

Award Accounts

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Development and Application of a Convergent Strategy for the Total Synthesis of Polycyclic Ether Natural Products

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The polycyclic ether class of marine natural products presents formidable and challenging synthetic targets due to their structural complexity and exceptionally potent biological activities. Over the past decade, however, their extremely limited availability from natural sources has precluded detailed biological studies on polycyclic ethers. Therefore, the supply of useful quantities of these natural products by chemical total synthesis has been strongly demanded. We developed a highly convergent strategy for the rapid assembly of a huge polycyclic ether array, which features Suzuki–Miyaura cross-coupling reaction of alkylboranes, generated from exocyclic enol ethers, with cyclic ketene acetal triflates or phosphates combined with reductive ring-closure. The utility of this strategy was demonstrated by its application to the convergent total synthesis of the natural products gambierol and gymnocin-A. These practical synthetic routes allowed for the first time systematic studies of the structure–activity relationships of the polycyclic ether class of natural products.

Marine organisms provide an important source of structurally diverse secondary metabolites with unique molecular architecture and significant biological activities. Among these marine natural products, polycyclic ethers have attracted considerable attention of chemists and biologists due to their complex and huge molecular structures coupled with exceptionally potent biological properties.[1] Since the structure of brevetoxin-B (**1**, Fig. 1) was first reported by Nakanishi and coworkers in 1981,[2] a number of polycyclic ether natural products have been isolated and structurally elucidated using modern spectroscopic techniques. These toxic metabolites, produced by marine unicellular algae, chiefly dinoflagellates, usually contain extended arrays of trans-fused cyclic ethers of sizes ranging from five- to nine-membered. Figure 1 shows a number of representative examples from this class of natural products, including brevetoxins-B (**1**) and -A (**2**),[3] ciguatoxin (**3**),[4] CTX3C (**4**),[5] gambierol (**5**),[6] gambieric acid A (**6**),[7] yessotoxin (**7**),[8] gymnocin-A (**8**),[9] and brevenal (**9**).[10,11] Despite the common polycyclic ether motif, they show diverse biological activities with extreme potency, i.e., neurotoxicity, cytotoxicity, and antifungal activity. However, the target receptor protein has only been identified for brevetoxins and ciguatoxins, which bind to and activate voltage-sensitive sodium channels of excitable membranes.[12–15] In addition, the biological aspects of many of these molecules have not been fully investigated mainly due to their very limited availability from natural sources and difficulties of chemical modifications. Therefore, chemical total synthesis is the only means for supply of these natural products to investigate and exploit their biological activities.

Over the past two decades, considerable efforts have been devoted toward the total synthesis of these polycyclic ether molecules.[16] In 1995, Nicolaou and co-workers have reported the total synthesis of brevetoxin-B (**1**) after a twelve-year endeavor, which is the first synthesis of a highly complex molecule of the polycyclic ether class.[17] This seminal work has been followed by the synthesis of brevetoxin-A (**2**) by the same group in 1998.[18] In the past six years, remarkable progress has been made in the total synthesis of these huge polycyclic ethers with the advance of innovative synthetic methodologies and strategies, especially the development of an efficient method for convergent assembly of a polycyclic ether system, which is an obviously indispensable issue in this field. These efforts have culminated in the total synthesis of CTX3C (**4**), 51-hydroxyCTX3C, and ciguatoxin (**3**) by the Hirama/Inoue group,[19,20] gambierol (**5**) by us[21] and the groups of Yamamoto/Kadota[22] and Rainier,[23] gymnocin-A (**8**) by our group,[25] and brevetoxin-B (**1**) by the Nakata[26] and Yamamoto/Kadota groups.[24]

The huge and complex structures of these natural products require a highly efficient synthetic strategy with excellent material throughput. Our own investigations in this area have focused on development and application of a practical methodology for coupling polycyclic ether fragments, which is suitable for complex fragment coupling in the advanced stage of the synthesis. In this account, the development of a *B*-alkyl

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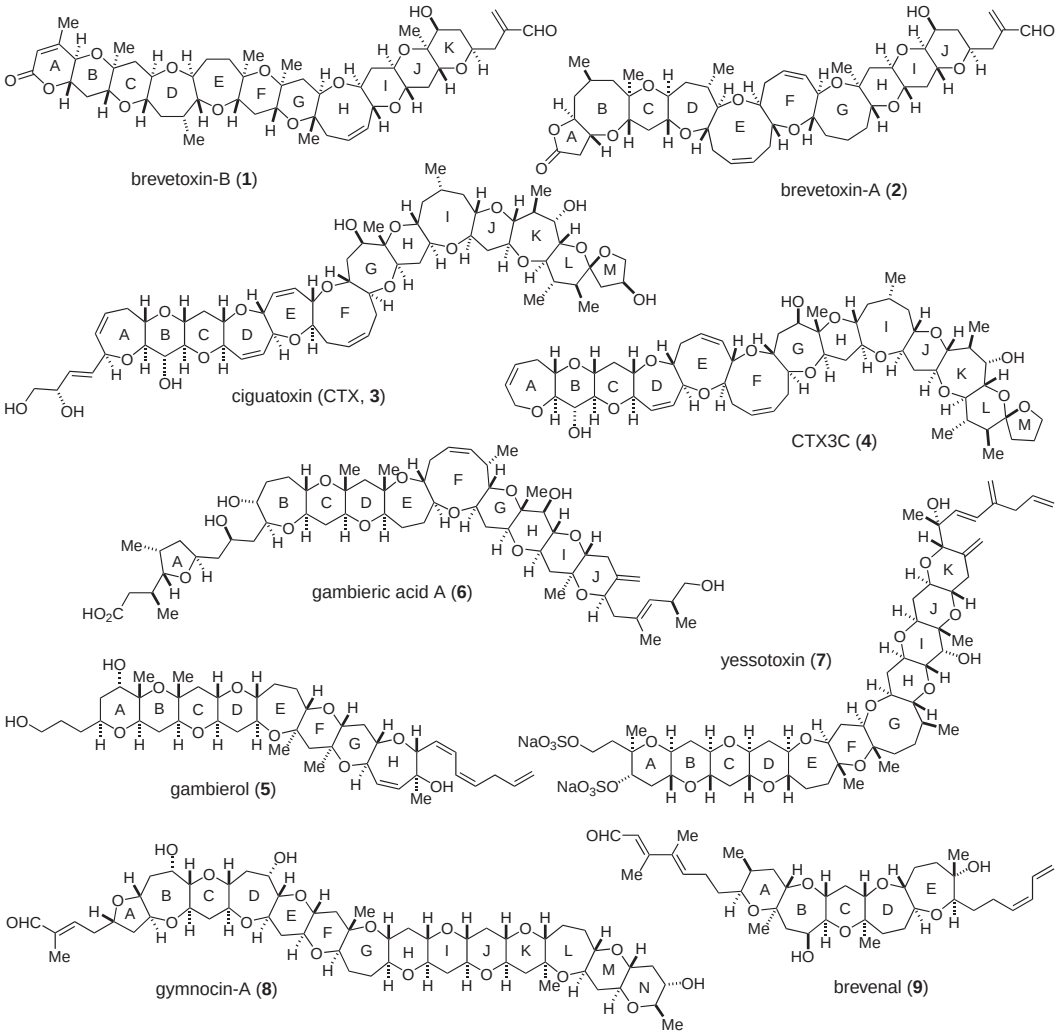


Fig. 1. Representative polycyclic ether marine natural products.

Suzuki–Miyaura coupling-based strategy for the convergent synthesis of polycyclic ethers and its successful applications to the total synthesis of natural products and their analogues as well as the studies of structure–activity relationships are described.

1. Suzuki–Miyaura Coupling Strategy for Polycyclic Ether Synthesis

1.1 Suzuki–Miyaura Reaction of Ketene Acetal Triflates.[27] Transition metal-catalyzed cross-coupling reactions have played an enormously decisive and important role in contemporary organic synthesis. Among palladium-catalyzed cross-coupling processes, the Suzuki–Miyaura coupling reaction has been one of the most versatile carbon–carbon bond-forming reactions.[28] The Suzuki–Miyaura coupling reaction has several significant advantages over other palladium-catalyzed cross-coupling reactions, such as the Stille[29] and the Mizoroki–Heck[30] reactions. Most notably, the Suzuki–Miyaura reaction is capable of generating not only the $C(sp^2)$–$C(sp^2)$ bond, but also $C(sp^3)$–$C(sp^2)$ linkage. The latter variant can be termed *B*-alkyl Suzuki–Miyaura coupling, and the first examples of this reaction have been reported in 1986.[31] In this reaction, the alkylborane, readily prepared through regio- and stereoselective hydroboration of the olefin precursor, can be utilized without isolation in the cross-coupling event under mild conditions, and an alkyl group is transferred from the organoborane component during the palladium-catalyzed coupling process with aryl or vinyl halides or triflates. Since its pioneering application in the total synthesis of (+)-quadrilure by the Mori group in 1990,[32] the *B*-alkyl Suzuki–Miyaura coupling has developed into a powerful tool for the total synthesis of natural products.[33] However, when our studies began in 1998, there existed no application of the Suzuki–Miyaura reaction to the synthesis of polycyclic ether natural products.

