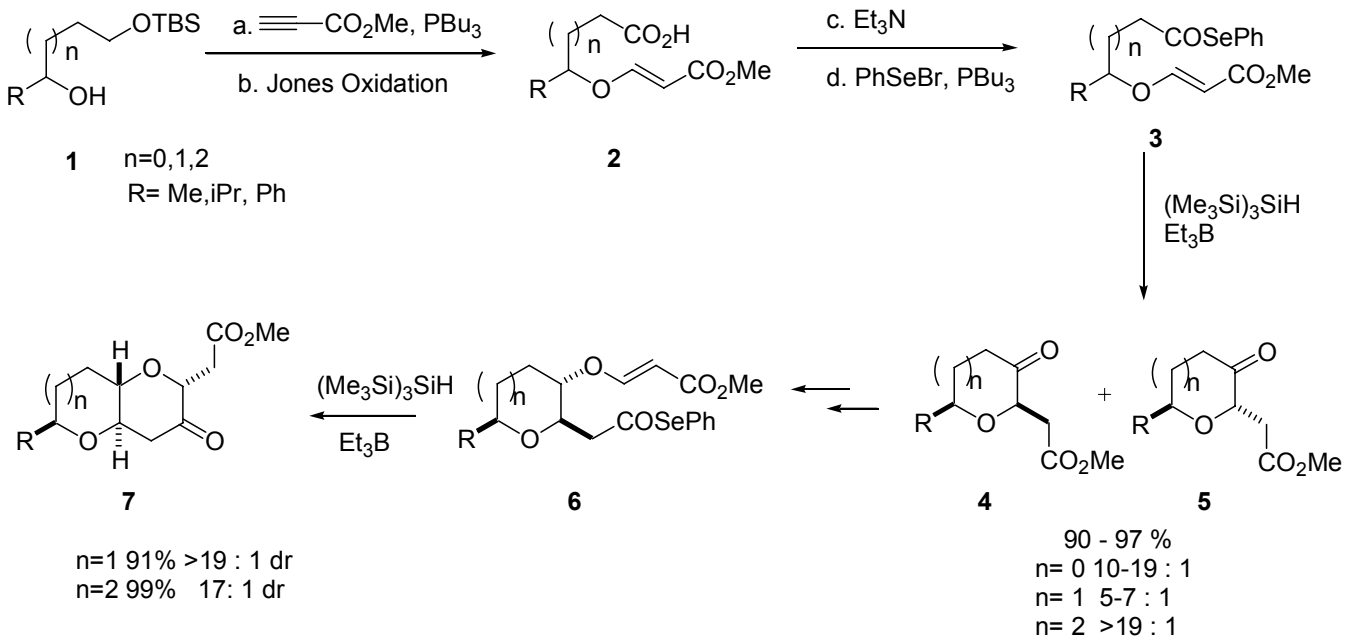
Figure 1. Structure of Brevetoxin A

ITERATIVE STRATEGIES

Acyl Radical Cyclizations

Evans and coworkers have reported the synthesis of polycyclic ethers through the radical closure of acyl selenides (Scheme 1).[8] The required acyl selenide **3** was prepared in four steps from secondary

Scheme 1



alcohol **1**. Radical cyclization provided diastereomers **4** and **5** in excellent yield and variable diastereoselectivity. The proposed chair transition states explain the formation of the *syn* product through transition state **I**, with the alkene positioned in a pseudo equatorial position (Figure 2). This avoids the diaxial interaction seen in **II**. This proposal explains the excellent selectivity observed in five and seven-membered ring formation but fails to account for the poor selectivity observed in closure to pyranones from acyclic precursor **3**. Reduction and selective protection of tetrahydropyranone **4** generates a new secondary alcohol for further manipulation to acyl selenide **6.**[9] In this manner, a series of five- six- and seven-membered fused cyclic ethers **7** can be prepared in excellent yield and diastereoselectivity.

