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RECENT PROGRESS IN THE SYNTHETIC STUDY OF AN ANTITUMOR MARINE MACROLIDE APLYRONINE A AND RELATED MOLECULES

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Abstract – Aplyronine A is a potent antitumor marine macrolide. The unique molecular structures of aplyronine A and its congeners, in conjunction with their potent biological activities, have made them attractive synthetic targets. This review discusses recent progress in the development of efficient routes to the synthesis of aplyronines and the related molecules.

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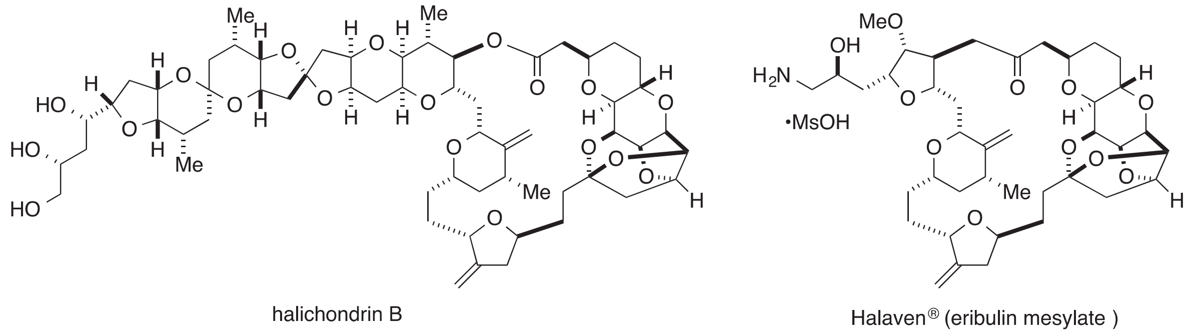
1. INTRODUCTION

The search for the seeds of novel types of drugs, such as antitumor agents, from marine animals and plants is ongoing all over the world.[1] For instance, Hirata and Uemura discovered halichondrin B, an antitumor polyether macrolide from a marine sponge, in 1985 (Figure 1).[2] In 2011, Eisai Co., Ltd., released Halaven® (eribulin mesylate) as a novel anticancer agent against breast cancer, which was inspired from halichondrin B through joint development by Eisai Research Institute and the Kishi group.[3] In this way, the development of novel types of drugs based on marine natural products is an important research field.

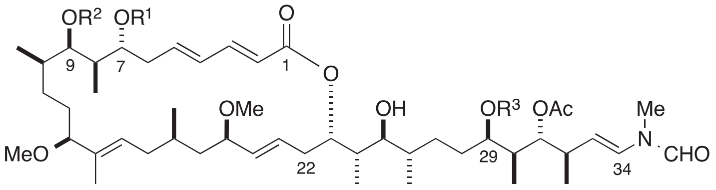


halichondrin B

Halaven® (eribulin mesylate)

Figure 1. Structures of halichondrin B and Halaven®

Aplyronine A (**1**) is another potent antitumor marine natural product (Figure 2).[4] In 1993, Yamada and co-workers isolated the aplyronines A (**1**)–C (**3**) from the Japanese sea hare *Aplysia kurodai*.[5] In 2012, they reported the isolation of five more analogues, aplyronines D (**4**)–H (**8**).[6] In addition, they investigated the synthesis,[7] biological activities,[8] and structure–activity relationships[9] of aplyronine A (**1**). Interestingly, aplyronine A (**1**) binds to actin, which is a major protein of the cytoskeleton in eukaryotic cells, and shows potent actin-depolymerizing activity.[8] Recently, Kigoshi and Kita reported very unique mechanisms of action of aplyronine A (**1**).[10] Thus, aplyronine A (**1**) forms a 1 : 1 : 1 heterotrimeric complex with actin and tubulin, and inhibits tubulin polymerization. Inhibitors of tubulin polymerization, such as vinblastine, have become clinically important drugs, especially for breast cancer.[11]



	R1	R2	R3
aplyronine A (**1**)	TMSer	H	DMAla
aplyronine B (**2**)	H	TMSer	DMAla
aplyronine C (**3**)	H	H	DMAla
aplyronine D (**4**)	TMSer	H	DMGly
aplyronine E (**5**)	= 22-methylaplyronine A		
aplyronine F (**6**)	TMSer	H	MMAla
aplyronine G (**7**)	DMSer	H	DMAla
aplyronine H (**8**)	H	DMSer	DMAla

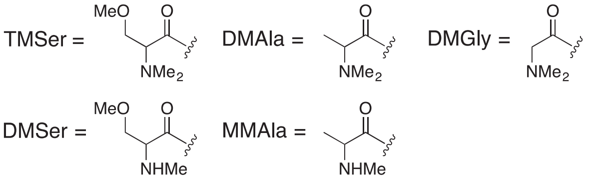


Figure 2. Structures of aplyronines A (**1**)–H (**8**)

The unique molecular structures of aplyronine A (**1**) and its congeners, in conjunction with their potent biological activities, have made them attractive synthetic targets. Several groups have reported approaches to synthesize aplyronines. In 2009, we reviewed the total synthesis of aplyronine A (**1**) and the synthetic study of aplyronines.[4] In the present review, we outline our synthetic study of aplyronines and introduce synthetic works since 2009.

2. TOTAL SYNTHESIS OF APLYRONINES

2.1. Yamada–Kigoshi's synthesis of aplyronines A–C

In 1994 Yamada, Kigoshi, and co-workers reported the first total synthesis of aplyronine A (**1**).[7] This synthesis confirmed the absolute configuration of aplyronine A (**1**) and determined the absolute configurations of aplyronines B (**2**) and C (**3**). Features of this synthesis were 1) construction of four contiguous stereogenic centers by using the Evans aldol reaction[12] and the Sharpless asymmetric epoxidation,[13] and 2) the coupling reaction of various segments by using the Julia olefination[14] as key steps (Figure 3).

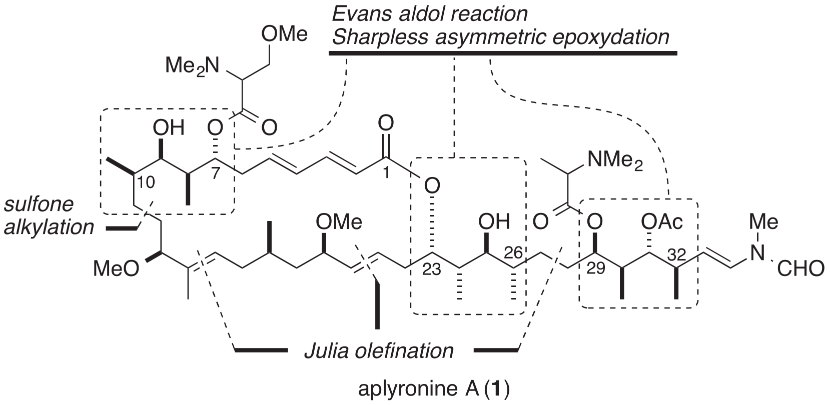
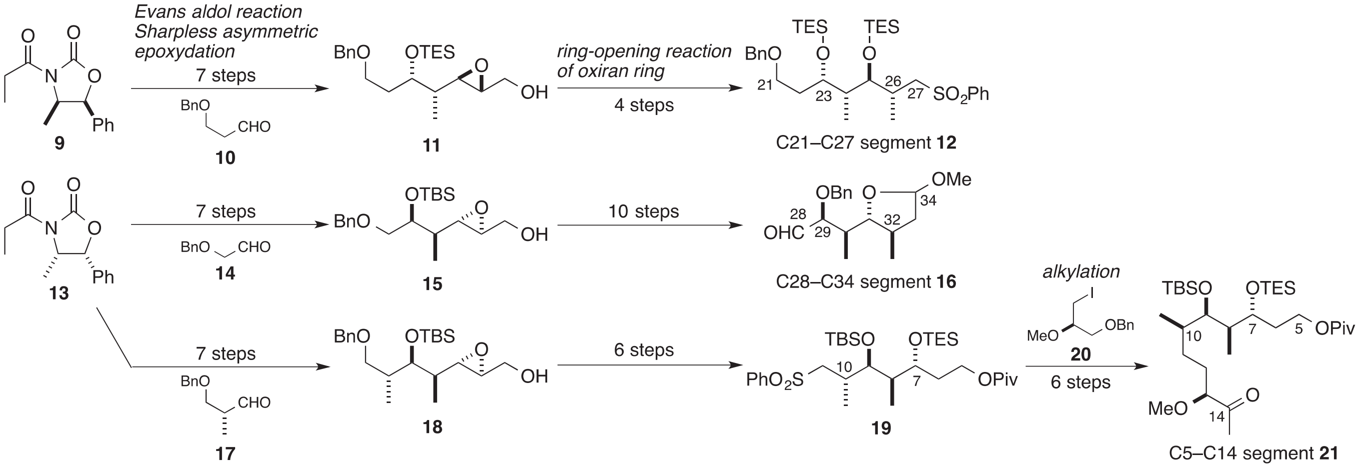


