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Enantioselective Total Synthesis of Brevetoxin 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 5-, 6-, 7-, 8-, and 9-membered oxacycles, as well as 22 tetrahedral stereocenters. Herein, we describe a unified approach to the B, E, G, and J rings based 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 completion of a convergent synthesis of brevetoxin A.

Keywords: asymmetric synthesis · chiral auxiliaries · glycolate alkylation · ring-closing metathesis · total synthesis

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 and co-workers through spectroscopic studies,[2c] features 10 rings (including 5-, 6-, 7-, 8-, and 9-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 **1** is attributed to strong binding to the α subunit of the voltage-sensitive sodium ion channels, effecting an increase in the mean channel open time and inhibiting channel inactivation.[3a] The landmark total synthesis of **1**, reported in 1998 by Nicolaou and co-workers,[4] stands as the only completed synthesis of this captivating target.

A fundamental goal in our vision for the total synthesis of **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 in the previous synthesis by Nicolaou and co-workers (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. Specifically, 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 that ultimately led to the completed total synthesis of **1**.[7] Described herein is the development of scalable routes to the four ring subunits **6**–**9**,

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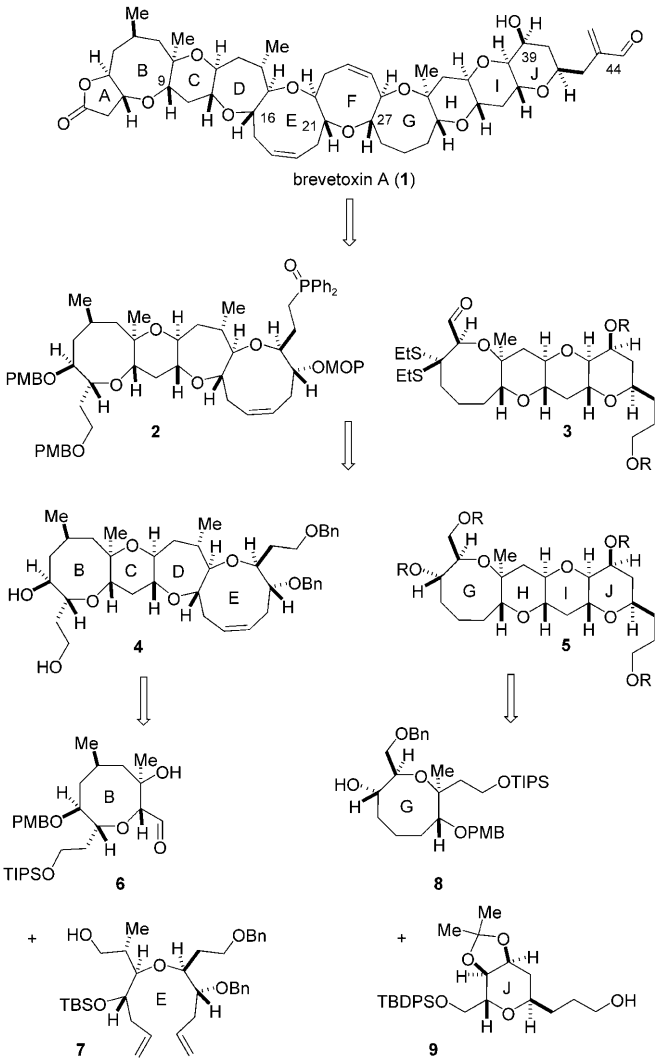


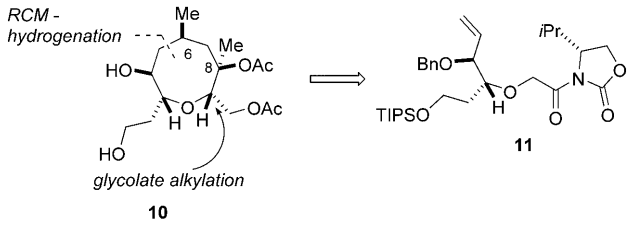
Scheme 1. Retrosynthetic analysis of **1**. TBDPS = *tert*-butyldiphenylsilyl.

which were prepared through ring-closing metathesis (RCM)[8] from acyclic diene precursors with stereodefined α-carbon atoms in the ether linkage. In the case of the B, E, and G rings, the stereogenicity of the α-carbon atoms would be established through the implementation of enolate technology developed in our laboratory.

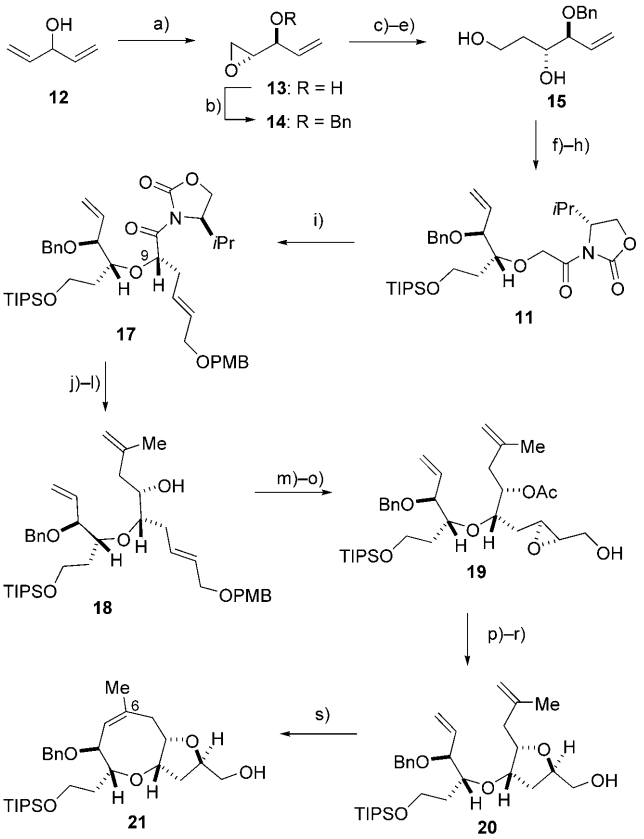
Results and Discussion

Synthesis of the B Ring: Efforts toward the total synthesis of **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 through a glycolate alkylation strategy to set the stereogenic centers of the ether linkage,[9] followed by RCM and hydrogenation to create the oxocane (Scheme 2).[10]

A Sharpless asymmetric epoxidation[11] of 1,4-pentadien-3-ol (**12**) conveniently provided an epoxide **13** as an enantioenriched 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 3). The epox-



Scheme 2. Initial retrosynthetic analysis of the B ring **10**. Bn = benzyl.

