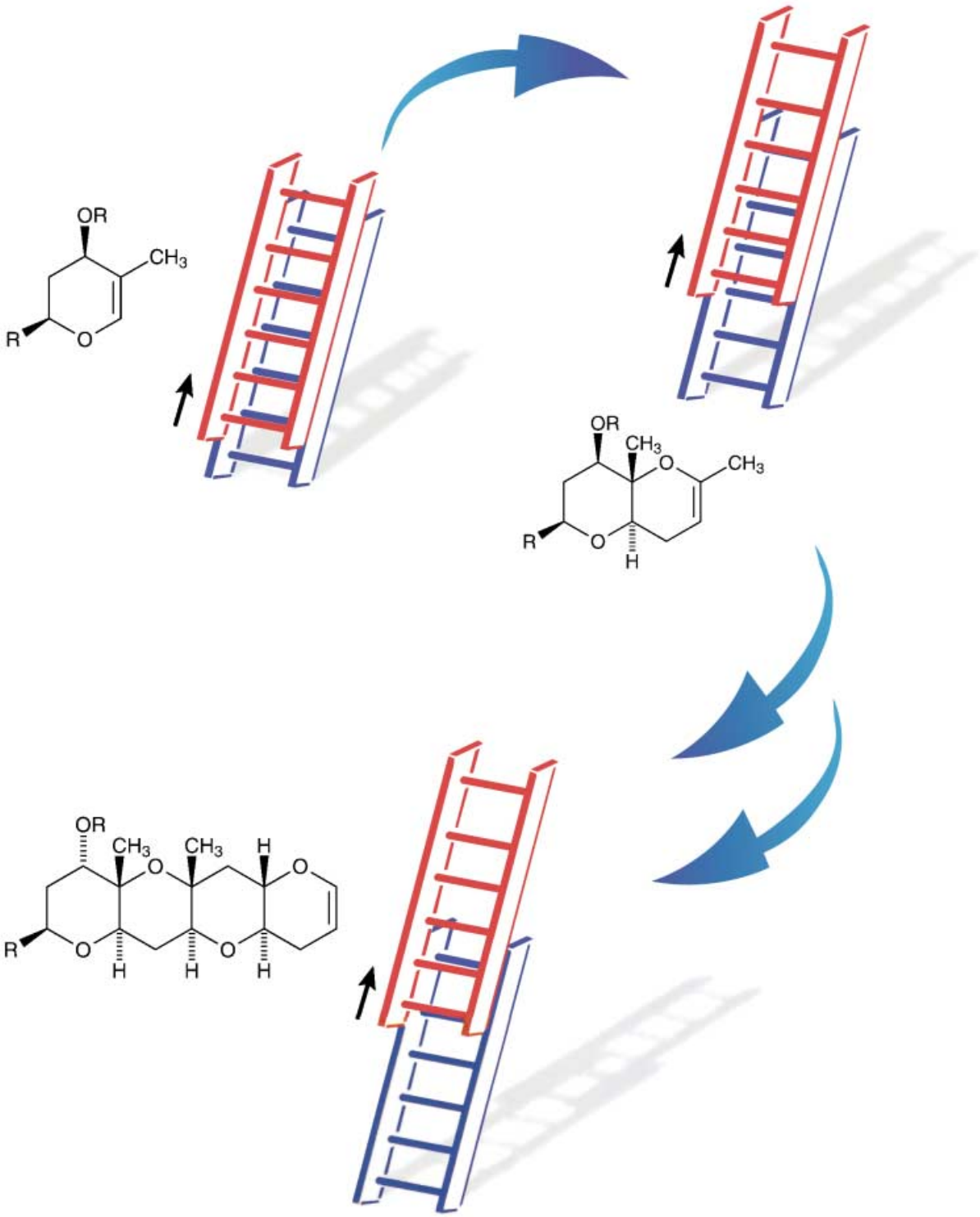
Ladder-Extension in the Synthesis of Marine Polyether Toxins



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New Efficient Iterative Approaches to Polycyclic Ethers

Fredrik P. Marmsäter[a] and Frederick G. West*[b]

Abstract: The imposing structures of the marine polyether ladder toxins have inspired synthetic chemists to develop many clever methods for assembling these complex skeletons. One intriguing strategy is to use a short and reliable sequence of reactions to build successive rings in an iterative fashion. The ideal approach should tolerate variation in ring size and substitution at the bridgehead positions. This paper offers an overview of recent progress in this field.