Figure 2 outlines our strategy for the convergent synthesis of polycyclic ethers based on the *B*-alkyl Suzuki–Miyaura coupling reaction. We became interested in the possibility that alkylborane **11**, readily obtainable from hydroboration of exocyclic enol ether **10** with 9-BBN, might react with ketene acetal triflate **12** under the Suzuki–Miyaura coupling conditions to afford the cross-coupled product **13**. Since elaboration of **13** to polycyclic ether system **16**, which involved stereoselective hydroboration of the endocyclic enol ether and oxidation of the resulting alcohol, followed by reductive etherification, has been reported by two research groups,[34] we surmised that polycyclic ether arrays could be constructed in a convergent man-

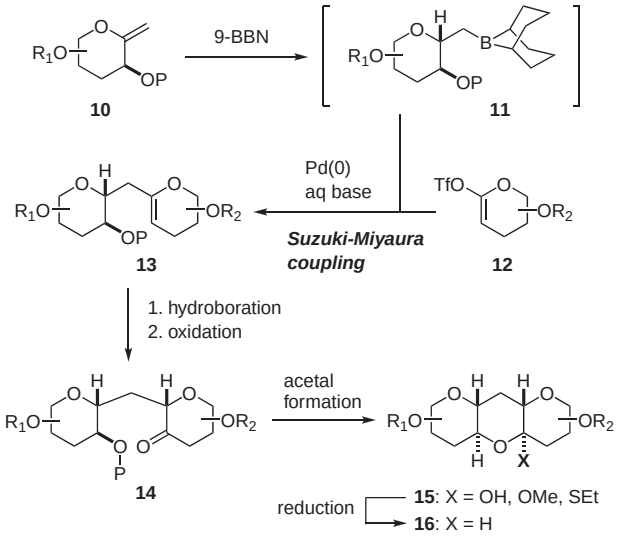
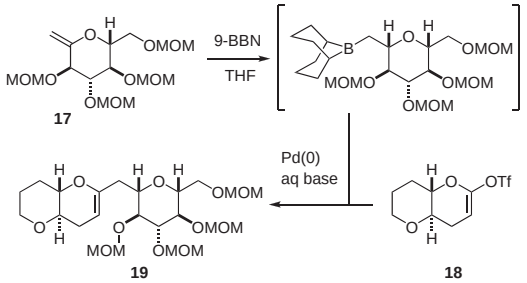


Fig. 2. *B*-Alkyl Suzuki–Miyaura coupling-based strategy for convergent synthesis of polycyclic ethers.

Table 1. Suzuki–Miyaura Coupling of Ketene Acetal Triflate **18** with Alkylborane[a)]



Entry	Pd cat	Base (equiv)[b)]	Ligand	Yield/%
1	$[PdCl_2(dppf)]$	aq K_3PO_4 (1.5)	none	40
2	$[PdCl_2(dppf)]$	aq Cs_2CO_3 (1.5)	none	51
3	$[PdCl_2(dppf)]$	aq Cs_2CO_3 (1.5)	Ph_3As	63
4	$[Pd_2(dba)_3]$	aq Cs_2CO_3 (3.0)	Ph_3As	80

a) 10 mol % Pd catalyst, 0.4 equiv ligand, 1.2 equiv KBr, DMF, room temperature, 20 h. b) 3 M aqueous solution.

ner by means of these reactions.

To test the feasibility of this Suzuki–Miyaura coupling reaction, we attempted to join exocyclic enol ether **17**[35] and bicyclic ketene acetal triflate **18** (Table 1). It was found that an alkylborane, prepared through hydroboration of **17** with 9-BBN, coupled with **18** in the presence of a catalytic amount of $[PdCl_2(dppf)]$ (dppf: 1,1′-bis(diphenylphosphino)ferrocene) and an aqueous base in THF/DMF at room temperature to give the desired product **19** in modest yield (Entries 1 and 2). After several experiments, it was found that the addition of Ph_3As as a co-ligand[36] improved the yield of **19** (Entry 3). Further efforts revealed the best source of the palladium(0) catalyst to be $[Pd_2(dba)_3]$ (dba: dibenzylideneacetone) (Entry 4).[37] As shown in Fig. 3, we were able to connect various six-membered ethers by the *B*-alkyl Suzuki–Miyaura coupling. It was noteworthy that, in any case, the hydroboration of exocyclic enol ethers with 9-BBN resulted in axial hydride delivery to form the equatorial products stereoselectively.[35,38]

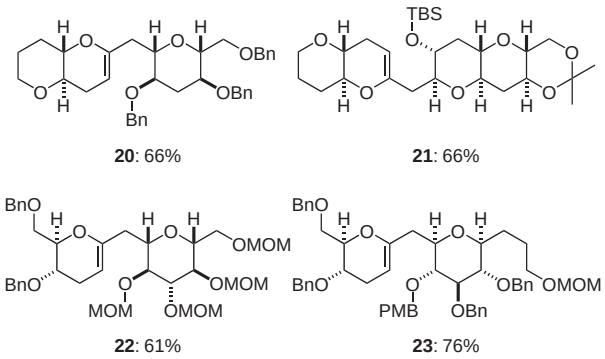


Fig. 3. Some examples of Suzuki–Miyaura coupling of six-membered ketene acetal triflates.

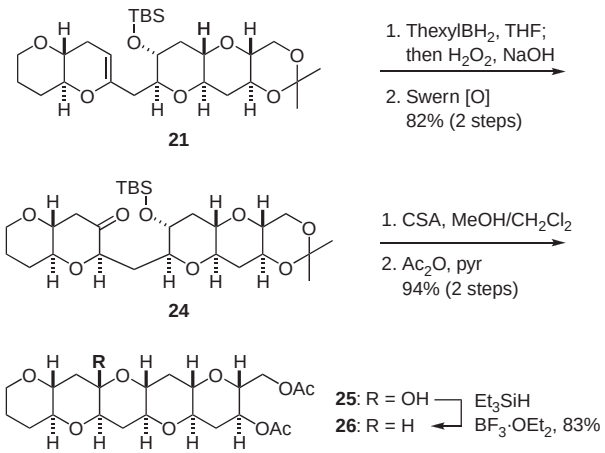


Fig. 4. Convergent synthesis of pentacyclic polypyran.

The success of the *B*-alkyl Suzuki–Miyaura coupling of six-membered ketene acetal triflates enabled us to perform a convergent synthesis of a polycyclic ether system. As an example, the synthesis of pentacyclic ether **26** from **21** is shown in Fig. 4. Stereoselective hydroboration of **21** with thexylborane followed by oxidation of the resulting secondary alcohol afforded ketone **24** in 82% yield for the two steps. Subsequent treatment of **24** with camphorsulfonic acid (CSA) affected the removal of the acetonide and *t*-butyldimethylsilyl (TBS) groups to give, after acetylation, hemiacetal **25** (94%, two steps). Finally, reduction with Et_3SiH and $BF_3 \cdot OEt_2$[39] delivered trans-fused pentacyclic polyether **26** in 83% yield. Thus, pentacyclic **26** was constructed rapidly and efficiently in only six steps from the coupling reaction.

1.2 Suzuki–Miyaura Coupling of Ketene Acetal Phosphates.[37,40] Having developed effective synthetic methodology for convergent synthesis of the polypyran system, we tried to extend the Suzuki–Miyaura coupling strategy to the synthesis of polycyclic ethers containing medium-sized rings. However, we soon encountered difficulty in utilizing medium-sized ketene acetal triflates as the coupling substrates in the present reaction due to their extreme lability. Indeed, seven-membered ketene acetal triflate **28** underwent rapid decomposition under the coupling conditions, and the desired product **29** could not be obtained (Fig. 5).

To overcome this issue arising from the labile nature of me-

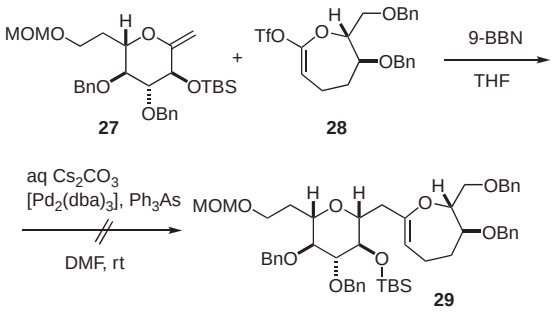


Fig. 5. Attempted coupling of seven-membered ketene acetal triflate.

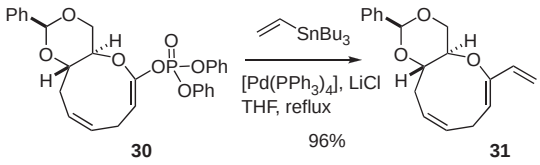
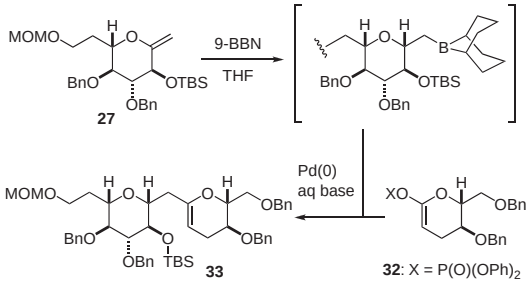


Fig. 6. Stille coupling of nine-membered ketene acetal phosphate.

dium-sized ketene acetal triflates, we considered the use of the corresponding ketene acetal phosphates in the *B*-alkyl Suzuki–Miyaura reaction. Medium-sized ketene acetal phosphates are stable enough to be isolated and purified by silica-gel chromatography. The use of a ketene acetal phosphate in organic synthesis has been demonstrated by Kane and Doyle in their total synthesis of zoapatanol in 1981,[41] and, recently, Nicolaou and co-workers have reported the successful use of cyclic ketene acetal phosphates in the Stille coupling reaction (Fig. 6),[42] which is one of the most important findings during the course of their total synthesis of brevetoxin-A.[18c] However, at the time that we initiated our studies, there existed, to the best of our knowledge, no literature precedent concerning the use of vinyl or aryl phosphates in the Suzuki–Miyaura coupling reaction.