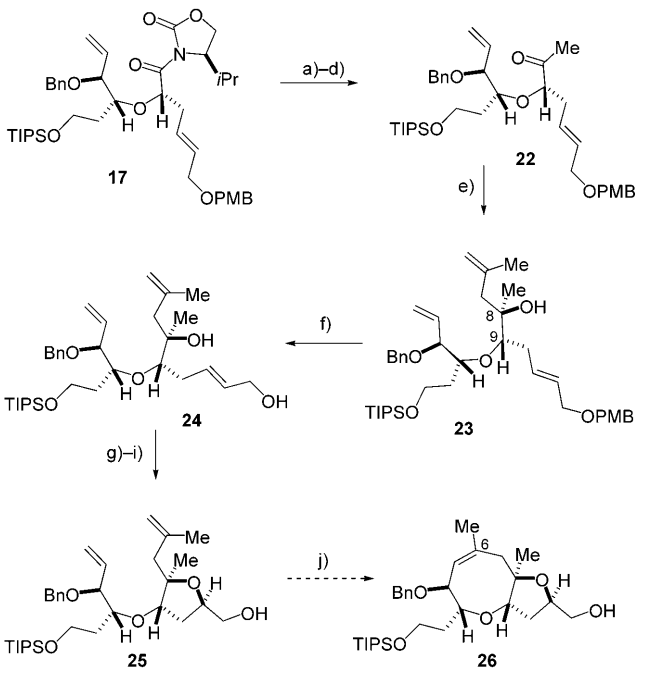


Scheme 3. First-generation B ring synthesis. Reagents and conditions: a) (+)-diisopropyl tartrate, [Ti(O-*i*Pr)$_4$], *t*BuOOH, CH_2Cl_2, 4 Å molecular sieves, −20 °C, 63%; b) NaH, BnBr, nBu$_4$NI, THF, 91%; c) KCN, $LiClO_4$, CH_3CN, 80 °C, 84%; d) NaOH, H_2O, MeOH, 65 °C; e) $LiAlH_4$, Et_2O, 35 °C, 78% for 2 steps; f) TIPSCl, imidazole, DMF, 89%; g) NaH, $BrCH_2CO_2H$, THF, 88%; h) PivCl (Piv = pivaloyl), Et_3N, (*R*)-5-lithio-4-isopropyloxazolidin-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)$_2BCH_2C(Me)=CH_2$ (^{d}Icr = isocaranyl), Et_2O, THF, −78 °C, 94% for two steps; m) Ac_2O, pyridine, 4-dimethylaminopyridine (DMAP), CH_2Cl_2, 92%; n) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), H_2O, CH_2Cl_2, 0 °C, 85%; o) (+)-diethyl tartrate (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 two steps; s) [Ru(=CHPh)Cl$_2$(Cy$_3$P)(sIMes)], CH_2Cl_2, 40 °C, 70%.

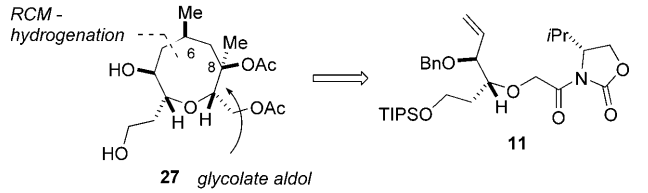
ide **14** was opened at its terminus with a cyanide ion and the resultant nitrile was transformed to the diol **15** by hydrolysis of the nitrile and reduction of the resulting acid. The primary alcohol was selectively protected as its triisopropylsilyl (TIPS) ether and the secondary alcohol was alkylated with sodium bromoacetate to produce a glycolic acid that was converted to its mixed anhydride. The mixed anhydride was utilized to acylate (*R*)-lithio-4-isopropyl-2-oxazolidinone, providing glycolyloxazolidinone **11** and staging an alkylation to stereoselectively install the C9 substituent.[9] In the event, alkylation of the sodium enolate of glycolate **11** with iodide **16** afforded diene **17** in 80% yield as a single detectable diastereomer (by ^{1}H NMR spectroscopy). Reductive removal of the auxiliary, oxidation[12] of the resultant alcohol to the aldehyde, and Brown asymmetric methallylation[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 (PMB) ether preceded a Sharpless asymmetric epoxidation[11] to provide diene **19** in high yield. RCM was attempted using diene **19** in the presence of the Grubbs second-generation catalyst [Ru(=CHPh)Cl_2(Cy_3P)(sIMes)] (Cy = cyclohexyl, sIMes = 1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene),[8a,b] but the desired oxocene was not observed.[14] Aware of precedent involving the facilitation of medium-ring synthesis through RCM 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, heating diene **20** at reflux in dichloromethane with the Grubbs second-generation catalyst 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 straightforward steps to methyl ketone **22** (Scheme 4). 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**, RCM could not be induced by using diene **25** or a variety of similar analogues 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 (Scheme 5). To accommodate this approach we anticipated that a temporary, removable tether would be required to facilitate the RCM. Rather than use a glycolate alkylation



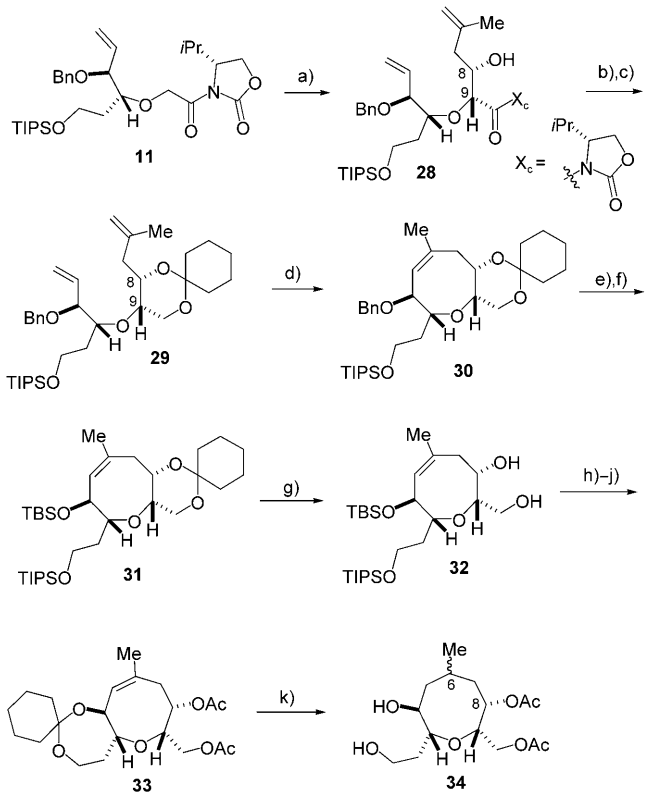
Scheme 4. Attempted incorporation of the C8 methyl. Reagents and conditions: a) $LiBH_4$, MeOH, Et_2O, 0°C, 96%; b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; c) MeMgI, Et_2O, 0°C, 90% for 2 steps; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; e) (4-^{d}Icr)$_2$BCH_2C(Me)=CH_2, Et_2O, THF, −78°C, 89% for two steps, 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) [Ru(=CHPh)Cl_2(Cy_3P)(sIMes)], CH_2Cl_2, 40°C, no reaction.



