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Total Synthesis and Biological Evaluation of (+)-Gambieric Acid A and Its Analogues

Kazuya Ishigai,[a] Haruhiko Fuwa,*[a] Keisuke Hashizume,[a] Ryo Fukazawa,[a] Yuko Cho,[b] Mari Yotsu-Yamashita,[b] and Makoto Sasaki*[a]

Abstract: In this study, we report the first total synthesis and complete stereostructure of gambieric acid A, a potent antifungal polycyclic ether metabolite, in detail. The A/B-ring exocyclic enol ether **32** was prepared through a Suzuki–Miyaura coupling of the B-ring vinyl iodide **18** and the alkylborate **33** and subsequent closure of the A-ring by using diastereoselective bromoetherification as the key transformation. Suzuki–Miyaura coupling of **32** with acetate-derived enol phosphate **49**, followed by ring-closing metathesis of the derived diene, produced the D-ring. Subsequent closure of the C-ring through a mixed thioacetalization completed the synthesis of the A/BCD-ring fragment **8**. The A/BCD- and F′GHIJ-ring fragments (i.e., **8** and **9**) were assembled through Suzuki–Miyaura coupling. The C25 stereogenic center was elaborated by exploiting the intrinsic conformational property of the seven-membered F′-ring. After the oxidative cleavage of the F′-ring, the E-ring was formed as a cyclic mixed thioacetal (i.e., **70**) and then stereoselectively allylated by using glycosylation chemistry. Ring-closing metathesis of the diene **3** thus obtained closed the F-ring and completed the polycyclic ether skeleton. Finally, the J-ring side chain was introduced by using a Julia–Kocienski olefination in the presence of $CeCl_3$ to complete the total synthesis of gambieric acid A (**1**), thereby unambiguously establishing its complete stereostructure. The present total synthesis enabled us to evaluate the antifungal and antiproliferative activities of **1** and several synthetic analogues.

Keywords: natural products · polycyclic ethers · structure–activity relationships · Suzuki–Miyaura coupling · total synthesis

Introduction

Gambieric acids (GAs) A–D were isolated as antifungal substances from a culture medium of the ciguatera causative dinoflagellate, *Gambierdiscus toxicus*, by Nagai, Yasumoto, and co-workers.[1] The skeletal structure of GAs consists of a nonacyclic polyether core involving six-, seven-, and nine-membered cyclic ethers, arranged with an isolated tetrahydrofuran ring (A-ring). GAs share the structural characteristics common to those of polycyclic ether neurotoxins, which are produced by *G. toxicus*, for example, ciguatoxin, maitotoxin, and gambierol.[2–4] However, Nagai and co-workers have reported that gambieric acid A (GAA, **1**) shows no toxicity in mice at a dose of 1 mg kg^{-1} (ip injection).[1,5] Moreover, Hirama and co-workers have reported that GAA only weakly inhibits the binding of tritiated dihydrobrevetoxin B ([^{3}H]PbTx-3) to site 5 of the voltage-gated sodium ion channels of excitable membranes.[6] Instead, the Nagai/Yasumoto group has shown that GAs exhibit potent antifungal activity against *Aspergillus niger*[5] and also suggested the possible role of GAA as an endogenous growth regulator of *G. toxicus*.[7]

The gross structure and relative stereochemistry of the polycyclic ether domain of GAs were established by 2D NMR spectroscopic analysis.[1] The complete stereostructure was later proposed on the basis of degradation experiments, application of chiral anisotropic reagents, chiral HPLC analysis, and NMR-based conformational analysis on gambieric acid B.[8] Satake and co-workers have determined the absolute configuration of the C9 stereogenic center by using the modified Mosher's method,[9] and the relative stereochemistry of C7/C9 and C9/C11 stereogenic centers was proposed on the basis of $^3J_{H,H}$ values and nuclear Overhauser effect (NOE) correlations. However, our previous studies on the synthesis and NMR spectroscopic analysis of the A/B-ring model compounds of GAs strongly suggested that the relative stereochemical relationship between the C9 and C11 stereogenic centers was erroneously assigned in the originally proposed structure, and the absolute configuration of the polycyclic ether domain of GAs must be opposite to that of the proposed structure.[10] However, our revised structure of GAs must be verified unambiguously by total synthesis.

[a] K. Ishigai, Prof. Dr. H. Fuwa, K. Hashizume, R. Fukazawa, Prof. Dr. M. Sasaki
Graduate School of Life Sciences
Tohoku University, 2-1-1 Katahira
Aoba-ku, Sendai 980-8577 (Japan)
Fax: (+81) 22-217-6214
E-mail: hfuwa@m.tohoku.ac.jp
masasaki@m.tohoku.ac.jp

[b] Dr. Y. Cho, Prof. Dr. M. Yotsu-Yamashita
Graduate School of Agricultural Science
Tohoku University, 1-1 Tsutsumidori-amamiya
Aoba-ku, Sendai 981-8555 (Japan)

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Stimulated by the structural and biological aspects of GAs, we embarked on the total synthesis of GAA (**1**), the representative congener of GAs.[11,12] Herein, we describe in detail the first total synthesis of GAA (**1**), culminating in the establishment of its complete stereostructure (Figure 1).[13] The salient features of our total synthesis of **1** include 1) convergent union of the two advanced polycyclic ether fragments of comparable structural complexity (the A/BCD- and F′GHIJ-ring fragments, **8** and **9**, respectively; Scheme 1) through Suzuki–Miyaura coupling;[14] 2) stereocontrolled elaboration of the C25 stereogenic center by exploiting the intrinsic conformational bias of the "unnatural" F′-ring; 3) stereoselective allylation of the E-ring cyclic mixed thioacetal using glycosylation chemistry; and 4) modified Julia–Kocienski olefination[15] to form the trisubstituted olefin within the J-ring side chain. Furthermore, we evaluated the antifungal and antiproliferative activities of GAA and its synthetic analogues, providing preliminary information on the structure–activity relationships of this intriguing natural product.

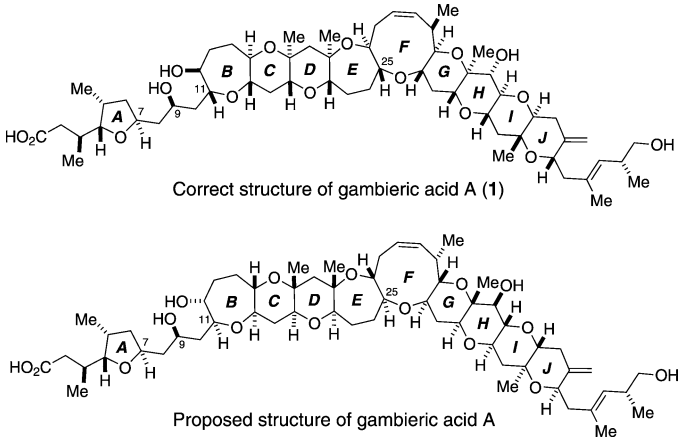
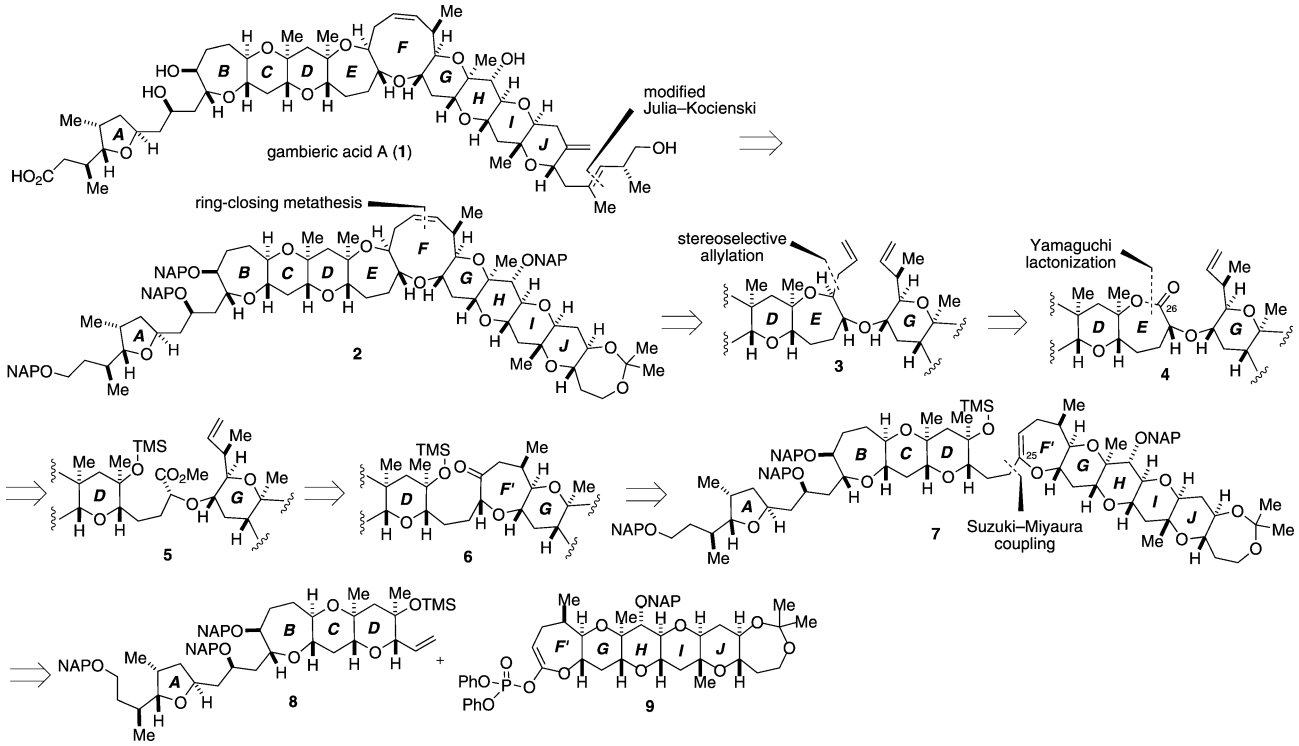


