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TOTAL SYNTHESIS OF GAMBIEROL

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Abstract – Gambierol is a marine polycyclic ether toxin isolated from the cultured cells of the ciguatera causative dinoflagellate *Gambierdiscus toxicus*. The fascinating molecular structure of gambierol, its association with ciguatera poisoning, and its potential biological activity have drawn significant attention from the synthetic community and provided a strong impetus for the development of an efficient path by which a total synthesis can be achieved. We recently accomplished the synthesis of gambierol based on an oxiranyl anion strategy. To date, four total syntheses have been reported. This review focuses on the efforts that culminated in the total synthesis of gambierol.

CONTENTS

1. INTRODUCTION

Dinoflagellate toxins constitute a large family of compounds, many of which exhibit a wide range of physiological activities. Accordingly, intense activity has been devoted to the isolation and structure determination of toxins. Ciguatera poisoning is a toxicological syndrome resulting from the ingestion of seafood contaminated by certain toxic polycyclic ethers produced by the epiphytic dinoflagellate *Gambierdiscus toxicus*. The toxin suite comprises ciguatoxins, maitotoxin, and gambierol.[1] The large complex architecture of these compounds and their potent neurotoxicity have attracted the attention of chemists and have made them the focus of numerous synthetic efforts.[2] Gambierol (**1**) was isolated as a

neurotoxin from the cultured cells of *G. toxicus* in 1993.[3] The absolute stereochemistry was later determined by NMR analysis of the (*S*)- and (*R*)-phenylmethoxy(trifluoromethyl)acetate (MTPA) derivatives.[4] The toxin exhibits potent toxicity against mice with an LD_{50} of 50 μg/kg (ip), and its symptoms occurring in mice resemble those displayed in ciguatoxins, indicating that gambierol is also responsible for ciguatera seafood poisoning. The ability of gambierol to inhibit the binding of dihydrobrevetoxin B to voltage-sensitive sodium channels[5] has also attracted attention, leading to structure-activity relationship (SAR) studies.[6] Further evaluation of its molecular target on the ion channels has revealed that gambierol inhibits the voltage-gated potassium channels in mouse taste cells,[7] which might be associated with the taste alteration caused by ciguatera intoxication, and modulates ion fluxes by acting as a partial agonist of sodium channels in human neuroblastoma cells.[8] Moreover, gambierol has been reported to act as a functional antagonist of neurotoxin site 5 on voltage-gated sodium channels in cerebellar granule neurons.[9]

Gambierol (**1**) consists of a ladder-shaped *trans*-fused octacyclic ring system that includes 18 stereogenic centers and a partially conjugated triene side chain, including a conjugated (Z,Z)-diene system (Figure 1). The complex architecture and the need for biologically active analogues for SAR study continue to interest organic chemists. To date, three convergent total syntheses by Sasaki's,[10] Kadota-Yamamoto's,[11] and Rainier's[12] groups and one linear iterative synthesis by Mori's group[13] have been achieved. Although, several synthetic efforts directed toward the target have been reported in the literature,[14] this review focuses on the works that culminated in the total synthesis of gambierol.

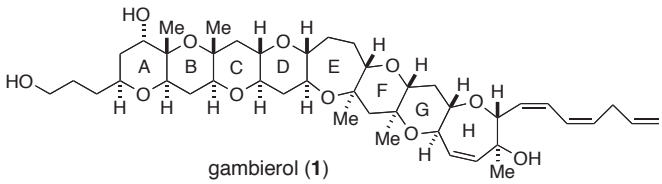


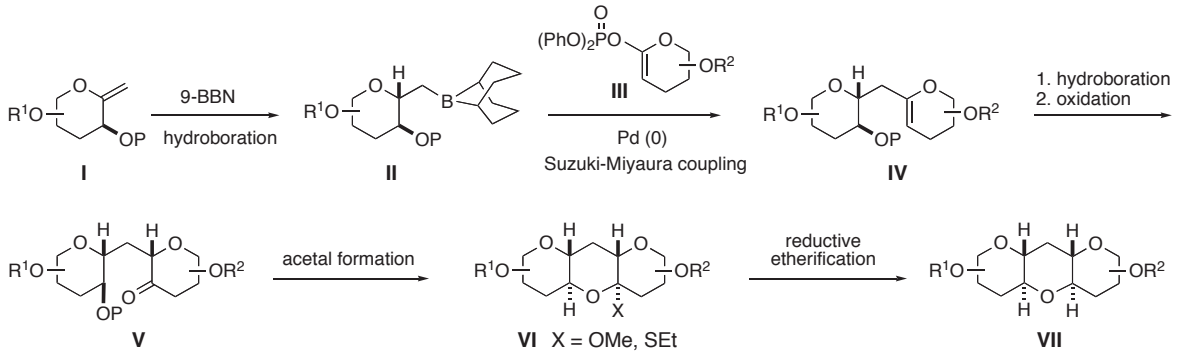
Figure 1. Structure of gambierol

2. SASAKI'S TOTAL SYNTHESIS

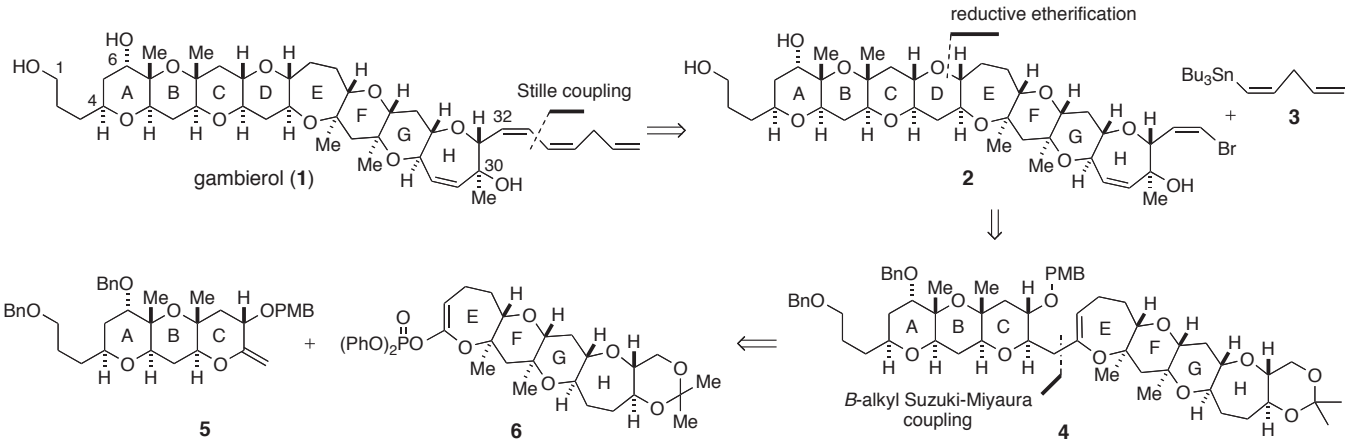
2.1. Retrosynthesis. The first total synthesis of gambierol was reported by Sasaki's group in 2002.[10] From the standpoint of developing a convergent strategy, Sasaki's synthesis provided a demonstration of the great efficacy of *B*-alkyl Suzuki-Miyaura coupling[15] for the convergent synthesis of six-membered ether rings.[16] Alkylborane **II**, prepared from hydroboration of exocyclic enol ether **I** with 9-BBN, reacted with ketene acetal phosphate **III** to afford the cross-coupling product **IV** (Scheme 1). Hydroboration and

oxidation provided ketone **V**, and subsequent acetal formation and reductive etherification enabled the construction of polycyclic ether framework **VII** in a convergent manner.

Sasaki planned to construct the triene side chain of gambierol (**1**) by Stille coupling[17] of vinyl bromide **2** and tributyl((*Z*)-penta-1,4-dienyl)stannane (**3**)[18] at a late stage of the synthesis according to the Kadota's protocol[19] (Scheme 2). Retrosynthetic disassembly of the octacyclic intermediate **2** via **4** based on the Suzuki-Miyaura coupling strategy provides the ABC-ring exocyclic enol ether **5** and the EFGH-ring ketene acetal phosphate **6**.



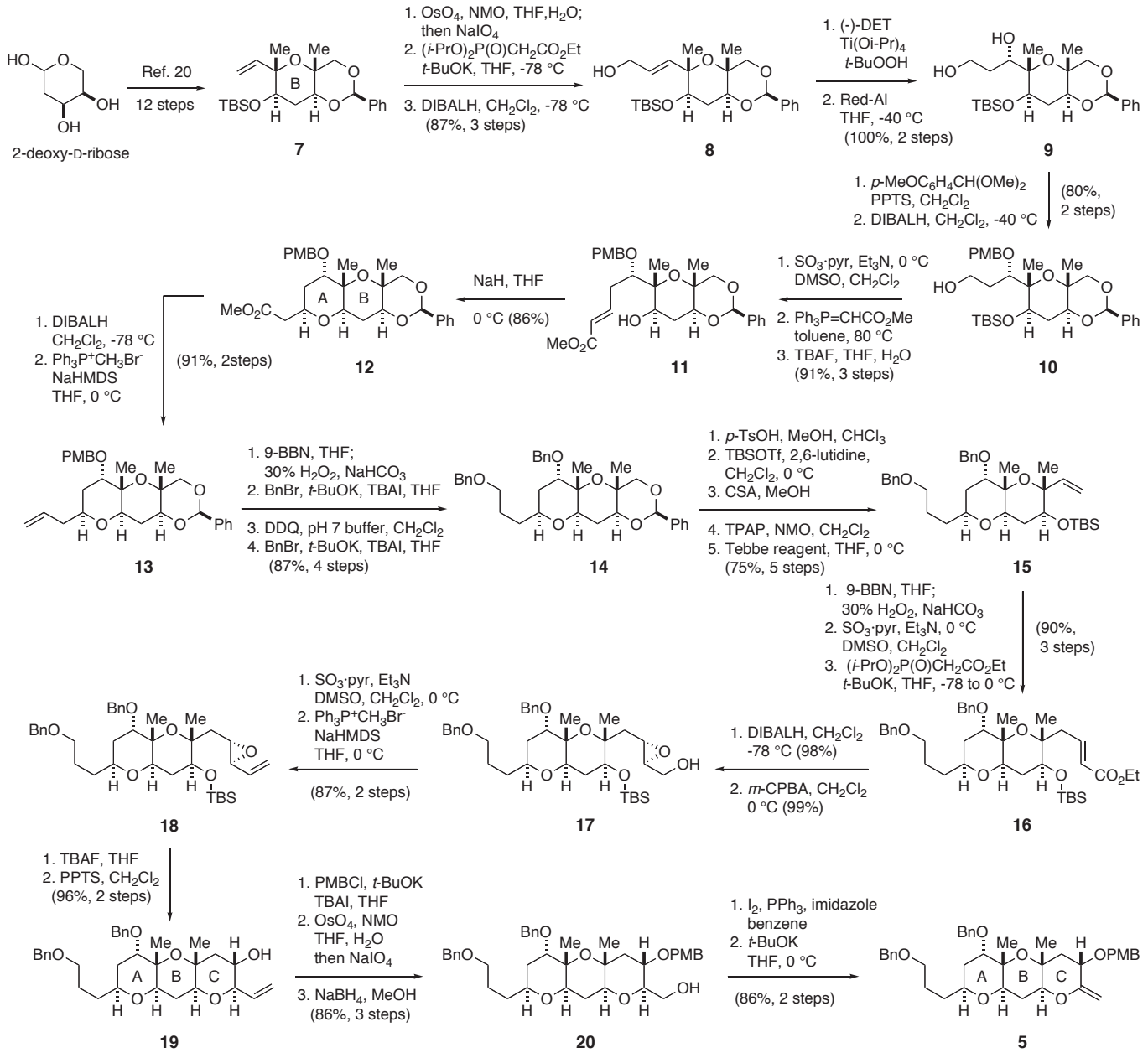
Scheme 1. *B*-Alkyl Suzuki-Miyaura coupling-based convergent strategy



