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Total Synthesis of Gambierol by Using Oxiranyl Anions

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Abstract: Gambierol was isolated as a neurotoxin from the cultured cells of the ciguatera causative dinoflagellate *Gambierdiscus toxicus* and classified as a member of the polycyclic ether family of marine toxins. The structure consists of a ladder-shaped *trans*-fused octacyclic ring system that includes 18 stereogenic centers, two 1,3-diaxial dimethyl-substituted tetrahydropyranyl rings, and a partially conjugated triene side chain. The total synthesis of gambierol has been achieved by utilizing an oxiranyl anion strategy in an iterative manner. Synthetic highlights of this route include direct carbon–carbon formation on epoxides, sulfonyl-assisted 6-*endo* cyclization, and an expansion reaction of the tetrahydropyranyl rings to oxepanes to forge the polycyclic architecture of the target molecule.

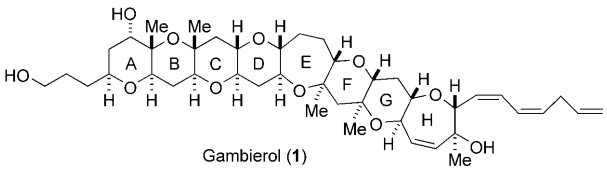
Keywords: cyclization · gambierol · oxiranyl anions · polycyclic ethers · ring expansion

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 spectroscopic analysis of the (*S*)- and (*R*)-phenylmethoxy(trifluoromethyl)acetate (MTPA) derivatives.[4] The toxin exhibits potent toxicity against mice at LD_{50} 50 μg kg^{-1} (ip), and its symptoms occurring in mice resemble those shown for ciguatoxins, which indicates 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 and to be a subtype selective voltage-gated potassium channel antagonist that binds to a novel binding site in cerebellar granule neurons.[9]

Gambierol 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



Gambierol (**1**)

(*Z*,*Z*)-diene system. The complex architecture and the need for biologically active analogues for SAR studies continue to interest organic chemists. To date, three total syntheses have been reported. The Sasaki group reported the first total synthesis based on the B-alkyl Suzuki–Miyaura cross-coupling strategy.[10] Shortly thereafter, Kadota and co-work-

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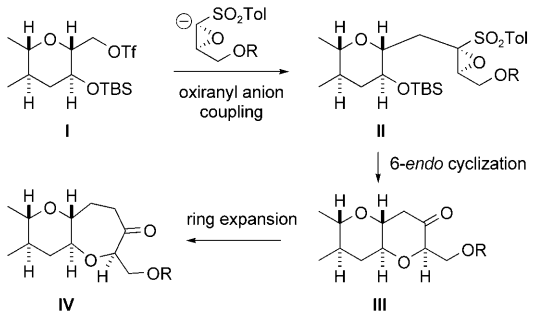
ers achieved the second synthesis by using the intramolecular allylation of α-chloroacetoxy ether followed by ring-closing metathesis.[11] Most recently, the Rainier group completed the third synthesis, with iterative C-glycoside/enol ether–olefin metathesis and olefin metathesis/carbonyl olefination reactions being employed.[12] Moreover, interesting approaches to the construction of the partial ring system of gambierol have been designed.[13]

We describe herein a full account of our total synthesis of gambierol based on our oxiranyl anion coupling methodology.[14]

Results and Discussion

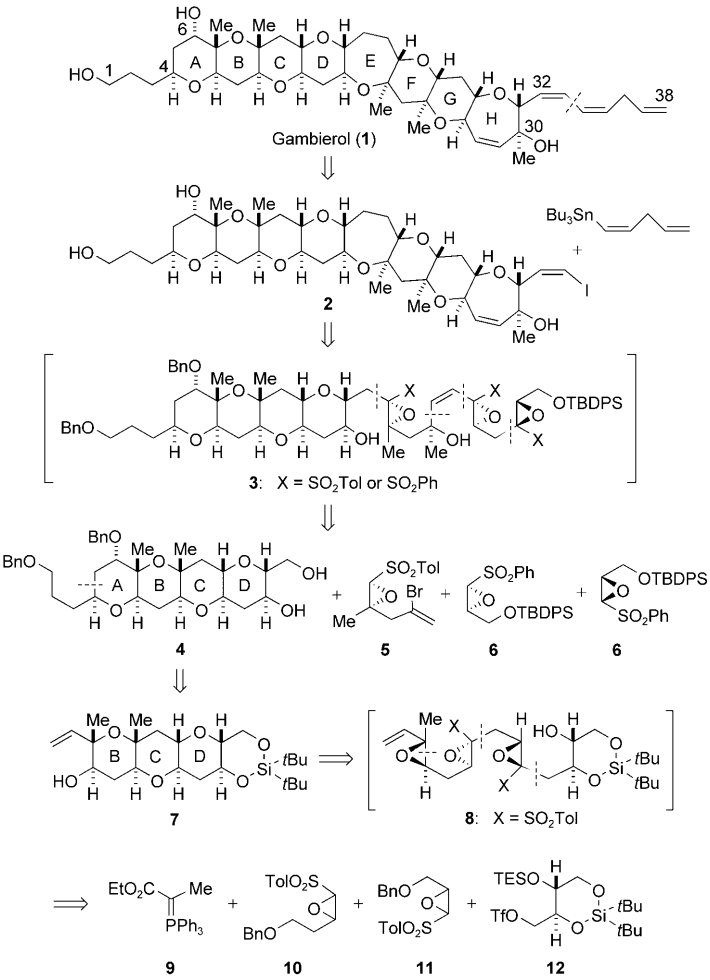
Retrosynthetic analysis: Our laboratory has been interested in the synthesis of bioactive polycyclic ether natural products through use of oxiranyl anions in an iterative manner. Along these lines, we have developed a unique method for the formation of tetrahydropyran **III** by the reaction of triflate **I** with an anion derived from an epoxide followed by a sulfonyl-assisted 6-*endo* cyclization of **II** (Scheme 1).[15] By



Scheme 1. Synthesis of six- and seven-membered rings by an oxiranyl anion strategy.

using this approach, we circumvent direct formation of oxepane **IV** by employing a ring-expansion reaction of **III**.[16] Such structural units found in gambierol make it an attractive target for possible applications of our methodology.