Scheme 5. Aldol-based retrosynthetic analysis of the B ring **27**.

and Brown methallylation 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.

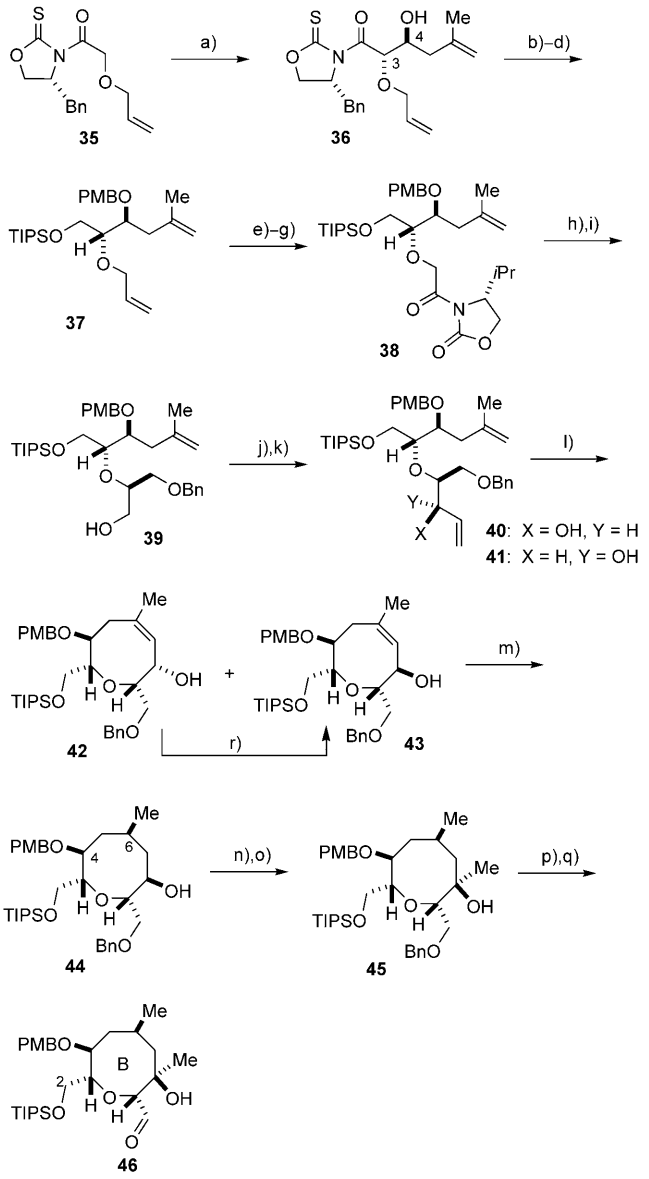
The chlorotitanium enolate of previously prepared glycolate **11** was treated with 3-methyl-3-butenal to afford the desired *syn* product **28** in approximately 70% yield (Scheme 6). Reduction of the chiral auxiliary and formation of the cyclohexylidene acetal provided diene **29**. With the cyclic constraint in place, RCM[8a,b] provided oxocene **30** in 83% yield.[19] Replacement of the benzyl ether with a *tert*-butyldimethylsilyl ether that would be compatible with the reduction of the olefin was accomplished in two straightforward operations. Stereoselective hydrogenation of the C5–



Scheme 6. Second-generation B ring synthesis. Reagents and conditions: a) $TiCl_4$, iPr_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, pyridinium *p*-toluenesulfonate (PPTS), $MgSO_4$, C_6H_6, 80 °C, 87 %; d) [Ru(=CHPh)Cl_2-(Cy_3P)(sIMes)], CH_2Cl_2, 40 °C, 83 %; e) Na, naphthalene, THF, 0 °C, 91 %; f) *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), 2,6-lutidine, CH_2Cl_2, 90 %; g) PPTS, EtOH, 78 °C, 72 %; h) Ac_2O, DMAP, CH_2Cl_2, 87 %; i) nBu_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.

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 transition-metal-catalyzed and transfer-hydrogenation conditions. Removal of the cyclohexylidene acetal provided diol **32**, which was also unreactive toward reductive conditions, including attempted hydrogenation by using the homogeneous Crabtree 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 the Pearlman 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 to allow for stereoselective establishment of C6 and the tertiary alcohol at C8 present in **1**.

At this stage, we adopted a third-generation approach to the B ring that utilized the *anti*-glycolate aldol methodology recently developed in our laboratory.[21] The chlorotitanium enolate of allyloxyglycolylimide **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 7).[6c] Removal of the chiral auxiliary and sequential protection of



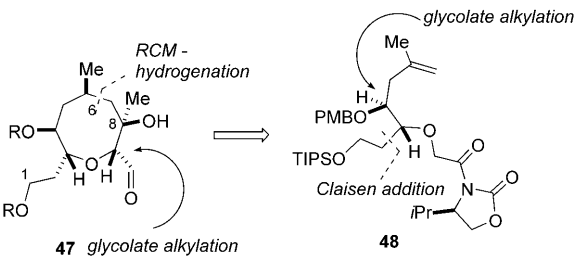
Scheme 7. First stereocontrolled completion of the B ring **46**. Reagents and conditions: a) $TiCl_4$, (−)-sparteine, $CH_2{=}C(Me)CH_2CHO$, CH_2Cl_2, −78 °C, 64 %, 9:1 dr; b) $LiBH_4$, MeOH, Et_2O, 0 °C, 78 %; c) TIPSCl, imidazole, DMF, 95 %; d) PMBBr, NaH, DMF, 86 %; e) Ti(O-*i*Pr)$_4$, *n*BuMgCl, Et_2O, 0 °C, 86 %; f) NaH, $BrCH_2CO_2H$, THF, DMF, 91 %; g) PivCl, Et_3N, (*R*)-5-lithio-4-isopropyloxazolidin-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) [Ru(=CHPh)Cl_2(Cy_3P)-(sIMes)], CH_2Cl_2, 40 °C, 75 %; m) [Ir(cod)(PCy_3)(pyr)]·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) lithium di-*tert*-butylbiphenylilde (LiDBB), THF, −78 °C, 98 %; q) Dess–Martin periodinane, CH_2Cl_2, 88 %; r) PPh_3, *p*-$NO_2C_6H_4CO_2H$, diethyl azodicarboxylate (DEAD), C_6H_6; *i*Bu_2AlH, CH_2Cl_2, −78 °C, 50 % for 2 steps.

