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Enantioselective Total Synthesis of Brevetoxin A: Convergent Coupling Strategy and Completion

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Abstract: A highly convergent, enantioselective total synthesis of brevetoxin A is reported. The development of a [X+2+X] Horner–Wadsworth–Emmons/cyclodehydration/reductive etherification convergent coupling strategy allowed a unified approach to the synthesis of two advanced tetracyclic fragments from four cyclic ether subunits. The Horner–Wittig coupling of the two tetracyclic fragments provided substrates that were explored for reductive etherification, the success of which delivered a late-stage tetraol intermediate. The tetraol was converted to the natural product through an expeditious selective oxidative process followed by methylenation.

Keywords: asymmetric synthesis · convergent strategy · ladder toxin · polycyclic ether · total synthesis

Introduction

In the preceding manuscript,[1] we described the development of efficient routes to the B, E, G, and J ring subunits **7**–**10** of brevetoxin A (**1**; Scheme 1), which provided multigram quantities of these key intermediates. Described herein is the convergent coupling of these subunits through a unified strategy to produce two advanced tetracyclic fragments **5** and **6**, the conversion of the tetracyclic fragments into Horner–Wittig coupling partners **3** and **4**, and the completion of **1** through the late-stage nonacycle **2**.[2]

Results and Discussion

Convergent coupling strategy for the synthesis of the BCDE and GHIJ fragments: In the context of the rapidly growing collection of synthetic strategies for the assembly of *trans*/*syn*/*trans*-fused polycyclic ether arrays,[3] we were attracted to the maximized convergency of the [X+2+X] concept,[3c] in which two individual rings are coupled, followed by the formation of two new, adjoining rings. Furthermore, based upon our overarching retrosynthetic analysis of **1** (Scheme 1), we recognized that a strategy of this type would be particularly well suited for the convergent construction of the individual BCDE and GHIJ subunits. Therefore, we designed a unique convergent coupling strategy that relies upon a Horner–Wadsworth–Emmons (HWE) reaction for the union of a cyclic ether functionalized as the β-keto phosphonate with another as the aldehyde (Scheme 2). The resulting enone intermediate would be subjected to 1,4-reduction, and an *endo*-selective cyclodehydration would provide a cyclic enol ether. Stereoselective hydration of the enol ether followed by a reductive etherification sequence would complete the tetracyclic subunit.

The HWE/cyclodehydration/reductive etherification strategy has several pertinent advantages. The mildness and reliable efficiency of the HWE reaction is particularly important for the stoichiometric coupling of advanced fragments—a critical consideration in the choice of assembly strategy. Also, the numerous methods for effecting 1,4-reduction of enones[4] and cyclodehydrations of δ-hydroxy ketones[5] bolster the potential for the success of the strategy. Finally, the hydration and reductive etherification of enol ethers is well known as one of the most powerful approaches for the closure of interior rings in a polycyclic ether array.[3] Strategically, for the BCDE tetracycle **5**, the B ring aldehyde **7** would be coupled with the E ring keto phosphonate **11**, which would derive from the E ring precursor **8**[1] (Scheme 3).

Preparation of the suitably functionalized E ring keto phosphonate **11** was accomplished by converting primary alcohol **8** into iodide **12**, which was displaced by cyanide to afford nitrile **13** (Scheme 4). Partial reduction of the nitrile

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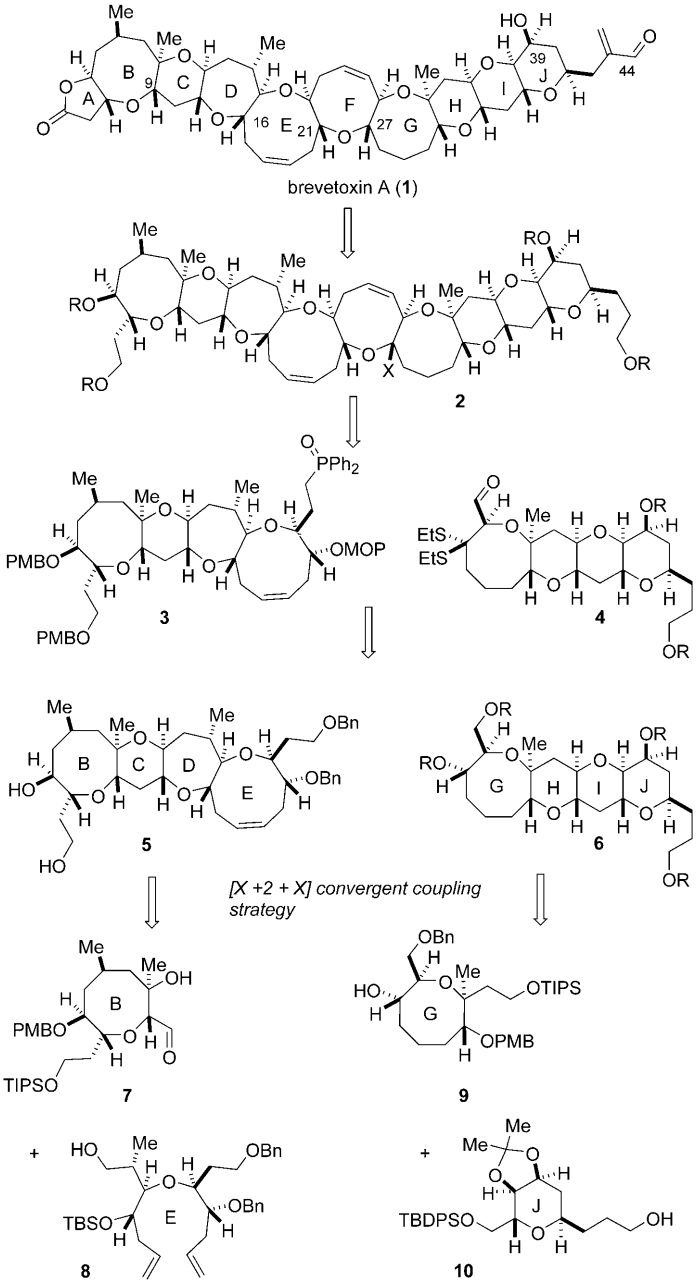
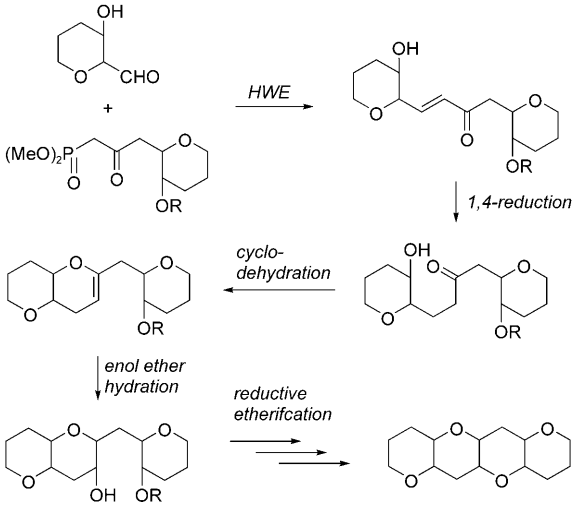
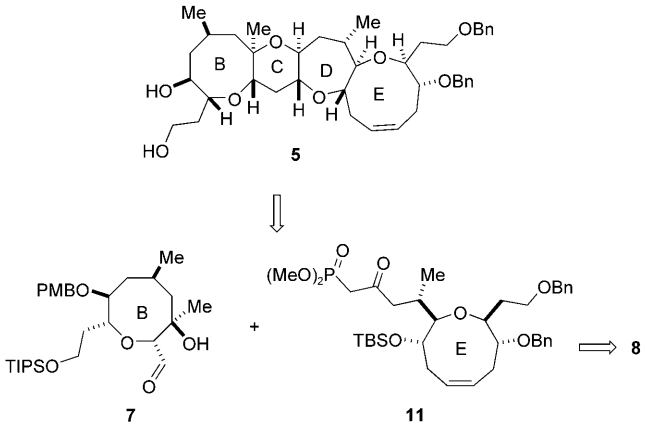