Keywords: cyclization · fused-ring systems · iterative synthesis · natural products · polyethers

Introduction

The marine ladder toxins, associated with the massive fish kills and human food poisoning from red tides, have attracted much attention in the chemistry community for their intriguing molecular structures and biological activity. This class of compounds, including the brevetoxins and ciguatoxins, produced by the marine organisms *Gymnodinium breve* and *Gambierdiscus toxicus*, are extremely scarce, highly potent and act to depolarize cell membranes by binding to or near Na^+ channels.[1] These properties, coupled with the very interesting structures, have been the driving force for the considerable efforts to synthesize this family of compounds. The Nicolaou group has been on the forefront of the synthetic endeavor with impressive total syntheses of brevetoxin B[2] and A.[3] More recently, the Hirama group disclosed a masterful total synthesis of ciguatoxin CTX3C.[4] However, the construction of these molecules can require in excess of seven steps per ring. This, in conjunction with the highly repetitive nature of these structures, has led several groups to investigate iterative approaches that would install each ring in 4–5 transformations. The successful iterative method must be general and able to assemble 6–9 membered polyether arrays and bridgehead stereocenters, including quarternary centers bearing axial methyl groups (Figure 1). In addition, the sheer sizes of these molecules require an iterative approach to be highly efficient with excellent material throughput. The topic of iterative synthesis of polypyrans was reviewed in 1997,[5] this article will examine some recent iterative methods, published after the 1997 review, and their application towards the synthesis of these natural products.

The Mori group has developed a novel iterative strategy towards polypyran domains based on the postulated biosynthesis of these agents.[6] The basic strategy is outlined in Scheme 1 and will be only briefly discussed as it has previously been reviewed.[5] The nucleophilic addition of oxiranyl anions such as **2** to triflate **1** creates the carbon backbone and installs the oxygenation required for the formation of the next ether ring. Treatment with acid effects the desired 6-*endo* epoxide opening to close the ring. Four steps are required to convert **4** to the next alkylation precursor **5**; thus, each iterative pyran synthesis requires six steps, all of which are very efficient. This method has also been successfully applied to systems bearing axial methyl groups and 1,3-diaxial methyl groups.[7]

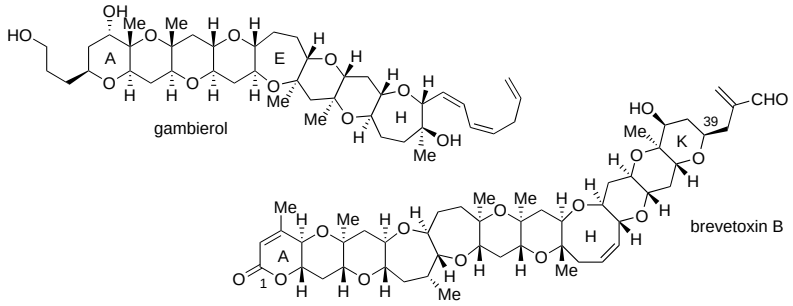

Figure 1. Structures of the marine ladder toxins gambierol and brevetoxin B.

The Mori group circumvented direct formation of oxepanes by employing a ring expansion reaction of pyrans.[8] Treatment of **4** with trimethylsilyl diazomethane under Lewis acid

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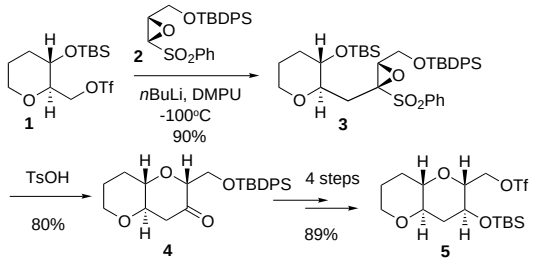
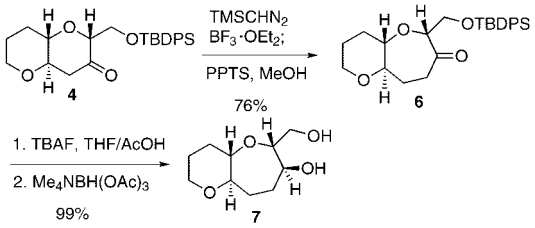


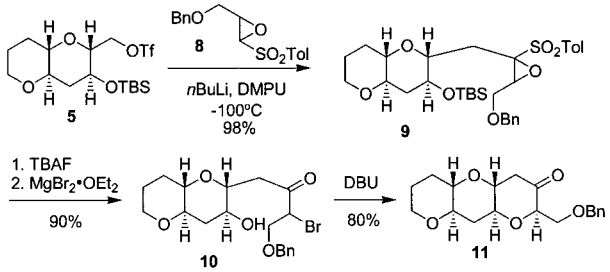
Scheme 1. Mori: Iterative polypyran synthesis via 6-*endo*-cyclization of epoxysulfones. TBS = *tert*-butyldimethylsilyl; Tf = trifluoromethanesulfonyl; TBDPS = *tert*-butyldiphenylsilyl; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2*H*-pyrimidinone.

catalysis followed by in situ silyl enol ether hydrolysis produced oxepane **6**, which was subjected to a hydroxyl directed reduction to afford the desired product **7** (Scheme 2).