Our model studies on Suzuki–Miyaura coupling of ketene acetal phosphate utilized exocyclic enol ether **27** and six-membered phosphate **32**. We first employed the reaction conditions established for the triflate coupling. However, the desired cross-coupled product **33** was not obtained at all, and unreacted phosphate **32** was recovered (Table 2, Entry 1). Use of $(2\text{-furyl})_3P$ as a ligand was also ineffective for this case (Entry 2). Given the fact that phosphate **32** remained unreacted under these conditions, it was supposed that the relatively less reactive **32** could not undergo oxidative addition to such electron-deficient palladium(0) species. Hence, we returned to the original Suzuki–Miyaura coupling conditions that employ electron-rich palladium(0) species. An alkylborane that was generated from **27** coupled with **32** under the influence of $[Pd(PPh_3)_4]$ catalyst and aqueous K_3PO_4 in THF/DMF, giving **33** in moderate yield (Entries 3 and 4). Under these strong basic conditions, hydrolysis of phosphate **32** occurred competitively. After many experiments, use of aqueous $NaHCO_3$ was found to suppress undesirable hydrolysis, and the yield of **33** was remarkably improved (Entry 5). Increasing the amounts of **32** further improved the yield of the coupling product (Entries 6 and 7).

Table 2. Suzuki–Miyaura Coupling of Six-Membered Ketene Acetal Phosphate **32** with Alkylborane[a)]



Entry	Pd cat	Base	Ligand	**32** /equiv	Yield /%
1[b)]	$[Pd_2(dba)_3]$	3 M aq Cs_2CO_3	Ph_3As	1.0	0
2[b)]	$[Pd_2(dba)_3]$	3 M aq Cs_2CO_3	$(2\text{-furyl})_3P$	1.0	0
3[b)]	$[Pd(PPh_3)_4]$	3 M aq K_3PO_4	none	1.0	46
4[c)]	$[Pd(PPh_3)_4]$	3 M aq K_3PO_4	none	1.0	56
5[c)]	$[Pd(PPh_3)_4]$	1 M aq $NaHCO_3$	none	1.0	72
6[c)]	$[Pd(PPh_3)_4]$	1 M aq $NaHCO_3$	none	1.4	84
7[c)]	$[Pd(PPh_3)_4]$	1 M aq $NaHCO_3$	none	2.0	98

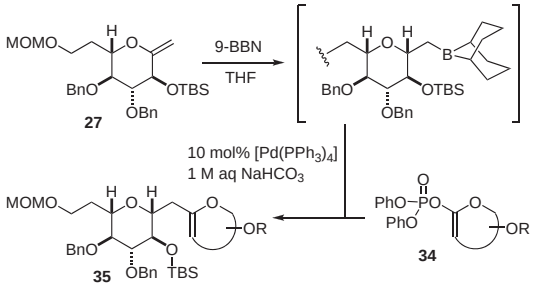
a) 10 mol % Pd catalyst, 3 equiv base, 0.4 equiv ligand. b) DMF at room temperature for 20 h. c) DMF at 50 °C for 20 h.

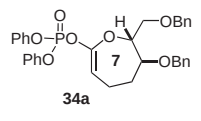
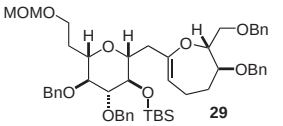
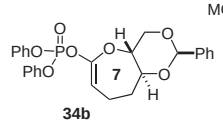
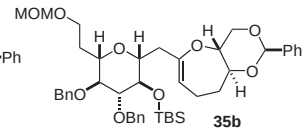
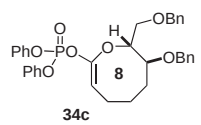
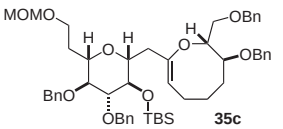
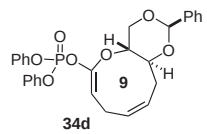
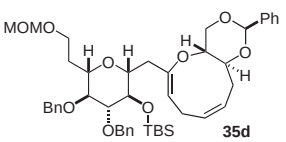
To ascertain the generality and scope of the *B*-alkyl Suzuki–Miyaura coupling of ketene acetal phosphates, a variety of substrates of different ring sizes were allowed to react under the optimal conditions. As shown in Table 3, the present reaction was successfully applied to seven- to nine-membered ketene acetal phosphates **34a**–**34d**, giving the desired products in excellent yields. Since the seven-membered ketene acetal triflates decomposed even under these mild conditions using $NaHCO_3$ as a base, use of a phosphate leaving group is essential for this cross-coupling reaction. The present method appears to be quite general and feasible for the union of various ether rings. Successful applications of the present reaction to the total synthesis of polycyclic ether natural products are described in the following sections.

2. Total Synthesis of Gambierol

In 1993, Yasumoto and co-workers have reported the isolation of gambierol (**5**) as a toxic constituent from the cultured cells of the ciguatera causative dinoflagellate *Gambierdiscus toxicus* collected at the Rangiroa Peninsula in French Polynesia.[6] The gross structure, including the relative stereochemistry, has been revealed by extensive NMR experiments[6a] and, subsequently, the absolute configuration has been determined by derivatization and application of the modified Mosher's method.[6b] Structurally, the toxin molecule consists of a trans-fused octacyclic polyether skeleton containing 18 stereogenic centers and a partially skipped triene side chain including a conjugated (*Z*,*Z*)-diene system. Gambierol exhibits potent neurotoxicity against mice (minimum lethal dose 50 $\mu g\,kg^{-1}$, ip) with symptoms resembling those shown by ciguatoxins, implying that gambierol is also involved in ciguatera seafood poisoning. However, as is often the case with other polycyclic ether compounds, the extremely limited availability of this toxin from natural sources has hampered detailed biological stud-

Table 3. Suzuki–Miyaura Coupling of Medium-Sized Ketene Acetal Phosphates **34** with Alkylborane[a)]



Entry	Ketene acetal phosphate	Coupling product	Yield/%
1			97
2			94
3			96
4			98

a) 3 equiv 1 M $NaHCO_3$, 10 mol % $[Pd(PPh_3)_4]$, 2 equiv phosphate, DMF, 50 °C for 20 h.

ies. In 2002, we accomplished the first total synthesis of gambierol,[21] which was the first successful application of our developed Suzuki–Miyaura coupling chemistry to the total synthesis of natural products. Shortly thereafter, the Yamamoto/Kadota group have reported the second total synthesis using their intramolecular allylstannane cyclization chemistry.[22] Subsequently, Rainier and co-workers have also accomplished their own total synthesis.[23]

2.1 Synthesis Plan. Our synthetic plan for the total synthesis of gambierol is summarized in Fig. 7. The labile triene side chain was planned to be installed at a late stage of the synthesis. For the C33–C34 bond formation, the Stille coupling between **36** and **37** was chosen as a promising candidate, as the Yamamoto/Kadota group has reported in their model study.[43] The (*Z*)-vinyl bromide **36** would be available through appropriate functionalization of the H-ring from the octacyclic polyether **38**, which was envisioned to be obtained by the convergent union of the ABC-ring exocyclic enol ether **39** and the EFGH-ring ketene acetal phosphate **40** through the foregoing Suzuki–Miyaura coupling chemistry.

2.2 Synthesis of the ABC-Ring Fragment.[21b,44] The ABC-ring fragment **39** was synthesized in a linear manner (B → AB → ABC), wherein the A-ring was constructed by

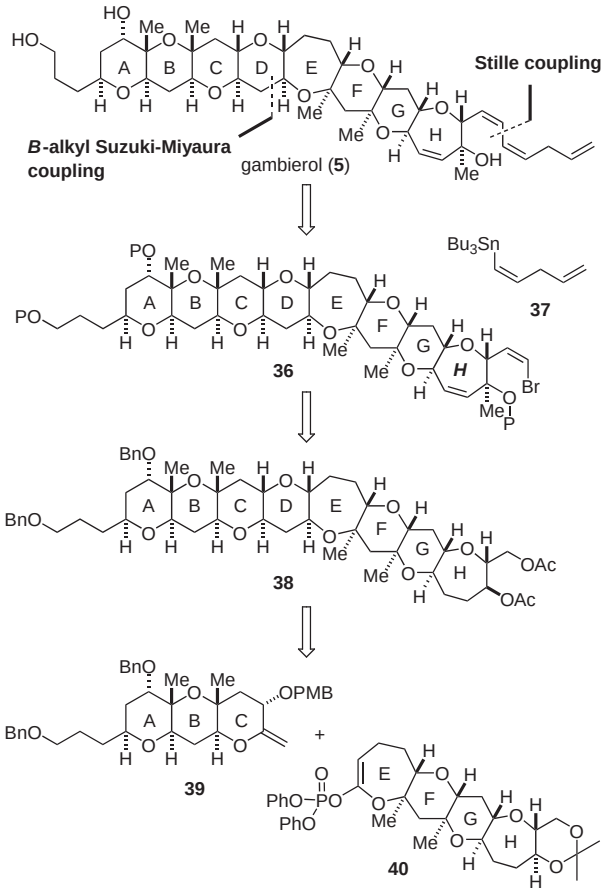


Fig. 7. Retrosynthetic analysis of gambierol.

an intramolecular hetero-Michael reaction and the C-ring was formed via a 6-endo cyclization.[45] The known olefin **41**[46] was elaborated to allylic alcohol **42** in a standard three-step sequence (Fig. 8). The hydroxy group at C6 was introduced by Sharpless asymmetric epoxidation (AE) followed by regioselective reductive opening of the resulting epoxy alcohol with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®).[47] The derived 1,3-diol **43** was then converted to hydroxy enoate **44** in a further five steps. Treatment of **44** with NaH effected an intramolecular hetero-Michael reaction to give tricyclic ester **45** as a single stereoisomer. Elongation of the side chain followed by a sequence of transformations led to allylic alcohol **46**. To set the stage for the construction of the C-ring, **46** was oxidized with *m*CPBA, leading exclusively to the desired α-epoxide. The resulting epoxy alcohol was further converted to vinyl epoxide **47**, which upon treatment with pyridinium *p*-toluenesulfonate (PPTS) generated tricyclic ether **48** via the 6-endo cyclization.[45] The requisite ABC-ring exocyclic enol ether **39** was synthesized from **48** without incident. Although the present synthesis is linear and requires 36 synthetic manipulations from **41**, the remarkably high overall yield (18%) allowed multi-gram preparation of the ABC-ring fragment **39**.