Scheme 1. Retrosynthetic analysis of brevetoxin A. Bn = benzyl, MOP = methoxypropyl, PMB = *p*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl, TBDPS = *tert*-butyldiphenylsilyl.



Scheme 2. Convergent coupling strategy to form tetracyclic polyether arrays.



Scheme 3. [X+2+X] strategy for the BCDE tetracycle **5**.

to the aldehyde was followed by an aldol reaction with the lithium carbanion of dimethyl(methylphosphonate) to produce β-hydroxy phosphonates **14** as an inconsequential mixture of diastereomers. Subsequent oxidation to the keto phosphonate[6] and ring-closing metathesis (RCM) provided the E ring **11** in excellent yield.

For the Horner–Wadsworth–Emmons coupling of B ring **7** and E ring **11**, exposure of the two fragments to aqueous $Ba(OH)_2$ provided a 96% yield of the desired enone **15** (Scheme 4).[7] A method was next developed to directly access enol ether **16** from enone **15.** By using the Wilkinson catalyst and Me_2PhSiH, the enone was reduced,[8] and subsequent addition of pyridinium *p*-toluenesulfonate (PPTS) to the reaction mixture provided enol ether **16** in a one-pot transformation.

The selective hydration of enol ether **16** in the presence of the E-ring endocyclic olefin proved particularly challenging. Because selective hydroboration could not be achieved under a variety of conditions, epoxidation of the electron-rich enol ether **16** and in situ reduction of the epoxide was explored. While dimethyldioxirane (DMDO) smoothly converted the enol ether to the corresponding epoxide with excellent chemoselectivity, the epoxide proved to be extremely unstable. Various conditions were explored, but only use of "acetone-free" DMDO to execute the epoxidation, followed by immediate exposure of the epoxide to iBu_2AlH at low temperature proved workable,[9] providing a mixture of diastereomeric secondary alcohols. Oxidation[10] of the alcohols produced a 3:1 mixture of ketones **17**/**18**, revealing that the epoxidation and in situ reduction had provided a 3:1 diaste-

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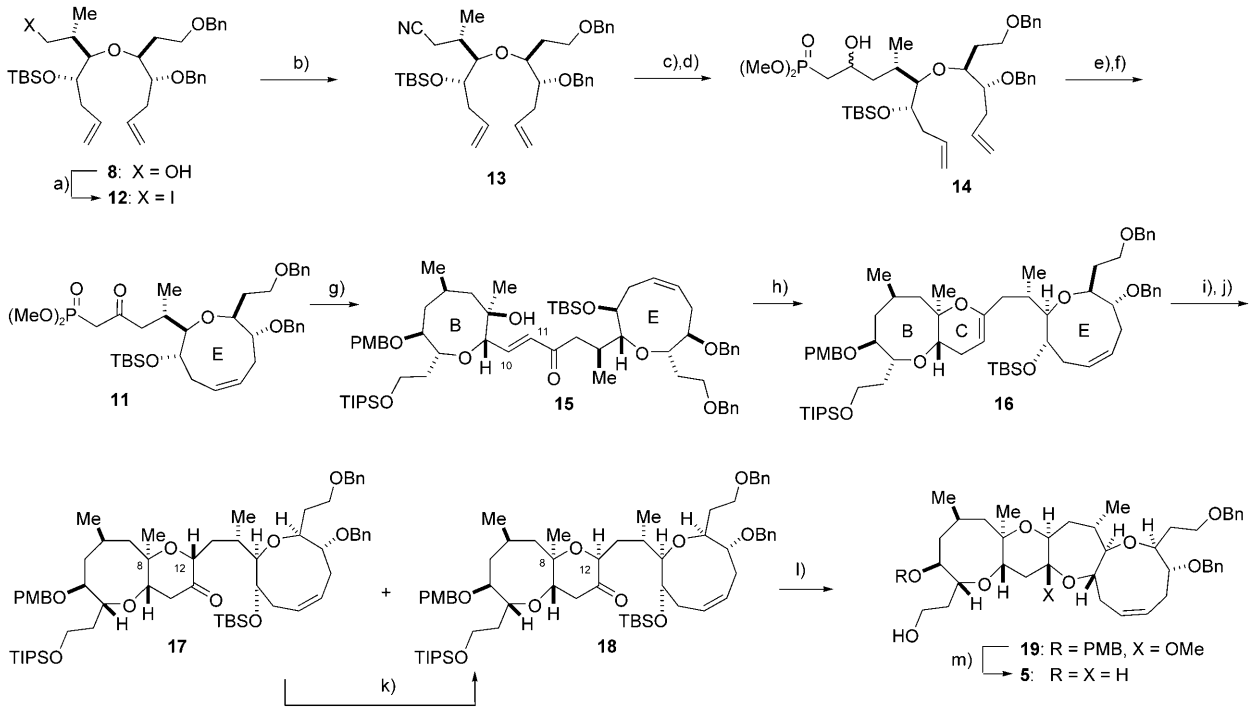
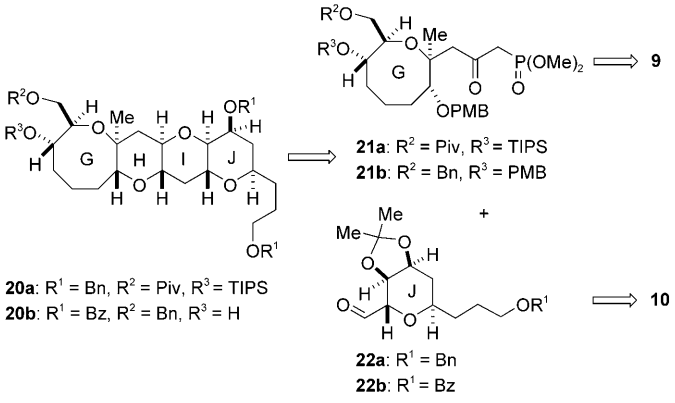