Scheme 2. Mori: Oxepane formation through ring expansion of pyrans. PPTS = pyridinium *p*-toluenesulfonate; TBAF = tetra-*n*-butylammonium fluoride.

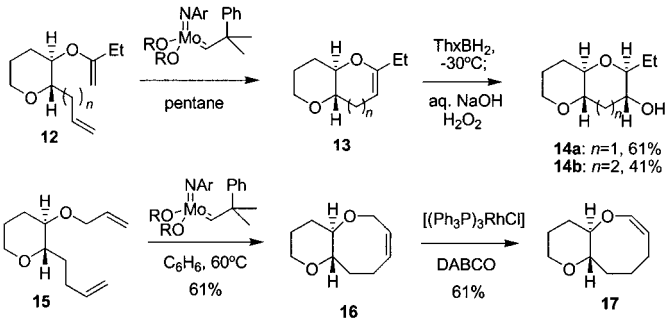
This approach was applied in the formal total synthesis of hemibrevetoxin B.[9] The lengthy synthesis of optically active epoxide **2** (eight steps from (*S*)-pentylideneglyceraldehyde) prompted the Mori group to pursue an alternate approach employing racemic *cis*- and *trans*- epoxy sulfones such as **8**, synthesized in three steps from allyl benzyl ether (Scheme 3).[10] Incorporation of this epoxy sulfone required



Scheme 3. Mori: Modified polypyran synthesis employing racemic epoxy sulfones. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

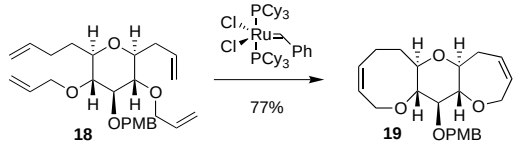
conversion into the α-bromo ketone **10** to allow for ring closure upon treatment with DBU. (Presumably, DBU also effects epimerization to the desired isomer.) In summary, the Mori approach utilizes a biomimetic 6-*endo* epoxide cyclization and requires six steps per iteration for polypyran synthesis. This method allows for the installation of the axial methyl groups and access to oxepane rings by a one carbon ring expansion of pyrans.

Clark and Kettle have reported an approach based on ring closing metathesis and hydroboration of enol ethers.[11] Exposure of compounds such as **12** to Schrock's molybdenum catalyst[12] and hydroboration of the resulting enol ether **13** gave rise to pyran **14a** and oxepane **14b** in good to moderate yields (Scheme 4).



Scheme 4. Clark: Iterative polyether synthesis through ring closing metathesis. Thx = 2,3-dimethyl-2-butyl; DABCO = 1,4-diazabicyclo[2,2,2]octane.

In the case of target-oriented synthesis, the ethyl group in the model system would be replaced by an appropriate carbon tether and a double bond surrogate, such as a selenide or protected alcohol, and revealed after the hydroboration. Formation of oxocenes by an analogous method was problematic and required the use of an allyl ether instead of a vinyl ether as the cyclization precursor. Exposure of **15** to Schrock's catalyst gave rise to **16**, which was isomerized using Wilkinson's catalyst to produce the desired oxocene **17**. A two-directional double metathesis version was later disclosed.[13] This strategy begins with a central ether ring such as compound **18** and constructs ether rings on both flanks using the above described RCM method to give rise to **19** (Scheme 5).



Scheme 5. Clark: Two-directional metathesis approach. PMB = *p*-methoxybenzyl.

A variety of different ether ring sizes were created using this method. However, differentiation between the east and west flanks by hydroboration or other methods was not demonstrated. In summary, Clark's ring-closing metathesis reaction gives rise to cyclic enol ethers which can be hydroborated to install the bridgehead stereocenters. Importantly, this method allows for the efficient formation of the elusive medium-sized ether rings. At this time, installation of the axial methyl groups has not yet been addressed, nor has a successful iteration been disclosed.