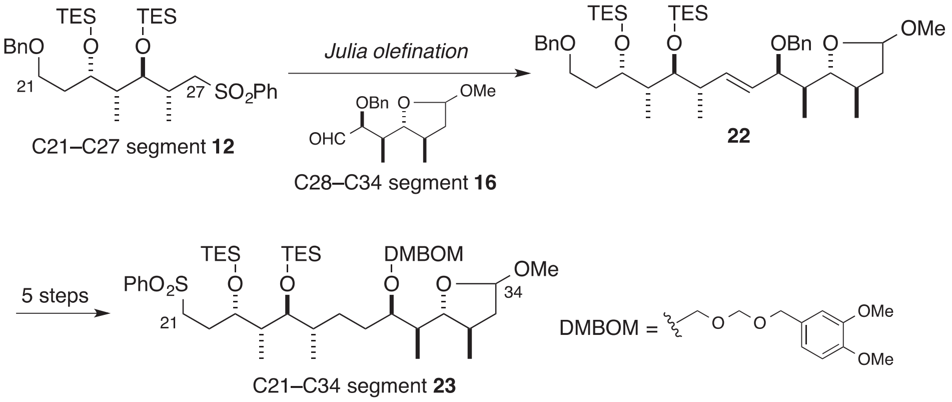
Figure 3. Strategy for the synthesis of aplyronine A (**1**) developed by Yamada and Kigoshi

The starting point for this work was the construction of four contiguous stereogenic centers at C7–C10, C23–C26, and C29–C32 by using the Evans aldol reaction[12] and the Sharpless asymmetric epoxidation[13] as key steps (Scheme 1). Thus, the Evans aldol reaction between chiral imide **9** or **13** and aldehyde **10**, **14**, or **17** gave optically active aldol adducts, which were transformed into C21–C27 segment **12**, C28–C34 segment **16**, and C5–C14 segment **21** by using Sharpless asymmetric epoxidation and the ring-opening reaction of the oxirane ring by the stereoselective introduction of a methyl group with Me_2CuLi (for **12** and **16**) or regioselective reduction with Red-Al (for **19**).



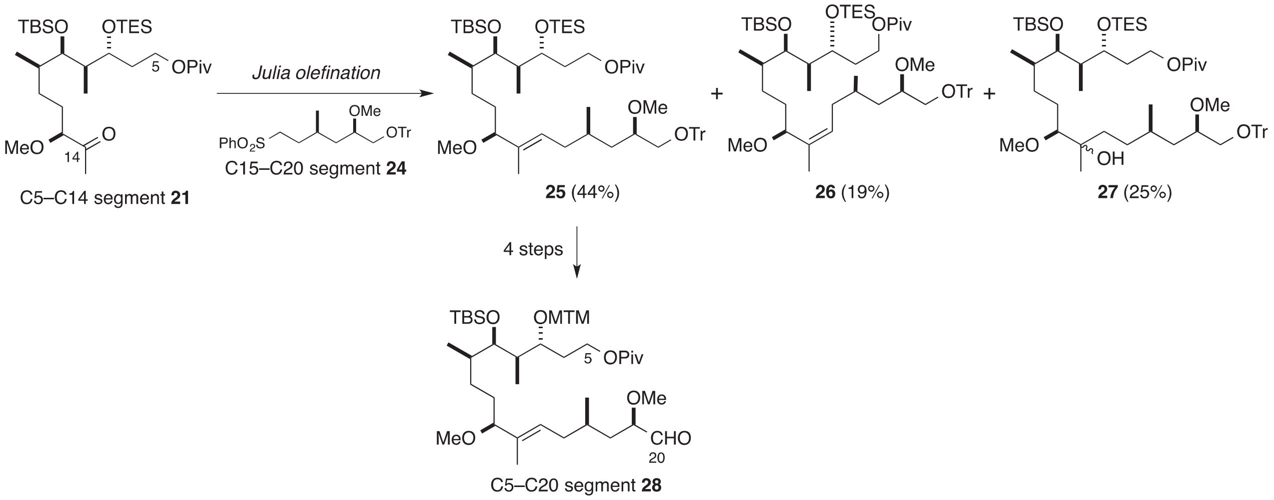
Scheme 1. Enantioselective synthesis of the four contiguous stereogenic centers by Yamada and Kigoshi

Coupling reaction of the C21–C27 and C28–C34 segments **12** and **16** by Julia olefination[14] afforded olefin **22** in good yield (Scheme 2). Olefin **22** was converted into the C21–C34 segment **23** in five steps. The DMBOM [{(3,4-dimethoxybenzyl)oxy}methyl] ether group[15] could be removed under mild conditions at the end game of the total synthesis.[7]



