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# DESIGN AND SYNTHESIS OF ARTIFICIAL LADDER-SHAPED POLYETHERS FOR EXPLORING BIOLOGICAL FUNCTIONS

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Dedicated to Professor Tohru Fukuyama on the occasion of his 70th birthday

**Abstract** – Ladder-shaped polyethers (LSPs) are marine natural products produced by dinoflagellates. The unique molecular structure and interesting biological activities have attracted considerable attention of the synthetic community. On the other hand, artificial ladder-shaped polyethers (ALPs) have been designed and synthesized for exploring biological functions. In this review, design and synthesis of ALPs are summarized focusing on the development of synthetic strategies and methodologies.

## CONTENTS

## 1. INTRODUCTION

Ladder-shaped polyethers (LSPs) are secondary metabolites produced by marine unicellular algae called dinoflagellates, and more than fifty LSPs including its congeners have been identified to date.[1] The first example of LSP named as brevetoxin B (**1**) and its congener brevetoxin A (**2**) were discovered in association with 'red tide' from the causative dinoflagellate *Karenia brevis* (Figure 1).[2] Brevetoxins are potent neurotoxic compounds, and are known to bind to voltage-sensitive sodium channels (VSSCs) in the nerve system.[3] In association with ciguatera seafood poisoning, ciguatoxin CTX1B (**3**) was isolated from the moray eels *Gymnothorax javanicus*,[4] and CTX3C (**4**) was produced by the causative dinoflagellate *Gambierdiscus toxicus*.[5] Ciguatoxins are also known to bind to VSSCs and share a common binding site on an α subunit with very high affinity in the nanomolar-subnanomolar range. On the other hand, Caribbean ciguatoxin C-CTX-1 (**5**) was isolated from *Caranx latus* living in Caribbean Sea.[6]

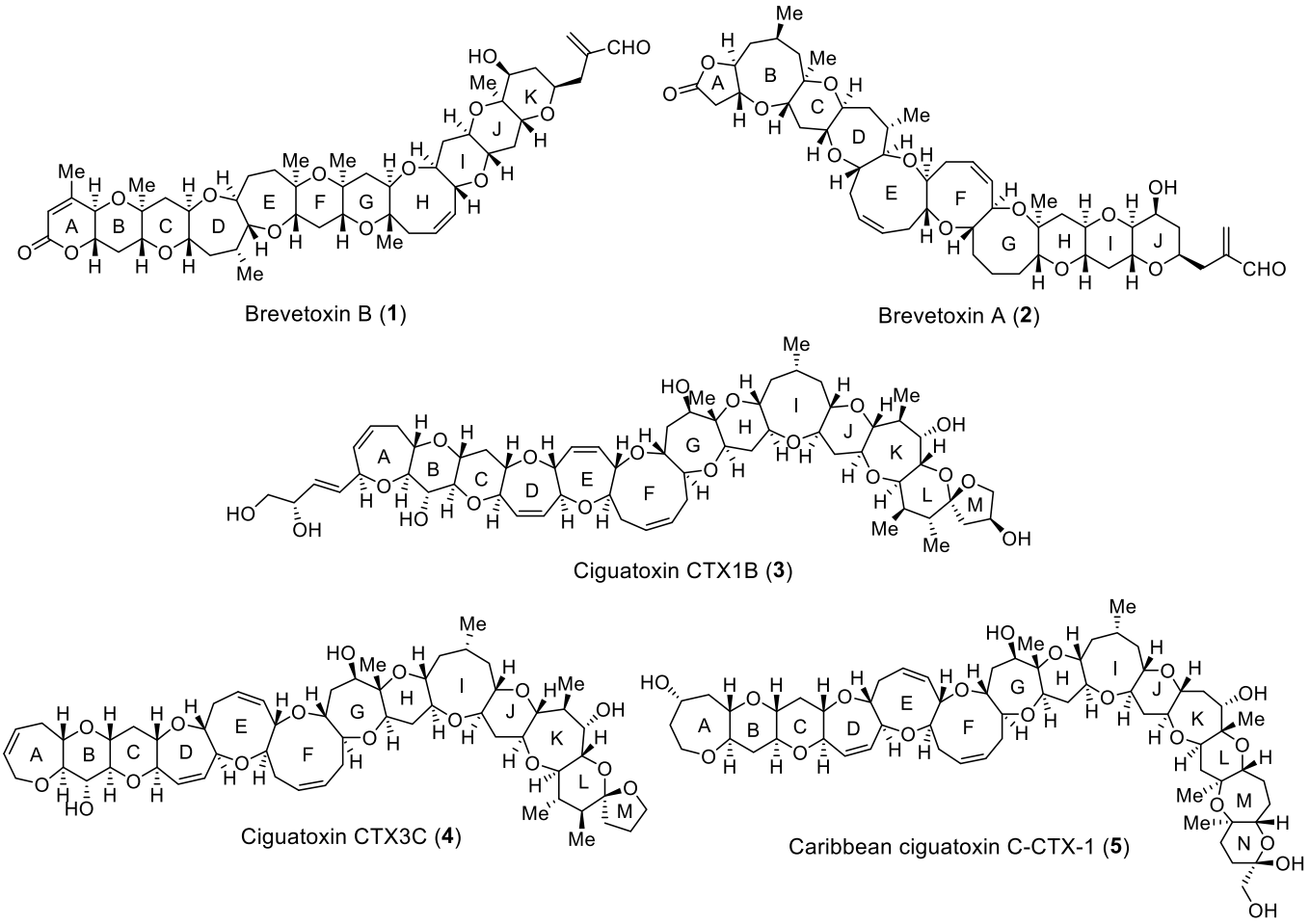



**Figure 1.** Structures of naturally occurring LSPs (Part 1)

Gambieric acid-A (**6**) was isolated from the dinoflagellate *Gambierdiscus toxicus* as a potent antifungal (Figure 2),[7] but it is not a neurotoxic compound. In association with shellfish poisoning, yessotoxin (**7**) was isolated from scallops but the origin is the dinoflagellate *Protoceratium reticulatum*.[8] In contrast to brevetoxins and ciguatoxins, yessotoxin does not bind VSSCs, but induces apoptosis via a mitochondrial signal transduction pathway.[9] Gymnocin-A (**8**)[10] and gymnocin-B (**9**)[11] were isolated from *Karenia mikimotoi*, which elicit cytotoxicity against P388 mouse leukemia cells.

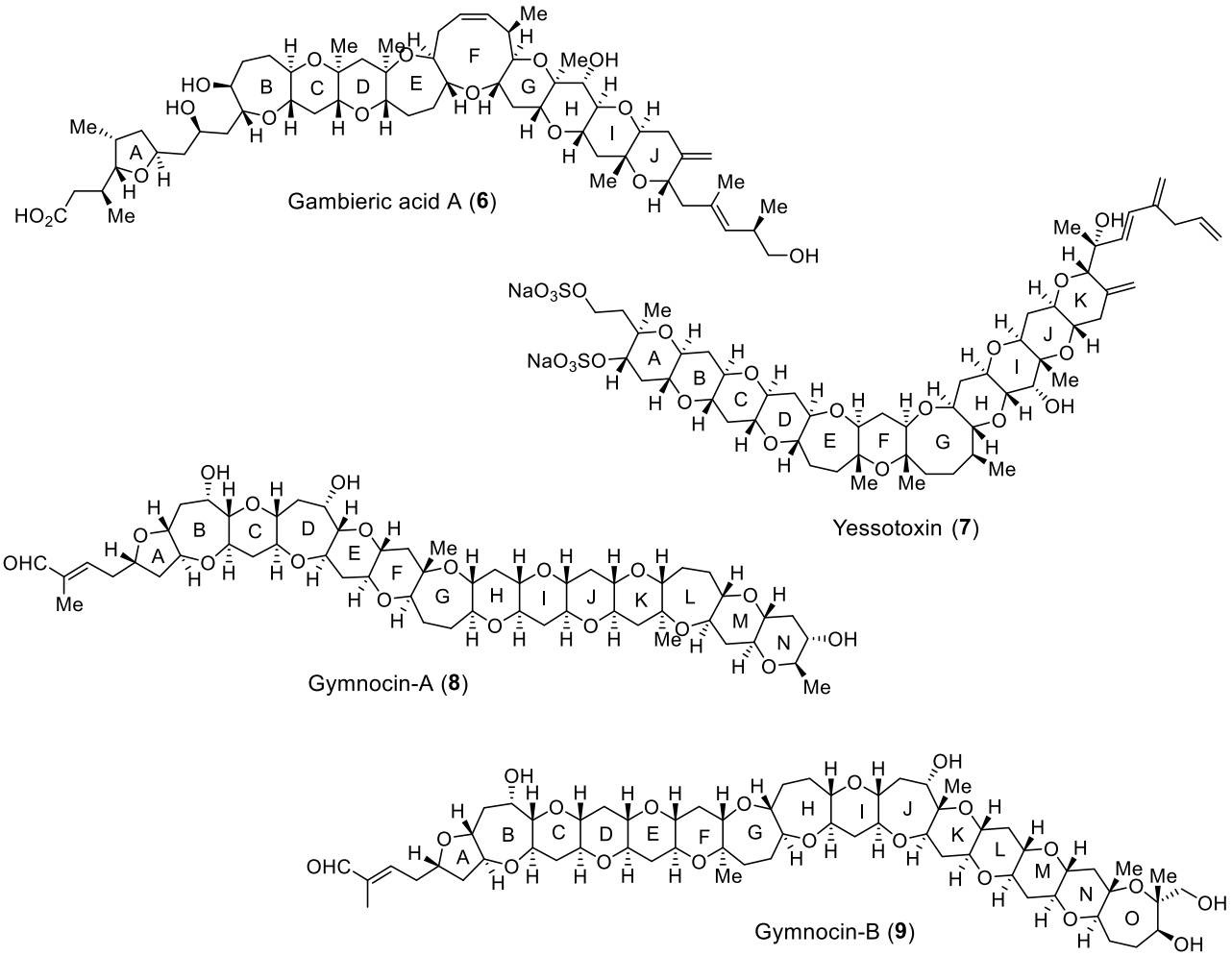



**Figure 2.** Structures of naturally occurring LSPs (Part 2)

On the other hand, LSPs comprised of shorter molecular length were also isolated (Figure 3). Gambierol (**10**) was isolated from the dinoflagellate *Gambierdiscus toxicus*.[12] The dinoflagellate *Karenia brevis* also produces a different type of LSPs; tamulamide A (**11**),[13] brevenal (**12**),[14] and hemibrevetoxin-B (**13**).[15] Brevisin (**14**) is comprised of linked two tricyclic ether systems.[16] Brevisamide (**15**) is comprised of monocyclic ether. It is suggested that a brevisamide like precursor lacking nitrogen could serve as the initiating unit in a cascade process leading to the formation of other polyethers.[17]

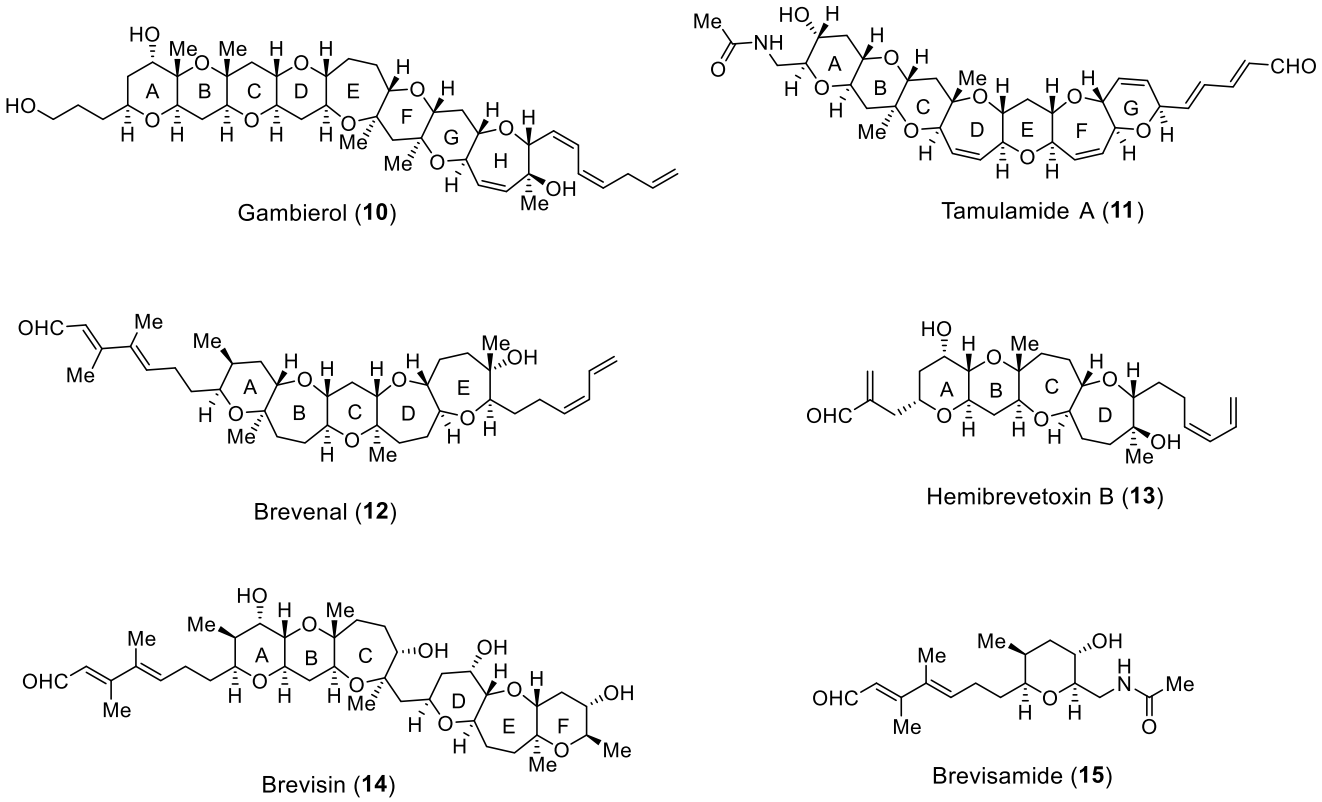



**Figure 3.** Structures of naturally occurring LSPs (Part 3)

On the other hand, LSPs possessing extreme long carbon framework were also isolated (Figure 4). Brevisulcenal-F (**16**) was isolated from the dinoflagellate *Karenia brevisulcata* in association with red tide causing massive fish-kills in Wellington Harbour, New Zealand.[18] The molecular weight of brevisulcenal-F is over 2,000. Among the LSPs whose structures were elucidated, maitotoxin (**17**) is the largest,[19] the molecular weight exceeds 3,000. Maitotoxin is different in the following points; it is comprised of hydrophobic part (the P-F'ring system) and hydrophilic part (the A-O ring system), and it induces $Ca^{2+}$ influx at extremely low concentration (0.3 nM).[20]