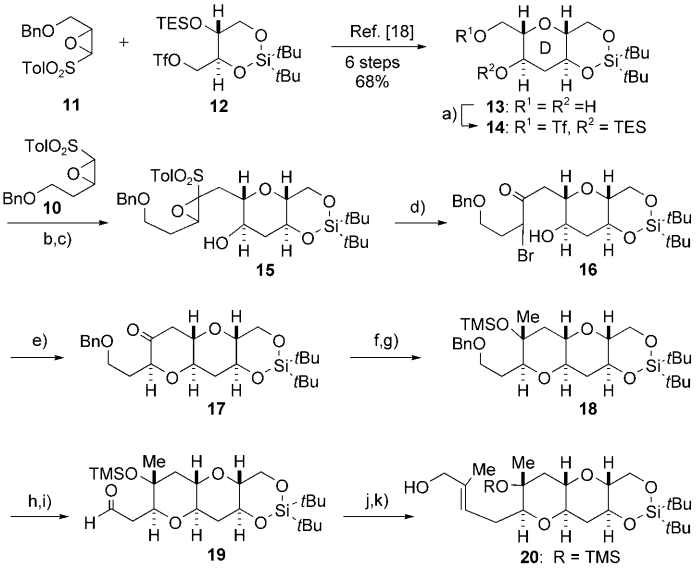
Our synthetic strategy is outlined in Scheme 2. The reported total syntheses have successfully employed the Stille coupling reaction of vinyl iodide **2** or the corresponding vinyl bromide with a (*Z*)-dienyl stannane at the final step.[10–12] This conversion to gambierol is efficient and reliable from the perspective of constructing the stereochemically labile conjugated (*Z*,*Z*)-diene system. As a result, our synthetic plan has focused on the construction of vinyl iodide **2**. We envisioned that two seven-membered E and H rings in **2** would be constructed by a ring-expansion reaction of tetrahydropyranyl rings at suitable stages of synthesis, so we tentatively regarded **3** as a hypothetical polyepoxide precursor for retrosynthetic disassembly. Disconnection of **3** at the indicated bonds with the aid of sulfonyl groups allowed for generation of the ABCD-ring diol **4** with the optically



Scheme 2. Retrosynthetic analysis of gambierol (**1**).

active epoxy sulfones **5** and **6** as building blocks. The advanced BCD-ring fragment **7** was then retrosynthetically broken by considering the hypothetical polyepoxide **8** to afford epoxy sulfones, **10** and **11**, and triflate **12** as potential starting materials. To facilitate the gram-scale preparation of the starting epoxy sulfones, we decided to employ racemic **10** and **11**, which could readily be prepared as a mixture of *cis* and *trans*-isomers according to the reported method.[17]

Synthesis of the CD rings: Our synthesis of gambierol commenced with the D-ring diol **13**, which was prepared from epoxy sulfone **11** and triflate **12** according to the previously reported procedure[18] (Scheme 3). Selective triflation of the primary alcohol of diol **13** with triflic anhydride at −80 °C followed by triethylsilylation of the secondary alcohol with TESOTf in one pot gave triflate **14** in high yield. Treatment of a mixture of epoxy sulfone **10** and triflate **14** with *n*BuLi in THF/HMPA at −100 °C afforded, after removal of the TES group, hydroxy epoxy sulfone **15** in 89 % overall yield. As the latter compound is a mixture of four diastereoisomers around the stereochemistry of the epoxide functionali-

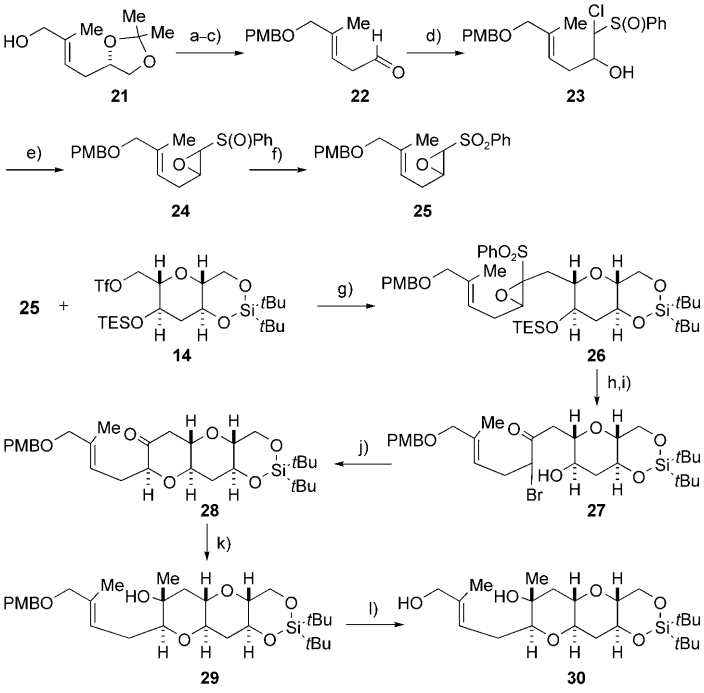


Scheme 3. Synthesis of the CD rings—the first approach: a) Tf_2O, 2,6-lutidine, CH_2Cl_2, −80 °C, then TESOTf, 94 %; b) **10**, *n*BuLi, THF, HMPA, −100 °C, 90 %; c) *p*TsOH·H_2O, CH_2Cl_2, MeOH, RT, 99 %; d) $MgBr_2$·OEt_2, LiBr, CH_2Cl_2, −15 to 0 °C, 99 %; e) DBU, CH_2Cl_2, 0 °C, 90 %; f) $AlMe_3$, CH_2Cl_2, −50 to −20 °C, 94 %; g) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 95 %; h) H_2, $Pd(OH)_2$/C, EtOAc, 94 %; i) Dess–Martin periodinane, py, CH_2Cl_2, RT, 91 %; j) **9**, toluene, RT, 96 %; k) DIBALH, CH_2Cl_2, −80 °C, 93 %. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIBALH = diisobutylaluminum hydride, HMPA = hexamethylphosphoramide, py = pyridine, TES = triethylsilyl, Tf_2O = trifluoromethanesulfonic anhydride, TMS = trimethylsilyl.

ty, the C ring was constructed in a stepwise manner according to the procedure developed in this laboratory.[19]

Thus, exposure of **15** to $MgBr_2$·OEt_2 in the presence of LiBr provided bromoketone **16** as a 1:1 mixture of diastereoisomers, which was then subjected to intramolecular etherification with DBU to afford the desired ketone **17** in 90 % yield with 95:5 diastereoselectivity. This cyclization has the advantage that neither the stereochemistry of bromoketone **16**, in turn, nor that of epoxy sulfone **15** is relevant, because the initial cyclization products undergo facile base-catalyzed equilibration to afford a thermodynamically more stable isomer possessing an equatorial side chain. Stereoselective introduction of the β-axial methyl group was accomplished by using an excess of $AlMe_3$ (3 equiv) to provide a tertiary alcohol with 95:5 selectivity,[20] and the alcohol was protected as a TMS ether to afford **18** in 89 % yield for the two steps. Removal of the benzyl group with H_2/$Pd(OAc)_2$ followed by oxidation of the resulting alcohol with Dess–Martin periodinane yielded aldehyde **19** in 86 % overall yield. The aldehyde was then subjected to the Wittig reaction with **9** to afford an unsaturated ester with high *E* selectivity (94:6), which was reduced with DIBALH to give a CD-ring fragment **20** containing an allylic alcohol side chain in 89 % yield for the two steps.