Scheme 2. Sasaki's retrosynthesis of gambierol

2.2. Synthesis of the ABC rings. The synthesis commenced with the known B-ring olefin **7**, an intermediate of Nicolaou's brevetoxin B synthesis, which was prepared from 2-deoxy-D-ribose in 12 steps (Scheme 3).[20] The olefin was transformed into allylic alcohol **8** in a conventional three-step operation. In order to introduce the C-6 hydroxy group of the A ring, **8** was subjected to Sharpless epoxidation with the (-)-DET chiral ligand followed by regioselective reductive opening of the resulting epoxy alcohol with Red-Al to afford diol **9**. The diol was converted to hydroxy α,β-unsaturated ester **11** in five-step sequences involving: (a) *p*-methoxybenzylidene acetal formation, (b) regioselective reductive

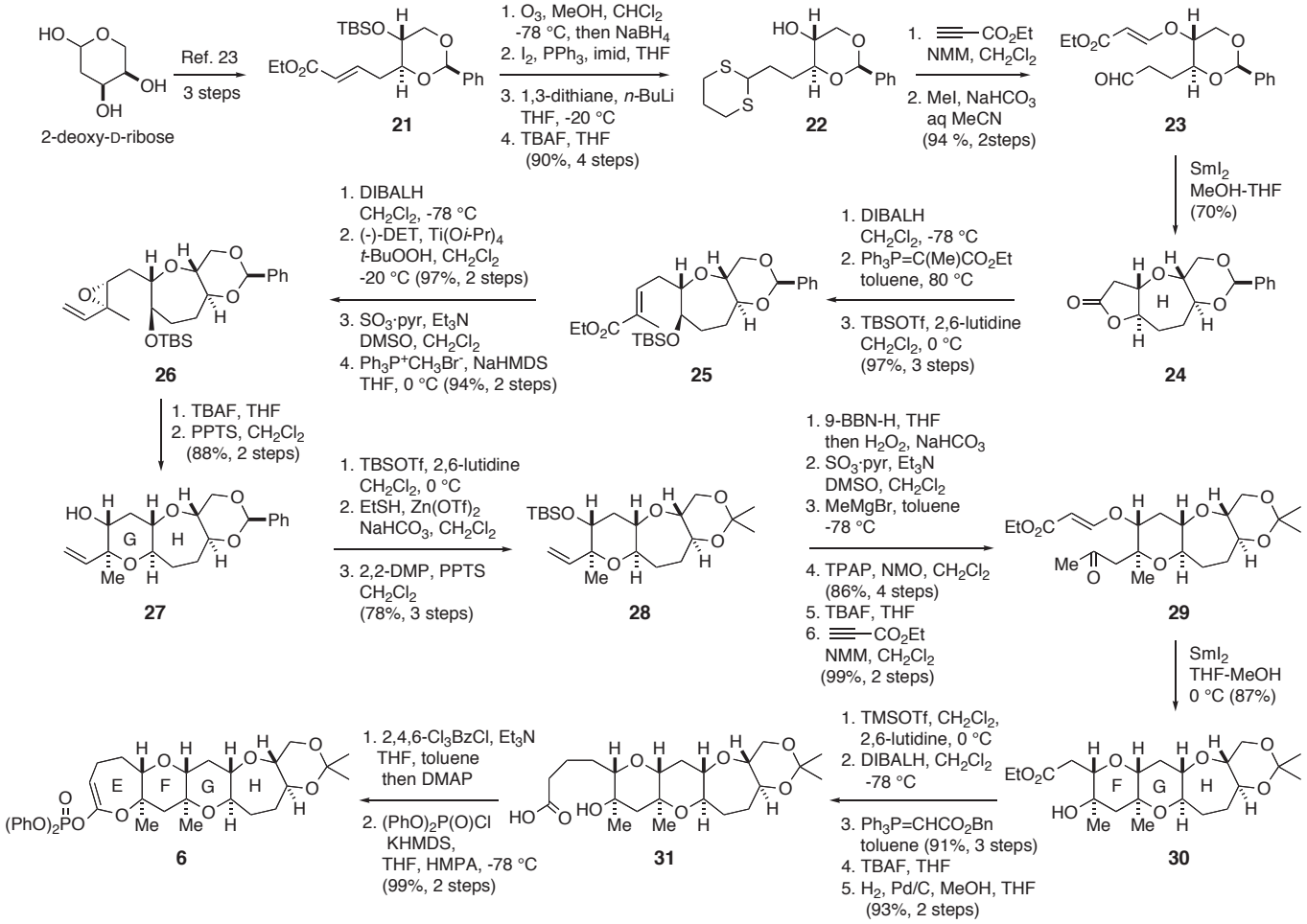
cleavage with DIBALH to form the PMB ether **10**, (c) oxidation of the primary alcohol, (d) Wittig reaction, and (e) removal of the TBS group. The A ring was constructed by the intramolecular hetero-Michael addition reaction of hydroxy α,β-unsaturated ester **11** with NaH in THF, resulting in the stereoselective formation of the AB-ring ester **12**. Homologation of the ester side chain of **12** and the following sequential manipulations of protecting groups to yield **14** required a six-step operation: DIBALH reduction of the ester, Wittig olefination of the resulting aldehyde to **13**, hydroboration/oxidation, benzylation of the primary alcohol, removal of the PMB group, and benzylation. Compound **14** was then converted to olefin **15** in five steps.



Scheme 3. Sasaki's synthesis of the ABC-ring fragment **5**

Construction of the C ring was performed in a straightforward manner by employing Nicolaou's 6-*endo* hydroxy-epoxide cyclization method.[21] Hydroboration/oxidation of the double bond of **15** followed by SO_3·pyridine oxidation produced an aldehyde, which was subsequently homologated by Horner-Wadsworth-Emmons reaction to give **16**. Conversion of **16** to epoxy alcohol **17** was accomplished by DIBALH reduction and *m*-CPBA epoxidation. Oxidation and Wittig reaction afforded vinyl epoxide **18**. The 6-*endo* cyclization of the desilylated compound of **18** into a tricyclic ring system **19** was carried out by treatment with PPTS in CH_2Cl_2. Protection of the newly formed secondary alcohol as the PMB ether, oxidative cleavage of the double bond, and the reduction of the derived aldehyde led to a primary alcohol **20**, which was transformed into the ABC-ring exocyclic enol ether **5** through iodination of the primary alcohol and elimination.

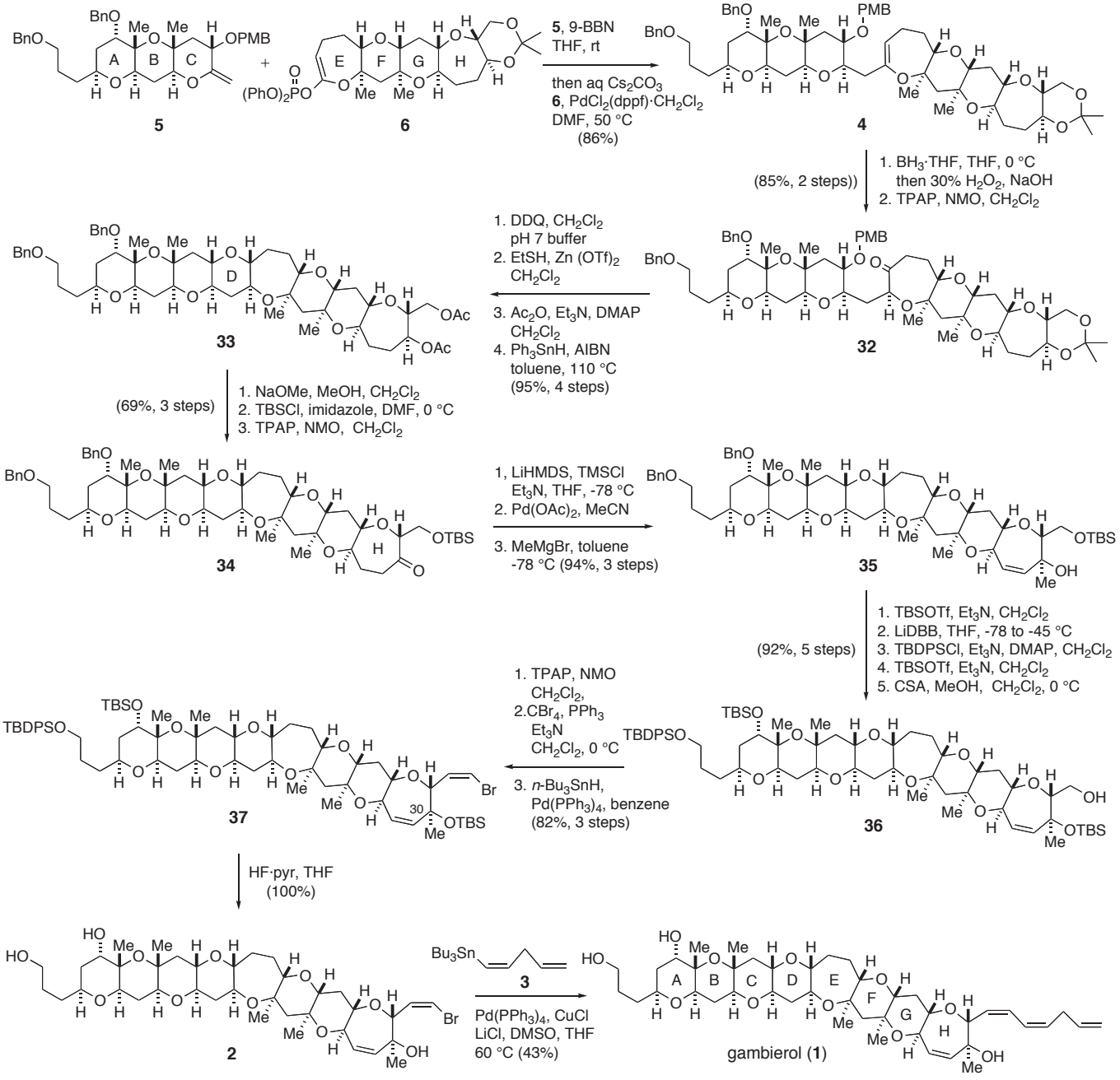
2.3. Synthesis of the EFGH rings. Sasaki initially attempted the synthesis of EFGH-ring fragment **6** by the *B*-alkyl Suzuki-Miyaura coupling between an F-ring exocyclic enol ether and an H-ring ketene acetal phosphate. However, the synthesis required 42 steps from compound **21** and its overall yield was only 6%.[10d] A more efficient and practical route was next explored; this route was based on the SmI_2-promoted reductive cyclization protocol developed by Nakata and co-workers,[22] which was employed for the construction of the H and F rings. The second approach for the EFGH-ring fragment **6** is illustrated in Scheme 4. Elaboration of compound **21**[23] to aldehyde **23**, a ketyl radical cyclization precursor, via dithiane **22** was carried out by a six-step sequence including the two-carbon diminution of the unsaturated ester side chain followed by the one-carbon extension with 1,3-dithiane, introduction of a β-alkoxy acrylate moiety by hetero-Michael addition with ethyl propiolate, and hydrolysis of dithioacetal. Treatment of **23** with SmI_2 induced reductive cyclization to afford stereoselectively the H-ring lactone **24**,[22] which was then converted to unsaturated ester **25** in excellent yield. The GH-ring system **27** containing an axial methyl group was constructed according to the Nicolaou's protocol.[20] Thus, the unsaturated ester **25** was transformed to vinyl epoxide **26** by a four-step manipulation, and treatment of the latter with TBAF followed by PPTS caused 6-*endo* cyclization to afford the GH-ring **27** in a stereocontrolled manner. The vinyl group of **28** was converted to a methyl ketone by a four-step operation, and, after removal of the TBS group, a β-alkoxy acrylate side chain was introduced to afford keto acrylate **29**. Exposure of **29** to SmI_2 again effected stereoselective ketyl radical cyclization[14a] to furnish the FGH-ring system **30** having angular 1,3-diaxial dimethyl groups. Chain extension of ester **30** to hydroxy carboxylic acid **31** via Wittig reaction followed by Yamaguchi lactonization[24] led to a seven-membered lactone, which was finally converted to the EFGH-ring ketene acetal phosphate **6** with KHMDS and $(PhO)_2P(O)Cl$.[25] This second approach to **6** had an overall yield of 22% for the 33 steps from **21**, which was much more favorable than the first approach.