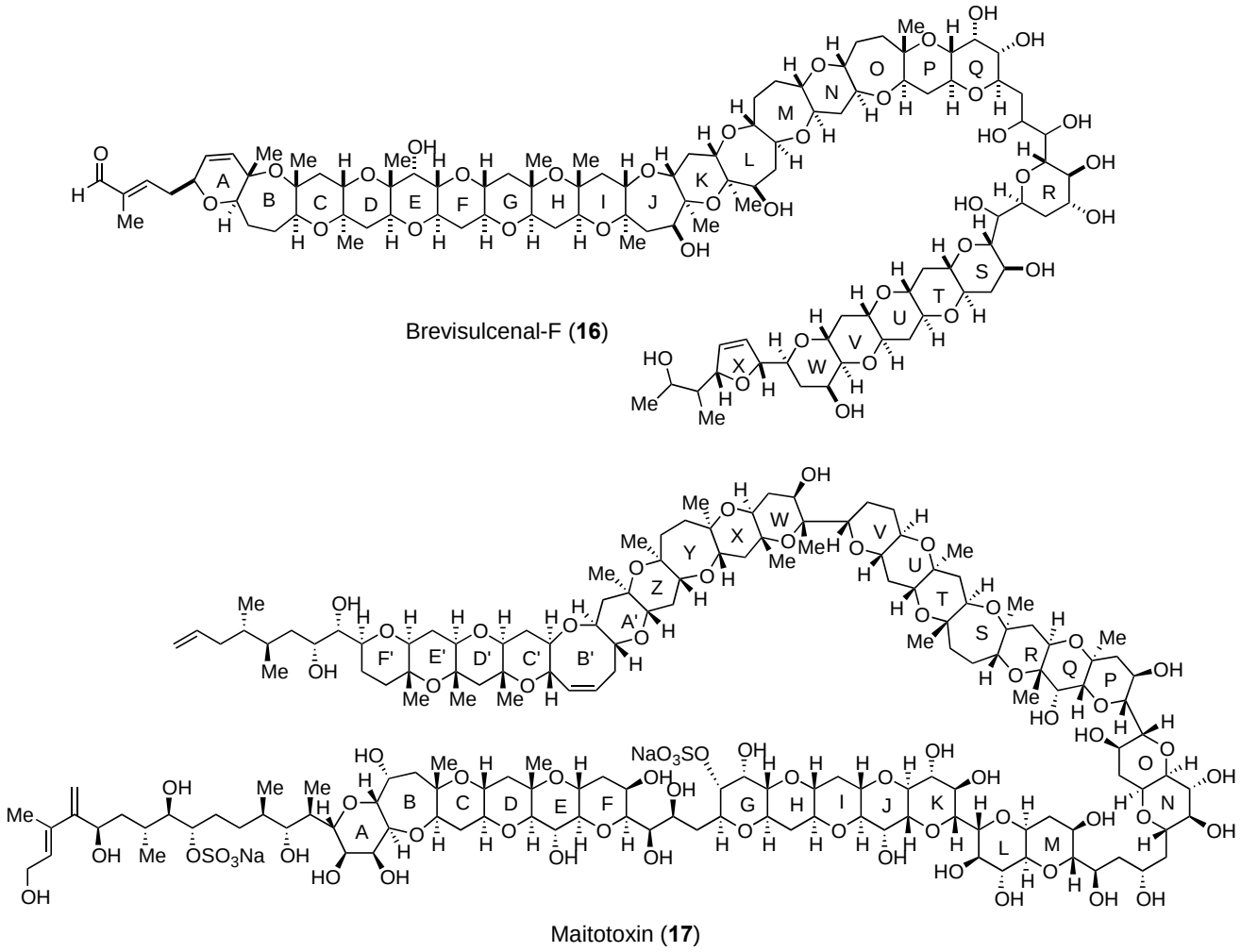



**Figure 4.** Structures of naturally occurring LSPs (Part 4)

Some of the targets proteins of LSPs have been identified, i. e. brevetoxins and ciguatoxins are known to bind to VSSC (vide supra), and gambierol is a selective inhibitor of the voltage-gated $K^+$ channels.[21] However, mode-of-action studies of LSPs have been hampered because of scarcity from natural sources. Therefore, total synthesis of the LSPs should be crucial to solve the problem, and remarkable progress has been made in the last two decades, which are summarized in excellent reviews.[22]

By using the methods for total synthesis of LSPs, syntheses of analogs of LSPs for structure-activity relationship studies have been reported. Nicolaou et al. reported the first example of design and synthesis of LSP (Figure 5),[23] an artificial truncated analog of brevetoxin B corresponding to the AFGHIJ-ring (**18**). However, biological studies with **18** revealed no binding to the brevetoxin B receptor, suggesting the importance of the molecular length.

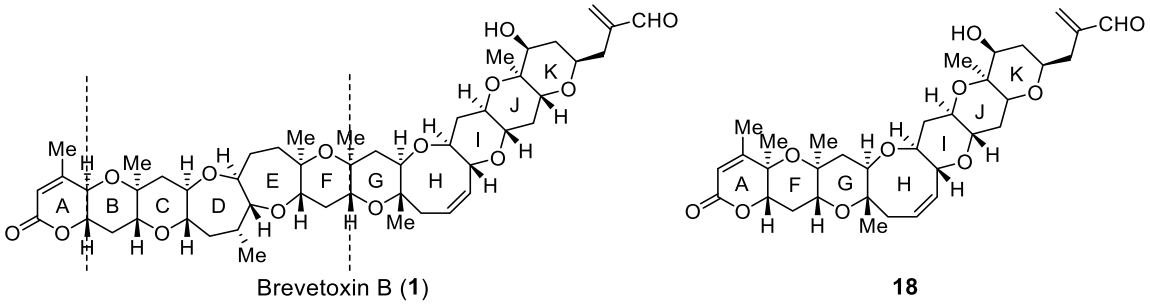



**Figure 5.** Structures of brevetoxin B (**1**) and its truncated analog corresponding to the AFGHIJK ring (**18**)

Hirama et al. reported design and synthesis of artificial analogs of 51-hydroxyCTX3C (**19**) with respect to the F-ring in order to estimate the importance on the biological activity (Figure 6).[24] The original nine-membered F-ring was changed to eight-membered ring (**20**) and open chain diene (**21**), respectively, and it was found that the nine-membered F-ring plays important role to elicit biological activities.

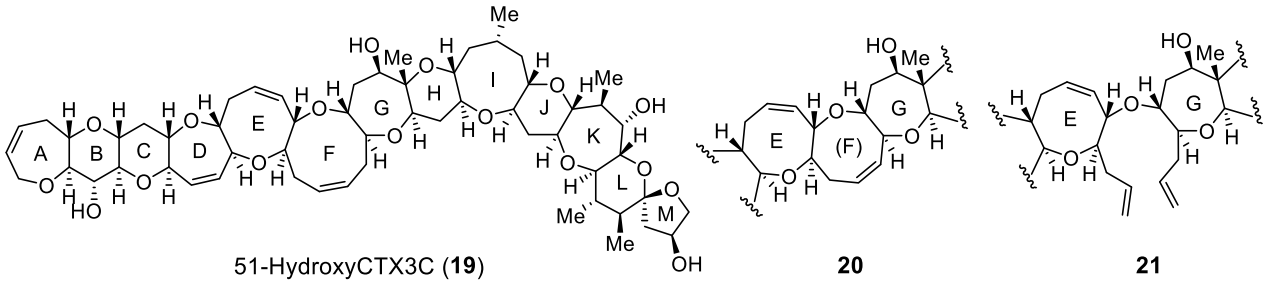



**Figure 6.** Structures of 51-hydroxyCTX3C (**19**), and its analogs with respect to the F ring, the eight-membered analog (**20**) and the open-chain analog (**21**)

As a part of the structure-activity relationship studies of gambierol (**10**), Sasaki et al. reported design and synthesis of artificial analogs, the heptacyclic (**22**) and tetracyclic (**23**) ethers corresponding to the BCDEFGH- and EFGH-ring system, respectively (Figure 7).[25] These compounds **22** and **23** inhibited voltage-gated potassium channel with similar potency as **10**.

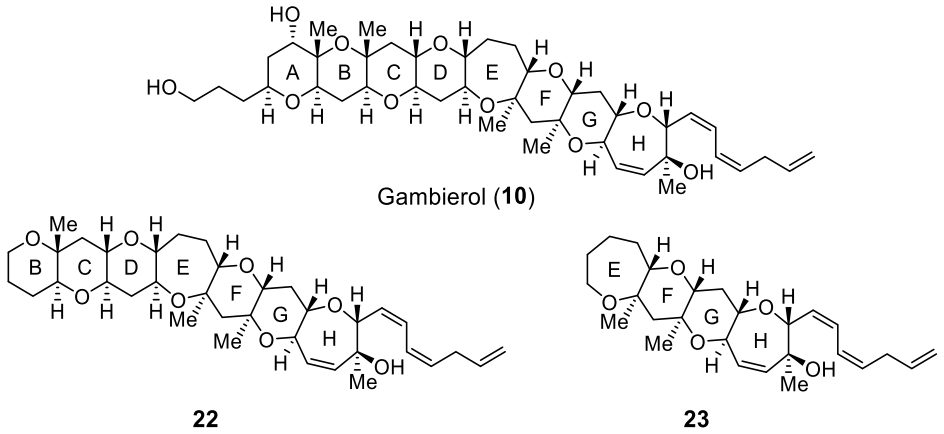



**Figure 7.** Structures of gambierol (**10**), and its analogs corresponding to the BCDEFGH-ring (**22**) and the EFGH-ring (**23**)

LSPs possess the general structural motif of continuous *trans/syn*-fused ether rings (Figure 8, left), and the structural diversity of LSPs are attributed to various combinations of the number and sizes of cyclic ethers ranging from five- to nine-membered rings, and the order of the ring connection. The targets proteins of brevetoxins, ciguatoxins, and gambierol are ion channels, a member of transmembrane proteins, therefore, it is suggested that membrane-integral α-helices are considered to be the interacting motif of LSPs. The distance between the neighboring skeletal oxygen atoms on the same side of the LSPs is consistent with the helix pitch around 5 Å (Figure 8, right), therefore, it is suggested that the oxygen atoms act as hydrogen bond acceptors to interact with membrane-integral α-helices.

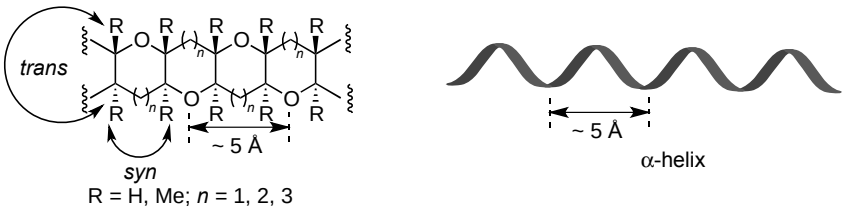


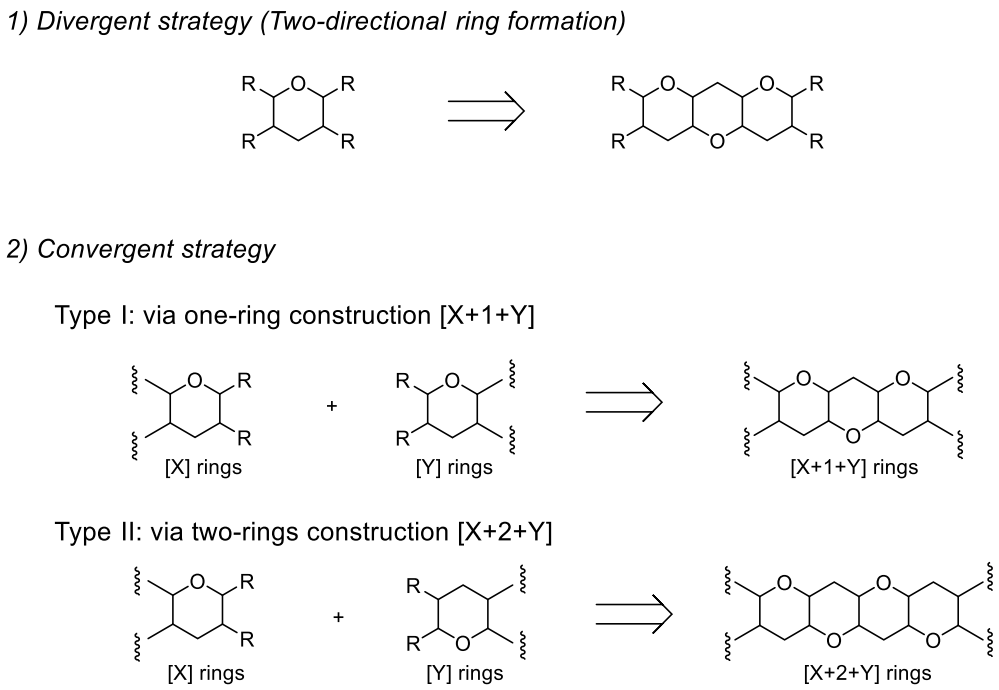

**Figure 8.** General structural feature of LSPs and α-helix

Inoue et al. reported interesting results that binding of PbTx-3 (a brevetoxin-B derivative) to VSSCs was competitively inhibited by the addition of not only brevetoxin B and ciguatoxin CTX1B (target proteins are VSSCs), but also gambieric acid-A and gambierol (target proteins are not VSSCs), while their affinities are $10^4$~$10^6$ times lower than that of ciguatoxin CTX1B.[26] These results suggest that gambieric acid-A and gambierol competitively bind to the identical receptor site, and presumably membrane-integral α-helices are common structural motif to interact with LSPs. However, the limited availability from natural sources and structural variety of LSPs, i.e. length of the molecule, combination

of the array and size of the ether rings, and structures of the side chains, have been obstacles for quantitative structure-activity relationship studies. In order to solve the problems, it is necessary to prepare model compounds as molecular probes by chemical synthesis.