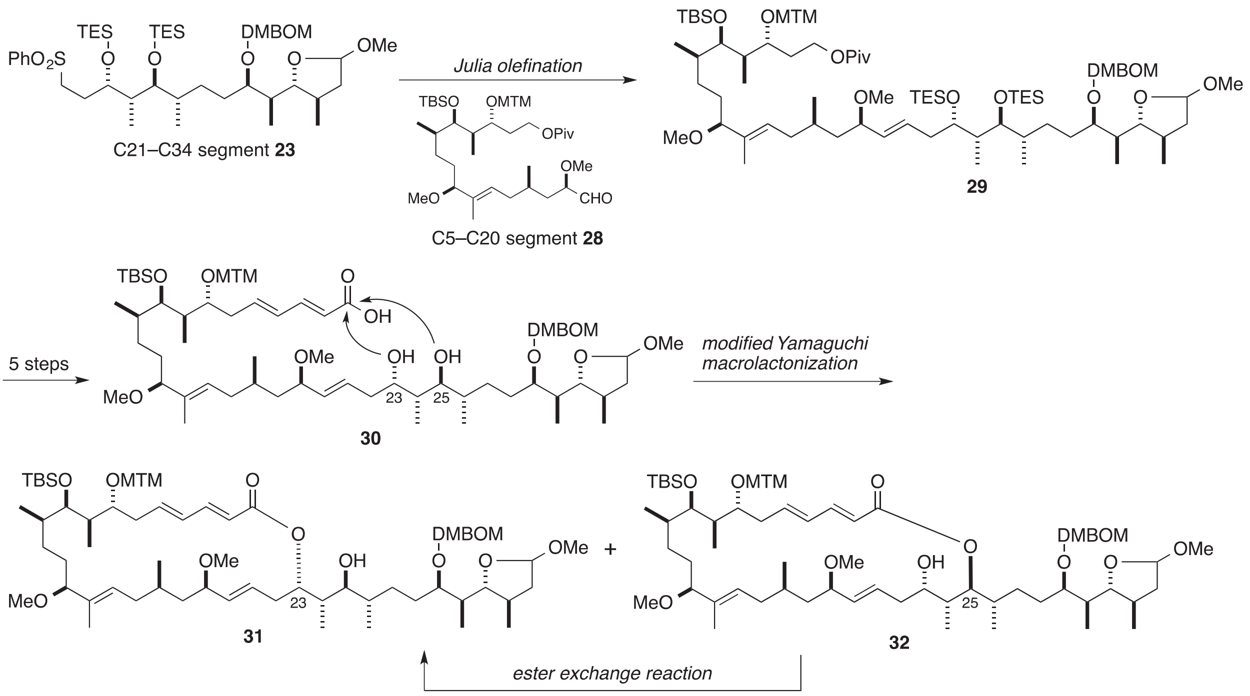
Scheme 2. Enantioselective synthesis of the C21–C34 segment **23** by Yamada and Kigoshi

On the other hand, Julia olefination[14] between the C5–C14 segment **21** and the C15–C20 segment **24** gave the desired *E*-olefin **25** in 44% yield (Scheme 3). The undesired *Z*-olefin **26** (19%) and tertiary alcohol **27** (25%) were obtained in this coupling conditions. The desired *E*-olefin **25** was transformed into aldehyde **28** as the C5–C20 segment in four steps.



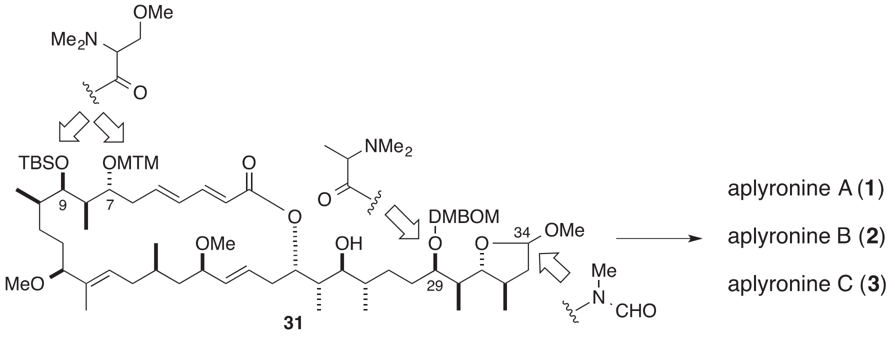
Scheme 3. Enantioselective synthesis of the C5–C20 segment **28** by Yamada and Kigoshi

The Julia olefination[14] between the C5–C20 segment **28** and the C21–C34 segment **23** gave a hydroxy sulfone, which was subjected to acetylation and reduction to furnish the coupling compound **29** (Scheme 4). Compound **29** was converted in five steps into seco acid **30**, which has two hydroxy groups at C23 and C25 as possible reaction sites. Macrolactonization under the modified Yamaguchi conditions[16,17] was carried out to afford the desired 24-membered lactone **31** and the undesired 26-membered lactone **32** in a ratio of ca. 4 : 3. The undesired 26-membered lactone **32** was isomerized to the desired 24-membered lactone **31** by using Ti(O*i*-Pr)$_4$.[18]



Scheme 4. Synthesis of common intermediate **31** of aplyronines by Yamada and Kigoshi

The desired lactone **31** was a common intermediate of aplyronines. Thus, the introduction of the *N*-methylformamide group at C34, the *N,N*-dimethylalanine ester group at C29, and the *N,N,O*-trimethylserine ester group (at C7 for aplyronine A (**1**), at C9 for aplyronine B (**2**)) afforded aplyronines A (**1**), B (**2**), and C (**3**) (Scheme 5).[7] This total synthesis of aplyronine A (**1**) yielded an amount sufficient for further biological studies, including animal experiments.

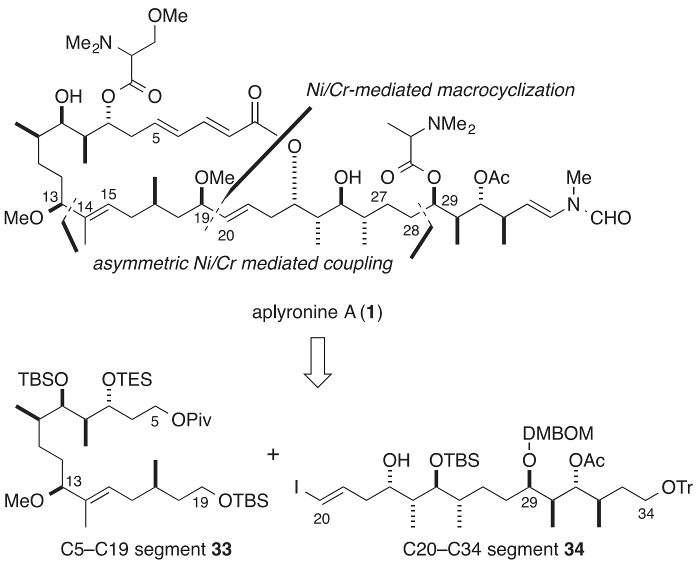


Scheme 5. Total synthesis of aplyronines A (**1**)–C (**3**) by Yamada and Kigoshi

2.2. Kigoshi's asymmetric Ni/Cr-mediated coupling approach for the second-generation synthesis of aplyronine A

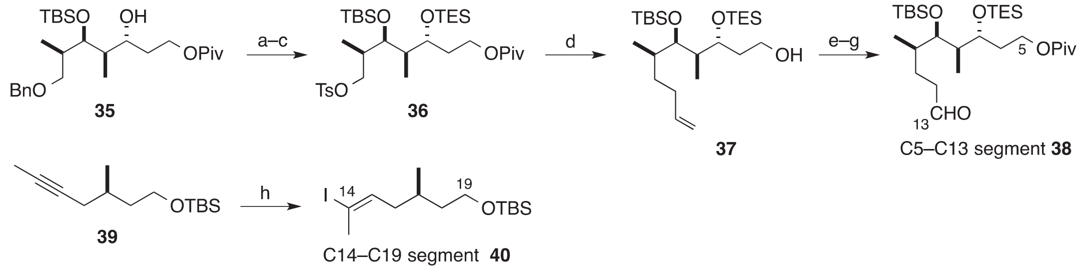
In section 2.1, we introduced the first total synthesis of aplyronines by Yamada and Kigoshi.[7] However, this synthetic strategy had a problem. Thus, Julia olefination[14] to construct a C14 trisubstituted double bond showed poor stereoselectivity: the desired (*E*)-olefin (44%), the undesired (*Z*)-olefin (19%), and the C14 tertiary alcohol (25%). Therefore, Kigoshi planned to improve the stereoselective construction of the C14–C15 (*E*)-trisubstituted double bond by using an asymmetric Ni/Cr-mediated coupling

(Nozaki–Hiyama–Takai–Kishi coupling)[19] as a key step for the second-generation total synthesis of aplyronine A (**1**) and the synthesis of related artificial analogues (Scheme 6). This strategy has the benefit of constructing the C14–C15 (*E*)-trisubstituted double bond and the C13 stereogenic center at once.