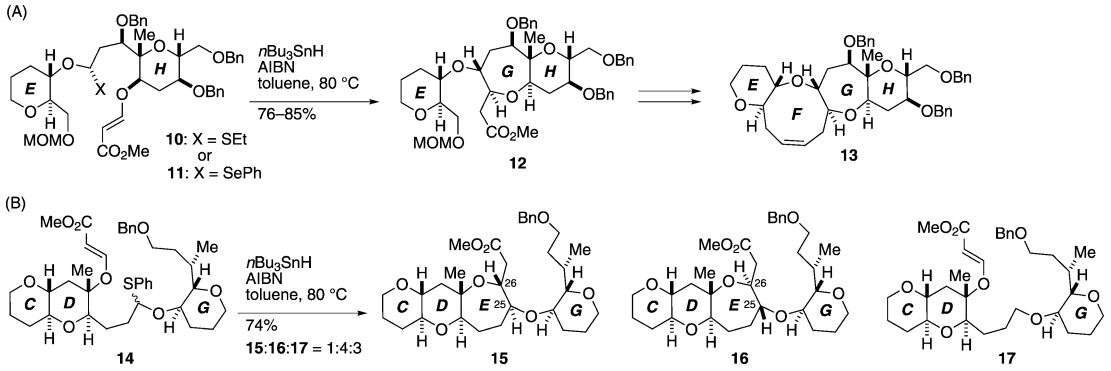
Figure 1. Structure of gambieric acid A.

Results and Discussion

Synthetic route toward GAA (1): Our synthetic route toward GAA (**1**) is illustrated in a retrosynthetic format in Scheme 1. The target molecule **1** could be obtained from polycyclic ether **2** through introduction of the J-ring side chain by using the Julia–Kocienski olefination[15] in a later stage. Considering the extraordinarily complex molecular architecture, we were completely aware from the outset that it was necessary to devise a convergent synthetic approach capable of building the entire polycyclic ether skeleton of **1**, preferably by assembling two polycyclic ether fragments of approximately equal complexity at the central domain of the molecule. Because it was evident that ring-closing metathesis (RCM)[16] is a suitable method for the construction of the nine-membered F-ring, the most significant challenge was how to synthesize the RCM precursor, an *O*-linked diene **3**, in a convergent fashion.



Scheme 1. Synthetic route toward **1**. NAP = 2-Naphthylmethyl, TMS = trimethylsilyl.

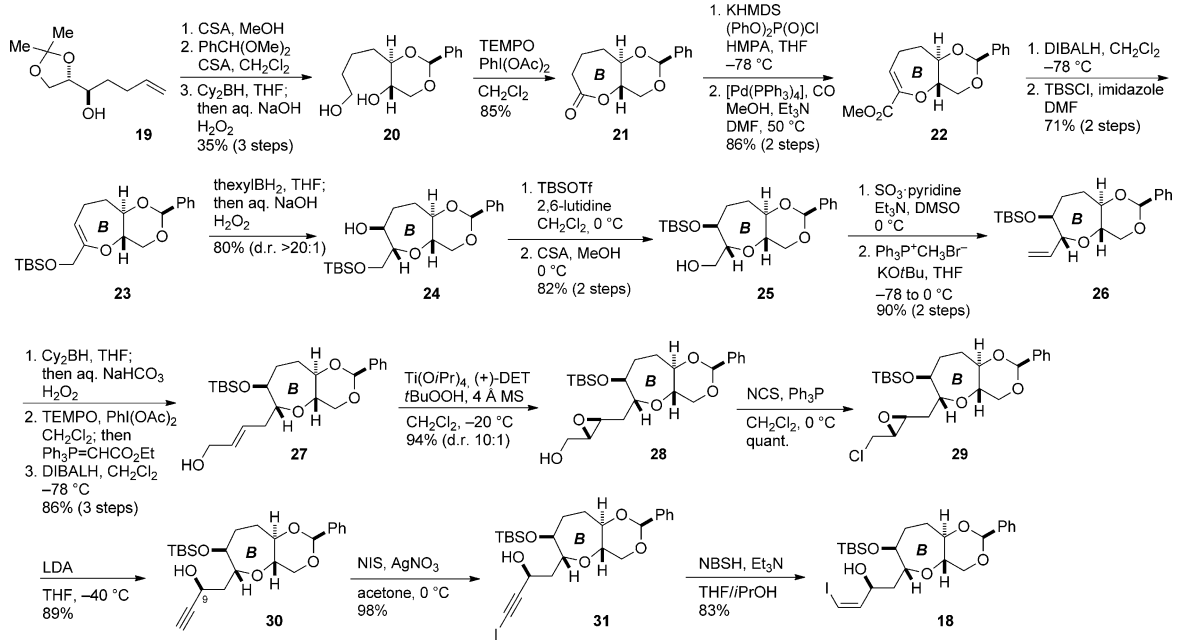


Scheme 2. Our earlier attempts at the construction of fused seven- and nine-membered ring systems. AIBN = 2,2′-Azobisisobutyronitril, Bn = benzyl, MOM = methoxymethyl.

In our previous studies, we have successfully demonstrated the synthesis of the fused seven- and nine-membered ring system of ciguatoxins, which is closely related to the central ring system of **1**, through radical cyclization of acrylate-tethered *O*,*S*- or *O*,*Se*-acetal (**10** or **11**, respectively; see Scheme 2A).[17] However, our model studies on applying the radical cyclization chemistry to GAs were not fruitful because of difficulties in controlling the C25 and C26 stereogenic centers (Scheme 2B).[12a,c]

Accordingly, we established a new strategy for the synthesis of the central domain of GAs by exploiting Suzuki–Miyaura coupling as the key transformation.[12e,f] The diene **3** could be obtained from the ester **5** through Yamaguchi lactonization[18] and stereoselective allylation at the C26 position. We envisioned that the ester **5** would be obtained from the ketone **6** through oxidative cleavage of the F′-ring, which is absent in the natural product. Here the seven-membered F′-ring was introduced for the following two purposes: 1) to control the stereochemistry at the C25 position by taking advantage of the intrinsic conformational property of seven-membered cyclic ethers and 2) to facilitate the union of cyclic ether fragments by Suzuki–Miyaura coupling.[19–22] Thus, the ketone **6** should be available from the endocyclic enol ether **7** through a sequence of hydroboration and oxidation. In turn, the compound **7** could be synthesized from the A/BCD-ring fragment **8** and F′GHIJ-ring fragment **9** through Suzuki–Miyaura coupling.