This review describe the design and synthesis of artificial ladder-shaped polyethers (ALPs) for exploring biological functions, mainly focused on the synthetic strategy. These ALPs, but not all, were used as molecular probes to evaluate the biological activity and the interaction with membrane-integral α-helices.

There are two different strategies for synthesizing ALPs as shown in Scheme 1; 1) divergent strategy (two-directional ring formation), and 2) convergent strategy. The convergent strategy is categorized into type I: two fragments [X] and [Y] are combined via one-ring construction [X+1+Y], and type II: via two-rings construction [X+2+Y].




**Scheme 1.** Strategies for synthesizing ALPs

## 2. TWO-DIRECTIONAL DIVERGENT STRATEGY: DOUBLE ALLYLATION AND RING CLOSING METATHESIS

In 2002, Martin et al. reported design and synthesis of ALPs possessing symmetrical structures (*meso* compounds).[27] The 6/7/7/7/6-pentacyclic ALP (**24a**) and the 6/7/7/7/7/7/6-heptacyclic ALP (**24b**) were designed (Figure 9). These compounds expected to possess conformational flexibility because of the presence of oxepane ring system. They developed two-directional divergent strategy (Scheme 2).

Intramolecular double allylation of bis-aldehyde **A** giving **B**, followed by double alkylation to furnish tetraene **C**, and double ring closing metathesis (RCM)[28] afforded **D**. Related two-directional divergent strategies have been reported by Clark et al. based on RCM,[29] and by Nakata et al. based on $SmI_2$-induced cyclization.[30]

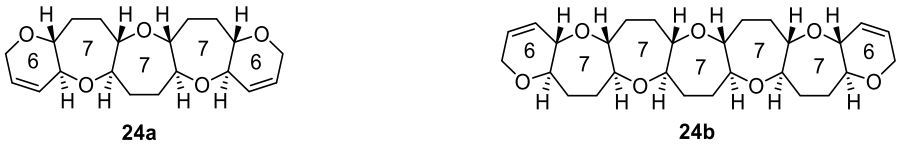
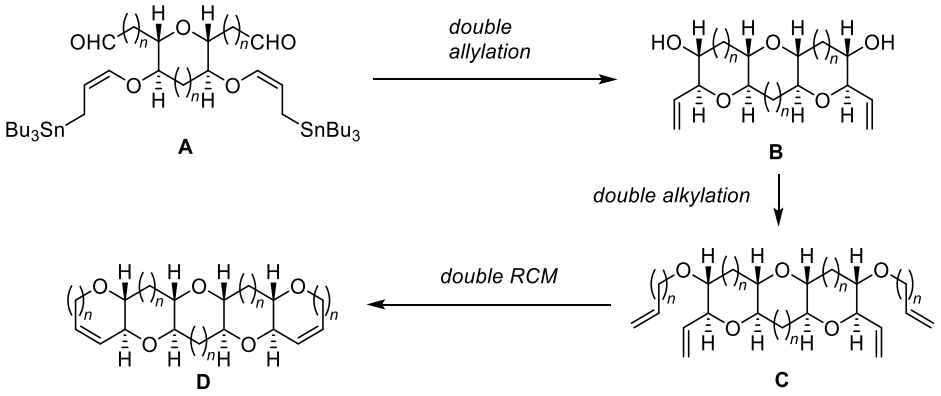


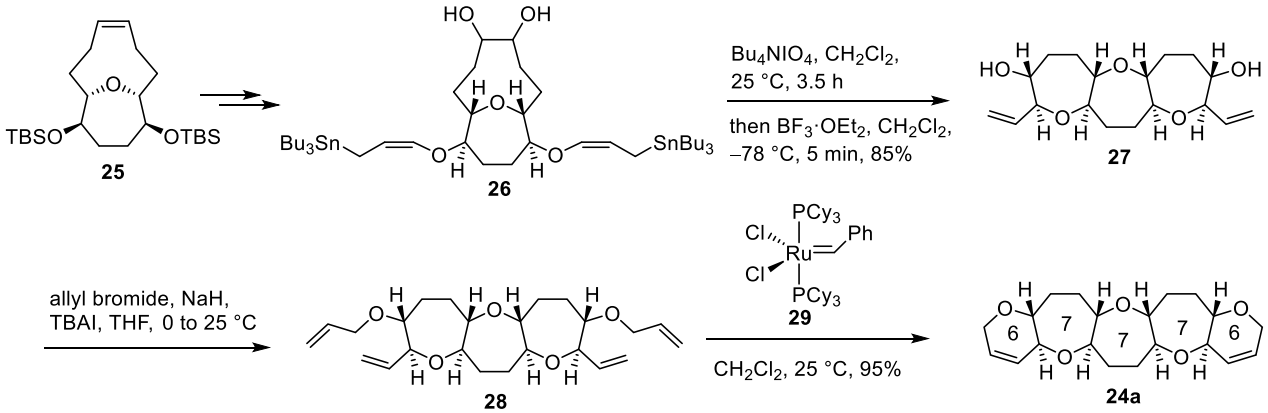

**Figure 9.** Design of the 6/7/7/7/6-pentacyclic and 6/7/7/7/7/7/6-heptacyclic ALPs (**24a** and **24b**)




**Scheme 2.** Two-directional divergent strategy via double allylation and RCM

Synthesis of the 6/7/7/7/6-pentacyclic ALP (**24a**) is shown in Scheme 3. The bis-allylstannane **26** was prepared form bicyclic compound **25**.[31] Cleavage of the *vic*-diol **20** with periodate resulted in the formation of bis-aldehyde, which was treated with $BF_3{\cdot}OEt_2$ to afford **27** via double allylation. The resulting diol was converted to bis-allyl ether **28**, and subsequent double RCM with Grubbs I catalyst **29** proceeded to afford **24a**. On the other hand, precise procedure to synthesize **24b** was unpublished.

Martin et al. evaluated biological activities of the ALPs **24a** and **24b** by using uterine strips in which VSSCs were cloned. Both **24a** and **24b** did not induce any significant contractile effect at 1 nM ~1 μM, while brevetoxin B (**1**) elicited rhythmic contractions at 30 nM. Although inhibitory effects on rhythmic contractions induced by **1** were also evaluated, both **24a** and **24b** inhibited neither the frequency nor the amplitude, suggesting that no binding of these ALPs to the receptor site of **1**.




**Scheme 3.** Synthesis of the 6/7/7/7/6-pentacyclic ALP (**24a**)

## 3. CONVERGENT STRATEGY VIA ONE-RING CONSTRUCTION: [X+1+Y]

3-1. Reductive Aldol/Reductive Etherification

Oguri, Hirama et al. designed the 6/6/6/6/6-pentacyclic ALP possessing hydroxy groups (**30**) as a template for molecular recognition with transmembrane α-helices (Figure 10),[32] because distance between skeletal oxygen atoms on the same side (4.8 Å) in the ALP is almost identical to the interval between side-chains in the α-helical peptides (ca. 5 Å). For the iterative synthesis of the 6/6/6/6/6-pentacyclic system, $SmI_2$-mediated reductive aldol reaction was used for coupling of the fragments **A** and **B**, and the resulting ketone **C** was converted to **D** via reductive etherification (Scheme 4).

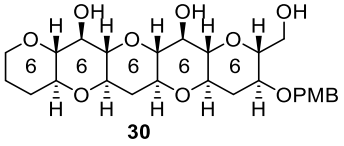
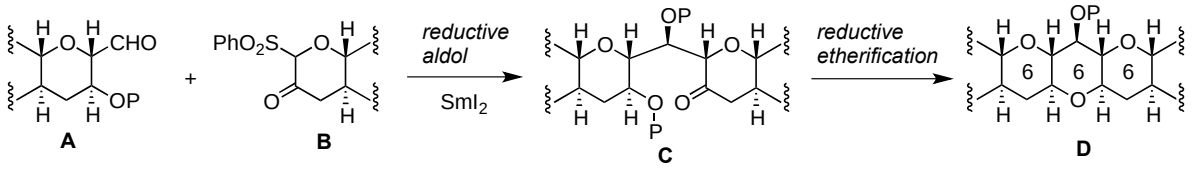


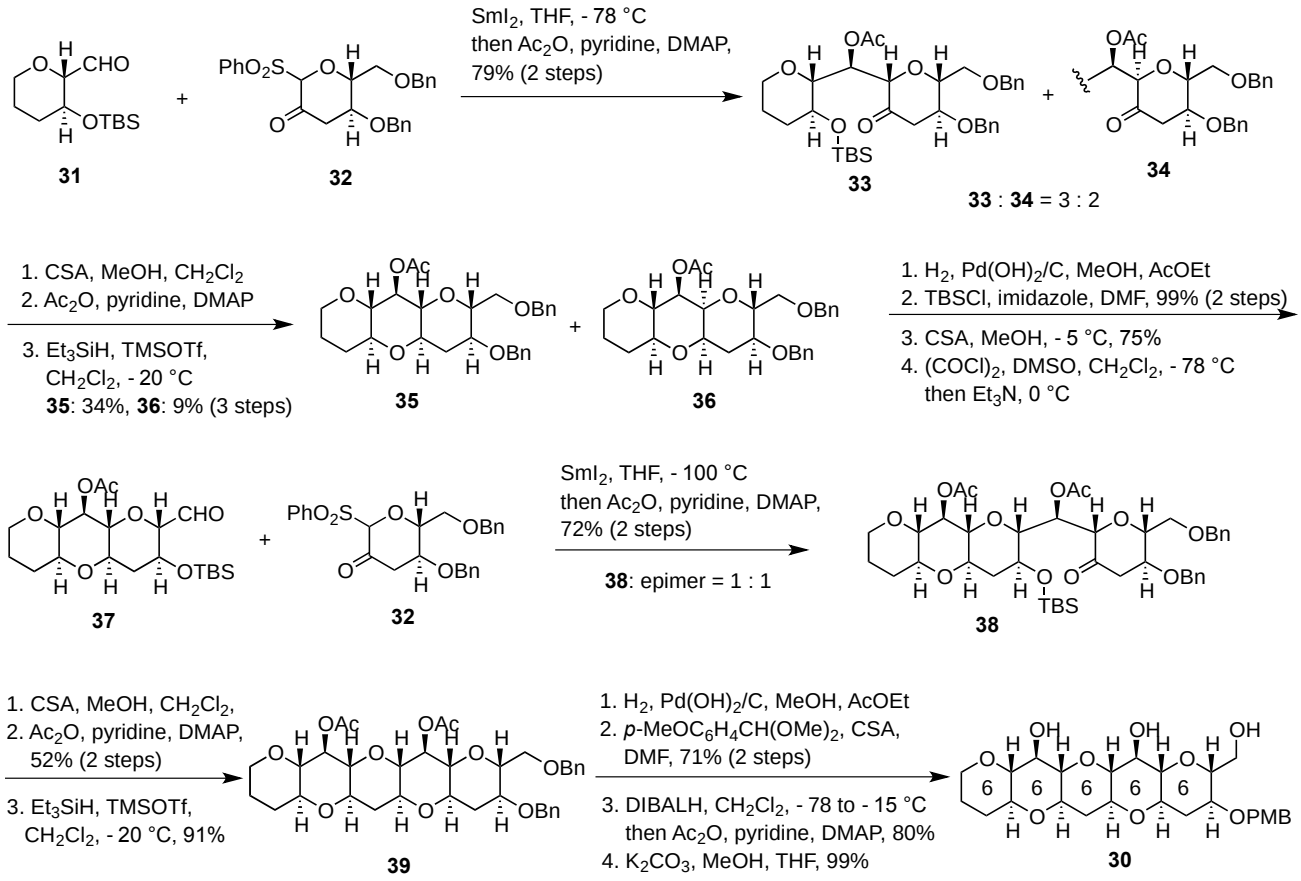

**Figure 10.** Design of the 6/6/6/6/6-pentacyclic ALP (**30**)




**Scheme 4.** Convergent strategy via reductive aldol and reductive etherification

Synthesis of the 6/6/6/6/6-pentacyclic ALP (**30**) is shown in Scheme 5. Sulfonyl ketone **32** was treated with $SmI_2$ to generate samarium enolate, which was coupled with aldehyde **31** to afford a mixture of **33** and epimer **34** in a 3 : 2 ratio. Removal of the TBS group with concomitant formation of methyl acetal,

followed by reductive etherification with $Et_3SiH$/TMSOTf afforded cyclized product **35** (34%) and epimer **36** (9%) for three steps. Protecting group manipulation of **35** and oxidation of the resulting primary alcohol gave aldehyde **37**, which was subjected second reductive aldol reaction with **32** to furnish **38** and its epimer at Cα of the ketone in a 1 : 1 ratio. Removal of the TBS group and concomitant formation of methyl acetal, followed by reductive etherification with $Et_3SiH$/TMSOTf afforded cyclized product **39**. Protecting group manipulation of **39** furnished triol **30**. Evaluation of biological activity of **30** has not been reported yet.




**Scheme 5.** Synthesis of the 6/6/6/6/6-pentacyclic ALP (**30**)

3-2. Suzuki-Miyaura Coupling/Reductive Etherification

Tachibana et al. reported design and synthesis of the 6/7/6/6/7-pentacyclic ALP (**40a**) and the 6/7/6/7/7-pentacyclic ALP (**40b**) (Figure 11),[33] because the importance of continuous oxepane rings of brevetoxin B was reported.[34] For the synthesis of the pentacyclic ALPs, the strategy based on Suzuki-Miyaura coupling[35] developed by Sasaki et al. was utilized (Scheme 6).[36] Hydroboration of the *exo*-enol ether **A** gave alkylborane **B**, which was coupled with enol triflate or enol phosphate **C** by the action of a palladium catalyst to afford enol ether **D**. Hydroboration/oxidation followed by reductive

etherification afforded tetracyclic system **E**. Based on this strategy, total syntheses of natural LSPs, brevenal,[37] gambierol,[38] gymnocin-A[39] and gambieric acid-A,[40] have been achieved by Sasaki et al.