Scheme 4. Synthesis of the BCDE tetracycle **5**. Reagents and conditions: a) PPh_3, I_2, imidazole, C_6H_6, 97%; b) NaCN, DMSO, 96%; c) *i*Bu_2AlH, CH_2Cl_2, 0°C, 84%; d) $(MeO)_2P(O)CH_3$, *n*BuLi, THF, −78°C, 88%; e) Dess–Martin periodinane, CH_2Cl_2, 96%; f) [Ru(=CHPh)Cl_2(Cy_3P)(sIMes)] (sIMes = 1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene), CH_2Cl_2, 40°C, (quant.); g) **7**, $Ba(OH)_2$, THF, H_2O, 96%; h) [RhCl(PPh_3)$_3$], Me_2PhSiH, PhMe, 50°C; PPTS, 92%; i) DMDO, CH_2Cl_2, −78°C; *i*Bu_2AlH; j) Dess–Martin periodinane, CH_2Cl_2, 67% (3:1 dr) for 2 steps; k) K_2CO_3, MeOH, 65°C, 66% (84% based on recovered starting material (brsm)); l) CSA, MeOH, 65°C, 76%; m) $BF_3{\cdot}OEt_2$, Me_2PhSiH, CH_2Cl_2, 0°C, 78%.

reomeric ratio (dr) at C12, favoring the undesired configuration. This result was certainly not unexpected based on the influence of the C8 angular methyl on the approach of electrophiles to the C11–C12 enol ether double bond of **16.** Additionally, because of the 1,3-relationship of the C8 angular methyl and the C12 substituent, it was anticipated that major isomer **17** might be readily epimerized to **18**. After investigating several bases and solvent systems, it was discovered that heating the mixture of ketones at reflux in methanol with potassium carbonate provided a 3:1 dr at C12, favoring the desired configuration **18**.[11] Furthermore, the minor isomer could then be recovered and exposed to the same equilibration conditions, ultimately providing an excellent yield of the desired ketone **18**. Heating ketone **18** at reflux in methanol with camphorsulfonic acid (CSA) provided the desired mixed methyl ketal **19** with loss of the primary triisopropylsilyl (TIPS) protecting group,[12] and reductive etherification delivered the targeted BCDE tetracycle **5**.[13]

Based upon the effectiveness of our approach to the BCDE ring system, our vision for the synthesis of the GHIJ fragment **20** involved analogous coupling of a G ring ketophosphonate with a J ring aldehyde (Scheme 5). We recognized that the choice of protecting groups employed in the GHIJ fragment synthesis would not only factor into the overall efficiency of the total synthesis, but could also prove critical in the success of key reactions. With preliminary experiments revealing that silyl protecting groups were unsuitable for the J ring (i.e., $R^1 = SiR_3$, Scheme 5) due to their lability under the acidic conditions used in the synthesis, two strategies were conceived. Although we were compelled by the robustness of the protecting groups in the coupling of G ring **21a** (R^2 = pivaloyl (Piv), R^3 = TIPS) and J ring **22a** (R^1 = Bn), we were also attracted to the expedient coupling of G ring **21b** (R^2 = Bn, R^3 = PMB) and J ring **22b** (R^1 = Bz), in which protecting-group manipulations from G ring intermediate **9** would be minimized. In either case, HWE coupling would lead to an enone intermediate and subsequent 1,4-reduction and cyclodehydration would lead to an enol ether poised for hydration and ultimate reductive



Scheme 5. [X+2+X] strategy for the GHIJ fragment.

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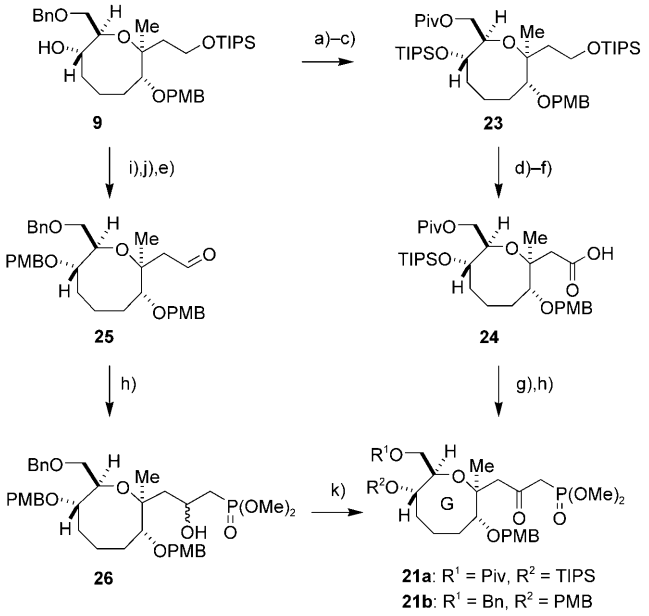
etherification to produce the desired tetracyclic fragment **20a** or **20b**. In the end, both protecting-group strategies were explored as viable routes toward the completion of the total synthesis.

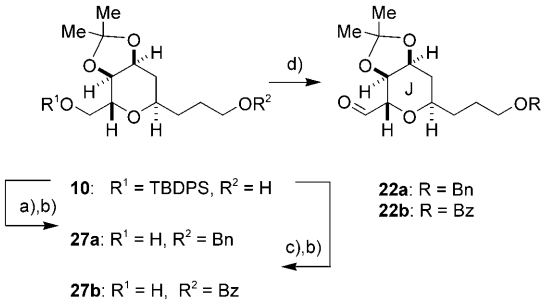
The G ring intermediate **9** (Scheme 6) was first converted to ketophosphonate **21a** through an eight-step sequence. After obtaining bis-TIPS ether **23** through a series of pro-



Scheme 6. Completion of G ring keto phosphonates **21a** and **21b**. Reagents and conditions: a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; b) LiDBB, THF, −78 °C; c) PivCl, DMAP, Et_3N, CH_2Cl_2, 90 % for 3 steps; d) trifluoroacetic acid (TFA), THF, H_2O, 96 %; e) 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), NaOCl, KBr, CH_2Cl_2, H_2O, 0 °C, 97 %; f) $NaClO_2$, Me_2C=CHMe, *t*BuOH, pH 4 buffer, 98 %; g) K_2CO_3, MeI, DMF, 96 %; h) $LiCH_2(O)P(OMe)_2$, THF, −78 °C, 87 % (for **21a**), 89 % (for **26**); i) NaH, PMBBr, $nBu_4N^+I^-$, THF, 0 °C to RT; j) H_2SiF_6, CH_3CN, 89 % for 2 steps; k) Dess–Martin periodinane, CH_2Cl_2, 92 %.