Synthesis of the B-ring fragment 18: The synthesis of the B-ring fragment **18** started with the known alcohol **19**[23] (Scheme 3). A three-step sequence involving acidic cleavage of the acetonide, benzylidene-acetal protection of the 1,3-diol moiety of the resultant triol, and subsequent hydroboration of the terminal olefin gave the diol **20**. Oxidative lacto-

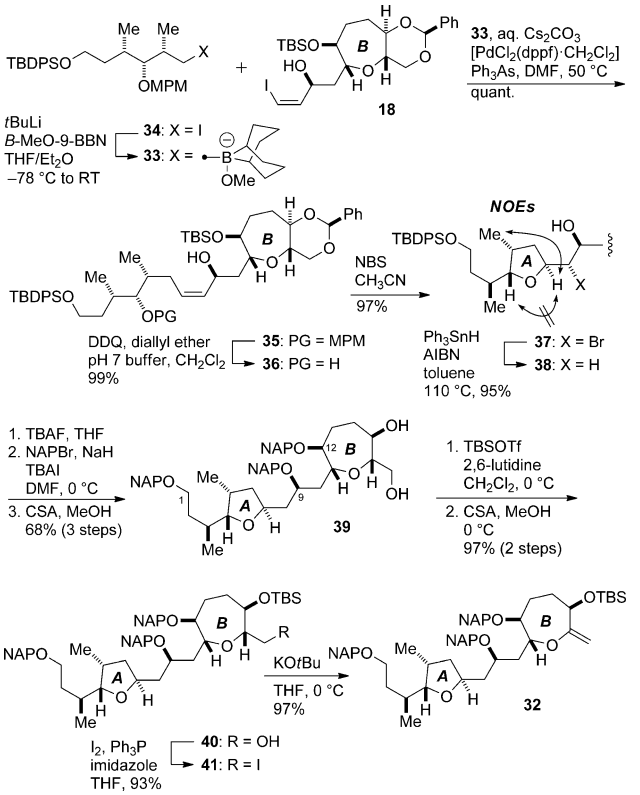


Scheme 3. Synthesis of the B-ring fragment **18**. CSA = (±)-10-Camphorsulfonic acid, Cy = cyclohexyl, MS = molecular sieves, NBSH = *o*-nitrobenzenesulfonyl hydrazide, Tf = trifluoromethanesulfonyl, thexyl = 2,3-dimethyl-2-butyl.

nization of **20** with 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO)/PhI(OAc)$_2$[24] directly gave the seven-membered lactone **21**. Treatment of **21** with potassium bis(trimethylsilyl)amide (KHMDS) in the presence of $(PhO)_2P(O)Cl$[25] gave the corresponding enol phosphate, whose palladium-catalyzed methoxycarbonylation ([Pd(PPh_3)$_4$], CO, Et_3N, MeOH/DMF, 50 °C) gave the α,β-unsaturated ester **22** (86 %, two steps).[26] Diisobutylaluminum hydride (DIBALH) reduction of **22**, followed by silylation of the resultant hydroxy group, gave the *tert*-butyldimethylsilyl (TBS) ether **23** (71 %, two steps). Hydroboration of **23** with thexylborane proceeded in a highly stereoselective manner to provide the alcohol **24** in 80 % yield (diastereomer ratio (d.r.) > 20:1). A two-step protective group manipulation sequence gave the alcohol **25** (82 %, two steps). Oxidation and Wittig methylenation yielded the olefin **26** (90 %, two steps). Hydroboration of the olefin **26**, followed by one-pot oxidation/Wittig reaction, gave an α,β-unsaturated ester, which was reduced with DIBALH to afford the allylic alcohol **27** (86 %, three steps). Sharpless asymmetric epoxidation of **27** by using (+)-diethyl tartrate (DET) gave the epoxy alcohol **28** (94 %, d.r. 10:1). Chlorination of **28** with *N*-chlorosuccinimide (NCS)/Ph_3P and subsequent treatment of the derived chloro-epoxide **29** with lithium diisopropylamide (LDA)[27] afforded the propargylic alcohol **30** in 89 % yield. At this stage, the minor C9 epimer was removed by flash column chromatography on silica gel. Iodination of **30** with NIS (*N*-iodosuccinimide)/$AgNO_3$ (98 %), followed by diimide reduction[28] of the resultant iodoalkyne **31**, gave the (*Z*)-vinyl iodide **18** in 83 % yield. The stereochemistry of the C9 position was unambiguously determined by derivatization of the alcohol **30** and the application of the modified Mosher's method.[9,29]

Synthesis of the A/B-ring fragment 32: Next, we performed a Suzuki–Miyaura coupling of the alkylborate **33** and the vinyl iodide **18** (Scheme 4). The alkylborate **33**, generated in situ from the iodide **34**[29] (*t*BuLi, *B*-methoxy-9-borabicyclo[3.3.1]nonane (*B*-MeO-9-BBN), THF/Et_2O, −78 °C to RT),[30] was coupled with the (*Z*)-vinyl iodide **18** ([$PdCl_2$(dppf)·CH_2Cl_2] (in which dppf = 1,1′-bis(diphenylphosphino)ferrocene), Ph_3As, Cs_2CO_3, aqueous THF/DMF, 50 °C) to give the olefin **35** quantitatively. The *p*-methoxyphenylmethyl (MPM) group of **35** was removed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation (99 %), and the resultant alcohol **36** was treated with *N*-bromosuccinimide (NBS) in acetonitrile, which gave the bromide **37** in 97 % yield (d.r. > 20:1). The stereochemical outcome of the bromoetherification was in accordance with that observed in our previous model study.[10b] Reduction of **37** with Ph_3SnH/AIBN delivered the compound **38** in 95 % yield. At this stage, the relative stereochemistry of the A-ring tetrahydrofuran was unambiguously confirmed by NOE experiments as shown.

Having established the A-ring tetrahydrofuran with complete stereocontrol, we performed routine protective group manipulations before the elaboration of the C- and D-rings.

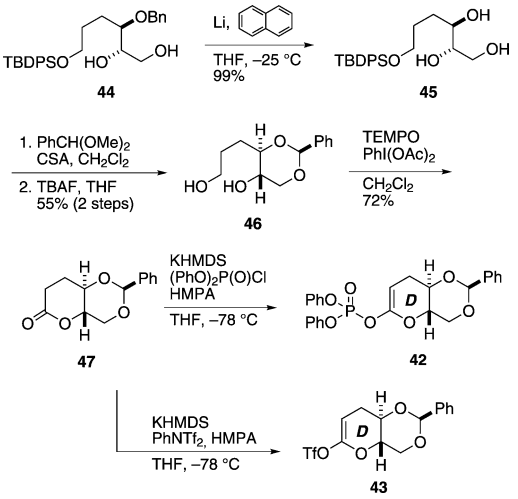


Scheme 4. Synthesis of the A/B-ring fragment **32**. 9-BBN = 9-Borabicyclo[3.3.1]nonyl, TBAI = tetra-*n*-butylammonium iodide, TBDPS = *tert*-butyldiphenylsilyl.

Here we masked the C1, C9, and C12 hydroxy groups as their NAP ethers; it has been shown that the NAP group tolerates strong acids and bases but can be selectively removed under mild conditions by using DDQ.[31] The primary alcohol **40** thus obtained was smoothly converted to the A/B-ring exocyclic enol ether **32** by iodination and base treatment.

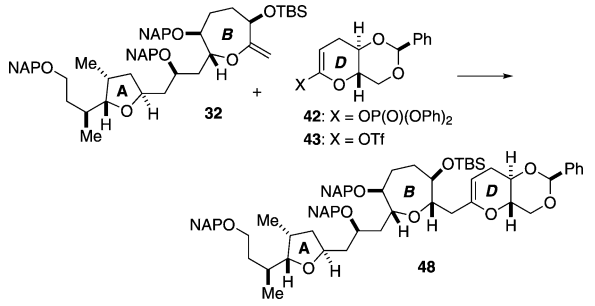
Synthesis of the D-ring enol phosphate 42 and enol triflate 43: Synthesis of the D-ring fragments **42** and **43** is summarized in Scheme 5. Reductive removal of the benzyl group from the known diol **44**[12h] with lithium naphthalenide[32] gave the triol **45** in 99 % yield. Protection of the 1,3-diol moiety of **45** as its benzylidene acetal and subsequent treatment with tetra-*n*-butylammonium fluoride (TBAF) afforded the diol **46** (55 %, two steps). Oxidative lactonization of **46** with TEMPO/PhI(OAc)$_2$[33] gave the lactone **47** (72 %), which was transformed into the enol phosphate **42** under standard conditions (KHMDS, $(PhO)_2P(O)Cl$, hexamethylphosphoramide (HMPA), THF, −78 °C).[25] The enol triflate **43** was readily prepared from the lactone **47** (KHMDS, $PhNTf_2$, HMPA, THF, −78 °C).[34]

Suzuki–Miyaura coupling of the A/B-ring exocyclic enol ether 32 and the lactone-derived D-ring enol phosphate 42 or enol triflate 43: We investigated Suzuki–Miyaura coupling of the A/B-ring exocyclic enol ether **32** and the D-ring



Scheme 5. Synthesis of the D-ring enol phosphate **42** and enol triflate **43**.