Scheme 4. Sasaki's synthesis of the EFGH-ring fragment **6**

2.4. Total synthesis. Completion of the synthesis was then achieved along the lines previously developed using the *B*-alkyl Suzuki-Miyaura coupling strategy.[16] Hydroboration of enol ether **5** with 9-BBN and cross coupling with ketene acetal phosphate **6** in the presence of $PdCl_2$(dppf) afforded **4** in 86% yield (Scheme 5).[10e] A stereoselective hydroboration with a BH_3·THF-oxidation sequence gave a secondary alcohol as a single isomer, which was further oxidized with TPAP to ketone **32**. It should be mentioned that if the same hydroboration-oxidation sequence was repeated by employing BH_3·SMe_2, a 7:1 mixture of diastereoisomers was produced. The D-ring was constructed by removal of the PMB group of **32**, mixed thioacetal formation with EtSH and $Zn(OTf)_2$, and desulfurization under radical reductions (Ph_3SnH, AIBN) to afford the octacyclic polyether **33** after acetylation. This diacetate **33** was transformed into ketone **34** in three steps. Elaboration of the H-ring of **34** continued with incorporation of the H-ring double bond by Ito-Saegusa oxidation[26] of the derived silyl enol ether with $Pd(OAc)_2$ in MeCN to form an α,β-unsaturated ketone and subsequent stereoselective installation of an axial methyl group with MeMgBr in toluene at -78 °C to afford tertiary alcohol **35** in 94% overall yield as the sole product.[27] In order to construct the triene side chain of gambierol, two benzyl groups of **35** were reductively removed

with LiDBB at this stage and the resulting diol was reprotected with TBDPS and TBS groups to afford alcohol **36** after selective removal of the TBS group of the primary alcohol in 92% overall yield for the five steps. Oxidation of the alcohol followed by Corey-Fuchs reaction[28] of the derived aldehyde gave a dibromoolefin, which was stereoselectively mono-debrominated with *n*-Bu_3SnH and $Pd(PPh_3)_4$[29] to afford (*Z*)-vinyl bromide **37** in 82% yield for the three steps.



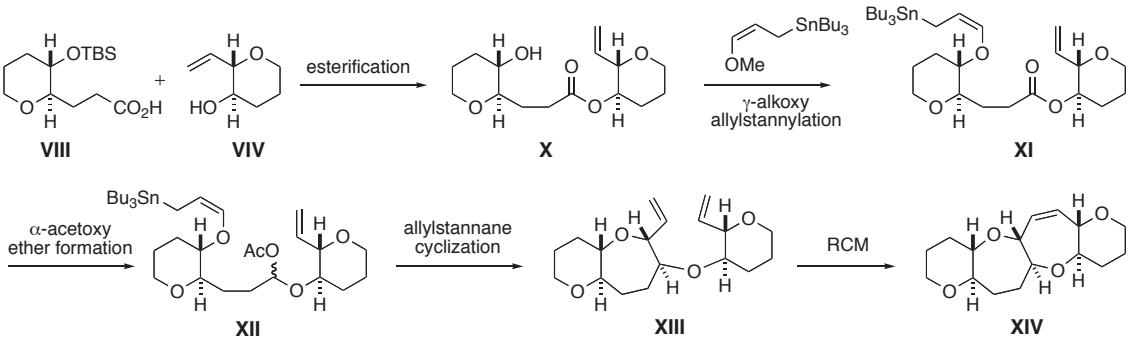
Scheme 5. Completion of Sasaki's total synthesis

Finally, the vinyl bromide side chain was converted into the requisite partially conjugated triene. The Stille coupling reaction of **37** with (*Z*)-vinyl stannane **3** employing $Pd(PPh_3)_4$/CuCl/LiCl[30] gave fully

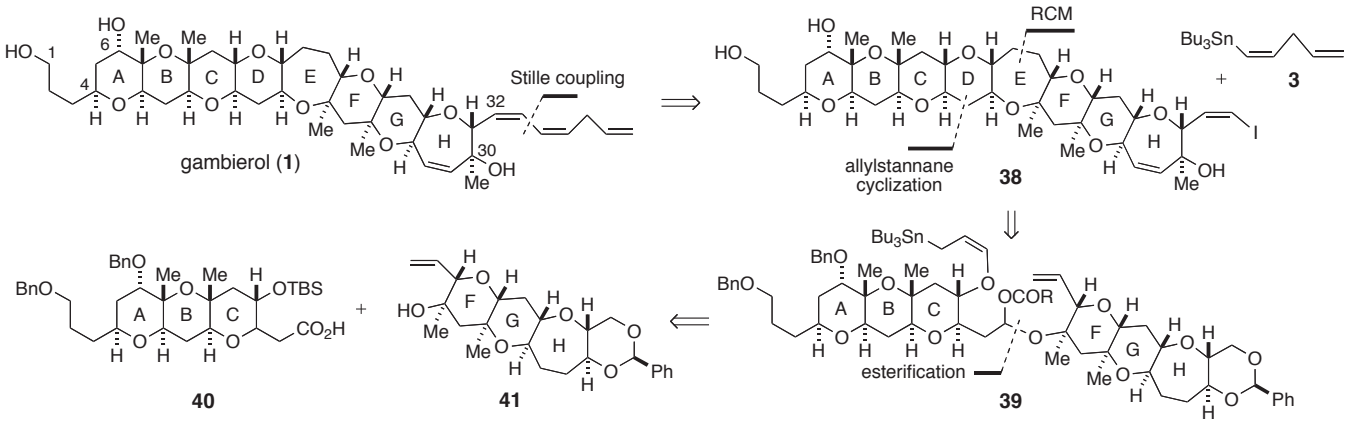
protected gambierol in 66% yield, which was then subjected to global deprotection. However, the sterically hindered C-30 TBS ether was not removed under various conditions, such as TBAF, HF·pyridine, and $Et_3N·3HF$. Completion of the synthesis was finally achieved by exchanging the order of the last two steps. Thus, removal of three silyl groups with excess HF·pyridine afforded triol **2**. The Stille coupling of the unprotected **2** with (*Z*)-vinylstannane **3**[18] provided gambierol (**1**) in 43% yield.

3. KADOTA-YAMAMOTO'S TOTAL SYNTHESIS

3.1. Retrosynthesis. Kadota and Yamamoto have exploited a novel approach to polycyclic ethers using intramolecular cyclization of γ-alkoxy allylstannanes to α-acetoxy ethers (Scheme 6).[31] Ester **X** prepared from acid **VIII** and alcohol **VIV** was converted to allylstannane **XI**. Partial reduction of the ester was followed by in-situ trapping of the resulting hemiacetal with acetic anhydride to afford α-acetoxy ether **XII**. Intramolecular allylation of **XII** with $MgBr_2·OEt_2$ induced the formation of a 7-membered ring to give **XIII**, which was then transformed to the tetracyclic ether-ring system **XIV** by a ring-closing metathesis (RCM) reaction. The rapid construction of two ether rings by means of this synthesis is noteworthy, and the technology was applied to the synthesis of gambierol.[11]



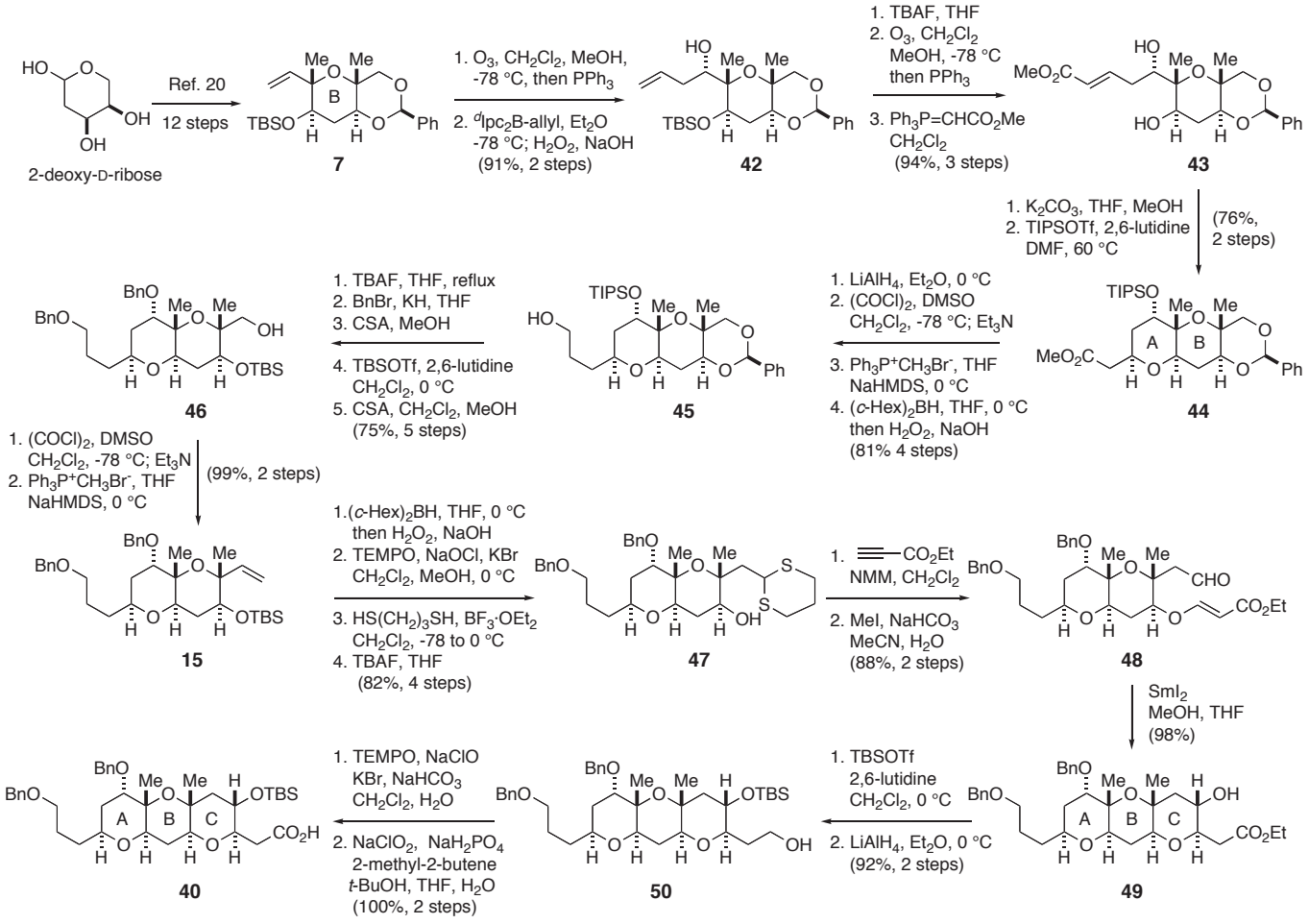
Scheme 6. Intramolecular allylation of α-acetoxy ether and ring-closing metathesis



Scheme 7. Kadota-Yamamoto's retrosynthesis of gambierol

A brief retrosynthesis of gambierol is illustrated in Scheme 7. According to the preliminary study for the synthesis of the H ring[19] and taking into account Sasaki's synthesis,[10b] the triene side chain would be constructed by the Stille coupling employing vinyl stannane **3** and vinyl iodide **38**, which is more reactive than vinyl bromide **2**. According to the strategy shown in Scheme 6, the D ring of **38** can be constructed by intramolecular allylation of an α-acyloxy ether, and the subsequent ring-closing metathesis would allow formation of the E ring. The key α-acyloxy ether **39** would be retrosynthetically broken down into the ABC-ring acid **40** and the FGH-ring alcohol **41**.

