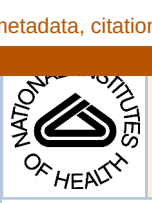

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Enantioselective Total Synthesis of Brevetoxin A: A Unified Strategy for the B, E, G, and J Subunits

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Abstract

Brevetoxin A is a decacyclic ladder toxin that possesses five-,six-, seven-, eight-, and nine-membered oxacycles, as well as 22 tetrahedral stereocenters. Herein, we describe a unified approach to the B, E, G, and J rings predicated upon a ring-closing metathesis strategy from the corresponding dienes. The enolate technologies developed in our laboratory allowed access to the precursor acyclic dienes for the B, E, and G medium ring ethers. The strategies developed for the syntheses of these four monocycles ultimately provided multigram quantities of each of the rings, supporting our efforts toward the convergent completion of brevetoxin A.

Keywords

asymmetric synthesis; glycolate alkylation; ring-closing metathesis; total synthesis; chiral auxiliary

Introduction

The marine ecosystem is a source of a multitude of structurally and biologically fascinating molecular metabolites, of which the ladder ether toxins are some of the most complex and intriguing small molecules ever discovered. The exquisite structures of marine polycyclic ether natural products, which characteristically contain a linear series of *trans*-fused ether rings of varying sizes from five to nine members with assorted methyl and hydroxyl substituents appended, have captured the imagination of synthetic chemists for over two decades. The development of novel technologies and strategies for the preparation of ladder toxin natural products has driven the total syntheses of a number of these targets.[1] As a representative member of this class, the structure of brevetoxin A (1), which was first elucidated in 1986 by Shimizu and co-workers[2a,b] through X-ray analysis and independently by Nakanishi through spectroscopic studies,[2c] features ten rings (including five-, six-, seven-, eight, and nine-membered oxacycles) fused in a linear array containing 22 tetrahedral stereocenters. Brevetoxin A is a highly toxic metabolite of *Karenia brevis*, which is known to cause the infamous red tide phenomenon responsible for massive fish kills as well as neurotoxic shellfish poisoning and bronchial irritation in humans.[3] The bioactivity of brevetoxin A is attributed to strong binding to the α subunit of the voltage-sensitive sodium ion channels, effecting an

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increase in the mean channel open time and inhibiting channel inactivation.[3a] The landmark total synthesis reported in 1998 by Nicolaou[4] stands as the only completed synthesis of this captivating target.

A fundamental goal in our vision for the total synthesis of brevetoxin A (**1**) was the incorporation of maximum convergency, particularly in three major disconnections. The first disconnection directed the simplification of the natural product into two tetracyclic halves of similar complexity (**2** and **3**), which would be united in a stereoselective Horner–Wittig reaction precedented by the previous synthesis by Nicolaou (Scheme 1). [4,5] The Horner–Wittig coupling partners **2** and **3** would be obtained from advanced fragments **4** and **5** respectively, which would be further disconnected into two subunits each. Specfically, the the BCDE fragment **4**[6a] would be prepared from the B and E ring subunits **6** and **7** through a novel convergent [X + 2 + X] strategy,[1c] and the GHIJ subunit **5**[6b] would be prepared in an analogous way from the G and J ring subunits **8** and **9**. The adjoining manuscript details the convergent [X + 2 + X] strategy, as well as the versatile endgame approach which ultimately led to the completed total synthesis of brevetoxin A.[7] Described herein is the development of scalable routes to the four ring subunits **6**-**9**, which were prepared via ring-closing metathesis [8] from acyclic diene precursors with stereodefined α-carbons in the ether linkage. In the case of the B, E and G rings, the stereogenicity of the α-carbons would be established through the implementation of enolate technology developed in our laboratory.

Results and Discussion

Synthesis of the B Ring

Efforts toward the total synthesis of brevetoxin A (1) commenced with the initial goal of preparing three of the four medium ring ethers present in the natural product, namely the B, E, and G rings. At the outset, the B ring **10** was targeted for assembly via a glycolate alkylation strategy to set the stereogenic centers of the ether linkage,[9] followed by ring-closing metathesis and hydrogenation to create the oxocane (Figure 1).[10]

A Sharpless asymmetric epoxidation[11] of 1,4-pentadien-3-ol (**12**) conveniently provided an epoxide **13** as a chiral starting material, and the secondary alcohol of the epoxide was protected as a benzyl ether to give the known epoxy ether **14** in 91% yield (Scheme 2). The epoxide **14** was opened at its terminus with cyanide ion, and the resultant nitrile was transformed to the diol **15** by hydrolysis of the nitrile and reduction of the resulting acid. The primary alcohol was selectively protected as its TIPS ether and the secondary alcohol was alkylated with sodium bromoacetate to produce a glycolic acid, which was converted to its mixed anhydride. The mixed anhydride of the glycolic acid was utilized to acylate (*R*)-lithio-4-isopropyl-2-oxazolidinone, providing glycolyl oxazolidinone **11** and staging an alkylation to stereoselectively install the C9 substituent.[9] In the event, alkylation of the sodium enolate of glycolate **12** with iodide **16** afforded an 80% yield of diene **17** as a single detectable diastereomer by ^{1}H NMR. Reductive removal of the auxiliary, oxidation[12] of the resultant alcohol to the aldehyde, and Brown asymmetric allylation[13] of the aldehyde provided stereodefined triene **18** in 90% yield for the three step sequence. Protection of the secondary alcohol as an acetate ester and oxidative removal of the *p*-methoxybenzyl ether preceded a Sharpless asymmetric epoxidation[b] to provide diene **19** in high yield. Ring-closing metathesis was attempted using diene **19** in the presence of the Grubbs second generation catalyst [$Cl_2(Cy_3P)$(sIMes)Ru=CHPh],[8a,b] but the desired oxocene was not observed.[14] Aware of precedent involving the facilitation of medium ring synthesis via ring-closing metathesis using cyclic constraints,[15] we chose to install a tetrahydrofuran as a temporary cyclic constraint. Base-induced cleavage of the acetate of diene **19** led to spontaneous cyclization to form a tetrahydrofuran, and the resultant 1,2-diol was oxidatively cleaved to provide an aldehyde that was reduced to afford alcohol **20**.[16] Gratifyingly, treatment of diene **20** with the Grubbs

second generation catalyst in refluxing dichloromethane for three days provided the targeted oxocene **21** in 70% yield, along with 14% of the recovered diene **20**.[17]

With this encouraging result, we set out to examine the stereoselective introduction of the C8 methyl stereocenter. Oxazolidinone **17** was converted in four straight-forward steps to methyl ketone **22** (Scheme 3). Exposure of ketone **22** to a Brown asymmetric methallylation delivered the tertiary alcohol **23** in excellent yield with a 10:1 diastereoselectivity. Cleavage of the PMB ether then produced the required allylic alcohol **24**. The allylic alcohol **24** was processed under standard Sharpless conditions leading to in situ formation of the desired tetrahydrofuran ring. Oxidative cleavage of the product diol and subsequent reduction of the intermediate aldehyde gave the alcohol **25**. Unfortunately, unlike diene **20**, ring-closing metathesis could not be induced using diene **25** and a variety of similar analogs to produce the oxocene **26**. This disappointing turn of events led to a reevaluation of the strategy for the B ring synthesis and led to the investigation of alternative routes.

In our revised approach to the B ring, we hoped to incorporate the C8 methyl group after the formation of the oxocene (Figure 2). To accommodate this approach we anticipated that a temporary, removable tether would be required to facilitate the ring-closing metathesis. Rather than use a glycolate alkylation and Brown allylation to establish the C8 and C9 stereocenters in separate steps, we hoped to employ a glycolate aldol reaction to introduce both centers stereoselectively in a single transformation.[18] This would also allow the incorporation of a 1,3-diol that could be used to introduce the required temporary tether.

The chlorotitanium enolate of previously prepared glycolate **11** was treated with 3-methyl-3-butenal to afford the desired *syn* product **28** in approximately 70% yield (Scheme 4). Reduction of the chiral auxiliary and formation of the cyclohexylidene acetal provided diene **29**. With the cyclic constraint in place, ring-closing metathesis provided the oxocene **30** in 83% yield.[8a,b] Replacement of the benzyl ether with a *t*-butyldimethylsilyl ether that would be compatible with the reduction of the olefin was accomplished in two straightforward operations. Stereoselective hydrogenation of the C5–C6 alkene was needed to establish the C6 methyl-bearing stereocenter, but unfortunately the trisubstituted olefin of oxocene **31** was unreactive under a variety of standard hydrogenation conditions.[19] Removal of the cyclohexylidene acetal provided diol **32**, which was also unreactive toward reductive conditions, including attempted hydrogenation using the homogeneous Crabtree's catalyst.[20] Postulating that the steric encumbrance of the silyl protecting groups was deterring the reduction of the olefin, the silyl ethers were replaced with a cyclohexylidene acetal to deliver oxocene **33** in three routine steps. Indeed, hydrogenation of oxocene **33** was possible in the presence of Pearlman's catalyst, at elevated pressure, providing the targeted oxocane **34** in 90% yield; however, the cyclohexylidene acetal was cleaved during this process, and the oxocane was isolated as a 1:1 diastereomeric mixture of epimers at C6. It was clear that a new strategy needed to be implemented for the B ring allowing for stereoselective establishment of C6 and the tertiary alcohol at C8 present in brevetoxin A (**1**).

At this stage, we adopted a third generation approach to the B ring that utilized the *anti*-glycolate aldol methodology that we had recently developed.[21] The chlorotitanium enolate of allyloxy glycolylimide **35** was treated with 3-methyl-3-butenal to provide the alcohol **36** in 64% yield and 9:1 dr, favoring the desired *anti* adduct (Scheme 5).[6c] Removal of the chiral auxiliary and sequential protection of the resultant diol provided diene **37**. The allyl protecting group was selectively removed in the presence of the 1,1-disubstituted olefin,[22] and the resultant alcohol was transformed to the glycolate **38** via the glycolic acid. Alkylation of the sodium enolate of glycolate **38** with benzyl iodomethyl ether (generated in situ from $(BnO)_2CH_2$ and TMSI) proceeded in 93% yield, and reduction of the oxazolidinone moiety delivered alcohol **39**.[9] Oxidation[12] of the primary alcohol followed by addition of

vinylmagnesium bromide gave dienes **40** and **41** in a 3:1 diastereomeric ratio. Ring-closing metathesis using the Grubbs second generation catalyst was possible in the absence of a cyclic constraint to produce oxocenes **42** and **43**,[8a,b] which were separable at this stage. The minor component **42** of this mixture was transformed to the desired oxocene **43** via a Mitsunobu inversion.[23] Crabtree's catalyst proved remarkably effective for the reduction of the trisubstituted olefin of oxocene **43**,[20] providing the oxocane **44** and its C6 epimer in a 3:1 ratio at 25 °C, 8:1 at −20 °C and a >19:1 ratio (93% yield) at −50 °C. The allylic hydroxyl effectively directs the hydrogenation of the C6–C7 alkene to the opposite face of the ring. Similar effects are observed in the directed Simmons–Smith cyclopropanation and directed epoxidation of cyclooctenol.[24,25] Next, oxidation[26] of the C8 hydroxyl and subsequent treatment of the ensuing ketone with methylmagnesium chloride provided the tertiary alcohol **45** in excellent yield and high diastereoselectivity (>19:1 dr).[27] The benzyl ether of oxocane **45** was reductively removed[28] in the presence of the more electron rich PMB ether to afford the primary alcohol, which was oxidized[26] to deliver the targeted B ring aldehyde **46**.

Much had been learned regarding the required functionality to facilitate the ring-closing metathesis and hydrogenation of the B ring during the course of our studies. However, while a viable approach to B ring aldehyde **46** was in place, a final improvement to this route was needed. Installation of C1 at an early stage of the synthesis was desired to obviate the need for a late-stage homologation at C2 of the B ring.

For the homologated B ring **47**, we envisioned the installation of C1 through a Claisen addition, and planned to then intercept the previous strategy prior to the glycolate alkylation (Figure 3).[6a] This would take advantage of the directed reduction of the C6–C7 double bond as before, and utilize the basic strategy for the construction of the oxocene and incorporation of the C8 methyl group from the third generation route.