Table 1. Investigation of the Suzuki–Miyaura coupling.[a]

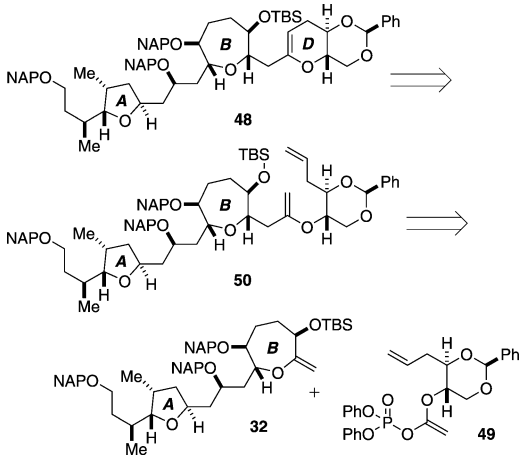


Entry	D-ring	Pd catalyst	Ligand	Base	Yield [%]
1[b]	**42**	$[Pd(PPh_3)_4]$	none	Cs_2CO_3	21
2[b]	**42**	$[Pd(PPh_3)_4]$	none	$NaHCO_3$	25
3[b]	**42**	$[PdCl_2(dppf)\cdot CH_2Cl_2]$	none	Cs_2CO_3	0
4[b]	**42**	$[PdCl_2(dppf)\cdot CH_2Cl_2]$	Ph_3As	Cs_2CO_3	0
5[c]	**43**	$[Pd_2(dba)_3]$	Ph_3As	Cs_2CO_3	15
6[c]	**43**	$[Pd_2(dba)_3]$	Ph_3As	$NaHCO_3$	26
7[c]	**43**	$[PdCl_2(dppf)\cdot CH_2Cl_2]$	Ph_3As	$NaHCO_3$	0

[a] All reactions were performed by using 2.6 equivalents of 9-BBN-H, a Pd catalyst (10 mol%), 2 equivalents of **42** or **43**, and 3 equivalents of base in THF/DMF. Yields are based on the *exo*-olefin **32**. [b] Reaction performed at 50 °C. [c] Reaction performed at RT.

enol phosphate **42** in detail (Table 1). We initially examined the Suzuki–Miyaura coupling by using Cs_2CO_3 as a base and $[Pd(PPh_3)_4]$ as a catalyst in aqueous THF/DMF at 50 °C. Unfortunately, the desired endocyclic enol ether **48** was isolated in only 21% yield (Table 1, entry 1). Changing the base to $NaHCO_3$ did not improve the yield of **48** (Table 1, entry 2), whereas the use of $[PdCl_2(dppf)\cdot CH_2Cl_2]$ alone or in combination with Ph_3As did not afford **48** (Table 1, entries 3 and 4). From these results, we considered that the low reactivity of the enol phosphate **42** might be the reason for the unsuccessful outcome. Hence, we examined the use of the more reactive enol triflate **43** as the coupling partner. However, we were disappointed to find that Suzuki–Miyaura coupling using **43** under the conditions specifically optimized for lactone-derived enol triflates ($[Pd_2(dba)_3]$ (dba = tris(dibenzylideneacetone)/Ph_3As, Cs_2CO_3, aqueous THF/DMF, RT)[20a] gave **48** in only 15% yield (Table 1, entry 5). Changing the base to $NaHCO_3$ slightly improved the yield of **48**, but the result remained unsatisfactory (Table 1, entry 6). The $[PdCl_2(dppf)\cdot CH_2Cl_2]/Ph_3As$-catalyst system was completely ineffective (Table 1, entry 7). Thus, we could not synthesize the endocyclic enol ether **48** in synthetically useful quantities.

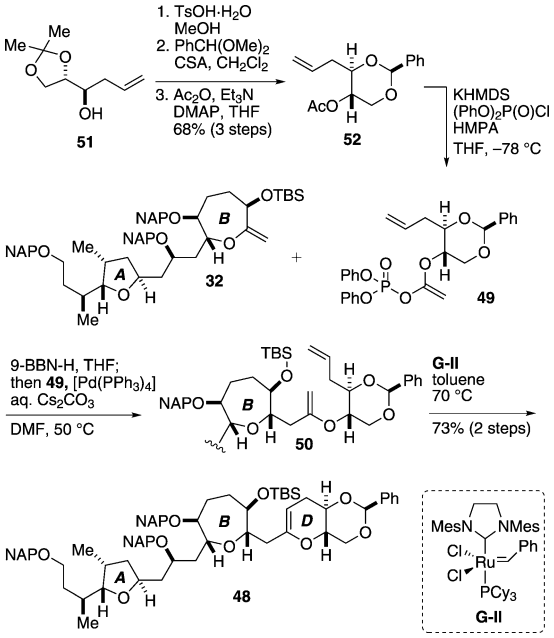
Synthesis of endocyclic enol ether 48 via Suzuki–Miyaura coupling/RCM sequence: We have previously reported the synthesis of endocyclic enol ethers based on a Suzuki–Miyaura coupling/RCM sequence, which utilized alkylboranes and acetate-derived enol phosphates as coupling partners.[35,36] This methodology has been shown to be particularly useful when it is difficult to prepare the corresponding lactone-derived enol triflates/phosphates, and/or they are insufficiently reactive toward palladium-catalyzed reactions. As shown in Scheme 6, this complementary methodology may enable the synthesis of the endocyclic enol ether **48** from the A/B-ring fragment **32** and the acetate-derived enol phosphate **49**.



Scheme 6. Alternative synthetic strategy for the endocyclic enol ether **48**.

The synthesis of the enol phosphate **49** is shown in Scheme 7. Removal of the acetonide group of the known alcohol **51**,[37] protection of the 1,3-diol moiety of the resultant triol with benzylidene acetal, and subsequent acylation of the resulting alcohol led to the acetate **52** in 68% yield for the three steps. Enolization of **52** with KHMDS in presence of $(PhO)_2P(O)Cl$ (HMPA, THF, −78 °C) gave the enol phosphate **49**.

Hydroboration of the A/B-ring exocyclic enol ether **32** with 9-BBN-H, followed by in situ reaction of the derived alkylborane with the enol phosphate **49** ($[Pd(PPh_3)_4]$, Cs_2CO_3, aqueous THF/DMF, 50 °C), proceeded smoothly to afford the diene **50**. This diene was immediately exposed to the Grubbs second-generation catalyst (**G-II**)[38] in toluene

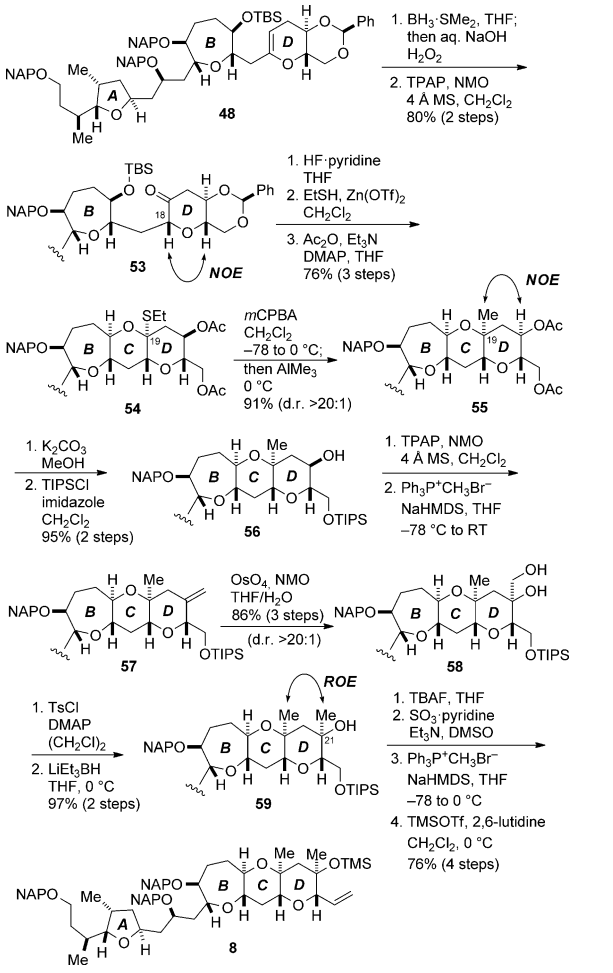


Scheme 7. Synthesis of the endocyclic enol ether **48**. DMAP = 4-Dimethylaminopyridine, Ts = *p*-toluenesulfonyl.

at 70 °C to give the desired enol ether **48** in 73 % yield for the two steps.