2.3 Synthesis of the EFGH-Ring Fragment.[21b] Our first approach to the EFGH-ring fragment **40** relied on the Suzuki–Miyaura coupling of the F- and H-rings. However, the synthesis lacked overall efficiency (42 steps in the longest linear sequence and 6% overall yield from the corresponding methyl

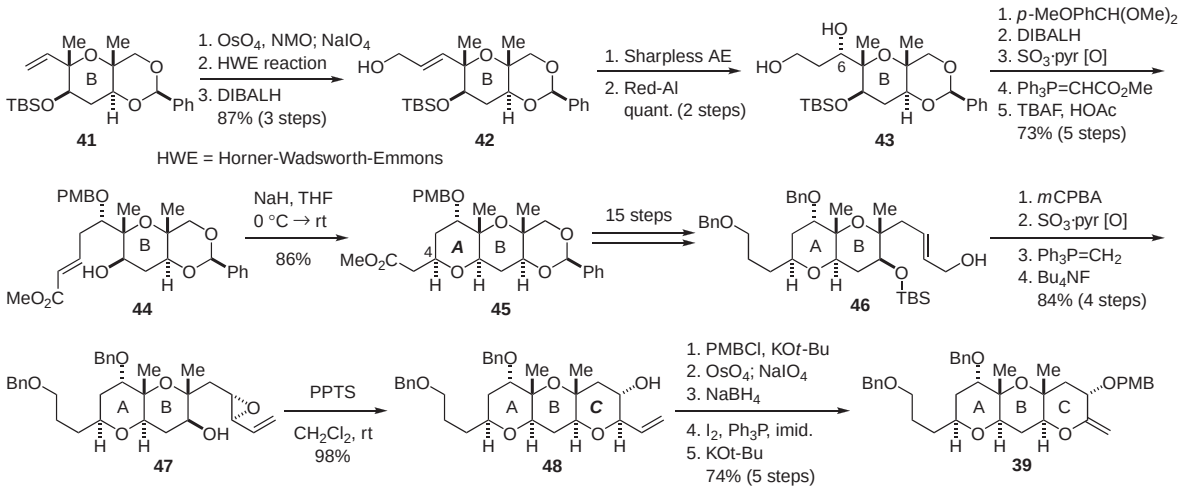


Fig. 8. Synthesis of the ABC-ring fragment of gambierol.

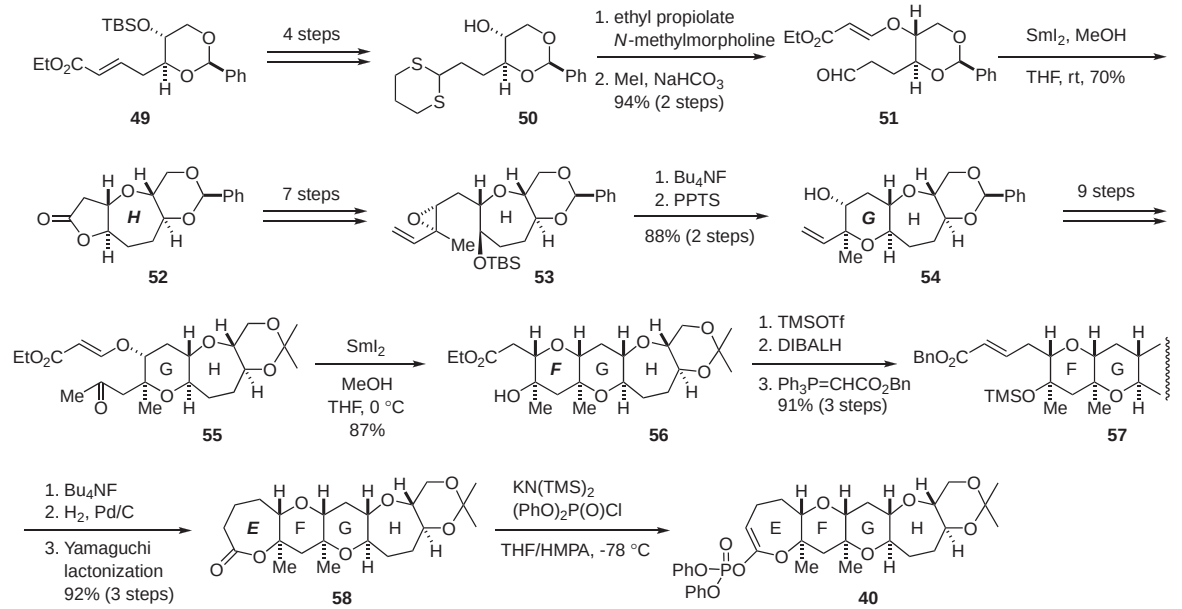


Fig. 9. Synthesis of the EFGH-ring fragment of gambierol.

ester of **49**),[48] which led us to explore an alternative route for the synthesis of **40**. An improved second-generation synthesis of the EFGH-ring fragment **40** utilized the SmI_2-promoted reductive cyclization protocol developed by Nakata and coworkers.[49] The synthesis started with the known ester **49**,[18c] which was converted in four steps to dithiane alcohol **50** (Fig. 9). The β-alkoxyacrylate unit was incorporated to the secondary alcohol (ethyl propiolate, 4-methylmorpholine (NMM)), and the thioacetal was hydrolyzed to afford aldehyde **51**. Treatment of **51** with SmI_2 in the presence of MeOH (THF, room temperature) effected reductive cyclization to form the seven-membered H-ring, giving γ-lactone **52** in 70% yield with complete stereocontrol.[49] For the construction of the G-ring, lactone **52** was converted to vinyl epoxide **53** in a seven-step sequence. After removal of the TBS group, treatment of the resulting alcohol with PPTS effected 6-endo cyclization[45] to give the GH-ring system **54**. Alcohol **54** was then transformed to methyl ketone **55** in a further nine steps. Reductive cyclization of **55** with SmI_2 proceeded again stereoselectively to afford the FGH-ring fragment **56** in 87% yield as a single stereoisomer.[49] Chain elongation of **56** and Yamaguchi lactonization[50] afforded seven-membered lactone **58**. Finally, treatment of **58** with $KN(TMS)_2$ and $(PhO)_2P(O)Cl$ (THF/HMPA, $-78\,^{\circ}C$)[42] afforded the EFGH-ring fragment **40**. The synthesis of **40** consisted of 33 synthetic operations with 22% overall yield, allowing the gram-scale synthesis of this key intermediate.

2.4 Synthesis of the Octacyclic Polyether Core.[21b,44] With the requisite key intermediates **39** and **40** in hand, we next turned our attention to the crucial coupling of these components via the Suzuki–Miyaura coupling strategy. Hydroboration of the ABC-ring exocyclic enol ether **39** with 9-BBN generated the intermediate alkylborane **59**, which was in situ reacted with the EFGH-ring ketene acetal phosphate **40** in the presence of $[PdCl_2(dppf)]$ and aqueous Cs_2CO_3 in THF/DMF at $50\,^{\circ}C$ (Fig. 10). The desired cross-coupled product

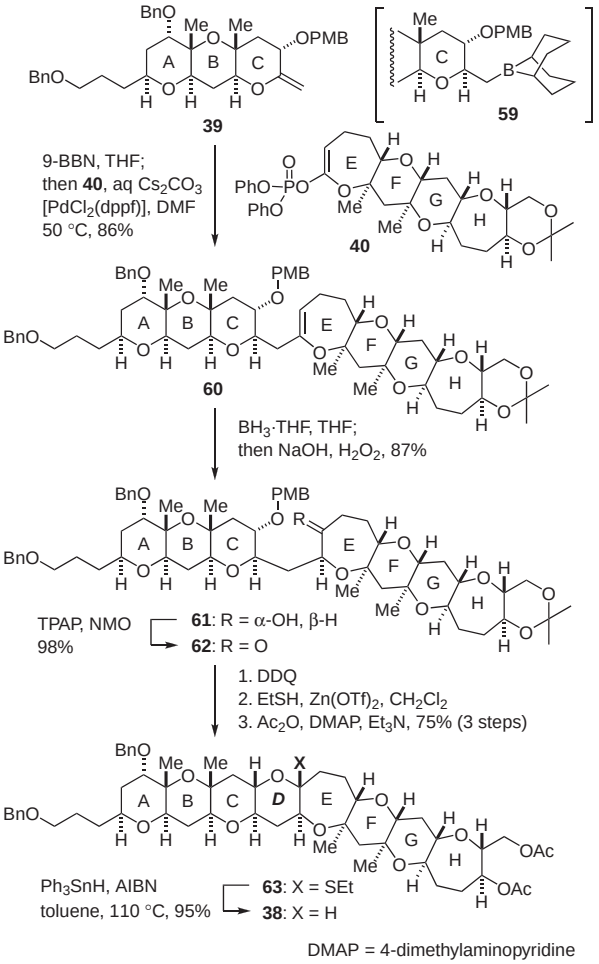


Fig. 10. Construction of the octacyclic polyether core of gambierol.

60 was obtained in a 86% yield. Subsequent hydroboration of the endocyclic enol ether with $BH_3 \cdot THF$ led stereoselectively to the desired alcohol **61**, which was then oxidized with tetra-*n*-propylammonium perruthenate (TPAP)/4-methylmorpholine *N*-oxide (NMO)[51] to afford ketone **62**. Oxidative removal of the *p*-methoxybenzyl (PMB) group from **62** followed by treatment with EtSH and $Zn(OTf)_2$ effected cyclization of the D-ring as the mixed thioacetal to yield, after acetylation, **63**. Finally, desulfurization under radical reduction conditions (Ph_3SnH, AIBN, toluene, 110 °C)[52] proceeded cleanly to furnish the desired octacyclic polyether skeleton **38** in 95% yield.