The sodium enolate of *p*-methoxybenzyloxy glycolylimide **49** was alkylated with methallyl iodide[9] and the resultant product **50** underwent an unprecedented Claisen condensation with the lithium enolate of ethyl acetate to afford the β-keto ester **51** directly (Scheme 6).[29] Exhaustive reduction with lithium aluminum hydride followed by selective protection of the primary alcohol as its TIPS ether, and finally oxidation[12] of the secondary alcohol provided ketone **52**.[30] Chelation-controlled reduction of ketone **52** mediated by $Zn(BH_4)_2$ delivered the targeted one-carbon homologated secondary alcohol **53**.[31] From this point, a similar sequence of transformations to those previously developed, with optimizations for large scale throughput, were employed. Glycolate **48** was prepared under standard conditions from alcohol **53**, and the alkylation of imide **48** with benzyl iodomethyl ether proceeded efficiently.[9] Reduction of the alkylation product afforded alcohol **54**, which was oxidized to the corresponding aldehyde.[12] The aldehyde was exposed to vinylmagnesium bromide whereupon ring-closing metathesis again gave a mixture of oxocenes **55** and **56** (3:1 dr) in just 2 h. Minor oxocene **56** was converted to the desired oxocene **55** via Swern oxidation and Luche reduction.[32] Hydrogenation of the allylic alcohol 55 with Crabtree's catalyst at −50 °C provided the oxocane in 94% yield (>19:1 dr).[20] Oxidation[12] of the C8 alcohol and addition of methylmagnesium chloride to the resultant ketone gave alcohol **57** as a single observable diastereomer. Removal of the benzyl ether using Raney nickel,[33] and oxidation[26] of the primary alcohol delivered the desired homologated B-ring aldehyde **6** in 81% yield over two steps. As a testament to the scalability of this route, >3 g of aldehyde **6** were prepared via this sequence in a single execution of the synthetic sequence.

Synthesis of the E Ring

The initial synthesis of the E ring fragment **58** was predicated upon a glycolate alkylation[9] and ring-closing metathesis strategy to prepare the functionalized oxonene (Figure 4).[10] An

asymmetric glycolate alkylation and a thiazolidinethione-mediated aldol addition were envisioned to establish three of the required stereocenters of the acyclic diene precursor.

Alkylation of the sodium enolate of glycolate **60** with allyl iodide, reduction to the primary alcohol, and oxidation under Swern conditions afforded aldehyde **61** (Scheme 7).[12] Addition of aldehyde **61** to the chlorotitanium enolate of oxazolidinethione propionate **62** provided the aldol adduct **59** as a single detectable diastereomer by ^{1}H NMR.[34] Subsequent reductive removal of the chiral auxiliary provided a 1,3-diol, which underwent selective protection of the primary alcohol as its TIPS ether to give secondary alcohol **63.** Alkylation of the secondary alcohol with sodium bromoacetate provided the corresponding glycolic acid derivative, which was converted to its mixed pivaloyl anhydride and exposed to (*R*)-5-lithio-4-isopropyl-oxazolidin-2-one to produce the required glycolyl oxazolidinone **64**. The C22 stereocenter was established by alkylation of the glycolyl oxazolidinone with prenyl iodide under standard conditions[9] to provide imide **65**. Reduction of the oxazolidinone gave a primary alcohol which was oxidized[12] to the aldehyde **66**. Brown allylation[13] of aldehyde **66** gave a triene in 89% yield as a single detectable diastereomer, and acetylation of the secondary alcohol afforded acetate **67**. The trisubstituted olefin **67** was selectively epoxidized followed by exposure of the resultant diene to the Grubbs catalyst [$Cl_2(Cy_3P)_2Ru$=CHPh] to effect ring-closing metathesis, which generated the oxonene **68** in 99% yield.[7] The epoxide was exposed to aqueous perchloric acid resulting in hydrolytic opening of the epoxde accompanied by partial cleavage of the primary silyl ether,[35] requiring conversion back to the TIPS ether. Oxidative cleavage of the 1,2-diol provided aldehyde **69**. Simultaneous reduction of the aldehyde and the acetate with $LiAlH_4$, protection of the resultant diol as the dibenzyl ether, and cleavage of the silyl ether realized the desired E ring **70** in 96% yield.

While a viable strategy for synthesis of the E ring had been developed, we hoped to improve the protecting group strategy and eliminate the need for the somewhat cumbersome oxidative cleavage of the prenyl substituent as a latent oxygen functionality. As previously demonstrated in the B ring synthesis (vide supra, Scheme 5), the *anti*-glycolate aldol reaction developed in our laboratory is a useful means for generating *anti*-1,2-diol units, which are commonly found in ladder ether toxins.[21,6c] To that end, previously described alcohol **63** was transformed to the oxazolidinethione glycolate **71** (Scheme 8). The chlorotitanium enolate of glycolate **71** underwent an aldol reaction with 3-butenal in 50% yield (89% brsm) and 5:1 dr to provide the aldol adduct **72**.[21] Reduction of the oxazolidinethione moiety gave alcohol **73**. At this stage, the benzyl ether was cleaved with sodium naphthalenide, and the resultant triol was protected as the tris-*p*-methoxybenzyl ether. Tetrabutylammonium fluoride-mediated removal of the primary silyl group gave alcohol **74**. Although this sequence had led to the diene **74** in a shorter sequence of transformations, the subunit was lacking C24, which had been present in our previous synthesis. Hoping to achieve a more practical synthesis of a homologated E ring, we once again revised our approach to this medium ring ether.

In the final plan for the E ring, as with the B ring (vide supra, Scheme 6), we hoped to incorporate all of the carbons of the E ring from the outset, avoiding the need for a late-stage homologation. Our third generation approach to the E ring[6a] commenced with an alkylation of the sodium enolate of glycolate **49**[9] with allyl iodide, followed by reductive removal of the oxazolidinone and oxidation of the resultant primary alcohol to deliver aldehyde **75** (Scheme 9).[12] A *syn*-aldol addition between the chlorotitanium enolate of (*R*)-*N*-propionyl-4-benzylthiazolidin-2-thione (**62**) and aldehyde **75** proceeded efficiently, generating the aldol adduct **76**. Exposure of the aldol adduct **76** to sodium borohydride gave a diol, which upon selective protection of the primary alcohol delivered the secondary alcohol **77.** Formation of the glycolic acid and subsequent conversion to the corresponding imide **78** set the stage for alkylation with bromoacetonitrile to diastereoselectively establish the C22 stereocenter.[9] Removal of the auxiliary under reductive conditions then provided alcohol **79** in 75% yield for

two steps. Oxidation[12] of alcohol **79** to the aldehyde preceded a substrate-controlled stereoselective allylation to afford diene **80** in 80% yield (7:1 dr).[36,37] Treatment of diene **80** with hydrochloric acid at 65 °C in methanol served to hydrolyze the nitrile to the carboxylic acid, which formed the γ-lactone in situ, and also cleaved the silyl and *p*-methoxybenzyl ethers in a single operation in 85% yield. The resultant diol was protected as the bis-TBS ether to give lactone **81**. The lactone **81** was reduced with lithium aluminum hydride, whereupon the resulting diol was transformed to the dibenzyl ether. Selective deprotection of the primary silyl ether provided the targeted diene **7**, with C24 in place.[38]

Synthesis of the G Ring

The first generation synthesis of the G ring was inspired by the initial success of the asymmetric glycolate alkylation/aldol/ring-closing metathesis approach to the E ring. In the case of the G ring (**82**, Figure 5), either an asymmetric aldol or glycolate alkylation could potentially be used to set the C26 stereocenter. Additionally, a latent C–O bond at C34 would be masked through the regioselective epoxidation of a triene intermediate, followed by ring-closing metathesis. Thus, a key intermediate would be a complex glycolyl oxazolidinone **83**, with the stereocenter at C32 envisioned to arise from a Sharpless kinetic resolution.

To investigate this approach, the glycolyl oxazolidinone **83** (Scheme 10) was pursued, beginning with the addition of allyl Grignard to methacrolein (**84**). Resolution of the resulting racemic mixture of secondary alcohols **85** through a Sharpless kinetic resolution provided epoxy alcohol **86** (98% ee at 43% conversion),[11b] which was protected as the benzyl ether **87**. Copper-assisted Grignard addition to form the secondary alcohol **88**, followed by *O*-alkylation with sodium bromoacetate, produced glycolic acid **89**. The glycolic acid was first coupled to (*S*)-4-benzyl-2-oxazolidinone to examine the aldol addition of the chlorotitanium enolate of imide **84a** with acrolein, which would install both the C26 stereocenter and the olefin required for subsequent ring-closing metathesis. Despite efforts toward optimization, only a 25% yield of the desired aldol adduct **90** could be obtained.

On the other hand, coupling of glycolic acid **89** with (*S*)-4-isopropyl-2-oxazolidinone allowed for the efficient alkylation of imide **84b** with $BnOCH_2I$ to provide alkylation product **91**.[9] Reductive removal of the auxiliary with $NaBH_4$ generated the primary alcohol, which underwent oxidation under Dess–Martin conditions to afford aldehyde **92**. Addition of vinylmagnesium bromide to the aldehyde gave an 80% yield of the triene as mixture of diastereomers, and selective epoxidation of the trisubstituted olefin with *m*-chloroperbenzoic acid furnished epoxy diene **93**. Treatment of diene **93** with Grubbs' second generation catalyst then led to an 85% yield of oxocene **83**.[8a,b] Attempts to perform the ring-closing metathesis with Grubbs' first generation catalyst led to a lower yield (50%).

The first generation synthesis of the G ring provided a preliminary route to an important intermediate in the brevetoxin synthesis, and further demonstrated the utility of the glycolate alkylation/ring-closing metathesis approach. However, the multigram quantities of G ring needed for further development of the total synthesis motivated the investigation of a second generation route optimized for scale-up. In particular, a chelation-controlled Grignard addition leading to *N*-glycolyl oxazolidinone **95** was envisioned as being a more efficient alternative to the Sharpless kinetic resolution for installation of the C32 stereocenter (Figure 6).

The second generation route to the G ring commenced with an asymmetric alkylation of imide *ent*-**48** (Scheme 11) with allyl iodide.[9] In an earlier report,[6b] the alkylation product **96** was treated with $LiBH_4$ for reductive removal of the auxiliary, and the resultant alcohol was oxidized under Swern conditions to the corresponding aldehyde *ent*-**75**. Addition of lithiated *t*BuOAc to aldehyde *ent*-**75** provided alcohols **97** as an inconsequential mixture of diastereomers, and exposure to $LiAlH_4$ led to diols **98**. While this five step sequence was high

yielding overall, our observation from the B ring synthesis that *N*-glycolyl oxazolidinones readily participate in Claisen addition reactions with lithiated esters provided a means to streamline the preparation of diols **98** (vide supra, Scheme 6).[6a] The addition of the lithium enolate of *t*BuOAc to alkylation product **96** proceeded smoothly to produce β-ketoester **99** in 85% yield. The reduction of β-ketoester **99** with $LiAlH_4$ was complicated somewhat by the presence of enol tautomers, which led to enolate intermediates resistant to reduction. Nonetheless, a 67% yield of diols **98** based on recovered starting material was reproducible.

Upon selective protection of the primary alcohol of diols **98** as the TIPS ether and oxidation to the ketone under Swern conditions (Scheme 12), the chelation-controlled addition of methylmagnesium chloride to the ketone **100** afforded tertiary alcohol **101** as a single isomer in excellent yield. After *O*-alkylation with sodium bromoacetate and coupling of the resulting glycolic acid with (*S*)-4-isopropyl-2-oxazolidinone, alkylation of the *N*-acyloxazolidinone **102** with $BnOCH_2I$ once again performed well, even on larger scale: over 100 g of alkylation product **103** have been prepared.

Similar to before, reductive removal of the chiral auxiliary from alkylation product **103**, oxidation of the resulting alcohol under Swern conditions, and addition of vinylmagnesium bromide to the aldehyde **104** provided the allylic alcohols as a mixture of diastereomers. Subsequent exposure of the diene to Grubbs' second generation catalyst furnished the oxocene **94** in high yield at up to 10 mM concentration.[8a,b]

To properly functionalize the G ring, we had originally reported[6b,d] the use of Crabtree's catalyst[20] under H_2 atmosphere for the hydrogenation of the endocyclic olefin. However, upon scale-up, these conditions led to a somewhat disappointing 70% yield of the desired oxocanes **105**, with loss of the PMB protecting group and epimerization at C26 via alkene isomerization accounting for undesirable portions of the mass balance. Alternatively, hydrogenation with *o*-$NO_2C_6H_4SO_2NHNH_2$[39] and Et_3N was found to cleanly afford the oxocanes **105** in 96% yield without any significant side reactions. For convergence of the C27 diastereomers, oxidation to the ketone under Swern conditions followed by treatment with *i*Bu_2AlH provided the alcohol **8** as a single isomer. This completed the second generation synthesis of G ring intermediate **8** in 16 steps, with an overall yield of 12%.

Synthesis of the J Ring

In formulating a synthetic plan for the J ring **106**, it was reasoned that a ring-closing metathesis approach would be particularly germane since the dihydropyran produced would be the required substrate for dihydroxylation to install the necessary *syn* diol (Figure 7). In our initial approach to the diene substrate **107** for ring-closing metathesis, an asymmetric acetate aldol and a glycolate alkylation were envisioned as key stereo-determining and C–C bond-forming steps.