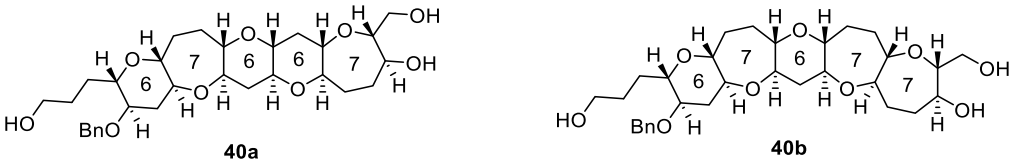
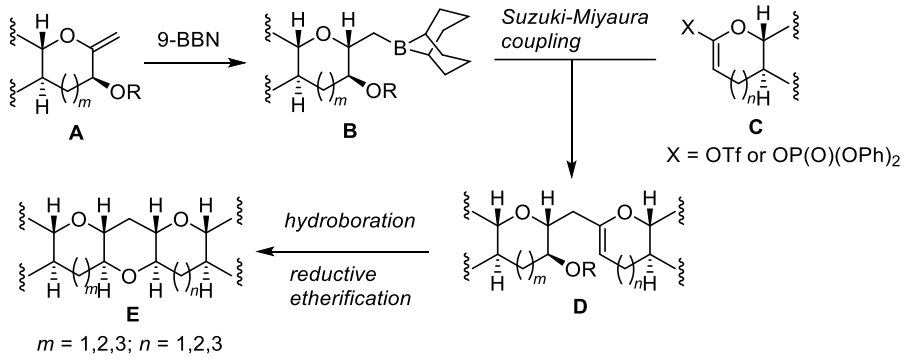


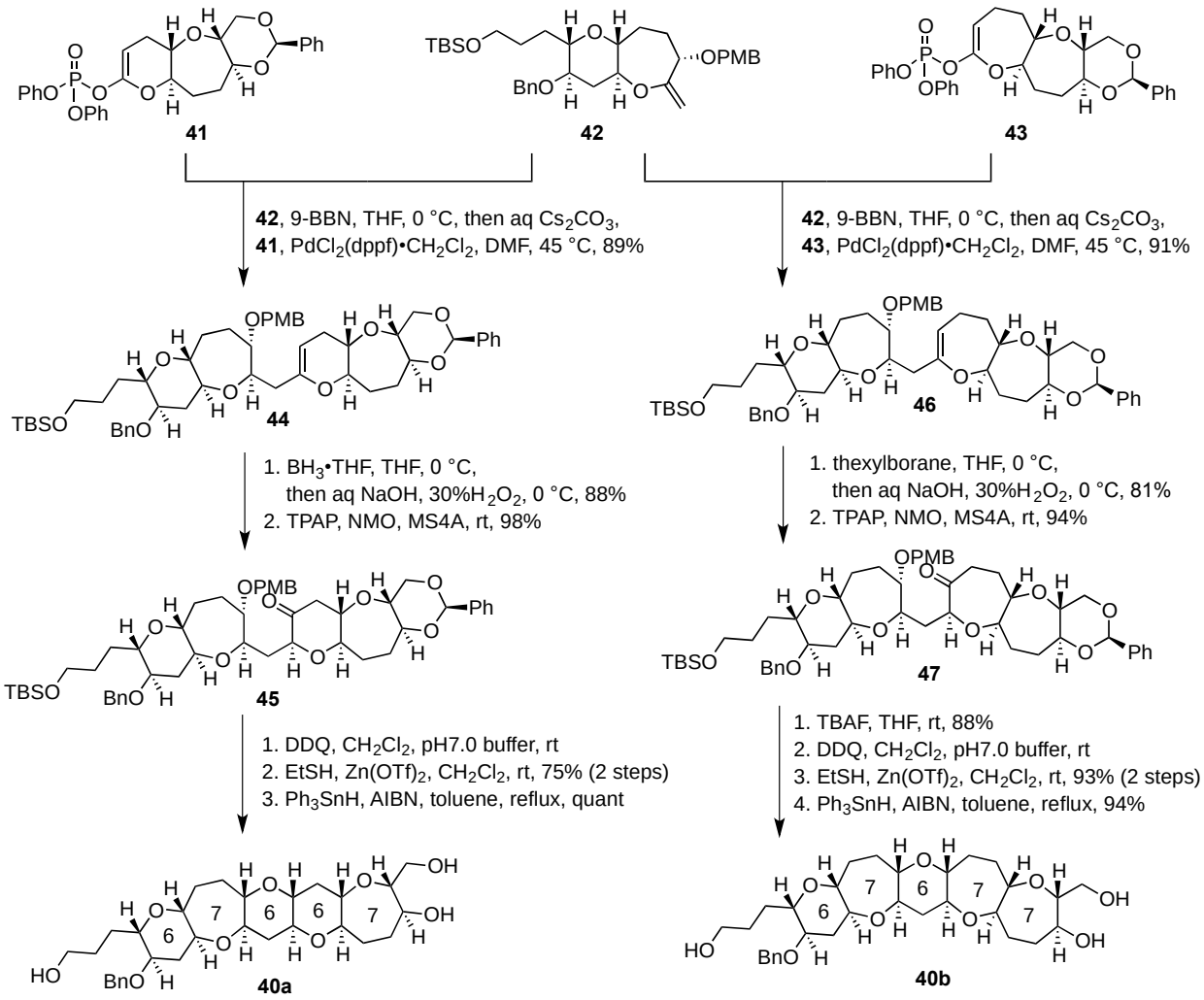

**Figure 11.** Design of the 6/7/6/6/7- and 6/7/6/7/7-pentacyclic ALPs (**40a** and **40b**)




**Scheme 6.** Convergent strategy via Suzuki-Miyaura coupling/reductive etherification

Synthesis of the 6/7/6/6/7- and 6/7/6/7/7-pentacyclic ALPs (**40a** and **40b**) is shown in Scheme 7. Hydroboration of enol ether **42** with 9-BBN, followed by coupling with enol phosphate **41** in the presence of $PdCl_2(dppf)\cdot CH_2Cl_2$ afforded coupling product **44**. Hydoboration/oxidation sequence giving keone **45**, which was converted to *S*,*O*-acetal and radical reduction furnished the 6/7/6/6/7-pentacyclic ALP **40a**. In an analogous sequence, the 6/7/6/7/7-pentacyclic ALP **40b** was synthesized via Suzuki-Miyaura coupling of **42** with enol phosphate **43** to afford **46**, hydroboration/oxidation giving **47**, and *S*,*O*-acetal formation/radical reduction.

Tachibana et al. evaluated interaction of the ALPs (**40a** and **40b**) with α-helical peptide, melittin (the principal venom component of European honey bee), by circular dichroism (CD) spectroscopy. Interestingly, only the 6/7/6/7/7-pentacyclic ALP (**40b**), not the 6/7/6/6/7-pentacyclic ALP (**40a**), stabilized the α-helical structure of melittin. These results suggested that a ring fusion pattern of the polycyclic structure is important to recognize membrane proteins.




**Scheme 7.** Synthesis of the 6/7/6/6/7- and 6/7/6/7/7-pentacyclic ALPs (**40a** and **40b**)

## 4. CONVERGENT STRATEGY VIA TWO-RINGS CONSTRUCTION: [X+2+Y]

4-1. Aldehyde-Alkyne Coupling/Alkyne Oxidation/Reductive Etherification

Oguri, Hirama et al. designed the 6/6/6/6-tetracyclic ALP (**48**) equipped with guanidium groups (Figure 12).[41] This model compound was designed as a template for elucidating interaction of the guanidium groups with the aspartate residues in the α-helical peptides.

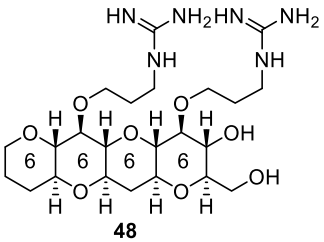
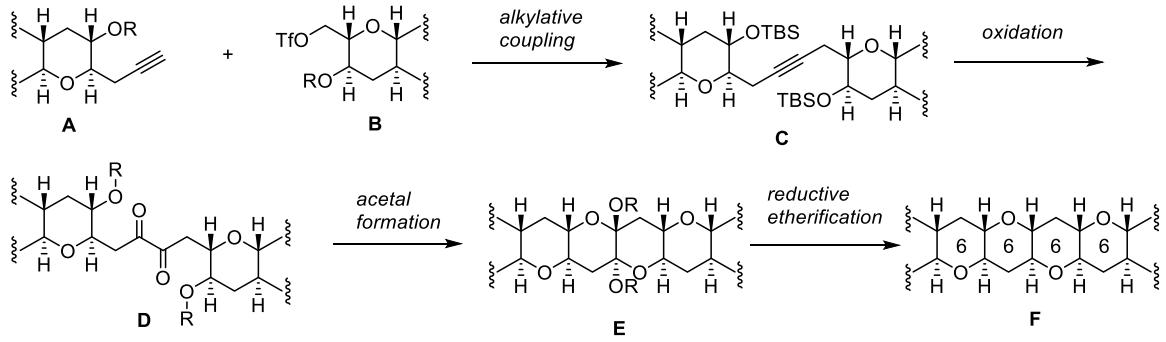


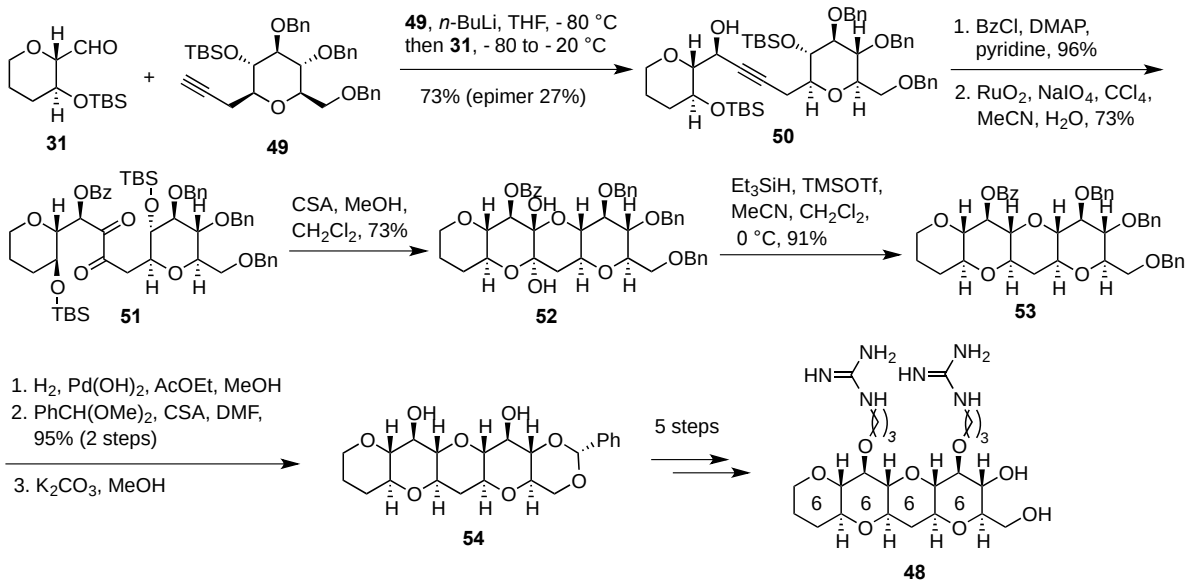

**Figure 12.** Design of the 6/6/6/6-tetracyclic ALP (**48**)

For the construction of the 6/6/6/6-tetracyclic ether system, Nakata, Mori, and Fujiwara et al. developed a convergent strategy via coupling of an acetylide and a triflate, independently (Scheme 8).[42] Coupling of acetylide **A** and triflate **B** gave alkyne **C**, which was oxidized to α-diketone **D**. Conversion to the 6/6/6/6-tetracyclic ether **F** was achieved via methyl acetal formation giving **E** followed by reductive etherification.




**Scheme 8.** Convergent strategy for synthesizing the 6/6/6/6-tetracyclic ether system via alkylative coupling, alkyne oxidation, and reductive etherification

Oguri, Hirama et al. modified the method for coupling of aldehyde **31** instead of a triflate (Scheme 9). Lithium acetylide derived from **49** with *n*-BuLi was coupled with aldehyde **31** to afford propargylic alcohol **50**. After protection of the hydroxy group of **50** as its benzoate, the alkyne was oxidized to α-diketone **51**, which was converted to the 6/6/6/6-tetracyclic system **53** via formation of bis-hemiacetal **52** followed by reductive etherification. Protecting group manipulation of **53** gave **54**, which was converted to **48** in five steps.

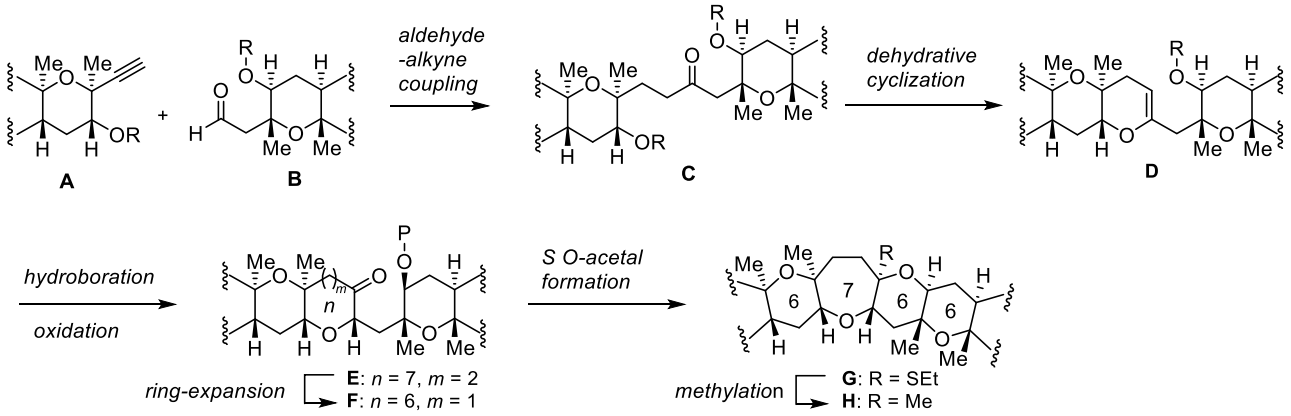



**Scheme 9.** Synthesis of the 6/6/6/6-tetracyclic ALP (**48**)

Oguri et al. evaluated the interaction between the 6/6/6/6-tetracyclic ALP (**48**) equipped with two guadinium groups and α-helical peptides containing *i* + *n* (*n* = 3, 4, 5, and 11) aspartates by CD titration. They found that **48** stabilized α-helical structure of the peptide containing *i* + 4 spaced aspartate, suggesting that specific recognition might present between guanidium groups of **48** and carboxylate groups of the peptide.