2.5 Completion of Total Synthesis of Gambierol.[21] For the functionalization of the H-ring, octacycle **38** was converted to ketone **64** in a three-step sequence (Fig. 11). Based on our preliminary model experiments, incorporation of the C28–C29 double bond was carried out by the Ito–Saegusa protocol.[53] Thus, the silyl enol ether was prepared from **64** and subsequently treated with $Pd(OAc)_2$, giving the corresponding enone. Stereoselective installation of the C30 methyl group was performed by the action of MeMgBr (toluene, −78 °C).[54] These three-step manipulations successfully transformed ketone **64** into tertiary alcohol **65** in 94% overall yield as a single stereoisomer. Protective group manipulations from **65** then generated primary alcohol **66**. Oxidation to the aldehyde and Corey–Fuchs reaction,[55] followed by stereoselective reduction of the resulting dibromoolefin by the Uenishi protocol,[56] led to (*Z*)-vinyl bromide **67** in good overall yield.

The final steps to complete the total synthesis required stereoselective construction of the triene side chain and global deprotection. However, both of these issues posed significant challenges. The Stille coupling of (*Z*)-vinyl bromide **67** with (*Z*)-vinyl stannane **37**[57] turned out to be more difficult than anticipated due to the low reactivity of these substrates. After extensive experimentation, it was finally found that the $[Pd(PPh_3)_4]$/CuCl/LiCl-promoted modified Stille coupling conditions, developed by Corey and co-workers,[58] were quite suitable for the present case. Under the optimal conditions, the Stille coupling of **67** with **37** furnished fully protected gambierol **68** in 66% yield (82% yield based on recovered **67**). However, all attempts to remove the silyl protective groups from **68** under various conditions were unsuccessful due to the labile nature of the triene side chain. After considerable experimentation, this critical issue was overcome as follows. Exposure of (*Z*)-vinyl bromide **67** to excess HF·pyridine facilitated clean deprotection of the three silyl groups, giving triol **69** in excellent yield. Finally, the Stille coupling of unprotected **69** with **37** under the established conditions ($[Pd(PPh_3)_4]$, CuCl, LiCl, DMSO/THF, 60 °C) furnished (−)-gambierol (**5**) in 43% isolated yield. The spectroscopic data (^1H and ^{13}C NMR, HR-MS, and CD) and mice lethality of the synthetic gambierol were identical to those of an authentic natural sample, confirming the structure of gambierol including the absolute configuration. Thus, the first total synthesis of gambierol (**5**) was completed in 0.57% overall yield over a 71-step longest linear sequence. The present synthesis clearly demonstrated the utility of the Suzuki–Miyaura coupling chemistry for the fragment coupling process in polycyclic ether synthesis.

2.6 Biological Studies of Gambierol.[59,60] Since ample quantities of gambierol could be supplied by our total synthesis, detailed studies aimed at understanding the molecular basis of the biological mode of action of this marine toxin were made possible.

The acute toxicological effects induced in mice by synthetic gambierol were first examined. The lethal doses were about $80\,\mu g\,kg^{-1}$ by intraperitoneal (ip) and intravenous (iv) injections, and $150\,\mu g\,kg^{-1}$ by oral administration. The main injury by this toxin was observed in the lung, and secondary in the heart, resulting in systemic congestion. Another toxic effect was seen in the stomach, inducing hypersecretion and ulceration.[59]

We next evaluated the effect of synthetic gambierol on the voltage-sensitive ion currents in mouse taste cells by using the patch-clamp technique. Taste cells are excitable cells endowed with voltage-sensitive sodium, potassium, and chloride ion currents (I_{Na}, I_K, and I_{Cl}, respectively). It was found that gambierol markedly inhibited I_K with an IC_{50} value of 1.8 nM, whereas it showed no significant effect on I_{Na} or I_{Cl} even at higher concentration (1 μM).[60a] In sharp contrast, CTX3C markedly affected the operation of voltage-sensitive sodium channels, but was ineffective on voltage-sensitive potassium channels.[60b] These results revealed that, unlike ciguatoxins that affect the function of voltage-sensitive sodium channels,

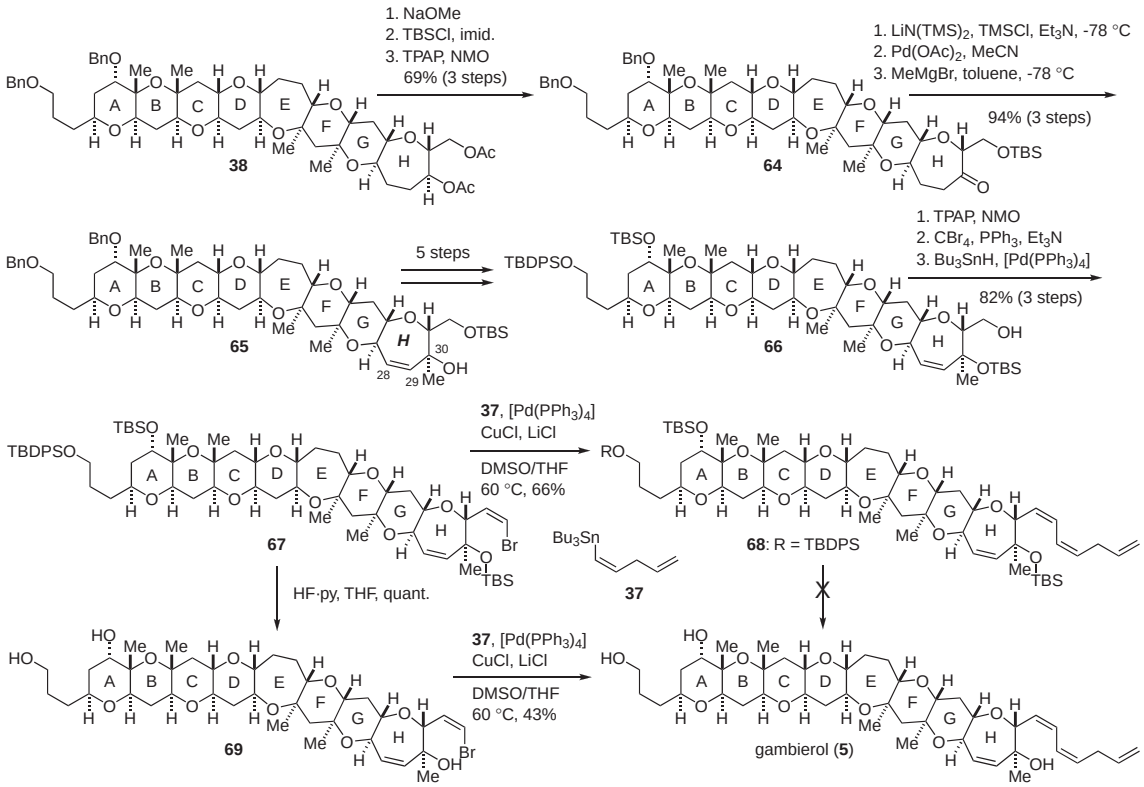


Fig. 11. Completion of the total synthesis of gambierol.

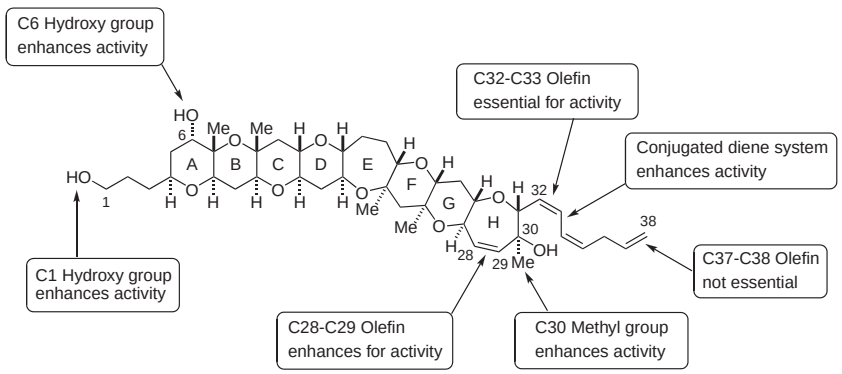


Fig. 12. Structure–activity relationships of gambierol.

the preferred molecular target of gambierol is the voltage-sensitive potassium channels at least in taste cells.

2.7 Structure–Activity Relationship Studies on Gambierol.[61] There exist only a few reports concerning structure–activity relationships (SAR) of marine polycyclic ether toxins.[62] Two major reasons for this are (i) extremely limited availability of these toxins from natural sources and (ii) difficulties of derivatization of the highly complex natural products themselves. In the case of gambierol, we solved the first problem by our efficient total synthesis, which realized the preparation of several hundred milligrams of this natural toxin. On the other hand, the second problem would be overcome by a "diverted total synthesis."[63] The synthetic route is diverted at the stage of an advanced intermediate, which has a simple structure and sufficient functional groups for further chemical manipulation. We selected octacyclic polyether **38**, which is now available in gram quantity, as a branching point for diverted total synthesis of gambierol analogues not accessible from the natural product itself. Thus, a series of structural analogues were synthesized starting from **38** and investigated for their toxicity against mice, thus allowing for the first time systematic SAR studies of this complex marine toxin. These SAR studies revealed that the structural elements of gambierol that are indispensable for exhibiting potent toxicity are (i) the C28–C29 double bond within the H-ring and (ii) the unsaturated side chain of specific length (Fig. 12). In contrast to these important structural elements, the C1 and C6 hydroxy groups, the C30 methyl group, and the C37–C38 double bond are not essential but are preferred functional groups for toxicity. The present results will enable rational design of photoaffinity labeling and/or biotin-tagged molecular probes useful for detailed biological studies on gambierol.

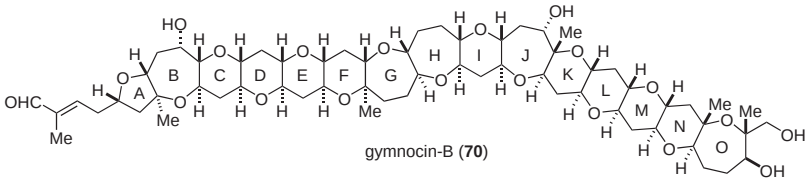


Fig. 13. Structure of gymnocin-B.