The original route to the J ring drew upon interest in our laboratory on aldol reactions involving the titanium enolates of *N*-acetylthiazolidinethione auxiliaries. Though we have recently shown that the mesityl-substituted auxiliary of this type undergoes aldol reaction with a variety of aldehydes in high yield and stereoselectivity,[40] at the outset of the J ring synthesis, the isobutyl-substituted *N*-acetylthiazolidinethione auxiliary was known to provide reasonable selectivity levels via the Urpí protocol, particularly with α,β-unsaturated aldehydes.[10b,41] Specifically, the aldol reaction of *N*-acetylthiazolidinethione **108** (Scheme 13) with *trans*-cinnamaldehyde led to a 76% yield of the major aldol adduct **109a** (90:10 dr). Because the olefin installed in the aldol reaction would undergo a ring-closing metathesis, the phenyl substituent on the olefin was inconsequential. Reductive removal of the auxiliary with $NaBH_4$ and selective protection of the resultant primary alcohol **110a** produced the TIPS ether **111a**. After *O*-alkylation of the secondary alcohol with sodium bromoacetate and coupling of

the corresponding glycolic acid to (*R*)-4-isopropyl-2-oxazolidinone, the alkylation of imide **112a** was attempted.[9] Unfortunately, alkylation with allyl iodide took place in only a 28% yield, with the major side-reaction involving 2,3-Wittig rearrangement of the sodium enolate.[42]

To circumvent the low yield of the glycolate alkylation, it was hypothesized that replacement of the phenyl group on the olefin with an aliphatic chain would reduce the rate of the competing 2,3-Wittig rearrangement. To this end, *trans*-2-hexenal was used as the aldehyde in the acetate aldol reaction (**108** to **109b**, Scheme 13). In this case, a 64% yield of the aldol adduct was obtained, with a slightly diminished diastereoselectivity (7:1). After the same four step sequence as before, the glycolate alkylation was attempted once again. Pleasingly, a 90% yield of the alkylation product **113b** was obtained.

Conversion of alkylation product **113b** to J ring **107** was then accomplished in four additional steps. Upon reductive removal of the chiral auxiliary, the resulting primary alcohol was protected as the benzyl ether **114.** As expected, ring-closing metathesis with Grubbs' catalyst afforded the dihydropyran in excellent yield,[8] and Upjohn dihydroxylation[43] occurred in 78% overall yield with a diastereoselectivity of 3:l to produce J ring **106**. The facial bias is presumably imparted by the bulky TIPS group. Alternatively, the Sharpless asymmetric dihydroxylation protocol[44] gave slightly improved selectivity (4:1), but in only 60% overall yield.

The first generation approach to the J ring confirmed the effectiveness of the ring-closing metathesis/dihydroxylation sequence for completing the ring core, but was limited in terms of throughput by the moderate yield and tedious separation of diastereomers associated with the acetate aldol. Furthermore, the C43 and C44 carbons would need to be added through subsequent manipulations, further lengthening the synthesis. Thus, a second generation synthesis targeting a J ring **115** possessing the C42–C44 side chain was formulated (Figure 8). It was also postulated that the acetate aldol and glycolate alkylation steps could be replaced by an epoxide-opening and a Hosomi–Sakurai reaction, respectively. This approach would involve a mixed acetal intermediate **116**, which could be rapidly prepared through transacetalization.

To begin the second generation synthesis of the J ring, known alcohol **118**[45] was prepared in two steps from (*R*)-glycidol (**117**) (Scheme 14). The smooth conversion of alcohol **118** to mixed acetal **116** was then accomplished through a transacetalization reaction under mild conditions. Ring-closing metathesis with the Grubbs catalyst proceeded in excellent yield as before, and the resulting dihydropyran was dihydroxylated stereoselectively with the $RuCl_3$/$NaIO_4$ oxidation system (8:1 dr),[46] with the bulky silyl protecting group once again providing the presumed facial bias. Protection of the diol **119** as the carbonate using 1,1′-carbonyldiimidazole (CDI) preceded the key Hosomi–Sakurai reaction,[47] which delivered pyran **121** in good yield and high diastereoselectivity (dr >10:1) via putative transition state **120.** Anticipating the need for a more robust diol protecting group, the carbonate group was removed under basic conditions, and the diol was re-protected as the acetonide **122**. Hydroboration of the terminal olefin with 9-BBN then delivered the primary alcohol **115** exclusively. In testament to the scalability of this route, over 21 g of alcohol **115** was prepared through this sequence.

Conclusion

In summary, scalable approaches to the B, E, G, and J rings of brevetoxin A have been developed, allowing the preparation of multi-gram quantities of each of these oxacycles. Ring-closing metathesis was utilized in each case for the cyclization event from the corresponding

acyclic diene. Enolate methodologies developed in our laboratory were exploited to introduce eight of the 22 stereocenters present within brevetoxin A. The routes described have proven suitable for supplying sufficient quantities of the B, E, G, and J rings to support our efforts toward a highly convergent synthesis of the decacyclic natural product, the completion of which [48] is reported in the accompanying manuscript.[7]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support of this work by the National Institute for General Medical Sciences (GM60567) is acknowledged with thanks.

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35. The hydrolysis gave 59% of the diol, and 27% of the triol (resulting from primary ether cleavage). The triol could be reprotected in 74% yield to merge the material.
36. The stereoinduction in this transformation is predictable based upon a non-chelated Felkin–Anh model. Allyltrimethylsilane was unreactive in the presence of trimethylaluminum. Allylmagnesium bromide was non-selective (1:1 dr). Brown allylation provided the product in >19:1 dr, but in only 30% yield.
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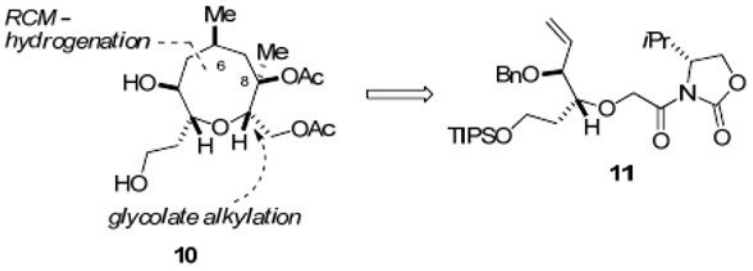


Figure 1.
Initial retrosynthetic analysis of the B ring **10**.

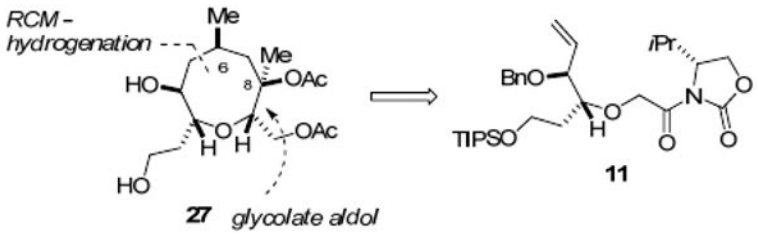


Figure 2.
Aldol-based retrosynthetic analysis of the B ring **27**.

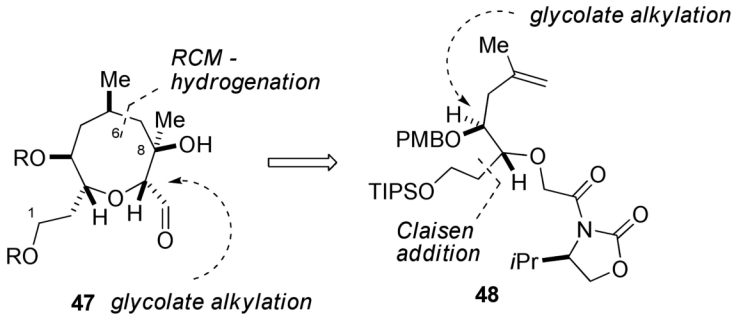


Figure 3.
Key features of the strategy for the B ring **47**.

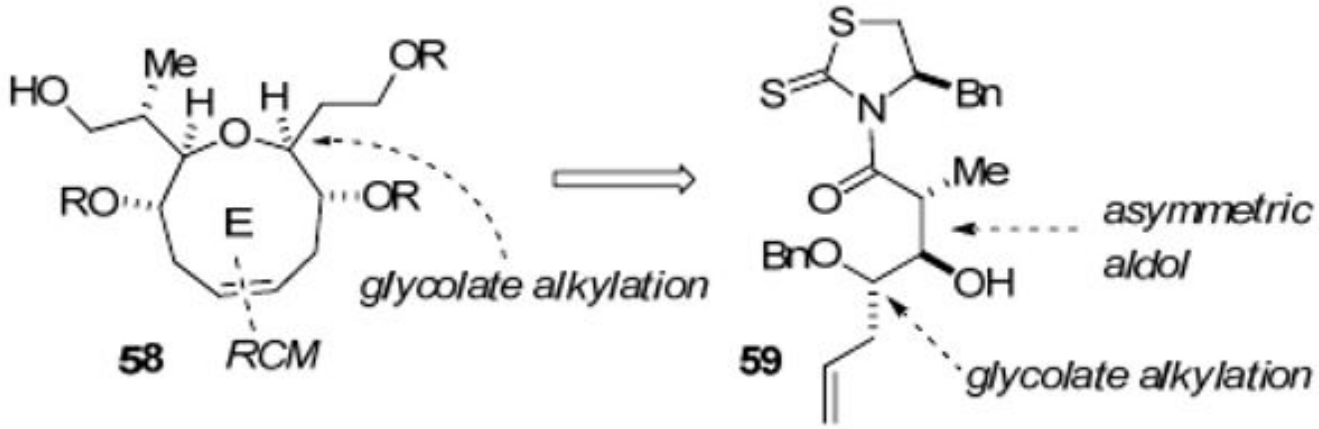


Figure 4.
Key strategic elements for the E ring synthesis.

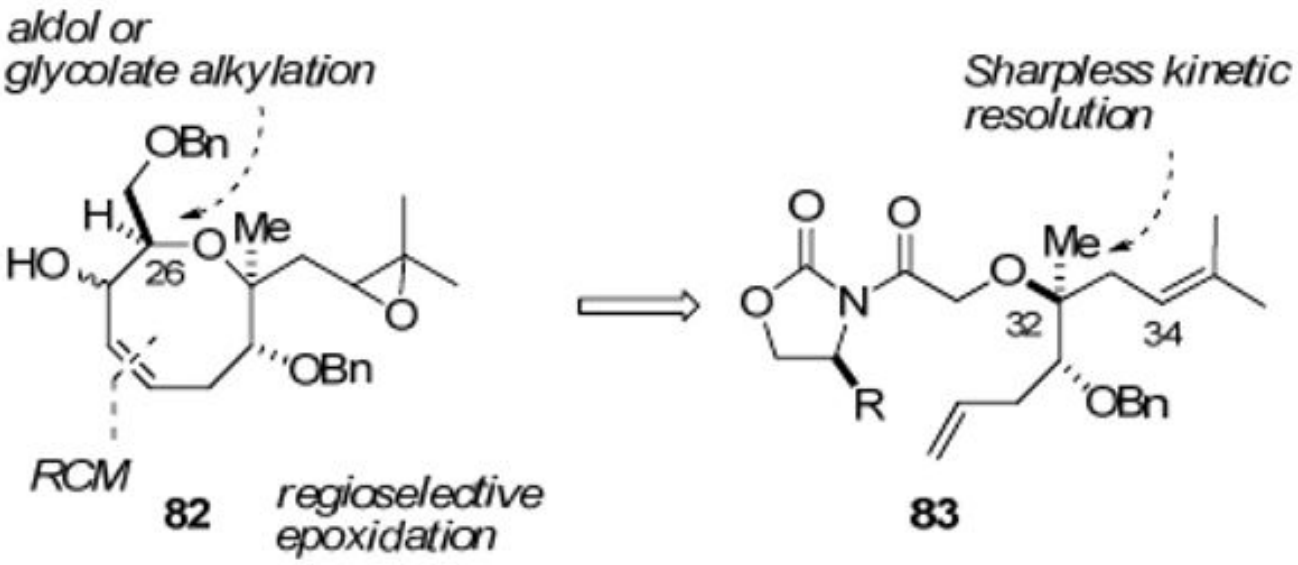


Figure 5.
Key features of the first generation synthesis of the G ring **82**.