tecting-group manipulations, selective removal of the primary TIPS group under acidic conditions followed by a two-step oxidation process[14] provided carboxylic acid **24** in excellent yield. Exposure to K_2CO_3 and MeI afforded the methyl ester, which underwent a Claisen condensation with lithiated dimethyl methylphosphonate to give the desired keto phosphonate **21a**. Alternatively, protection of G ring intermediate **9** as the bis-*p*-methoxybenzyl (PMB) ether, rapid removal of the TIPS group with H_2SiF_6,[15] and oxidation of the resultant alcohol with catalytic 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) revealed aldehyde **25** in 87 % yield over three steps.[16] In this case, direct reaction of the aldehyde with lithiated dimethyl(methylphosphonate) was high yielding and oxidation of the resultant β-hydroxyphosphonates **26** (inconsequential mixture of diastereomers) under Dess–Martin conditions afforded ketophosphonate **21b.** Although ketophosphonate **21a** required three more steps from intermediate **9** than ketophosphonate **21b**, the overall yield was quite similar in both cases.

The J ring alcohol **10** was used to quickly access aldehydes **22a** and **22b** through three-step sequences (Scheme 7). For aldehyde **22a**, protection of the primary alcohol as the



Scheme 7. Completion of J ring aldehydes **22a** and **22b**. Reagents and conditions: a) KH, BnBr, $nBu_4N^+I^-$, THF, 0 °C, 88 %; b) nBu_4NF, THF, 99 % (for **27a**), 100 % (for **27b**); c) BzCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 91 %; d) TEMPO, NaOCl, KBr, CH_2Cl_2, H_2O, 0 °C, 87 % (for **22a**), 70 % (for **22b**). Bz = benzoyl.

benzyl ether and removal of the *tert*-butyldiphenylsilyl (TBDPS) group with nBu_4NF yielded alcohol **27a**. Although a host of oxidants were found to be unsuitable for alcohol **27a** due to epimerization and overoxidation to the carboxylic acid, the use of TEMPO was found to reliably give aldehyde **22a** in 87 % yield.[16] Alternatively, J ring alcohol **10** was protected with benzoyl chloride in the presence of *N*,*N*′-dimethylaminopyridine (DMAP) to provide the benzoate ester, which was subjected to nBu_4NF as before to deliver alcohol **27b** in 91 % over two steps. Once again, TEMPO proved to be the oxidant of choice for the formation of the sensitive aldehyde **22b**.

The HWE coupling of the G and J rings was first explored for keto phosphonate **21a** and aldehyde **22a** (Scheme 8). As in the BCDE synthesis, exposure to $Ba(OH)_2$ smoothly furnished enone **28a** in 80 % yield. Clean 1,4-reduction with 40 mol % of Stryker's reagent produced the ketone and the acetonide protecting group was swiftly removed by heating at reflux in methanol with TFA to afford diol **29a** in 88 % yield over two steps. The ketophosphonate **21b** and aldehyde **22b** were coupled and converted to the corresponding diol **29b** following the same three-step protocol, though in slightly diminished yield.

The cyclodehydration of ketodiol **29a** to form the I ring (Scheme 9) was met with considerable resistance because both the desired enol ether and the starting material were observed to degrade into a complex mixture of intractable products under even moderately acidic conditions, particularly upon heating above 50 °C. Furthermore, conversion of the starting material was often sluggish, indicating the need for rigorous removal of water. It was hoped that the reaction would proceed at room temperature in the presence of strong acid and molecular sieves, but in practice, successful reaction required increased temperature. Eventually it was found that reaction with PPTS in benzene at 40 °C with azeotropic removal of water under aspirator vacuum

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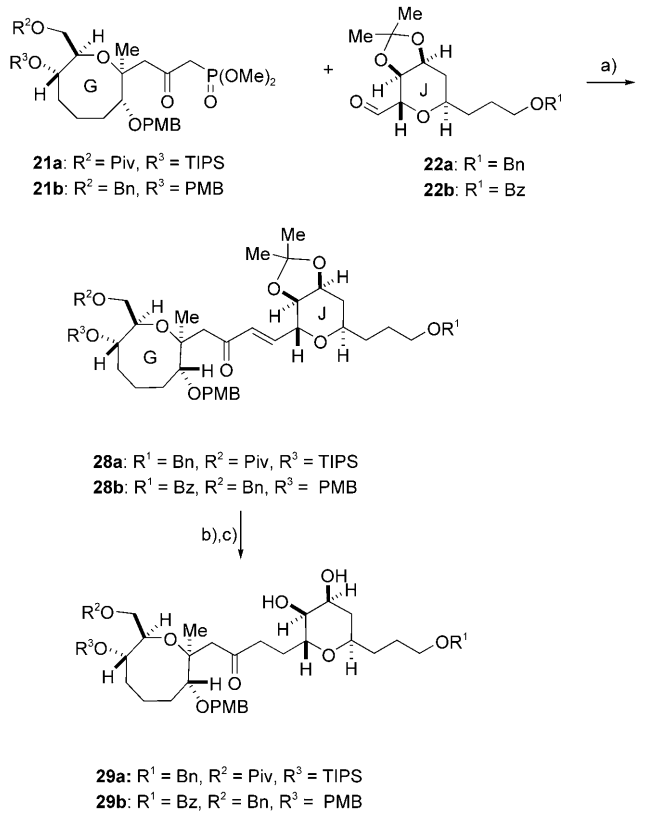
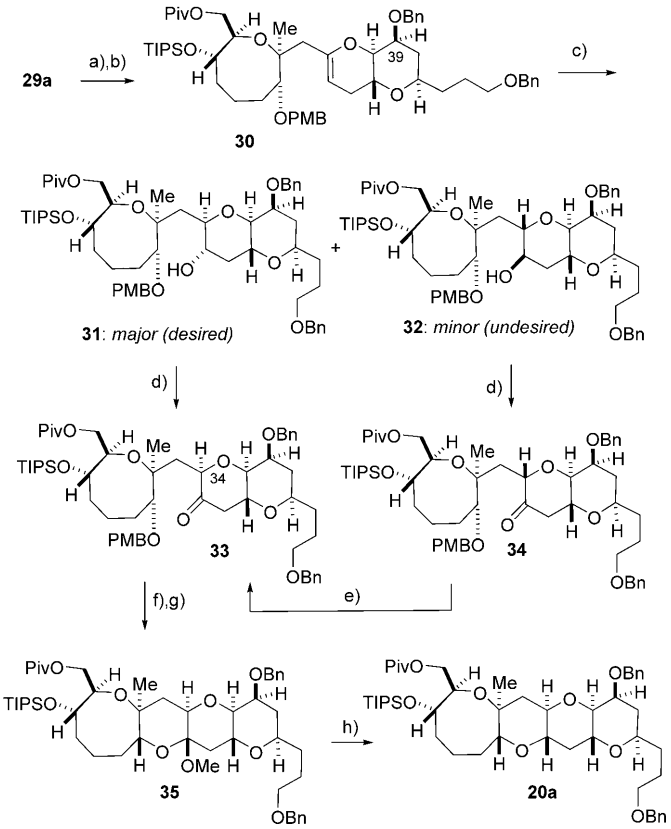


Scheme 8. HWE coupling of the G and J rings. Reagents and conditions: a) $Ba(OH)_2$, H_2O, THF, 80%; b) $[CuH(Ph_3P)]_6$ (40 mol%), PhMe, 95% (from **28a**), 89% (from **28b**); c) TFA, MeOH, 65°C, 93% (for **29a**), 83% (for **29b**).