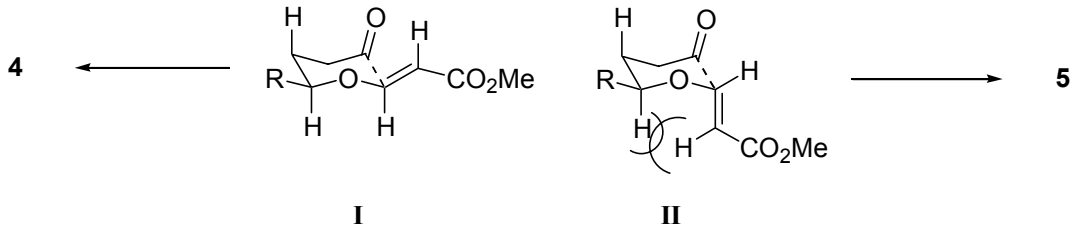
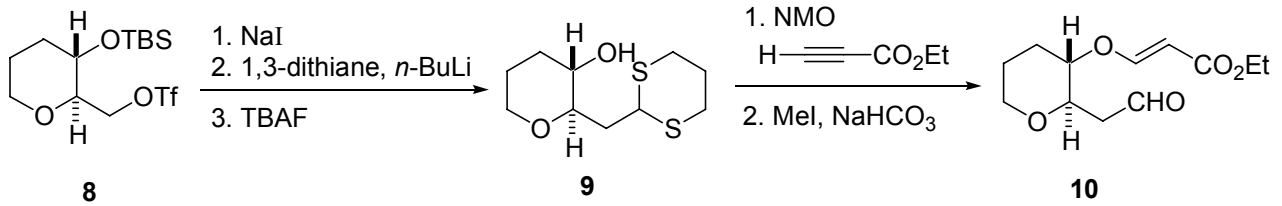


Figure 2. Transition states for ring closure.

SmI_2- Induced Cyclization

In a process similar to Evans' acyl selenide chemistry, Nakata has reported a method for radical cyclization induced by SmI_2.[10,11] This strategy requires the preparation of aldehyde **10,** which is analogous to the acyl selenide **6**. This key precursor can be prepared from optically active triflate **8**. Conversion of the triflate to the iodide followed by 1,3-dithiane addition and deprotection of the alcohol to give thioacetal **9** (Scheme 2). Conjugate addition to ethyl propiolate and deprotection of the thioacetal

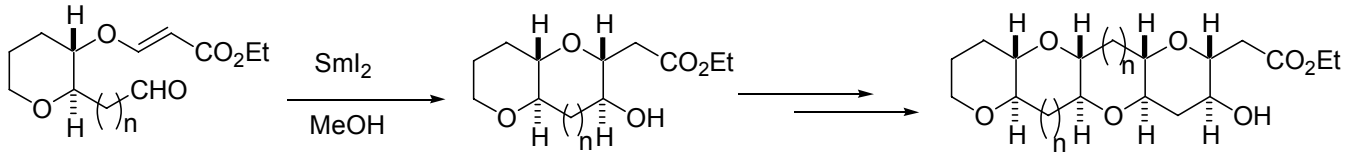
Scheme 2



8 **9** **10**

yields aldehyde **10**. Treatment with 2.2 equivalents of SmI_2 in methanol results in closure to the trans-fused cyclic ether **11** with complete diastereoselectivity (Scheme 3).

Scheme 3



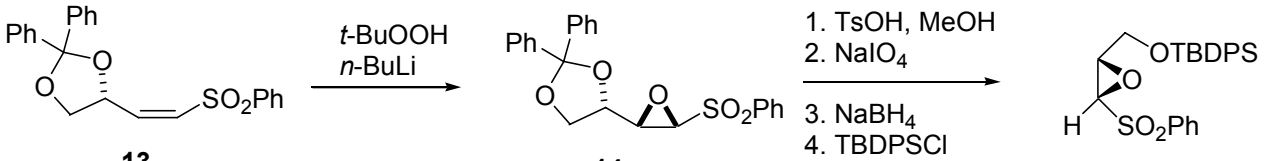
10 n=1,2 **11** **12** n = 1, 2

Further manipulation of bicyclic product **11** allows for the preparation tri- and tetra-cyclic products **12** through repetition of previous steps. Polycyclic ether **12** has been prepared with 6,6,6- 6,7,6- and 6,7,7-membered ring fusions.[12] The products are formed with high stereoselectivity with the exception of 6,7,7- ring systems, which suffer from significant leakage to the *cis*-fused products.