Synthesis of the A/BCD-ring fragment 8: Stereoselective hydroboration of **48** with $BH_3{\cdot}SMe_2$, followed by alkaline oxidative workup, gave an alcohol, which was oxidized by tetra-*n*-propylammonium perruthenate (TPAP)/*N*-methylmorpholine *N*-oxide (NMO)[39] to provide the ketone **53** (80 %, two steps, d.r. > 20:1) (Scheme 8). The stereochemistry of the C18 stereogenic center of **53** was confirmed by an NOE experiment, as shown. After the removal of the TBS group with HF·pyridine, treatment of the resultant hemiacetal with EtSH/$Zn(OTf)_2$[40a] promoted the mixed thioacetalization and spontaneous cleavage of the benzylidene acetal. Subsequent acetylation of the liberated hydroxy groups gave the diacetate **54** (76 %, three steps). The C19 axial methyl group was stereoselectively installed by the one-pot oxidation/methylation protocol (*meta*-chloroperoxybenzoic acid (*m*CPBA), CH_2Cl_2, −78 °C; then excess Me_3Al, 0 °C)[40b] to give the tetracyclic ether **55** in 91 % yield (d.r. > 20:1). The stereochemistry of the C19 stereogenic center was established by an NOE experiment, as shown.

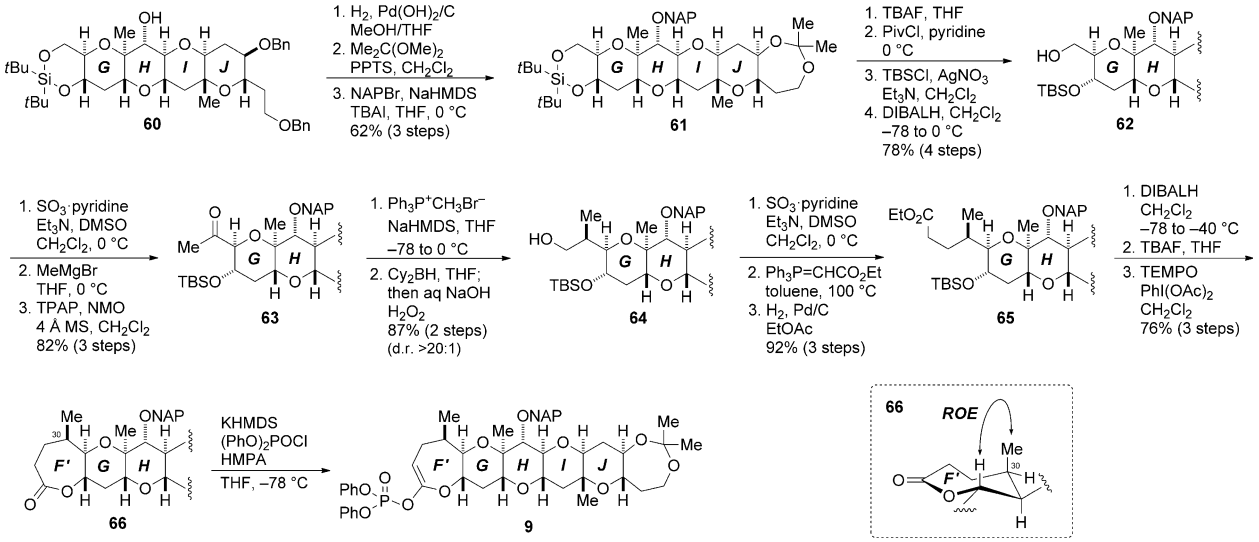
Toward the formation of the A/BCD-ring fragment **8**, the C21 axial methyl group was introduced according to the methodology previously developed in our laboratory.[40a] After removal of the acetyl groups of **55**, the primary hydroxy group was selectively protected as the triisopropylsilyl (TIPS) ether **56** (95 %, two steps). Oxidation of **56** with TPAP/NMO[39] and Wittig methylenation of the derived ketone gave the *exo*-olefin **57**. Dihydroxylation of **57** with OsO_4/NMO exclusively gave the diol **58** in 86 % yield for the three steps (d.r. > 20:1). Tosylation of **58**, followed by



Scheme 8. Synthesis of the A/BCD-ring fragment **8**. NaHMDS = Sodium bis(trimethylsilyl)amide.

treatment with $LiEt_3BH$ (THF, 0 °C), gave the tertiary alcohol **59** in 97 % yield for the two steps. The relative stereochemistry of the C21 stereogenic center was determined by a rotating-frame Overhauser effect (ROE) experiment, as shown. Finally, a four-step sequence that involved removal of the TIPS group, oxidation of the resultant primary alcohol, Wittig methylenation, and silylation of the tertiary alcohol gave the A/BCD-ring fragment **8** (76 %, four steps).

Synthesis of the F′GHIJ-ring fragment 9: The synthesis of the F′GHIJ-ring enol phosphate **9** started with the previously reported tetracyclic ether **60**[12g,h] (Scheme 9). A sequence of routine protective group manipulations gave the alcohol **62**. This alcohol was then converted to the methyl ketone **63** in three steps (82 % overall yield). Wittig methylenation of **63**, followed by stereoselective hydroboration of the derived olefin with dicyclohexylborane, gave the alcohol **64** (87 %, two steps, d.r. > 20:1).[41] Oxidation of **64**, Wittig reaction of the derived aldehyde by using $Ph_3P{=}CHCO_2Et$, and hydrogenation of the resultant enoate delivered the ester **65** (92 %, three steps). Reduction of **65** with DIBALH, removal of the TBS group, and TEMPO/$PhI(OAc)_2$-mediated oxida-

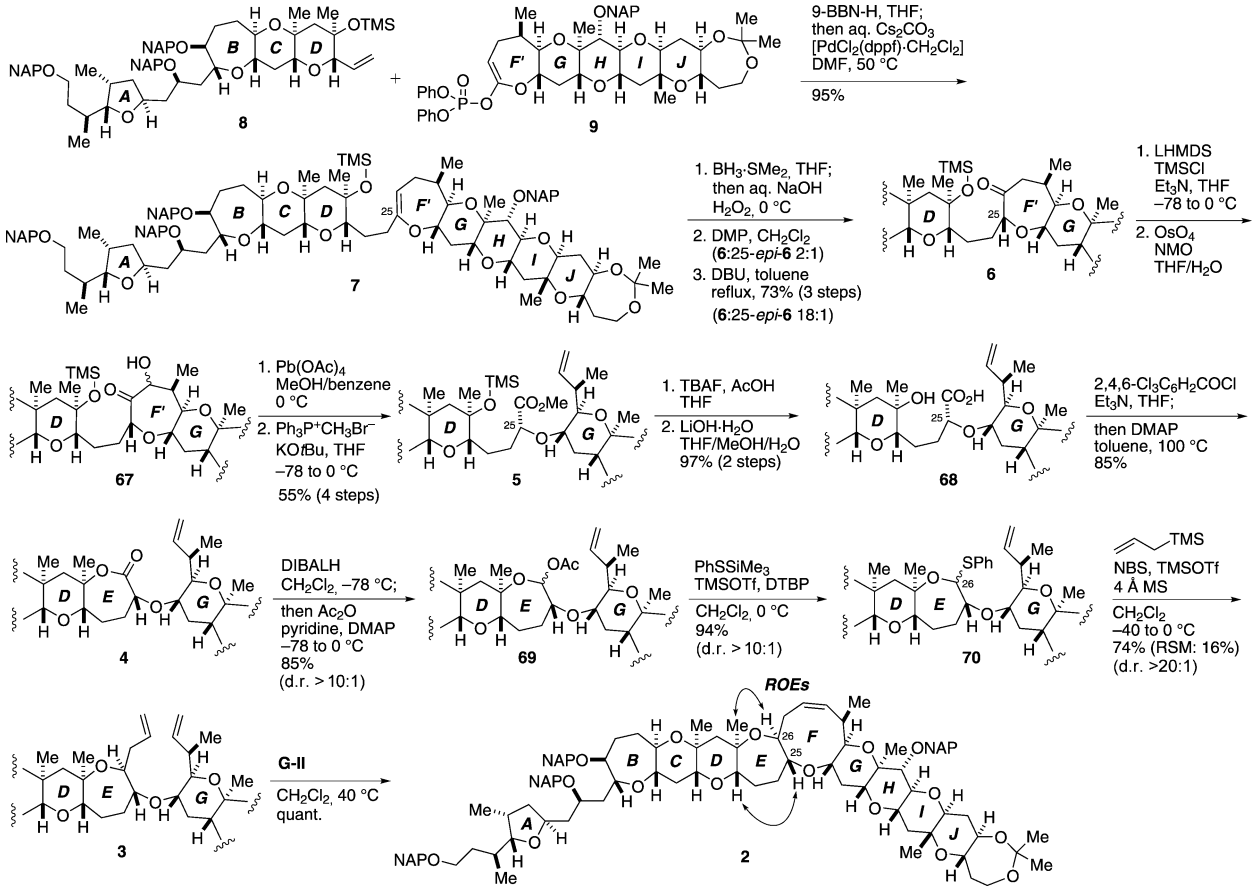


Scheme 9. Synthesis of the F′GHIJ-ring fragment **9**. Piv = Pivaloyl, PPTS = pyridinium *p*-toluenesulfonate.

tive lactonizaton[24] afforded the seven-membered lactone **66** (76%, three steps). At this stage, the configuration of the C30 stereogenic center was determined by a ROE experiment, as shown. Finally, treatment of **66** with KHMDS/$(PhO)_2P(O)Cl$ gave the F′GHIJ-ring enol phosphate **9**, which was immediately used in subsequent Suzuki–Miyaura coupling.