Scheme 9. Completion of GHIJ fragment **20a**. Reagents and conditions: a) PPTS, C_6H_6, 40°C, 50 mm Hg, 82% brsm; b) $KN(SiMe_3)_2$, BnBr, $Bu_4N^+I^-$, THF, 0°C to RT, 92%; c) BH_3·THF, THF, 0°C, 91% (3:1 dr); d) Dess–Martin periodinane, CH_2Cl_2, 96% (from **31**), 80% (from **32**); e) DBU, CH_2Cl_2, 40°C, 85% brsm; f) DDQ, CH_2Cl_2, pH 7 buffer, 89%; g) PPTS, MeOH, 65°C, 87%; h) BF_3·OEt_2, Et_3SiH, CH_2Cl_2, −30 to 0°C, 96%.

(≈25 mm Hg) smoothly produced the desired endocyclic enol ether in good yield with minimal decomposition. Protection of the axially disposed C39 hydroxyl as its benzyl ether with potassium hexamethyldisilazide (KHMDS) and BnBr then yielded ether **30.**

The stage was then set for the critical enol ether hydration/oxidation sequence. Although selective olefin hydration was achieved in the BCDE system through the use of DMDO/*i*Bu_2AlH, the absence of other double bonds in the GHIJ system allowed for hydroboration/oxidation of the I ring enol ether **30**. Although BH_3·DMS was unsatisfactory, BH_3·THF allowed for a 91% yield of a 3:1 mixture of separable diastereomers **31** and **32** after alkaline peroxide workup.[17] The isomers were separately oxidized under Dess–Martin conditions to the corresponding ketones **33** and **34**, respectively. Whereas the minor epimer **34** was isomerized to the major epimer **33** with 1,8-diazabicycloundec-7-ene (DBU) at 40°C in good yield, the major epimer **33** could not be isomerized to the minor ketone **34** under identical conditions. The major isomer was therefore reasoned to have the desired configuration at C34, since having the G ring substituent in an equatorial position on the I ring would be more thermodynamically favorable.

To complete the GHIJ fragment, the PMB protecting group of ketone **33** was oxidatively removed with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), and the resulting hemiketal was treated with PPTS in MeOH to form mixed methyl ketal **35**. Reductive etherification mediated by BF_3·Et_2O and Et_3SiH then completed the GHIJ tetracycle **20a** in excellent yield as a single isomer.[18]

To our surprise, the cyclodehydration of ketodiol **29b** (Scheme 10) did not proceed well under the previously employed conditions. However, treatment with P_2O_5 in toluene at −30°C delivered the endocyclic enol ether in good yield. Acylation of the C39 hydroxyl with benzoyl chloride and DMAP in pyridine with heating provided the benzoate-protected enol ether **36**. Similar to before, BH_3·THF was effective (95% yield) for the hydroboration of the enol ether, but in this case, the hydration product obtained after oxidative workup was an inseparable mixture of diastereomers (2:1 dr). Other reagents for hydroboration, including 9-borabicyclo[3.3.1]nonane (9-BBN) and enantiopure isopinocampheylborane ($IpcBH_2$),[19] were probed with the intention of increasing the diastereoselectivity of the reaction, but inferior results were obtained. Thus, the mixture of diastereomers was oxidized to ketone **37** (2:1 mixture of inseparable epimers) under Dess–Martin conditions and exposure

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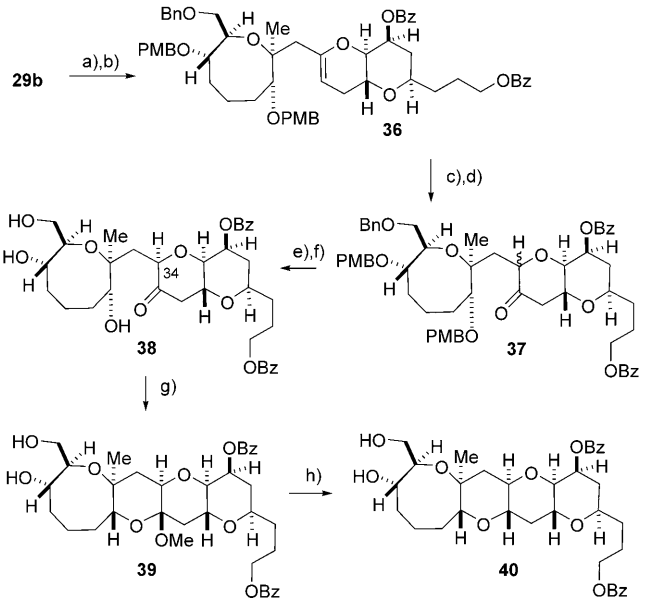
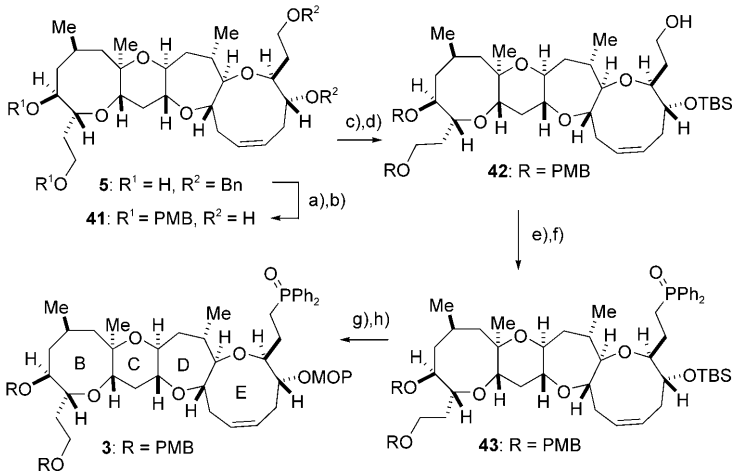


Scheme 10. Completion of alternative GHIJ fragment **40**. Reagents and conditions: a) P_2O_5, PhMe, −30 °C, 80% (95% brsm); b) BzCl, DMAP, pyridine, 60 °C, 95%; c) BH_3·THF, THF, 0 °C; d) Dess–Martin periodinane, CH_2Cl_2, 87% for 2 steps, 2:1 dr; e) DBU, CH_2Cl_2, 40 °C; f) H_2, $Pd(OH)_2$, THF, 68% for 2 steps; g) PPTS, MeOH, 65 °C, 80%; h) BF_3·OEt_2, Et_3SiH, CH_2Cl_2, −30 to 0 °C, 95%.