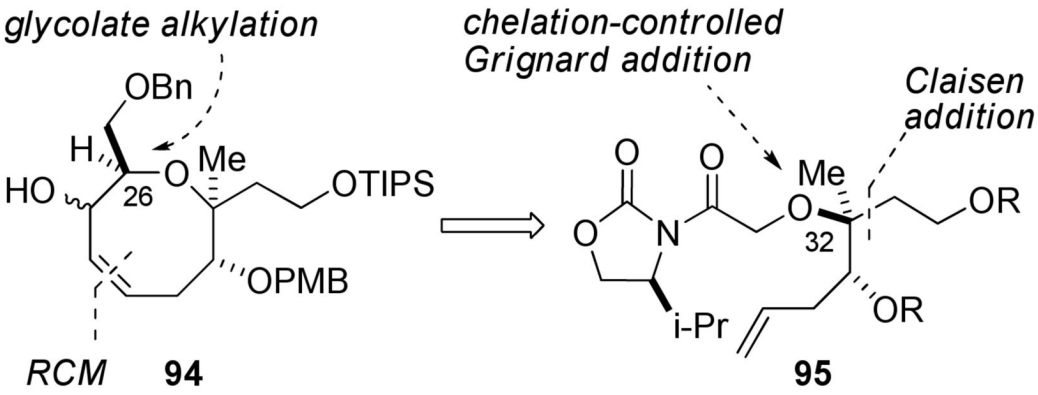


Figure 6.
Key features of the second generation synthesis of the G ring.

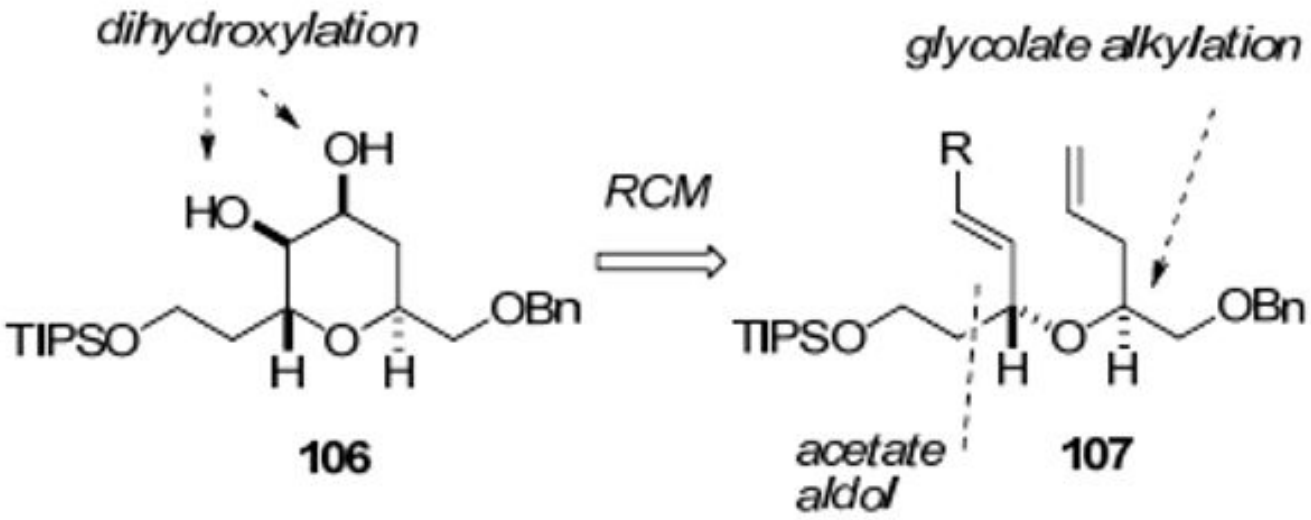


Figure 7.
Key features of the first generation synthesis of the J ring **106**.

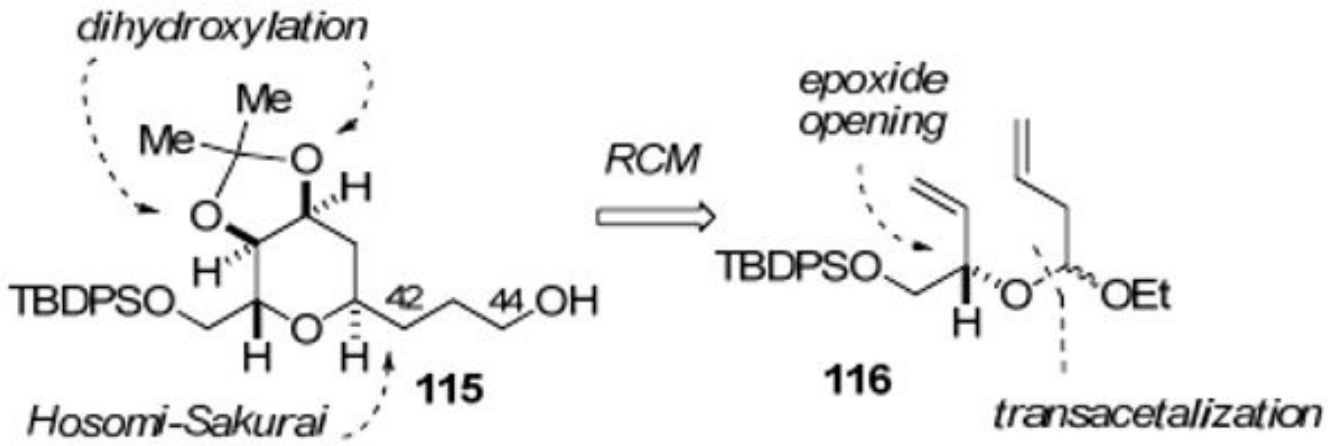
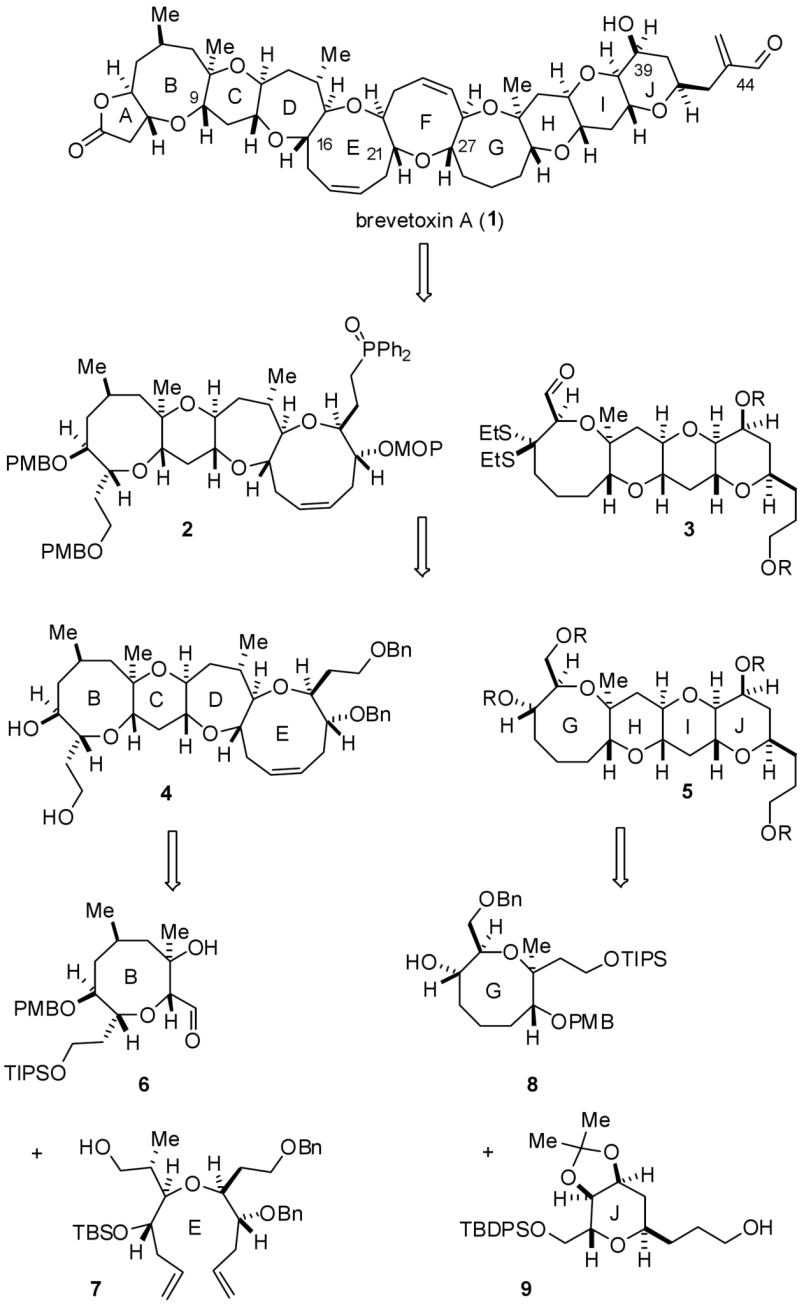
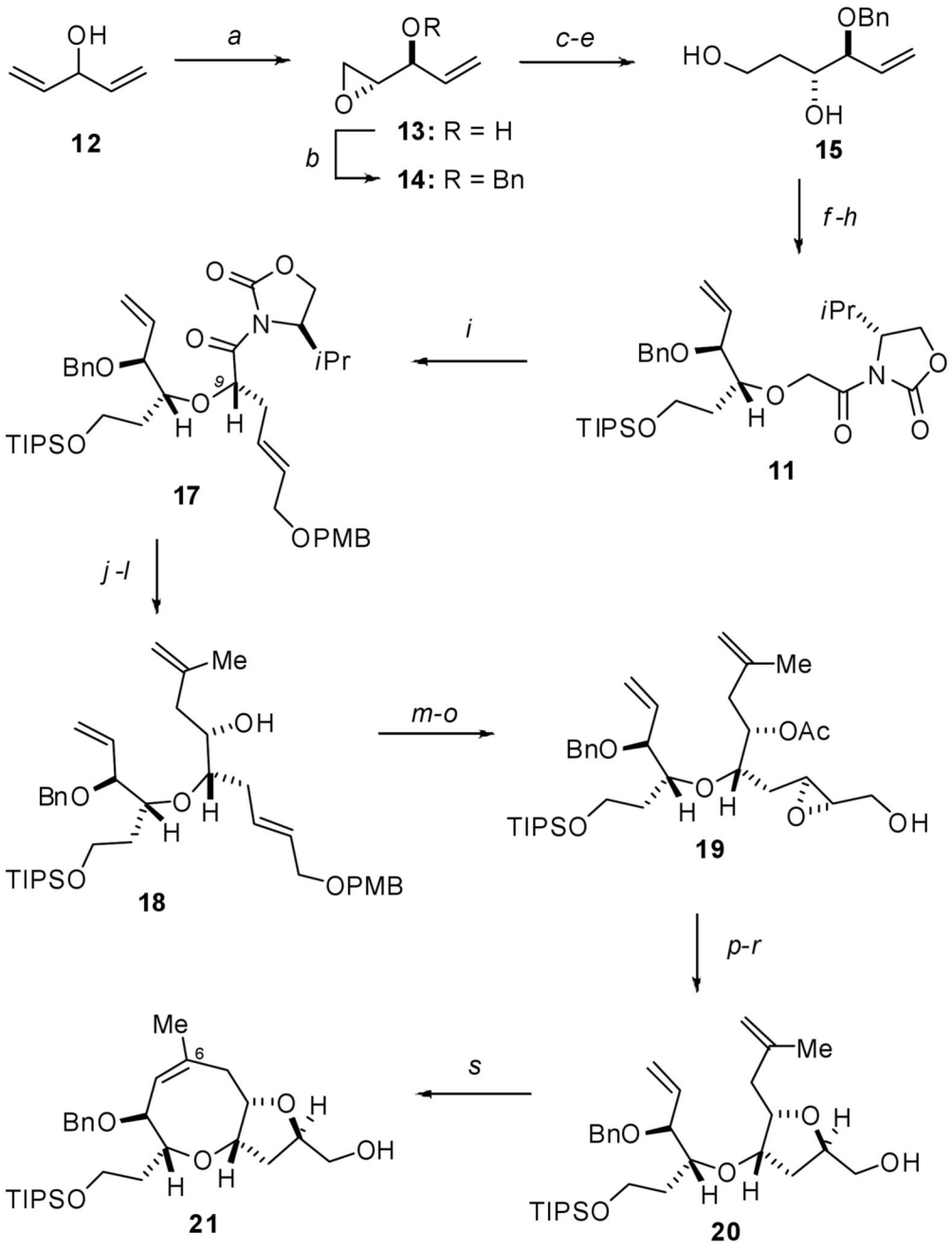


Figure 8.
Key features of the second generation synthesis of the J ring **115**.