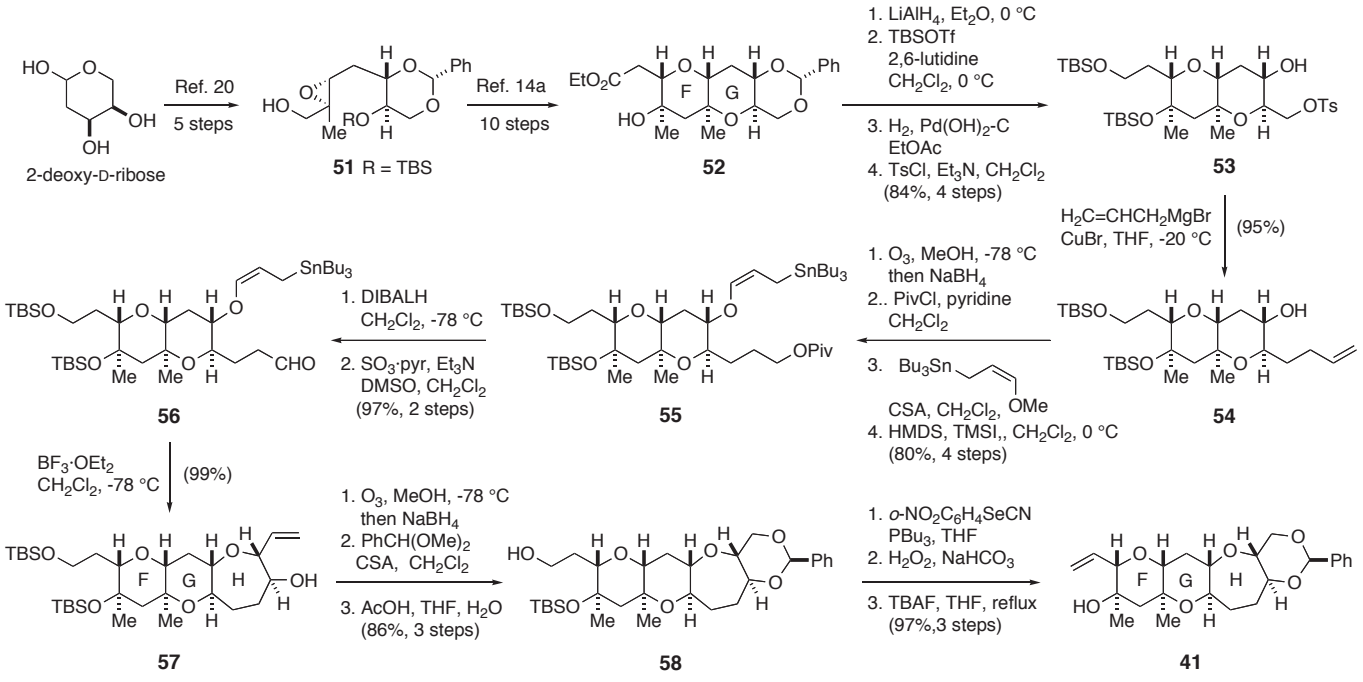
3.2. Synthesis of the ABC rings. Synthesis of the ABC rings began with Brown's asymmetric allylation[32] of the aldehyde prepared from the known olefin **7**[20] to afford homoallylic alcohol **42** as the sole product (Scheme 8). Chain extension to α,β-unsaturated ester **43** was achieved by ozonolysis followed by Wittig condensation. Exposure of **43** to K_2CO_3 in THF-MeOH resulted in the formation of the desired AB-ring system **44** by intramolecular hetero-Michael reaction, which still required an additional carbon atom to form the A-ring side chain.



Scheme 8. Kadota's synthesis of the ABC-ring fragment **40**

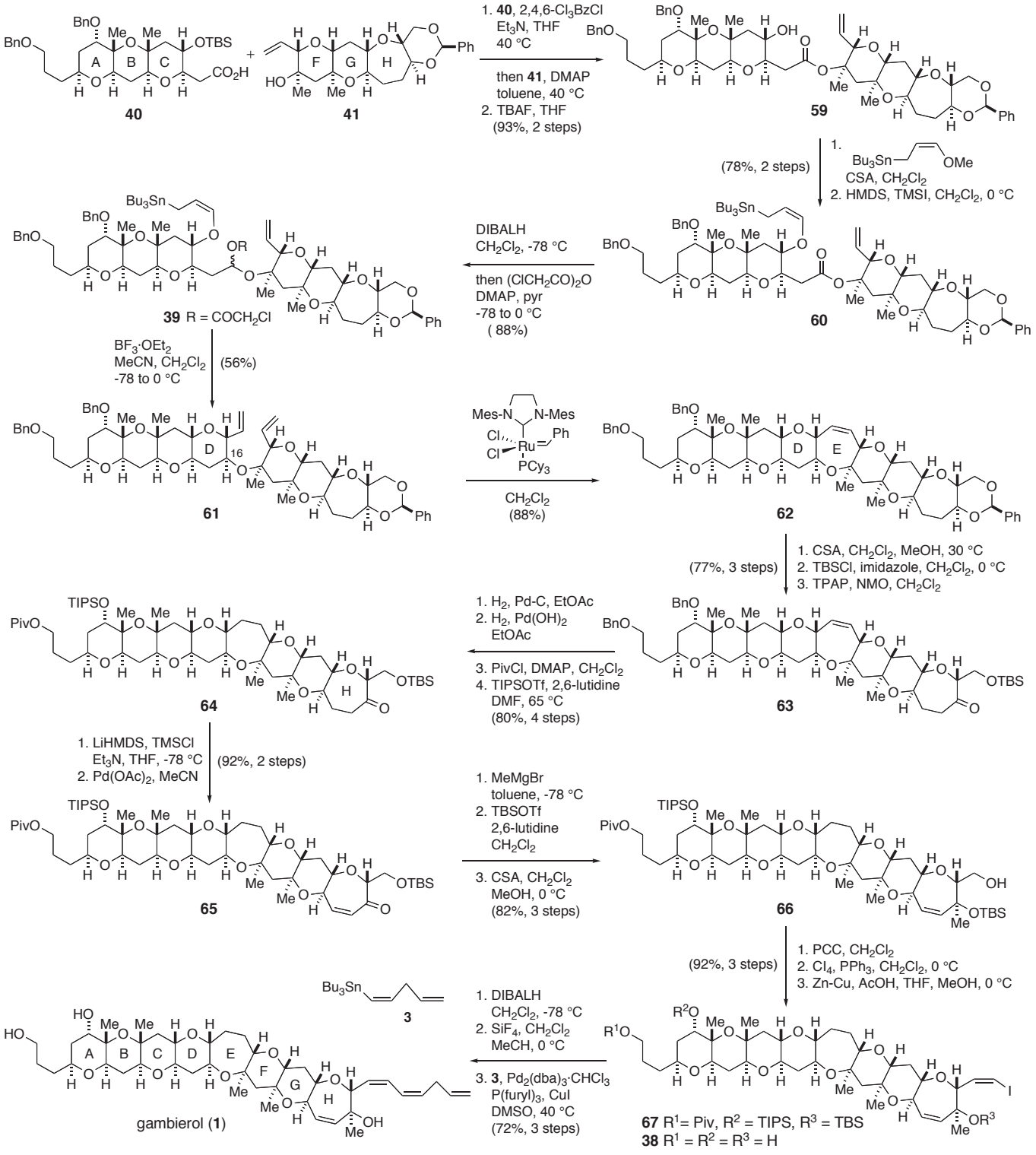
This homologation was then accomplished via Wittig olefination and hydroboration/oxidation to afford alcohol **45** in four steps. Five-step protecting group manipulation followed by oxidation of **46** to aldehyde and subsequent methylenation led to the Sasaki's AB-ring fragment **15**.[10e] This intermediate was then converted into aldehyde **48** via hydroxy dithioacetal **47** in six steps. Construction of the C-ring was performed by the SmI_2-induced ketyl radical cyclization of **48** to give hydroxy ester **49** in an excellent yield. Protection of the secondary alcohol, reduction of the ester, and oxidation of the resulting primary hydroxy group of **50** produced the ABC-ring acid **40** in quantitative yield.

3.3. Synthesis of the FGH rings. Construction of the second fragment corresponding to the FGH rings began with the transformation of the known ester **52**,[14a] prepared from 2-dexoy-D-ribose via **51**[20] in fifteen steps, to tosylate **53** in 84% yield for the four steps (Scheme 9). This intermediate was then coupled with allylmagnesium bromide in the presence of CuBr to afford olefin **54**. Ozonolysis/reduction and protection of the primary alcohol as a pivalate was followed by acid-catalyzed mixed-acetal formation with tributyl((*Z*)-3-methoxyallyl)stannane and subsequent elimination of MeOH to furnish (*Z*)-allylic stannane **55**.[33] Reductive removal of the pivaloyl group with DIBALH followed by oxidation with SO_3·pyridine gave aldehyde **56**. Cyclization of **56** mediated by BF_3·OEt_2 afforded the tricyclic FGH-ring **57** in 99% yield as a single diastereoisomer.[34] Ozonolysis of the double bond followed by reduction, benzylidene acetal formation, and selective desilylation of the primary TBS ether provided alcohol **58**. Synthesis of the required FGH-ring olefinic alcohol **41** from **58** was completed by selenylation, oxidative elimination, and desilylation.



Scheme 9. Kadota' synthesis of the EFGH-ring fragment **41**

3.4. Total synthesis. Union of the two segments **40** and **41** was now effected by Yamaguchi conditions,[24] and subsequent removal of the TBS group afforded ester **59** in 93% yield for the two steps (Scheme 10). Acetal formation with (*Z*)-methoxyallylstannane and acetal cleavage furnished allylic stannane **60**.

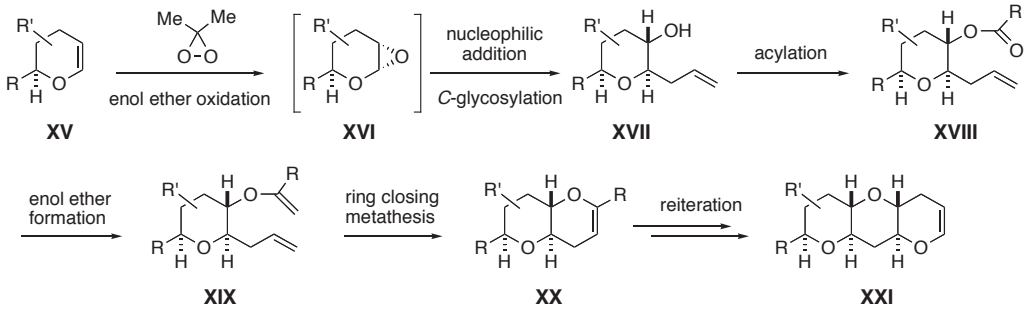


Scheme 10. Completion of Kadota's total synthesis

The ester **60** was then converted to a 3:2 mixture of α-chloroacetoxy ether **39** by partial reduction with DIBALH followed by in-situ acylation with chloroacetic anhydride according to the Rychnovsky protocol.[35] Construction of the D ring was initially attempted using **39** (R = $COCH_3$) with $MgBr_2 \cdot OEt_2$ to give a 36:64 ratio of **61** and its C-16 epimer. The ratio was finally improved to 64:36 by treatment of α-chloroacetyl derivative **39** (R = $COCH_2Cl$) with $BF_3 \cdot OEt_2$, and the desired product **61** was isolated in 56% yield. This diene was then subjected to RCM reaction using the second-generation Grubbs catalyst[36] to provide octacyclic ether **62** in 88% yield. A series of hydrolysis, selective protection, and oxidation steps provided ketone **63**. Hydrogenation followed by a protecting group exchange afforded ketone **64**. Saegusa oxidation[26] of the derived silyl enol ether afforded enone **65**, which was stereoselectively methylated with MeMgBr in toluene[27] to give the primary alcohol **66** after a protection-deprotection sequence. Finally, completion of the synthesis was accomplished by oxidation of **66** with PCC, diiodoolefination with PPh_3/CI_4, and stereoselective hydrogenolysis with Zn-Cu/AcOH to provide (*Z*)-vinyl iodide **67**. Removal of the pivaloyl group with DIBALH and the two silyl groups with SiF_4 yielded trihydroxy (*Z*)-vinyl iodide **38**, which was subjected to modified Stille coupling with **3** using $Pd_2(dba)_3 \cdot CHCl_3/P(furyl)_3/CuI$ conditions[19,37] to afford synthetic gambierol (**1**) in 72% yield.