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** through the glycolic acid. Alkylation of the sodium enolate of glycolate **38** with benzyl iodomethyl ether (generated in situ from $(BnO)_2CH_2$ and trimethylsilyl iodide (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. RCM using the Grubbs second-generation catalyst was possible in the absence of a cyclic constraint to produce oxocenes **42** and **43**, which were separable at this stage. The minor component (**42**) of this mixture was transformed to the desired oxocene **43** through a Mitsunobu inversion.[23] The Crabtree 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, an 8:1 ratio 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.[19] 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**.

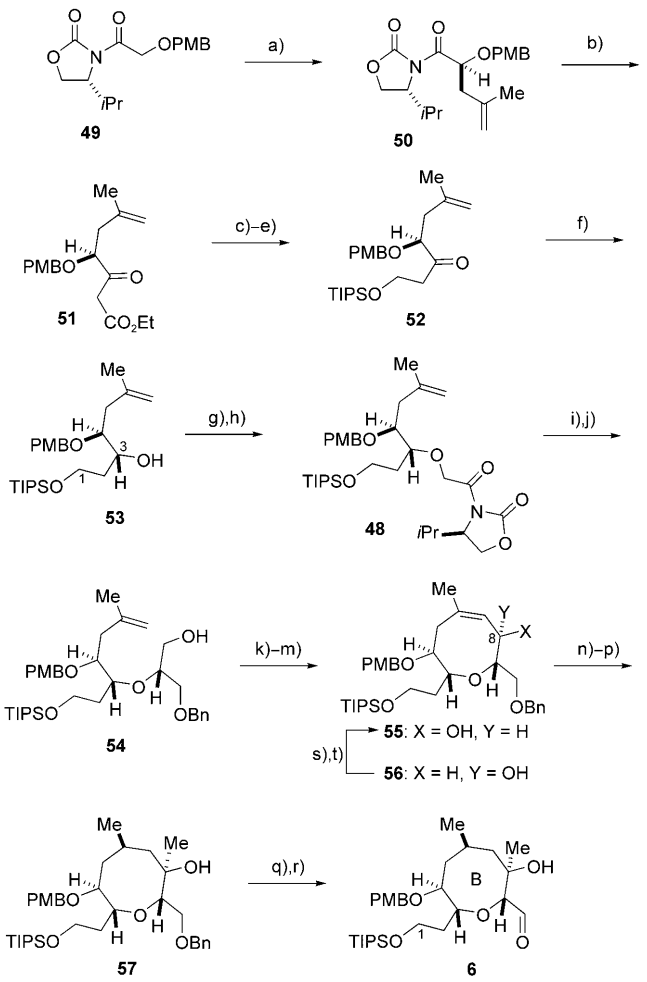
Much had been learned regarding the required functionality to facilitate the RCM and hydrogenation of the B ring during the course of our studies. However, although a viable approach to B ring aldehyde **46** was in place, a final improvement to this route was needed. Installation of C1 at an early stage 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 (Scheme 8).[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*-methoxybenzyloxyglycolylimide **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 9).[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



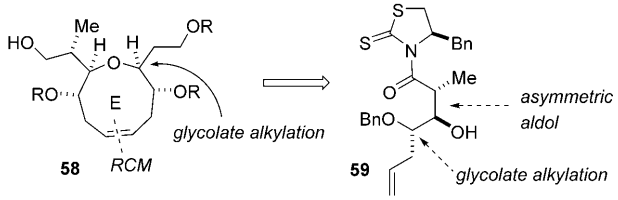
Scheme 8. Key features of the strategy for the B ring **47**.



Scheme 9. 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, imidazole, 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) $[Ru(=CHPh)Cl_2(Cy_3P)(sIMes)]$, CH_2Cl_2, 40°C, 71%; n) $[Ir(cod)(PCy_3)(pyr)]\cdot PF_6$, 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) $[CeCl_3]\cdot 7H_2O$, $NaBH_4$, MeOH, 82%.

$Zn(BH_4)_2$ 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, was employed. Glycolate **48** was prepared under standard conditions from alcohol **53** and the alkylation of imide **48** with benzyliodomethyl 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 RCM 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** through Swern oxidation and Luche reduction.[32] As before, hydrogenation of the allylic alcohol **55** with the Crabtree catalyst at −50 °C provided the oxocane in 94% yield (>19:1 dr). 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, more than three grams of aldehyde **6** were prepared by using this sequence in a single execution of the synthetic sequence.

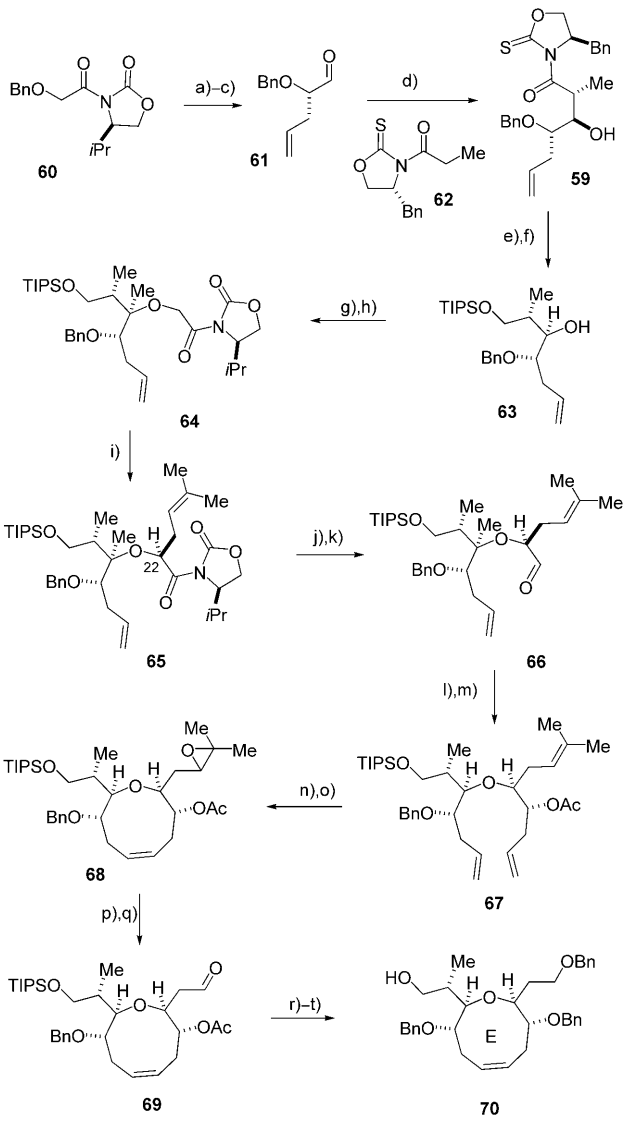
Synthesis of the E ring: The initial synthesis of the E ring fragment **58** was based upon a glycolate alkylation[9] and RCM strategy to prepare the functionalized oxonene (Scheme 10).[10] An asymmetric glycolate alkylation and a



Scheme 10. Key strategic elements for the E ring synthesis.