McDonald and Bowman have developed an iterative synthesis of polypyran domains based on a 6-*endo* cyclization of a tungsten vinylidine intermediate.[14] Treatment of **20**

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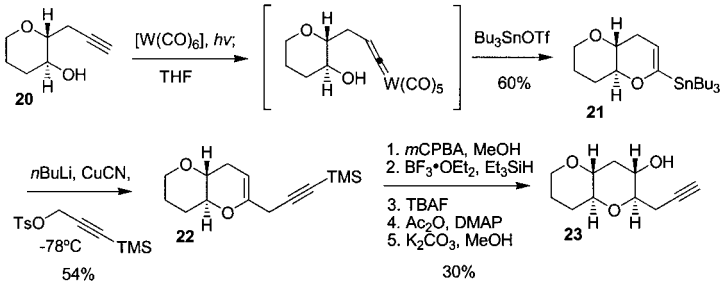
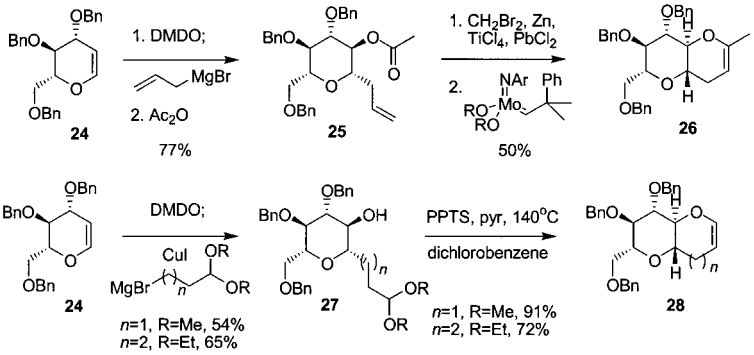
(synthesized from dihydropyran in four steps) with a photogenerated solution of $[W(CO)_5(thf)]$ and subsequent stannylation produced **21** (Scheme 6). This transformation serves to close the pyran ring through formation of the carbon–oxygen bond and establishes a handle for further functionalization. Tin lithium exchange followed by alkylation gave rise to **22**, which has all the carbons of the next ether ring in place. Facially selective oxidation with *m*CBPA/MeOH followed by a stereoselective reduction of the resulting mixed ketal installs the bridgehead stereocenters. The reduction produced a 3:1 mixture of inseparable diastereomers favoring the desired isomer. Following deprotection of the alkyne, separation required conversion into the corresponding acetates. Subsequent removal of the acetate gave rise to **23** in 30% overall yield from **22**. Compound **23** could be cyclized in analogy to **20** to furnish the corresponding tricyclic stannylated dihydropyran. This method requires seven steps per iteration in an overall yield of 10% for the synthesis of polypyran domains.



Scheme 6. McDonald: Polypyran synthesis through 6-*endo*-cyclization of tungsten vinylidine intermediate. *m*CPBA = *m*-chloroperoxybenzoic acid.

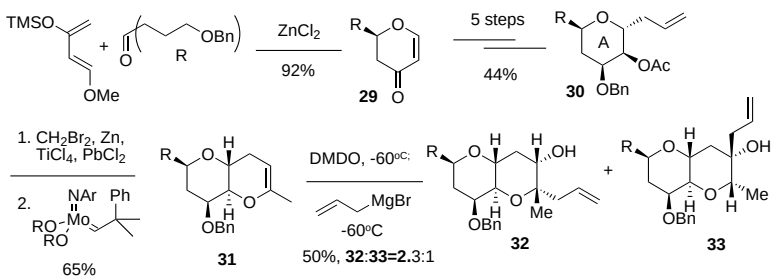
Rainier and co-workers have developed two closely related iterative approaches which, like Clark's and McDonald's, rely on the formation and functionalization of enol ethers as the key transformations. One method employs a ring closing metathesis reaction,[15] the other an acid mediated cyclization/elimination event[16] to accomplish ring closure and enol ether formation (Scheme 7). Starting with tri-*O*-benzyl-D-glucal (**24**), both strategies share a one-pot epoxidation/alkylation protocol, which installs the carbon backbone and the bridgehead stereocenters, to afford **25** and **27**, respectively. Exposure of acetate **25** to Takai's conditions[17] to methylenate the acetate group and subsequent ring closing metathesis with Schrock's alkylidine catalyst produced the desired methyl substituted enol ether **26** in 50% overall yield. Use of the corresponding formate ester results in low yields in the Takai reaction. Treatment of acetal **27** with acid and heat effected ring closure and elimination to provide enol ether **28** in high yield. This second process allows for the iterative synthesis of both pyrans and oxepanes in three steps/two pots in a highly efficient manner. These methods were used in combination in the formal total synthesis of hemibrevetoxin B.[18]