4. RAINIER'S TOTAL SYNTHESIS

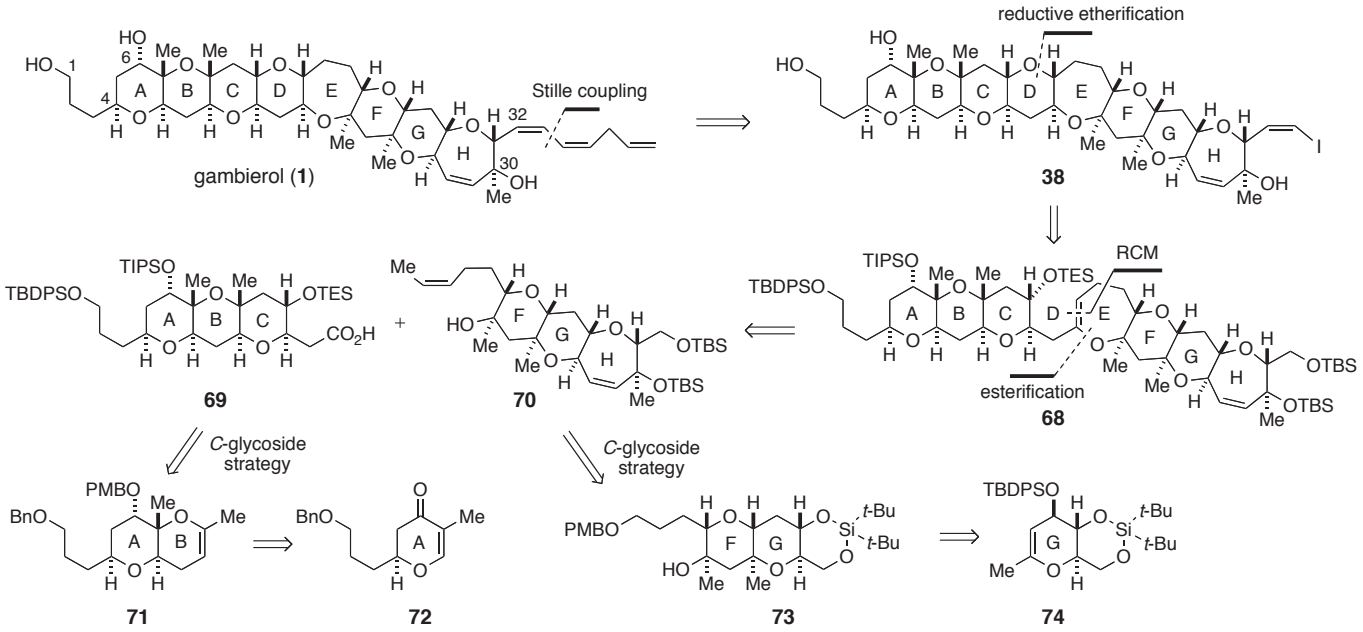
4.1. Retrosynthesis. The third synthesis in this area is that of Rainier in 2005.[12] An iterative strategy developed to synthesize polycyclic ethers was the generation of *C*-glycoside **XVII** from cyclic enol ether **XV** via nucleophilic addition of organometalic reagents to epoxide **XVI** (Scheme 11). Transformation of the acylated *C*-glycoside **XVIII** into cyclic enol ether **XX** was performed through the use of an enol ether-olefin RCM reaction of **XIX**.[38]



Scheme 11. Generation of *C*-glycosides from cyclic enol ethers and enol ether-olefin RCM

Rainier's plan to synthesize gambierol was a convergent one that centered on the combined use of the above *C*-glycosylation and enol ether-olefin RCM reactions (Scheme 12). The octacyclic (*Z*)-vinyl iodide **38** would be dissected to cyclic enol ether **68**. Disassembly of **68** based on the enol ether-olefin RCM strategy would provide the ABC-ring acid **69** and the FGH-ring **70**, which could be prepared from **72** and

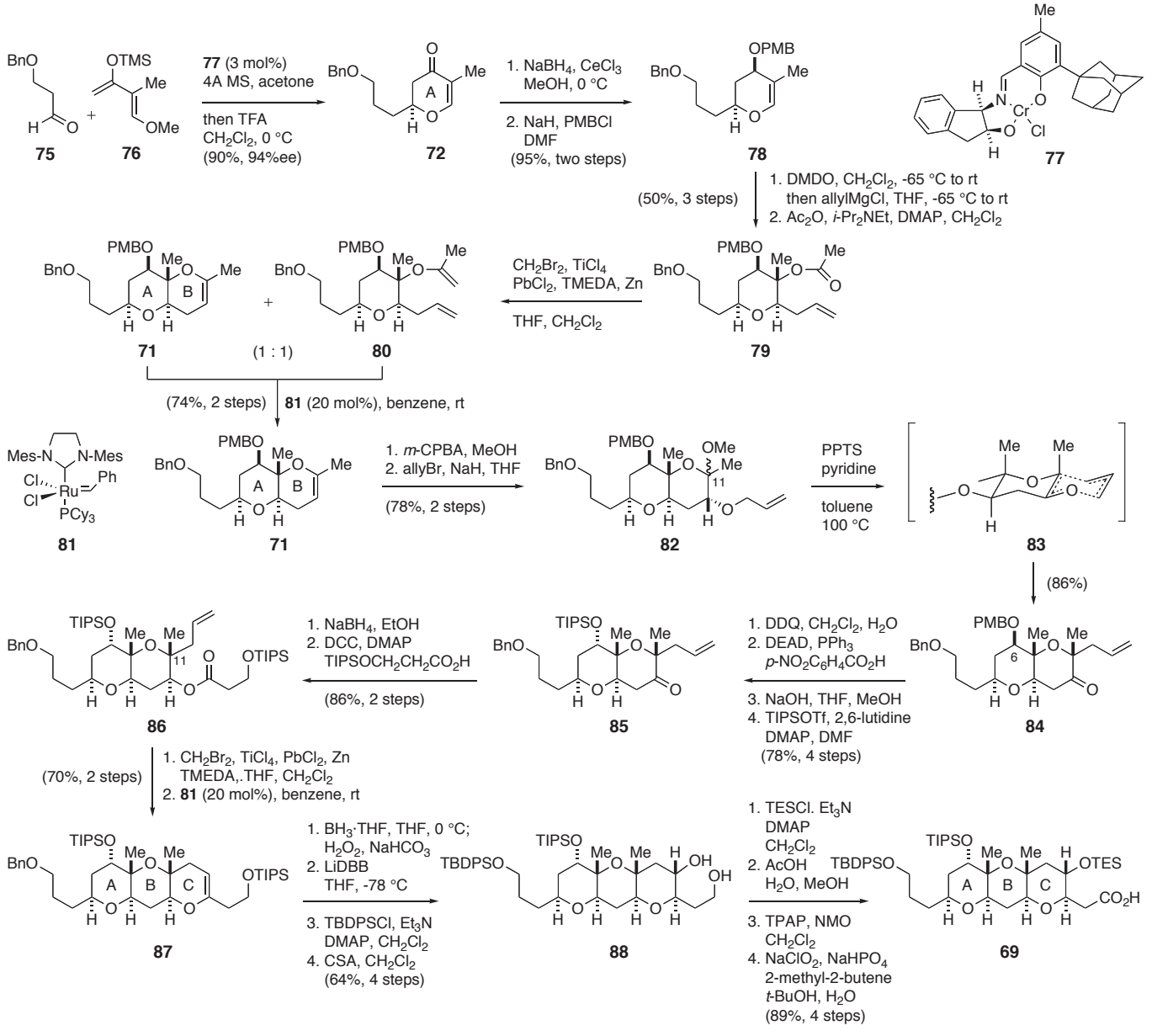
74, respectively, by iteration of the *C*-glycosylation strategy. Final steps to incorporate the skipped triene side chain using Kadota' protocol[11] were planned.



Scheme 12. Rainier's retrosynthesis of gambierol

4.2. Synthesis of the ABC rings. Preparation of the ABC-ring fragment **69** was initiated by asymmetric hetero Diels-Alder cycloaddition between aldehyde **75** and Danishefsky's diene **76**[12d] (Scheme 13). Jacobsen's tridentate Cr(III) catalyst **77**[39] catalyzed the reaction to give the A ring unit **72** in both high yield and enantiomeric purity. Reduction of the ketone using Luche conditions[40] followed by protection with a PMB group afforded **78**. Although the C-6 stereocenter was epimeric to that needed for gambierol, this center was employed to control the facial selectivity in the subsequent epoxidation with DMDO. Reaction of **78** with DMDO followed by addition of allylmagnesium chloride afforded β-glycoside in 78% yield with 7.5:1 diastereoselectivity, which was acetylated to give acetate **79**. When the acetate was subjected to the Takai-Utimoto reagent,[41] a 1:1 mixture of cyclic and acyclic enol ethers, **71** and **80**, was isolated. Further treatment of the mixture with the Grubbs II catalyst **81** yielded cyclic enol ether **71** in 74% yield. Iteration of the above *C*-glycoside strategy (**78** → **79**) could be used to construct the ester **86** from **71**. However, this strategy was unsuccessful because the addition of allylmagnesium chloride to the epoxide derived from **71** resulted in the formation of the undesired C-11 diastereoisomer. This problem was solved by the use of a Claisen rearrangement of an allyl enol ether. Thus, treatment of **71** with *m*-CPBA in MeOH followed by *O*-allylation provided **82**. Claisen rearrangement of **82** in pyridine in the presence of PPTS at 100 °C afforded **84** in 86% yield. Inversion of the C-6 stereogenic center of **84** was accomplished in four steps involving a Mitsunobu reaction to give **85**, which was subjected to reduction