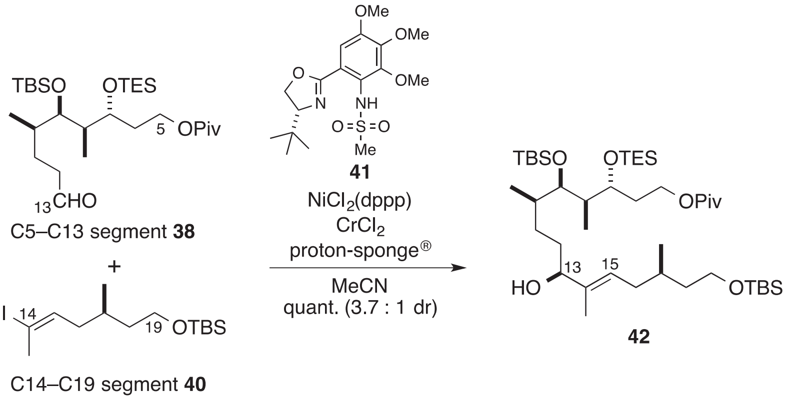
Scheme 6. Strategy for the second-generation synthesis of aplyronine A (**1**) and the key intermediates **33** and **34**

The C5–C13 segment **38** was prepared from synthetic intermediate **35**[7] in the first-generation total synthesis of aplyronine A (**1**) in seven steps (Scheme 7). Also, the C14–C19 segment **40** was synthesized from **39**[20] by using regioselective hydrozirconation with Cp_2ZrHCl.[21]



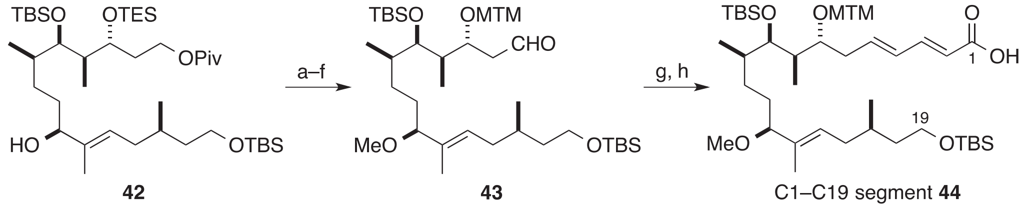
Scheme 7. Enantioselective synthesis of the C5–C13 segment **38** and the C14–C19 segment **40** by the Kigoshi group. *Reagents and conditions*: (a) TESCl, imidazole, DMF, 96%; (b) H_2, Pd/C, EtOH, 98%; (c) *p*-TsCl, pyridine, 99%; (d) allylmagnesium bromide, Et_2O, 92%; (e) PivCl, DMAP, pyridine, CH_2Cl_2, quant.; (f) OsO_4, NMO, THF, H_2O; (g) $NaIO_4$, THF, H_2O, 97% in two steps; (h) Cp_2ZrHCl, I_2, THF, 70%.

An asymmetric Ni/Cr-mediated coupling reaction between fragments **38** and **40** was carried out (Scheme 8). Based on the procedure reported by Kishi,[19] the modified ligand **41**,[20] which has a large *t*-Bu group on the oxazoline ring, a small methyl group on the sulfonamide group, and three electron-donating methoxy groups on the benzene ring, was employed to give coupling compound **42** with the best diastereoselectivity (desired **42** : undesired stereoisomer = 3.7 : 1) and yield in this ligand screening.



Scheme 8. Construction of the C14–C15 (*E*)-trisubstituted double bond and the C13 stereogenic center via asymmetric Ni/Cr-mediated coupling by the Kigoshi group

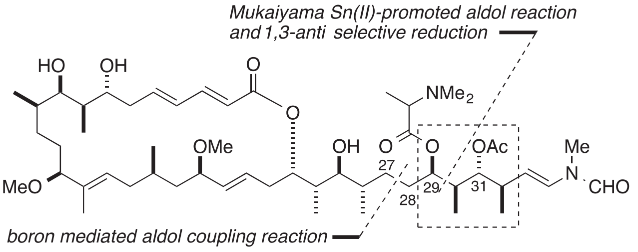
Coupling compound **42** was converted into the C1–C19 segment **44** by the Kigoshi group's use of their first-generation synthetic strategy (Scheme 9). The group employed this strategy in the synthesis of aplyronine A–mycalolide B hybrid molecule **76** (see Section 3.2).[22]



Scheme 9. Enantioselective synthesis of the C1–C19 segment **44** by the Kigoshi group. *Reagents and conditions*: (a) NaH, MeI, THF, quant.; (b) AcOH, H_2O, THF; (c) TBSCl, Et_3N, DMF, 98% in two steps; (d) DMSO, Ac_2O, AcOH, 83%; (e) DIBAL, CH_2Cl_2, 98%; (f) Dess–Martin periodinane, CH_2Cl_2, quant.; (g) LDA, $(EtO)_2P(O)CH_2CH=CHCO_2Et$, THF, 86%; (g) LiOH, MeOH, H_2O, 74%.

2.3 Paterson's synthesis of aplyronine C

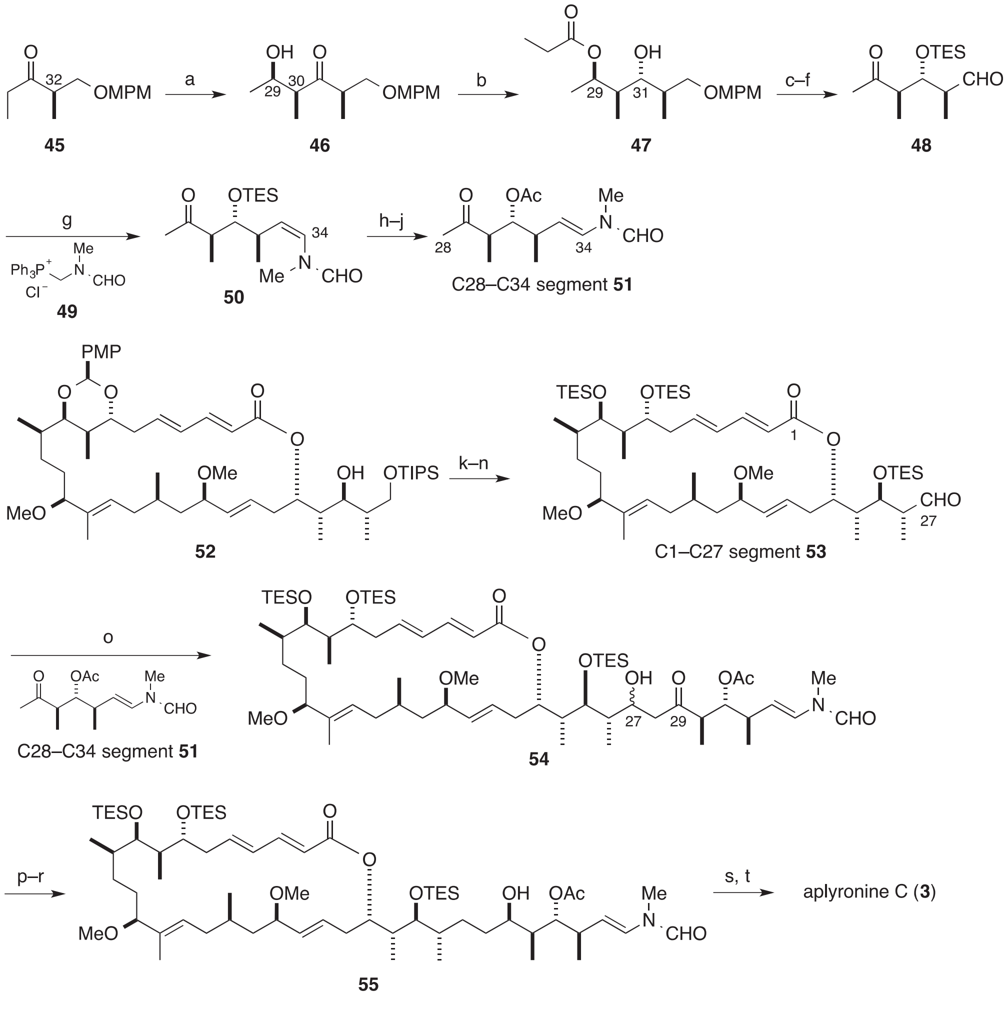
Paterson and co-workers achieved the total synthesis of aplyronine C (**3**) in 2013.[23] Their strategy involved a key fragment coupling between the C1–C27 segment **53** and the C28–C34 segment **51** using a boron-mediated aldol coupling reaction (Figure 4).[24]