4-2. Aldehyde-Alkyne Coupling/Dehydrative Cyclization/*S*,*O*-Acetal Formation

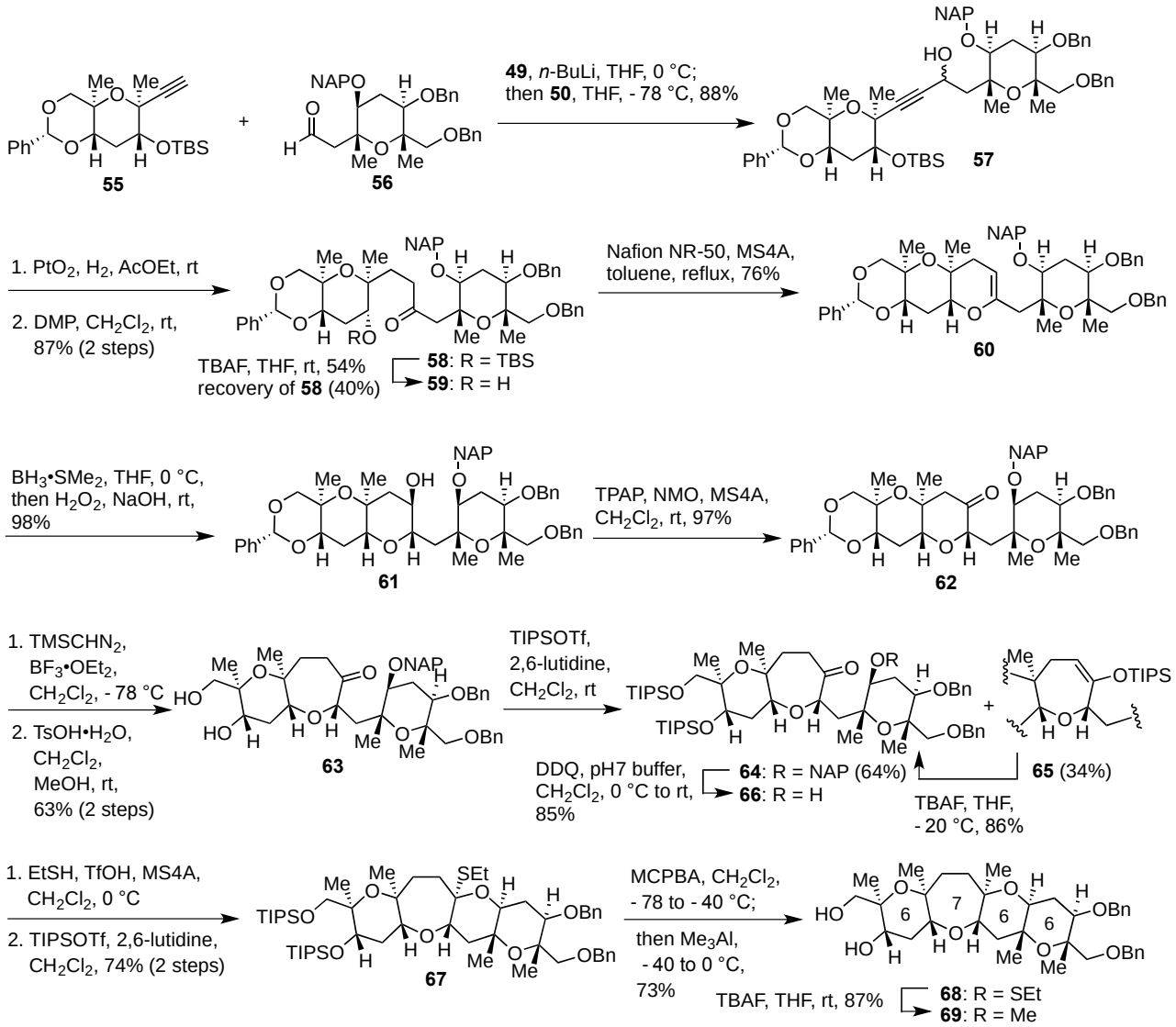
Oishi et al. reported the extension of the convergent method via aldehyde-alkyne coupling to construct 6/7/6/6-tetracyclic ether system possessing consecutive angular methyl groups (Scheme 10), because the similar ring system are found in the structures of brevisulcenal-F (**16**) and maitotoxin (**17**).[43] Coupling of aldehyde **A** and alkyne **B** followed by hydrogenation/oxidation sequence furnished ketone **C**. Dehydrative cyclization giving **D** and subsequent hydroboration/oxidation sequence gave six-membered ring ketone **E**. Ring-expansion of **E** to seven-membered ring ketone **F**, followed by *S*,*O*-acetal formation and methylation of **G** afforded 6/7/6/6-tetracyclic ether system **H**.




**Scheme 10.** Convergent method for synthesizing 6/7/6/6-tetracyclic ether system via aldehyde-alkyne coupling, dehydrative coupling, ring-expansion, and *S*,*O*-acetal formation

Synthesis of the 6/7/6/6-tetracyclic ether **69** is shown in Scheme 11. Treatment of alkyne **55** with BuLi followed by addition of aldehyde **56** gave coupling product **57**. Hydrogenation of the alkyne **57** and oxidation of the secondary alcohol furnished ketone **58**, and removal of the TBS group gave hydroxy ketone **59**. Dehydrative cyclization was achieved by treating with cation-exchange resin (Nafion NR-50) to afford dihydropyran derivative **60**. Hydroboration of **60** giving **61** and subsequent oxidation of the secondary alcohol **61** furnished ketone **62**. Ring-expansion of the six-membered ring ketone **62** to the seven-membered one was achieved by treatment with trimethylsilyldiazomethane in the presence of $BF_3 \cdot OEt_2$,[44] and subsequent hydrolysis afforded diol **63**. Protection of the resulting diol as TIPS ethers

gave **64** with concomitant formation of silyl enol ether **65**, which was recovered to form **64** by treatment with TBAF at −20 °C. After removal of the NAP group of **64** giving hydroxy ketone **66**, mixed-thioacetal **67** was obtained by treating with EtSH in the presence of TfOH. Introduction of the angular methyl group was achieved by treatment with MCPBA followed by $Me_3Al$[45] to afford **68**, and, removal of the TIPS group with TBAF furnished the 6/7/6/6-tetracyclic ether **69** corresponding to the WXYZ ring of MTX. This strategy was applied to the convergent synthesis of the HIJK ring of brevisulcenal-F.




**Scheme 11.** Synthesis of the 6/7/6/6-tetracyclic ether (**69**) possessing contiguous angular methyl groups

4-3. *S*, *O*-Acetal Formation/Radical Cyclization/Ring Closing Metathesis

Hirama et al. reported design and synthesis of 6/*n*/7/6-tetracyclic (*n* = 7, 8, 9) ALPs (**70a**~**70d**) as the initial phase of detailed structure-activity relationship studies of LSPs (Figure 13).[46] Coupling of alcohol **A** and α-chlorosulfide **B** via *S*,*O*-acetal formation followed by introduction of ß-alkoxy acrylate furnished

**C**. Stereoselective radical cyclization of **C** afforded the common intermediate **D**, which was converted to the diene **E**. RCM of the dienes afforded the 6/*n*/7/6-tetracyclic (*n* = 7, 8, 9) ALP **F**. The strategy was utilized for total synthesis of ciguatoxin CTX3C (**4**)[47] and CTX1B (**3**).[48]

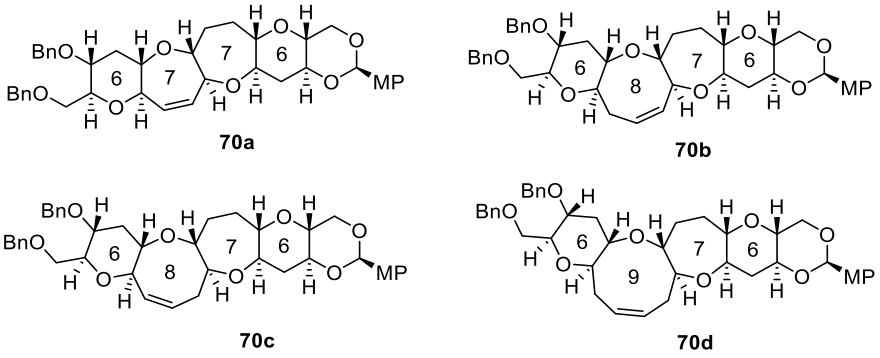
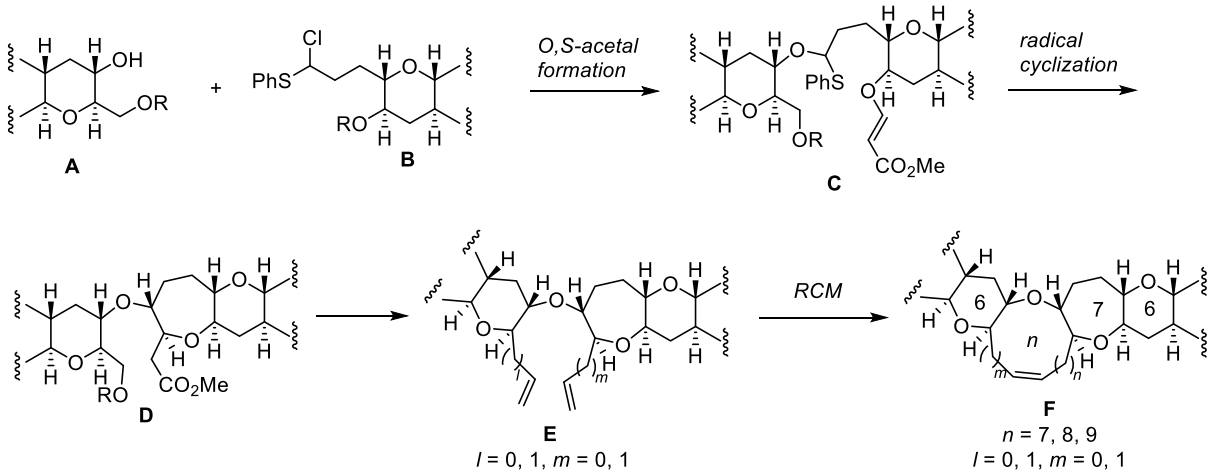
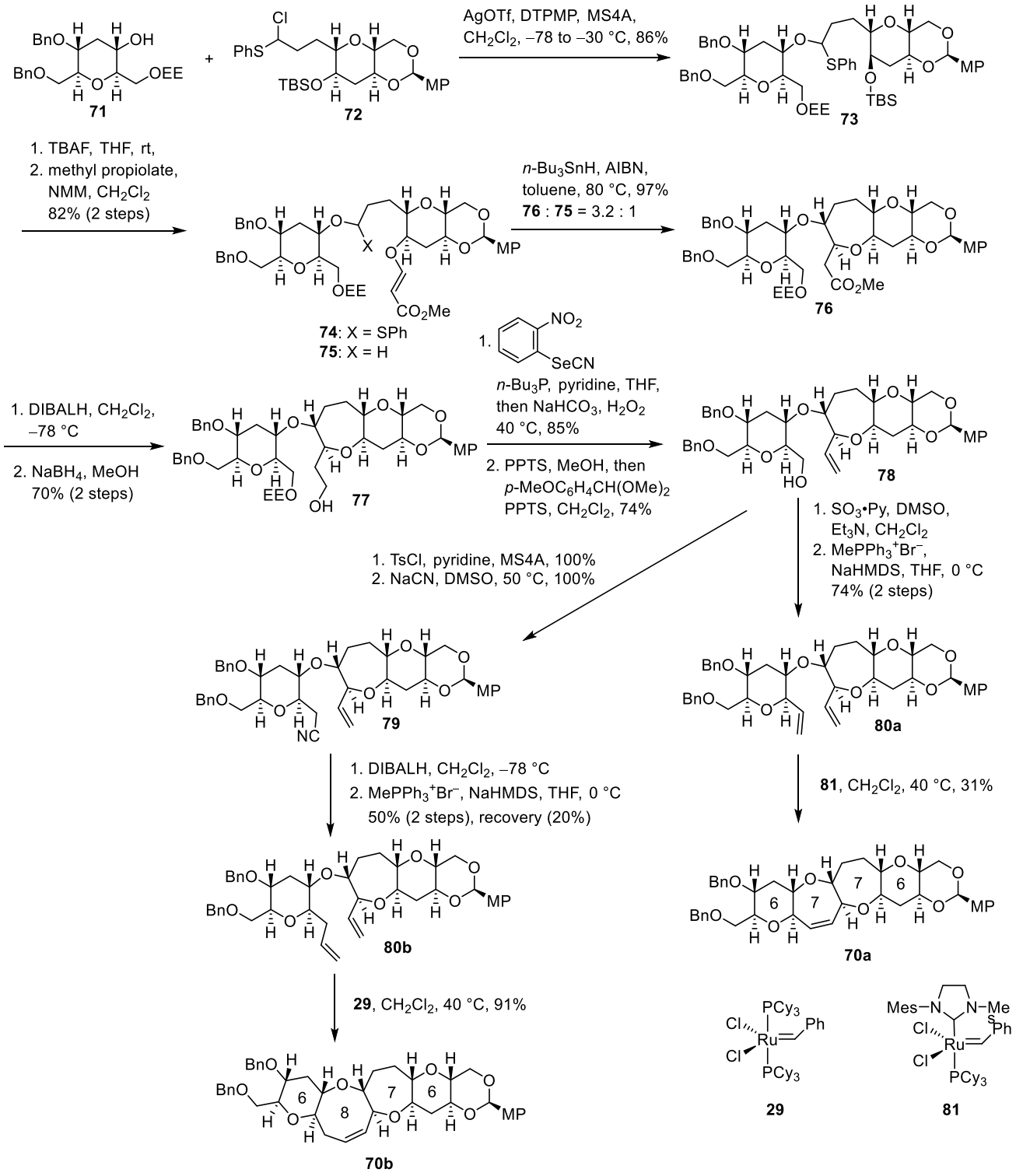