The route described above was effective for reaching the CD rings but was laborious, especially for the stepwise elaboration of the allylic alcohol side chain, which required 10 steps from triflate **14**. We therefore decided to explore an alternative route requiring the use of epoxy sulfone **25**, an advanced building block with an allylic alcohol moiety preinstalled into epoxy sulfone **10**, at the second oxiranyl anion coupling step (Scheme 4). The epoxy sulfone **25** was prepared from the known alcohol **21**.[21] Protection of the primary alcohol as the PMB ether was followed by removal of the acetonide, and oxidative cleavage of the resulting diol with $NaIO_4$ provided aldehyde **22**. Addition of the anion derived from chloromethyl phenyl sulfoxide and LiHMDS proceeded in good yield to give chlorohydrin **23** as a diastereoisomeric mixture. Cyclization of the chlorohydrin to epoxide **24** by using *t*BuOK and careful chemoselective oxidation of the sulfoxide in the presence of a trisubstituted olefin with MMPP[22] in MeOH at 0 °C afforded epoxy sulfone **25** as a mixture of racemic *cis* and *trans*-isomers in 57 % yield for the three steps.

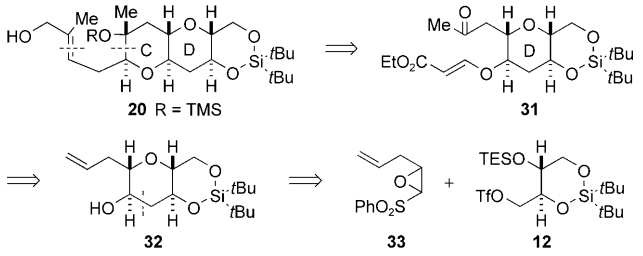


Scheme 4. Synthesis of the CD rings—the second approach: a) PMBCl, NaH, DMF, RT, 91 %; b) *p*TsOH·H_2O, MeOH, RT, 93 %; c) $NaIO_4$, MeOH, H_2O, RT, 97 %; d) chloromethyl phenyl sufoxide, LiHMDS, THF, −80 °C, 87 %; e) *t*BuOK, *t*BuOH, CH_2Cl_2, 0 °C to RT, 88 %; f) MMPP, MeOH, 0 °C, 75 %; g) *n*BuLi, THF, HMPA, −100 °C, 89 %; h) *p*TsOH·H_2O, CH_2Cl_2, MeOH, RT, 99 %; i) $MgBr_2$·OEt_2, CH_2Cl_2, 4 Å MS, 0 °C, 60 %; j) DBU, CH_2Cl_2, 0 °C, 90 %; k) $AlMe_3$, CH_2Cl_2, −50 to −20 °C, 90 %; l) DDQ, CH_2Cl_2, H_2O, 0 °C, then $NaBH_4$, $CeCl_3$, MeOH, 92 %. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, LiHMDS = lithium hexamethyldisilazide, PMBCl = *p*-methoxybenzyl chloride, MMPP = monoperoxyphtalic acid magnesium salt.

With the requisite epoxy sulfone **25** in hand, we turned our attention to the oxiranyl anion coupling reaction with triflate **14**.[23] This was accomplished by using the same conditions employed for **10** to provide **26** in 89 % yield. After removal of the TES group, transformation of **26** to bromo-

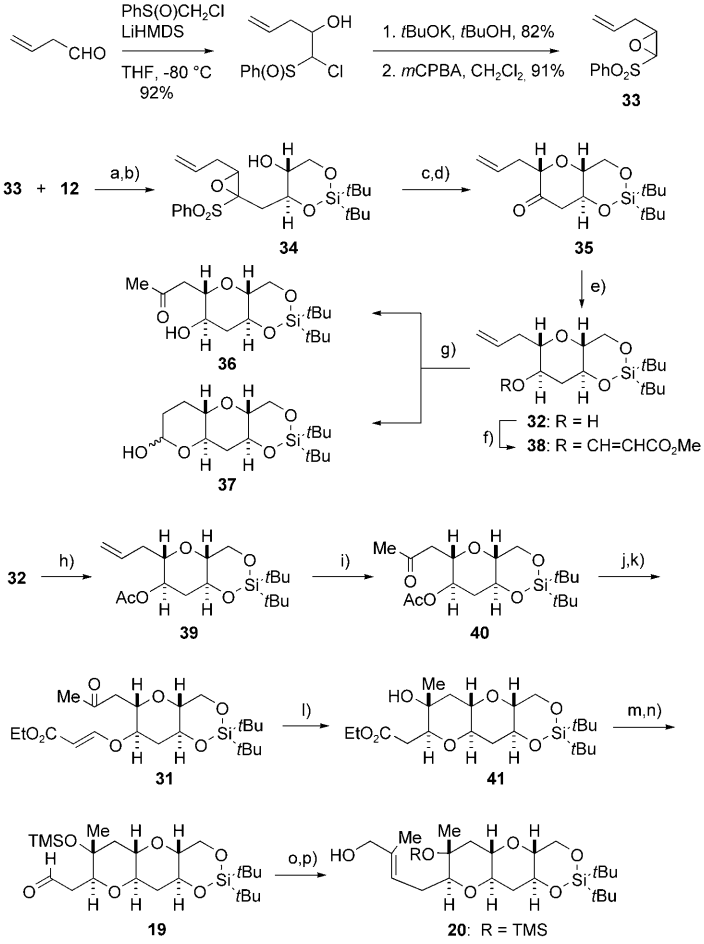
ketone **27** under the standard conditions ($MgBr_2$·OEt_2, LiBr, CH_2Cl_2, −15 °C) proved to be less effective than the preceding case, yielding **27** in only 47% yield. The major side reaction observed was a 1,2-shift of the sulfonyl group, leading to the corresponding α-sulfonyl ketone. Efforts to optimize the yield by changing the reaction conditions to $MgBr_2$·OEt_2/4 Å MS/CH_2Cl_2/0 °C improved the yield up to 60%. The subsequent cyclization with DBU (diastereomeric ratio d.r. 94:6) to ketone **28** and methylation with $AlMe_3$ (d.r. 94:6) proceeded without trouble to afford tertiary alcohol **29** in 80% yield for the two steps. Removal of the PMB group with DDQ gave a 3:2 mixture of an allylic alcohol and the corresponding unsaturated aldehyde. To avoid handling the labile aldehyde, the reaction mixture was further treated with $NaBH_4$ in one pot, yielding allylic alcohol **30** in 92% yield. Utilization of the advanced epoxy sulfone **25** enabled us to diminish the number of reaction steps from 17 steps in the first approach (34% overall yield) to 13 steps to reach **30** from triflate **12**. However, the overall yield (18%) of the second approach was lower than we anticipated. The lengthy synthesis of epoxy sulfone **25**, the moderate yield of bromoketone **27**, and the extra reductive workup at the DDQ oxidation step made the second route impractical as a means of acquiring a sufficient quantity of **30**.