Scheme 11. Formation of phosphine oxide **3**. Reagents and conditions: a) NaH, PMBBr, DMF, 91%; b) LiDBB, THF, −78 °C, 89%; c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 96%; d) HF·pyridine, THF, 86%; e) MsCl, Et_3N, 0 °C; f) *n*BuLi, $HPPh_2$, THF, 0 °C; H_2O_2, 94% for 2 steps; g) nBu_4NF, THF, 94%; h) 2-methoxypropene, PPTS, 0 °C, 90%.

to DBU increased the diastereomeric ratio to 6:1. At this point, it was postulated that removal of one or more of the hydroxyl protecting groups might allow for separation of the epimers. Although we favored selective removal of the PMB groups with DDQ at this juncture to access the targeted tetracycle **20b** (Scheme 5), the resulting diols remained an inseparable mixture. On the other hand, hydrogenolysis of both PMB groups and the benzyl group by using the Pearlman catalyst led to triol **38**,[20] from which the minor, undesired isomer 34-*epi*-**38** was easily removed by chromatography. Ketalization with PPTS in MeOH led to mixed methyl ketal **39** and reductive etherification under conditions used before accomplished a shortened synthesis of the GHIJ fragment **40** in excellent yield.

Coupling of the BCDE and GHIJ fragments and completion of 1: The planned approach for the completed total synthesis of **1** focused on an endgame that would exploit the selective manipulation of nonacycle **2** (see above, Scheme 1). Nonacycle **2** would derive from a stereoselective Horner–Wittig coupling[21] of phosphine oxide **3** and aldehyde **4**, which found precedent in the strategy previously reported by Nicolaou and co-workers.[2] We recognized that the dithioketal moiety of aldehyde **4** offered versatility because it could serve as a stabilized precursor to a mixed ketal (**2**, X = OMe) or lead to a mixed *S*,*O*-ketal (**2**, X = SO_2Et) in the event that formation or reductive etherification of the less-activated nonacycle proved to be problematic.

The next task became the manipulation of the tetracyclic fragments **5** and **20a** or **40** to the required Horner–Wittig coupling partners. To this end, the conversion of diol **5** to phosphine oxide **3** (Scheme 11) commenced with protection of diol **5** as the bis-*p*-methoxybenzyl ether with subsequent reductive cleavage of the benzyl ethers with lithium di-*tert*-butyl diphenyl (LiDBB) to form diol **41**. Protection of the diol as the bis-*tert*-butyldimethylsilyl (TBS) ether and selective cleavage of the primary TBS ether with HF·pyridine afforded alcohol **42**. Smooth transformation to phosphine oxide **43** was then accomplished through mesylation of the alcohol, nucleophilic displacement of the mesylate to provide the phosphine, and finally, oxidative workup of the phosphine with H_2O_2.[2,21] Cleavage of the silyl ether **43** with nBu_4NF and formation of the methoxypropyl (MOP) acetal delivered the required phosphine oxide **3** in high yield.[22]

For the GHIJ fragment, tetracycle **20a** was treated with nBu_4NF and the resultant secondary alcohol was oxidized to ketone **44** under Dess–Martin conditions (Scheme 12). Reaction of ketone **44** with $Zn(OTf)_2$ and EtSH produced the dithioketal[23] and reductive cleavage of the pivaloate ester delivered alcohol **45**. Although most conditions proved to be unsuitable for the subsequent oxidation of the primary alcohol to dithioketal aldehyde **46** due to undesired oxidation of the dithioketal, the use of stoichiometric nPr_4NRuO_4 cleanly provided the desired aldehyde.[24]

As for the alternative GHIJ tetracycle **40**, the primary hydroxyl was selectively protected as the TBS ether (Scheme 13) and the remaining secondary hydroxyl was oxidized under buffered Dess–Martin conditions to afford ketone **47**. Removal of the silyl protecting group with H_2SiF_6 provided the hydroxy ketone and exposure to $Zn(OTf)_2$ in 1:1 EtSH/CH_2Cl_2 reliably gave dithioketal **48**. As before, reaction with one equivalent of nPr_4NRuO_4 delivered aldehyde **49** in good yield.

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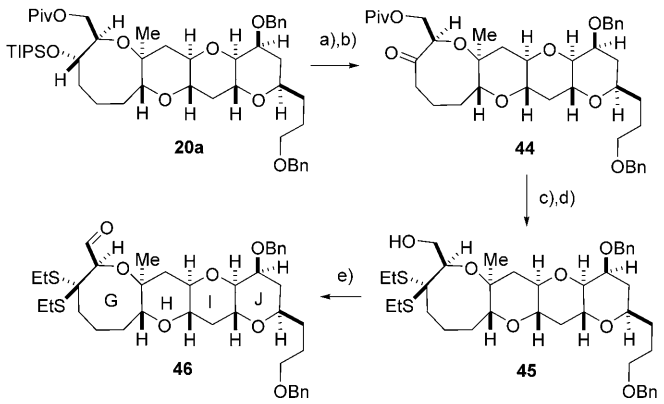
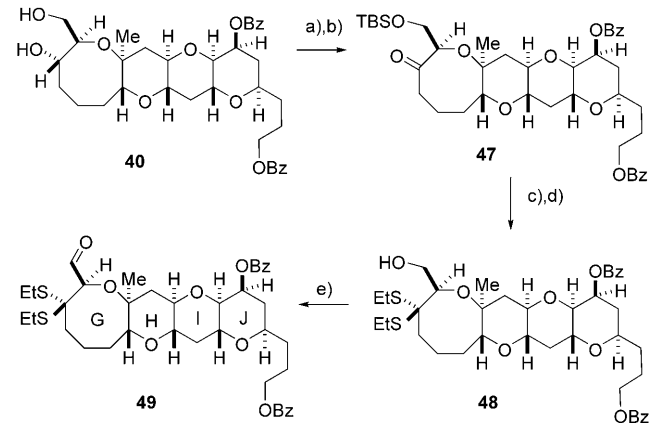