**Figure 13.** Design of the 6/*n*/7/6-tetracyclic (*n* = 7, 8, 9) ALPs (**70a**~**70d**)




**Scheme 12.** Convergent strategy via *S*,*O*-acetal formation, radical cyclization, and RCM

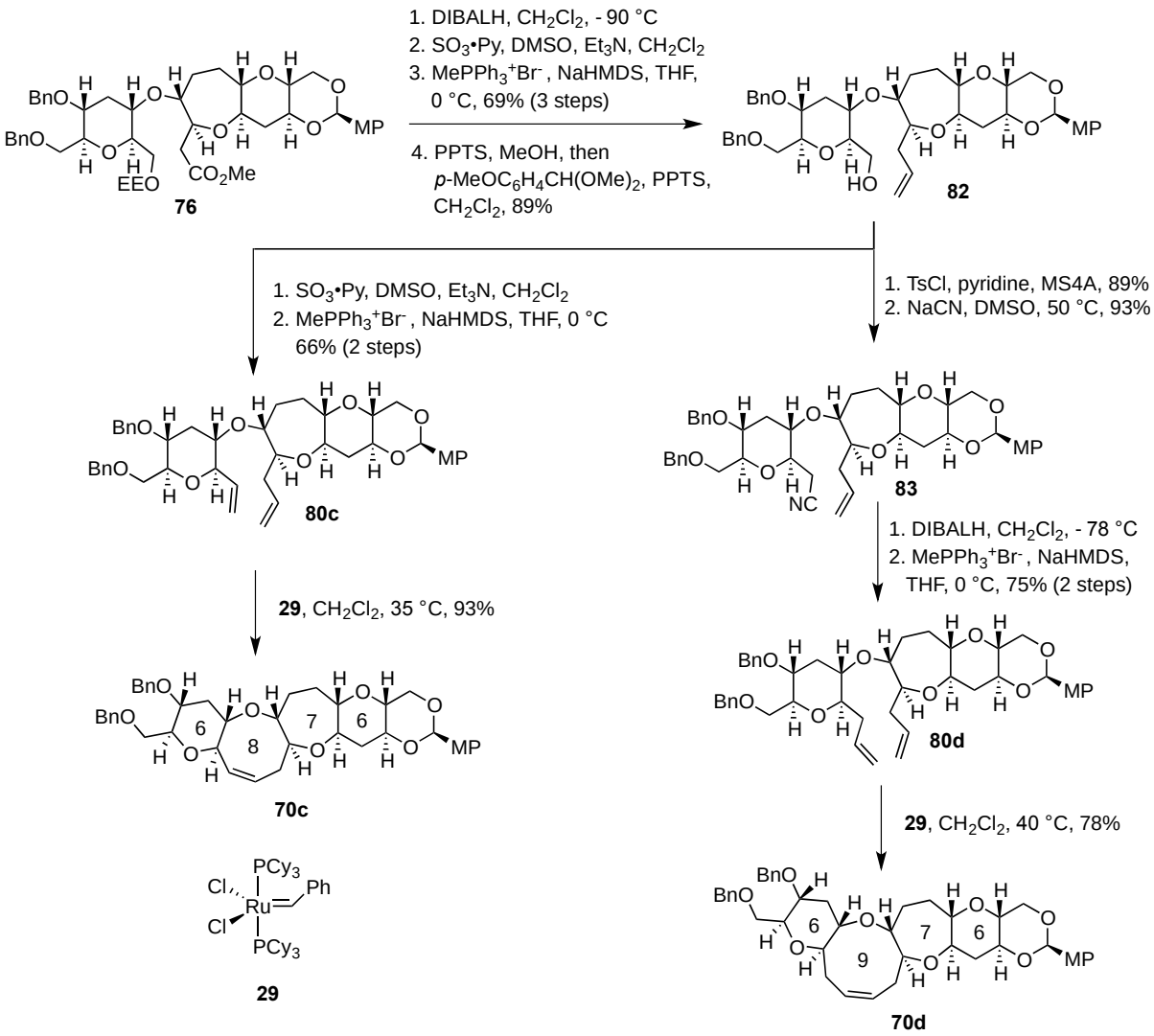
Synthesis of the 6/7/7/6- and 6/8/7/6-tetracyclic ALPs (**70a** and **70b**) is shown in Scheme 13. Coupling of the alcohol **71** and α-chlorosulfide **72** was achieved by the action of AgOTf to afford *S*,*O*-acetal **73**. Removal of the TBS group followed by oxa-Michael addition with methyl propiolate furnished β-alkoxyacrylate **74**. Treatment of **74** with *n*-$Bu_3SnH$ in the presence of AIBN afforded **76** via 7-*exo* radical cyclization. After reduction of the ester **76**, the resulting alcohol **77** was converted **78** via Nishizawa-Grieco reaction.[49] The common intermediate **78** was converted to the 6/7/7/6-tetracyclic ALP **70a** via oxidation, Wittig olefination, and RCM with Grubbs II catalyst **81**. Alternatively, the common intermediate **78** was converted to the 6/8/7/6-tetracyclic ALP **70b** through the one-carbon elongation via nitrile **79** and reduction/Wittig olefination sequence giving **80b** and subsequent RCM with Grubbs I catalyst **29**.




**Scheme 13.** Synthesis of the 6/7/7/6- and 6/8/7/6-tetracyclic ALPs (**70a** and **70b**)

Synthesis of the 6/8/7/6- and 6/9/7/6-tetracyclic ALPs (**70c** and **70d**) form the common intermediate **76** is shown in Scheme 14. After reduction/oxidation/Wittig olefination sequence, **76** was converted to olefin **82**. The common intermediate **82** was converted to the 6/8/7/6-tetracyclic ALP **70c** via oxidation/Wittig olefination/RCM sequence. Alternatively, the common intermediate **82** was converted the

6/9/7/6-tetracyclic ALP **70d** through the one-carbon elongation via nitrile **83** and reduction/Wittig olefination/RCM sequence. Evaluation of biological activity of **70a**~**70d** has not been reported yet.




**Scheme 14.** Synthesis of the 6/8/7/6- and 6/9/7/6-tetracyclic ALPs (**70c** and **70d**)

4-4. Esterification/Takeda Reaction/Reductive Etherfication

Oishi et al. reported design and synthesis of the 6/6/7/6-tetracyclic ALP (**84**) system which is frequently found in the structure of LSPs (Figure 14).[50] Synthetic strategy of **84** is shown in Scheme 15. The two fragments **A** and **B** are to be combined by esterification and intramolecular carbonyl olefination of the dithioacetal **C** mediated by a low-valent titanium complex (Takeda reaction),[51] would afford cyclic enol ether **D**, which could be converted dithioacetal **F** via hydroboration/oxidation sequence. Hydroxy dithioacetal cyclization would afford mixed thioacetal **G**, and which could be converted to **H** via oxidation/methylation sequence. This strategy was utilized for the convergent synthesis of the IJKLM ring system of CTX3C.[52]

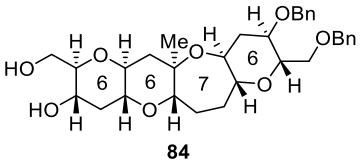
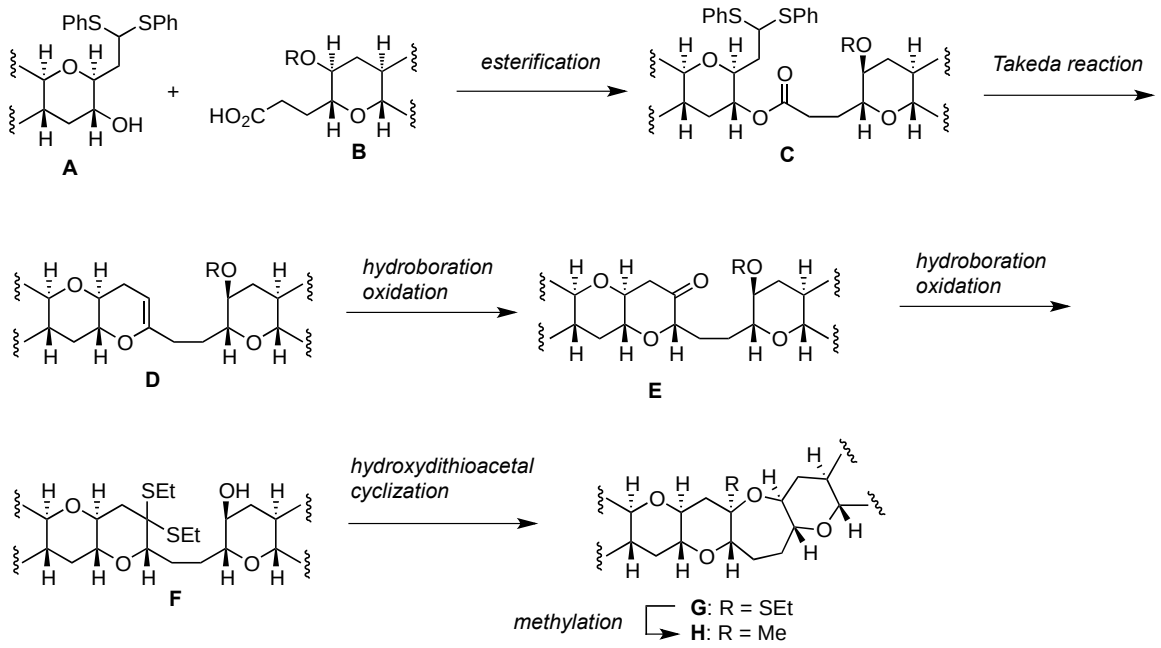
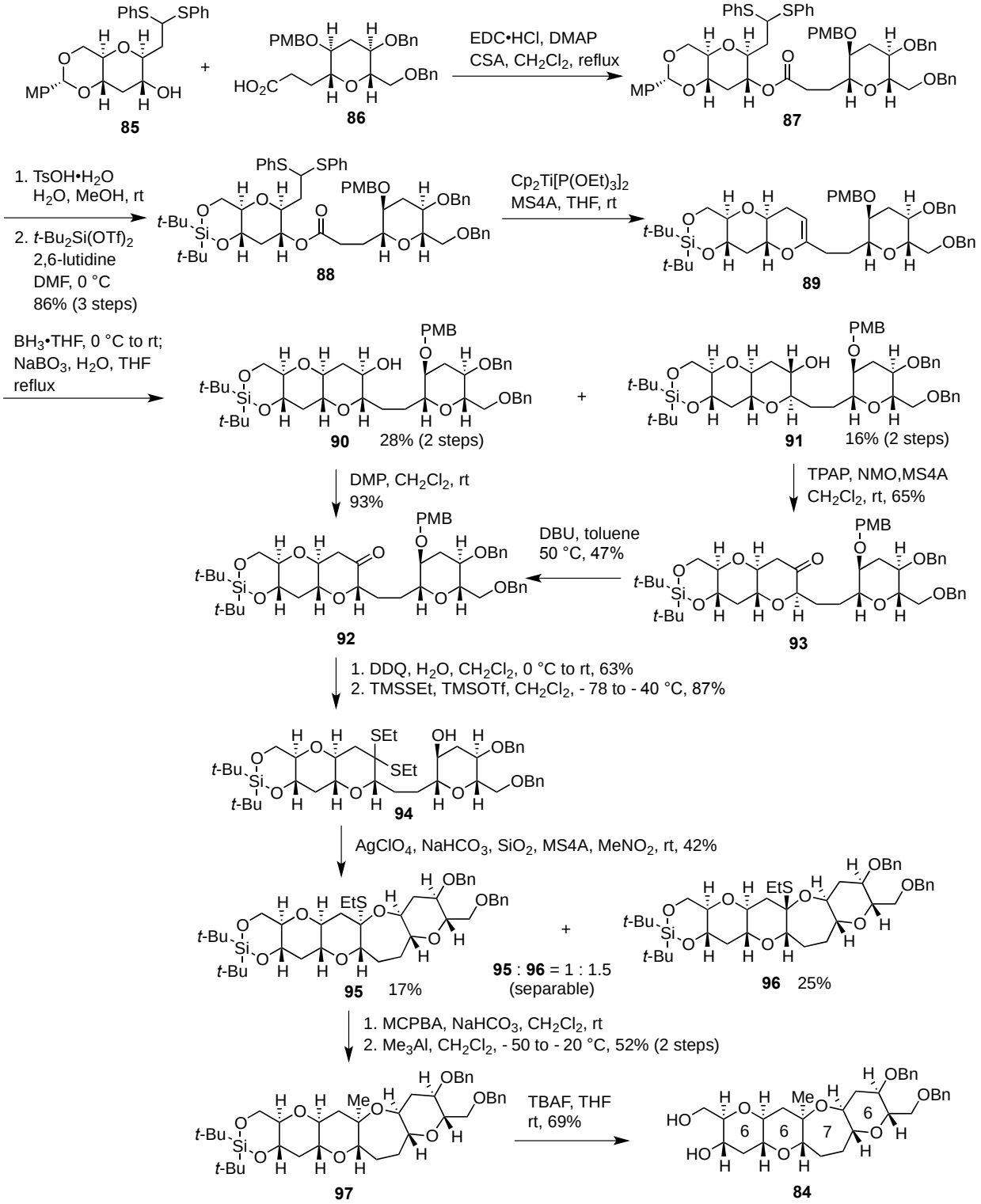



**Figure 14.** Design of the 6/6/7/6-tetracyclic ALP (**84**)




**Scheme 15.** Convergent strategy based on esterification and Takeda reaction

Synthesis of the 6/6/7/6-tetracyclic ether **84** is shown in Scheme 16. Condensation of alcohol **85** with carboxylic acid **86** afforded ester **87**. After protecting group manipulation, dithioacetal **88** was subjected to intramolecular carbonyl olefination (Takeda reaction) mediated by a low-valent titanium complex ($Cp_2Ti[P(OEt)_3]_2$)[51] to yield dihydropyran **89**. Hydroboration of **89** gave a separable mixture of the desired alcohol **90** and its diastereomer **91**. Oxidation of the alcohols **90** and **91** furnished ketones **92** and **93**, respectively, and the undesired **93** was converted to **92** by treating with DBU. Removal of the PMB group of **92** giving a hydroxy ketone, which was converted to hydroxy dithioacetal **94**. The formation of the seven-membered ring was then achieved by means of Nicolaou's method.[53] Thus, dithioacetal **94** was treated with $AgClO_4$ in the presence of silica gel in nitromethane at room temperature to afford mixed thioacetal **95** and *cis*-fused epimer **96**. The methylation of the *S*,*O*-acetal was performed via oxidation of mixed thioacetal **95** with MCPBA followed by treatment with $Me_3Al$ to afford **97** as a single isomer. Finally, removal of the silyl group of **97** with TBAF furnished the tetracyclic ether **84**.