aplyronine C (**3**)

Figure 4. Strategy for the synthesis of aplyronine C (**3**) developed by the Paterson group

The C28–C34 segment **51** was prepared with the Mukaiyama Sn(II)-promoted aldol reaction[25] as a key step (Scheme 10). Thus, the treatment of ketone **45** and acetaldehyde with $Sn(OTf)_2$ gave *syn* aldol adduct **46**. 1,3-Anti-selective reduction of aldol adduct **46** under the Evans–Tishchenko conditions[26] and regioselective acylation afforded ester **47**. Ester **47** was converted into aldehyde **48** in four steps. Introduction of *N*-methylformamide group to **48** gave (*Z*)-vinyl formamide **50**, which was isomerized into the desired (*E*)-vinyl formamide **51** as the C28–C34 segment. The C1–C27 segment **53** was prepared from Paterson's previous synthetic intermediate **52** in four steps.[27] Aldol coupling reaction between the C1–C27 segment **53** and the C28–C34 segment **51** with *c*-Hex_2BCl/Et_3N furnished β-hydroxy ketone **54** as a diastereomeric mixture of alcohols at C27.[24] Deoxygenation of the C27 hydroxy group and stereoselective reduction of ketone at C29 with $ZnBH_4$ gave compound **55**. To convert compound **55** into aplyronine C (**3**), they followed Yamada–Kigoshi's procedure[7] to achieve the total synthesis of aplyronine C (**3**).



Scheme 10. Total synthesis of aplyronines C (**3**) by the Paterson group. *Reagents and conditions*: (a) MeCHO, $Sn(OTf)_2$, Et_3N, CH_2Cl_2, 97%, 15 : 1 dr; (b) SmI_2, EtCHO, THF, 98%, >95 : 5 dr; (c) TESOTf, 2,6-lutidine, CH_2Cl_2, 99%; (d) DDQ, buffer (pH 9), CH_2Cl_2; (e) DIBAL, CH_2Cl_2, 92% in two steps; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (g) **49**, LHMDS, THF, 75% in two steps, *Z* : *E* = 8 : 1; (h) *n*-Bu_4NF, AcOH, THF, 98%; (i) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (j) I_2, CH_2Cl_2, 94% in two steps; (k) HF aq., MeCN;

(l) TESOTf, 2,6-lutidine, CH_2Cl_2; (m) AcOH, H_2O, THF; (n) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 81% in four steps; (o) *c*-Hex_2BCl, Et_3N, Et_2O, then **53**, 61%; (p) $Et_3NSO_2NCO_2Me$, THF; (q) $[Ph_3P·CuH]_6$, wet toluene, 91% in two steps; (r) $Zn(BH_4)_2$, Et_2O, 90%, 10 : 1 dr; (s) (*S*)-*N,N*-dimethylalanine, DCC, CSA, DMAP, CH_2Cl_2; (t) HF·pyridine, pyridine, THF, 66% in two steps.

3. SYNTHETIC APPROACHES TOWARD APLYRONINES AND THE RELATED MOLECULES

3.1. Fuchs's ring-opening reaction of chiral cyclic vinyl sulfones approach

In 2011, Fuchs and co-workers reported the synthesis of the C1–C20 and C15–C27 segments **68** and **75** of aplyronine A (**1**).[28] They previously established the stereoselective synthesis of vinyl sulfone **56** as a starting material of the C15–C20 part (Figure 5).[29] They also developed a stereoselective method of synthesizing seven-membered vinyl sulfones **59** and **69** involving four contiguous stereogenic centers by using the double Lawton S_N2' addition as a key step.[30] These vinyl sulfones **59** and **69** were used as precursors of C5–C11 and C21–C27 segments **62** and **73**, respectively.