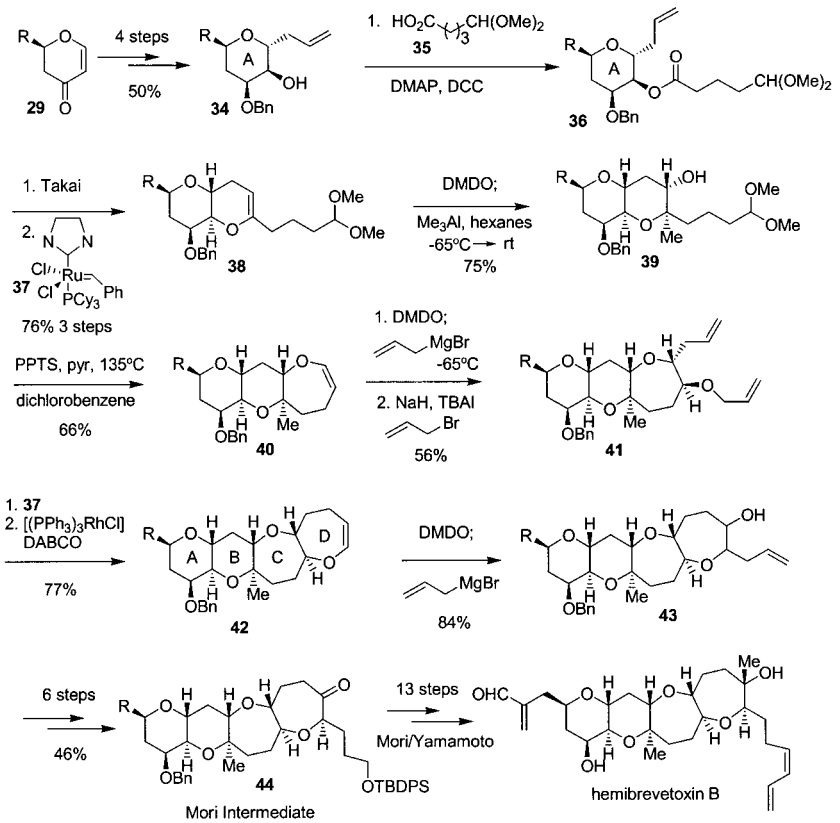
Scheme 7. Rainier: Polyether synthesis ring closing metathesis or annulation reaction. Bn = benzyl; DMDO = 2,2-dimethyldioxirane; pyr = pyridine.

Rainier employed a hetero-Diels–Alder reaction to produce **29**, which was converted to the A-ring surrogate **30** in five steps (Scheme 8). To allow for installation of the axial methyl group, the RCM method was chosen for the formation of the B-ring. Hence, **30** was exposed to the Takai conditions followed by the ring closing metathesis reaction to afford enol ether **31**.[19] Facially selective epoxidation was accomplished (directed by the C-3 benzyloxy group) but the addition reaction produced the undesired *trans–syn–cis* stereoisomer **32** as well as compound **33**, which might arise from a hydride shift of an oxocarbenium intermediate.

The Rainier group solved this problem by introducing the carbons needed for the C-ring before the metathesis event and then installing the axial methyl group, effectively inverting the stereochemistry at the bridgehead center. Hence, **34** was coupled with acid **35**, which possessed the carbon backbone and the acetal needed for formation of the C-ring (Scheme 9). The B-ring was produced by the Takai/ring closing metathesis procedure, utilizing Grubbs' catalyst **37**,[20] to afford bicyclic enol ether **38** in good yield. Epoxidation and treatment with Me_3Al at $-65\,^{\circ}C$ delivered **39** with the correct *trans–syn–trans* stereochemistry through a postulated aluminum-ate complex and intramolecular methyl addition. The acid mediated annulation reaction furnished the seven-membered C-ring to give rise to **40** in 66% yield. According to the synthetic plan, formation of the D-ring was to follow the model substrate (**27** → **28**, $n = 2$): epoxidation and coupling with an acetal cuprate followed by the acid mediated annulation reaction. However, coupling of the epoxide of **40** with the acetal cuprate was unsuccessful. Interestingly, propenylmagnesium chloride added efficiently, and after allyl



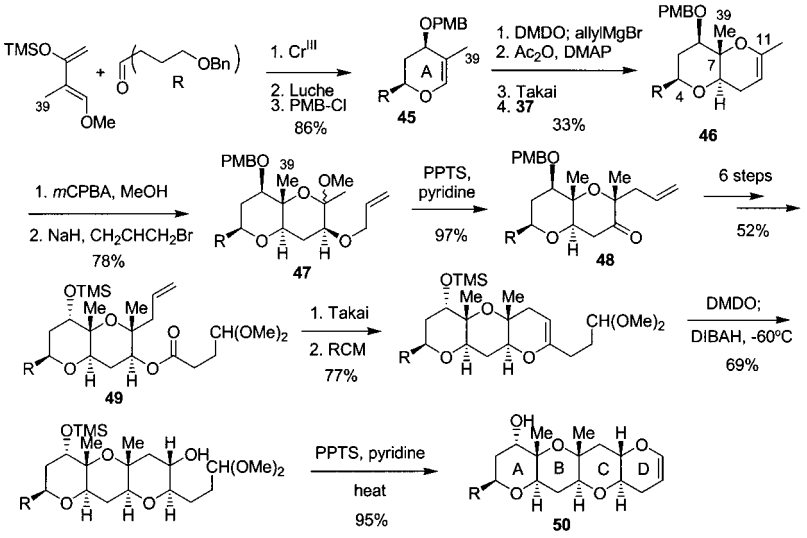
Scheme 8. Rainier: Initial unsuccessful approach to hemibrevetoxin B. TMS = trimethylsilyl.