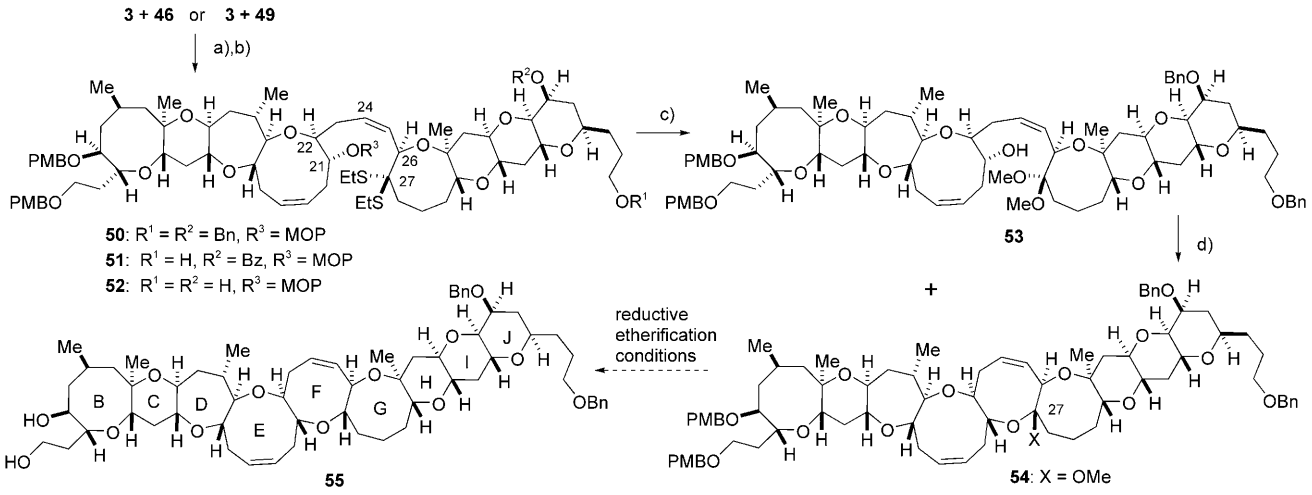
Scheme 12. Preparation of aldehyde **46**. Reagents and conditions: a) nBu$_4$NF, THF, 0°C, 94%; b) Dess–Martin periodinane, CH_2Cl_2, 95%; c) $Zn(OTf)_2$, EtSH, CH_2Cl_2, 97%; d) $LiAlH_4$, Et_2O, 0°C, 85%; e) nPr$_4$NRuO$_4$, 4 Å MS, CH_2Cl_2, 75%.



Scheme 13. Preparation of aldehyde **49**. Reagents and conditions: a) TBSCl, imidazole, CH_2Cl_2, 94%; b) Dess–Martin periodinane, pyridine, CH_2Cl_2, 87%; c) H_2SiF_6, CH_3CN, H_2O, 97%; d) $Zn(OTf)_2$, EtSH, CH_2Cl_2, 87%; e) nPr$_4$NRuO$_4$, 4 Å MS, CH_2Cl_2, 75%.

Having both phosphine oxide **3** and aldehydes **46** and **49** in hand, we then explored their assembly under Horner–Wittig conditions (Scheme 14).[2,21] After some experimentation, addition of three equivalents of lithium diisopropylamide (LDA) to a solution of phosphine oxide **3** and aldehyde **46** at −78°C was found to produce 63% of the Horner–Wittig adduct. It is noteworthy that no epimerization of aldehyde **46** was observed despite the presence of superstoichiometric base.[25] Exposure of the intermediate hydroxyphosphine oxide to $KN(SiMe_3)_2$ provided the desired *Z*-olefin **50** in 74% yield. In contrast, when phosphine oxide **3** and aldehyde **49** were reacted in the presence of three equivalents of LDA, the desired Wittig adduct was obtained in only 28% yield, along with an additional 14% of adduct in which the primary benzoate ester had been cleaved. Treatment of the Wittig adducts with $KN(SiMe_3)_2$ was also complicated by the loss of benzoate protecting groups and unidentified degradation, producing olefins **51** and **52** in an unacceptable 32% combined yield. Further attempts to identify cleaner elimination conditions by altering the base, solvent, and temperature were unsuccessful.

After carrying out the effective coupling of the BCDE **3** and GHIJ **46** fragments, we focused on mixed methyl ketal **54** as a precursor to the targeted nonacycle **55** (Scheme 14). Despite the rarity of the conversion of 7-hydroxy ketones or ketals to eight-membered cyclic ketals found in the literature, we believed that the formation of mixed ketal **54** should be possible due to the structural preorganization appearing in olefin **50**. Specifically, we expected the C24–C25 *Z* olefin, along with the conformational constraints about the C21–C22 and C26–C27 bonds, to facilitate the required cyclization event. In addition, based upon the reported use of $(F_3CCO_2)_2$IPh in alcoholic solvent to convert dithioketals to dialkoxy ketals,[26] we presumed that treating olefin **50** with the hypervalent iodine reagent in MeOH would lead to the dimethyl ketal **53** or to mixed ketal **54** directly. In the event, treatment of olefin **50** with $(F_3CCO_2)_2$IPh in MeOH



Scheme 14. Coupling of tetracyclic fragments **3** and **46**. Reagents and conditions: a) LDA, THF, −78°C, 63% (from **3**+**46**), 42% (from **3**+**49**); b) KN(SiMe$_3$)$_2$, DMF, 74% (for **50**), 32% (for **51** and **52**, combined yield); c) $(F_3CCO_2)_2$IPh, MeOH; d) PPTS, $CH(OMe)_3$, PhMe, 50°C, 80% for 2 steps.

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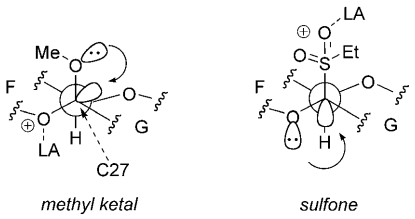
rapidly removed the MOP protecting group and led to a mixture of the expected ketal products in a 4:1 ratio, favoring the dimethyl ketal **53**.[27] Upon exposure of the crude mixture to PPTS, an 80% overall yield of mixed methyl ketal **54** was obtained.