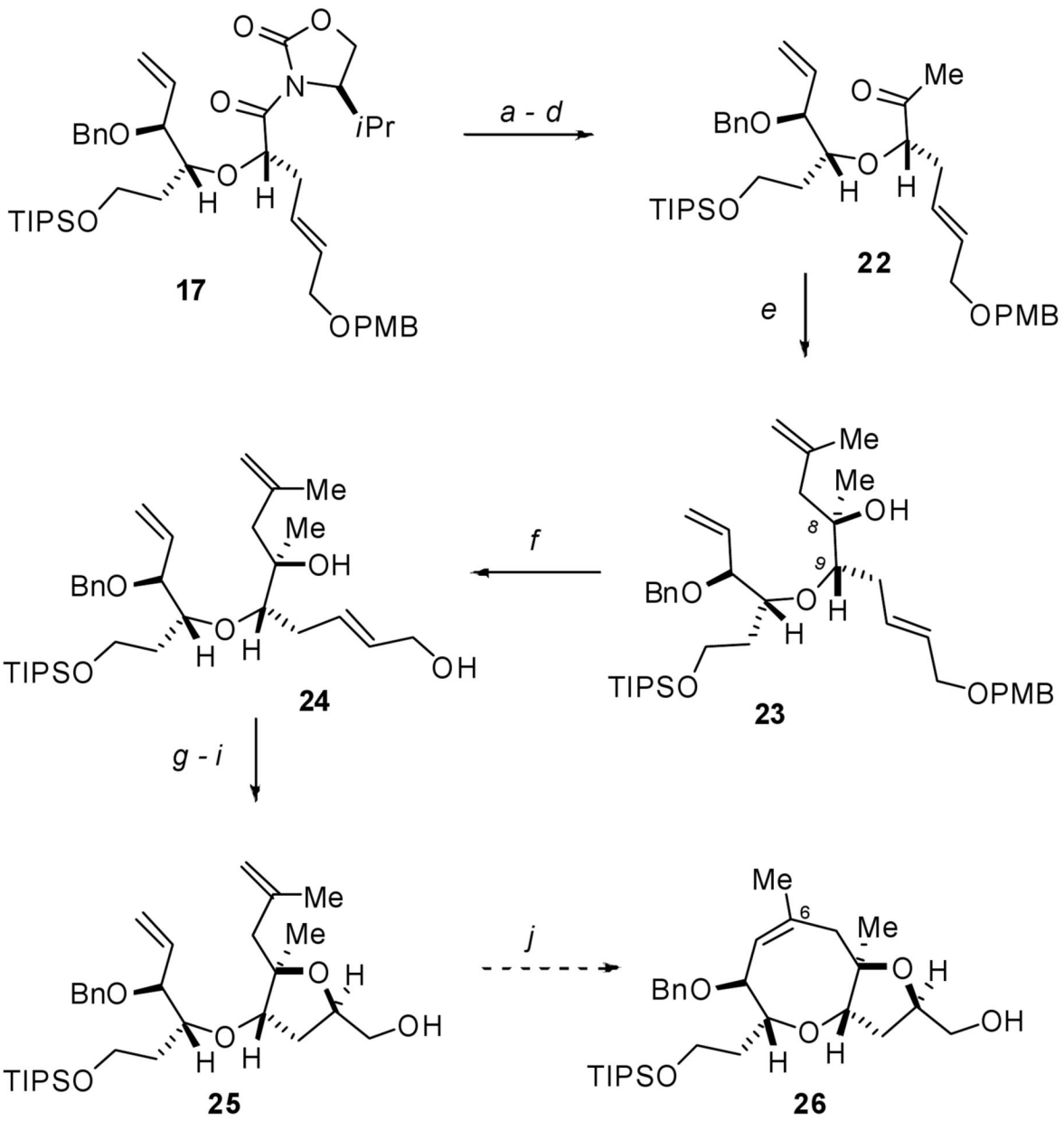
Scheme 1.
Retrosynthetic analysis



Scheme 2.

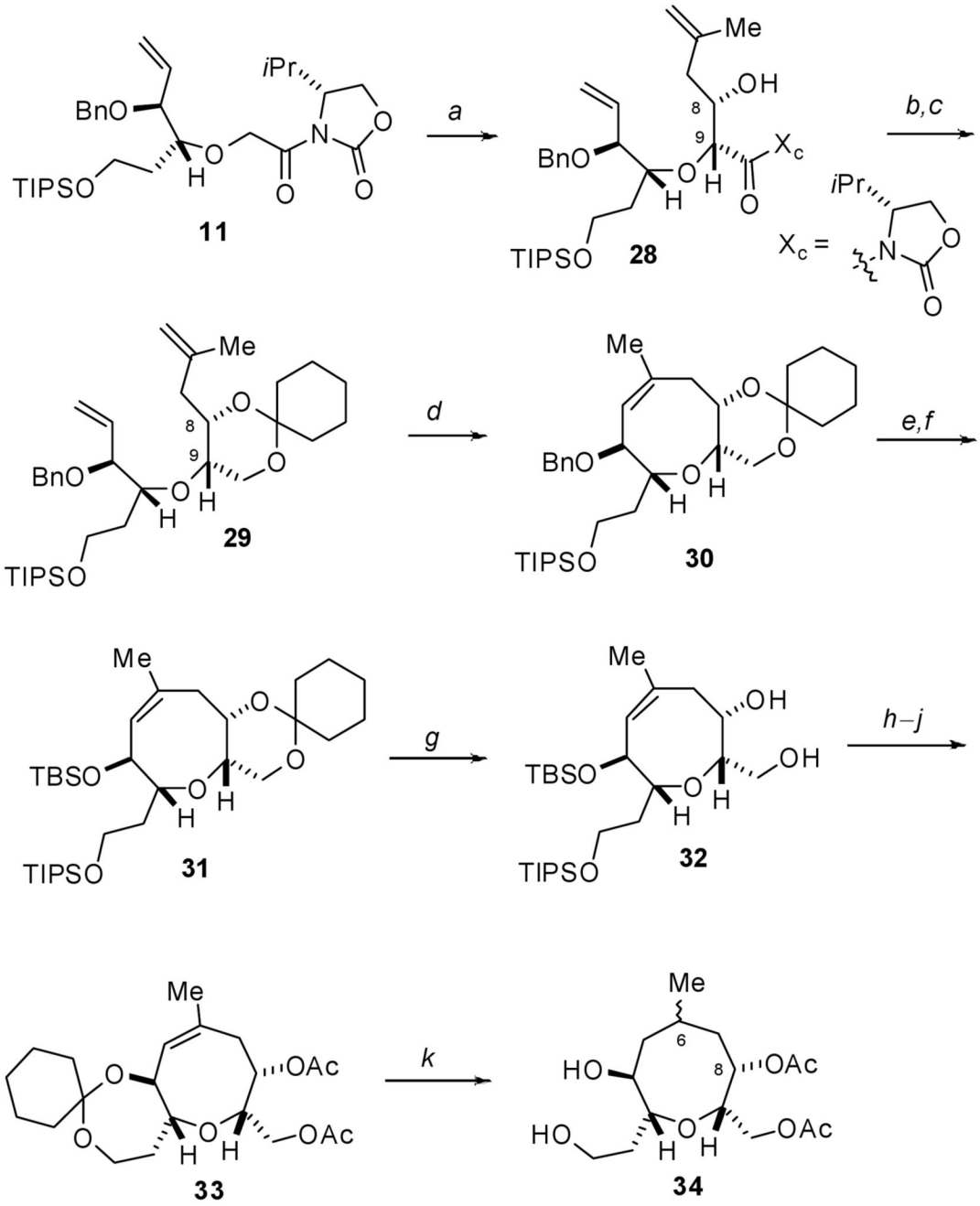
First generation B ring synthesis. Reagents and conditions: a) (+)-DIPT, Ti(O-*i*Pr)$_4$, *t*BuOOH, CH_2Cl_2, 4 Å MS, −20 °C, 63%; b) NaH, BnBr, *n*Bu$_4$NI, THF, 91%; c) KCN, $LiClO_4$, CH_3CN, 80 °C, 84%; d) NaOH, H_2O, MeOH, 65 °C; e) $LiAlH_4$, Et_2O, 35 °C, 78% for 2 steps; f) TIPSCl, imid., DMF, 89%; g) NaH, $BrCH_2CO_2H$, THF, 88%; h) PivCl, Et_3N, (*R*)-5-lithio-4-isopropyl-oxazolidin-2-one, THF, 80%; i) $NaN(SiMe_3)_2$, *E*-$ICH_2CH{=}CHCH_2OPMB$ (**16**), THF, PhMe, −78 to −45 °C, 80%; j) $LiBH_4$, MeOH, Et_2O, 0 °C, 96%; k) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; l) (4-^{d}Icr)$_2BCH_2C(Me){=}CH_2$, Et_2O, THF, −78 °C, 94% for 2 steps; m) Ac_2O, pyr., DMAP, CH_2Cl_2, 92%; n) DDQ, H_2O, CH_2Cl_2, 0 °C, 85%; o) (+)-DET, Ti(O-*i*Pr)$_4$, *t*BuOOH, CH_2Cl_2, 4 Å MS, −20 °C, 93%; p) K_2CO_3, MeOH, Et_2O, 89%; q) $NaIO_4$, THF,

H_2O; r) $NaBH_4$, EtOH, 0 °C, 92% for 2 steps; s) $Cl_2(Cy_3P)(IMes)Ru{=}CHPh$, CH_2Cl_2, 40 °C, 70%.



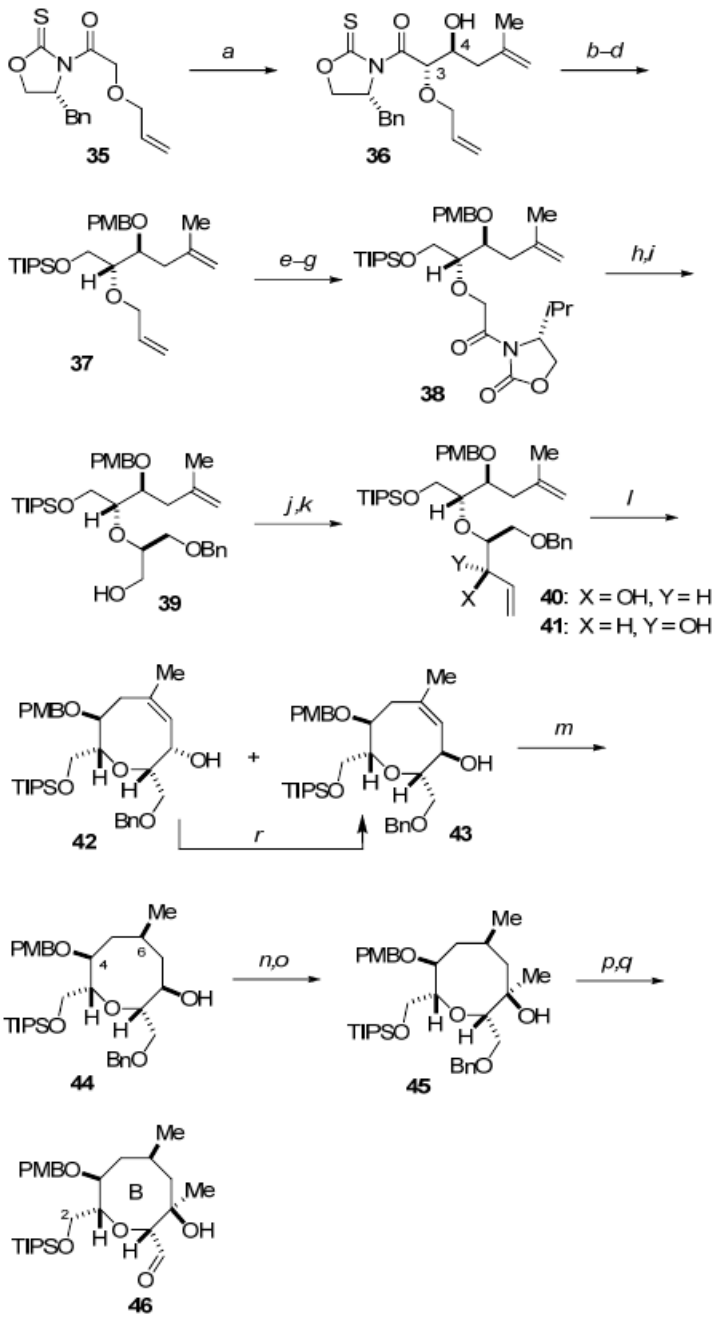
Scheme 3.

Attempted incorporation of the C8 methyl. Reagents and conditions: a) $LiBH_4$, MeOH, Et_2O, 0 °C, 96%; b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; c) MeMgI, Et_2O, 0 °C, 90%; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; e) $(4\text{-}^{d}Icr)_2BCH_2C(Me)=CH_2$, Et_2O, THF, −78 °C, 89% for 2 steps, 10:1 dr; f) DDQ, H_2O, CH_2Cl_2, 0 °C, 85%; g) (+)-DET, Ti(O-*i*Pr)$_4$, *t*BuOOH, CH_2Cl_2, 4 Å MS, −20 °C, 93%; h) $NaIO_4$, THF, H_2O; i) $NaBH_4$, EtOH, 0 °C, 92% for 2 steps; j) $Cl_2(Cy_3P)(IMes)Ru=CHPh$, CH_2Cl_2, 40 °C, *no reaction.*



Scheme 4.