Oxiranyl Anions

The first iterative strategy to be successfully applied to total synthesis utilizes a oxiranyl anion derived from aryl sulfone **15** as a synthon for hemibrevetoxin B (**19**). Synthesis of the optically active suflone is initiated through epoxidation of Z-vinyl sulfone **13** to give epoxide **14 (**Scheme 4). Deprotection to the diol and oxidative cleavage gives the corresponding aldehyde, which can be reduced and protected to provide enantiopure **15**.

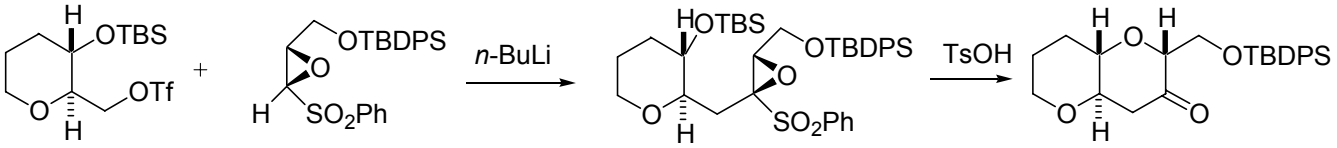
Scheme 4



13 **14** **15**

Developed by Mori, this approach is initiated by alkylation of sulfone **15** with triflate **16** (Scheme 5).[13] The resulting epoxide **17** then undergoes 7-*endo* cyclization upon deprotection of the TBS ether to give bicyclic ketone **18**. Selective reduction gives the desired *trans-syn-trans* ring fusion. While this approach directly forms tetrahydropyrans exclusively, Mori has demonstrated oxepane formation through one-carbon homologation of the tetrahydropyran with trimethylsilyldiazomethane.[14]

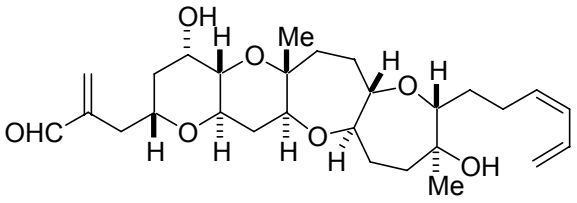
Scheme 5



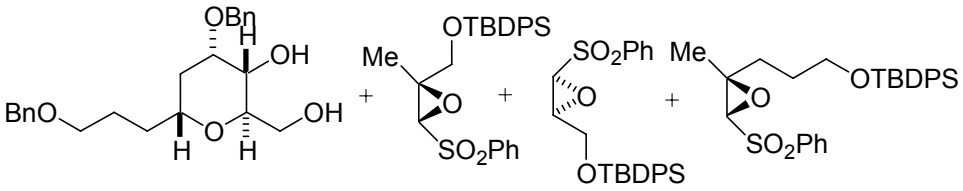
16 **15** **17** **18**

Mori's retrosynthetic analysis of the simplest ladder toxin hemibrevetoxin B **19** demonstrates the strength of the oxiranyl anion strategy (Scheme 6).[15] By sequentially adding three readily prepared epoxides to the diol precursor **20**, the tetracyclic backbone of Hemibrevetoxin B is easily constructed.

Scheme 6



19 Hemibrevetoxin B

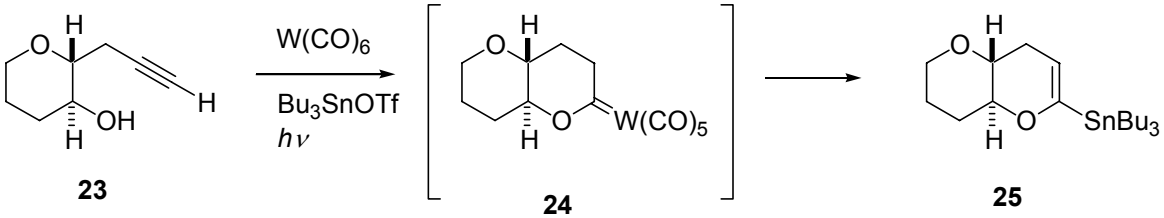


20 **21** **15** **22**

Carbene Insertion

Another approach to polypyrans developed by McDonald relies upon cyclization of alkynols **23** as a key step (Scheme 7).[16] Ring closure is achieved by tungsten hexacarbonyl-initiated cyclization of 1-alkyn-5-ols **23** to provide the stable tungsten oxacarbene intermediate **24**.[17] In the presence of tributyltin triflate, oxacarbene **24** reacts to give pure bicyclic stannane **25** in moderate yield.