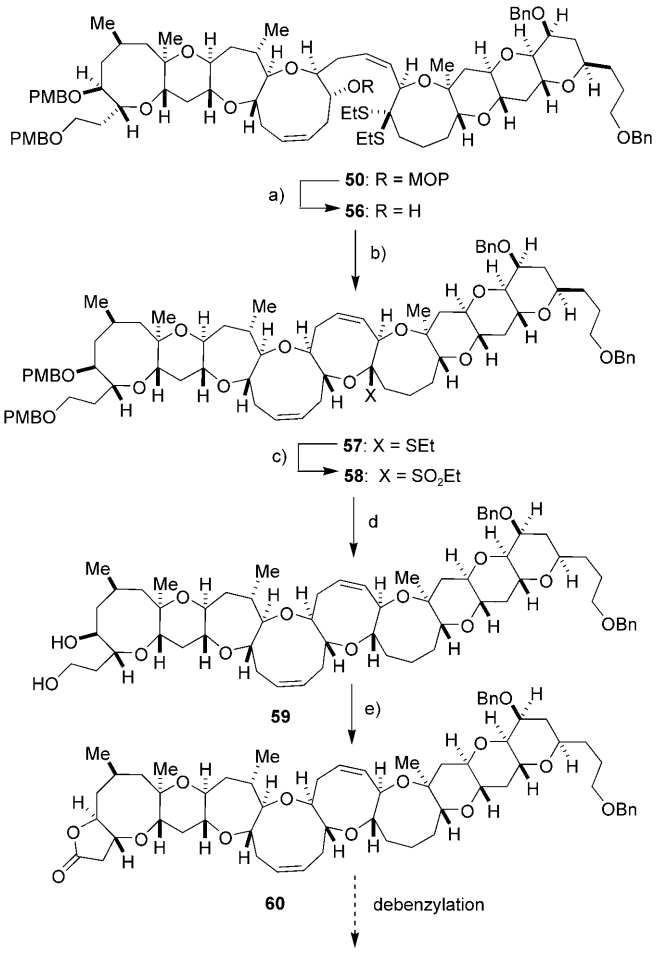
In view of our previous successes in the reductive etherification of precursors to the BCDE and GHIJ fragments (see above, Schemes 4, 9, and 10), it was anticipated that treatment of ketal **54** with an appropriate Lewis acid in the presence of a trialkylsilane would deliver the expected nonacycle **55**. Despite extensive screening of Lewis acids ($BF_3{\cdot}OEt_2$, $TiCl_4$, trimethylsilyl trifluoromethanesulfonate (TMSOTf)), solvents, and silanes (Et_3SiH, Me_2PhSiH), only traces of the desired product **55** were observed. Instead, hydrolysis of the ketal and intractable decomposition were repeatedly observed.[28] Drying agents (4 Å molecular sieves, BaO) were investigated in an effort to suppress hydrolysis, but under these conditions, cleavage of the central oxocene (producing the C27 methyl ether) was the major product. This result indicated that the kinetically preferred mode of C–X bond cleavage for the methyl ketal substrate involved good $n_O \rightarrow \sigma^*_{C27-O}$ orbital overlap (Scheme 15), leading to a ring-opened oxocarbenium ion that is intercepted by silane. We reasoned that the precedented sulfone leaving group[2,29]



Scheme 15. Favored modes of C–X bond cleavage for methoxy ketal and sulfone substrates.

would circumvent this unwanted stereoelectronic effect, since the absence of lone pair electrons on sulfur would render the $n \rightarrow \sigma^*_{C27-O}$ interaction inoperative. Instead, the required mode of bond cleavage should be favored (Scheme 15). The increased lability of the sulfinate leaving group relative to the methoxide nucleofuge was also expected to facilitate the desired reactivity.

Turning our attention to the reductive etherification of sulfone **58** (Scheme 16), the MOP acetal was removed from olefin **50** under acidic conditions, and the resulting hydroxy dithioketal **56** was treated with $AgClO_4$ to provide the mixed *S,O*-ketal **57**.[2] Subsequent oxidation with *m*-CPBA led to sulfone **58** and reductive etherification with concomitant removal of the PMB protecting groups was smoothly accomplished to give diol **59** in 85% yield. Whereas the A ring lactone **60** was readily accessible in 83% yield from diol **59** through exposure to $PhI(OAc)_2$ and catalytic TEMPO,[30] clean debenzylation was not observed under a variety of conditions. Nevertheless, compound **1** was accessed in three steps from diol **59** (Scheme 17). Reductive



Scheme 16. Closure of the A and F rings. Reagents and conditions: a) PPTS, MeOH, 0°C, 96%; b) $AgClO_4$, $NaHCO_3$, 4 Å MS, $MeNO_2$, 65%; c) *m*-CPBA, CH_2Cl_2, 0°C, 74%; d) $BF_3{\cdot}OEt_2$, Et_3SiH, CH_2Cl_2, −78 to 0°C, 85%; e) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 83%.

cleavage of the benzyl ethers with LiDBB[31] delivered tetraol **61**, which was exposed to $PhI(OAc)_2$ and catalytic TEMPO to selectively form the A-ring lactone and the C44 aldehyde, while leaving the axially-disposed C39 secondary alcohol untouched.[30] The unpurified decacyclic aldehyde **62** was treated with Eschenmoser's salt in the presence of Et_3N[2,32] to complete the synthesis of **1**.[33] Synthetic **1** was identical in all respects (^1H and ^{13}C NMR and IR spectroscopies, mass spectrometry, and $[\alpha]_D$) to an authentic sample.[2a,d,34]

Conclusion

The second total synthesis of **1** has been accomplished in a highly convergent, enantioselective fashion. The synthesis hinges on the selective oxidation of a late-stage nonacyclic tetraol. Access to the key tetraol intermediate was explored through the rare cyclization of a medium-ring mixed methyl ketal, which was assessed as a substrate for oxocene-forming reductive etherification. In the end, a sulfone-based ap-

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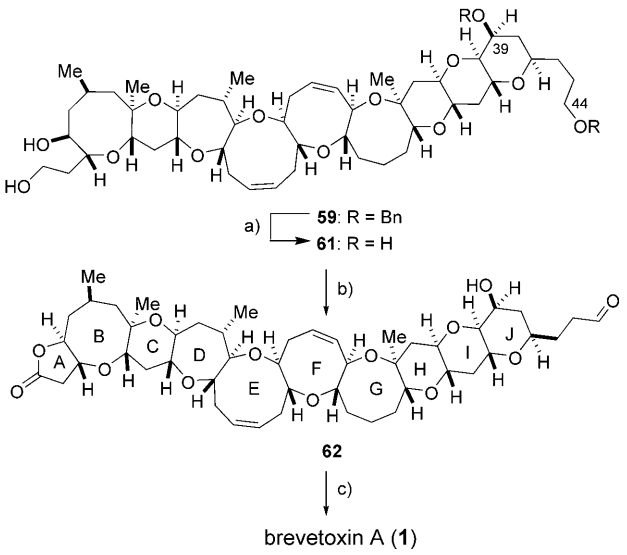

Scheme 17. Completion of **1**. Reagents and conditions: a) LiDBB, THF, −78 °C, 86%; b) TEMPO, $PhI(OAc)_2$, CH_2Cl_2; c) $H_2C{=}NMe_2{}^+I^-$, Et_3N, CH_2Cl_2, 48% for 2 steps.

proach proved to be a superior path to the nonacyclic tetraol. A Horner–Wittig olefination of two advanced tetracyclic subunits assembled the eventual tetraol precursor, with the tetracyclic units being constructed through a common [X+2+X] strategy by using a HWE coupling and subsequent cyclodehydration/reductive etherification protocol. Each of the monocyclic units for the construction of the tetracyclic BCDE and GHIJ units was prepared from a RCM of an acyclic diene precursor with stereodefined ether linkages. Enolate methodologies developed in our laboratory were exploited to introduce 8 of the 22 stereocenters present within **1**.

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