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 11).[12] Addition of aldehyde **61** to the chlorotitanium enolate of (*R*)-*N*-propionyl-4-benzylthiazolidin-2-one **62** provided the aldol adduct **59** as a single detectable diastereomer by ^{1}H NMR spectroscopy.[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

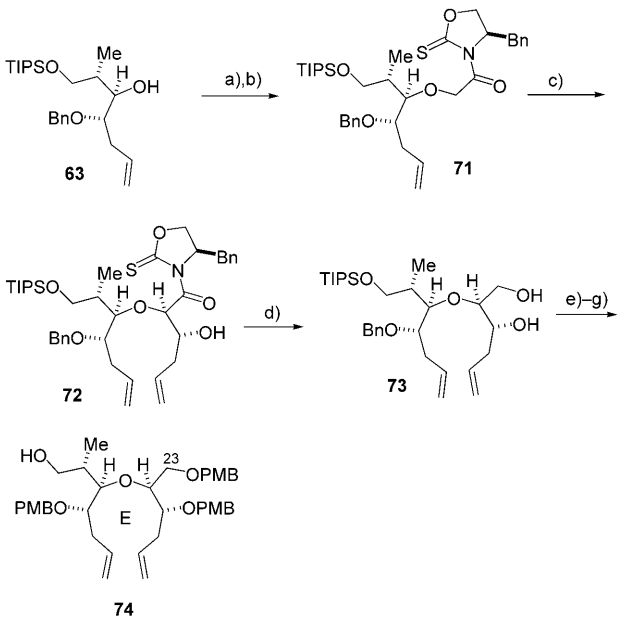


Scheme 11. Initial E ring synthesis. Reagents and conditions: a) $NaN(SiMe_3)_2$, CH_2=$CHCH_2I$, THF, −78 °C, 82%; b) $NaBH_4$, H_2O, THF, 95%; c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; d) propionate **62**, $TiCl_4$, (−)-sparteine, NMP, CH_2Cl_2, 92% for 2 steps; e) $LiBH_4$, MeOH, Et_2O, 0 °C, 91%; f) TIPSCl, imidazole, DMF, 70 °C, 96%; g) NaH, $BrCH_2CO_2H$, THF, 81%; h) PivCl, Et_3N, (*R*)-5-lithio-4-isopropyloxazolidin-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) $(2\text{-}^dIcr)_2BCH_2CH$=$CH_2$, 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) $[Ru(=CHPh)Cl_2(PCy_3)]$, CH_2Cl_2, 40 °C, 99%; p) $HClO_4$, H_2O, THF, 59%; q) $NaIO_4$, nBu_4NHSO_4, THF, H_2O, 92%; r) $LiAlH_4$, Et_2O, 0 °C, 96%; s) NaH, BnBr, DMF, THF, 40 °C, 75%; t) nBu_4NF, THF, 96%.

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 [Ru(=CHPh)Cl_2(Cy_3P)$_2$] to effect RCM, which generated the oxonene **68** in 99% yield.[7] The epoxide was exposed to aqueous perchloric acid, resulting in hydrolytic opening of the epoxide 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 bis(benzyl) ether, and cleavage of the silyl ether gave the desired E ring **70** in 96% yield.

Although 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 (see above, Scheme 7), 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 12). The chlorotitanium enolate of glycolate **71** underwent an aldol reaction with 3-butenal in 50% yield (89% based on recovered starting material (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 led to 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.

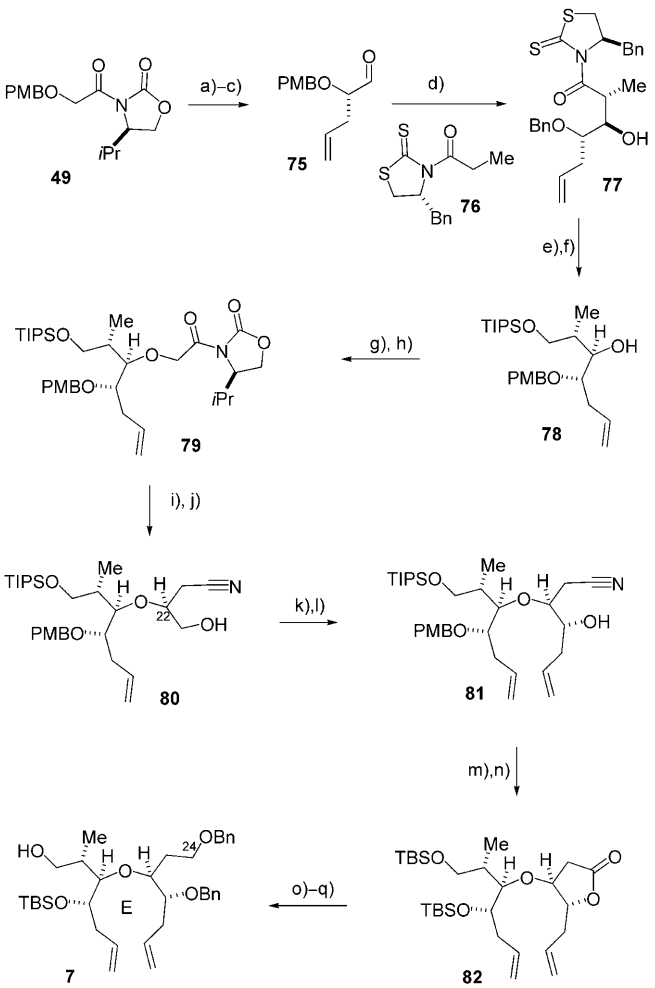


Scheme 12. Second-generation E ring synthesis. Reagents and conditions: a) NaH, $BrCH_2CO_2H$, THF, 81%; b) PivCl, Et_3N, (*S*)-5-lithio-4-benzyl-2-oxazolidinethione, THF, 66%; c) $TiCl_4$, (−)-sparteine, CH_2=$CHCH_2CHO$, CH_2Cl_2, −78°C, 50% (5:1 dr), 89% brsm; d) $LiBH_4$, MeOH, Et_2O, 0°C, 80%; e) Na, naphthalene, THF, 0°C, 98%; f) NaH, PMBBr, DMF; g) $n$$Bu_4NF$, THF, 90% for 2 steps.