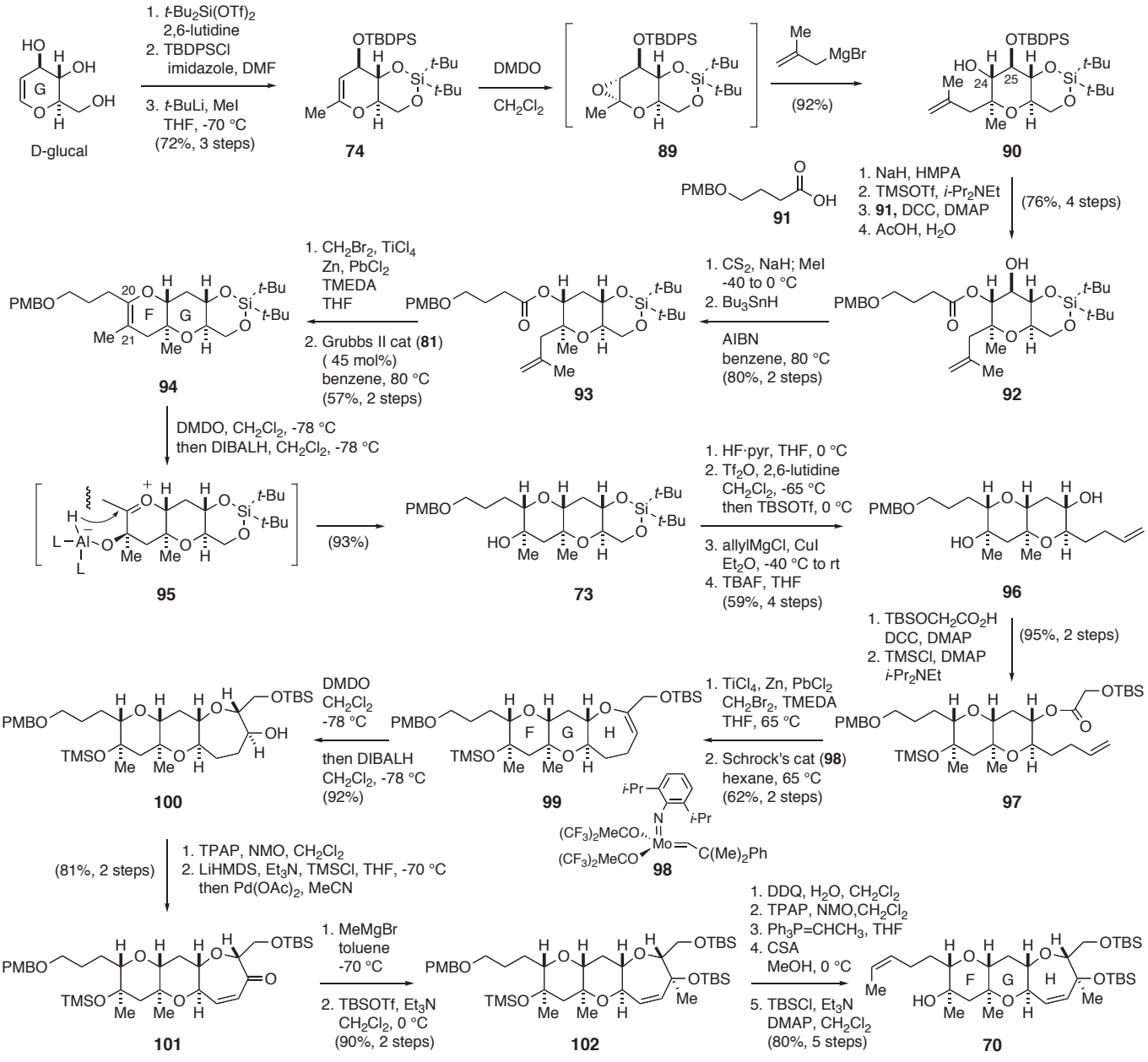
with $NaBH_4$ and esterification with 3-(triisopropylsilyloxy)propanoic acid to provide olefinic ester **86**. Acyclic enol ether formation using the Takai-Utimoto protocol followed by enol ether-olefin RCM afforded the tricyclic enol ether **87** in 70% yield. Hydroboration followed by exchange of the benzyl ether for a TBDPS ether and hydrolysis of the primary TIPS ether yielded the diol **88**. Finally, bis-TES ether formation, selective hydrolysis of the primary TES ether, and oxidation afforded the ABC-ring acid **69** in 89% overall yield.



Scheme 13. Rainier's synthesis of the ABC-ring fragment **69**

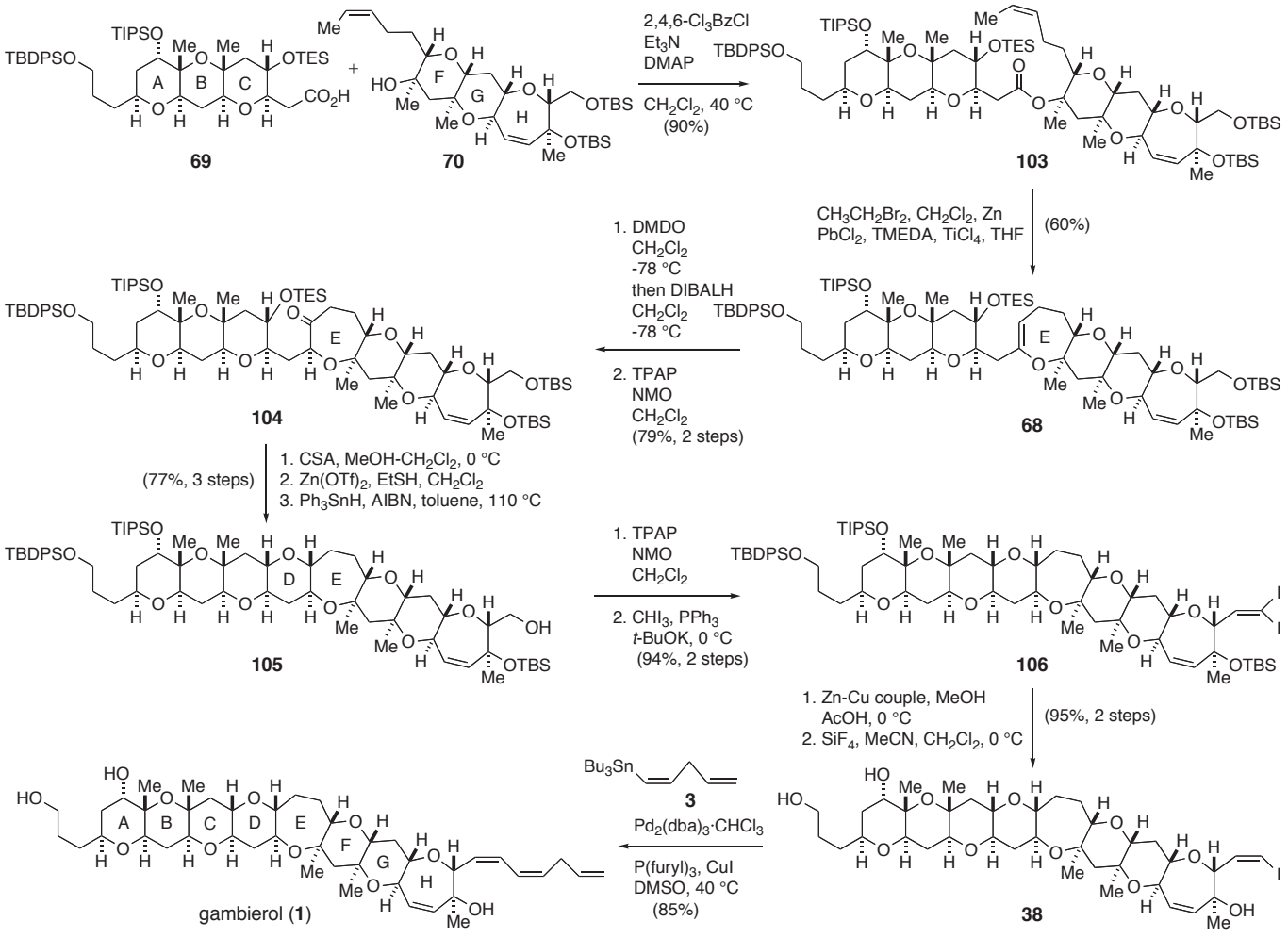
4.3. Synthesis of the FGH rings. Synthesis of the FGH-ring fragment **70** began with D-glucal (Scheme 14).[12c] Oxidation of **74** with DMDO under Messengeur's acetone free conditions[42] followed by addition of 2-methyl-2-propenymagnesium chloride gave **90** in 92% yield. Removal of the TBDPS group with NaH in HMPA, selective silylation of the C-25 hydroxy group, and esterification with acid **91** afforded

hydroxy ester **92** after hydrolysis of the TMS ether. The Barton-McCombie deoxygenation of the remaining hydroxy group with Bu_3SnH led to olefinic ester **93**, which was converted into the FG-ring enol ether **94** in 52% yield by Takai-Utimoto reaction followed by RCM reaction using the Grubbs II catalyst **81**. Construction of the F-ring still required the additional C-20 and C-21 stereocenters. To this end, **94** was subjected to DMDO oxidation and subsequent DIBALH reduction to afford the desired isomer **73** in a >30:1 diastereomeric ratio. The cyclic silylene group was removed and the resulting triol was transformed into the primary triflate and secondary TBS ether derivative. Coupling reaction of the triflate with allylmagnesium chloride in the presence of CuI[43] provided diol **96** after desilylation.



Scheme 14. Rainier's synthesis of the FGH-ring fragment **70**

Esterification of the secondary alcohol with (*t*-butyldimethylsilyloxy)acetic acid followed by trimethylsilylation of the tertiary alcohol gave olefinic ester **97**. Sequential exposure of **97** to the Takai-Utimoto conditions and Schrock's molybdenum catalyst **98**[44] afforded a 62% yield of the FGH tricyclic enol ether **99** over the two steps. The Grubbs II catalyst was less effective than the Schrock catalyst, resulting in the generation of **99** in 35-39% overall yield from **97**. The DMDO oxidation and DIBALH reduction gave alcohol **100** as a single diastereoisomer. The remaining transformation required the introduction of a double bond and a tertiary methyl group to the H-ring. Accordingly, **100** was converted to enone **101** by TPAP and Saegusa oxidations. Addition of MeMgBr in toluene followed by silylation afforded **102**. A series of deprotection, oxidation, olefination, deprotection, and reprotection steps provided the FGH-ring fragment **70**.



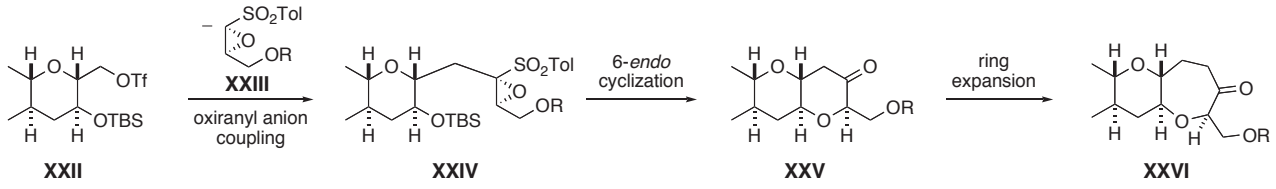
Scheme 15. Completion of Rainier's synthesis

4.4. Total synthesis. Coupling of the two fragments **69** and **70** was then effected by the Yamaguchi method[24] to provide ester **103** (Scheme 15). Subsequent RCM reaction with Takai-Utimoto ethylidene reagent generated from dibromoethane afforded the cyclic enol ether **68** in 60% yield. The attempted

RCM reactions employing titanium methylidene reagent prepared from dibromomethane were not successful in this case, producing **68** in a capricious 10-30% yield. Single-flask DMDO oxidation of the cyclic enol ether **68** and reduction of the resulting epoxide with DIBALH led to a secondary alcohol, which was oxidized with TPAP to provide ketone **104**. Construction of the D ring was achieved by desilylation, cyclic *O*,*S*-acetalization, and reductive desulfurization under radical conditions to afford the octacyclic alcohol **105** in 77% yield. Completion of the synthesis was then accomplished along the lines previously developed by the Kadota-Yamamoto group.[11] Thus, oxidation of **105** to the aldehyde was followed by Corey-Fuchs reaction to form diiodoolefin **106**. Stereoselective reduction of **106** to (*Z*)-vinyl iodide and global deprotection afforded triol **38**. Stille coupling of the resulting triol **38** with dienyl stannane **3** provided synthetic gambierol (**1**) in 85% yield.