We then devised a new plan based on the modified retrosynthetic analysis shown in Scheme 5. In this third approach, we envisaged constructing the C ring by using ketyl radical



Scheme 5. The third approach for the CD-ring fragment **20**.

cyclization of ketone **31**. The ketone would be accessed from hydroxy olefin **32**, which could be built up by using an oxiranyl anion coupling reaction between the unsaturated epoxy sulfone **33** and triflate **12**. The requisite epoxy sulfone **33** was prepared from 4-butenal[24] and chloromethyl phenyl sulfoxide as a mixture of racemic *cis* and *trans*-stereoisomers by a three-step procedure (Scheme 6). Reaction of the oxiranyl anion derived from epoxy sulfone **33** with triflate **12** followed by removal of the TES group afforded hydroxy epoxy sulfone **34** in 88% overall yield. The reaction of **34** with $MgBr_2$·OEt_2 proceeded without any trouble to provide bromoketones in 94% yield, and the DBU-mediated cyclization afforded ketone **35** quantitatively with 94:6 diastereoselectivity. Reduction of the ketone with $NaBH_4$ furnished a diastereoisomeric mixture of alcohols, from which the desired alcohol **32** was isolated in 91% yield. Transformation of the double bond to a methyl ketone proved to be more



Scheme 6. Synthesis of the CD rings—the third approach: a) *n*BuLi, THF, HMPA, −100 °C, 94%; b) *p*TsOH·H_2O, CH_2Cl_2, MeOH, RT, 94%; c) $MgBr_2$·OEt_2, LiBr, CH_2Cl_2, −15 to 0 °C, 94%; d) DBU, CH_2Cl_2, 0 °C, 100% (d.r. 94:6); e) $NaBH_4$, MeOH, CH_2Cl_2, −80 °C, 91%; f) methyl propiolate, NMM, CH_2Cl_2, RT, 90%; g) $PdCl_2$, CuCl, CH_3CN, H_2O, RT, **36** (44%), **37** (44%); h) Ac_2O, py, DMAP, CH_2Cl_2, 86%; i) $PdCl_2$, DMF, H_2O, RT, 73%; j) K_2CO_3, MeOH, RT, 93%; k) ethyl propiolate, NMM, CH_2Cl_2, RT, 97%; l) SmI_2, THF, MeOH, 0 °C, 100%; m) TMSOTf, 2,6-lutidine, 0 °C, CH_2Cl_2, 96%; n) DIBALH, CH_2Cl_2, −80 °C, 99%; o) **9**, toluene, RT, 96%; p) DIBALH, CH_2Cl_2, −80 °C, 93%. DMAP = 4-dimethylaminopyridine; NMM = *N*-methylmorpholine.

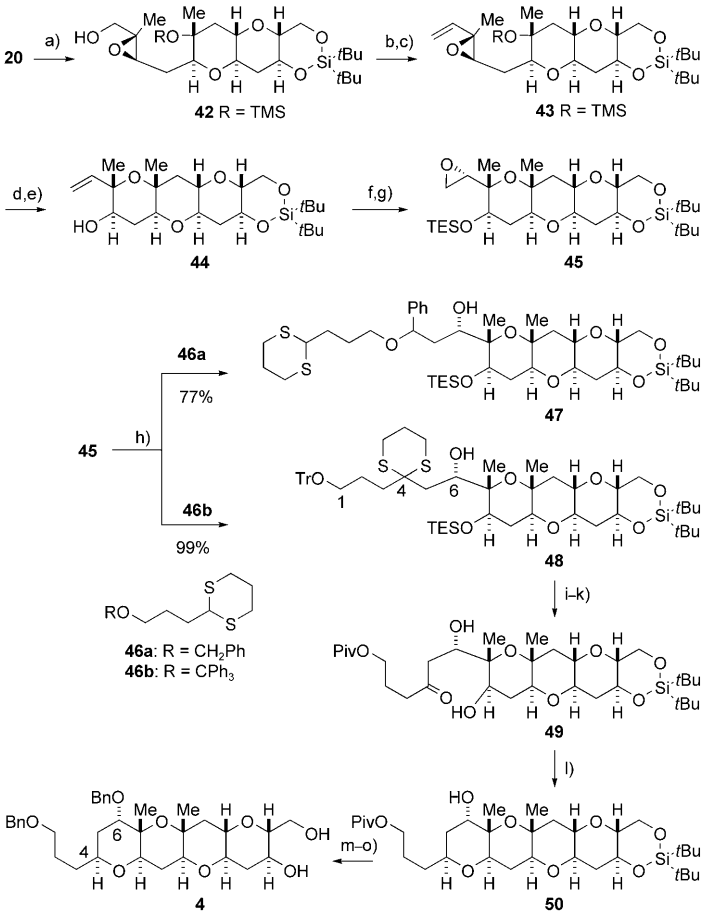
difficult than anticipated. Wacker oxidation[25] of **32** gave the desired hydroxy ketone **36** in a disappointing 44% yield. The byproduct of this oxidation was hemiacetal **37**, which was also obtained in 44% yield. To prevent the undesired hemiacetal formation, the hydroxy group was protected as a β-alkoxy acrylate by reaction with methyl propiolate in the presence of *N*-methyl morpholine, leading to **38** in 90% yield. Wacker oxidation of **38**, however, resulted in the same outcome, yielding a 1:1 mixture of **36** and **37**, due to the rapid hydrolysis of the alkoxy acrylate group under acidic conditions.

These disappointing results forced us to protect the hydroxy group with an appropriate protecting group that would be tolerable under acidic conditions. To this end, the hydroxy group of **32** was protected as an acetate. When ace-

tate **39** was subjected to Wacker oxidation under noncatalytic conditions,[26] the desired ketone **40** was produced in 73% yield. Removal of the acetyl group followed by installation of a β-alkoxy acrylate group afforded keto acrylate **31** in 90% overall yield. Treatment of **31** with SmI_2 in the presence of MeOH[27] effected ketyl radical cyclization to afford quantitatively bicyclic ester **41** as a single stereoisomer. Elaboration of the ester to allylic alcohol **20** via **19** was carried out in 85% overall yield by a four-step sequence involving: 1) protection of the tertiary alcohol with a TMS group, 2) reduction of the ester with DIBALH, 3) Wittig olefination with **9**, and, finally, 4) the DIBALH reduction of the unsaturated ester. This third approach to **20** has a favorable overall yield of 34% for the 14 steps from **12**, compared with the first and second approaches.

Synthesis of the ABCD rings:[23] With an ample supply of the CD-ring fragment **20**, we then turned our attention to the construction of the AB ring as shown in Scheme 7. The B ring containing sterically congested 1,3-diaxial dimethyl groups was synthesized according to the Nicolaou's protocol.[28] Thus, epoxidation of allylic alcohol **20** with *m*CPBA proceeded with a high diastereomeric ratio of 96:4 to afford epoxide **42** in 96% yield. Subsequent oxidation with SO_3·py gave an aldehyde, which was subjected to methylenation to afford epoxy olefin **43** in 75% overall yield. Removal of the TMS group with one equivalent of nBu$_4$NF at −10°C followed by exposure of the resulting hydroxy epoxide to PPTS at 0°C led to the B-ring vinyl alcohol **44** in 74% yield over the two steps.