Convergent synthesis of the polycyclic ether skeleton 2: After completing the formation of the A/BCD-ring fragment **8** and F′GHIJ-ring fragment **9**, we focused on their assembly and the construction of the entire polycyclic ether skeleton of GAA (**1**). Hydroboration of **8** with 9-BBN-H gave the corresponding alkylborane, which was coupled in situ with the enol phosphate **9** under our previously optimized conditions ($[PdCl_2(dppf)\cdot CH_2Cl_2]$, Cs_2CO_3, aqueous THF/DMF, 50 °C)[21a] to give the endocyclic enol ether **7** in 95% yield (Scheme 10). Hydroboration of **7** with BH_3·SMe_2, followed by oxidative workup under basic conditions, gave a 2:1 mixture of diastereomeric alcohols. The disappointingly low stereoselectivity of hydroboration was in sharp contrast to that observed for the B-ring endocyclic enol ether **23** (Scheme 3). Our plausible explanation for the observed stereoselectivity of the hydroboration of **7** and **23** is summarized in Figure 2. In the case of **7**, two possible conformers **A** and **B** can be considered, and the energy difference between these conformers is likely to be small (2.9 kJ mol^{-1} as estimated by ab initio calculations on a model compound).[42] By avoiding unfavorable steric repulsion,[43] hydroboration would occur from the upper face of the conformer **A** or from the lower face of the conformer **B**, leading to the transition state **TS-A** or **TS-B**, respectively. Since it is known that hydroboration proceeds via a four-membered transition state that occurs very early along the reaction coordinate,[44] the transition state of hydroboration must reflect the ground state conformation of a starting alkene.[45] Thus, we can consider that the energy difference between **TS-A** and **TS-B** is likewise small. Consequently, the hydroboration would produce a mixture of the desired and undesired alcohols. Meanwhile, two conformers **C** and **D** can similarly be considered for **23**, but in this case the energy difference between these conformers was estimated to be quite large (12 kJ mol^{-1} by ab initio calculations). Accordingly, **TS-C** must be significantly lower in energy than **TS-D**, and it is most conceivable that the hydroboration of **23** would preferentially proceed via **TS-C** to give the desired alcohol. Despite the disappointing diastereoselectivity of the hydroboration of **7**, oxidation of the resultant diastereomeric mixture of alcohols with Dess–Martin periodinane (DMP)[46] and ensuing treatment with excess 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene heated at reflux allowed us to enrich the thermodynamically favored **6** in 73% yield from **7** (d.r. 18:1).[12e,f]

Having successfully secured the C25 stereogenic center, the F′-ring was oxidatively cleaved prior to the elaboration of the E- and F-rings. Enolization of the ketone **6** with lithium bis(trimethylsilyl)amide (LHMDS) in the presence of trimethylsilyl chloride (TMSCl)/Et_3N (THF, −78 to 0 °C) gave the corresponding enol silyl ether, which was immediately oxidized with OsO_4/NMO to afford the α-hydroxy ketone **67** as a 1:1 mixture of inconsequential diastereomers (Scheme 10). Treatment of **67** with $Pb(OAc)_4$ in MeOH/benzene at 0 °C resulted in the cleavage of the F′-ring,[47] and the resultant aldehyde ester was immediately exposed to $Ph_3P{=}CH_2$ to give the ester **5** (55%, four steps). The ^{1}H NMR analysis of **5** indicated that no epimerization occurred at the C25 position during the four-step transformation of **6**. After removal of the TMS group with TBAF/AcOH, saponification of the ester provided the hydroxy acid **68** (97%, two steps). Lactonization of **68** under Yamaguchi conditions[18] gave the seven-membered lactone **4** in 85% yield. Reduction of **4** with DIBALH and in situ acetylation[48] gave the α-acetoxy ether **69** as a 10:1 mixture of dia-



Scheme 10. Completion of the polycyclic ether skeleton **2**. RSM = Recovered starting material.

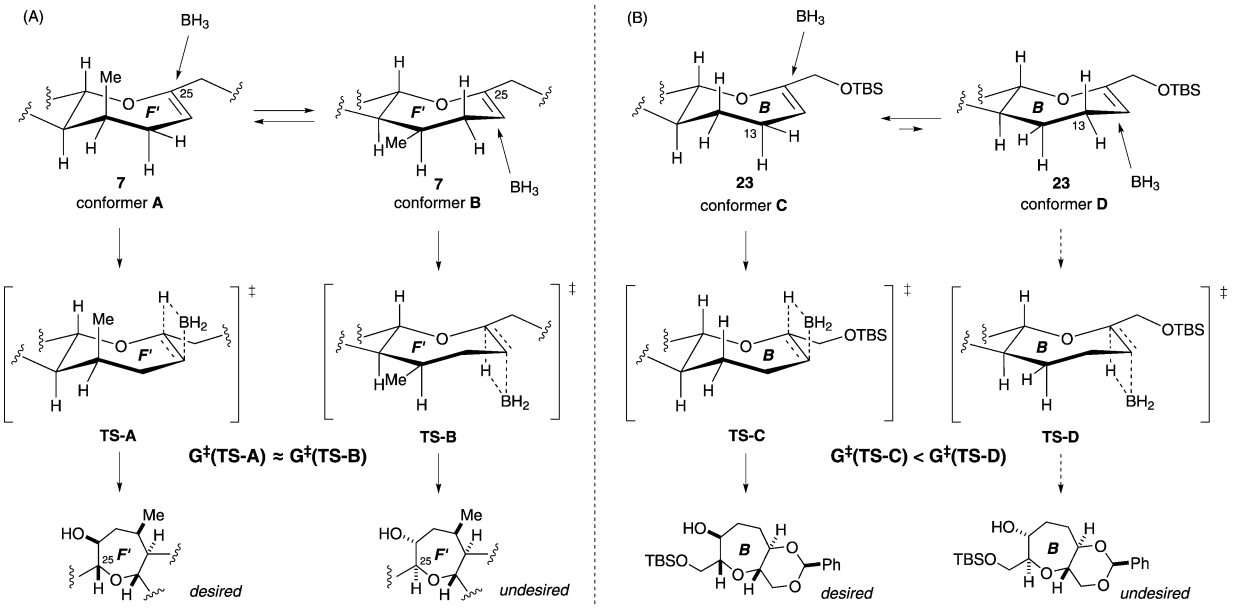
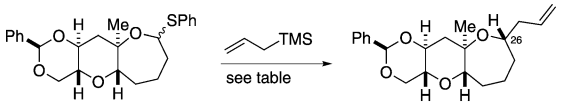


Figure 2. Rationale for the stereoselective hydroboration of seven-membered endocyclic enol ethers.

stereomers in 85% yield, which was converted to the mixed thioacetal **70** by treatment with TMSSPh in the presence of TMSOTf and 2,6-di-*tert*-butylpyridine (DTBP; 94%, d.r. 10:1, stereochemistry not determined).