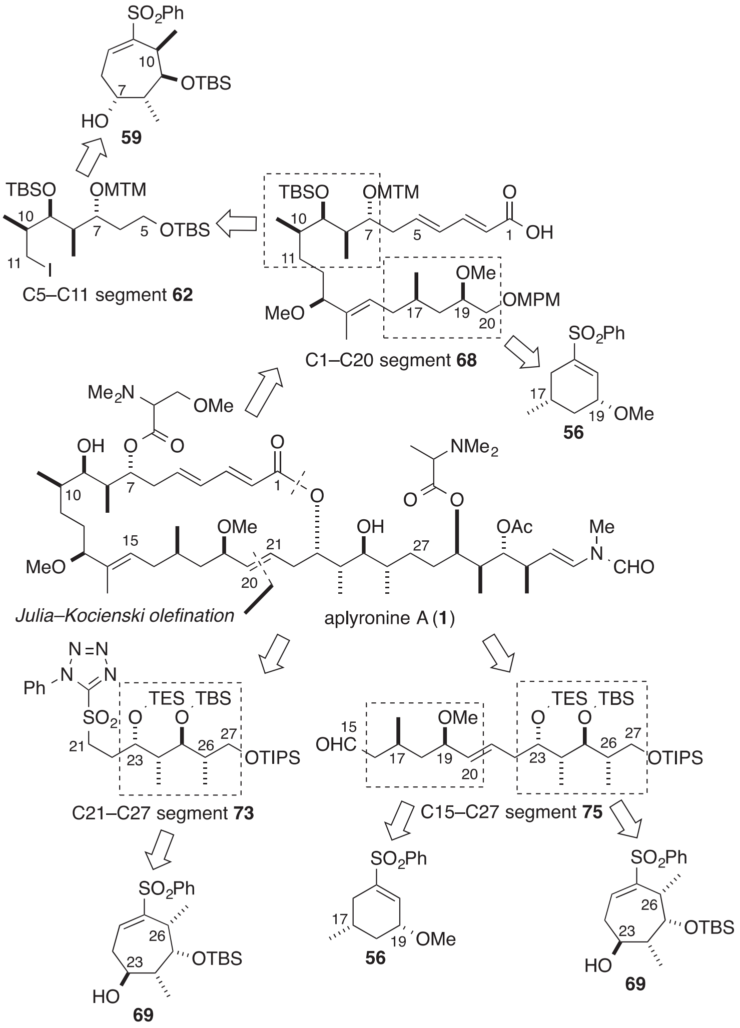
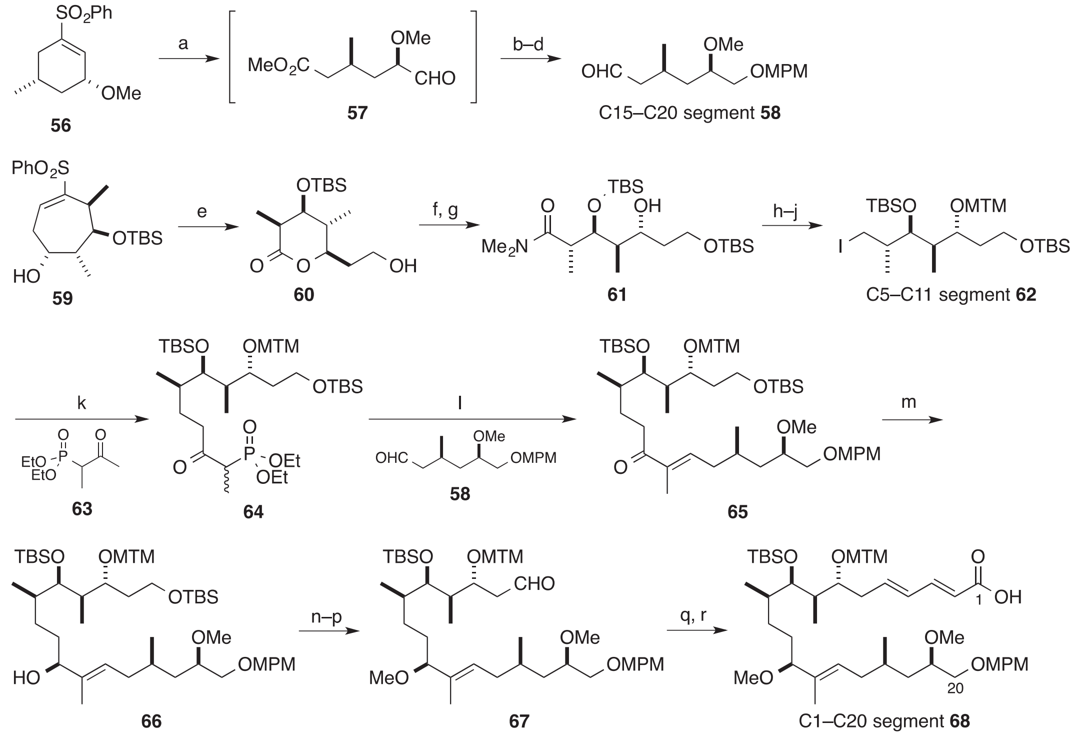


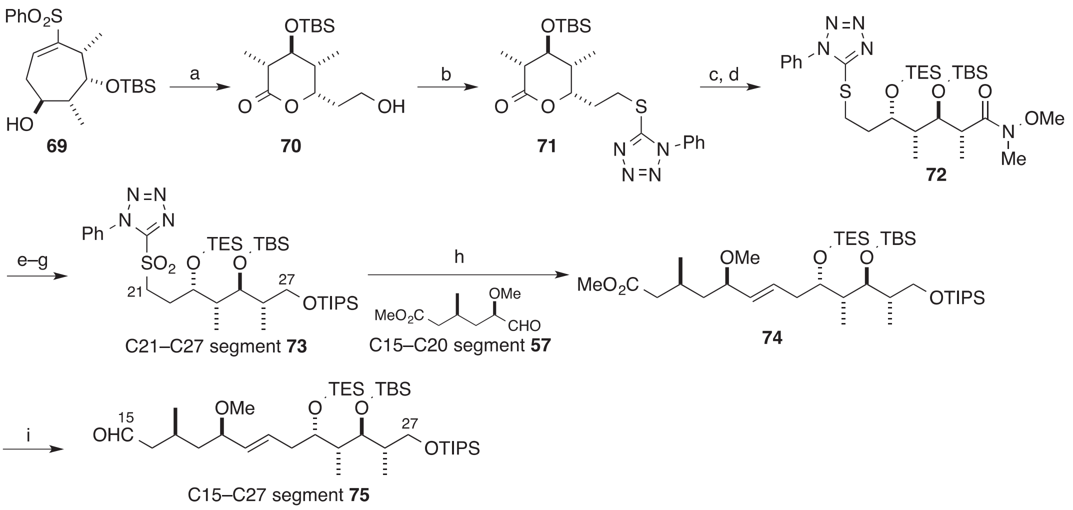
Figure 5. Strategy for the synthesis of aplyronine A (**1**) developed by the Fuchs group

Synthesis of the C15–C20 segment **58** is shown in Scheme 11. The vinyl sulfone **56**[29] was converted into aldehyde **58** as the C15–C20 segment in four steps. Synthesis of the C1–C20 segment **68** started from seven-membered vinyl sulfone **59**[30] (Scheme 11). Thus, oxidation of vinyl sulfone **59** by ozone followed by reduction with $BH_3 \cdot t\text{-}BuNH_2$ gave lactone **60**. Protection of the primary hydroxy group of lactone **60** and the subsequent ring-opening reaction afforded amide **61**. Reduction of the dimethyl amide group in **61** and iodination of the resulting hydroxy group gave iodide **62**. To convert iodide **62** into the C1–C20 segment **68**, the Fuchs group followed Paterson's[27] and Yamada–Kigoshi's[7] synthetic strategies for aplyronines.



Scheme 11. Enantioselective synthesis of the C1–C20 segment **68** by the Fuchs group. *Reagents and conditions*: (a) O_3, $NaHCO_3$, CH_2Cl_2, MeOH; (b) $BH_3 \cdot t\text{-}BuNH_2$; (c) MPM imidate, TfOH, Et_2O; (d) DIBAL, toluene, 50% in four steps; (e) O_3, CH_2Cl_2, then $BH_3 \cdot t\text{-}BuNH_2$, 76%; (f) TBSOTf, 2,6-lutidine, CH_2Cl_2; (g) $Me_2NH \cdot HCl$, *i*-PrMgCl, THF, 83% in two steps; (h) Me_2S, $(PhCOO)_2$, MeCN; (i) $LiBEt_3H$, THF; (j) I_2, PPh_3, imidazole, Et_2O, MeCN, 71% in three steps; (k) **63**, NaH, *n*-BuLi, THF, 86%; (l) $Ba(OH)_2$, THF, H_2O, then **58**, 67%; (m) (*R*)-MeCBS, $BH_3 \cdot Me_2S$, molecular sieves, THF, 91%; (n) NaH, MeI, THF, 90%; (o) CSA, $(CH_2Cl)_2$, MeOH, 89%; (p) Dess–Martin periodinane, CH_2Cl_2; (q) LHMDS, $(EtO)_2P(O)CH_2CH{=}CHCO_2Et$, THF, 77%, $E : Z = 14 : 1$; (r) LiOH, MeOH, H_2O, 78%.

On the other hand, they synthesized the C15–C27 segment **75** by using Julia–Kocienski olefination[31] as a key step (Scheme 12). Thus, they followed Yamada–Kigoshi's synthetic strategy[7] with modification. The seven-membered vinyl sulfone **69**,[30] which was a diastereomer of vinyl sulfone **59**, was converted into lactone **70**. Introduction of a thio tetrazole group at the hydroxy group of lactone **70** by Mitsunobu reaction[32] and the subsequent ring-opening reaction afforded Weinreb amide **72**. This amide was transformed into sulfone **73** as a precursor of Julia–Kocienski olefination.[31] Treatment of sulfone **73** with LHMDS in DMF/HMPA followed by the addition of aldehyde **57** furnished coupling compound **74** in 60% yield (83% based on recovered starting material), which was converted into aldehyde **75** as the C15–C27 segment.