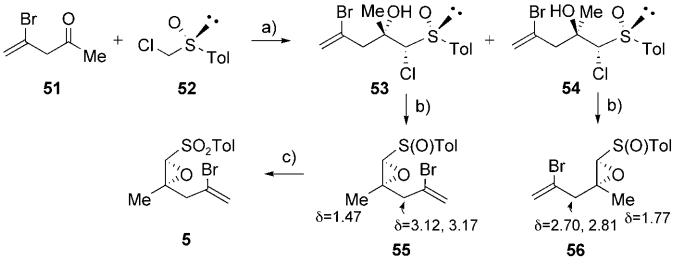
Construction of the A ring is a challenging issue, because an α-axial hydroxy group at C(6) and a β-equatorial C_3 side chain at C(4) have to be installed stereoselectively. To introduce the C(6) axial hydroxy group, Sasaki and Yamamoto/Kadota's syntheses employed reduction of a hydroxy epoxide[10] or asymmetric allylation of an aldehyde,[11] in which the hydroxy epoxide and the aldehyde were prepared from the vinyl derivatives similar to **44**. We envisioned that the C(6) hydroxyl group and the C_3-side chain could be introduced by the reaction of epoxide **45** with 2-(3-benzyloxypropyl)-1,3-dithiane (**46a**). To this end, vinyl alcohol **44** was subjected to the homoallylic hydroxy-directed epoxidation with *tert*-butyl hydroperoxide in the presence of [VO(acac)$_2$][29] (acac = acetylacetone) to afford the desired epoxide with 93:7 diastereoselectivity, and the remaining hydroxy group was protected as a TES ether to provide epoxide **45** in 82% yield over the two steps. Reaction of the epoxide with the lithiodithiane derived from **46a** under standard conditions (nBuLi, THF, −20°C, 2 h)[30] resulted in only 28% yield of the desired product. The lack of reactivity of lithiated **46a** was found to be due to decomposition of the lithiodithiane during anion formation, which was confirmed by the isolation of 2-allyl-1,3-dithiane. When the reaction was carried out under in situ trapping conditions at 0°C, an unexpected product **47** was obtained in 77% yield.[31] To avoid this undesired reaction, the trityl ether derivative **46b**, which has no benzylic protons, was reacted with epoxide **45**.



Scheme 7. Synthesis of the ABCD-ring fragment **4**: a) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0°C, 96% (d.r. 96:4); b) SO_3·py, Et_3N, DMSO, 0°C to RT; c) $Ph_3P^+CH_3$·Br^-, KHMDS, THF, −80°C to RT, 87% (2 steps); d) nBu$_4$NF, THF, −10°C, 100%; e) PPTS, CH_2Cl_2, 74%; f) *t*BuOOH, [VO(acac)$_2$], CH_2Cl_2, 35°C, 85% (d.r. 93:7); g) TESCl, Et_3N, DMAP, CH_2Cl_2, 96%; h) **46b**, nBuLi, THF, 0°C, **48** (99%); i) *p*TsOH·H_2O, MeOH, CH_2Cl_2, RT, 97%; j) PivCl, DMAP, py, CH_2Cl_2, 0°C, 98%; k) $Hg(ClO_4)_2$, THF, H_2O, 0°C, 90%; l) Et_3SiH, $SnCl_4$, CH_2Cl_2, −40°C, 91%; m) DIBALH, CH_2Cl_2, −80°C, 98%; n) NaH, BnBr, DMF, 86%; o) nBu$_4$NF, THF, RT, 97%. KHMDS = potassium hexamethyldisilazide, *m*CPBA = *meta*-chloroperbenzoic acid, PivCl = pivaloyl chloride, PPTS = pyridinium *p*toluenesulfonate, TESCl = chlorotriethylsilane.

In this case, the desired hydroxy dithioacetal **48** was obtained in 99% yield. The dithioacetal was then transformed into β,δ-dihydroxy ketone **49** in 85% overall yield in a three-step sequence: removal of the TES and trityl groups with *p*TsOH, protection of the primary alcohol as its pivaloate, and hydrolysis of the dithioacetal group. The reductive cycloetherification of hydroxy ketone **49** was best accomplished with triethylsilane in the presence of $SnCl_4$ at −40°C to proceed with complete stereochemical control, leading to the ABCD-ring fragment **50** containing an equatorial side-chain group in 91% yield. Finally, reductive removal of the pivaloyl group followed by dibenzylation of the C(1) and C(6) hydroxy groups and desilylation afforded the ABCD-ring diol **4** in 82% yield for the three steps.

Synthesis of the ABCDEF rings: Elaboration of the ABCD rings to the hexacyclic ABCDEF rings required constructing seven and six-membered ring systems with sterically congested 1,3-diaxial dimethyl groups. To this end, the requisite building block **5** to be coupled to the ABCD-ring fragment was prepared from 4-bromo-4-pent-2-enone (**51**) and (*R*)-(−)-chloromethyl *p*-tolyl sulfoxide (**52**) (Scheme 8).[32]

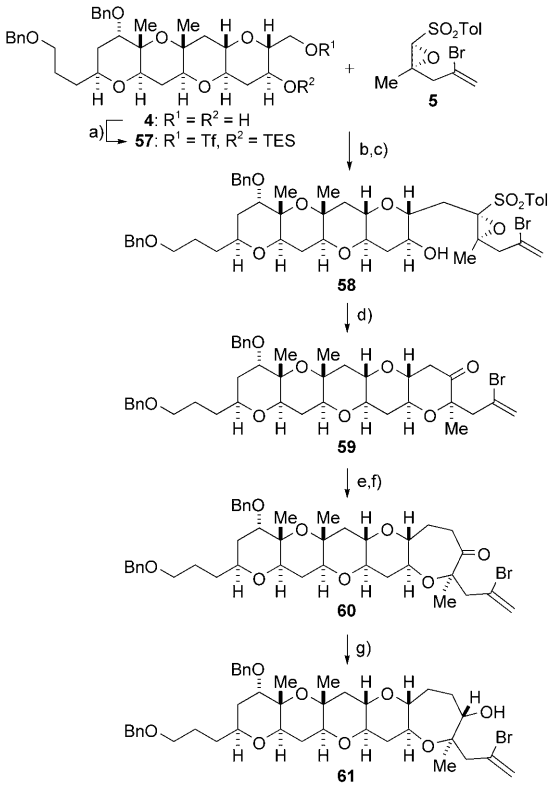


Scheme 8. Preparation of epoxy sulfone **5**: a) **52**, LiHMDS, THF, −80 °C, then **51**, **53** (40 %), **54** (40 %); b) *t*BuOK, *t*BuOH, CH_2Cl_2, 0 °C, **55** (90 %), **56** (83 %); c) *m*CPBA, CH_2Cl_2, 0 °C, 94 %. LDA = lithium diisopropylamide.

Chlorohydrins **53** and **54** were subjected to exposure to *t*BuOK to afford the epoxy sulfoxides **55** and **56**, respectively, in good yields.