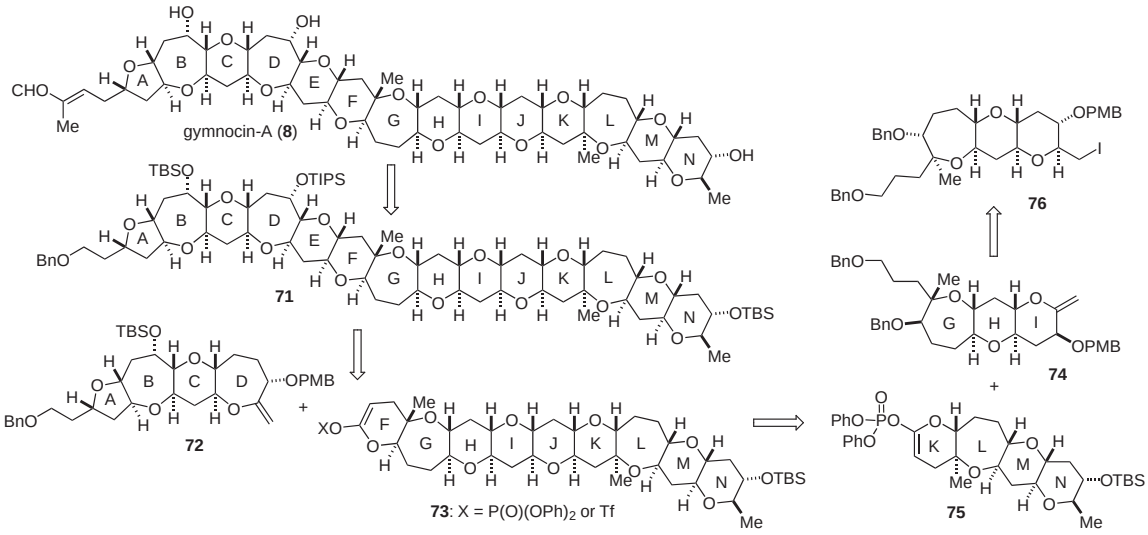


Fig. 14. Retrosynthetic analysis of gymnocin-A.

3. Total Synthesis of Gymnocin-A

Gymnocin-A (**8**) is a polycyclic ether toxin that has been isolated by Satake and co-workers from the dinoflagellate, *Karenia mikimotoi*, which is one of the most notorious red tide species that causes devastating damages to aquaculture and marine ecosystems worldwide.[9] The toxin is a rare polycyclic ether natural product that displays in vitro cytotoxicity against P388 leukemia cells ($EC_{50} = 1.3\,\mu g\,mL^{-1}$). Several congeners of **8**, including gymnocin-B (**70**, $EC_{50} = 1.7\,\mu g\,mL^{-1}$, Fig. 13),[64] have also been isolated, and some of them have displayed far stronger cytotoxicity than **8**, though their structures has not been determined. The structure of gymnocin-A has been elucidated on the basis of extensive 2D NMR analysis and collision-induced MS/MS experiments. Furthermore, the absolute configuration has also been determined by the modified Mosher's method. Structurally, gymnocin-A is characterized by 14 contiguous saturated ether rings, including two repeating 6/6/7/6/6 ring systems (the EFGHI- and JKLMN-rings), and a 2-methyl-2-butenal side chain. In 2000, we started a program toward its total synthesis aimed at assessing whether our Suzuki–Miyaura coupling chemistry was suitable for the construction of such a huge molecule.

3.1 Synthesis Plan. The most formidable challenge in the total synthesis of gymnocin-A is apparently the construction of the huge tetradecacyclic polyether skeleton. In this context, we planned to assemble the polycyclic ether backbone **71** by a particularly challenging Suzuki–Miyaura cross-coupling between the ABCD- and FGHIJKLMN-fragments (**72** and **73**, respectively, Fig. 14). The symmetry elements of the latter fragment **73** allowed further disconnection at the J-ring into two fragments, the GHI- (**74**) and KLMN-rings (**75**), both of which would be derived from a common precursor **76**.

3.2 Synthesis of ABCD-Ring Fragment.[24b] The synthesis of the ABCD-ring fragment **72** started with convergent union of the AB- and D-rings (**77** and **78**, respectively). Hydroboration of exocyclic enol ether **78** with 9-BBN, followed by in situ reaction with **77**, afforded cross-coupled product **79** in 84% yield (Fig. 15). Subsequent hydroboration with thexylborane followed by oxidation of the derived alcohol with TPAP/NMO produced ketone **80** in 71% overall yield. For the stereoselective introduction of the C10 hydroxy group, ketone **80** was first converted to the corresponding silyl enol ether **81** ($LiN(TMS)_2$, TMSCl, Et_3N, THF, $-78\,^\circ C$). Oxidation of **81** with catalytic OsO_4 and NMO delivered α-hydroxy ketone **82** in 84% overall yield as an inseparable 8.5:1 mixture of diastereomers. After protection as the triisopropylsilyl (TIPS) ether, the resulting siloxy ketone **83** was separated in a pure form by silica-gel chromatography. Subsequent treatment of **83** with EtSH and $Zn(OTf)_2$ in CH_2Cl_2, however, produced a mixture of hemiacetal **84** (55%) and mixed thioacetal **85** (29%). The hemiacetal **84** was readily separated by column chromatography and resubjected to EtSH and $Zn(OTf)_2$ in $CH_2Cl_2/MeNO_2$ (1:1) to give thioacetal **85** in 95% yield. Thus, the desired **85** was obtained in 81% combined yield. In this transformation, direct treatment of ketone **83** with EtSH and $Zn(OTf)_2$ in $CH_2Cl_2/MeNO_2$ (1:1) resulted in a variable yield of **85**. After protection as the *p*-methoxybenzylidene acetal, the thioacetal moiety was cleanly reduced under radical conditions (Ph_3SnH, AIBN, toluene, $100\,^\circ C$) to give, after de-

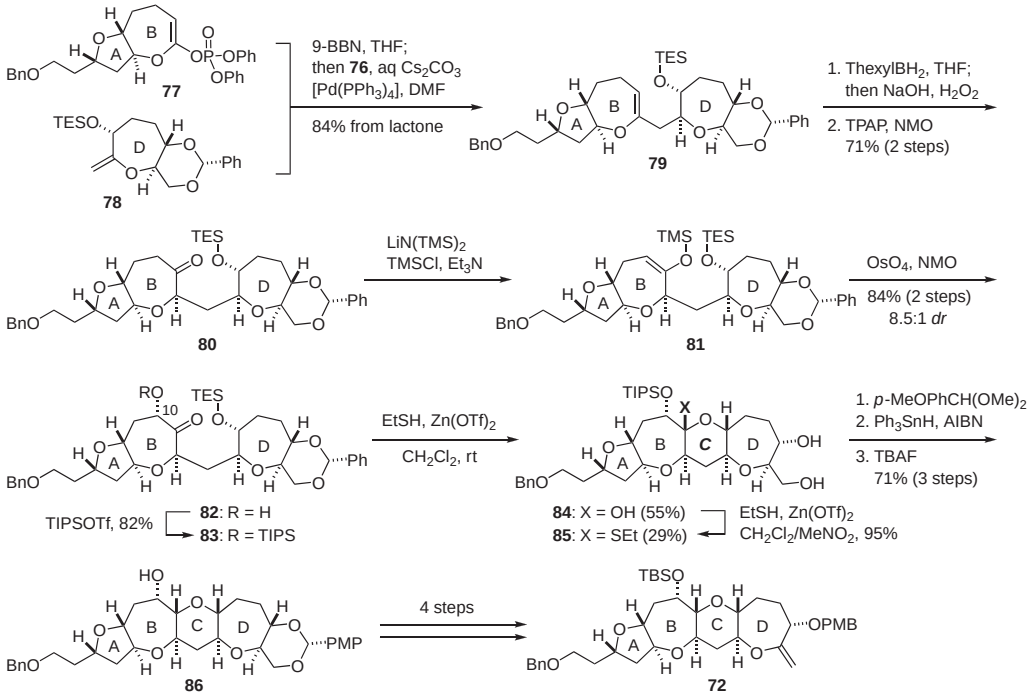


Fig. 15. Synthesis of the ABCD-ring fragment of gymnocin-A.

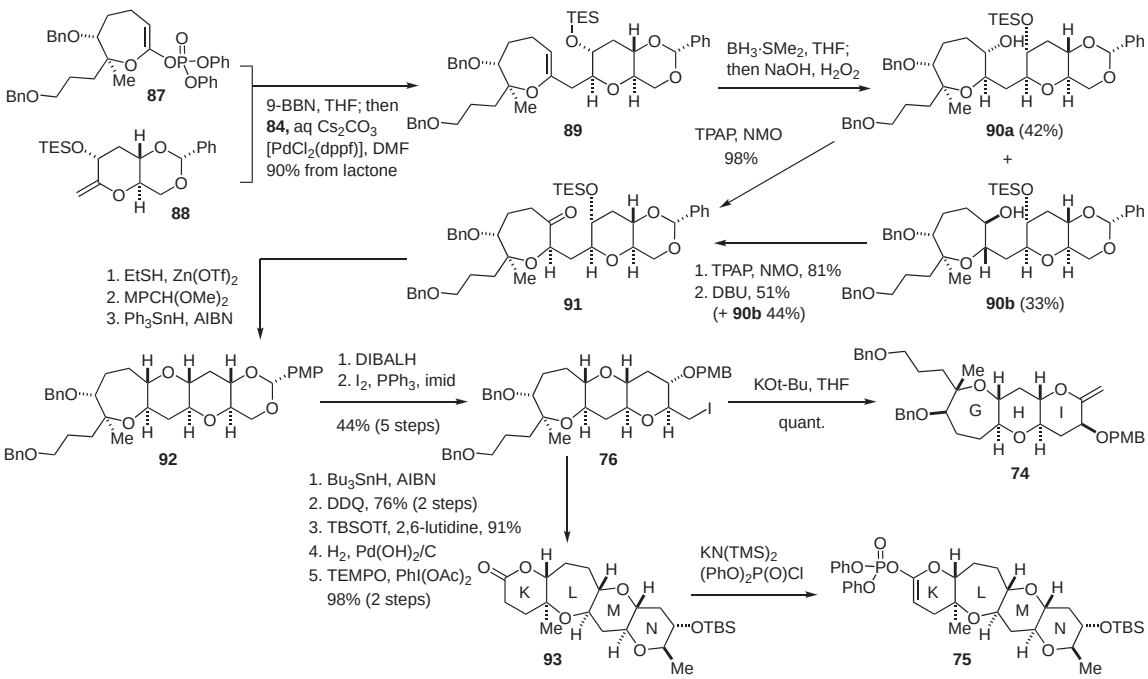


Fig. 16. Synthesis of the GHI- and KLMN-ring fragments of gymnocin-A.

silylation, alcohol **86** in 71% yield for the three steps. A further four-step sequence was required to complete the synthesis of the ABCD-ring fragment **72**.