5. MORI'S TOTAL SYNTHESIS

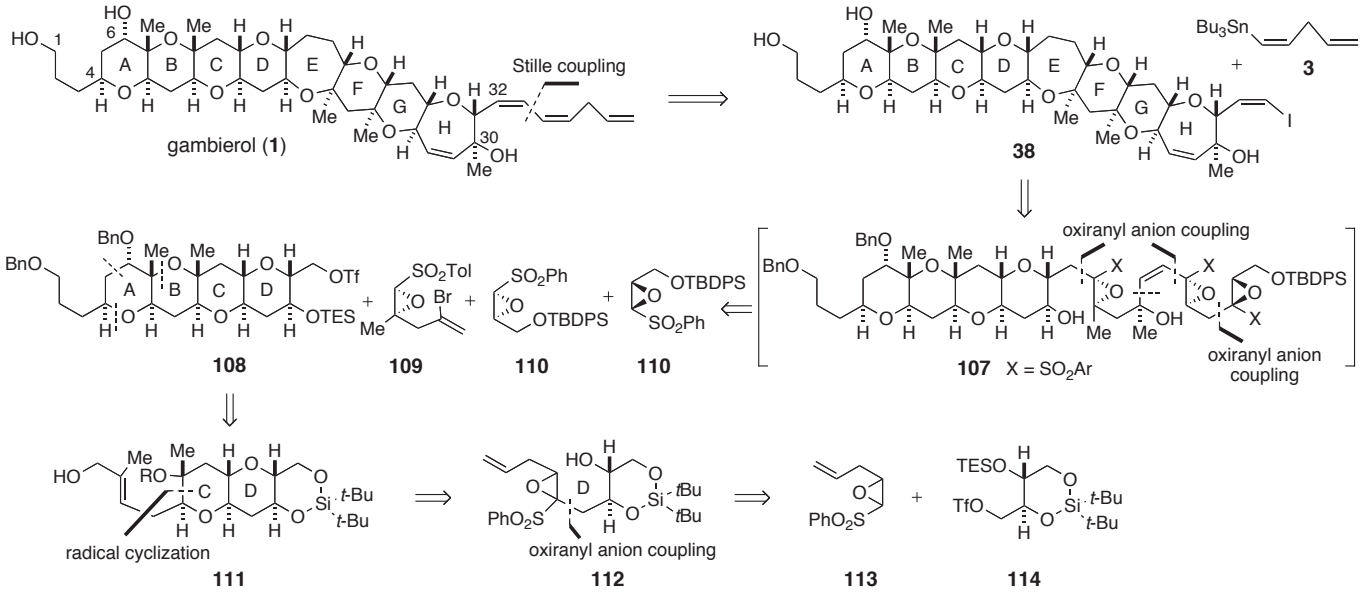
5.1. Retrosynthesis. Our laboratory has been interested in the synthesis of bioactive polycyclic ether natural products through the use of oxiranyl anions in an iterative manner. We have developed a unique method for the formation of tetrahydropyran **XXV** by the reaction of triflate **XXII** with oxiranyl anion **XXIII** followed by a sulfonyl-assisted 6-*endo* cyclization of the product **XXIV** (Scheme 16).[45] Using this approach, we achieved direct formation of oxepane **XXVI** by employing a ring-expansion reaction of **XXV**.[46] Such structural units found in gambierol make it an attractive target for possible applications of our methodology, and we have completed the fourth synthesis of gambierol based on the iterative use of oxiranyl anion chemistry.[13]



Scheme 16. Synthesis of 6- and 7-membered ether rings by an oxiranyl anion strategy

Our linear synthetic strategy is outlined in Scheme 17. The reported total syntheses have successfully employed the Stille coupling reaction of (*Z*)-vinyl bromide **2** or the corresponding vinyl iodide **38** with a (Z)-dienyl stannane **3** at the final step. This conversion to gambierol is efficient and reliable from the perspective of constructing the stereochemically labile conjugated (Z,Z)-diene system. As a result, our synthetic plan has also focused on the construction of **38**. We envisioned that two seven-membered E and H rings in **38** would be constructed by a ring-expansion reaction of tetrahydropyranyl rings at suitable stages of synthesis, so we tentatively regarded **107** as a hypothetical polyepoxide precursor for

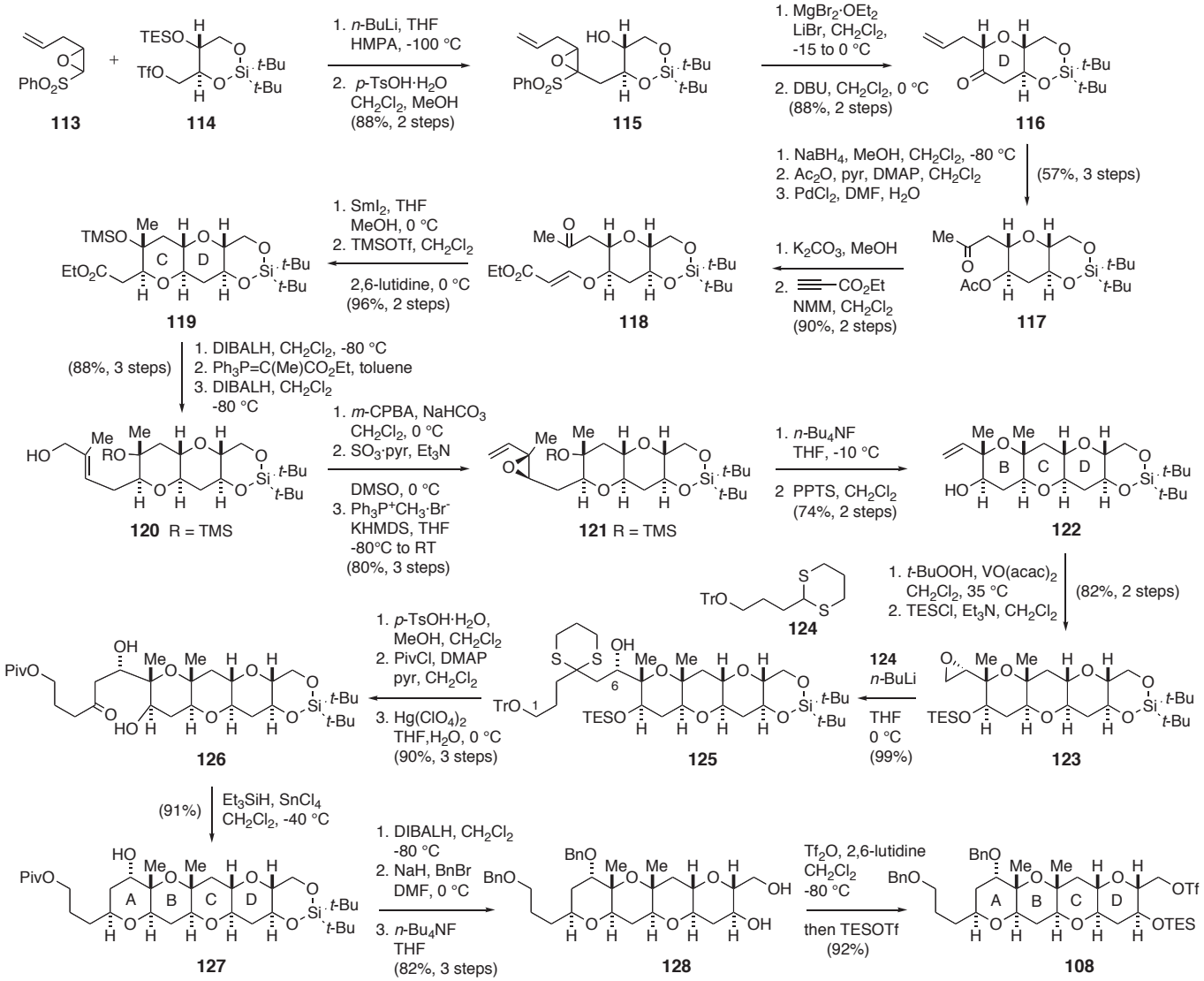
retrosynthetic disassembly. Disconnection of **107** at the indicated bonds with the aid of sulfonyl groups allowed for generation of the ABCD-ring fragment **108**, the optically active epoxy sulfones **109**, and **110** as building blocks. The advanced CD-ring fragment **111** was then retrosynthetically broken by considering the intermediate **112** to afford epoxy sulfone **113** and triflate **114** as potential starting materials. In order to facilitate the gram-scale preparation of the starting epoxy sulfone, we decided to employ racemic **113**, which could readily be prepared as a mixture of *cis*- and *trans*-isomers according to the reported method.[47]



Scheme 17. Mori's retrosynthesis of gambierol

5.2. Synthesis of the ABCD rings. According to the retrosynthesis, rings D, C, B, and A were annulated sequentially in this order, starting with an oxiranyl anion coupling between epoxy sulfone **113** and triflate **114** (Scheme 18). The triflate **114** was prepared from D-glucal in four steps.[48] The product **115** obtained in 88% yield was treated with $MgBr_2 \cdot OEt_2$ to give a 1:1 mixture of α-bromoketones, which was then subjected to cycloetherification with DBU to afford the D-ring ketone **116** in 88% yield for the two steps.[49] Reduction of the ketone, protection of the resulting alcohol as the acetate, and subsequent Wacker oxidation of the double bond gave ketone **117**. Deacetylation followed by hetero-Michael addition with ethyl propiolate provided keto acrylate **118** in 90% overall yield. Treatment of **118** with SmI_2 effected ketyl radical cyclization[22] to afford, after silylation, the CD ring ester **119** as a single diastereoisomer. Elaboration of the ester to allylic alcohol **120** was carried out by a three-step sequence involving reduction of the ester with DIBALH, Wittig olefination, and the DIBALH reduction of the unsaturated ester. Construction of the B ring containing sterically congested 1,3-diaxial dimethyl groups was achieved according to the Nicolaou's protocol.[20] Thus, stereoselective epoxidation of the allylic alcohol **120**

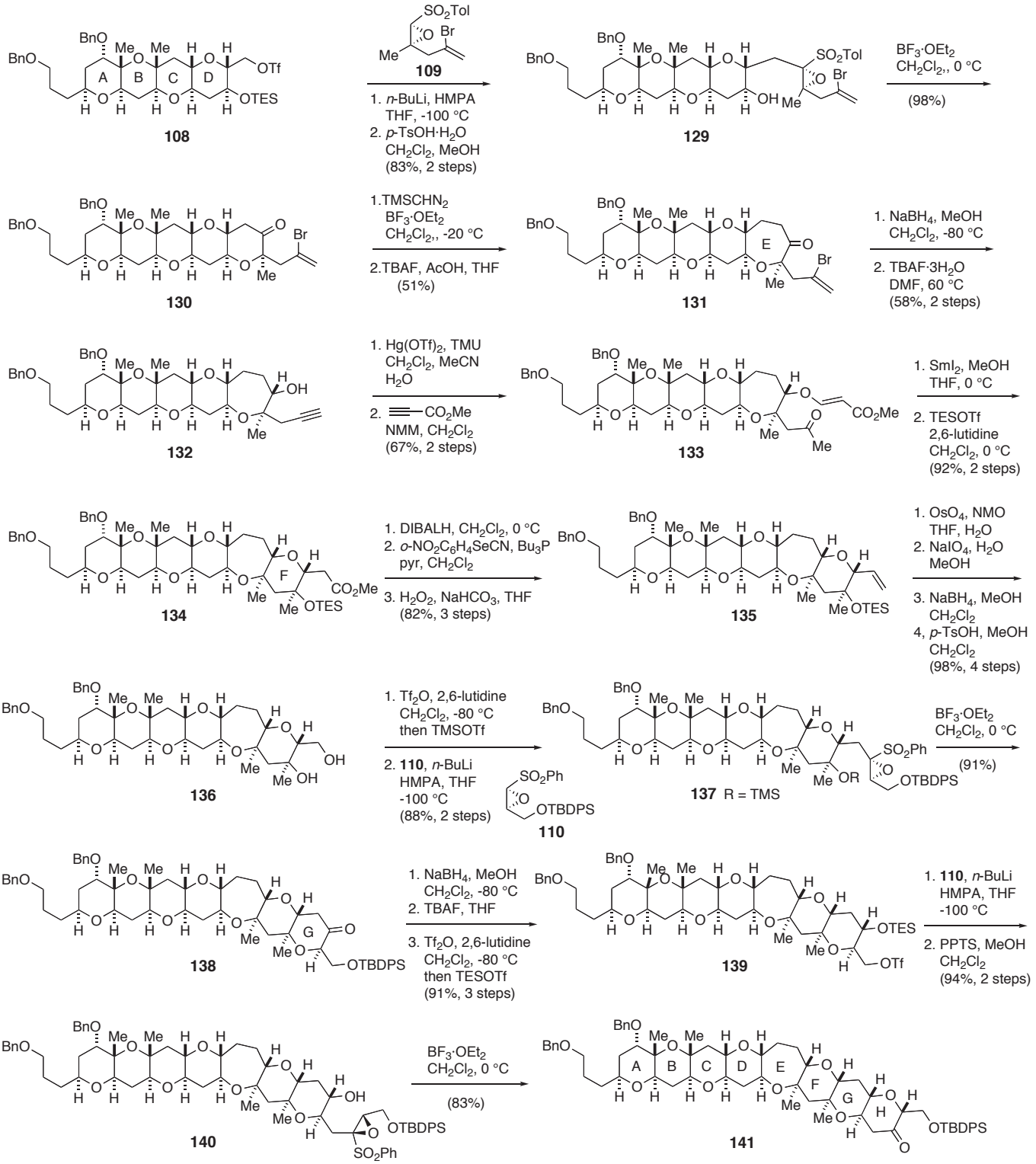
followed by oxidation and Wittig olefination provided epoxy olefin **121**. Detrimethylsilylation followed by treatment with PPTS effected 6-*endo* cyclization to afford the BCD-ring fragment **122** in good yield.