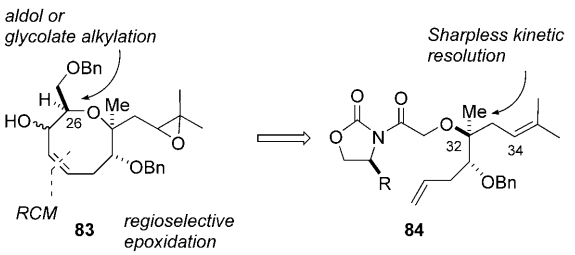
In the final plan for the E ring, as with the B ring (see above, Scheme 9), we hoped to incorporate all of the carbon atoms of the E ring from the outset, avoiding the need for a late-stage homologation. Our third-generation approach to the E ring[6a] commenced with an alkylation of the sodium enolate 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 13).[12] A *syn*-aldol addition of the chlorotitanium enolate of (*R*)-*N*-propionyl-4-benzylthiazolidin-2-thione (**76**) to aldehyde **75** proceeded efficiently, generating the aldol adduct **77**.[34] Exposure of the aldol adduct **77** to sodium borohydride gave a diol, which upon selective protection of the primary alcohol delivered the secondary alcohol **78.** Formation of the glycolic acid and subsequent conversion to the corresponding imide **79** set the stage for alkylation with bromoacetonitrile to diastereoselectively establish the C22 stereocenter.[9] Removal of the auxiliary under reductive conditions then provided alcohol **80** in 75% yield for two steps. Oxidation[12] of alcohol **80** to the aldehyde preceded a substrate-controlled stereoselective allylation to afford diene **81** in 80% yield (7:1 dr).[36,37] Treatment of diene **81** 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 **82**. Compound **82** was reduced with lithium aluminum hydride, whereupon the resulting diol was transformed to the bis-benzyl 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/RCM approach to the E ring. In the case of the G ring (**83**, Scheme 14), 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 RCM. Thus, a key intermediate would be complex glycolyl oxazolidinone **84**, with the stereocenter at C32 envisioned to arise from a Sharpless kinetic resolution.

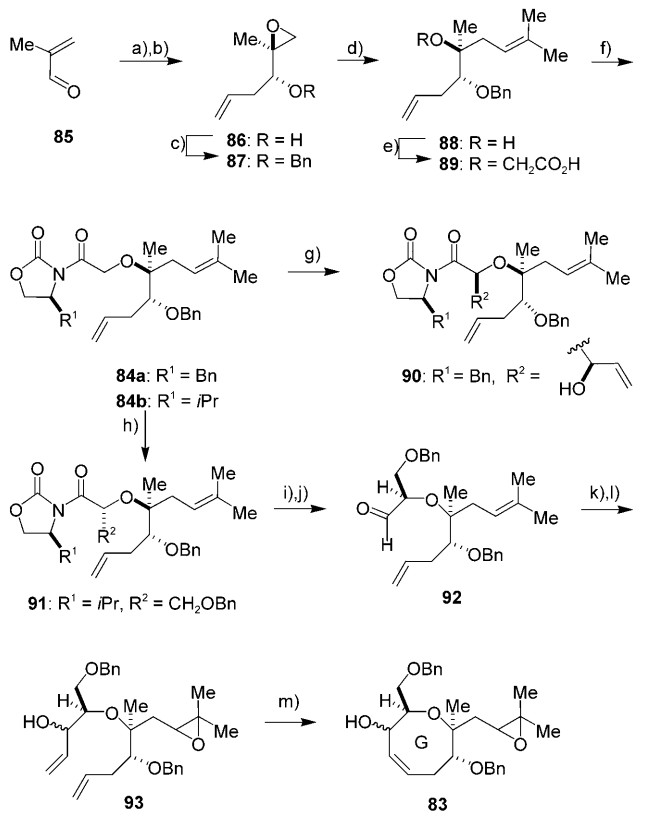
To investigate this approach, glycolyl oxazolidinone **84** was pursued, beginning with the addition of allylmagnesium bromide to methacrolein (**85**) (Scheme 15). Resolution of the resulting racemic mixture of secondary alcohols through a Sharpless kinetic resolution provided epoxy alcohol **86** (98% *ee* at 43% conversion),[11b] which was protected as the



Scheme 13. 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 **76**, $TiCl_4$, (−)-sparteine, NMP, CH_2Cl_2; e) $NaBH_4$, H_2O, THF, 78 % for 3 steps; f) TIPSCl, imidazole, CH_2Cl_2, 97 %; g) NaH, $BrCH_2CO_2H$, THF, DMF, 92 %; h) PivCl, Et_3N, (*R*)-5-lithio-4-isopropyloxazolidin-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) $CH_2{=}CHCH_2Sn(nBu)_3$, $AlMe_3$, CH_2Cl_2, −78 °C; m) HCl, MeOH, 65 °C, 69 % for 3 steps; n) TBSCl, imidazole, DMF, 80 °C, 80 %; o) $LiAlH_4$, Et_2O, −20 °C, 88 %; p) NaH, BnBr, DMF, 98 %; q) HF·pyridine, THF, 72 %.



Scheme 14. Key features of the first-generation synthesis of the G ring **83**.