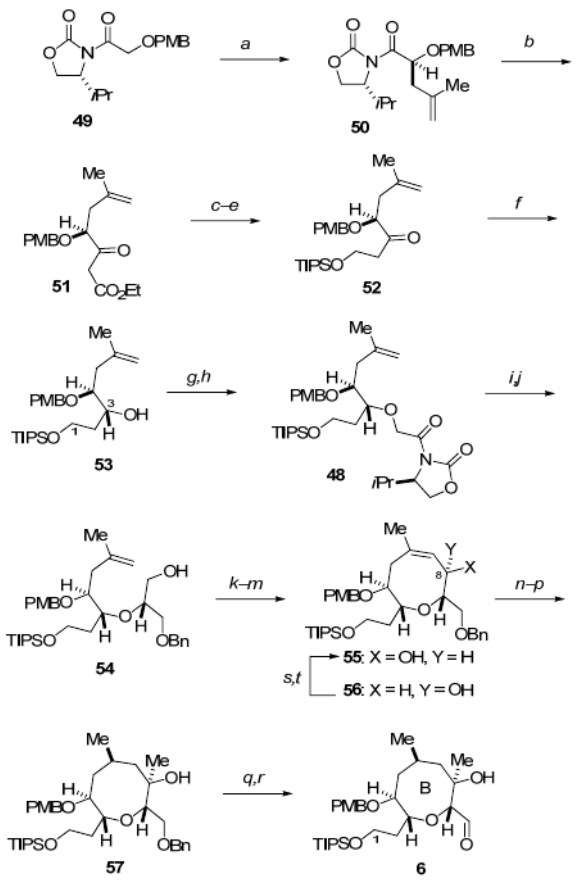
Second generation B ring synthesis. Reagents and conditions: a) $TiCl_4$, *i*Pr_2NEt, CH_2=C(Me) CH_2CHO, CH_2Cl_2, −78 °C; b) $LiBH_4$, MeOH, Et_2O, 0 °C, 58% for 2 steps; c) cyclohexanone, PPTS, $MgSO_4$, C_6H_6, 80 °C, 87%; d) $Cl_2(Cy_3P)$(IMes)Ru=CHPh, CH_2Cl_2, 40 °C, 83%; e) Na, naphthalene, THF, 0 °C, 91%; f) TBSOTf, 2,6-lut., CH_2Cl_2, 90%; g) PPTS, EtOH, 78 °C, 72%; h) Ac_2O, DMAP, CH_2Cl_2, 87%; i) *n*Bu_4NF, THF, 100%; j) cyclohexanone, PPTS, $MgSO_4$, C_6H_6, 80 °C, 94%; k) $Pd(OH)_2$/C, H_2 (45 psi), EtOH, 90%, 1:1 dr.



Scheme 5.

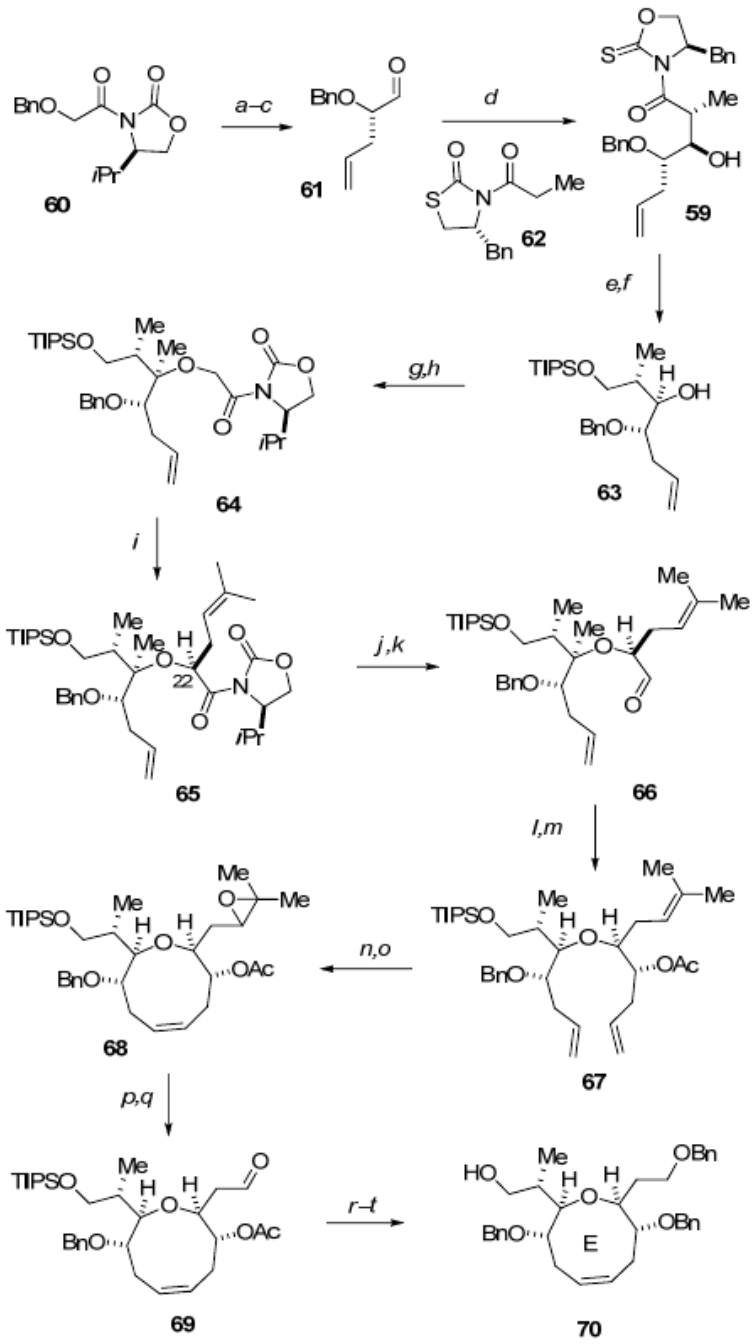
First stereocontrolled completion of the B ring **46**. Reagents and conditions: a) $TiCl_4$, (−)-sparteine, CH_2=C(Me)CH_2CHO, CH_2Cl_2, −78 °C, 64%, 9:1 dr; b) $LiBH_4$, MeOH, Et_2O, 0 °C, 78%; c) TIPSCl, imid., DMF, 95%; d) PMBBr, NaH, DMF, 86%; e) Ti(O-*i*Pr)$_4$, *n*BuMgCl, Et_2O, 0 °C, 86%; f) NaH, $BrCH_2CO_2H$, THF, DMF, 91%; g) PivCl, Et_3N, (*R*)-5-lithio-4-isopropyl-oxazolidin-2-one, THF, 90%; h) $NaN(SiMe_3)_2$, $(BnO)_2CH_2$, TMSI, THF, −78 °C, 93%; i) $LiBH_4$, MeOH, Et_2O, 0 °C, 81%; j) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; k) CH_2=CHMgBr, THF, 0 °C, 76% for 2 steps, 3:1 dr; l) $Cl_2(Cy_3P)$(IMes)Ru=CHPh, CH_2Cl_2, 40 °C, 75%; m) [PCy_3] [COD] [pyr]$Ir^+PF_6^-$, H_2, CH_2Cl_2, −50 °C, 93%; n) Dess–Martin periodinane, CH_2Cl_2, 89%; o) MeMgCl, Et_2O, −78 °C, 89%; p) LiDBB, THF, −78 °C, 98%;

q) Dess–Martin periodinane, CH_2Cl_2, 88%; r) PPh_3, *p*-$NO_2C_6H_4CO_2H$, DEAD, C_6H_6; *i*Bu_2AlH, CH_2Cl_2, −78 °C, 50% for 2 steps.



Scheme 6.

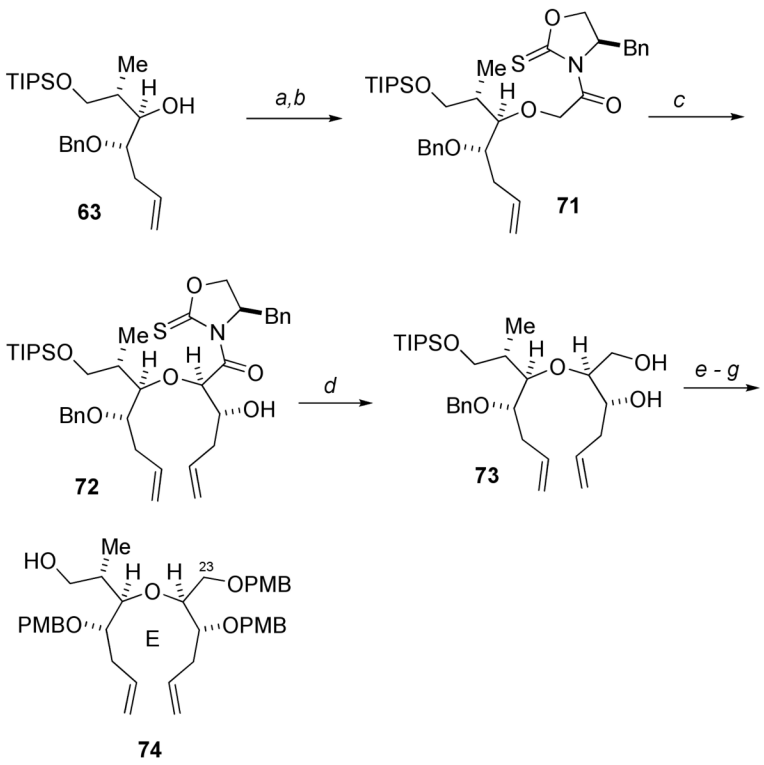
Homologated B ring synthesis. Reagents and conditions: a) $NaN(SiMe_3)_2$, $CH_2=C(Me)CH_2I$, THF, −78 °C, 78%; b) LDA, EtOAc, THF, −78 °C, 84%; c) $LiAlH_4$, Et_2O, 0 °C, 80%; d) TIPSCl, imid., CH_2Cl_2, 100%; e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 100%; f) $Zn(BH_4)_2$, Et_2O, −25 °C, 79%; g) NaH, $BrCH_2CO_2H$, THF, DMF, 90%; h) PivCl, Et_3N, (*R*)-5-lithio-4-isopropyl-oxazolidin-2-one, THF, 90%; i) $NaN(SiMe_3)_2$, $(BnO)_2CH_2$, TMSI, THF, −78 °C, 83%; j) $LiBH_4$, MeOH, Et_2O, 0 °C, 86%; k) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 99%; l) $CH_2=CHMgBr$, THF, 0 °C, 86% (3:1 dr); m) $Cl_2(Cy_3P)(IMes)Ru=CHPh$, CH_2Cl_2, 40 °C, 71%; n) $[PCy_3]$ [COD] $[pyr]Ir^+PF_6^-$, H_2, CH_2Cl_2, −50 °C, 94%; o) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 95%; p) MeMgCl, Et_2O, −78 °C, 88%; q) Raney Ni, H_2, EtOH, 95%; r) Dess–Martin periodinane, CH_2Cl_2, 85%; s) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 64%; t) $CeCl_3•7H_2O$, $NaBH_4$, MeOH, 82%.



Scheme 7.

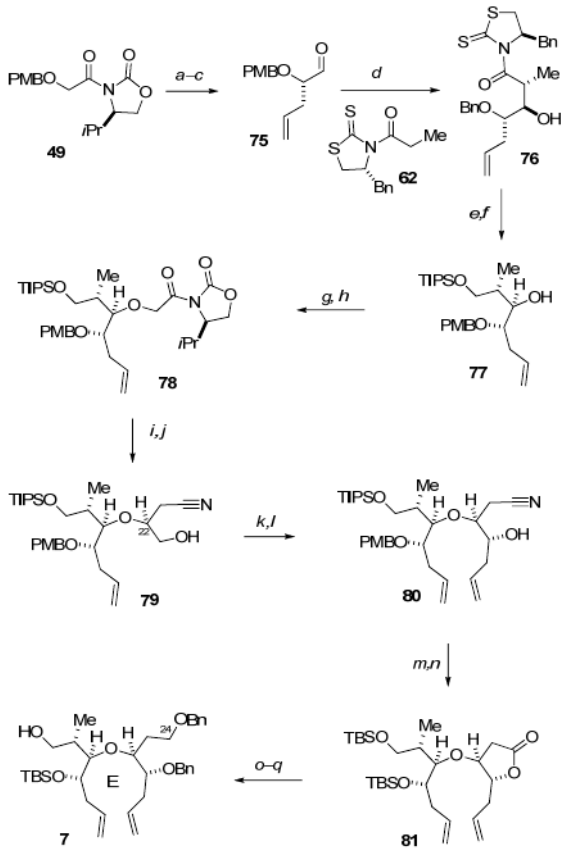
Initial E ring synthesis. Reagents and conditions: a) $NaN(SiMe_3)_2$, $CH_2{=}CHCH_2I$, THF, −78 °C, 82%; b) $NaBH_4$, H_2O, THF, 95%; c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; d) Propionate **62**, $TiCl_4$, (−)-sparteine, NMP, CH_2Cl_2, 92% for 2 steps; e) $LiBH_4$, MeOH, Et_2O, 0 °C, 91%; f) TIPSCl, imid., DMF, 70 °C, 96%; g) NaH, $BrCH_2CO_2H$, THF, 81%; h) PivCl, Et_3N, (*R*)-5-lithio-4-isopropyl-oxazolidin-2-one, THF, 77%; i) $NaN(SiMe_3)_2$, $(Me)_2C{=}CHCH_2I$, −78 °C, 83%; j) $LiBH_4$, MeOH, Et_2O, 0 °C, 87%; k) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; l) $(2\text{-}^{d}Icr)_2BCH_2CH{=}CH_2$, Et_2O, THF, −78 °C, 89% for 2 steps; m) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 96%; n) *m*-CPBA, CH_2Cl_2, −20 °C, 97%; o) $Cl_2(PCy_3)Ru{=}CHPh$, CH_2Cl_2, 40 °C,

99%; p) $HClO_4$, H_2O, THF, 59%; q) $NaIO_4$, nBu$_4$NHSO$_4$, THF, H_2O, 92%; r) $LiAlH_4$, Et_2O, 0 °C, 96%; s) NaH, BnBr, DMF, THF, 40 °C, 75%; t) nBu$_4$NF, THF, 96%.