Scheme 18. Mori's synthesis of the ABCD-ring fragment **108**

Construction of the A ring is a challenging issue, because the α-axial hydroxy group at C-6 and the β-equatorial side chain at C-4 have to be installed stereoselectively. To this end, vinyl alcohol **122** was subjected to the homoallylic hydroxy-directed epoxidation with *t*-BuO_2H in the presence of $VO(acac)_2$ to afford the desired epoxide with 93:7 diastereoselectivity.[50] Protection of the hydroxyl group as a TES ether provided epoxide **123** in 82% yield for the two steps. Addition of lithiodithiane generated from **124** gave dithioacetal **125** quantitatively. It should be mentioned that when the benzyl-protected derivative of **124** was employed only 28% yield of the product was realized because of decomposition of the benzyl-protected dithiane via anion formation at the benzylic position. The dithioacetal **125** was then transformed to the dihydroxy ketone **126** in three steps including hydrolysis of the dithioacetal group.

Reductive etherification of **126** was accomplished with triethylsilane in the presence of $SnCl_4$ to afford the ABCD-ring system **127** in 91% yield as the sole product. A three-step protecting group manipulation provided diol **128**,[13a] which underwent a subsequent one-pot triflation and triethylsilylation to afford the ABCD-ring triflate **108**.



Scheme 19. Mori's synthesis of the A-H ring system **141**

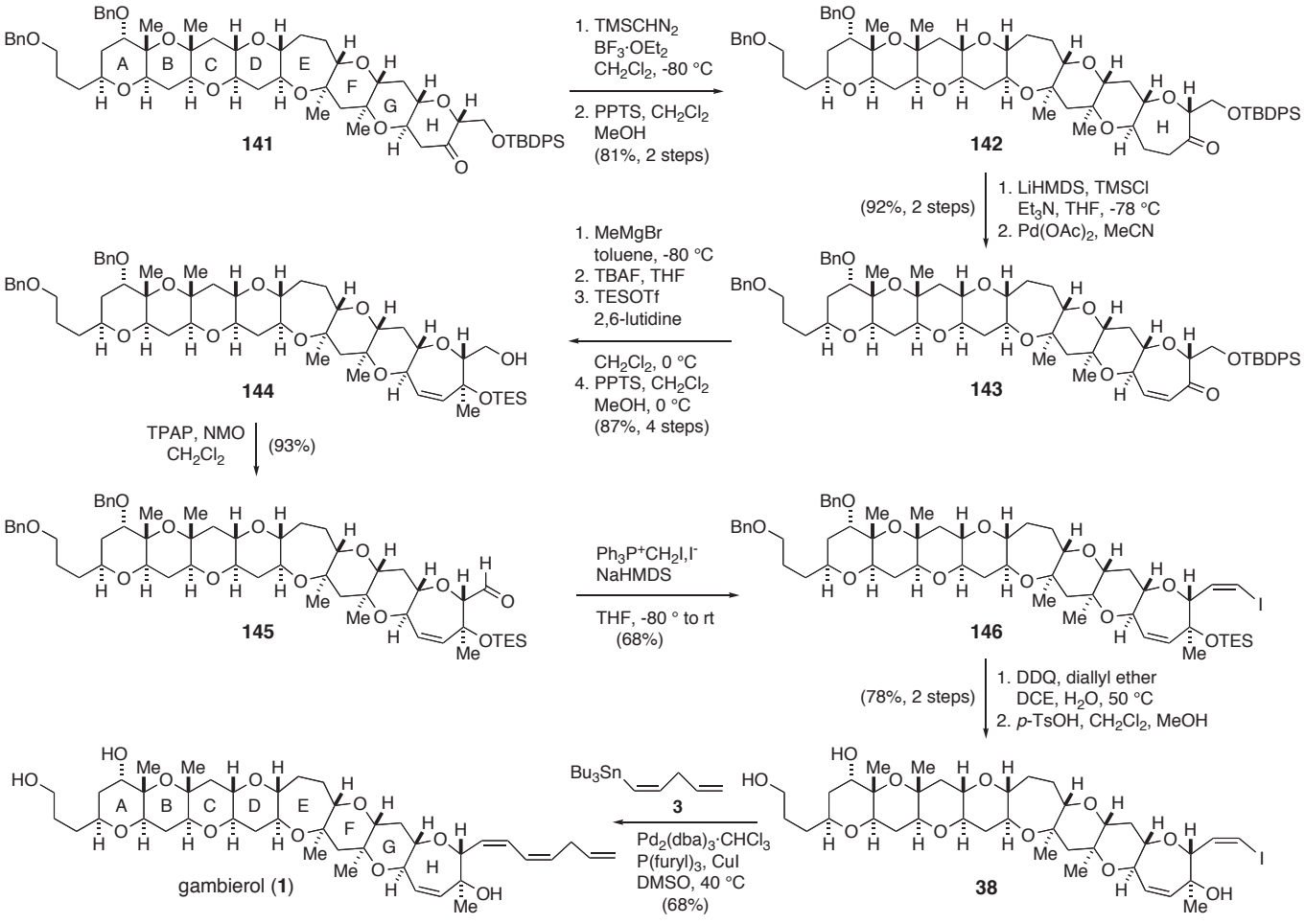
5.3. Synthesis of the ABCDEFGH rings. Construction of the seven-membered E-ring began with the coupling reaction of triflate **108** and the oxiranyl anion derived from epoxy sulfone **109** with *n*-BuLi at -100 °C to give, after desilylation, hydroxy epoxy sulfone **129** in 83% yield (Scheme 19). Treatment with $BF_3{\cdot}OEt_2$ effected 6-*endo* cyclization to give **130** quantitatively,[45b] which was followed by ring expansion with trimethylsilyldiazomethane in the presence of $BF_3{\cdot}OEt_2$ and desilylation of the resulting α-trimethylsilyl ketone with TBAF to afford the ABCDE-ring ketone **131**.[46] Reduction of the ketone and dehydrobromination of vinyl bromide with TBAF in DMF gave acetylene **132**.[51] Mercuric triflate-catalyzed hydration[52] of the terminal acetylene followed by reaction with methyl propiolate provided keto acrylate **133**. Treatment of **133** with SmI_2-induced reductive cyclization to afford the ABCDEF-ring fragment **134** as a single diastereoisomer after silylation of the secondary hydroxy group. Elaboration of **134** to **136** required the one-carbon diminution of the ester side chain. To this end, the ester was converted to olefin **135** by reduction and selenylation-oxidative elimination. Oxidative cleavage of the double bond followed by reduction and desilylation provided diol **136**, from which point the oxiranyl anion chemistry could be repeated for the construction of the G and H rings.

Triflation and trimethylsilylation of **136** in one pot gave triflate, which was then treated with the oxiranyl anion generated from **110** to afford epoxy sulfone **137** in 93% yield. Exposure of **137** to $BF_3{\cdot}OEt_2$ caused desilylation and 6-*endo* cyclization to form the G-ring ketone **138** in 91% yield. Stereoselective reduction followed by removal of the TBDPS group and one-pot triflation and silylation furnished triflate **139** in 91% yield for the three steps. The sequence described above was employed iteratively with equal efficiency to construct the H-ring. Thus, lithiation of **110** in the presence of **139** with *n*-BuLi at -100 °C afforded, after desilylation, **140** in 92% yield. Cyclization of **140** was then induced by exposure of $BF_3{\cdot}OEt_2$, which gave rise to octacyclic ketone **141** in 83% yield.

5.4. Total synthesis. With construction of the quasi-octacyclic core **141** of gambierol completed, conversion to the target required the elaboration of the six-membered H ring to the fully functionalized seven-membered H ring having a skipped triene side chain. To this end, ketone **141** was subjected to ring expansion with trimethylsilyldiazomethane and desilylation of the derived α-trimethylsilyl ketone with PPTS to afford the requisite octacyclic core **142** in 81% yield (Scheme 20). The remaining functionalization of the H ring was then achieved along the lines previously developed for gambierol.[10,11] Thus, Saegusa oxidation of the silyl enol ether derived from **142** afforded enone **143**. Methylation with MeMgBr in toluene gave a tertiary alcohol as a single diastereoisomer, which was followed by removal of the TBDPS group, bis-triethylsilylation, and selective mono-desilylation to provide the primary alcohol **144** in good yield.

In the work previously performed by Sasaki's and Kadota's groups, the robust C-1 and C-6 benzyl protecting groups were replaced by more easily removable silyl groups or silyl and pivaloyl groups prior

to installation of a (*Z*)-vinyl bromide or vinyl iodide, respectively. However, if debenzylation were feasible in the presence of the vinyl iodide functionality, a straightforward route to reaching triol **38** would be made possible. Accordingly, alcohol **144** was oxidized with TPAP to furnish aldehyde **145**, which was subjected to iodomethylenation with iodomethyltriphenylphosphonium iodide and NaHMDS[53] to afford (*Z*)-vinyl iodide **146** in 63% yield for the two steps. Debenzylation was now critical for the successful completion of our route, as it needed to be executed in the presence of the labile (*Z*)-vinyl iodide, cyclic allylic ether, and TES ether functionalities. Upon considerable experimentation, it was finally accomplished by heating **146** with DDQ in the presence of water and diallyl ether in dichloroethane at 50 °C for 3 h,[54] leading to, after removal of the TES ether, the desired triol **38** in 78% overall yield. Stille coupling of **38** with dienyl stannane **3** using Kadota's conditions afforded a 68% yield of gambierol.



Scheme 20. Completion of Mori's synthesis

CONCLUSION

Gambierol stood for more than ten years as a challenge to synthetic chemists. The necessity for the development of new synthetic methods for the construction of gambierol's skeletons stimulated the invention of convergent and iterative protocols for the regio- and stereoselective polytetrahydropyran and oxepane ring system. These synthetic methods demonstrated the great efficiency in the total synthesis of gambierol and have proved to be applicable to complex polycyclic ether natural products. However, the syntheses still required more than 70 steps in total: Sasaki's synthesis, 107 steps (the longest linear sequence from 2-deoxy-D-ribose is 71 steps with 0.57% overall yield); Kadota's synthesis, 102 steps (the longest linear sequence from 2-deoxy-D-ribose is 66 steps with 1.2% overall yield); Rainier' synthesis, 69 steps (the longest linear sequence from D-glucal is 44 steps with 1.5% overall yield); Mori's synthesis, 74 steps (the longest linear sequence from tri-*O*-acetyl D-glucal is 74 steps with 0.1% overall yield). Therefore, the development of more efficient and concise synthetic routes is a remaining challenge.

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