**Scheme 16.** Synthesis of the 6/6/7/6-tetracyclic ALP (**84**) based on esterification/Takeda reaction strategy

4-5. Double Reaction Strategy

Oishi et al. envisaged that the convergent method for synthesizing the 6/6/7/6-tetracyclic ALP (**84**) could be doubly applied to the construction of the 6/6/7/6/6/7/6-heptacyclic ALP (**98**) (Figure 15),[54] it was named as double reaction strategy (Scheme 17). In the double reaction strategy, two discrete reaction sites

are manipulated in a single synthetic operation, resulted in significant reduction of the total number of steps. Interestingly, the major product was not **98** but *cis*,*cis*-fused **99** (Figure 15).

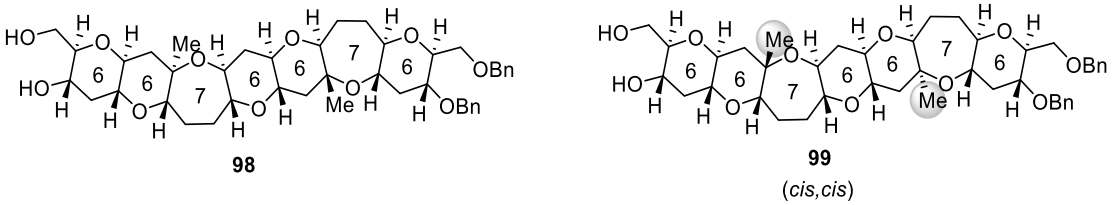
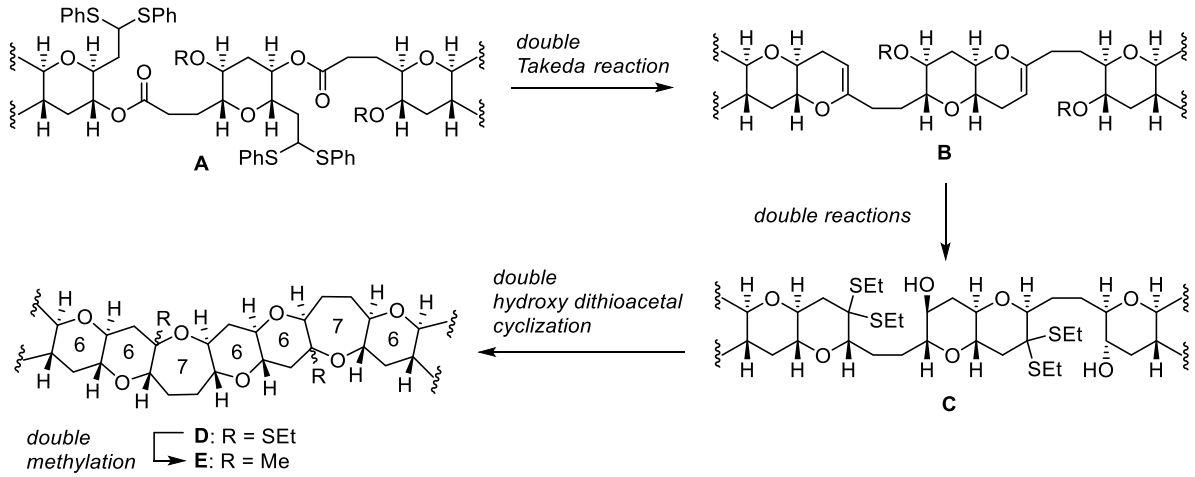
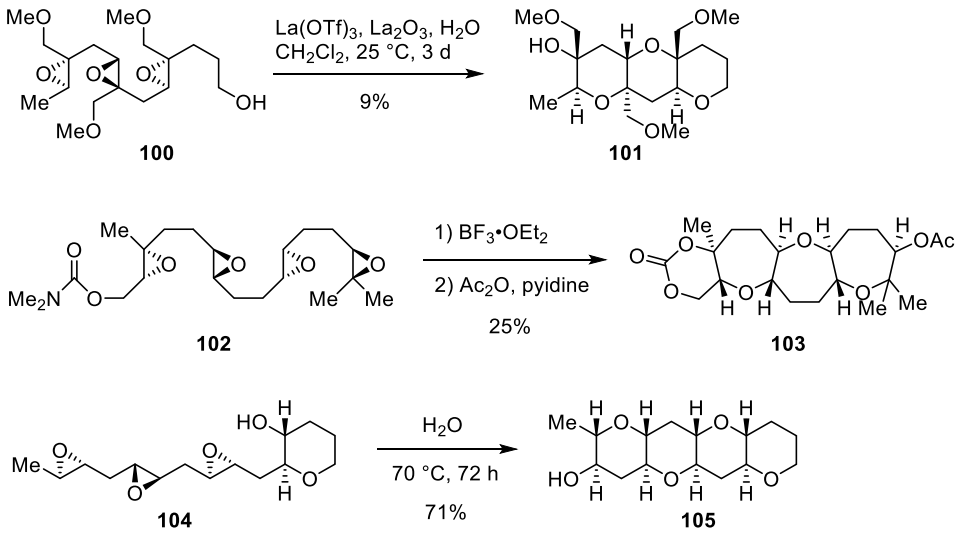



**Figure 15.** Design of a 6/6/7/6/6/7/6-heptacyclic ALP (**98**) and actually obtained *cis*,*cis*-fused ALP (**99**)



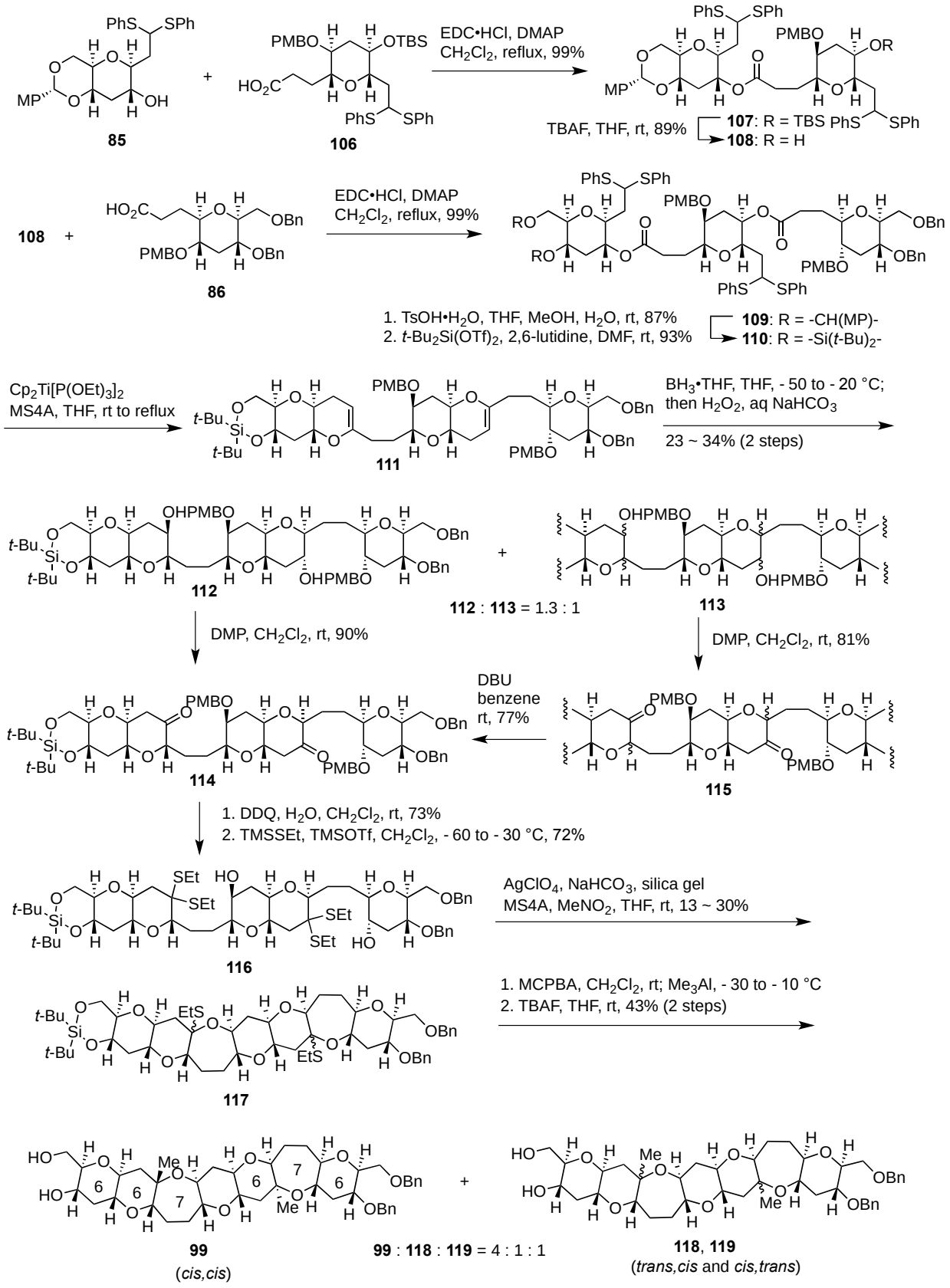

**Scheme 17.** Double reaction strategy for synthesizing the 6/6/7/6/6/7/6-heptacyclic ALP

Alternative one-pot strategies have been reported via epoxide-opening cascade reactions based on the hypothetical biosynthetic pathways proposed by Nakanishi et al.[2] Fujiwara et al. reported cascade 6-*endo* cyclization of triepoxide **100** equipped with methoxymethyl groups adjacent to the epoxide, expecting activation of the epoxides via chelation of Lewis acids, giving 6/6/6-fused tricyclic ether **101**.[55] McDonald e al. reported cascade 7-*endo* cyclization of tetraepoxide **102** by the action of Lewis acids to afford 7/7/7-fused tricyclic ether **103** possessing cyclic carbonate.[56] Jamison et al. succeeded in cascade 6-*endo* cyclization of triepoxide **104** in water to construct 6/6/6-tricyclic ether system **105** in 71% yield.[57]




**Scheme 18.** Tandem cyclization strategy for synthesizing ALPs

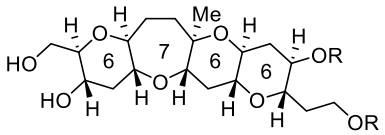
Synthesis of the 6/6/7/6/6/7/6-heptacyclic ALP (**99**) is shown in Scheme 19. Sequential coupling of three building blocks **85**, **106**, and **86** through iterative esterification via **107** and **108** afforded diester **109**. The first key step of the double reaction strategy, double cyclization of the diester **110** equipped with two dithioacetal moieties by means of Takeda reaction with the low valent titanium complex $Cp_2Ti[P(OEt)_3]_2$ resulted in the formation of bis-cyclic enol ether **111**. Subsequent hydroboration-oxidation sequence furnished the desired diol **112** with concomitant formation of **113** as an inseparable mixture of the other three possible diastereomers (**112** : **113** = 1.3 : 1). Oxidation of **112** gave diketone **114**. The undesired isomers **113** were also successfully converted to **114** through the oxidation and epimerization of **115** by treatment with DBU. After conversion of **114** to bis-hydroxy dithioacetal **116**, the second key reaction, formation of the bis-mixed thioacetal was achieved by Nicolaou's procedure with $AgClO_4$ to afford **117** as an inseparable mixture of diastereomers. The final double methylation was achieved through successive one-pot oxidation of **117** with MCPBA followed by treatment with $Me_3Al$. Finally, deprotection with TBAF afforded the 8,9-*cis*-18,19-*cis* heptacyclic ALP (**99**) and the other two diastereomers (**118**) and (**119**). Although the yields of the key cyclization steps should be improved, the double reaction strategy realized the expeditious synthesis of the heptacyclic ether (**99**) in only thirteen steps from the building blocks.



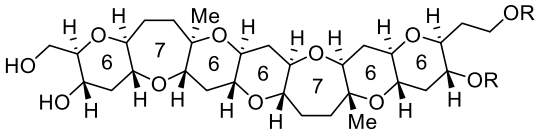

**Scheme 19.** Synthesis of the 6/6/7/6/6/7/6-heptacyclic ALP (**99**) based on double reaction strategy

4-6. Convergent Method via α-Cyano Ethers

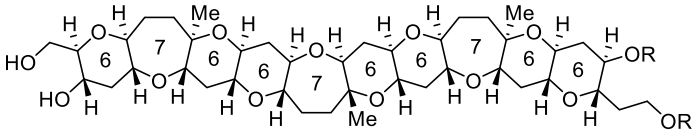
Oishi et al. reported design and systematic synthesis of ALPs with 6/7/6/6-tetracyclic (**120**), 6/7/6/6/7/6/6-heptacyclic (**121**), and 6/7/6/6/7/6/6/7/6/6-decacyclic (**122**) systems, which possess a common iterative 6/7/6-ring system with different molecular length (Figure 16).[58] In order to sort out the size effects of the polycyclic region from other factors on the biological activities, it is necessary to prepare model compounds as molecular probes that are composed of a consistent ring sequence with different length, which are unavailable from natural sources. One of the terminal sides is functionalized as diol to increase water solubility, and the other side was equipped with hydroxy groups (ALPA series) or benzyloxy groups (ALPB series) to assess the hydrophilic or hydrophobic effects of the side chains.