3.3 Synthesis of FGHIJKLMN-Ring Fragment.[24b,65] The synthesis of the GHI- and KLMN-ring fragments (**74** and **75**, respectively) started with the *B*-alkyl Suzuki–Miyaura coupling of **87** and **88** (Fig. 16). Hydroboration of **88** with 9-BBN, followed by coupling with ketene acetal phosphate **87**, which was prepared from geraniol,[66] delivered cross-coupled product **89** in 90% yield. Subsequent hydroboration produced a separable 4:3 mixture of the desired alcohol **90a** and the corresponding diastereomer **90b**. The poor stereoselectivity in this reaction is presumably due to the steric hindrance of the tertiary methyl group on the seven-membered ring. Oxidation of **90a** provided ketone **91** in excellent yield, whereas the undesired **90b** could be recycled by oxidation and base-induced isomerization. The resulting ketone **91** was then subjected to EtSH and $Zn(OTf)_2$ to generate a mixed thioacetal, which

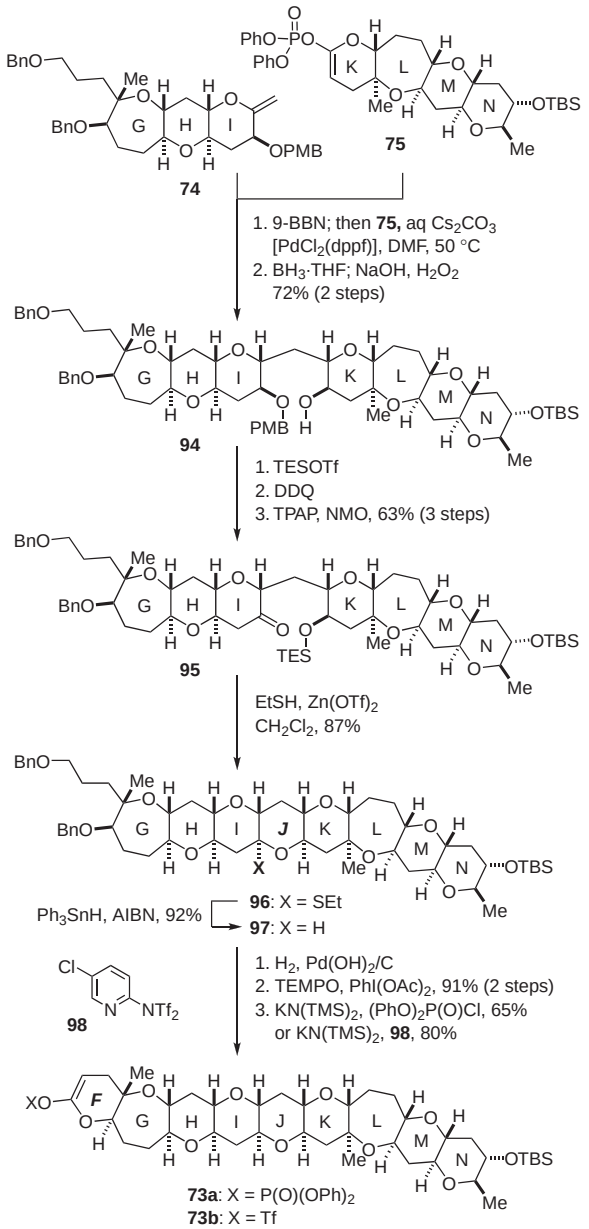


Fig. 17. Synthesis of the FGHIJKLMN-ring fragments of gymnocin-A.

was reprotected and reduced under radical conditions to afford tricyclic ether **92**. Reductive opening of the *p*-methoxybenzylidene acetal with DIBALH gave a primary alcohol, which was then iodinated to furnish the common intermediate **76**. Treatment of **76** with KO*t*-Bu led to the GHI-ring exocyclic enol ether **74**. On the other hand, radical reduction of **76** and protective group manipulations, followed by oxidation of the 1,5-diol with 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and $PhI(OAc)_2$,[67] provided lactone **93**, which was then converted to the KLMN-ring ketene acetal phosphate **75**.

Hydroboration of **74** with 9-BBN followed by reaction with **75** in the presence of aqueous Cs_2CO_3 and $[PdCl_2(dppf)]$ (DMF, 50 °C) proceeded smoothly to give the cross-coupled product, which was then subjected to a second hydroboration, giving alcohol **94** in 72% overall yield (Fig. 17). Triethylsilyl (TES) protection, PMB deprotection, and oxidation with TPAP/NMO gave ketone **95**. Subsequent exposure to EtSH and $Zn(OTf)_2$ generated mixed thioacetal **96**, which was reduced under radical conditions to give octacyclic polyether **97**. Removal of the benzyl groups under hydrogenolysis followed by TEMPO oxidation of the resulting 1,5-diol[67] provided a δ-lactone, which was readily converted to the FGHIJKLMN-ring ketene acetal phosphate **73a** in 65% yield.[42] The corresponding triflate **73b** was also prepared in 80% yield by use of Comins reagent **98**.[68]

3.4 Completion of Total Synthesis of Gymnocin-A.[24] With the advanced key fragments **72** and **73** in hand, the stage was now set for their crucial coupling by using the *B*-alkyl Suzuki–Miyaura reaction (Fig. 18). However, ketene acetal phosphate **73a** proved to be a poor substrate for this complex fragment coupling. Hydroboration of **72** with 9-BBN and attempted cross-coupling with **73a** under the optimized conditions did not yield any desired product, and unreacted **73a** was recovered. In contrast, it was discovered that the pivotal fragment coupling could be realized by using more reactive triflate **73b**. Thus, hydroboration of **72** with 9-BBN, followed by in situ coupling with **73b** in the presence of aqueous Cs_2CO_3 and $[Pd(PPh_3)_4]$ in DMF at room temperature, afforded the desired cross-coupled product **99** in excellent yield (81%). Considering the complexity and size of the fragments, this remarkable yield represents the power and reliability of the Suzuki–Miyaura cross-coupling reaction.

Cross-coupled product **99** was then subjected to hydroboration ($BH_3 \cdot SMe_2$; then H_2O_2, NaOH) to give alcohol **100** in 75% yield as a single stereoisomer. For the introduction of the C17 hydroxy group, **100** was elaborated to ketone **101** by a three-step sequence including TES protection, PMB deprotection, and oxidation. Conversion of **101** to the corresponding silyl enol ether followed by oxidation with OsO_4/NMO installed the C17 hydroxy group with complete stereocontrol, to give, after silyl protection, the desired α-siloxy ketone **102** in good overall yield.

The next task was to cyclize the E-ring by radical reduction of mixed thioacetal **104**. In sharp contrast to the preceding protocol (e.g. **95** → **96**), treatment of **102** with EtSH and $Zn(OTf)_2$ in CH_2Cl_2 resulted in only a poor yield of **104**. After some experiments, it was found that the choice of solvent was critical for this cyclization. Use of $MeNO_2$ as a solvent cleanly produced the desired **104**. Some of the TBS group on the N-ring was cleaved in this sequence, but the desilylated **103** was easily silylated to give **104**. Finally, reductive desulfurization of **104** proceeded cleanly to afford the tetradecacyclic polyether skeleton **71** in excellent yield.

The final stage of the synthesis involved the incorporation of a 2-methyl-2-butenal side chain. Initial attempts to cleave the TBS and TIPS protecting groups after introduction of the enal side chain or its equivalent were unsuccessful probably because of the lability of the side chain. Accordingly, these protecting groups were replaced with the more readily cleaved TES ethers at the stage of **71** (Fig. 19). Subsequent reductive removal of the benzyl group with lithium di-*t*-butylbiphenylide (LiDBB)[69] afforded primary alcohol **105** in good overall yield. Oxidation to the aldehyde followed by Wittig reaction with methyl 2-(triphenylphosphoranylidene)propionate installed