Stereoselective allylation of the C26 position required extensive model studies. We learned from our previous studies that the stereoselective allylation of lactone-derived α-acetoxy ethers promoted by a Lewis acid and allyltrimethylsilane required harsh conditions and gave the corresponding allylated products only in moderate yields.[12e,f] Hence, we strove to develop a new methodology for the stereoselective allylation, which can tolerate a wide range of functionalities. Hirama and co-workers have reported the allylation of a seven-membered cyclic mixed thioacetal by using NIS/AgOTf as an activator although the scope of the substrate remained elusive.[49] Accordingly, we investigated the application of glycosylation chemistry to cyclic mixed thioacetals in greater detail. We used the cyclic mixed thioacetal **71**[29] as the DE-ring model compound to investigate suitable reaction conditions for allylation (Table 2). We first attempted

Table 2. Stereoselective allylation of the mixed thioacetal **71**.[a]



71 **72**

Entry	Activator (equiv)	Triflate (0.1 equiv)	Additive	*T* [°C]	Yield [%]
1	NIS (1.3)	none	None	−78 to 0	0
2	NIS (1.3)	TMSOTf	None	−78 to 0	19
3	NIS (1.3)	TMSOTf	4 Å MS	−78 to 0	51
4	NBS (1.3)	TMSOTf	4 Å MS	−78	49
5	NBS (1.3)	TfOH	4 Å MS	−40	61
6	NBS (1.3)	MeOTf	4 Å MS	−40	56
7	NBS (3.0)	TMSOTf	4 Å MS	−40	72

[a] All reactions were performed in the presence of excess allyltrimethylsilane in CH_2Cl_2. In all cases, product **72** was isolated as a single stereoisomer.

to activate **71** with NIS, but found that the desired reaction did not occur (Table 2, entry 1). On the other hand, the addition of TMSOTf was found to be beneficial[50] although **72** was isolated only in 19% yield (Table 2, entry 2). The yield of **72** was considerably improved to 51% when the reaction was performed in the presence of 4 Å molecular sieves (Table 2, entry 3). By using NBS instead of NIS,[51] the reaction proceeded even at −78°C to give **72** in 49% yield (Table 2, entry 4). Changing the activator of NBS resulted in moderate yields of **72** (Table 2, entries 5 and 6). Finally, we found that increasing the molar amount of NBS was effective for achieving an optimal result (72%, Table 2, entry 7).[52] The acid-sensitive benzylidene acetal was not affected under these conditions.

The configuration of the newly formed C26 stereogenic center was determined by an NOE experiment, as shown in Figure 3, and the stereoselectivity of the allylation of **71** was in accordance with that observed for the *O*-glycosylation of septanosides.[53] The stereochemical outcome can be explained by a stereoelectronic effect (Figure 4A). The pseudoaxial lone pair of the ether oxygen would stabilize the

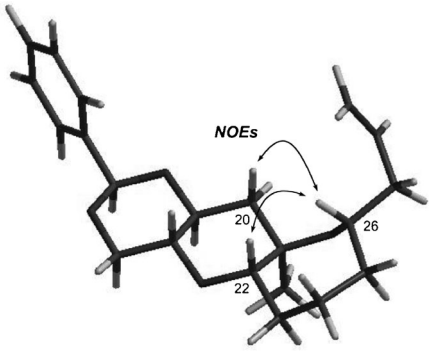


Figure 3. Stereochemistry of the allylated product **72**.

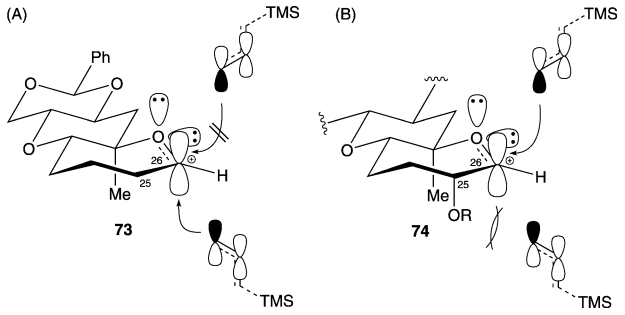
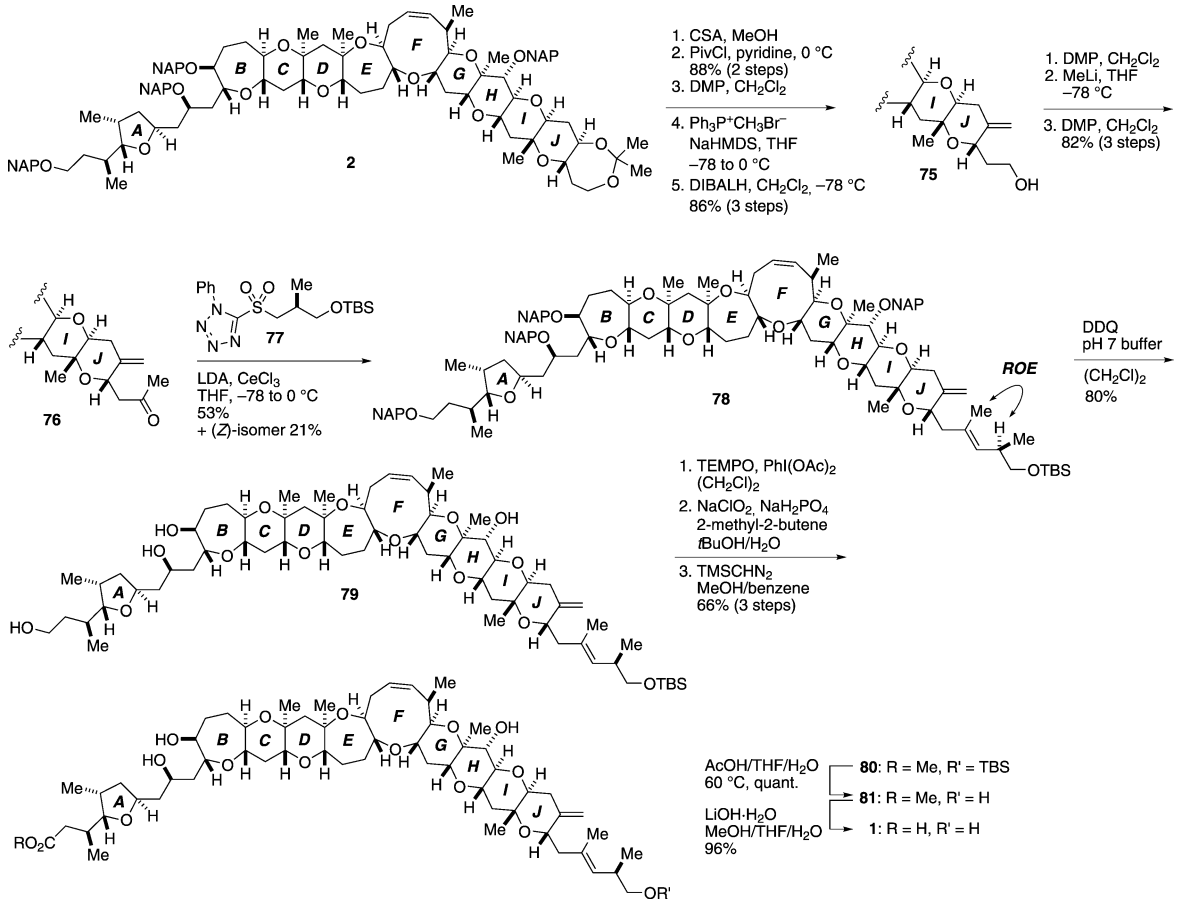


Figure 4. Rationale for the stereoselective allylation of cyclic mixed thioacetals.

generated oxocarbenium cation **73**, and allyltrimethylsilane approaches from the α-face to maximize orbital overlapping. In contrast, the nucleophilic attack of allyltrimethylsilane from the β-face would cause an unfavorable interaction between the pseudoaxial lone pair of the ether oxygen and the HOMO of allyltrimethylsilane. Notably, the stereoselectivity of the allylation of **71** was opposite to that expected for the real substrate, i.e., the cyclic mixed thioacetal **70**. However, as previously demonstrated with a model compound,[12e,f] we considered that in the real substrate, the C25 bulky substituent must be pseudoaxially oriented, which makes the α-face sterically crowded and prevents the approach of allyltrimethylsilane from the α-face of oxocarbenium cation **74** (Figure 4B). Consequently, allyltrimethylsilane would be forced to access from the less-hindered β-face so as to give the allylated product with the correct stereochemistry at C26.

In the event, stereoselective allylation of **70** was performed under optimized conditions (allyltrimethylsilane, NBS, TMSOTf, 4 Å MS, CH_2Cl_2, −40 to 0°C) to afford the diene **3** in 74% yield (d.r. > 20:1), along with the recovered starting material (16%) (Scheme 10). RCM of the diene **3** by its exposure to **G-II**[38] in CH_2Cl_2 at 40°C gave the nonacyclic polyether core **2** quantitatively. The relative configuration of the stereogenic centers along the E- and F-rings was established at this stage by ROE experiments, as shown, thereby supporting our proposed allylation model, illustrated in Figure 4B.



Scheme 11. Total synthesis of GAA (**1**).