Scheme 9. Rainier: Formal total synthesis of hemibrevetoxin B. DMAP = 4-*N*,*N*-dimethylaminopyridine; DCC = dicyclohexyldicarbodiimide; TBAI = tetra-*n*-butylammonium iodide.

ether formation gave rise to **41** in 56% isolated yield. Ring closing metathesis using **37** followed by isomerization gave rise to **42**. At this point, the complete ring system of hemibrevetoxin B has been achieved in an impressive 11 steps from A-ring surrogate **34**. The single flask epoxidation/alkylation protocol then provided **43**, which in six steps intercepted Mori intermediate **44**. The Rainier group accomplished the synthesis of **44** in 24 steps from Danishefsky's diene. In comparison, the Mori group synthesized **44** in 30 steps from tri-*O*-acetyl-D-glucal.[21]

Rainier and Cox have also applied the above described methods to the synthesis of the A–D ring system of gambierol (Figure 1).[22] This segment contains the challenging 1,3-diaxial methyl groups. The A-ring precursor was prepared by an asymmetric hetero-Diels–Alder reaction utilizing Jacobsen's Cr^{III} catalyst[23] which, after Luche reduction and PMB protection, provided **45** in good yield (Scheme 10). This sequence assembled the A-ring in three steps and 86% isolated yield. Subjection of **45** to the RCM protocol generated **46** with the C-7 axial methyl group in place. The success of this sequence is surprising in light of the failure of the very similar transformation **31** → **32** (Scheme 8). Interestingly, epoxidation of **46** and addition of allyl nucleophiles resulted in the undesired C-11 epimer. A rather elegant solution to this problem was realized by oxidation of **46** with *m*CPBA/MeOH, which after allyl ether formation furnished **47**. Treatment with acid produced the corresponding enol ether which underwent an in situ Claisen rearrangement to provide **48** with both the C-7 and C-11 methyl groups in place. The synthesis continued with inversion of the C-6 center (which in its axial position served to direct the facial selectivity in the epoxidation of the A-ring) and conversion into RCM precursor **49** followed by the efficient formation of the C- and D-rings to provide **50**. In summary, the Rainier approach has demonstrated the ability to efficiently provide all of the challenging structural features of hemibrevetoxin B and gambierol through formation and stereoselective functionalization of enol ethers. Interestingly, the Rainier syntheses required the use of a different method for the formation of each ring and did not utilize a truly iterative approach. These modified sequences demonstrate the need for a modular approach, which can address difficult transformations not encountered in the model study.



Scheme 10. Rainier: Synthesis of the A–D ring system of gambierol. DIBAH = diisobutylaluminum hydride.