The stereochemistry of epoxides **55** and **56** was determined by ^{1}H HMR spectroscopic analysis: the chemical shifts of the allylic hydrogen atoms of the desired isomer **55** lay downfield relative to those of the isomer **56** due to the anisotropic effect of the adjacent sulfinyl group. Oxidation of the isomer **55** with *m*CPBA afforded the desired epoxy sulfone **5** in 85 % yield for the two steps. We also attempted to prepare allylic or propargylic analogues of **5** from 4-pent-2-enone or 4-pent-2-ynone, respectively. However, the reactions of those ketones with the anion derived from **52** were unsuccessful due to the facile enolization of the starting ketones.

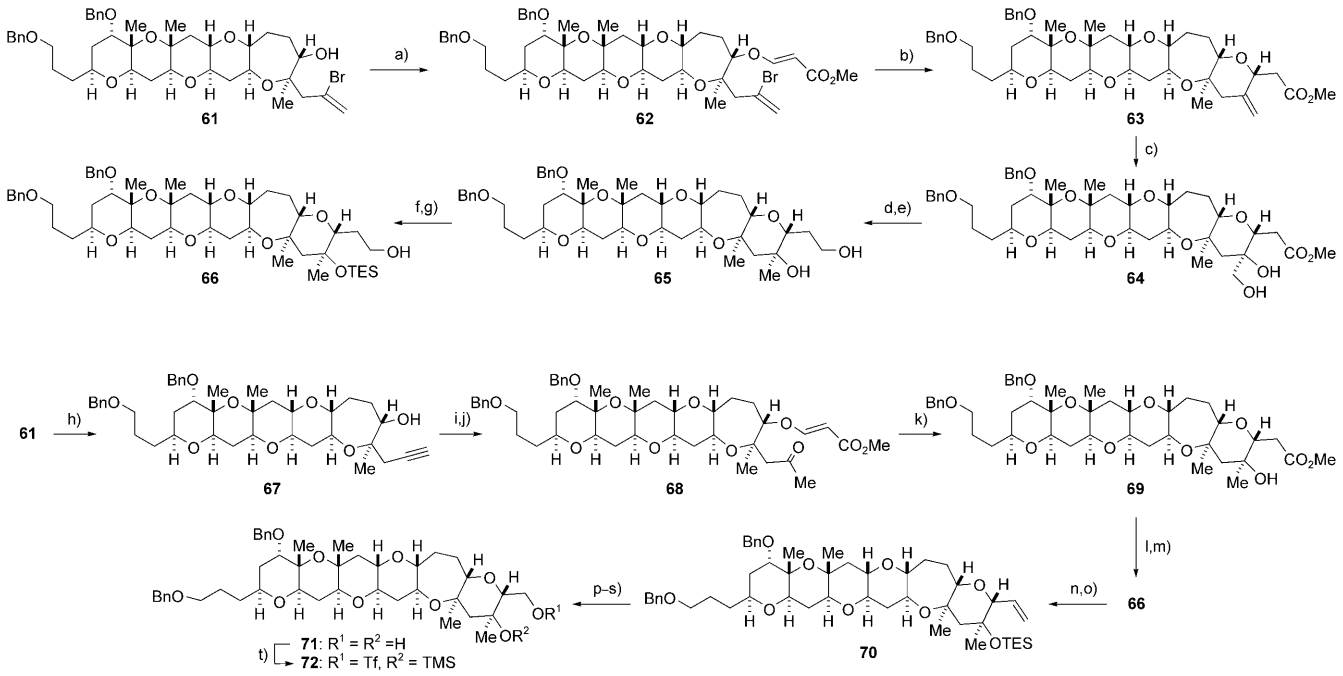
Construction of the E ring began with the anion coupling of epoxy sulfone **5** with the ABCD-ring triflate **57** prepared from diol **4** (Scheme 9). Thus, treatment of a mixture of **5** and **57** with *n*BuLi at −100 °C followed by desilylation with *p*TsOH afforded hydroxy epoxy sulfone **58** in 83 % overall yield. A sulfonyl-assisted 6-*endo* cyclization was carried out with $BF_3{\cdot}OEt_2$ to afford ketone **59** quantitatively. The ketone was then subjected to a ring-expansion reaction with trimethylsilyldiazomethane[16] in the presence of $BF_3{\cdot}OEt_2$ followed by desilylation of the resulting α-trimethylsilyl ketone with nBu_4NF to furnish the desired seven-membered ketone **60** in 51 % yield for the two steps. Reduction of the ketone with $NaBH_4$ gave a 3:2 separable mixture of the desired α-alcohol **61** and the undesired β-isomer in 59 and 41 % yields, respectively. The latter isomer could be recycled by oxidation and reduction, allowing the overall yield for the **60**→**61** conversion to be raised to 89 % after a three-cycle operation.



Scheme 9. Synthesis of the ABCDE-ring system **61**: a) Tf_2O, 2,6-lutidine, −80 °C, CH_2Cl_2, then TESOTf, 92 %; b) **5**, *n*BuLi, THF, HMPA, −100 °C, 91 %; c) *p*TsOH·H_2O, CH_2Cl_2, MeOH, RT, 91 %; d) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −80 °C, 98 %; e) $TMSCHN_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −20 °C, 53 %; f) nBu_4NF, THF, AcOH, RT, 97 %; g) $NaBH_4$, CH_2Cl_2, MeOH, −80 °C, 59 % (+ isomer 41 %). $TMSCHN_2$ = trimethylsilyldiazomethane.

At this stage we envisioned two options for forming the F ring: one was a vinyl radical cyclization route and the other was a ketyl radical cyclization route (Scheme 10). The vinyl radical approach proceeded through alkoxy acrylate **62**, which was prepared from **61** by a hetero-Michael reaction with methyl propiolate in 95 % yield. Treatment of **62** with Bu_3SnH in the presence of AIBN in toluene at reflux furnished the olefinic ester **63** in 81 % yield along with the debrominated product (15 %). Dihydroxylation of **63** with OsO_4 provided the diol **64** in 88 % yield as a single diastereoisomer. Selective mesylation of the primary alcohol followed by reduction with $LiEt_3BH$ afforded diol **65** containing 1,3-diaxial dimethyl groups in 94 % overall yield.[33] The primary alcohol **66** was then prepared by a two-step procedure involving bis-triethylsilylation followed by selective monodesilylation in 89 % overall yield.