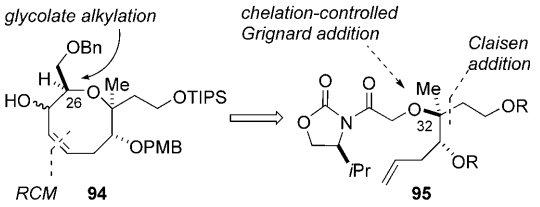
Scheme 15. First-generation synthesis of the G ring **83**. Reagents and conditions: a) $CH_2{=}CHCH_2MgBr$, Et_2O, 35 °C, 80 %; b) (−)-dicyclohexyl tartrate (DCHT), $Ti(iPrO)_4$, *t*BuOOH, 4 Å molecular sieves, CH_2Cl_2, −20 °C, 43 % (98 % *ee*); c) BnBr, NaH, THF, 87 %; d) $Me_2C{=}CHMgBr$, CuI, THF, 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 % for 2 steps; l) *m*-CPBA, CH_2Cl_2, −20 °C, 80 %; m) [Ru(=CHPh)Cl_2(PCy_3)(sIMes)], CH_2Cl_2, 40 °C, 85 %.

benzyl ether **87**. Copper-assisted Grignard addition to form 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** to acrolein, which would install both the C26 stereocenter and the olefin required for subsequent RCM. 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 by using Dess–Martin conditions to afford aldehyde **92**. Addition of vinylmagnesium bromide to the aldehyde gave an 80 % yield of the triene as a mixture of diastereomers, and selective epoxidation of the trisubstituted olefin with *m*-

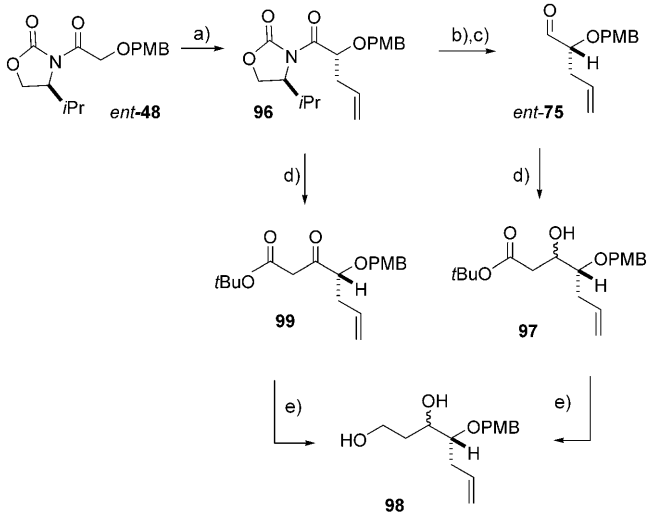
chloroperbenzoic acid (*m*-CPBA) gave epoxy diene **93**. Treatment of diene **93** with the Grubbs second-generation catalyst then led to an 85% yield of oxocene **83**.[8a,b] Attempts to perform the RCM with the Grubbs first-generation catalyst led to a lower yield (50%).

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/RCM 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 a more efficient alternative to the Sharpless kinetic resolution for installation of the C32 stereocenter (Scheme 16).



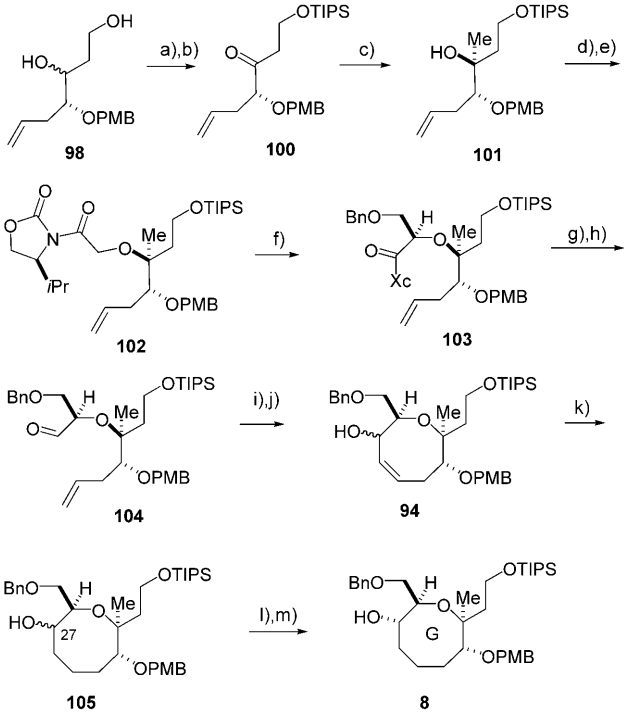
Scheme 16. Key features of the second-generation synthesis of the G ring.

The second-generation route to the G ring commenced with an asymmetric alkylation of imide *ent*-**49** (Scheme 17) 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**. Although 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** (see above, Scheme 9).[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 that were resistant to reduction. Nonetheless, a 67% yield of diols **98** based on recovered starting material was reproducible.



Scheme 17. 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) $tBuO_2CCH_2Li$, THF, −78°C, 85% from **96**, 75% from *ent*-**75**; e) $LiAlH_4$, Et_2O, 0°C, 92% from **97**, 67% from **99** brsm.

Upon selective protection of the primary alcohol of diols **98** as the TIPS ether and oxidation to the ketone under Swern conditions (Scheme 18), the chelation-controlled addition of methylmagnesium chloride to 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-oxazoli-



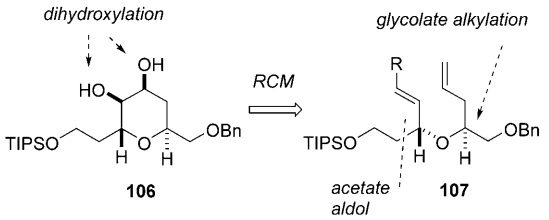
Scheme 18. Second-generation synthesis of the G ring **8**. Reagents and conditions: a) TIPSCl, imidazole, CH_2Cl_2, 99%; b) $(COCl)_2$, DMSO, diisopropyl ethylamine (DIEA), CH_2Cl_2, −78 to 0°C, 94%; c) MeMgCl, Et_2O, −78°C, 97%; d) $BrCH_2CO_2H$, NaH, DMF, 30 h, 84% (after 1 recycle); e) PivCl, Et_3N, 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% for 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) [Ru(=CHPh)Cl_2(PCy_3)(sIMes)], CH_2Cl_2, 40°C, 85%; k) *o*-$NO_2C_6H_4SO_2NHNH_2$, Et_3N, dimethoxyethane (DME), 85°C, 95%; l) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0°C, 96%; m) iBu_2AlH, CH_2Cl_2, −78°C, 98%.

dinone, alkylation of the *N*-acyloxazolidinone **102** with $BnOCH_2I$ once again performed well, even on larger scale: over 100 g of alkylation product **103** has 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 aldehyde **104** provided the allylic alcohols as a mixture of diastereomers. Subsequent exposure of the diene to the Grubbs second-generation catalyst gave oxocene **94** in high yield at up to 10 mM concentration.[8a,b]