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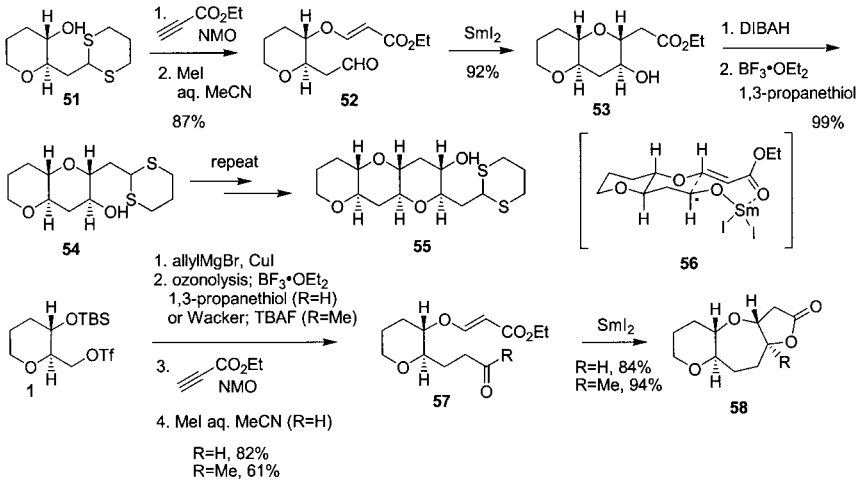
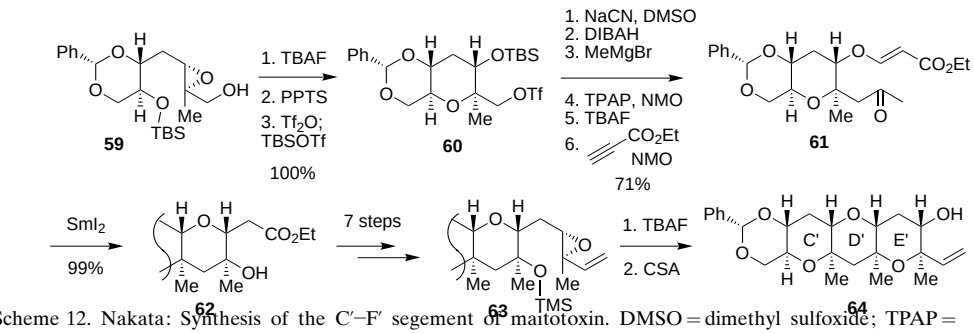
Nakata and co-workers have disclosed a very efficient approach to polypyrans based on a stereoselective SmI_2-induced reductive cyclization.[24] In contrast to the methods developed by Clark, McDonald and Rainier, which rely on enol ether formation and stereoselective oxidation or hydroboration, the reductive cyclization reaction utilized by the Nakata group constructs a carbon–carbon bond which sets both of the bridgehead stereocenters. Hetero-Michael addition of compound **51** (synthesized in two steps from **1**) into ethylpropiolate followed by deprotection of the dithioacetal produced cyclization precursor **52** in good yield (Scheme 11). Treatment with SmI_2 effects the reductive cyclization to produce the desired compound **53** via postulated transition state **56**. Half-reduction and protection completes the iteration. Polypyran domains are thus accomplished in five steps per iteration in an impressive 79% overall yield. The analogous reaction can be applied to substrates like **57** to produce oxepanes such as **58** in excellent yields.[25]



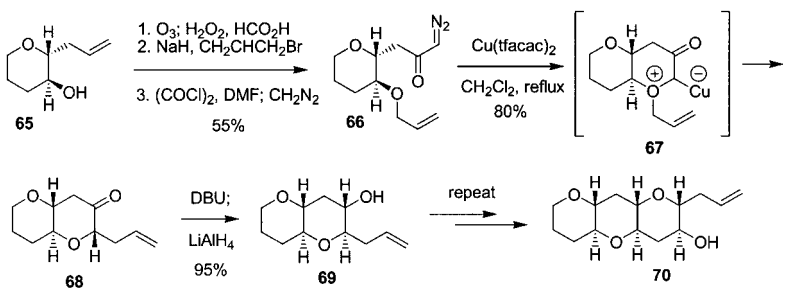
Scheme 11. Nakata: Iterative polyether synthesis through reductive cyclization. NMO = *N*-methylmorpholine-*N*-oxide.

The lactone can be opened by a half reduction with Dibal-H (for formation of a subsequent pyran ring) or by a Wittig reaction with Ph_3CHOMe (for formation of a subsequent oxepane ring). This chemistry has been applied towards the synthesis of the C′D′E′F′ ring system of maitotoxin which contains 1,3,5-triaxial methyl groups (Scheme 12).[26] The Nakata group utilized a 6-*endo* cyclization of methyl epoxide **59** to produce **60**.[27] Conversion into **61** followed by the SmI_2-induced reductive cyclization afforded **62** with the 1,3-diaxial methyl groups installed in excellent yield. Application of the methyl epoxide method for the installation of the third axial methyl group was not as efficient as the Nicolaou protocol,[28] which was then utilized to produce **64** with the 1,3,5-triaxial methyl groups in place. It is interesting to observe that, like the Rainier syntheses, each ring was assembled using a different method, so the preparation of this fragment cannot properly be viewed as an iterative synthesis.



Scheme 12. Nakata: Synthesis of the C′–F′ segement of maitotoxin. DMSO = dimethyl sulfoxide; TPAP = tetrapropylammonium perruthenate; CSA = camphorsulfonic acid.