The second approach to elaborate the F ring by ketyl radical cyclization began with the dehydrobromination of **61** with nBu_4NF in DMF at 60 °C[34] to afford alkyne **67** in 99 % yield. Hydration of the terminal alkyne with a catalytic amount of $Hg(OTf)_2$[35] followed by reaction with methyl propiolate provided keto acrylate **68** in 67 % overall yield. Treatment of **68** with SmI_2 in the presence of MeOH induced reductive cyclization to afford hydroxy ester **69** quan-

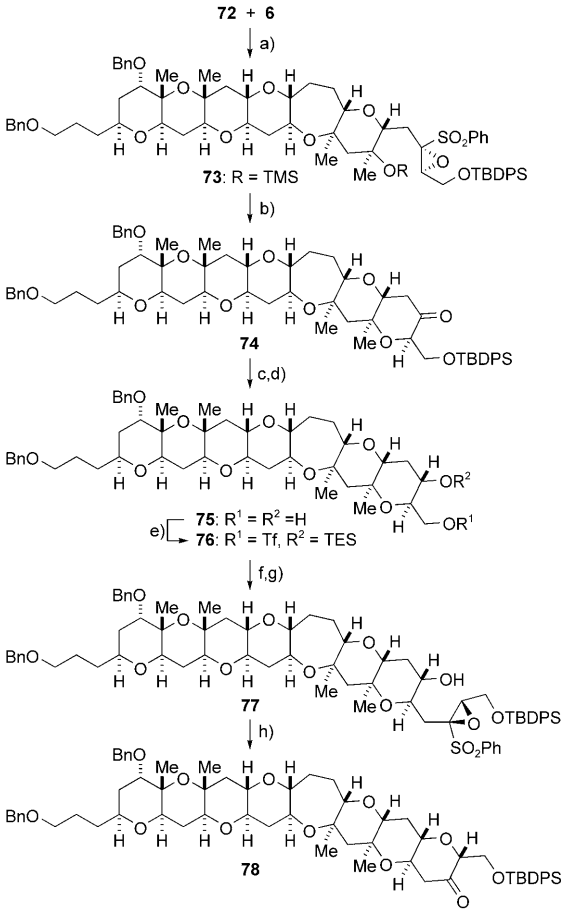


Scheme 10. Synthesis of the ABCDEF-ring triflate **72**: a) methyl propiolate, NMM, CH_2Cl_2, RT, 95%; b) nBu$_3$SnH, AIBN, toluene, 110°C, 81%; c) OsO_4, NMO, THF, H_2O, RT, 88%; d) MsCl, Et_3N, CH_2Cl_2, −10°C, 96%; e) $LiEt_3BH$, THF, 0°C, 98%; f) TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 94%; g) PPTS, MeOH, CH_2Cl_2, 0°C, 95%; h) nBu$_4$NF·3H$_2$O, DMF, 60°C, 99%; i) Hg(OTf)$_2$, TMU, CH_2Cl_2, MeCN, H_2O, RT, 82%; j) methyl propiolate, NMM, CH_2Cl_2, RT, 82%; k) SmI_2, THF, MeOH, 0°C, 100%; l) TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 92%; m) DIBALH, CH_2Cl_2, 0°C, 96%; n) o-$NO_2PhSeCN$, nBu$_3$P, CH_2Cl_2, py, RT; o) H_2O_2, $NaHCO_3$, THF, RT, 85% (2 steps); p) OsO_4, NMO, THF, H_2O, RT; q) $NaIO_4$, MeOH, H_2O, RT; r) $NaBH_4$, CH_2Cl_2, MeOH, RT, 98% (3 steps); s) pTsOH·H$_2$O, CH_2Cl_2, MeOH, RT, 100%; t) Tf_2O, 2,6-lutidine, CH_2Cl_2, −80°C, then TMSOTf, 95%. AIBN = 2,2′-azobisisobutyronitrile, TMU = 1,1,3,3,-tetramethylurea.

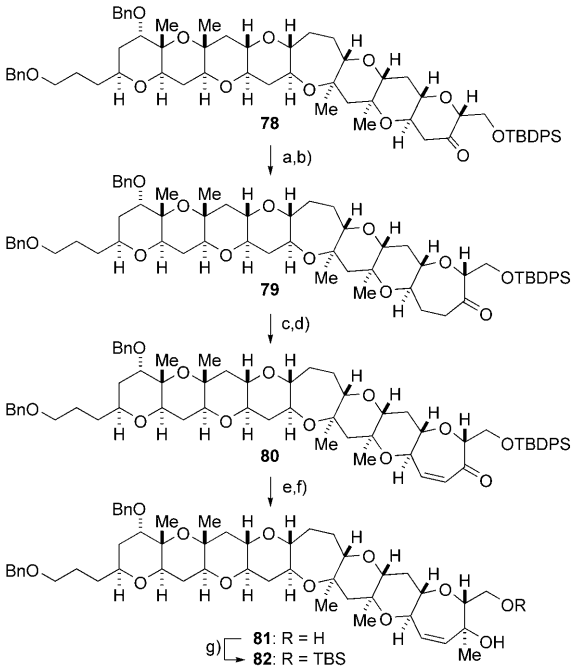
titatively as a single diastereoisomer. After protection of the hydroxy group as a TES ether, the ester was reduced with DIBALH to furnish alcohol **66** in 88% yield for the two steps. The lack of need for the deoxygenation step (**64**→**65**) made the second approach more practical. The elaboration of alcohol **66** to diol **71** required the one-carbon diminution of the side chain. Thus, alcohol **66** was converted to olefin **70** via *o*-nitrophenyl selenide in 82% overall yield.[36] Subsequent oxidative cleavage of the double bond was performed by a three-step procedure involving dihydroxylation with OsO_4, oxidation with $NaIO_4$, and $NaBH_4$ reduction to afford the primary alcohol. Removal of the TES group of the latter compound with acid provided diol **71** in 98% overall yield from **70**. Triflation and trimethylsilylation of the diol in one pot afforded triflate **72** in 95% yield, setting the stage for the construction of the G and H rings.

Synthesis of the octacyclic ring system of gambierol: With the hexacyclic ring system **72** in hand, we then turned our attention to the construction of the GH rings. Installation of the G and H rings was based on the use of an oxiranyl anion strategy (Scheme 11). Treatment of **6**[15] with *n*BuLi in the presence of triflate **72** at −100°C afforded epoxy sulfone **73** in 93% yield. Exposure of **73** to BF_3·OEt_2 caused detrimethylsilylation and 6-*endo* cyclization to form the G-ring ketone **74** in 91% yield. Stereoselective reduction of the ketone with $NaBH_4$ and removal of the *tert*-butyldiphenylsilyl (TBDPS) group with nBu$_4$NF afforded the diol **75**, which was then subjected to one-pot triflation and silylation to furnish triflate **76** in 91% yield for the three steps. The sequence described above was employed iteratively with equal efficiency to construct the H-ring precursor **78**. Thus, the second coupling reaction of **76** with the oxiranyllithium of **6** provided, after desilylation, epoxy sulfone **77** in 94% yield. The BF_3-promoted cyclization of **77** resulted in the formation of octacyclic ketone **78** in 83% yield.