ALP4A (**120a**): R = H
ALP4B (**120b**): R = Bn



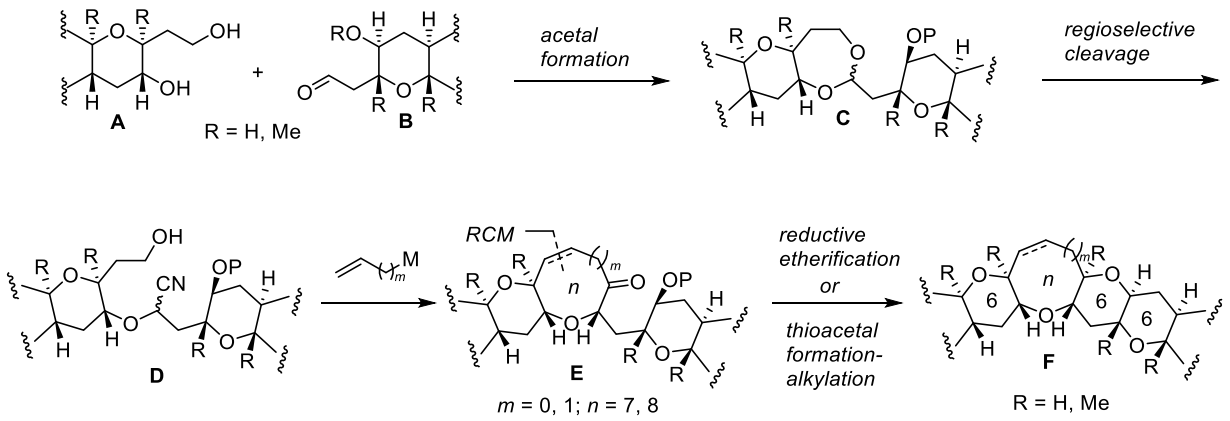
ALP7A (**121a**): R = H
ALP7B (**121b**): R = Bn



ALP10A (**122a**): R = H
ALP10B (**122b**): R = Bn

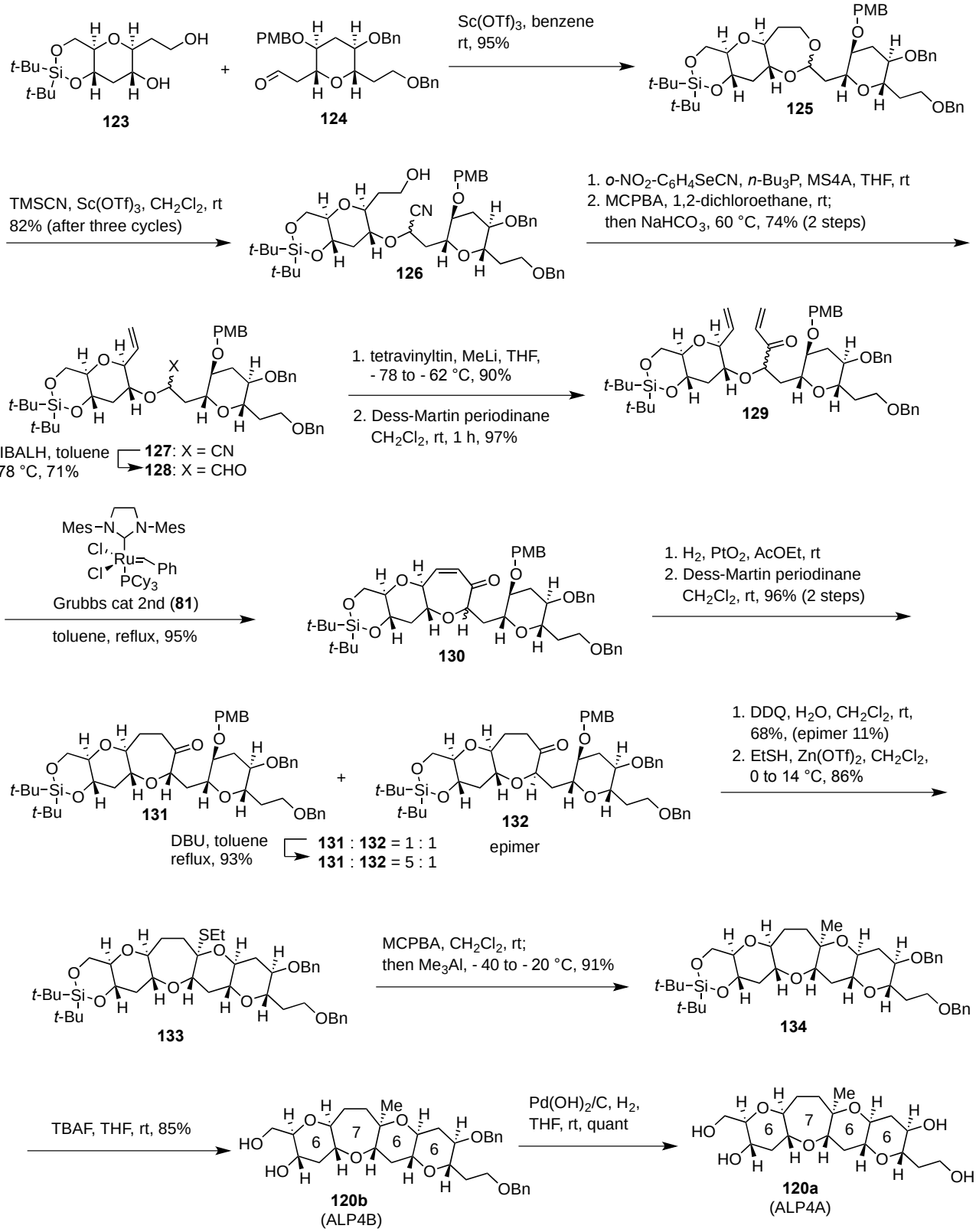
**Figure 16.** Design of the 6/7/6/6-tetracyclic (**120**), 6/7/6/6/7/6/6-heptacyclic (**121**), and 6/7/6/6/7/6/6/7/6/6-decacyclic (**122**) ALPs

For the synthesis of the ALPs (**120**~**122**), convergent strategy via α-cyano ethers (α-cyano ether method)[59] was utilized as shown in Scheme 20. Coupling of a diol **A** and an aldehyde **B** by acetal formation giving seven-membered ring acetal **C**, followed by regioselective cleavage of the acetal furnished an α-cyano ether **D**. Elimination of the primary alcohol giving terminal olefin and introduction of viniyl ($m$ = 0) or allyl ($m$ = 1) group to furnish diene, which were converted to seven- or eight-membered cyclic ethers by RCM. Although the α-cyano ether **D** was a mixture of diastereomers, undesired isomer was epimerized to afford ketone **E**. Construction of the six-membered ring was achieved by reductive etherification, or *S*,*O*-acetal formation followed by methylation. The α-cyano ether method was successfully applied to the convergent synthesis of the ABCDEFGHIJ ring system of yessotoxin[60] and the WXYA'B'C' ring system of maitotoxin.[61]



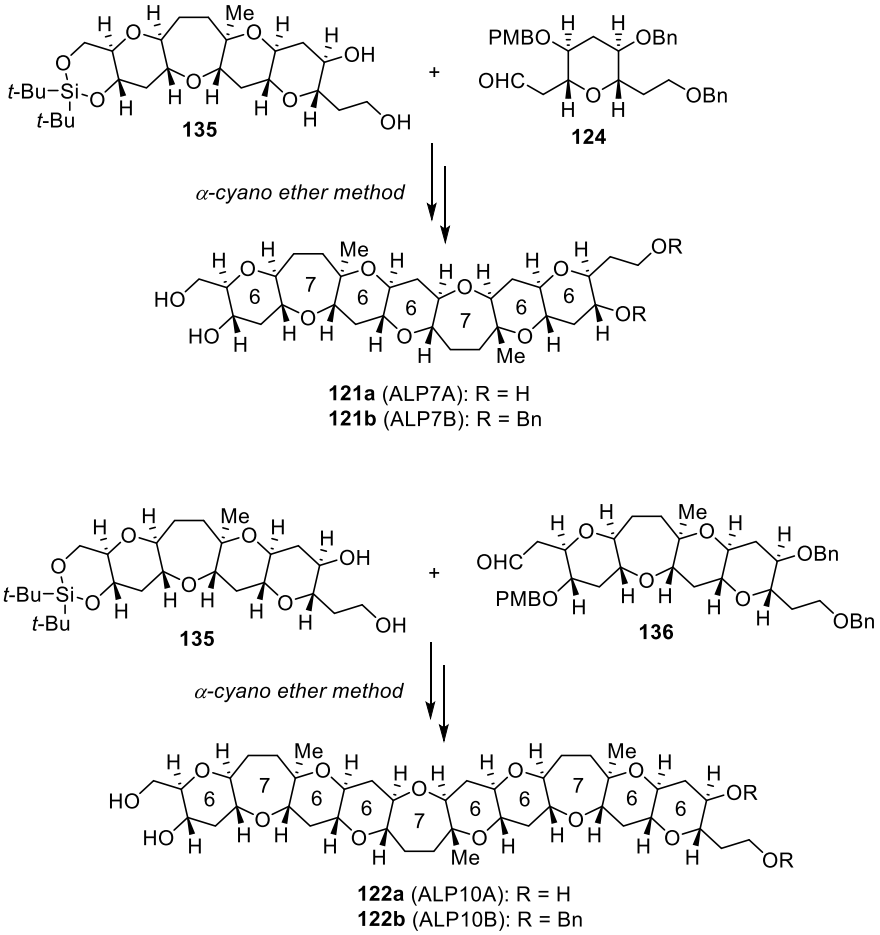

**Scheme 20.** Convergent method via α-cyano ethers (α-cyano ether method)

Synthesis of the 6/7/6/6-tetracyclic ALP (**120**) based on the α-cyano ether method is shown in Scheme 21. Condensation of diol **123** and aldehyde **124** proceeded smoothly by the action of $Sc(OTf)_3$ to give seven-membered cyclic acetal **125**. Regioselective opening of the acetal was achieved by treatment with TMSCN in the presence of $Sc(OTf)_3$ to form α-cyano ether **126**. Sequential conversion of primary alcohol **126** into terminal olefin **127** by Nishizawa-Grieco method, and reduction of the nitrile **127** with DIBALH gave aldehyde **128**, which was converted into enone **129** by treatment with vinyllithium followed by oxidation. RCM of the diene **129** by the action of Grubbs II catalyst **81** proceeded smoothly to afford seven-membered cyclic enone **130**. Hydrogenation of the olefin followed by conversion of the undesired epimer **132** into **131** was achieved by treatment with DBU in toluene at 110 °C (**131** : **132** = 5 : 1). Removal of the PMB group, followed by treatment with EtSH in the presence of $Zn(OTf)_2$ yielded cyclic mixed thioacetal **133**. Stereoselective introduction of an angular methyl group was successfully achieved through oxidation of mixed thioacetal **133** with MCPBA toward sulfone, and one-pot treatment of the reaction mixture with $Me_3Al$ to afford **134** as a single isomer. Removal of the silyl group of **134** with TBAF yielded **120b** (ALP4B). Thus, 6/7/6/6-tetracyclic ALP4B was synthesized from monocyclic building blocks (**123** and **124**) in 14% overall yield for fourteen steps (87% average yield). Hydrogenolysis of the benzyl ether **120b** afforded tetraol **120a** (ALP4A).




**Scheme 21.** Convergent synthesis of the 6/7/6/6-tetracyclic ALPs (**120**) based on α-cyano ether method

The heptacyclic ALPs (**121a** and **121b**) was synthesized in an analogous sequence as tetracyclic ALPs based on the α-cyano ether method (Scheme 22), starting from diol **135** and aldehyde **124** in 6.6% overall yield and in 82% average yield for fourteen steps. The α-cyano ether method was successfully applied to the decacyclic ALP10A and ALP710B (**122a** and **122b**), the most challenging molecule in the ALPs, irrespective of the size of the synthetic intermediates (Scheme 22). The average yield from **135** and **136** for fourteen steps was 83% (6.8% total yield), which is comparable to that of the heptacyclic ALP.




**Scheme 22.** Convergent synthesis of the 6/7/6/6/7/6/6-heptacyclic ALPs (**121a** and **121b**) and the 6/7/6/6/7/6/6/7/6/6-decacyclic ALPs (**122a** and **122b**) based on α-cyano ether method

The interaction of the ALPs (**120~122**) with α-helical transmembrane (TM) proteins, glycophorin A (GpA) and integrin $\alpha_1\beta_1$, which are known to form dimers in the lipid bilayer membranes, was evaluated by SDS-PAGE and surface plasmon resonance (SPR). The ALP7B (**121b**) exhibited notable activity to induce dissociation of GpA dimers to monomers, and the $K_D$ value between ALP7B and TM domain of GpA (GpA-TM) was determined to be 48 μM. The ALP10A (**122a**) exhibited an intriguing phenomenon to induce precipitation of GpA dose-dependently under the low concentration of SDS. ALP10A also

induced precipitation of integrin $\alpha_1\beta_1$. Based on these results, the concept of 'hydrophobic matching' was proposed. ALPs elicit potent affinity when the length of the hydrophobic region including the side chains of ALPs matches the lengths of the hydrophobic region of α-helical TM proteins (ca. 25Å). Furthermore, it is noteworthy that ALP7B inhibited $Ca^{2+}$-influx activity induced by MTX (**17**, Figure 4) with the $IC_{50}$ value at 2 μM, which is the most potent inhibitor that has ever reported.[62]

## 5. SUMMARY

In this review, design and synthesis of artificial ladder-shaped polyethers (ALPs) are summarized. There are two different strategies for synthesizing ALPs; 1) divergent strategy (two-directional ring formation), and 2) convergent strategy. The convergent strategy is categorized into type I: two fragments [X] and [Y] are combined via one ring construction [X+1+Y], and type II: via two rings construction [X+2+Y]. The latter strategy is also extended to the double reaction strategy. Although not all the ALPs were subjected to evaluation of biological activities, some of the examples offer important information on the interaction with α-helical TM proteins. Design and synthesis of ALPs with development of more efficient synthetic strategies and methodologies is expected in future.

## ACKNOWLEDGMENTS

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