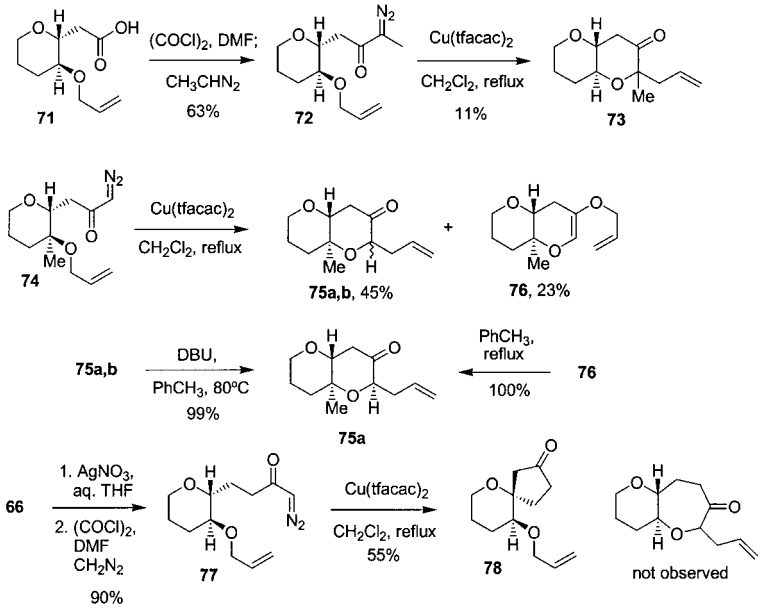
Marmsäter and West have recently described an iterative approach based on the [2,3]-shift of cyclic oxonium ylides.[29] This strategy is fundamentally different from the 6-*endo* cyclizations of epoxides employed by Mori and Nakata, and the enol ether based approaches of Clark, McDonald and Rainier. A closer analogy can be found in the reductive cyclization strategy developed by the Nakata group, as the key step accomplishes the ring formation and sets the bridgehead stereocenters. For example, compound **65** could be converted to diazoketone **66**, which upon treatment with catalytic copper(II) trifluoroacetylacetonate furnished bicyclic **68** via intermediate oxonium ylide **67** (Scheme 13). Surprisingly, compound **68** possessed the undesired stereochemistry at the



Scheme 13. West: Iterative polypyran synthesis through tandem oxonium ylide formation/[2,3]-shift process. DMF = *N*,*N*-dimethylformamide; tfacac = trifluoroacetylacetonate.

newly formed center, with the allyl chain axially disposed. This compound was isomerized and reduced by a one-pot procedure to produce an 8:1 mixture of **69** and its epimer in 98% yield to complete the iteration. The isomeric material could be recycled (oxidation/epimerization/reduction) to increase the effective yield of **69** to 95%.

As was seen in the examples discussed earlier, an important challenge in the assembly of polypyran arrays is the introduction of angular methyl groups at the bridgehead positions. Marmsäter and West investigated several approaches. Methylation via enolate intermediates derived from **68** was unsuccessful, and incorporation of the methyl group in the diazoketone (e.g. **72**) furnished the ylide rearrangement product **73** in disappointingly low yields (Scheme 14).[30] On the other hand, tertiary allylic ether **74** underwent conversion to **75a**,**b** in moderate yield.[31] Interestingly, allyl vinyl ether **76**, arising from an apparent [1,4]-shift, was also isolated. Both **75b** and **76** could be converted into **75a**, thus producing the desired compound in 68% yield from **74**. To investigate the formation of medium sized heterocycles, diazoketone **77** was subjected to the copper(II) conditions. Unfortunately, the desired oxepane was not observed; instead, spirocyclic C–H insertion product **78** was isolated. While direct formation of oxepanes via seven-membered oxonium ylides appears to be problematical, they should be accessible from the pyran-3-one intermediates using Mori's ring-expansion methodology.



Scheme 14. West: Installation of axial methyl groups and attempts to form medium size ether rings.

In conclusion, all of the methods described in this article can produce simple polypyran domains in a relatively short number of steps. The acid mediated annulation strategy of Rainier and the SmI_2 cyclization employed by Nakata are especially efficient and can produce polypyrans and oxepanes in 3–5 operations per iteration and in very high yields. In these examples, installation of the axial bridgehead methyl groups requires extra steps or a different strategy altogether, and results in reduced yields. In others, such as the West or Mori methods, access to medium sized ether rings is either inefficient or requires seven or more steps. To date, no natural product in this class of marine toxins, or segment thereof, has succumbed to a strictly iterative synthesis. This highlights the current absence of an iterative approach that is equipped to tackle these very complex and demanding structures, suggesting that iterative synthesis might not be the ideal strategy for these targets. However, as demonstrated by the formal synthesis of hemibrevetoxin B by Rainier and co-workers and the synthesis of the C′D′E′F′ segment of maitotoxin by the Nakata group, successful examples of powerful, efficient and modular methods have emerged from this endeavor. The concept of a common intermediate, such as a cyclic enol ether, used in an iterative sense in each ring forming sequence has been demonstrated. From such an adduct, the synthetic chemist can choose a number of methods for the efficient formation of the following ring based on ring size and substitution required. In addition, ring-closing metathesis of vinyl ethers has emerged as a very powerful reaction for the formation of medium sized ether rings. A combination of these synthetic strategies to provide bi-, tri-, or tetracyclic segments in conjunction with several coupling events, such as those used in some convergent polyether strategies,[32] will undoubtedly result in some very efficient syntheses of these agents and provide material for further study.

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