Scheme 12. Enantioselective synthesis of the C15–C27 segment **75** by the Fuchs group. *Reagents and conditions*: (a) O_3, EtOAc, then $BH_3 \cdot t\text{-}BuNH_2$, 65%; (b) DCAD (di-*p*-chlorobenzyl azodicarboxylate), PPh_3, 1-phenyltetrazole-5-thiol, CH_2Cl_2, 84%; (c) MeONHMe·HCl, *i*-PrMgCl, THF; (d) TESCl, imidazole, $(CH_2Cl)_2$, 80% in two steps; (e) DIBAL, CH_2Cl_2, then EtOH, $BH_3 \cdot t\text{-}BuNH_2$, 90%; (f) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 88%; (g) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 71%; (h) LHMDS, THF, DMF, HMPA, then **57**, 60%, $E : Z = 12 : 1$; (i) DIBAL, toluene, 92%.

3.2. Kigoshi's synthesis of an aplyronine A–mycalolide B hybrid molecule

The hybrid molecule consisting of the macrolactone part of aplyronine A (**1**) and the side-chain part of mycalolide B (**77**)[33] was designed by Kigoshi and co-workers (Figure 6). Hybrid molecule **76** is expected to possess stronger actin-depolymerizing activity and cytotoxicity than aplyronine A for three reasons. First, the side-chain moiety in aplyronine A is crucial for both cytotoxicity and actin-depolymerizing activity.[9] Second, the synthetic artificial analogue consisting of only the side-chain part of mycalolide B exhibits stronger actin-depolymerizing activity than that of aplyronine A.[34] Third, the macrolactone part of aplyronine A significantly emphasizes its cytotoxicity.[9] Thus, they synthesized aplyronine A–mycalolide B hybrid molecule **76** to evaluate its biological activity.

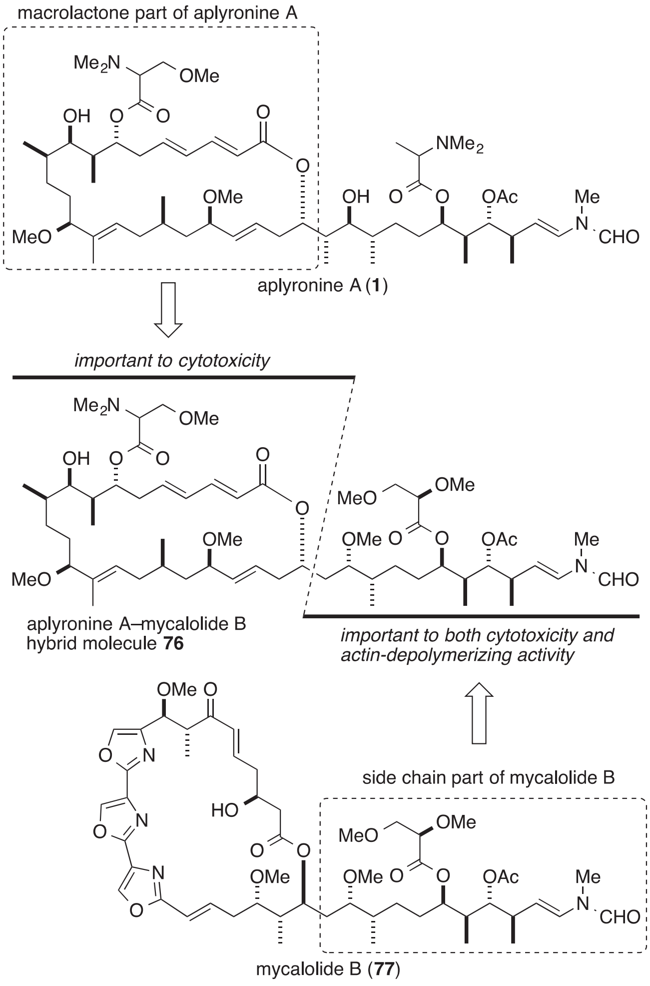
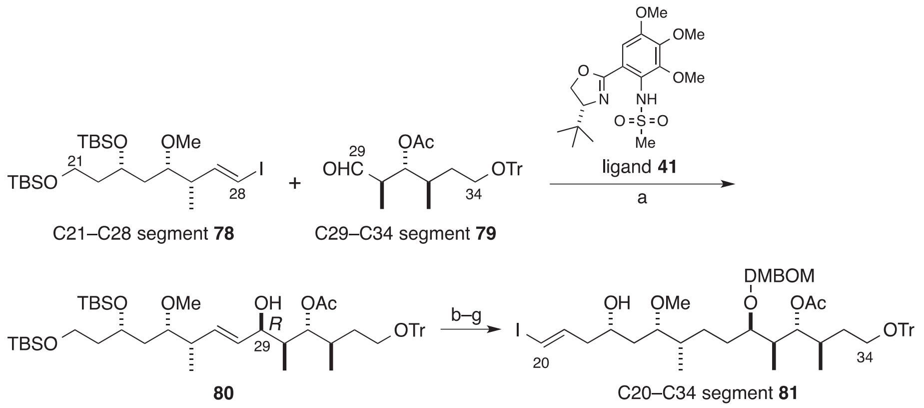


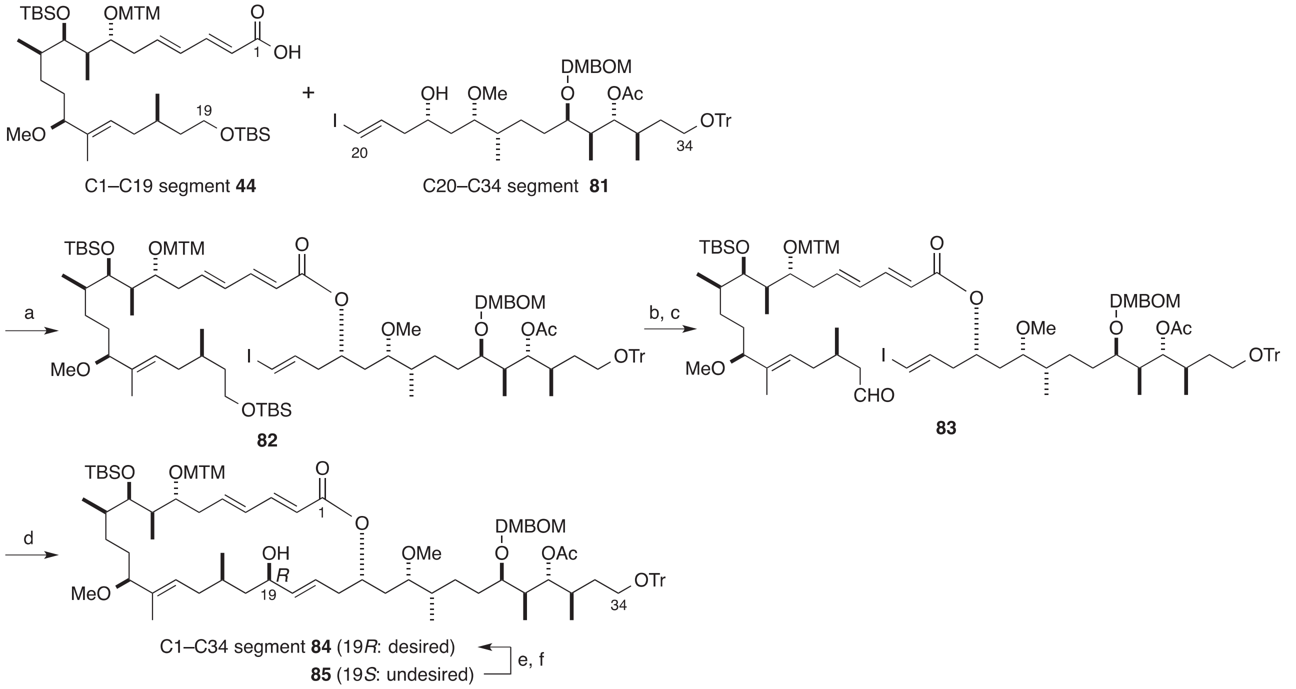
Figure 6. Design of aplyronine A–mycalolide B hybrid molecule **76** by the Kigoshi group