Scheme 7

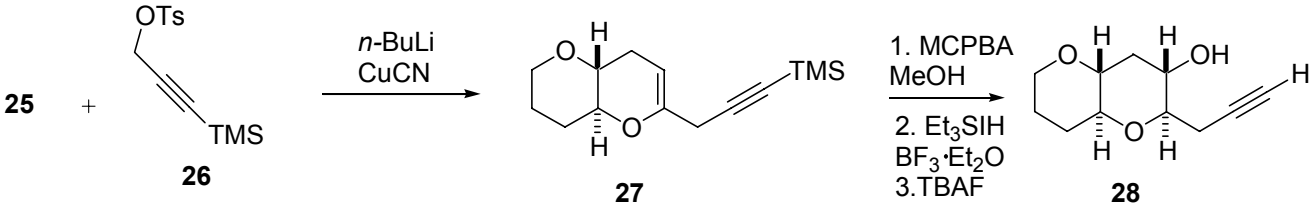


23 **24** **25**

The iterative cycle continues by lithiation of the stannane, transmetalation to copper, and alkylation with triflate **26** (Scheme 8). Oxidation with *m*-CPBA followed by hydride reduction and deprotection gives bicyclic 1-alkyn-5-ol **28** which can then undergo subsequent ring closure. To date, only fused pyrans have been prepared through this methodology. However, it is conceivable that

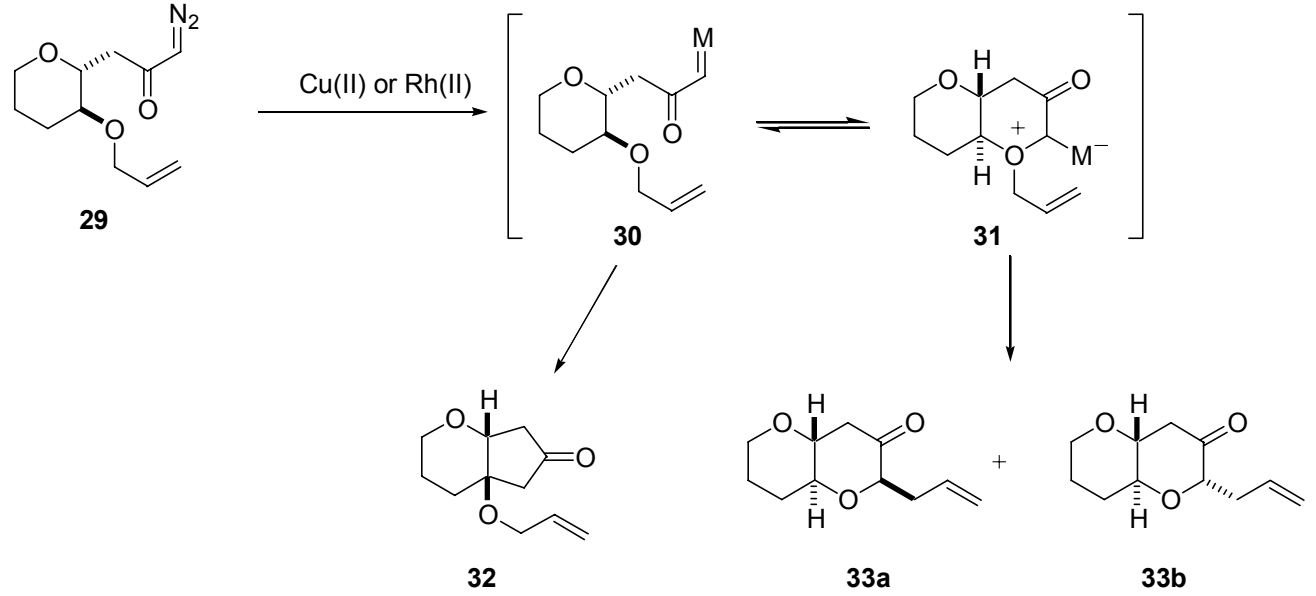
replacement of tosylate **26** with other alkynes could allow for entry into seven- through nine-membered ethers.