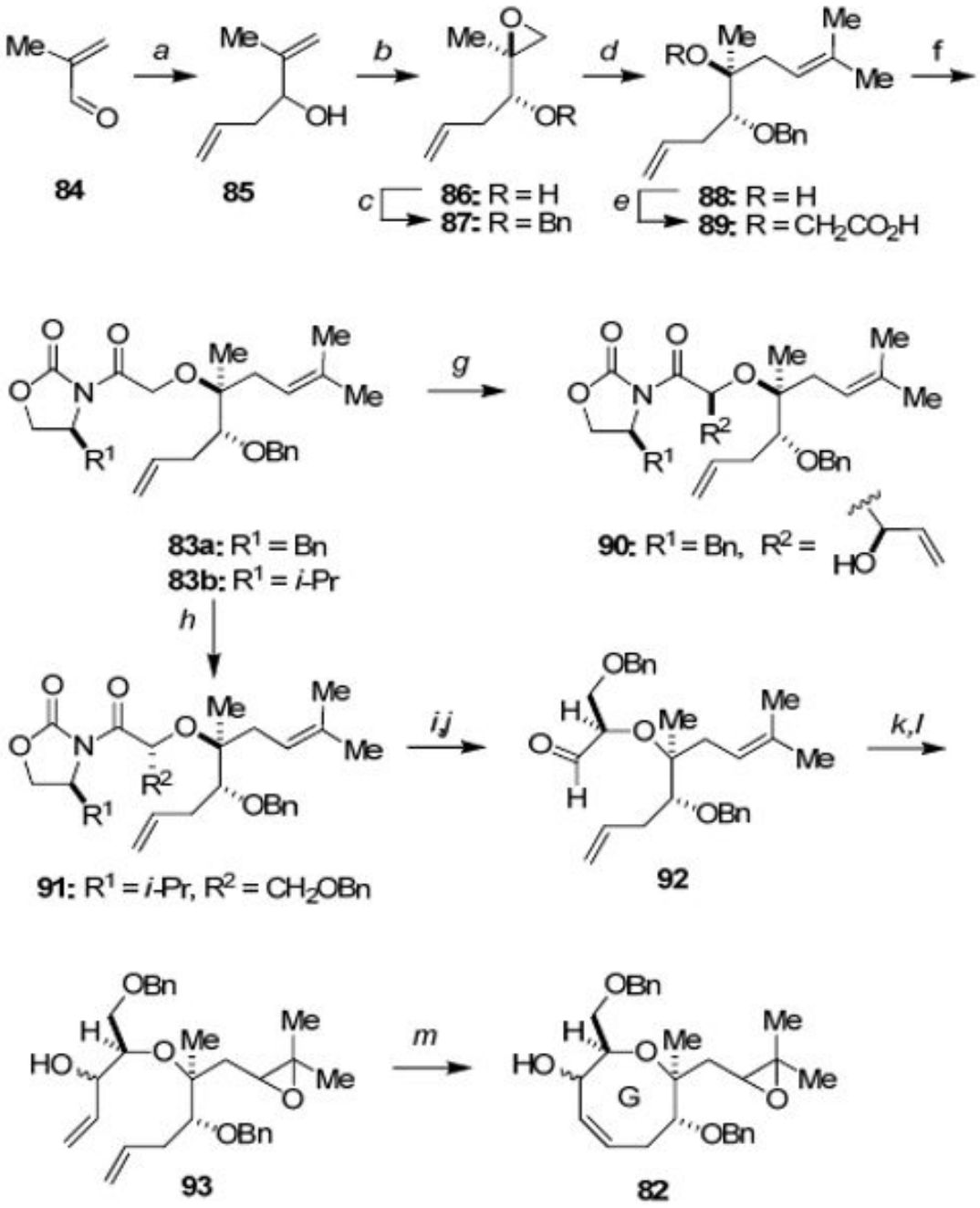
Scheme 8.

Second generation E ring synthesis. Reagents and conditions: a) NaH, $BrCH_2CO_2H$, THF, 81%; b) PivCl, Et_3N, (*S*)-5-lithio-4-benzyl-2-oxazolidinethione, THF, 66%; c) $TiCl_4$, (−)-sparteine, CH_2=$CHCH_2CHO$, CH_2Cl_2, −78 °C, 50% (5:1 dr), 89% brsm; d) $LiBH_4$, MeOH, Et_2O, 0 °C, 80%; e) Na, naphthalene, THF, 0 °C, 98%; f) NaH, PMBBr, DMF; g) *n*Bu_4NF, THF, 90% for 2 steps.



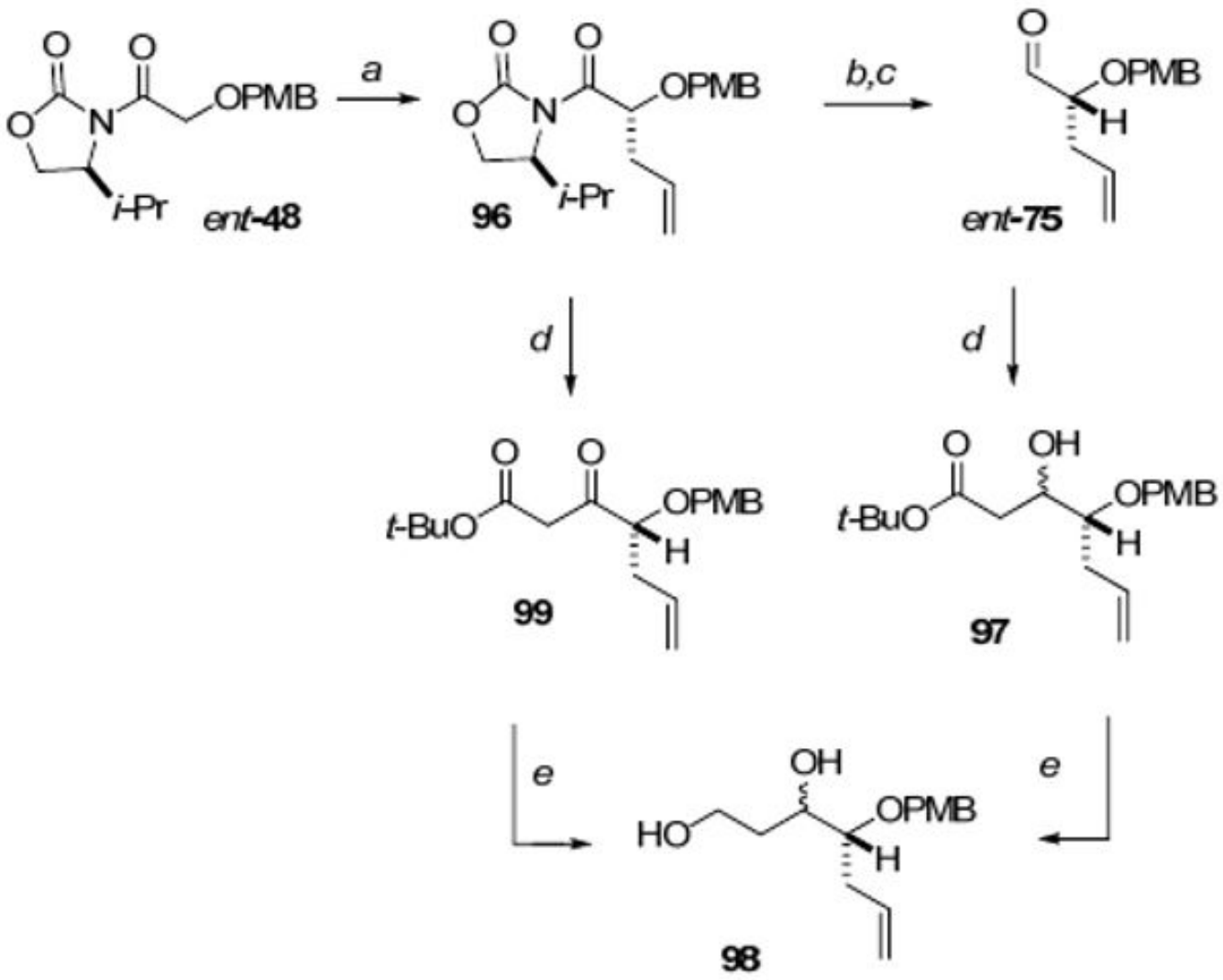
Scheme 9.

Third generation E ring synthesis. Reagents and conditions: a) $NaN(SiMe_3)_2$, $CH_2{=}CHCH_2I$, THF, −78 °C, 76%; b) $NaBH_4$, H_2O, THF, 93%; c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; d) Propionate **62**, $TiCl_4$, (−)-sparteine, NMP, CH_2Cl_2; e) $NaBH_4$, H_2O, THF, 78% for 3 steps; f) TIPSCl, imid., CH_2Cl_2, 97%; g) NaH, $BrCH_2CO_2H$, THF, DMF, 92%; h) PivCl, Et_3N, (*R*)-5-lithio-4-isopropyl-oxazolidin-2-one, THF, 89%; i) $NaN(SiMe_3)_2$, $BrCH_2CN$, −78 °C; j) $NaBH_4$, H_2O, THF, 75% for 2 steps; k) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; l) $CH_2{=}CHCH_2SnBu_3$, $AlMe_3$, CH_2Cl_2, −78 °C; m) HCl, MeOH, 65 °C, 69% for 3 steps; n) TBSCl, imid., DMF, 80 °C, 80%; o) $LiAlH_4$, Et_2O, −20 °C, 88%; p) NaH, BnBr, DMF, 98%; q) HF•pyr, THF, 72%.



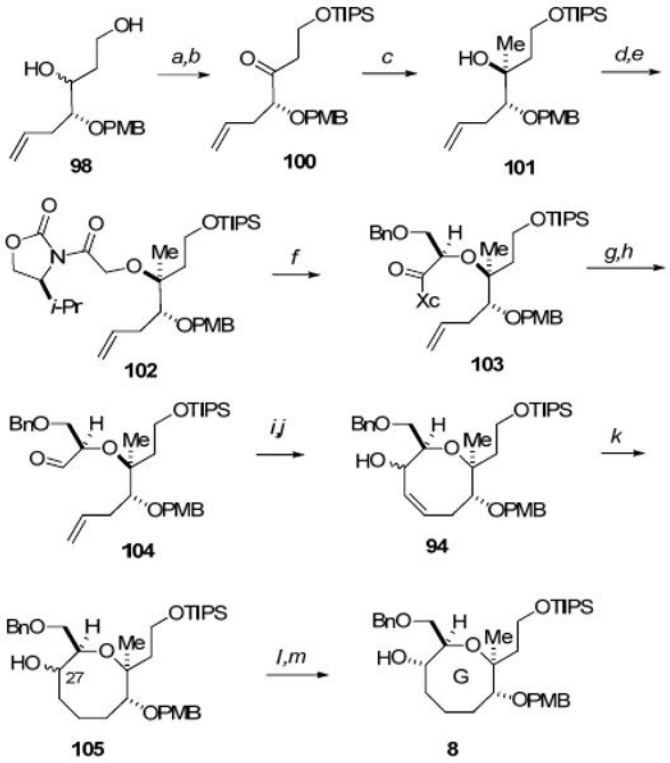
Scheme 10.