Completion of the total synthesis of (+)-GAA (1): Having completed the synthesis of the polycyclic ether skeleton **2**, we next developed the J-ring side chain (Scheme 11). Removal of the acetonide group of **2** with acidic methanol was followed by selective acylation of the primary alcohol (PivCl, pyridine) to deliver a pivaloyl ester (88%, two steps). Dess–Martin oxidation, Wittig methylenation of the resultant ketone, and reductive removal of the pivaloyl group gave the alcohol **75** (86%, three steps). This alcohol was converted to the methyl ketone **76** by using a three-step sequence involving oxidation, methylation, and a second oxidation (82%, three steps). Our earlier model studies have demonstrated that methyl ketones such as **76** are challenging substrates for Julia–Kocienski olefination because of their propensity for enolization or retro-oxa-Michael reaction.[12g,h] However, as we previously reported, these undesired side reactions could be suppressed by using $CeCl_3$ as an additive.[12g,h] Thus, the Julia–Kocienski reaction of **76** with the sulfone **77**[12g,h] in the presence of $CeCl_3$ (LDA, THF, −78°C) afforded the trisubstituted (*E*)-olefin **78** in 53% yield along with the corresponding (*Z*)-isomer in 21% yield. The stereochemistry of **78** was confirmed by a ROE experiment, as shown. Removal of all the NAP groups with DDQ[31] gave the tetraol **79** in 80% yield. Selective oxidation of the primary alcohol of **79** with TEMPO/PhI(OAc)$_2$[54] proceeded smoothly to deliver the corresponding aldehyde, which was immediately oxidized with $NaClO_2$ and then esterified with $TMSCHN_2$ to provide the methyl ester **80** (66%, three steps). Finally, cleavage of the TBS group with acetic acid and saponification of the derived methyl ester **81** with aqueous LiOH gave GAA (**1**) in 96% overall yield. The ^{1}H and ^{13}C NMR, IR, and HRMS data of our synthetic material were identical with those of the natural product. Furthermore, the specific rotation value of synthetic (+)-**1** ($[\alpha]_D^{25} = +22.5$ ($c = 0.40$ in MeOH)) was in accordance with that of the authentic sample ($[\alpha]_D^{20} = +33$ ($c = 0.488$ in MeOH)).[1] Thus, we concluded that our revised complete stereostructure of GAA, as shown structure **1**, was accurate.[10]

Evaluation of the antifungal and antiproliferative activities of synthetic GAA and its analogues: We investigated the biological activity of **1** and its synthetic analogues by taking advantage of our total synthesis. We prepared five synthetic analogues; that is, the GAA methyl ester **81** (Scheme 11), (46*Z*)-GAA (**82**), J-ring side chain truncated analogue **83**, truncated A/BCD-ring analogue **84**, and truncated GHIJ-ring analogue **85** (Figure 5). The preparation of analogues **82–85** is included in the Supporting Information.

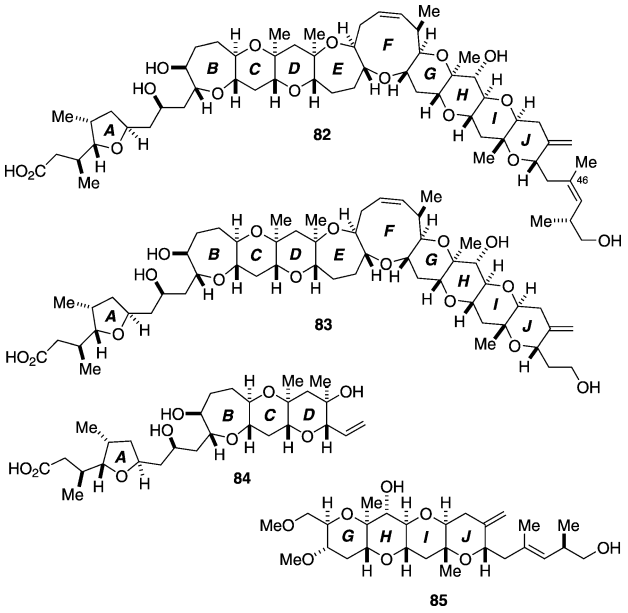


Figure 5. Synthetic analogues of GAA (**1**).

Table 3. Antifungal and antiproliferative activities of synthetic GAA (**1**) and its analogues.[a]

Compound	Antifungal activity [ng disk^{-1}][b]		Antiproliferative activity IC_{50} [μM][c]
	Sporulation inhibition	Growth inhibition	
GAA (**1**)	10	500	5.1
81	1000	>10000	11
82	10	500	1.0
83	100	10000	>30
84	>10000	>10000	>30
85	>10000	>10000	>30

[a] For details of assay procedures, see the Supporting Information. [b] Against *A. niger* by disk diffusion. [c] Against P388 cells.

We first evaluated the antifungal activity of synthetic GAA (**1**) and its analogues against *A. niger* by disk diffusion assay, and the results are summarized in Table 3. GAA (**1**) inhibited the sporulation of *A. niger* at 10 ng disk^{-1}, and the total growth was inhibited at a higher dose (500 ng disk^{-1}). These results were in accordance with those reported for the natural product.[5] The (46*Z*)-GAA (**82**) was found to be equipotent to GAA, showing that the geometry of the trisubstituted olefin within the J-ring side chain is not relevant to the antifungal activity. On the other hand, the activities of the J-ring side chain truncated analogue **83** and GAA methyl ester **81** were 10- to 100-fold lower than that of GAA, indicating the importance of the C1 carboxy group and the length of the J-ring side chain. Truncated analogues **84** and **85** were completely inactive at a dose of 10 μg disk^{-1}.

In addition, we evaluated the antiproliferative activity of GAA (**1**) and the synthetic analogues in cultured P388 mouse lymphoma cells by using the WST-8 assay.[55] GAA inhibited the growth of P388 cells with an IC_{50} value of 5.1 μM. The (46*Z*)-GAA (**82**) was slightly more potent (approximately five-fold) than GAA. Interestingly, the antiproliferative activity of the GAA methyl ester **81** was only two-fold less active than that of the parent GAA. On the other hand, the J-ring side chain truncated analogue **83** was inactive at a concentration of 30 μM. These results raised the possibility that the antifungal and antiproliferative activities of GAA might not be correlated. Truncated analogues **84** and **85** were completely inactive at 30 μM.

Conclusion

In this study, we described the first total synthesis and complete stereostructure of (+)-GAA (**1**) in detail. The synthesis of the A/BCD-ring fragment **8** featured Suzuki–Miyaura coupling of the B-ring vinyl iodide **18** and the alkylborate **33**, stereoselective bromoetherification to forge the A-ring tetrahydrofuran, and application of our Suzuki–Miyaura coupling/RCM sequence for the convergent assembly of the BCD-ring domain. The synthetically challenging central domain of **1** was constructed in a convergent fashion by using the "unnatural" seven-membered F′-ring. Thus, the A/BCD- and F′GHIJ-ring fragments (**8** and **9**, respectively) were assembled through a Suzuki–Miyaura coupling. Although the hydroboration of the coupling product, the endocyclic enol ether **7**, provided a mixture of diastereomeric alcohols, the C25 stereogenic center was successfully formed by the subsequent oxidation and base-promoted equilibration under thermodynamic control to give the ketone **6**. After oxidative cleavage of the F′-ring, stereoselective allylation of the cyclic mixed thioacetal **70**, based on the glycosylation chemistry, was utilized for the elaboration of the E-ring. Subsequently, the F-ring was formed through RCM. Stereoselective introduction of the J-ring side chain was achieved by using our modified Julia–Kocienski olefination to complete the total synthesis of **1**. Our total synthesis proceeded in 84 steps (longest linear sequence) from commercially available L-gulonolactone in 0.012% overall yield. The spectroscopic properties and specific rotation value of **1** matched those of the natural product, which resulted in an unambiguous determination of the absolute configuration of **1**. Thus, our total synthesis of **1** successfully confirmed that our previously revised structure was actually correct and demonstrated the vital role of organic synthesis in the structure elucidation of complex natural products.[56] From a biosynthetic perspective, the stereostructure of gambieric acids B–D should also be revised similarly. Moreover, we evaluated the antifungal and antiproliferative activities of **1** and several synthetic analogues and investigated the preliminary structure–activity relationships of **1**.

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Marine Science and Technology) for his useful suggestions. This work was financially supported in part by Grants-in-Aid (Nos. 21241050, 23681045, 23102016, and 24102517) from MEXT, Japan, and a grant from ERATO Murata Lipid Active Structure Project from JST. The Astellas Foundation for Research on Metabolic Disorders and the Banyu Life Science Foundation International are acknowledged for financial support. K.I. is a recipient of the Research Fellowship for Young Scientists from JSPS.

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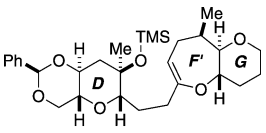

I

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