Scheme 8

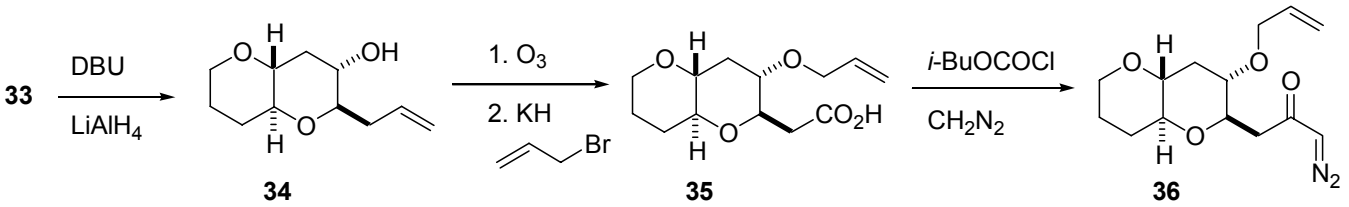


A similar method developed by West also relies upon carbene formation to initiate cyclization. This cyclization can be effected with catalytic decomposition of diazoketone **29** with copper (II) or rhodium (II) to give the metal carbene **30** (Scheme 9).[18,19] This carbene can then close to an oxonium ylide **31**, which then undergoes a [2,3]-sigmatropic rearrangement to provide diastereomers **33a** and **33b**. While rhodium catalysts favor desired diastereomer **33a**, significant C-H insertion product **32** is also observed. By contrast, copper catalysts do not give C-H insertion, but favor the opposite diastereomer. The unfavorable diastereoselectivity of copper is circumvented by epimerization and reduction of the diastereomeric mixture with DBU and $LiAlH_4$ to give the desired diastereomer of the corresponding alcohol in 7:1 selectivity (Scheme 10).

Scheme 9



Scheme 10

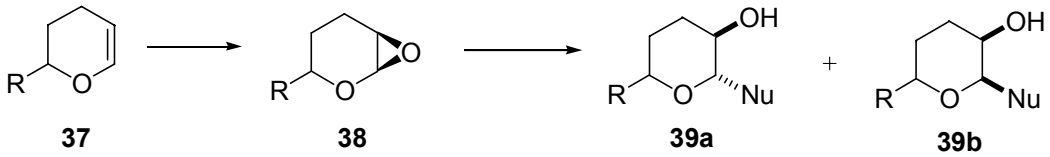


The product alcohol **34** is prepared for further iteration through ozonolysis and allyl ether formation to give intermediate carboxylic acid **35**. Activation of the acid and treatment with diazomethane provides the necessary diazoketone **36**.

C-Glycosides

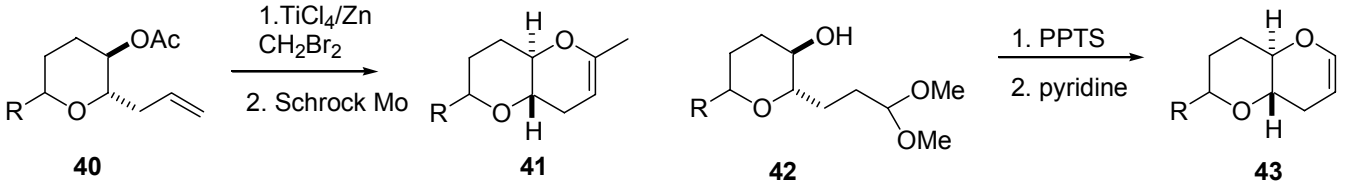
Perhaps the most promising approach to date involves the application of the diverse chemistry of *C*-glycosides to set the ring juncture stereochemistry.[20,21] This general method involves oxidation of a dihydropyran **37** to provide an epoxide **38** (Scheme 11). Nucleophilic opening of the epoxide gives an alcohol **39**. The stereochemistry of the ring opening can be controlled through careful selection of the nucleophile. Grignard reagents provide *trans* products **39a**, wheras aluminum nucleophiles favor *cis* products **39b**.[22] This allows for additional flexibility in cases where the ring fusion is quaternary, because either substituent can be utilized as the carbon nucleophile.