First generation synthesis of the G ring **82**. Reagents and conditions: a) CH_2=$CHCH_2MgBr$, Et_2O, 35 °C, 80%; b) (−)-DCHT, Ti(*i*PrO)$_4$, *t*BuOOH, 4Å mol. sieves, CH_2Cl_2, −20 °C, 43% (98% ee); c) BnBr, NaH, THF, 87%; d) Me_2C=$CHMgBr$, CuI, THF, 86%; e) $BrCH_2CO_2H$, NaH, THF, 87%; f) PivCl, Et_3N, THF; then (*S*)-5-lithio-4-benzyl-2-oxazolidinone (R^1= Bn) or (*S*)-5-lithio-4-isopropyl-2-oxazolidinone (R^1= *i*Pr), −78 to 0 °C, 80% or 85% respectively; g) $TiCl_4$, (−)-sparteine, acrolein, CH_2Cl_2, -78 to 0 °C, 25%; h) $NaN(SiMe_3)_2$, $(BnO)_2CH_2$, TMSI, THF, −78 to -45 °C, 70%; i) $NaBH_4$, THF, H_2O, 88%; j) Dess–Martin periodinane, CH_2Cl_2; k) CH_2=$CHMgBr$, THF, −78 °C, 80% (2 steps); l) *m*-CPBA, CH_2Cl_2, −20 °C, 80%; m) $Cl_2(PCy_3)$(sIMes)Ru=CHPh, CH_2Cl_2, 40 °C, 85%.



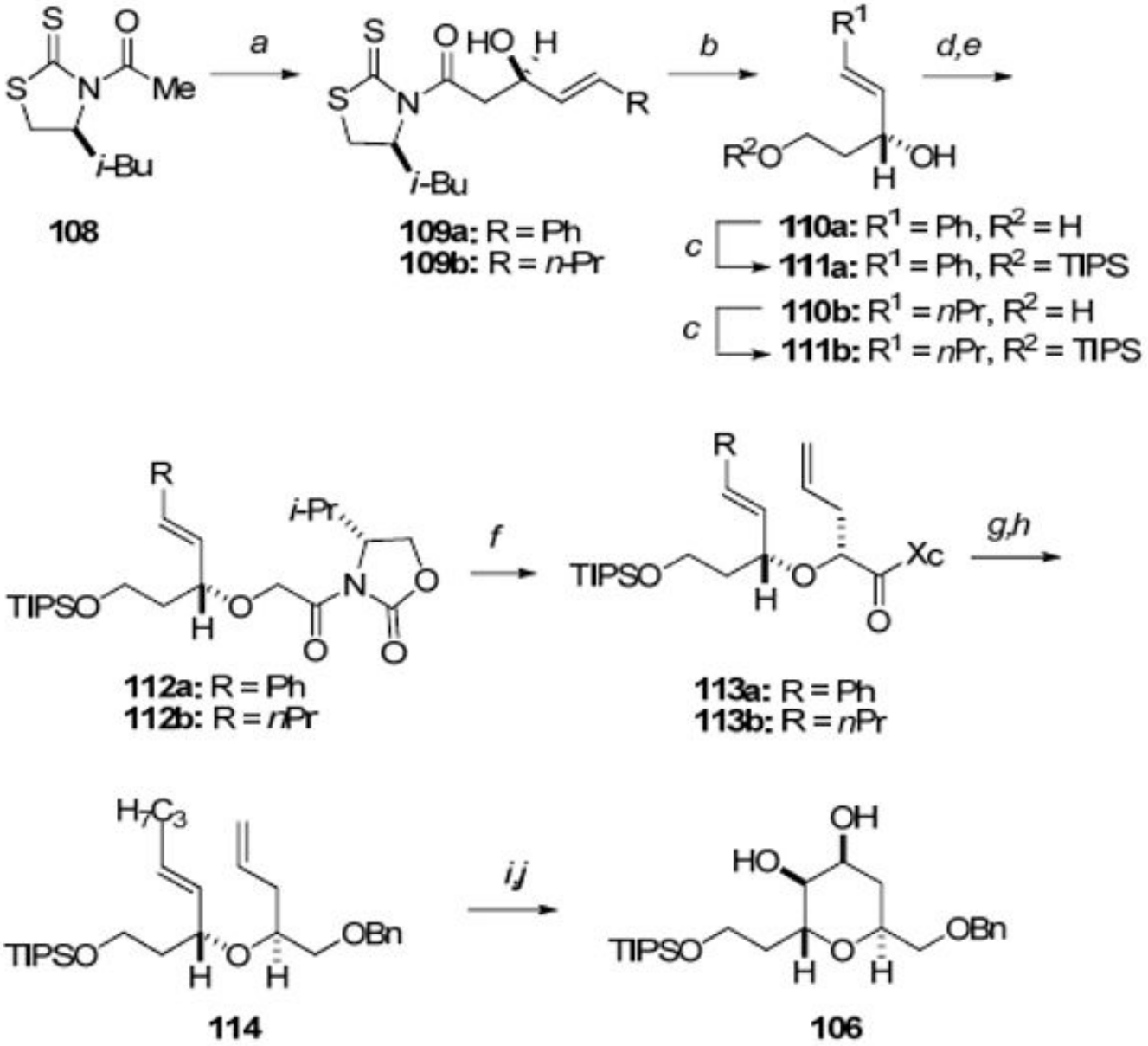
Scheme 11.

Preparation of Diols **98**. Reagents and conditions: a) $NaN(SiMe_3)_2$, $CH_2{=}CHCH_2I$, THF, -78 to -45 °C, 80%; b) $LiBH_4$, MeOH, Et_2O, 0 °C, 90%; c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, 97%; d) tBuO$_2$CCH$_2$Li, THF, −78 °C, 85% from **96**, 75% from *ent*-**75**; e) $LiAlH_4$, Et_2O, 0 °C, 92% from **97,** 67% from **99** brsm.



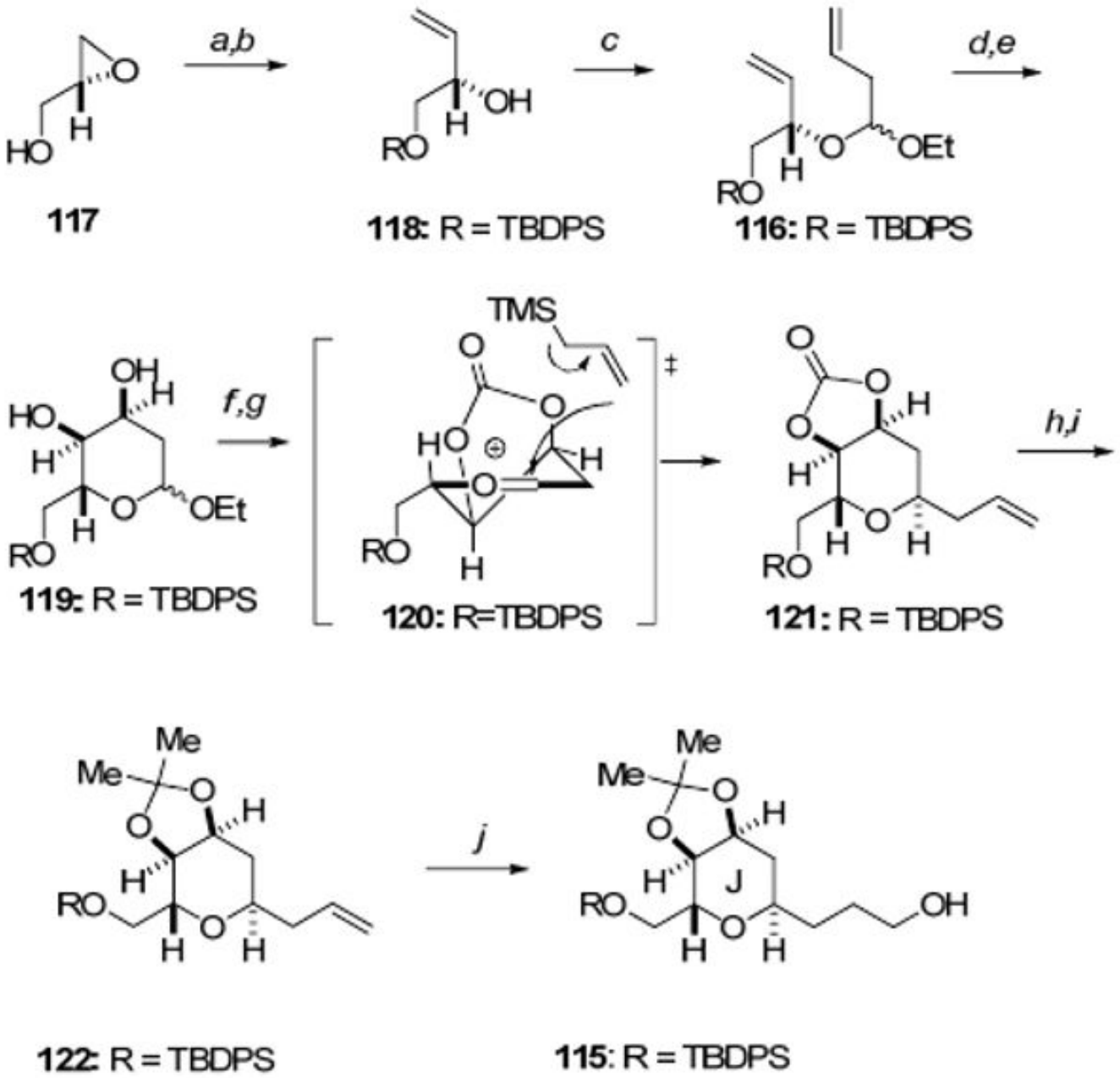
Scheme 12.

Second generation synthesis of the G ring **8**. Reagents and conditions: a) TIPSCl, imid., CH_2Cl_2, 99%; b) $(COCl)_2$, DMSO, DIEA, CH_2Cl_2, −78 to 0 °C, 94%; c) MeMgCl, Et_2O, -78 °C, 97%; d) $BrCH_2CO_2H$, NaH, DMF, 30 h, 84% (after 1 recycle); e) PivCl, Et_3N, THF; then (*S*)-5-lithio-4-isopropyl-2-oxazolidinone, -78 to 0 °C, 86%; f) $NaN(SiMe_3)_2$, $(BnO)_2CH_2$, TMSI, THF, −78 °C; g) $LiBH_4$, MeOH, Et_2O, 0 °C, 70% (2 steps); h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, 99%; i) CH_2=CHMgBr, THF, 0 °C, 80%; j) $Cl_2(PCy_3)$(sIMes) Ru=CHPh, CH_2Cl_2, 40 °C, 85%; k) *o*-$NO_2C_6H_4SO_2NHNH_2$, Et_3N, DME, 85 °C, 95%; l) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, 96%; m) *i*Bu_2AlH, CH_2Cl_2, −78 °C, 98%.



Scheme 13.

First Generation Synthesis of the J Ring **106**. Reagents and conditions: a) $TiCl_4$, DIEA, CH_2Cl_2, −78 °C; then *trans*-cinnamaldehyde or *trans*-2-hexenal, 76% (dr = 10:1) or 64% (dr = 7:1), respectively; b) $NaBH_4$, H_2O, THF, 80% (R = Ph), 82% (R = *n*Pr); c) TIPSCl, imid., DMF, 92% (R = Ph), 73% (R = *n*Pr); d) $BrCH_2CO_2H$, NaH, THF, 83% (R = Ph), 87% (R = *n*Pr); e) PivCl, Et_3N, THF; then (*R*)-5-lithio-4-isopropyl-2-oxazolidinone, −78 to 0 °C, 80% (R = Ph), 67% (R = *n*Pr); f) $NaN(SiMe_3)_2$, $CH_2{=}CHCH_2I$, THF, −78 to −45 °C, 28% (R = Ph), 90% (R = *n*Pr); g) $NaBH_4$, H_2O, THF, 86%; h) BnBr, NaH, THF, 99%; i) $Cl_2(PCy_3)_2Ru{=}CHPh$, CH_2Cl_2, 40 °C, 95%; j) OsO_4, NMO, THF, H_2O, 78% (dr = 3:1).



Scheme 14.

Second generation synthesis of the J ring **115**. a) TBDPSCl, imid., CH_2Cl_2, 0 °C to RT, 95%; b) $Me_3S^+I^-$, BuLi, THF, 0 °C, 86%; c) $(EtO)_2CHCH_2CH{=}CH_2$, PPTS, C_6H_6, 60 °C, 35 mm Hg, 87%; d) $Cl_2(PCy_3)_2Ru{=}CHPh$, CH_2Cl_2, 40 °C, 95%; e) $RuCl_3$, $NaIO_4$, H_2O, EtOAc, CH_3CN, 75%; f) CDI, THF, 65 °C, 90%; g) $CH_2{=}CHCH_2SiMe_3$, TMSOTf, CH_3CN, −10 °C, 87% (dr >10:1); h) K_2CO_3, MeOH, 76%; i) PPTS, $(MeO)_2CMe_2$, 92%; j) 9-BBN, THF; NaOH, H_2O_2 (aq), 90%.