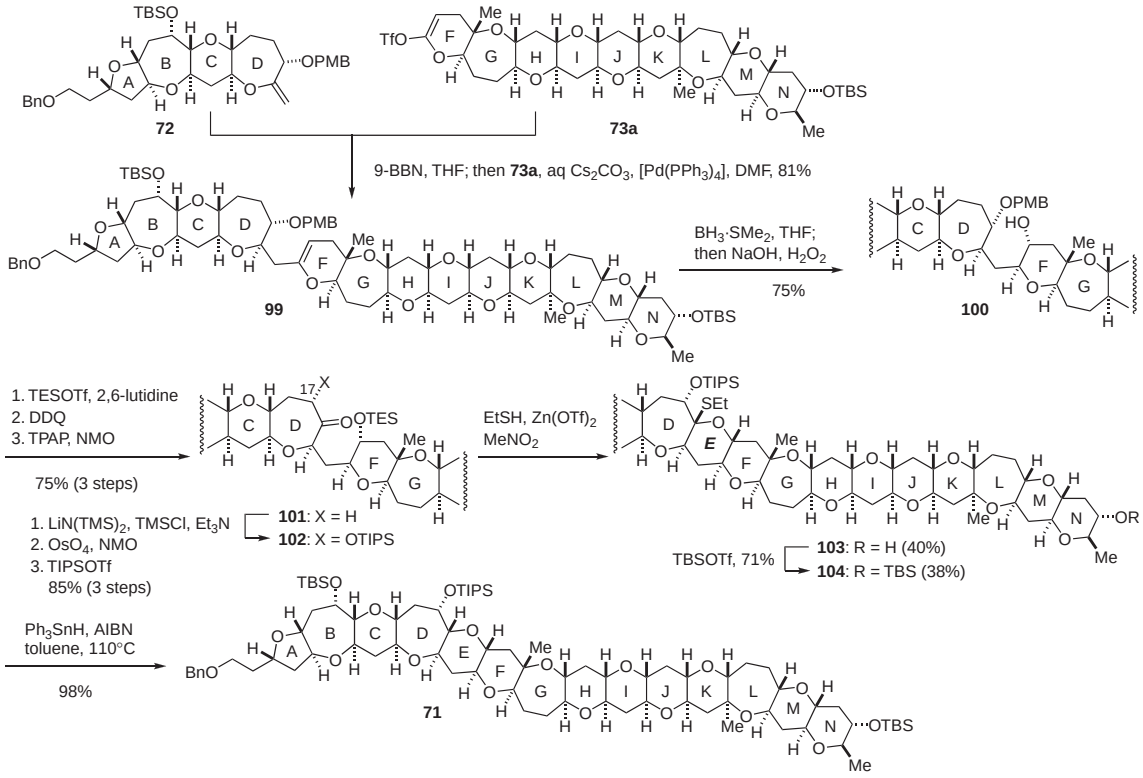


Fig. 18. Construction of tetradecacyclic polyether core of gymnocin-A.

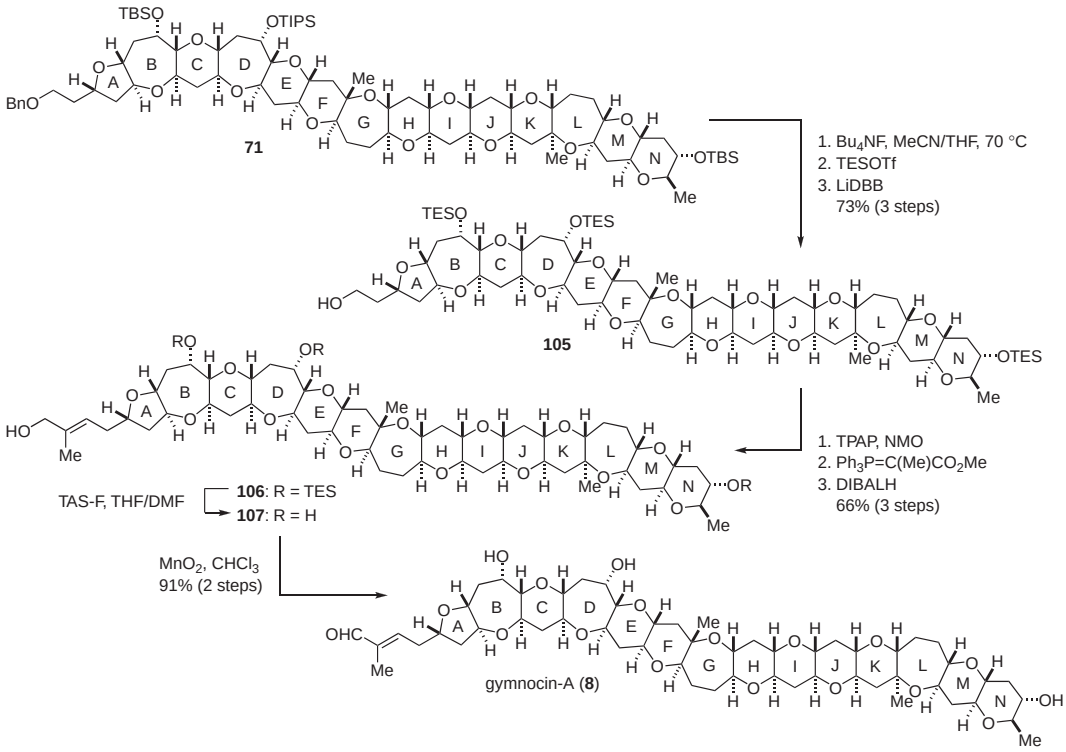


Fig. 19. Completion of the total synthesis of gymnocin-A.

the side chain as the corresponding ester, and subsequent DIBALH reduction gave allylic alcohol **106**. Finally, removal of the TES groups with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F)[70] followed by chemoselective oxidation of the allylic alcohol with MnO_2 completed the total synthesis of gymnocin-A (**8**). The synthetic gymnocin-A was identical to the natural sample by ^{1}H and ^{13}C NMR and MS spectra, thus confirming the structure of gymnocin-A.

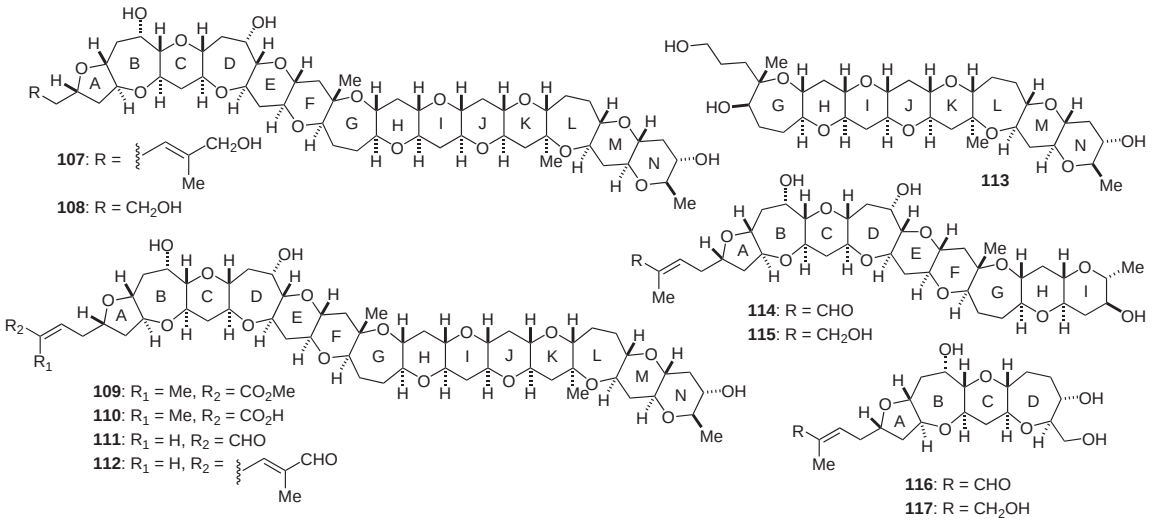


Fig. 20. Structures of synthetic analogues of gymnocin-A.

Table 4. Cytotoxicity of Gymnocin-A (**8**) and Synthetic Analogues (**107**–**117**) against P388 Murine Leukemia Cells

Compounds	Cytotoxicity $IC_{50}/\mu M$
8	1.3
107	>100
108	>100
109	>100
110	>10
111	1.0
112	2.9
113	>100
114	>100
115	>100
116	>100
117	>100

3.5 Structure–Activity Relationship Studies on Gymnocin-A.[24b,71] After the completion of the total synthesis, we focused our attention on elucidation of the structural elements required for cytotoxicity of gymnocin-A. Our convergent synthesis of gymnocin-A employing three fragments of equal complexity (**72**, **74**, and **75**) is well-suited for the preparation of numerous analogues with modified side chain and molecular length for detailed SAR studies. A series of structural analogues (**107**–**117**, Fig. 20) of gymnocin-A was synthesized, and their cytotoxicity against the P388 murine leukemia cells was evaluated using the XTT assay.[72] The results are summarized in Table 4. Among analogues examined, α,β-unsaturated aldehydes **111** and **112** alone exhibited cytotoxicity comparable to that of the natural gymnocin-A. These results clearly indicated that the α,β-unsaturated aldehyde functionality is crucial for its cytotoxicity. This is probably due to nucleophilic addition of biological macromolecules to a reactive electrophile center. In addition, nonacyclic analogue **114** somewhat decreased proliferation of P388 cells at 100 μM, whereas other truncated analogues **115**–**117** showed no detectable cytotoxicity even at 100 μM. Consequently, the molecular length was also important for exhibiting cytotoxicity.

4. Conclusion

We demonstrated that cyclic ketene acetal triflates or phosphates undergo palladium-catalyzed Suzuki–Miyaura cross-coupling reaction with alkylboranes, derived from exocyclic enol ethers. This variant of the Suzuki–Miyaura coupling reaction combined with reductive ring-closure process was successfully applied to the development of a convergent strategy for the synthesis of trans-fused polycyclic ether system. Using this strategy, the first total synthesis of gambierol and gymnocin-A was accomplished. These syntheses proved that the synthetic strategy that we developed is one of the most general and reliable complex fragment-coupling processes in polycyclic ether synthesis. In view of the high convergence, our synthetic strategy allows for the preparation of a diverse set of structural analogues of these natural products in order to clarify the structure–activity relationship profiles. We hope that chemical synthesis of these fascinating natural and unnatural polycyclic ether molecules will open the way for elucidating their biological functions and molecular mechanism of action.

I would like to express my sincere appreciation to all the coworkers, whose names are cited in the references, for their valuable contribution. This work was financially supported in part by a research grant from CREST, Japan Science and Technology Agency (JST), Suntory Institute for Bioorganic Research (SUNBOR), Nagase Science and Technology Foundation, Japan Society for the Promotion of Science (JSPS), and the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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