Conversion of the ketone **78** to the seven-membered H ring ketone **79** proceeded smoothly with trimethylsilyldiazomethane in the presence of BF_3·OEt_2 (Scheme 12). We were pleased to find that this ring enlargement was achieved in a high 81% yield compared with the case of E-ring formation. To then complete the H-ring functionalities, it remained to introduce the C(28)=C(29) double bond and the C(30) tertiary alcohol. This transformation was carried out according to the procedure employed in the previous syntheses.[10,11] Thus, treatment of ketone **79** with LiHMDS in the presence of TMSCl and Et_3N afforded the corresponding enol silyl ether, which was subjected to Saegusa oxidation[37] with Pd(OAc)$_2$ in acetonitrile to provide enone **80** quantitatively. Methylation with MeMgBr in toluene followed by removal of the TBDPS group with nBu$_4$NF afforded diol **81** in 93% yield as a single diastereoisomer. At this point, we decided to carry out an additional manipulation on the diol to reach compound **82**, an intermediate synthesized by Sasaki et al.[10]



Scheme 11. Synthesis of ketone **78**: a) *n*BuLi, THF, HMPA, −100 °C, 93 %; b) BF_3·OEt_2, CH_2Cl_2, 0 °C to RT, 91 %; c) $NaBH_4$, CH_2Cl_2, MeOH, −80 °C, 100 %; d) nBu_4NF, THF, RT, 96 %; e) Tf_2O, 2,6-lutidine, CH_2Cl_2, −80 °C, then TESOTf, 95 %; f) **6**, *n*BuLi, THF, HMPA, −100 °C, 94 %; g) PPTS, CH_2Cl_2, MeOH, RT, 100 %; h) BF_3·OEt_2, CH_2Cl_2, 0 °C to RT, 83 %.



Scheme 12. Synthesis of the ABCDEFGH-ring diol **81**: a) $TMSCHN_2$, BF_3·OEt_2, CH_2Cl_2, −80 °C; b) PPTS, CH_2Cl_2, MeOH, RT, 81 % (2 steps); c) LiHMDS, TMSCl, Et_3N, THF, −80 °C; d) $Pd(OAc)_2$, MeCN, RT, 98 % (2 steps); e) MeMgBr, toluene, −80 °C, 93 %; f) nBu_4NF, THF, RT, 100 %; g) TBSOTf, 2,6-lutidine, CH_2Cl_2, −80 °C, 86 %.

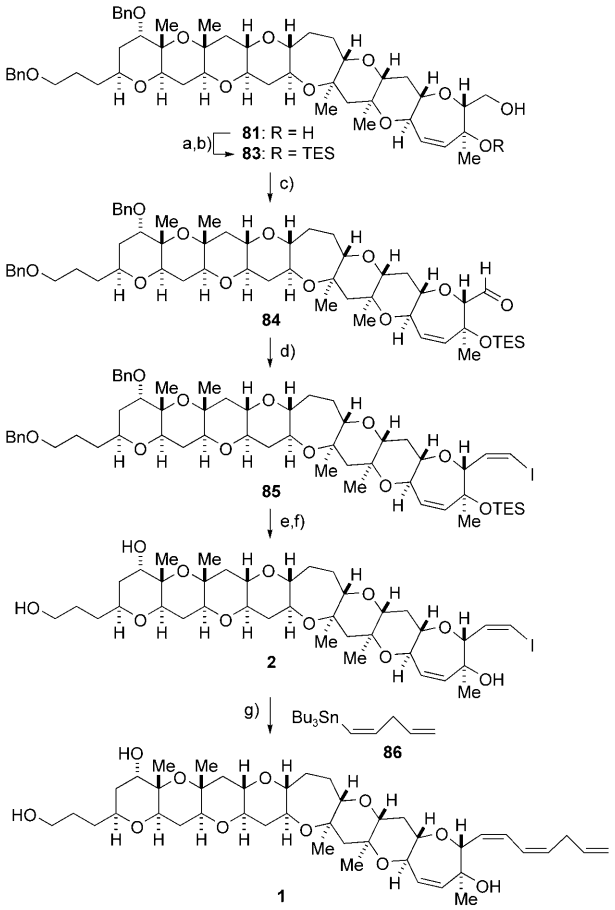
Selective silylation of the primary hydroxy group as a TBS ether led to compound **82**. Indeed, the ^1H and ^{13}C NMR spectroscopic data and the optical rotation of our synthetic material matched those reported for **82**, thus confirming the structure and stereochemical assignments of **81**.

Completion of the total synthesis: The last remaining challenge in the total synthesis of gambierol (**1**) required incorporation of the skipped triene side chain. This task was accomplished as summarized in Scheme 13. In the work previously performed by Sasaki's and Kadota's groups,[10,11] the robust C(1) and C(6) benzyl groups of **82** and the TBS derivative of **79** were replaced by more easily removable silyl groups or silyl and pivaloyl groups prior to installation of a (*Z*)-vinyl iodide moiety, respectively. However, if debenzylation of **85** were feasible in the presence of the vinyl iodide functionality, a straightforward route to reaching **2** would be made possible. To this end, the primary alcohol **83** was prepared from **81** by a two-step procedure involving bis-silylation followed by selective monodesilylation in 93 % overall yield. Subsequent oxidation of the alcohol with TPAP furnished aldehyde **84**, which was subjected to iodomethylenation with iodomethyltriphenylphosphonium iodide[38] and NaHMDS to afford the (*Z*)-vinyl iodide **85** in 63 % yield for the last two steps.

Debenzylation of **85** 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 discovered that gentle heating of **85** with DDQ in the presence of water and diallyl ether in 1,2-dichloroethane at 50 °C for 3 h smoothly promoted debenzylation,[39] leading to, after removal of the TES ether, the desired triol **2** in 78 % yield. The above reaction conditions are critical: extending the reaction time or elevated temperatures resulted in decomposition and decreased the yield. Finally, Stille coupling of triol **2** with dienyl stannane **86**[40] was carried out by using Kadota's protocol[11] to provide gambierol (**1**) in 68 % yield. The spectroscopic and physical data for synthetic gambierol were identical to those reported previously.[10,11]

Conclusion

Total synthesis of gambierol has been achieved by utilizing an oxiranyl anion strategy in an iterative manner. The salient features of the route include: 1) direct carbon–carbon bond formation on an oxirane ring and the subsequent sul-



Scheme 13. Completion of the total synthesis: a) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 95 %; b) PPTS, CH_2Cl_2, MeOH, 0 °C, 98 %; c) TPAP, NMO, CH_2Cl_2, RT, 93 %; d) $Ph_3P^+CH_2I \cdot I^-$, NaHMDS, THF, −80 °C to RT, 68 %; e) DDQ, H_2O, diallyl ether, DCE, 50 °C; f) pTsOH·H_2O, CH_2Cl_2, MeOH, RT, 78 % (2 steps); g) **86**, $[Pd_2(dba)_3]\cdot CHCl_3$, $P(furyl)_3$, CuI, DMSO, 40 °C, 68 %. dba = dibenzylideneacetone, DCE = 1,2-dichloroethane. TPAP = tetra-*n*-propylammonium perruthenate, NMO = 4-methylmorpholine-*N*-oxide.

fonyl-assisted 6-*endo* cyclization, 2) a ring-expansion approach to seven-membered ether rings, 3) a successful implementation of debenzylation in the presence of labile functional groups. Further application of this oxiranyl anion coupling strategy to other marine polycyclic ethers is in progress.

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