The aplyronine A–mycalolide B hybrid molecule **76** was synthesized by a strategy similar to that for the second-generation synthesis of aplyronine A (**1**) (Section 2.2). They attempted the synthesis of the C20–C34 segment **81**[22] by an asymmetric Ni/Cr-mediated coupling[19] between the C21–C28 and the C29–C34 segments **78** and **79** (Scheme 13). The asymmetric Ni/Cr-mediated coupling of **78** and **79** with our modified chiral sulfonamide ligand **41**[20] also worked successfully to afford the best yield and stereoselectivity (desired **80** : undesired stereoisomer = 17.6 : 1) among several known sulfonamide ligands. The coupling compound **80** was converted into an aldehyde by a modification of Yamada–Kigoshi's synthetic method,[7] which was subjected to Takai olefination[35] and removal of the TBS group to furnish the C20–C34 segment **81**.



Scheme 13. Enantioselective synthesis of the C20–C34 segment **81** by the Kigoshi group. *Reagents and conditions*: (a) $NiCl_2(dppp)$, $CrCl_2$, proton-sponge®, ligand **41**, MeCN, 88% (undesired isomer: 5%); (b) H_2, Pd/C, EtOH, 84%; (c) DMBOMCl, *i*-Pr_2NEt, CH_2Cl_2, 89%; (d) NH_4F, MeOH, 96%; (e) Dess–Martin periodinane, pyridine, CH_2Cl_2, 99%; (f) $CrCl_2$, CHI_3, THF, 86%; (g) *n*-Bu_4NF, THF, 88%.

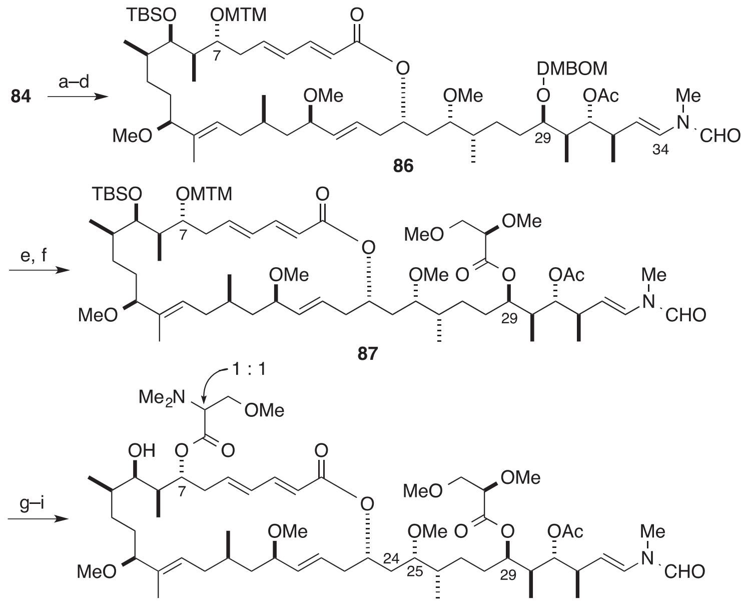
The C1–C19 segment **44**[20] and the C20–C34 segment **81**[22] were connected by using Yamaguchi esterification[16] to afford ester **82**, which was transformed into aldehyde **83** as a precursor of Ni/Cr-mediated macrocyclization (Scheme 14).[36] The Ni/Cr-mediated macrocyclization proceeded smoothly to give **84** (46%) and **85** (49%) even at a higher concentration (*c* = 10 mM)[37] than that of the modified Yamaguchi macrolactonization[16,17] in the Yamada–Kigoshi's total synthesis of aplyronine A (*c* = 0.39 mM). The undesired C19 epimer **85** could be transformed into the desired isomer **84** by using a sequence of Dess–Martin oxidation and CBS reduction.[38]



Scheme 14. Enantioselective synthesis of the C1–C34 segment **84** by the Kigoshi group. *Reagents and conditions*: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, THF, toluene, quant.; (b) NH_4F, MeOH,

99%; (c) Dess–Martin periodinane, CH_2Cl_2, 94%; (d) $NiCl_2$, $CrCl_2$, DMSO, 46% (undesired stereoisomer **85**: 49%); (e) Dess–Martin periodinane, pyridine, CH_2Cl_2, 94%; (f) (*S*)-CBS, $BH_3{\cdot}Me_2S$, THF, 80% (undesired stereoisomer **85**: 19%).

Compound **84** was transformed into hybrid molecule **76** following their first-generation total synthesis of aplyronine A (**1**)[7] and the synthesis of a side-chain analogue of mycalolide B[34] (Scheme 15). Thus, they introduced the *N*-methylformamide group at C34, the *O*,*O*-dimethylglyceric ester group at C29, and the *N,N,O*-trimethylserine ester groups at C7 to furnish aplyronine A–mycalolide B hybrid molecule **76**.[22]



aplyronine A–mycalolide B hybrid molecule **76**

Scheme 15. Synthesis of aplyronine A–mycalolide B hybrid molecule **76** by the Kigoshi group. *Reagents and conditions*: (a) NaH, MeI, THF, 99%; (b) HCO_2H, Et_2O, 99%; (c) Dess–Martin periodinane, pyridine, CH_2Cl_2, 88%; (d) MeNHCHO, PPTS, hydroquinone, 3 Å molecular sieves, benzene, 67%; (e) DDQ, buffer (pH 6), CH_2Cl_2, *t*-BuOH, quant.; (f) 2,3-di-*O*-methyl-D-glyceric acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, benzene, quant.; (g) $AgNO_3$, 2,6-lutidine, H_2O, THF; (h) *N*,*N*,*O*-trimethylserine ($S : R = 2 : 1$), 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, benzene, CH_2Cl_2, 95%; (i) HF·pyridine, pyridine, 81%.

The hybrid molecule **76** showed more potent actin-depolymerizing activity (EC_{50} = 1.0 μM) than that of aplyronine A (**1**) (EC_{50} = 1.4 μM). On the other hand, the cytotoxicity of hybrid molecule **76** (IC_{50} = 12 nM) proved to be about 1000-fold weaker than that of aplyronine A (**1**) (IC_{50} = 0.010 nM).[22] These results indicate that there is no direct correlation between actin-depolymerizing activity and cell-growth inhibitory activity, and they are consistent with the finding of tubulin as the second target protein.[8–10,34]

4. CONCLUSION

In this review, we discussed the development of efficient synthetic routes of aplyronines and related compounds to enable further biological evaluations of these compounds. Because aplyronine A shows potent antitumor activity and a unique mechanism of action, it and its related compounds may serve as lead compounds for novel types of anti-cancer chemotherapeutic agents. The development of a more effective method of synthesizing aplyronine A is anticipated.

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