Scheme 11



With the requisite stereochemistry set, ring closure can be effected by either of two methods. Allyl glycoside **40** can be treated with Takai's low valent titanium reagent followed by ring closing metathesis to provide cyclic enol ether **41** (Scheme 12). The same net transformation can be achieved from acetal **42** through acid mediated cyclization followed by elimination.

Scheme 12

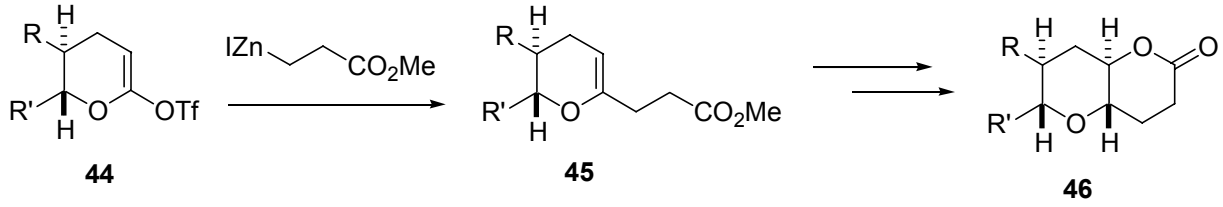


Rainier demonstrates the utility of this methodology through the formal total synthesis of Hemibrevetoxin B (**19**).[23,24] With the combination of nucleophilic epoxide opening and ring closing methods already discussed, the tetracyclic core of hemibrevetoxin B was prepared in racemic form.

Other Methods

It should be noted that a number of other iterative methods have been published. Yamamoto has recently published a method based upon Negishi coupling of an triflate **44** followed by lactonization (Scheme 13).[25] Currently, this method suffers from significant competing formation of the *trans-anti-trans* product during lactonization. A ring-closing enyne methathesis method has also been published by Clark, which has potential for use in the formation of eight- and nine-membered cyclic ethers.[26] However, this methodology has not yet been demonstrated in the formation of polycyclic structures.

Scheme 13



44 **45** **46**

CONCLUSIONS AND FUTURE DIRECTIONS

Despite the recent proliferation of iterative methods for polycyclic ether synthesis, a truly general approach has yet to be realized. Preparations of fused pyrans and oxepanes have been well documented. However, little progress has been reported on the preparation of eight- and nine-membered cyclic ethers. Likewise, many of the current methodologies suffer from poor diastereoselectivity when setting the *trans-syn-trans* ring junctions. Until these shortcomings can be overcome, the application of fully iterative methods to the total synthesis of the larger ladder toxins cannot be realized. Even with the development of more general iterative approaches, the most likely future for this technology is in the preparation of advanced intermediates such as the B-E and G-J ring systems of Gambieric acid A (Figure 2). This would allow the advantages of both iterative and convergent approaches to be utilized in the total synthesis of these complex natural products.

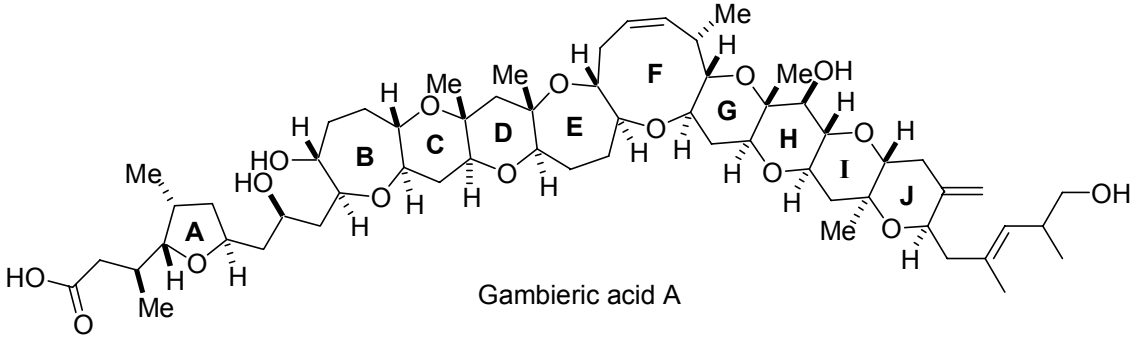


Figure 2. Structure of Gambieric acid A

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