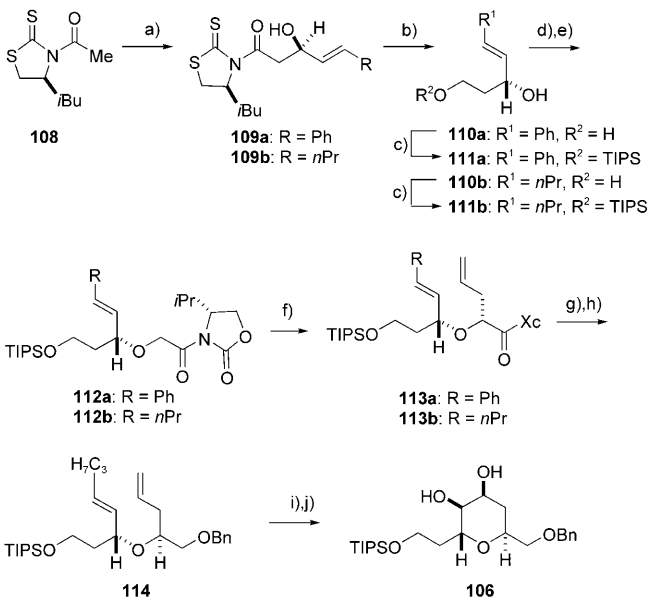
To properly functionalize the G ring, we had originally reported[6b,d] the use of the Crabtree catalyst[20] under a hydrogen atmosphere for the hydrogenation of the endocyclic olefin. However, upon scale up, these conditions led to a somewhat disappointing 70% yield of the desired oxocanes **105**, with loss of the PMB protecting group and epimerization at C26 by 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 RCM approach would be of particular interest because the dihydropyran produced would be the required substrate for dihydroxylation to install the necessary *syn* diol (Scheme 19). In our initial approach to the diene substrate **107** for RCM, an asymmetric acetate aldol and a glycolate alkylation were envisioned as key stereodetermining and C–C bond-forming steps.



Scheme 19. Key features of the first-generation synthesis of the J ring **106**.

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 through the Urpí protocol, particularly with α,β-unsaturated aldehydes.[10b,41] Specifically, the aldol reaction of *N*-acetylthiazolidinethione **108** (Scheme 20) with *trans*-cinnamaldehyde led to a 76% yield of the major aldol adduct **109a** (9:1 dr). Because the olefin installed in the aldol reaction would undergo a RCM, 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 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 28% yield, with the major side reaction involving 2,3-Wittig rearrangement of the sodium enolate.[42]



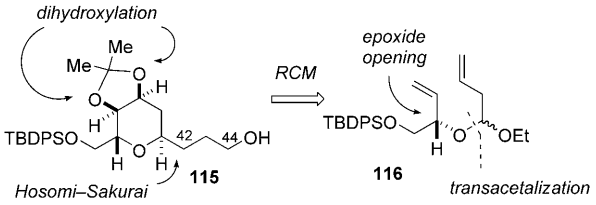
Scheme 20. First-generation Synthesis of the J Ring **106**. Reagents and conditions: a) $TiCl_4$, DIEA, CH_2Cl_2, −78 °C; then *trans*-cinnamaldehyde or *trans*-2-hexenal, 76% (9:1 dr) or 64% (7:1 dr), respectively; b) $NaBH_4$, H_2O, THF, 80% (R = Ph), 82% (R = *n*Pr); c) TIPSCl, imidazole, DMF, 92% (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) $[Ru(=CHPh)Cl_2(PCy_3)_2]$, CH_2Cl_2, 40 °C, 95%; j) OsO_4, *N*-methylmorpholine *N*-oxide (NMO), THF, H_2O, 78% (3:1 dr).

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 20). 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 benzyl ether **114.** As expected, RCM with the Grubbs catalyst afforded the dihydropyran in excellent yield,[8] and Upjohn dihydroxylation[43] occurred in 78% overall yield with a diastereoselectivity of 3:1 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.

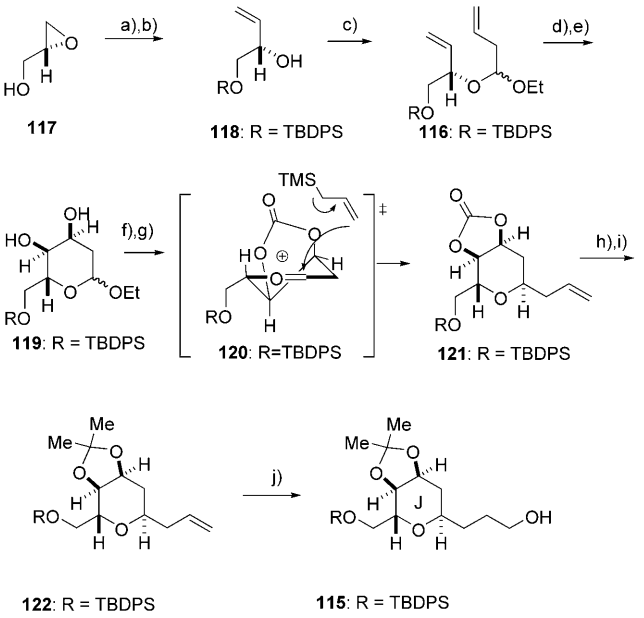
The first-generation approach to the J ring confirmed the effectiveness of the RCM/dihydroxylation sequence for completing the ring core, but was limited in terms of throughput by the moderate yield and tedious separation of diastereomers associated with the acetate aldol. Furthermore, the C43 and C44 carbon atoms would need to be added through subsequent manipulations, further lengthening the synthesis. Thus, a second-generation synthesis targeting J ring **115** possessing the C42–C44 side chain was formulated (Scheme 21). It was also postulated that the acetate



Scheme 21. Key features of the second-generation synthesis of the J ring **115**.

aldol and glycolate alkylation steps could be replaced by an epoxide opening and a Hosomi–Sakurai reaction, respectively. This approach would involve the 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 22). The smooth conversion of alcohol **118** to mixed acetal **116** was then accomplished through a transacetalization reaction under mild conditions. RCM 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 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 reprotected as acetonide **122**. Hydroboration of the terminal olefin with 9-borabicyclo[3.3.1]nonane (9-BBN) then delivered primary alcohol **115** exclusively. In testament to the scalability of this route, over 21 g of alcohol **115** was prepared through this sequence.



Scheme 22. Second-generation synthesis of the J ring **115**. a) TBDPSCl, imidazole, 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) $[Ru(=CHPh)Cl_2(PCy_3)_2]$, CH_2Cl_2, 40 °C, 95%; e) $RuCl_3$, $NaIO_4$, H_2O, EtOAc, CH_3CN, 75%; f) CDI, THF, 65 °C, 90%; g) $CH_2{=}CHCH_2SiMe_3$, trimethylsilyl trifluoromethanesulfonate (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%.

Conclusion

Scalable approaches to the B, E, G, and J rings of **1** have been developed, allowing the preparation of multigram quantities of each of these oxacycles. RCM 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 **1**. 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]

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